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**Self-Assembled Main-Group Metal Coordination Cages Directed by
Ligand Topology and Stoichiometry**

**Memoria para optar al grado de doctor
presentada por:**

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Fecha de lectura: 27 de enero de 2026

Bajo la dirección del doctor:

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Huelva, 2026





**Universidad
de Huelva**

**Self-Assembled Main-Group Metal Coordination
Cages Directed by Ligand Topology and
Stoichiometry**

**Programa de Doctorado:
Ciencia y Tecnología Industrial y Ambiental**

**Ignacio Izquierdo Sánchez
Tesis Doctoral 2025**

Self-Assembled Main-Group Metal Coordination Cages Directed by Ligand Topology and Stoichiometry

por

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Trabajo presentado para aspirar al
Título de Doctor en Ciencias Químicas

Huelva, octubre 2025

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Note: Full synthetic protocols, experimental details, and complete characterisation data (including NMR, DOSY NMR, HRMS, IR, X-ray crystallography, elemental analyses, and computational details) for all compounds described in this Thesis are provided electronically as Annexes on the USB device accompanying this Doctoral Dissertation.

Abbreviations and Symbols

Abbreviations and Symbols

Å	Angstrom
acac	Acetylacetonate anion (<i>Anión acetilacetonato</i>)
AcOEt	Ethyl acetate (<i>Acetato de etilo</i>)
bipy	2,2'–bipyridine (<i>2,2'–bipiridina</i>)
br	Broad (<i>Ancho</i>)
Bu	Butyl group (<i>Grupo butilo</i>)
°C	Celsius, Degree Celsius (<i>Celsius, Grados Celsius</i>)
CD	Circular Dichroism (<i>Dicroísmo Circular</i>)
CD ₂ Cl ₂	Deuterated dichloromethane (<i>Diclorometano deuterado</i>)
CDCl ₃	Deuterated chloroform (<i>Cloroformo deuterado</i>)
COSY	Correlation Spectroscopy (<i>Espectroscopía de Correlación</i>)
C _q	Quaternary carbon atom (<i>Átomo de carbono cuaternario</i>)
CuAAc	Copper–Catalysed Azide–Alkyne Cycloaddition (<i>Cicloaddición Azida–Alquino Catalizada por Cobre</i>)
Cy	Cyclohexyl group (<i>Grupo ciclohexilo</i>)
d	Doublet (<i>Doblete</i>)
D	Diffusion coefficient (<i>Coeficiente de difusión</i>)
D ₂ O	Deuterium oxide (<i>Agua deuterada</i>)
DCI	Deutero–hydrochloric acid (<i>Ácido clorhídrico deuterado</i>)
DCM	Dichloromethane (<i>Diclorometano</i>)
dd	Doble doublet (<i>Doble doblete</i>)
DFT	Density Functional Theory (<i>Teoría del Funcional de la Densidad</i>)
d _H	Hydrodynamic diameter (<i>Diámetro hidrodinámico</i>)

DMF	Dimethylformamide (<i>Dimetilformamida</i>)
DMF- d_7	Deuterated dimethylformamide (<i>Dimetilformamida deuterada</i>)
DMPA	2,2-dimethoxy-2-phenylacetophenone (<i>2,2-dimetoxi-2-phenilacetofenona</i>)
DMSO	Dimethylsulfoxide (<i>Dimetilsulfóxido</i>)
DMSO- d_6	Deuterated dimethylsulfoxide (<i>Dimetilsulfóxido deuterado</i>)
DNA	Deoxyribonucleic Acid (<i>Ácido desoxirribonucleico</i>)
DOSY	Diffusion Ordered Spectroscopy (<i>Espectroscopia Ordenada por Difusión</i>)
DTE	Dithienylethene (<i>Dietinileteno</i>)
EDTA	Ethylenediaminetetraacetic acid (<i>Ácido etilendiaminotetraacético</i>)
EEM	Electronegativity Equalization Method (<i>Método de Ecuación de Electronegatividades</i>)
en	Ethylenediamine (<i>Etilendiamina</i>)
Eq	Equivalents (<i>Equivalentes</i>)
ESI	Electrospray Ionisation (<i>Ionización por Electrospray</i>)
ESP	Electrostatic Potential (<i>Potencial Electrostático</i>)
Et	Ethyl group (<i>Grupo etilo</i>)
Et ₂ O	Diethyl ether (<i>Éter dietílico</i>)
EtCyHex	cis-(1R,2R)-N,N'-diethyl-1,2-diaminocyclohexane (<i>cis-(1R,2R)-N,N'-dietil-1,2-diaminociclohexano</i>)
EtOH	Ethanol (<i>Etanol</i>)
G	Gibbs energy (<i>Energía de Gibbs</i>)
g	Grams (<i>Gramos</i>)
h	Hours (<i>Horas</i>)
H	Enthalpy (<i>Entalpía</i>)
HCPK	1-hydroxycyclohexyl phenyl ketone (<i>1-hidroxiciclohexil fenil cetona</i>)
HMBC	Heteronuclear Multiple Bond Correlation spectroscopy (<i>Espectroscopia de Enlaces Múltiples Heteronucleares</i>)

HMPP	2-hydroxy-2-methylpropiophenone (<i>2-hidroxi-2-metilpropiofenona</i>)
HRMS	High Resolution Mass Spectrometry (<i>Espectrometría de Masas de Alta Resolución</i>)
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy (<i>Espectroscopia de Correlación Heteronuclear de un Único Cuanto</i>)
Hz	Hertz
iPr	Isopropyl group (<i>Grupo isopropilo</i>)
IR	Infrared Spectroscopy (<i>Espectroscopía de Infrarojo</i>)
ITC	Isothermal Titration Calorimetry (<i>Calorimetría de Titulación Isotérmica</i>)
J	Coupling constant (<i>Constante de acoplamiento</i>)
K	Kelvin, Degree Kelvin (<i>Kelvin, Grados Kelvin</i>)
K	Kilo
K	Equilibrium constant (<i>Constante de equilibrio</i>)
K _a	Affinity constant (<i>Constante de afinidad</i>)
L	Ligand (<i>Ligando</i>)
L	Litre (<i>Litro</i>)
M	Metal (<i>Metal</i>)
M	Molar
m	Mili
m	Metro
m	Multiplet (<i>Multiplete</i>)
M	Mega
Me	Methyl group (<i>Grupo metilo</i>)
MeO	Methoxy groups (<i>Grupos metóxido</i>)
MeOH	Methanol (<i>Metanol</i>)
MIM	Mechanically Interlocked Materials (<i>Materiales Mecánicamente Interconectados</i>)

n	Nano
n-BuOH	Normal butanol (<i>Butanol normal</i>)
NaOD	Sodium deuterioxide (<i>Deuteróxido de sodio</i>)
NMR	Nuclear Magnetic Resonance (<i>Resonancia Magnética Nuclear</i>)
NOESY	Nuclear Overhauser Effect Spectroscopy (<i>Espectroscopía del Efecto Nuclear Overhauser</i>)
PivCl	Pivaloyl Chloride (<i>Cloruro de pivaloilo</i>)
PivOH	Pivalic Acid (<i>Ácido piválico</i>)
ppm	Parts Per Million (<i>Partes Por Millón</i>)
Pr	Propyl group (<i>Grupo propilo</i>)
R ₄ N ⁺	Ammonium organic cations (<i>Cationes orgánicos amonio</i>)
RNA	Ribonucleic Acid (<i>Ácido ribonucleico</i>)
ROESY	Rotating-frame Overhauser Effect Spectroscopy (<i>Espectroscopía del Efecto Overhauser en el Marco Giratorio</i>)
s	Singlet (<i>Singulete</i>)
S	Entropy (<i>Entropía</i>)
s	Seconds (<i>Segundos</i>)
SCC	Supramolecular Coordination Cage (<i>Caja de Coordinación Supramolecular</i>)
t	Triplet (<i>Triplete</i>)
T	Temperature (<i>Temperatura</i>)
TBAF	Tetrabutylammonium Fluoride (<i>Fluoruro de tetrabutilamonio</i>)
TFA	Trifluoro Acetic Acid (<i>Ácido trifluoroacético</i>)
TGA	Thermogravimetric Analysis (<i>Análisis Termogravimétrico</i>)
THF	Tetrahydrofuran (<i>Tetrahidrofurano</i>)
TLC	Thin Layer Chromatography (<i>Cromatografía en Capa Fina</i>)
tmeda	N,N,N,N-tetramethylethylenediamine (<i>N,N,N,N-tetrametiletilendiamina</i>)

TMS	Trimethylsilyl group (<i>Grupo trimetilsililo</i>)
TMSA	Tetramethylsilylacetylene (<i>Acetileno tetrametilsililo</i>)
TOF	Time Of Flight (<i>Tiempo De Vuelo</i>)
UV	Ultraviolet light (<i>Luz ultravioleta</i>)
V	Volt (<i>Voltio</i>)
Vis	Visible light (<i>Luz visible</i>)
δ	Chemical shift in ppm (<i>Desplazamiento químico en ppm</i>)
μ	Micro

Resumen

Resumen

El empleo de metales en la construcción de cajas supramoleculares de coordinación (SCC) es un área de creciente interés en química supramolecular. La mayoría de los ejemplos descritos hasta la fecha se basan en metales de transición y han dado lugar a arquitecturas muy diversas y robustas. Por otro lado, el uso de elementos del bloque p, pese a su claro potencial para generar sistemas tipo caja, ha experimentado un desarrollo comparativamente limitado. Entre los avances más notables destacan los que emplean metales del Grupo 13, en particular, Al^{3+} y Ga^{3+} han mostrado una notable capacidad para formar arquitecturas estables con ligandos orgánicos dadores de oxígeno o nitrógeno. Estos resultados ponen de relieve que las jaulas basadas en elementos del bloque p, apoyadas en el diseño racional de nuevos ligandos, pueden competir con sus análogas construidas con metales de transición.

Por ello, esta *Tesis* Doctoral se centra en la síntesis, caracterización y estudio de nuevas SCC basadas en Al^{3+} , Ga^{3+} y Fe^{3+} , que exhiben propiedades supramoleculares relevantes. En concreto, se presenta un estudio sistemático de sus estructuras en estado sólido y un análisis de su comportamiento en disolución, poniendo de manifiesto su capacidad de encapsular moléculas de interés mediante procesos anfitrión–huésped, así como los factores que gobiernan su estabilidad y reactividad.

La *Tesis* consta de tres *Capítulos* interconectados, cada uno dedicado a SCC de Al^{3+} , Ga^{3+} y Fe^{3+} que presentan estructuras y geometrías distintas y propiedades de encapsulación diferenciadas. Se presta especial atención al diseño de ligandos con topologías diversas, a la influencia de los contraiones orgánicos (R_4N^+) y a la estequiometría metal–ligando empleada para dirigir el autoensamblaje hacia el ensamblaje deseado. Asimismo, se examinan en detalle las estructuras supramoleculares en el estado sólido y su correlación con el comportamiento y las propiedades en disolución, estableciendo criterios de diseño transferibles a nuevas familias de SCC.

Capítulo I

Autoensamblaje y Estructuras de Cajas de Coordinación de Tipo Helicato/Mesocato Ga_2L_3 y Fe_2L_3

El *Capítulo I* se centra en el desarrollo sintético, caracterización y estudio de cajas supramoleculares de coordinación de Ga^{3+} y Fe^{3+} de tipo M_2L_3 , formadas por dos cationes metálicos y tres ligandos orgánicos ditópicos basados en 1,2,3-triazoles y catecol/naftalendiol. Una parte de este trabajo se inspira en los ejemplos desarrollados por Stack y Raymond, quienes en la década de 1990 describieron sistemas de coordinación de tipo M_2L_3 con Ga^{3+} y ligandos basados en catecoles. Estos ejemplos representan los primeros estudios que demuestran el uso de metales del Grupo 13 en la formación de cajas supramoleculares de coordinación robustas y análogas a las descritas previamente por Fujita con metales de transición. A pesar de que los ejemplos descritos de cajas M_2L_3 con metales de los grupos principales son muy limitados, estos sistemas demuestran gran potencial y aplicabilidad en procesos de encapsulación de tipo anfitrión–huésped. Inspirado por estos ejemplos, el *Capítulo I* detalla el diseño, aislamiento y estudio de nuevas SCC de Ga^{3+} y Fe^{3+} de tipo M_2L_3 basadas en nuevos ligandos de tipo 1,2,3–triazol–catecol/naftalendiol.

Para la síntesis y aislamiento de estas cajas aniónicas $[M_2L_3]^{6-}$ ($M = Ga$ y Fe), se prepararon una familia de ligandos simétricos ditópicos basados en 1,2,3-triazoles con grupos catecol y naftalendiol, L^1 – L^5 (Figura 1), obtenidos mediante una ciclación 1,3–dipolar (CuAAC) entre azidas y alquinos catalizada por Cu. Las azidas utilizadas presentan grupos metoxi (OMe) como protectores, que tras la desprotección generan los dioles de tipo catecol/naftalendiol que actúan como puntos de anclaje del ligando al catión metálico. El alquino aromático define el núcleo del ligando, separado del sitio de anclaje por los anillos 1,2,3–triazol como nexos de unión.

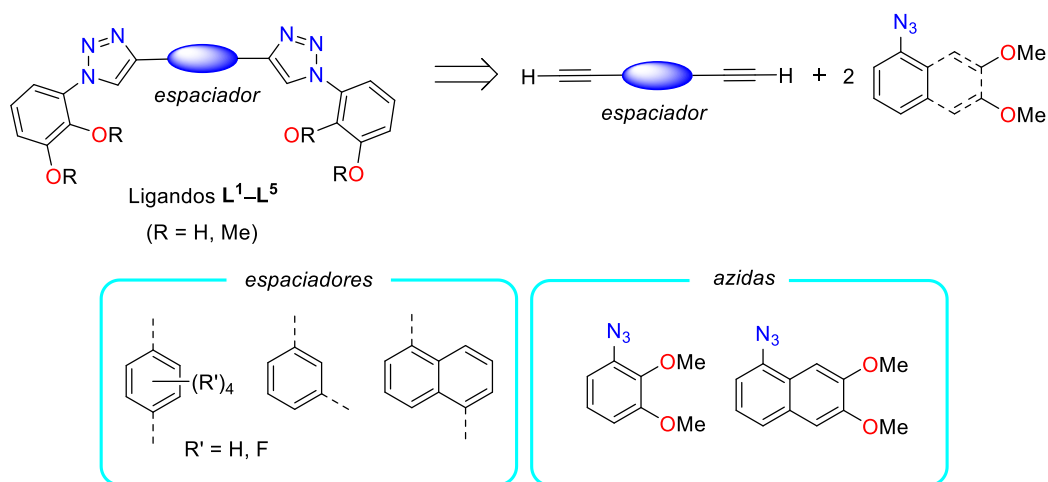


Figura 1. Síntesis de ligandos ditópicos L^1-L^5 descritos en el *Capítulo I*.

Estos ligandos forman cajas de coordinación robustas de tipo M_2L_3 con metales oxófilos como Ga^{3+} o Fe^{3+} (Figura 2). Para la formación de las cajas M_2L_3 se empleó KOH como base fuerte para desprotonar los grupos catecol y naftalendiol, y favorecer la coordinación de los diversos ligandos a los cationes metálicos. Se emplearon los derivados de acetil acetonato de cada metal, $M(acac)_3$, como fuente de los iones metálicos en disolución. Además, en algunos casos se añadió bromuro de tetraetilamonio (Et_4NBr) para favorecer la precipitación y el aislamiento de las cajas M_2L_3 . La formación de estas arquitecturas supramoleculares se estudió mediante RMN (1H , ^{13}C y DOSY), difracción de rayos-X y espectrometría de masas de alta resolución. Los estudios realizados mediante cristalografía de estas cajas de coordinación de tipo M_2L_3 permitieron conocer la naturaleza heterometálica de estas cavidades supramoleculares en estado sólido, debido a la encapsulación de iones K^+ en el interior. Estos iones K^+ permanecen unidos a los oxígenos de los grupos catecolato y naftalendiolato.

Entre las modificaciones electrónicas y estéricas de los ligandos orgánicos estudiadas en este *Capítulo*, se observó que las modificaciones estéricas, como, por ejemplo, la introducción de grupos naftalendiol como puntos de anclaje a los cationes metálicos en M_2L_3 , es uno de los efectos que mayor impacto tienen en la solubilidad, la geometría y el tamaño de la cavidad de las cajas resultantes.

Capítulo I
Cajas M_2L_3

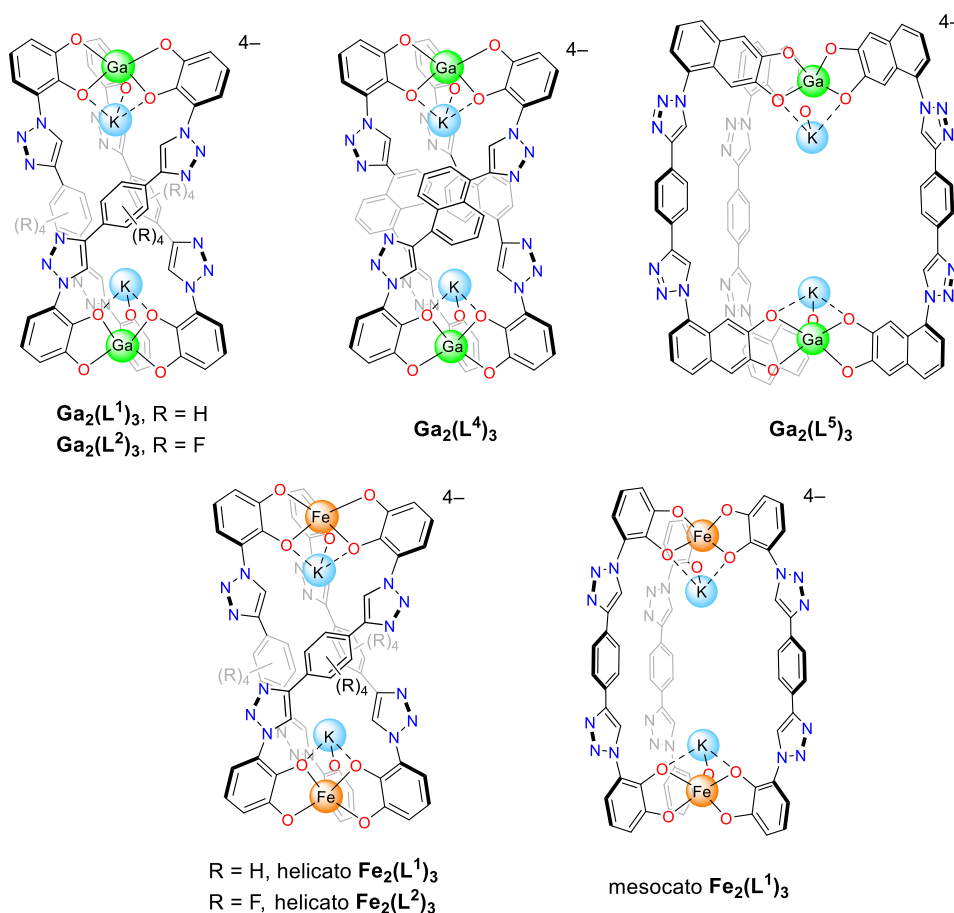


Figura 2. Cajas de coordinación M_2L_3 descritas en el *Capítulo I*.

Además, observamos que la presencia o ausencia de cationes amonio puede influir drásticamente en el proceso de autoensamblaje de las cajas Fe_2L_3 dirigiendo la síntesis hacia la formación de cajas de tipo helicatal o mesocatal, respectivamente (Figura 2). Así, los cationes Et_4N^+ son capaces de estabilizar de forma selectiva la formación de helicatos de tipo Fe_2L_3 . Este es un proceso selectivo que depende del metal, observándose tal selectividad únicamente para las cajas Fe_2L_3 , no existiendo el mismo efecto para los sistemas de Ga_2L_3 .

Por tanto, el *Capítulo I* pone de manifiesto que metales del Grupo 13 como Ga y metales de transición como Fe forman SCC estables y robustas de tipo M_2L_3 con ligandos ditópicos 1,2,3-triazol-catecol/naftalendiol, mostrando cavidades que pueden alojar K^+ . Además, mediante el diseño de estos nuevos ligandos ditópicos y el control de los contraiones, es posible dirigir selectivamente el autoensamblaje hacia geometrías específicas de tipo mesocatal o helicatal Fe_2L_3 , modulando de forma directa las dimensiones de estas cavidades. Más allá de ampliar el número

de sistemas y ejemplos sintéticos de cajas de tipo M_2L_3 , este trabajo sienta las bases para futuras aplicaciones de estos sistemas como posibles interruptores moleculares, potencial aplicación en química de encapsulación anfitrión–huésped y en catálisis supramolecular, donde las propiedades electrónicas, la presencia de K^+ encapsulados y el tamaño/forma de la cavidad podrían proporcionar nuevas propiedades.

Capítulo II

Autoensamblaje, Estructuras y Química Anfitrión–Huésped de Cajas de Coordinación Tetraédricas Al_4L_4 y Ga_4L_4

En el *Capítulo II* se detalla el estudio de la química supramolecular de coordinación de ligandos tritópicos basados en 1,2,3-triazoles, centrándonos en la obtención de cajas tetraédricas M_4L_4 ($M = Al^{3+}$ y Ga^{3+}). Aquí, a diferencia del *Capítulo I*, se desarrollan ligandos tritópicos específicos L^6 – L^{10} (Figura 3), siguiendo un protocolo sintético de química “Click” mediante triples cicloadiciones de tipo 3+2.

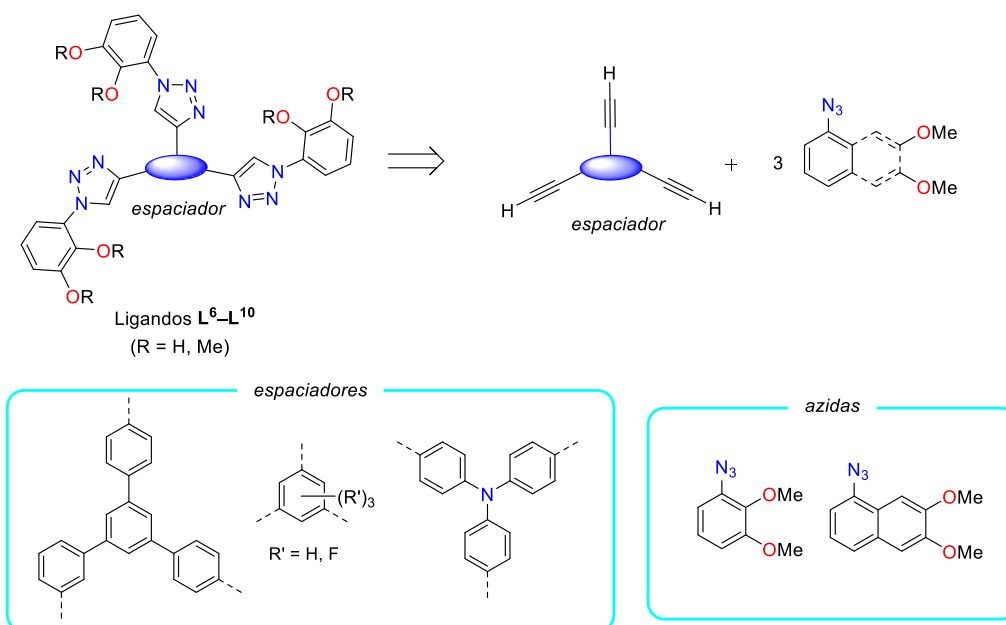


Figura 3. Síntesis de ligandos tritópicos L^6 – L^{10} descritos en el *Capítulo II*.

Parte de este trabajo se inspira en el descrito por Raymond, quien en 1998 presentó la primera caja tetraédrica aniónica Ga_4L_6 con ligandos ditópicos amida–

catecol. En estos sistemas los ligandos constituyen las aristas del tetraedro y los cationes metálicos los vértices. Estas arquitecturas ofrecen cavidades con potencial para encapsular huéspedes catiónicos (sales de amonio o complejos organometálicos), y han demostrado tener propiedades catalíticas mediante el confinamiento o encapsulación de especies catalíticamente activas. Por ejemplo, se han aplicado en transformaciones orgánicas como Aza–Cope o en la hidrólisis de ortoformatos, así como en adición oxidante y procesos de eliminación reductora de complejos organometálicos de metales de transición encapsulados en su interior. Debido a los escasos ejemplos de cajas de coordinación supramoleculares del tipo M_nL_m descritos en la actualidad con metales distintos a los de transición, el *Capítulo II* detalla el diseño, autoensamblaje, estudio estructural y aplicación en química anfitrión–huésped de una nueva familia de cajas tetraédricas M_4L_4 de Ga^{3+} y Al^{3+} (Figura 4) basadas en ligandos 1,2,3-triazol–catecol tritópicos (L^6 – L^9), incluyendo además, una variante expandida con naftalendiol (L^{10}).

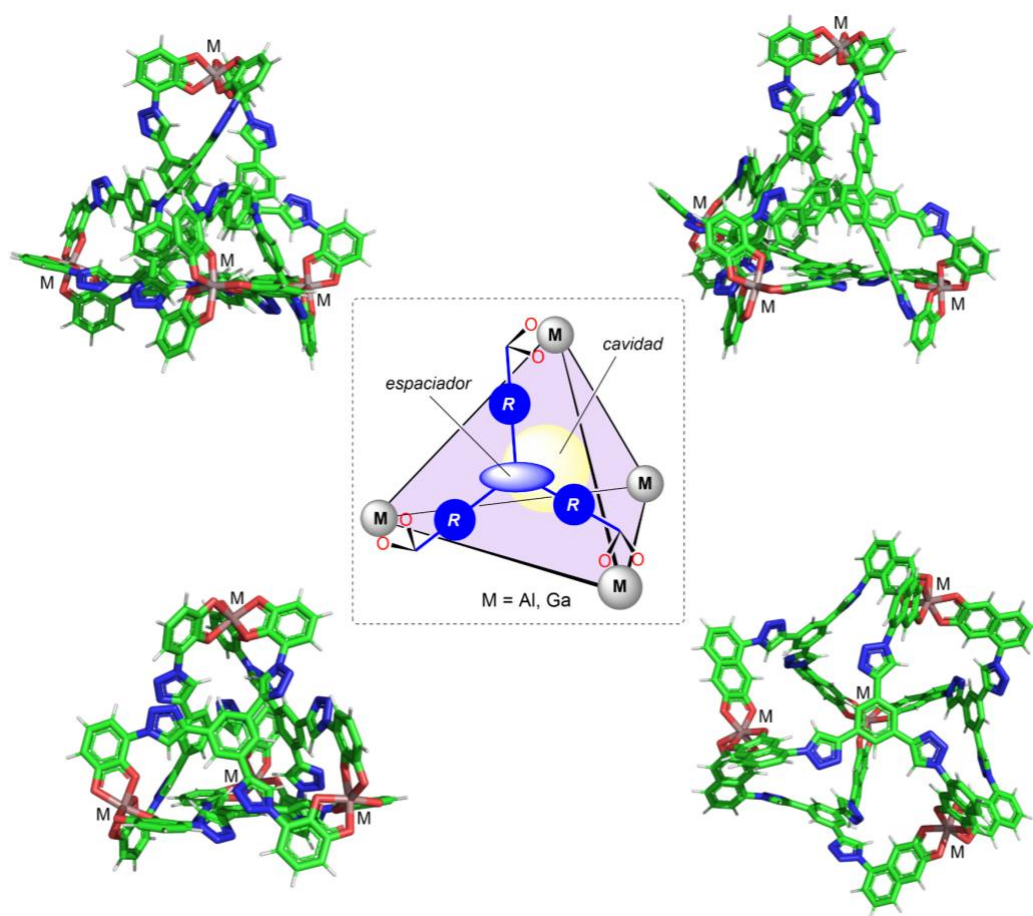


Figura 4. Familia de cajas tetraédricas M_4L_4 descritas en el *Capítulo II*.

Por ello, para la síntesis y aislamiento de estas cajas M_4L_4 de Ga^{3+} y Al^{3+} , se empleó KOH para la desprotonación de los ligandos tritópicos y las sales de acetilacetato $M(acac)_3$ como fuente de dichos metales. Además, en algunos casos se añadió bromuro de tetraetilamonio (Et_4NBr) para favorecer la precipitación y el aislamiento de las cajas. La estequiometría metal–ligando $M:L$ 1:1 usada en este *Capítulo* es clave para la formación selectiva de cajas tetraédricas de tipo M_4L_4 con ligandos tritópicos. La formación de estas cajas M_4L_4 se estudió por RMN (1H , ^{13}C y DOSY), por difracción de rayos-X y por masas de alta resolución. Los estudios cristalográficos ponen de manifiesto cavidades heterometálicas en sólido por encapsulación de K^+ , análogo a lo observado en M_2L_3 del *Capítulo I*. Desde el punto de vista estructural, los ligandos tritópicos L^6 – L^{10} permiten modular el volumen de cavidad y la flexibilidad de las cajas M_4L_4 . Este efecto es comúnmente conocido como respiración de las cajas supramoleculares de coordinación o “*breathing*” en disolución. Por ejemplo, la caja $Ga_4(L^6)_4$ (ligando basado en catecol y espaciador C_6H_3) puede expandirse en presencia de moléculas de disolvente en su interior (cavidad vacía $86 \text{ \AA}^3 \rightarrow$ cavidad con microsolvatación $503 \text{ \AA}^3$), mientras que $Ga_4(L^{10})_4$ (ligando basado en naftalendiol y el mismo espaciador C_6H_3) exhibe una cavidad grandes dimensiones (cavidad vacía $1148 \text{ \AA}^3$). Por otro lado, las cajas $Ga_4(L^8)_4$ (ligando basado en catecol y espaciador de tipo amina) y $Ga_4(L^9)_4$ (ligando basado en catecol y espaciado de tipo trifenilbenceno) presentan cavidades de pequeñas dimensiones (cavidades vacías $< 25 \text{ \AA}^3$) debido a la congestión estérica que presenta los sistemas ensamblados y la presencia de interacciones de tipo $\pi \cdots \pi$ entre ligandos. Estas tendencias explican los efectos de expansión/contracción de las cajas y la diversidad de tamaños de sus cavidades en disolución (H_2O), y, por ende, evidencia los procesos de *breathing* en estas cajas supramoleculares tetraédricas M_4L_4 .

Para profundizar en el comportamiento en disolución de las cajas tetraédricas M_4L_4 en disolución, se estudió la capacidad encapsulante de la caja tetraédrica $M_4(L^6)_4$ ($M = Al, Ga$) en presencia de cationes amonio R_4N^+ (Me_4N^+ , Et_4N^+ , Pr_4N^+ y Bu_4N^+) en agua, dada su naturaleza aniónica y las adecuadas dimensiones de sus cavidades hidrofóbicas (Figura 5). Los estudios de encapsulación anfitrión–huésped mediante RMN (1H , NOESY, DOSY) y calorimetría isotérmica ITC muestran que la afinidad depende predominantemente del tamaño del huésped. Los cationes Me_4N^+ , Et_4N^+ y Pr_4N^+ son encapsulados de forma eficiente con constantes de afinidad K_a en el rango 10^3 – 10^4 M^{-1} , con estequiometría 1:1 y formando complejos anfitrión–

huésped estables, mientras que el Bu_4N^+ es demasiado voluminoso para ser encapsulado. Los perfiles termodinámicos ITC indican procesos predominantemente dirigidos por entropía (liberación de moléculas de disolvente del interior de la cavidad), con afinidades K_a siguiendo el orden $\text{Et}_4\text{N}^+ > \text{Me}_4\text{N}^+ > \text{Pr}_4\text{N}^+$. Además, existen comportamientos diferenciados entre la caja Al_4L_4 y la de Ga_4L_4 . La caja Al_4L_4 tiende a preferir huéspedes más pequeños (Me_4N^+), mientras que la caja análoga Ga_4L_4 favorece la encapsulación de huéspedes de mayor tamaño (Et_4N^+ y Pr_4N^+), y requiere además, menor saturación para alcanzar condiciones de equilibrio (Pr_4N^+ se sitúa en la frontera de tamaño y Bu_4N^+ no se encapsula). Estas observaciones evidencian el cumplimiento de la “*regla de Rebek*” con ocupaciones durante la encapsulación de los diversos cationes amonio ~45–65 % del volumen de cavidad.

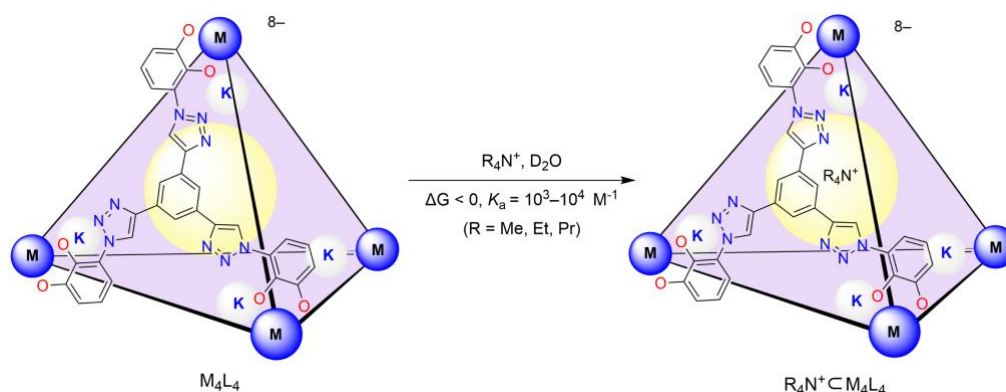


Figura 5. Encapsulación de cationes R_4N^+ en cajas tetraédricas $\text{M}_4(\text{L}^6)_4$ ($\text{M} = \text{Al, Ga}$) descritas en el *Capítulo II*.

Es por todo esto, que el *Capítulo II* representa un avance significativo en química supramolecular de coordinación, al desarrollarse nuevas cajas tetraédricas, Ga_4L_4 y Al_4L_4 , como alternativas a las cajas de metales de transición, y ampliar el número de sistemas SCC a metales del bloque p. La posibilidad de modular el volumen de cavidad mediante el diseño de los nuevos ligandos tritópicos (L^6 – L^{10}) y la demostrada encapsulación anfitrión–huésped selectiva de cationes orgánicos, sugieren aplicaciones en catálisis supramolecular y encapsulación selectiva de moléculas huésped de interés, donde tamaño/forma de cavidad, flexibilidad y naturaleza del metal determinan el reconocimiento y la afinidad.

Capítulo III

Ensamblaje Reversible y Cooperativo de Cajas de Coordinación Triplemente Interconectadas Al_6L_4 y Ga_6L_4

El *Capítulo III* describe cajas supramoleculares triplemente interconectadas (“*triply interlocked [2]catenanes*”) de Al^{3+} y Ga^{3+} de estequiometría M_6L_4 , totalmente distintas en geometría, estructura y propiedades de las cajas M_2L_3 presentadas en el *Capítulo I* y aquellas cajas tetraédricas M_4L_4 detalladas en el *Capítulo II*. Bajo condiciones acuosas básicas, una estequiometría $M:L \sim 1:1$ produce cajas tetraédricas M_4L_4 (por ejemplo, $[M_4L_4]^{12-}$ en el *Capítulo 2*), mientras que al aumentar la estequiometría de metal a $M:L \sim 3:2$ se favorece la formación de cajas M_6L_4 de tipo [2]catenano doblemente entrelazadas en el *Capítulo 3* (Figura 6). Los ejemplos previos de este tipo de cajas triplemente interconectadas, de tipo [2]catenano de coordinación, han sido exclusivamente estudiadas con metales de transición. Aunque en los años noventa Stack y Raymond demostraron la viabilidad de cajas con metales del bloque p, y Fujita describió los primeros ensamblajes de cajas de coordinación interconectadas con Pd y Pt, la obtención y estudio de cajas de este tipo con metales del bloque p ha permanecido completamente inexplorado. Los ejemplos descritos en este *Capítulo* son las primeras estructuras supramoleculares de cajas interconectadas con metales distintos a los de transición.

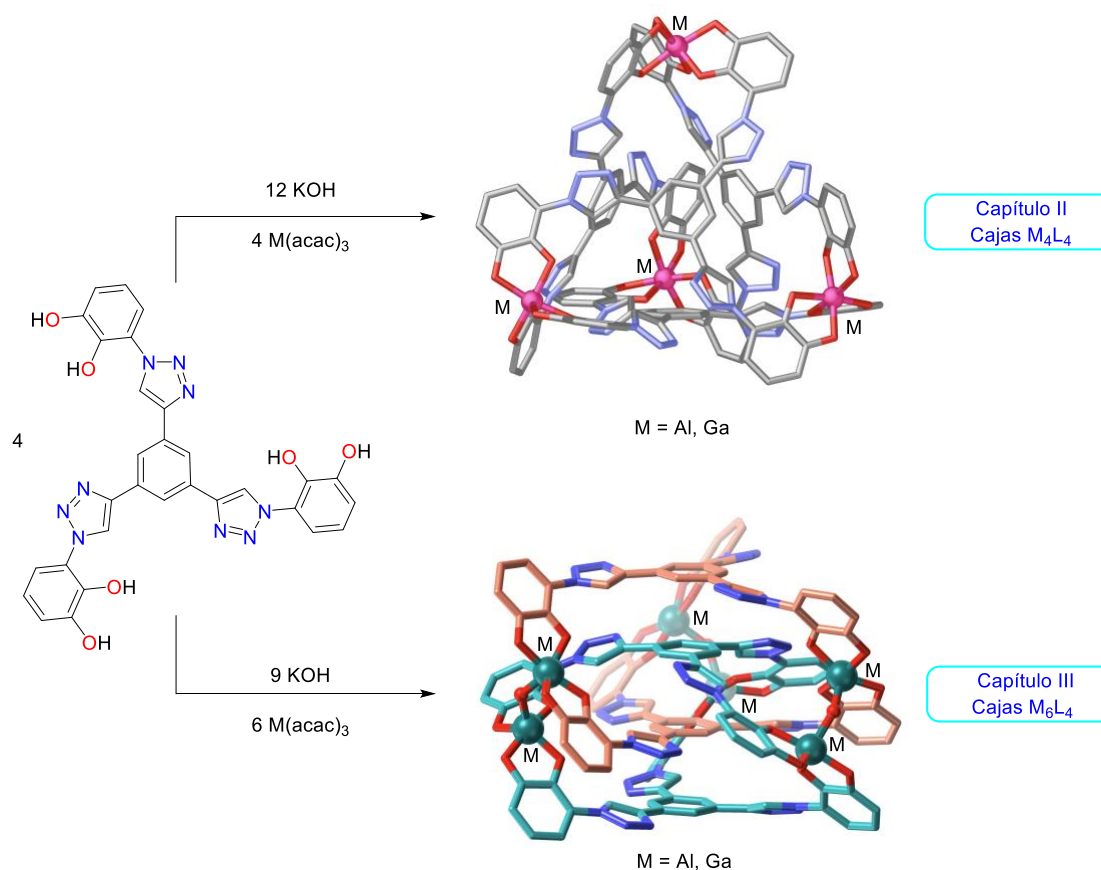


Figura 6. Cajas tetraédricas M₄L₄ (*Capítulo II*) e interconectadas M₆L₄ (*Capítulo III*).

Aprovechando el conocimiento adquirido con las cajas M₂L₃ y M₄L₄, en el *Capítulo III* se presenta una serie de estudios de autoensamblaje de ligandos tritópicos 1,2,3-triazol–catecol (**L**⁶ y su análogo fluorado **L**⁷) y su capacidad para formar cajas interconectadas de tipo M₆L₄ con Al³⁺ y Ga³⁺, ampliando así, por primera vez, la familia de cajas de este tipo al bloque p (Figura 6). La estequiometría metal–ligando (6:4) empleada en este *Capítulo* es clave para la formación selectiva de cajas interconectadas de tipo M₆L₄, evitando así la formación de cajas tetraédricas M₄L₄ con ligandos tritópicos.

Los estudios espectroscópicos mediante RMN, DOSY y NOESY, así como los estructurales por difracción de rayos-X, revelan similitudes y diferencias clave respecto a los análogos con metales de transición. En concreto, estos [2]catenanos de coordinación triplemente intreconectados presentan helicidad M/P, donde dos subunidades monoméricas M₃L₂ quedan entrelazadas mediante seis enlaces metal–catecolato y tres puentes μ-OH, estabilizadas además por la presencia de contactos de tipo π⋯π y de interacciones C–H⋯O. Además, estas estructuras muestran reversibilidad durante su formación (procesos de ensamblaje y desensamblaje

reversibles) en H_2O a temperatura ambiente, mediante cambios de pH (ácido/base, ensamblaje/desensamblaje). Estos procesos de formación fueron monitorizados por RMN, observándose que siguen rutas mecanísticas altamente cooperativas hacia el ensamblaje directo de cajas interconectadas M_6L_4 , sin detección de intermedios monoméricos M_3L_2 , a diferencia de lo que ocurre habitualmente en sistemas del bloque d.

Para profundizar en la naturaleza reversible de estos procesos de autoensamble, se realizaron estudios termodinámicos mediante calorimetría isotérmica ITC. Los análisis demuestran que el desensamblaje de estas cajas M_6L_4 está dirigido entrópicamente, mientras que el re-ensamblaje está fuertemente dirigido por una contribución entálpica. La caja Ga_6L_4 resulta ~500 veces más estable que la caja análoga Al_6L_4 , efecto que es atribuido a una coordinación Ga–O más fuerte entre el metal y los ligandos catecolato y $\mu\text{-OH}$, además de una contribución estabilizadora mucho más importante del apilamiento de tipo π en la caja de Ga_6L_4 . Esto demuestra que el mecanismo de desensamblaje y re-ensamblaje, además de ser reversible, es dependiente del metal (Al vs Ga).

Estos hallazgos demuestran que las cajas mecánicamente interconectadas M_6L_4 son estructuras reversibles y capaces de modificar su topología según las condiciones de pH. Estas evidencias experimentales proporcionan un conocimiento fundamental sobre los procesos de autoensamblaje cooperativo de sistemas de coordinación supramoleculares M_6L_4 más allá de los sistemas convencionales del bloque d, ofreciendo nuevas oportunidades para el desarrollo de materiales y ensamblajes supramoleculares con respuesta a estímulos externos.

Summary

Summary

The use of metals to construct Supramolecular Coordination Cages (SCCs) is a rapidly evolving area in supramolecular chemistry. Most reported examples rely on transition metals, giving a diverse and robust set of M_nL_m coordination architectures. In contrast, the use of p-block metals, despite their clear potential to generate cage-type M_nL_m systems, has experienced limited development. Among the most notable advances are those involving Group 13 metals, particularly Al^{3+} and Ga^{3+} , which have shown a remarkable ability to form stable architectures with oxygen- or nitrogen-donor organic ligands. These results highlight that p-block metal M_nL_m cages, supported by the rational design of new ligands, can compete with their transition-metal-based cage analogues.

Therefore, this *Doctoral Thesis* is focused on the synthesis, characterisation, and study of new SCCs based on Al^{3+} , Ga^{3+} and Fe^{3+} , which exhibit relevant supramolecular properties. Specifically, a systematic study is presented on the solid-state new M_nL_m cages and an analysis of their behaviour in solution, demonstrating their ability to encapsulate guest molecules through host-guest processes, as well as the factors that govern their self-assembly, stability and reactivity.

The *Thesis* comprises three interconnected *Chapters*, each dedicated to M_nL_m cages of Al^{3+} , Ga^{3+} and Fe^{3+} , which display distinct topologies and encapsulation properties. Special attention is paid to the design of new ligands with diverse geometries, the influence of secondary metal (K^+) and organic counterions (R_4N^+), and the metal-ligand stoichiometry used to direct the self-assembly toward the desired architecture. Furthermore, the supramolecular cage structures are scrutinised and correlated with their solution behaviour, providing transferable design criteria for designing and developing SCCs based on main-group metals.

Chapter I

Self-Assembly and Structures of Helicate/Mesocate

Coordination Cages Ga_2L_3 and Fe_2L_3

Chapter I focuses on the synthetic development, characterisation, and study of M_2L_3 supramolecular coordination cages, assembled from two metal cations (Ga^{3+} and Fe^{3+}) and three ditopic organic ligands based on 1,2,3-triazoles and catechol/naphthalenediol units. Part of this work is inspired by the examples developed by Stack and Raymond, who in the 1990s described the first M_2L_3 cage systems with Ga^{3+} and catechol-based ligands. These examples demonstrate the use of Group 13 metals in the formation of robust supramolecular coordination cages, analogous to those previously described by Fujita using d block metals. Although reported examples of M_2L_3 cages with main group metals are very limited, these cages show great potential and applicability in host–guest encapsulation processes. Building on this, *Chapter I* details the design, isolation, and study of new Ga_2L_3 and Fe_2L_3 cages based on novel 1,2,3-triazole–catechol/naphthalenediol ligands.

For the synthesis and isolation of these anionic cages $[\text{M}_2\text{L}_3]^{6-}$ ($\text{M} = \text{Ga}^{3+}$ and Fe^{3+}), a new family of symmetrical ditopic ligands based on 1,2,3-triazoles bearing catechol and naphthalenediol groups, $\text{L}^1\text{--L}^5$ (Figure 1), was prepared. These ligands were obtained via a Cu-catalysed 1,3-dipolar cycloaddition (CuAAC) between azides and bis(alkynes). The azides used feature methoxy (OMe) groups as protecting groups, which, upon deprotection, yield the catechol/naphthalenediol groups that anchor the ligands to the metal cations. The aromatic bis(alkyne) units define the ligand cores, linked to the binding through 1,2,3-triazole rings.

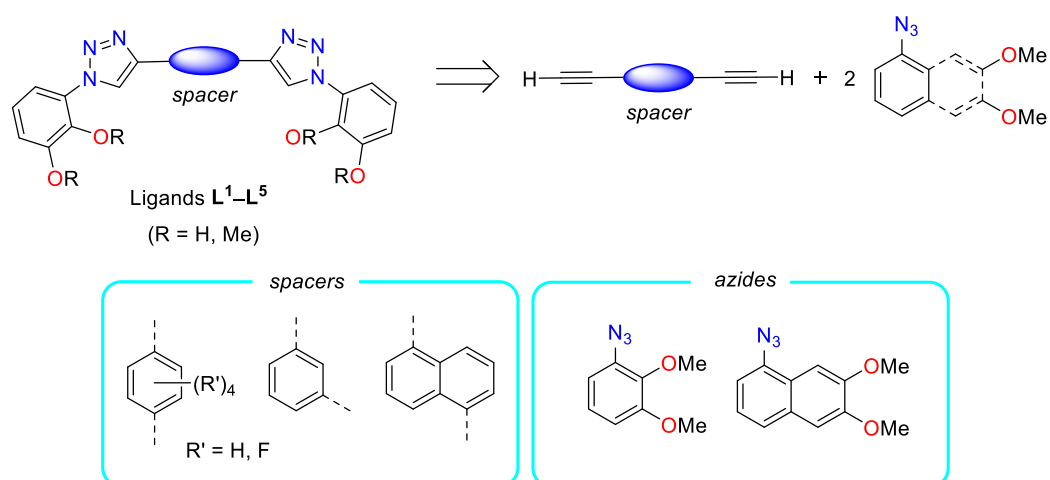


Figure 1. Synthesis of ditopic ligands L^1 – L^5 described in *Chapter I*.

These ligands form robust M_2L_3 coordination cages with oxophilic metals Ga^{3+} and Fe^{3+} (Figure 2). The assembly of the M_2L_3 cages was performed in the presence of KOH to deprotonate the catechol and naphthalenediol groups and promote coordination the Ga^{3+} and Fe^{3+} metal joints. Metal acetylacetonate reagents, $M(acac)_3$, provided the Ga^{3+} and Fe^{3+} metal ions in solution. Additionally, in selected cases, tetraethylammonium bromide (Et_4NBr) was added to aid precipitation and isolation of the M_2L_3 cages. The formation of these supramolecular architectures was elucidated by NMR spectroscopy (1H , ^{13}C and DOSY), X-ray diffraction, and high-resolution mass spectrometry. Crystallographic studies of the M_2L_3 cages revealed the heterometallic nature of the supramolecular cavities in the solid state, due to the encapsulation of K^+ ions within their internal cavities. These K^+ ions remain coordinated to the inner oxygen atoms of the catecholate and naphthalenediolate groups.

Among the electronic and steric modifications of the organic ligands studied in this *Chapter*, radial steric modifications such as the introduction of naphthalenediol (vs catechol) groups at the metal anchoring site in M_2L_3 cages, has a pronounced impact on solubility, geometry, and cavity size of the resulting M_2L_3 cages.

Chapter I
M₂L₃ Cages

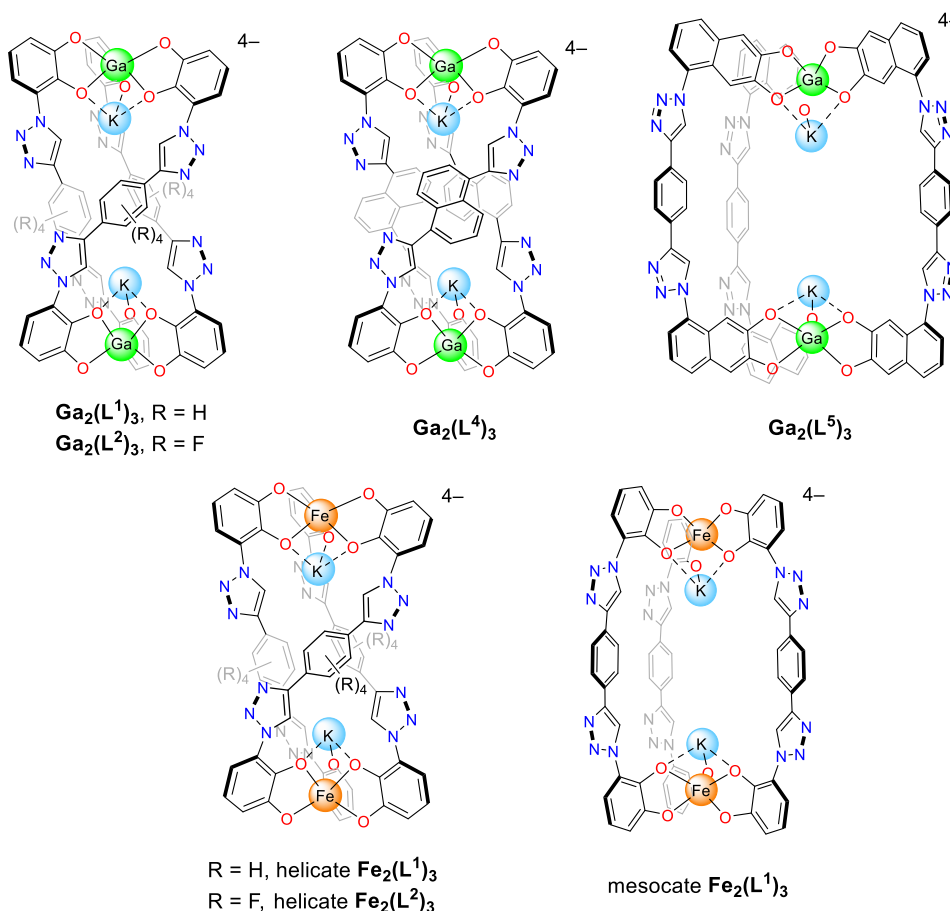


Figure 2. M₂L₃ coordination cages described in *Chapter I*.

Furthermore, we observed that the presence or absence of ammonium cations can drastically influence the self-assembly process of Fe₂L₃ cages, directing the self-assembly toward the formation of either helicate or mesocate M₂L₃ cages, respectively (Figure 2). In particular, Et₄N⁺ cations are capable of selectively stabilizing the formation of Fe₂L₃ helicates. This metal-dependent selectivity is observed for Fe₂L₃, but not for Ga₂L₃, which remain helicates under analogous conditions.

Thus, *Chapter I* shows that both Group 13 metals such as Ga³⁺ and transition metals such as Fe³⁺ form stable and robust M₂L₃ cages with 1,2,3-triazole-catechol/naphthalenediol ditopic ligands, displaying cavities capable of encapsulating K⁺ ions. Moreover, through the design of these new ditopic ligands and counterion-control, it is possible to selectively direct the self-assembly toward either mesocate or helicate Fe₂L₃ cages, thereby modulating cavity dimensions. Beyond expanding the synthetic repertoire of M₂L₃ cages, this *Chapter* lays the

groundwork for new molecular switching, host–guest encapsulation, and supramolecular catalysis, where electronic properties, encapsulation of K^+ ions, and cavity size/shape could unlock new functions in developing main–group metal bases M_2L_3 cage systems.

Chapter II

Self-Assembly, Structures and Host–Guest Chemistry of Tetrahedral Coordination Cages Al_4L_4 and Ga_4L_4

Chapter II explores the supramolecular coordination chemistry of tritopic ligands based on 1,2,3–triazoles, focusing on the formation of tetrahedral M_4L_4 cages ($M = Al^{3+}$, Ga^{3+}). Akin to *Chapter I*, here the tritopic ligands L^6 – L^{10} (Figure 3) were developed via a click 3+2 cycloaddition protocol from tris–alkyne and aromatic azide precursors.

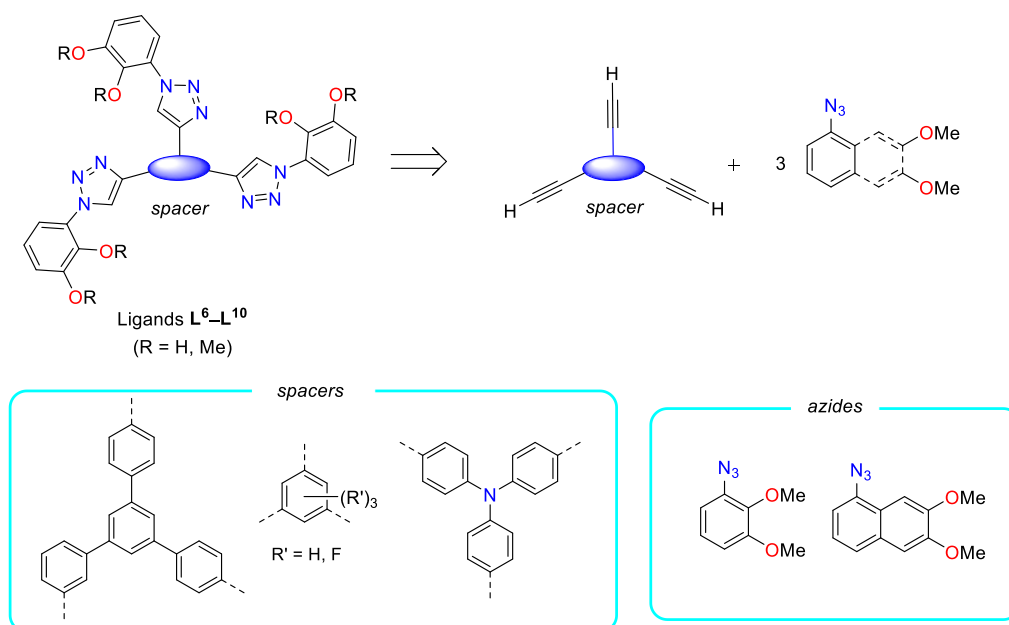


Figure 3. Synthesis of tritopic ligands L^6 – L^{10} described in *Chapter II*.

This work is partially inspired by the developments from Raymond, who in 1998 reported the first anionic tetrahedral cages Ga_4L_6 , assembled from ditopic amide–catechol ligands. In these systems, the ligands constitute the edges of the

tetrahedron, while the metal cations occupy the vertices. These architectures offer cavities with potential for encapsulating cationic guests, such as ammonium ions or organometallic complexes, and have demonstrated catalytic properties through the confinement or encapsulation of reactive species. For instance, they have been applied to catalyse organic transformations such as the Aza–Cope rearrangement, hydrolysis of orthoformates, as well as in oxidative addition and reductive elimination processes involving transition metal organometallic complexes encapsulated within these Ga_4L_6 cages. Given the limited number of supramolecular coordination cages of the M_nL_m type reported to date that incorporate metals different than transition metals, *Chapter II* details the design, self-assembly, structural study, and host-guest chemistry of a new family of tetrahedral M_4L_4 cages of Ga^{3+} and Al^{3+} (Figure 4), assembled from tritopic 1,2,3-triazole–catechol ligands (L^6 – L^9), including an expanded variant with a naphthalenediol unit (L^{10}).

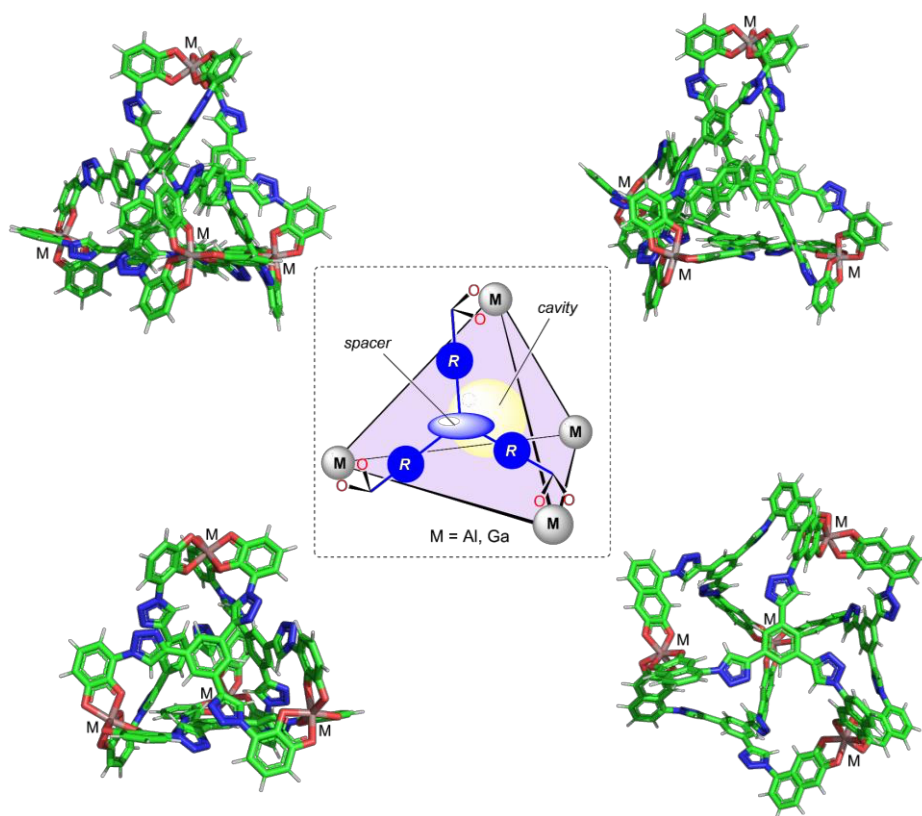


Figure 4. Family of tetrahedral M_4L_4 cages described in *Chapter II*.

The synthesis and isolation of these Al_4L_4 and Ga_4L_4 cages involved the use of KOH to deprotonate the tritopic ligands, along with the corresponding metal

acetylacetonate salts $M(\text{acac})_3$ as metal source. Additionally, in some cases, tetraethylammonium bromide (Et_4NBr) was added to promote the precipitation and isolation of the M_4L_4 cages. The metal–ligand $M:L$ 1:1 stoichiometry used in this *Chapter* is key for the selective formation of tetrahedral M_4L_4 cages with the tritopic ligands. The formation of these M_4L_4 architectures was studied by NMR spectroscopy (^1H , ^{13}C y DOSY), X-ray diffraction, and high-resolution mass spectrometry. Crystallographic studies revealed heterometallic cavities in the solid state through K^+ encapsulation, analogous to the behaviour observed in the M_2L_3 cages described in *Chapter 1*. From a structural perspective, the tritopic ligands L^6 – L^{10} allow for modulation of both cavity volume and flexibility in the M_4L_4 cages. This effect is commonly referred to as the "breathing" behaviour of supramolecular coordination cages in solution. For example, the $\text{Ga}_4(L^6)_4$ cage (based on a catechol ligand with a C_6H_3 core) can expand in the presence of solvent molecules within the cavity (from an empty cavity of $86 \text{ \AA}^3$ to a microsolvated cavity of $503 \text{ \AA}^3$), whereas $\text{Ga}_4(L^{10})_4$ (based on a naphthalenediol ligand with the same C_6H_3 core) exhibits a large intrinsic cavity (empty cavity of $1148 \text{ \AA}^3$). On the other hand, $\text{Ga}_4(L^8)_4$ (a catechol–based ligand with an amine–type spacer) and $\text{Ga}_4(L^9)_4$ (a catechol–based ligand with a triphenylbenzene spacer) form cages with much smaller cavity volumes (empty cavities $< 25 \text{ \AA}^3$), due to the steric congestion in the assembled systems and the presence of $\pi \cdots \pi$ interactions between ligands. These trends explain expansion/contraction effects and the range of cavity sizes observed in H_2O , thus providing clear evidence of the "breathing" processes in these tetrahedral M_4L_4 cages in solution.

To further investigate their behaviour of the tetrahedral M_4L_4 cages in solution, the encapsulation capacity of the $M_4(L^6)_4$ cage ($M = \text{Al}, \text{Ga}$) was studied in the presence of ammonium R_4N^+ (Me_4N^+ , Et_4N^+ , Pr_4N^+ y Bu_4N^+) in water, given the anionic nature of the cage and the suitable dimensions of its hydrophobic cavities (Figure 5). Host–guest encapsulation studies were monitored by NMR (^1H , NOESY, DOSY) and isothermal titration calorimetry (ITC), revealing that affinity is predominantly governed by the size of the guest. The cations Me_4N^+ , Et_4N^+ y Pr_4N^+ are efficiently encapsulated with association constants (K_a) in the range of 10^3 – 10^4 M^{-1} , following a 1:1 host–guest stoichiometry and forming stable complexes, while Bu_4N^+ is too bulky to be encapsulated.

The ITC thermodynamic profiles indicate entropy–driven encapsulation processes (due to the release of solvent molecules from the cavity interior and

desolvation of the guests), with affinities following the trend $\text{Et}_4\text{N}^+ > \text{Me}_4\text{N}^+ > \text{Pr}_4\text{N}^+$. Moreover, distinct behaviours were observed between the Al_4L_4 and Ga_4L_4 cages. The Al_4L_4 cage tends to prefer smaller guests (Me_4N^+), whereas the analogous Ga_4L_4 cage favours the encapsulation of larger guests (Et_4N^+ and Pr_4N^+), and requires lower saturation to reach equilibrium conditions (Pr_4N^+ lies at the size threshold, while Bu_4N^+ is not encapsulated). These observations are consistent with “*Rebek’s rule*”, with guest occupancies during encapsulation ranging from approximately 45–65% of the cavity volume.

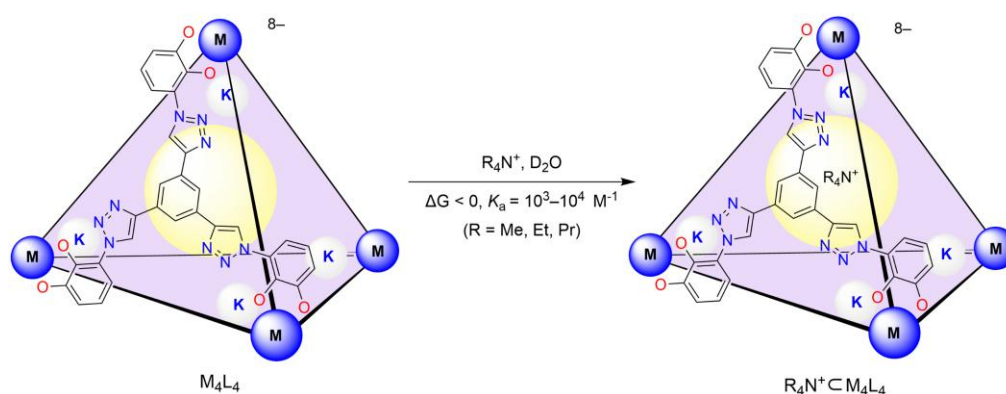


Figure 5. Encapsulation of R_4N^+ cations in the $\text{M}_4(\text{L}^6)_4$ tetrahedral cages ($\text{M} = \text{Al}, \text{Ga}$) described in *Chapter II*.

Overall, *Chapter II* represents a significant advance in supramolecular coordination chemistry by delivering a method to selectively assemble tetrahedral, Al_4L_4 and Ga_4L_4 cages as alternatives to transition metal cages, thereby broadening the scope of SCC systems to p-block metals. The ability to tune cavity volume through ligand design (L^6 – L^{10}) and the selective encapsulation of organic cations suggest applications in supramolecular catalysis and selective guest uptake, where cavity size/shape, flexibility, and metal identity dictate recognition and guest affinity.

Chapter III

Cooperative Reversible Assembly of Triply Interlocked Coordination Cages Al_6L_4 and Ga_6L_4

Chapter III describes triply interlocked [2]catenane cages of Al^{3+} and Ga^{3+} with an M_6L_4 stoichiometry, which are completely distinct in geometry, structure, and properties from the M_2L_3 cages presented in *Chapter I* and the tetrahedral M_4L_4 cages detailed in *Chapter II*. Across the tritopic ligand series, the global M:L ratio dictates the resulting self-assembled M_nL_m topology. Under basic aqueous conditions, M:L $\sim$ 1:1 yields tetrahedral M_4L_4 cages (e.g., $[\text{M}_4\text{L}_4]^{12-}$ in *Chapter 2*), whereas increasing the metal to M:L $\sim$ 3:2 favours triply interlocked [2]catenane M_6L_4 cages in *Chapter 3* (Figure 6). Previous examples of such triply interlocked [2]catenane coordination cages have been exclusively studied with transition metals. Although in the 1990s Stack and Raymond demonstrated the feasibility of cages with p-block metals, and Fujita described the first assemblies of interlocked coordination cages with Pd and Pt, the synthesis and study of these types of interwoven cages with p-block metals has remained entirely unexplored. The examples described in this *Chapter* represent the first interlocked cages built exclusively from p-block metals.

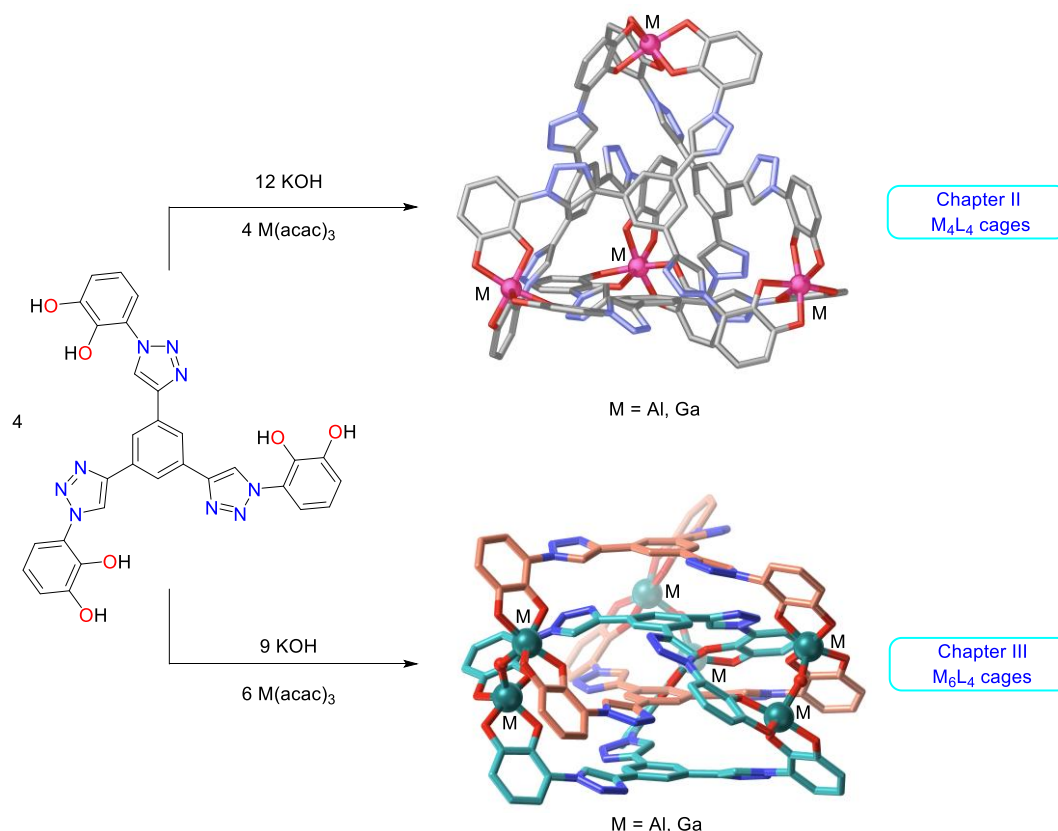


Figure 6. Tetrahedral M₄L₄ cages (*Chapter II*) and interlocked M₆L₄ cages (*Chapter III*).

Building on the insights from previous *Chapters* and the M₂L₃ and M₄L₄ cages, *Chapter III* demonstrates that tritopic 1,2,3-triazole–catechol ligands (**L**⁶ and its fluorinated analogue **L**⁷) self-assemble to form interlocked M₆L₄ cages with Al³⁺ and Ga³⁺, thereby extending the concept of interlocked cages to p-block metals for the first time.

Spectroscopic studies by NMR, DOSY, and NOESY, along with structural analysis by X-ray diffraction, reveal key similarities and differences compared to transition metal interlocked cage M_nL_m analogues. Specifically, these triply interlocked coordination [2]catenanes exhibit M/P helicity, where two monomeric M₃L₂ subunits are intertwined through six metal–catecholate bonds and three μ-OH bridges, further stabilized by π⋯π contacts and C–H⋯O interactions. Additionally, these structures show reversibility during their formation (reversible assembly and disassembly processes) in H₂O at room temperature, controlled by pH changes (acid/base, assembly/disassembly). These formation processes were monitored by NMR, revealing highly cooperative mechanistic pathways toward the direct assembly of interlocked M₆L₄ cages, without detection of monomeric M₃L₂ intermediates, unlike what is commonly observed in d-block systems.

To further explore the reversible nature of these self-assembly processes, thermodynamic studies were performed using isothermal titration calorimetry (ITC). The analyses demonstrate that the disassembly of these M_6L_4 cages is entropy-driven, whereas the reassembly is strongly enthalpy-driven. The Ga_6L_4 cage is approximately 500 times more stable than the analogous Al_6L_4 cage, an effect attributed to stronger Ga–O coordination between the metal and catecholate and μ -OH ligands, as well as a significantly greater stabilizing contribution from π -stacking interactions in the Ga_6L_4 cage. This demonstrates that the disassembly and reassembly mechanism is not only reversible but also metal-dependent (Al vs. Ga).

These findings show that the new mechanically interlocked M_6L_4 cages are reversible structures capable of modifying their topology in response to pH changes. This experimental evidence provides fundamental insights into the cooperative self-assembly processes of supramolecular coordination M_6L_4 systems beyond conventional d-block frameworks, opening opportunities for stimuli-responsive materials and adaptive supramolecular assemblies.

CHAPTER I

Self-Assembly and Structures of Helicate/Mesocate Coordination Cages Ga_2L_3 and Fe_2L_3

1.1 Introduction

1.1.1 Historical Development: From Crown Ethers to Supramolecular Metal–Organic M_nL_m Cages

Supramolecular chemistry is a multidisciplinary field that focuses on studying non-covalent interactions between molecules and the organised structures resulting from these interactions. Unlike conventional molecular chemistry, which investigates the formation and reactivity of covalent bonds, supramolecular chemistry explores how molecules recognise, interact, and assemble into larger, functional complex assembled architectures.^[1] At its core, supramolecular association is driven by a combination of non-covalent interactions such as hydrogen bonding, van der Waals forces, hydrophobic effect, π – π stacking and electrostatic interactions. These forces are weaker than covalent bonds but collectively are highly directional and selective, enabling precise molecular recognition and self-assembly.^[2]

In 1894, Emil Fischer proposed the model “*Lock and Key*”.^[3] In this study, Fischer describes the binding mechanism of enzymes highlighting that only the substrate can be encapsulated and react due to its specific shape to fit the enzyme cavity. Since then, due to the lack of 1H NMR or X-ray sources, supramolecular chemistry progressed slowly for a long period until the 1960s. In 1967, Pedersen made an important discovery by accident. While he was synthesizing a bisphenol derivative, he noticed an unexpected by-product within a reaction mixture (Figure 1).^[4] This unexpected, compound **I** (dibenzo-18-crown-6), had a cyclic structure and could increase the solubility of potassium permanganate ($KMnO_4$) in non-polar solvents, as well as its own solubility in methanol when inorganic Na^+ salts were added. Because its shape looked like a crown when binding to an electropositive metal ion (M^{n+}), forming a metal-crown adduct, Pedersen named this novel cyclic molecule as crown ether. Crown ethers are a class of cyclic polyether molecules characterised by a ring containing several ether ($-O-$) groups, typically spaced by ethylene bridging ($-CH_2CH_2-$) units, that can coordinate to metal cations, especially alkali (M^+) and alkaline earth (M^{2+}) metals.

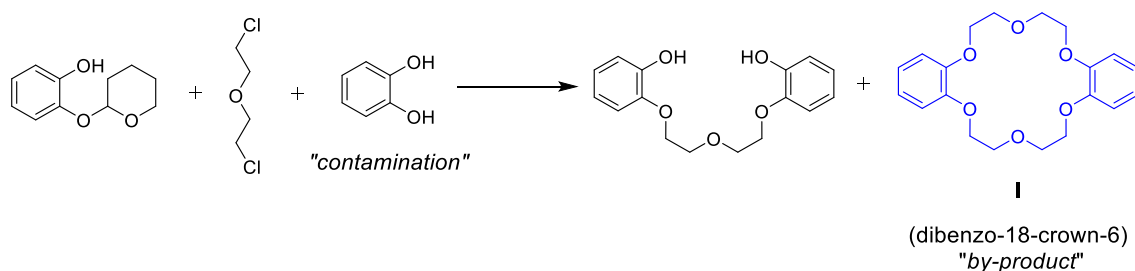


Figure 1. Synthesis of the first crown ether (dibenzo-18-crown-6) by Pedersen.

Two years later, in 1969, Jean-Marie Lehn extended this work by designing 3-dimensional host molecules, coined as cryptand **II** (Figure 2A), capable of binding metal cations (M^{n+}) selectively depending on their size and shape complementarity.^[5] Following these discoveries, in 1979, Cram reported the first spherand (Figure 2B).^[6] In contrast to cryptands, spherands are rigid and spherical macrocyclics which are highly preorganised featuring central aromatic rings and alkoxyethylene chains ($-OCH_2CH_2-$) that define the internal binding site for alkali cations (Li^+ , Na^+ , K^+ and etc). The rigid macrocyclic spherand host **III** is composed of six metaphenylene units functionalised with methoxy groups (MeO) that point toward the centre of the cyclic molecule. Thanks to its well-arranged binding sites, spherand **III** showed higher binding affinities to alkali metal ions (Li^+-Cs^+) than crown ether **I** or cryptand **II**.^[7]

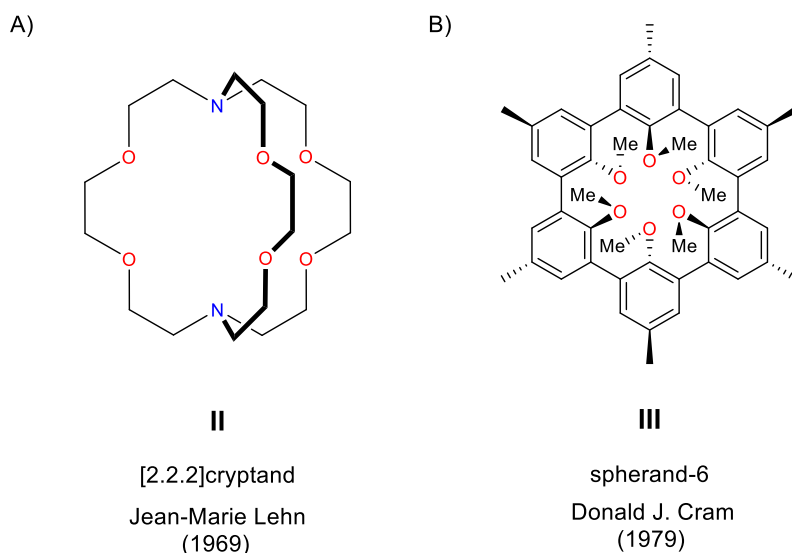


Figure 2. First examples of [2.2.2]cryptand **II** and spherand-6 **III**.

As a consequence of these discoveries, in 1987, Lehn, Pedersen and Cram were awarded the Nobel Prize in Chemistry for the development of cyclic organic molecules with tailor-made structure-specific interactions for high selectivity with specific substrates. Since then, the field expanded with a focus on self-assembly processes, hydrogen bonding, and other non-covalent interactions. For example, in 1983, Sauvage reported the first catenane **IV**, a mechanically interlocked architecture composed of two macrocyclic polyethers incorporating phenanthroline units, which was formed using Cu^+ as the metal ion template (Figure 3A).^[8] Following this, in 1991, Stoddart introduced the first molecular shuttle **V** (Figure 3B),^[9] a system based on a mechanically bonded rotaxane molecule. This structure consists of a linear unit interlaced through a cyclic ring and equipped at both ends with sterically bulky groups as stoppers to keep the ring from slipping away, forming a functional molecule. By adjusting the pH, the ring can move back and forth along the thread. Following these principles, Stoddart reported more precise molecular machines in the following years such as molecular elevators,^[10] and molecular muscles,^[11] and the field rapidly advanced, evolving into a multidisciplinary area with significant implications in biomedicine^[12] and catalysis.^[13]

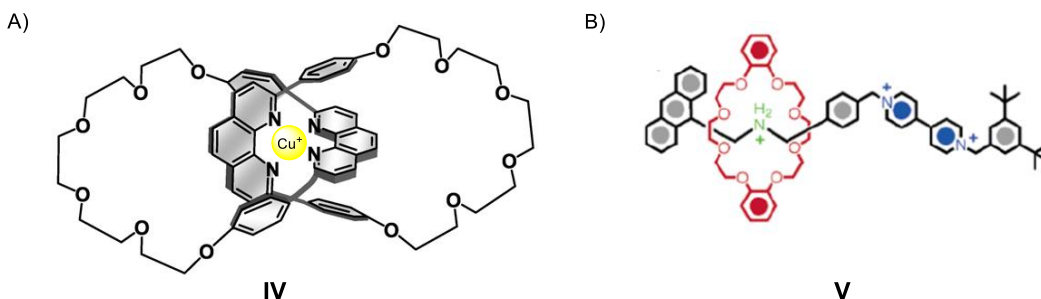


Figure 3. First examples of catenane **IV** and rotaxane **V** molecules.

In supramolecular chemistry, Supramolecular Coordination Compounds (SCCs) represent a fascinating subset, where metal ions (M^{n+}) act as central nodes, coordinating with organic ligands (L) to form well-defined Metal–Organic cage assemblies of the type M_nL_m . These compounds follow the principles of coordination chemistry, the study of metal–ligand interactions, to create supramolecular structures with diverse cage geometries such as tetrahedra,^[14] cubes,^[15] octahedra,^[16] cuboctahedra,^[17] dodecahedra,^[18] and others (Figure 4).^[19] The formation of SCCs relies on the predictable coordination behavior of metal ions (M^{n+}) and the

tailor-made design of ligands with specific binding sites and functionalities. Transition metals, lanthanides, and even main-group metals can serve as coordination nodes, offering a variety of coordination numbers and geometries. Ligands are typically designed with different functional groups and can be bidentate such as carboxylates,^[20] and catecholates,^[21] or monodentate such as pyridines,^[22] and phosphines,^[23] and they can bind to metal ions (M^{n+}) in a directional and robust manner. Self-assembly is an important feature of SCCs, driven by the thermodynamic minimisation of free energy (ΔG) and guided by the principles of molecular recognition.

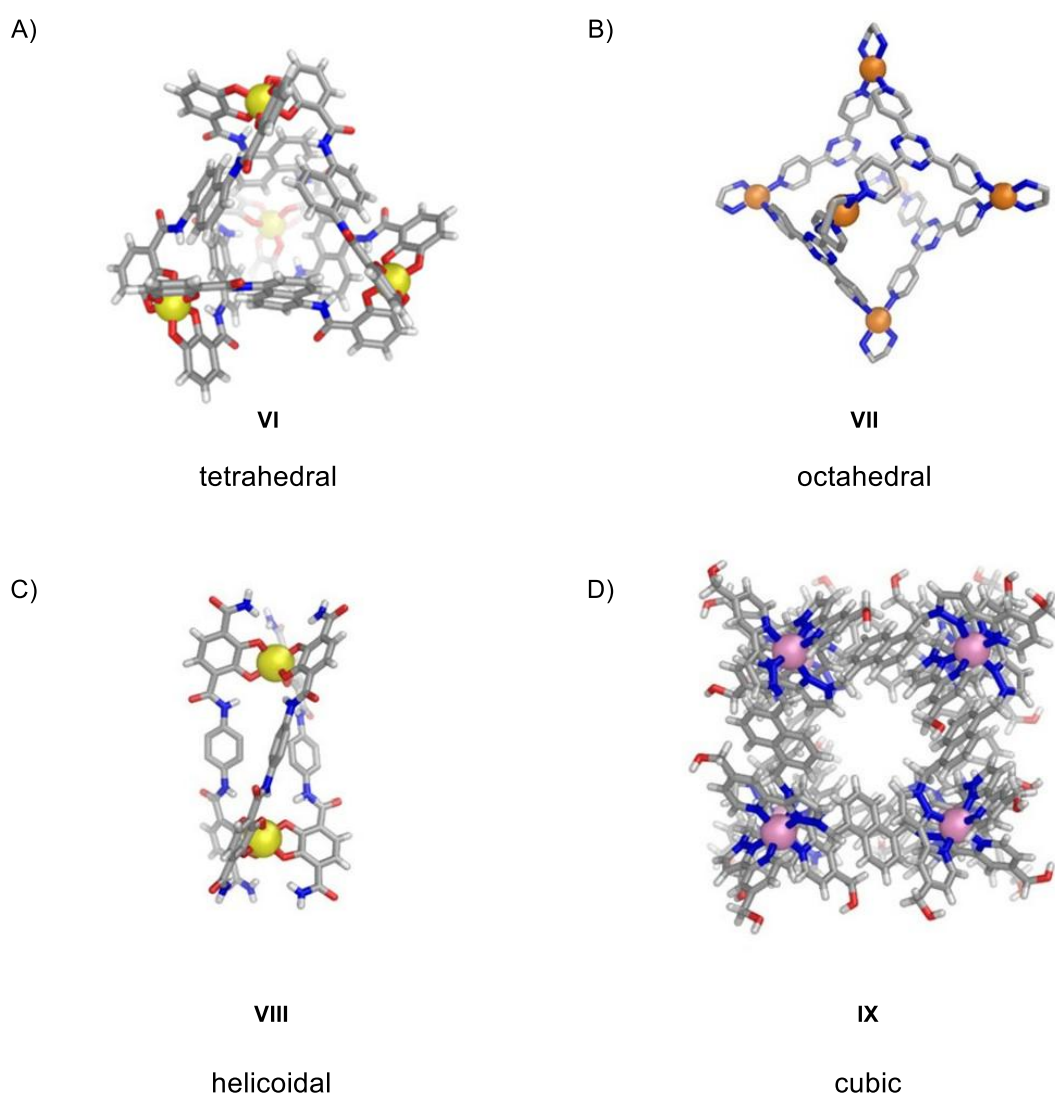


Figure 4. Examples of different types of Metal–Organic Cages.

Metal–organic cages present applications in fields such as molecular storage and transport, catalysis, sensing and detection and material science.^[24] These compounds can encapsulate molecules such as progesterone, ibuprofen and naphthalene, making them useful for gas storage,^[25] drug delivery,^[26] and selective molecular separation.^[27] Recently, Nitschke reported a tetrahedral metallacage Zn_4L_4 synthesised through the coordination–driven self–assembly of truxene–based organic ligand, 2–formylpyridine and Zn^{2+} .^[28] The cage **X** is able to selectively encapsulate hydrocarbon gases such as methane, ethane and ethene, in solution and the solid–state. The central cavity of this metallacage is hydrophobic due to the modification of six ethyl groups in the triazatruxene ligand (Figure 5A). Half of the six ethyl groups protrude to the interior of the cavity, making the central cavity hydrophobic and suitable for adsorbing aliphatic hydrocarbons.^[28]

SCCs show potential applications in catalysis as well, due to their confined spaces can create microenvironments that enhance catalytic activity and selectivity, mimicking the active sites of enzymes.^[29] For instance, Raymond, Toste and Bergman encapsulated an Au^+ –phosphine complex by a tetrahedral cage Ga_4L_6 host **XI** and they investigated the catalytic activity of the resulting complexes for the intramolecular hydroalkoxylation of allenes (Figure 5B). The catalytic activity of Me_3PAuBr was increased 8–fold by encapsulation, as determined by initial rate kinetics, and they observed up to 67 catalytic turnovers by Me_3PAu^+ encapsulated in Ga_4L_6 .^[29a] Moreover, this Ga_4L_6 cage has been used in others important reactions such as Aza–Cope rearrangement,^[30] hydrolysis of orthoformates,^[31] and Nazarov cyclisation.^[32]

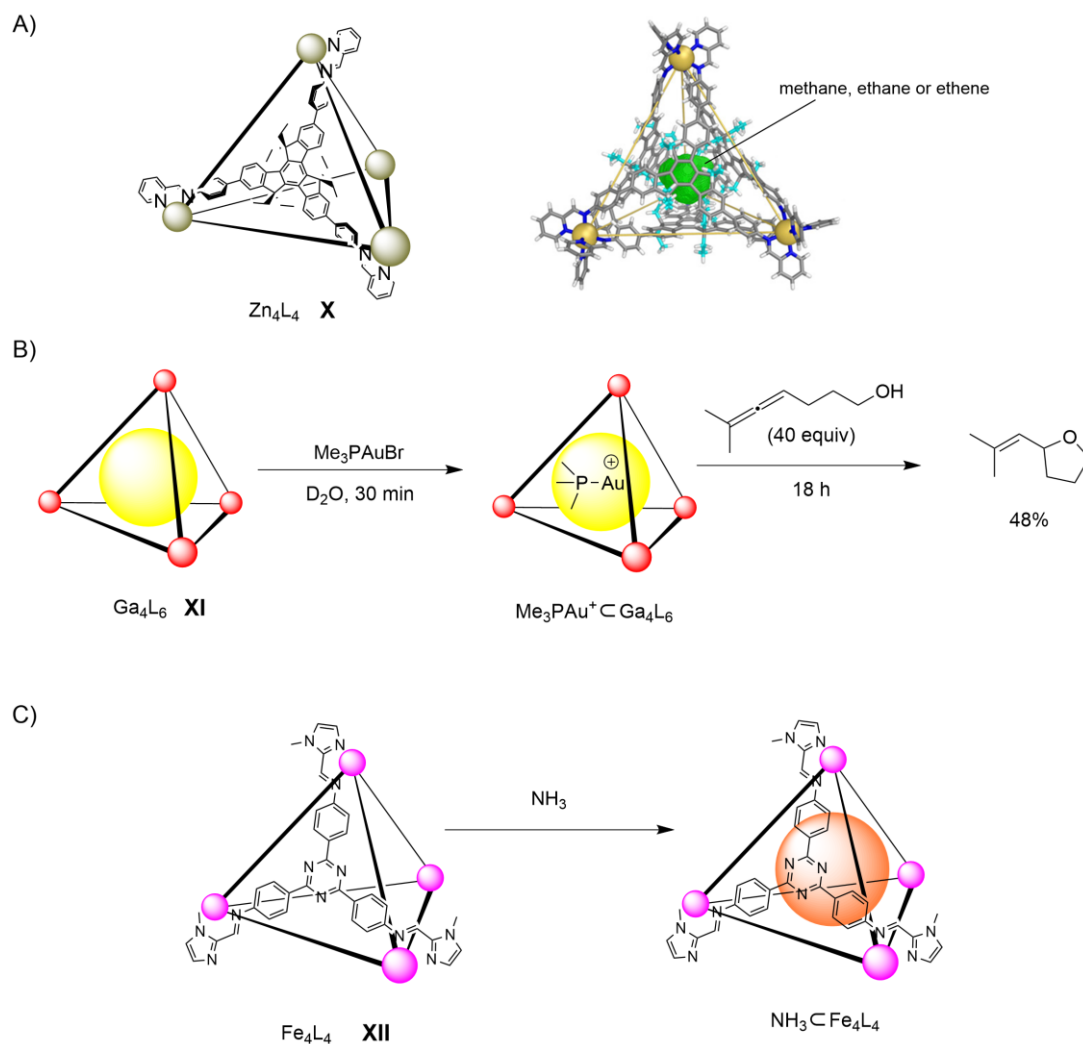


Figure 5. A) Hydrocarbons encapsulation in a Zn_4L_4 cage, B) Hydroalkoxylation catalyzed by $Me_3PAu^+ \cdot Ga_4L_6$ and C) NH_3 encapsulation in a Fe_4L_4 cage.

Furthermore, SCCs can be designed to selectively bind guest molecules, leading to changes in optical or electronic properties that enable sensing applications.^[33] For example, García reported the chiral supramolecular metal–organic cage **XII** (Figure 5C) capable of encapsulating $NH_{3(g)}$ at room temperature.^[33a] The metallacage **XII** exhibits superior selectivity for $NH_{3(g)}$ and twelve other substrates including common solvents ($CHCl_3$, MeOH, AcOEt) and amines (Et_3N , diethylenetriamine) opening new possibilities in NH_3 sensing, relevant for human health and food safety.

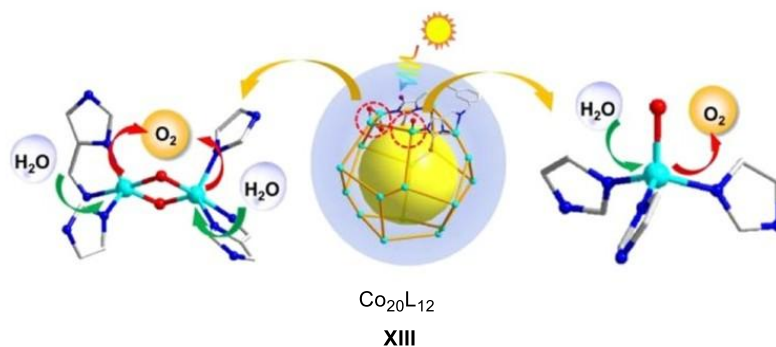


Figure 6. A $Co_{20}L_{12}$ metal–organic cage with applications in water oxidation.

Furthermore, SCCs have gained significant interest in others fields such as material science.^[34] For instance, Dan Li reported the metallacage **XIII** with two different active sites (Figure 6).^[35] This $Co_{20}L_{12}$ cage has visible–light driven water oxidation properties, opening new possibilities in artificial photosynthesis.

1.1.2 Dinuclear Metal–Organic M_nL_m Cages

1.1.2.1 M_2L_4 Cages

Supramolecular M_2L_4 cages are discrete, self–assembled structures formed by the coordination of two metal ions (M^{n+}) with four ligand molecules (L). The assembly of M_2L_4 cages typically involves the use of metal ions (M^{n+}) with specific coordination geometries, such as square–planar, square–pyramidal, or octahedral coordination.^[36] The most studied metals in the literature for obtaining this type of cages have been Pd,^[22b, 37] and Pt.^[38] These transition precious metals, with square–planar coordination environments, led to the formation of very robust M_2L_4 supramolecular structures. For example, Clever has reported a new series of Pd_2L_4 cages based on photochromic dithienylethene (DTE) ligands.^[39] These metal–organic cages are photoactive and have the ability to change their supramolecular topology by irradiation, modifying in this way, their cavity, morphology, and host–guest properties. Due to the switching properties of DTE ligands, these Pd_2L_4 cages can change between open (o–L) **XIV** and closed form (c–L) **XV**, under UV–visible light irradiation (Figure 7A).

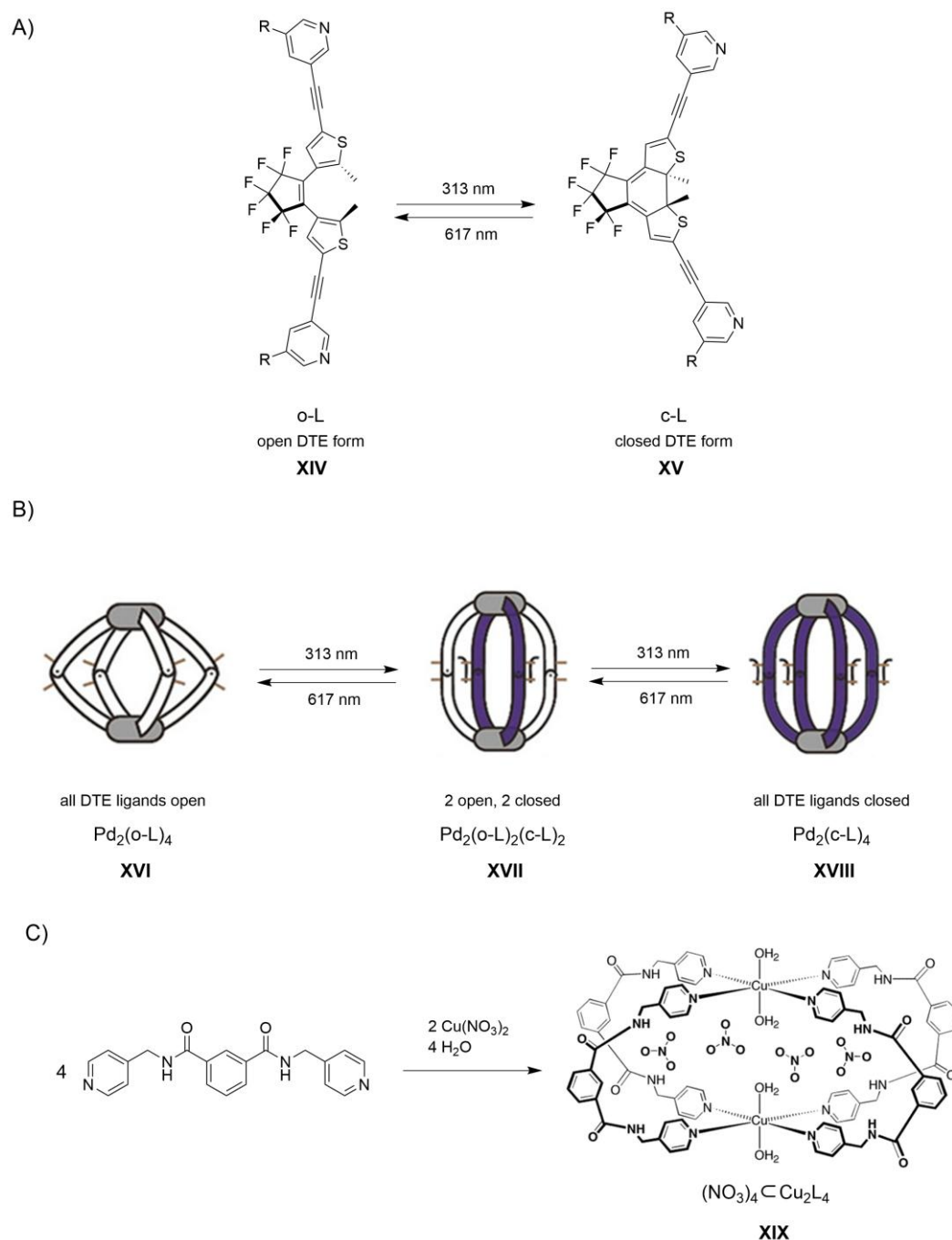


Figure 7. A) Reversible photo-switching of the dithienylethene-based ligands from open form to closed isomer, B) cartoon representations of different Pd_2L_4 isomers and C) synthesis of the cage $(NO_3)_4Cu_2L_4$.

Because of the differences in size and shape for the open and closed cages, Clever studied the binding abilities of the anionic $Pd_2(o-L)_4$ **XVI** and $Pd_2(c-L)_4$ **XVIII** assemblies towards a series of fluoroborate guests through NMR titrations. They concluded that guests as $[B_{12}F_{12}]^{2-}$, show higher affinities with the flexible open cage $Pd_2(o-L)_4$ ($3.2 \times 10^4 M^{-1}$) than with the rigid closed cage $Pd_2(c-L)_4$ ($6.7 \times 10^2 M^{-1}$).

Other metal–organic cages of the type M_2L_4 have been obtained and studied using transition metal centres with octahedral coordination environments such as $Co^{[40]}$ and $Cu^{[41]}$. For example, Atwood reported a dinuclear macro–tricyclic complex in which two octahedral Cu^{2+} ions are linked by four bridging ligands to form the Cu_2L_4 cage **XIX** (Figure 7C). All four equatorial positions on each metal centre are occupied by pyridyl groups while the axial positions are occupied by coordinated water molecules. The crystal structure of **XIX** also demonstrated that its positive charge is balanced by the presence of at least four encapsulated NO_3 anions within its cavity to give $(NO_3)_4 \subset Cu_2L_4$.

1.1.2.2 M_2L_3 Cages: Helicates and Mesocates

Lehn introduced a new and special class of metallo–supramolecular aggregates featuring two or more metal centres coordinating linear ligands forming a double stranded helical M_nL_m arrangement.^[42] In this study, he introduced the term “helicate” to describe this class of helicoidal metal–organic cages. The trinuclear Cu^+ complex **XX** wrapped by two linear tris(2,2'–bipyridine) ligands was presented by Lehn as the first example of a double helicate Cu_3L_2 (Figure 8A). In this complex, the bis(bipyridine) copper units adopt a distorted tetrahedral geometry. Three of such tetrahedra are covalently connected twice resulting in the observed double–stranded helical motif. This double coordination compound was defined as helicate due to ligands and metal ions (M^{n+}) forming spontaneously helicoidal structures by self–assembly. Later, Albrecht observed the formation of metal–organic M_nL_m mesocates, supramolecular compounds analogous to helicates that do not present a chiral twist in their structures. These are the first examples of the supramolecular coordination mesocate **XXI** arrays, which were obtained by self–assembly of three bis–catecholate ligands and two Ti^{4+} ions resulting with Ti_2L_3 cages (Figure 8B).^[43]

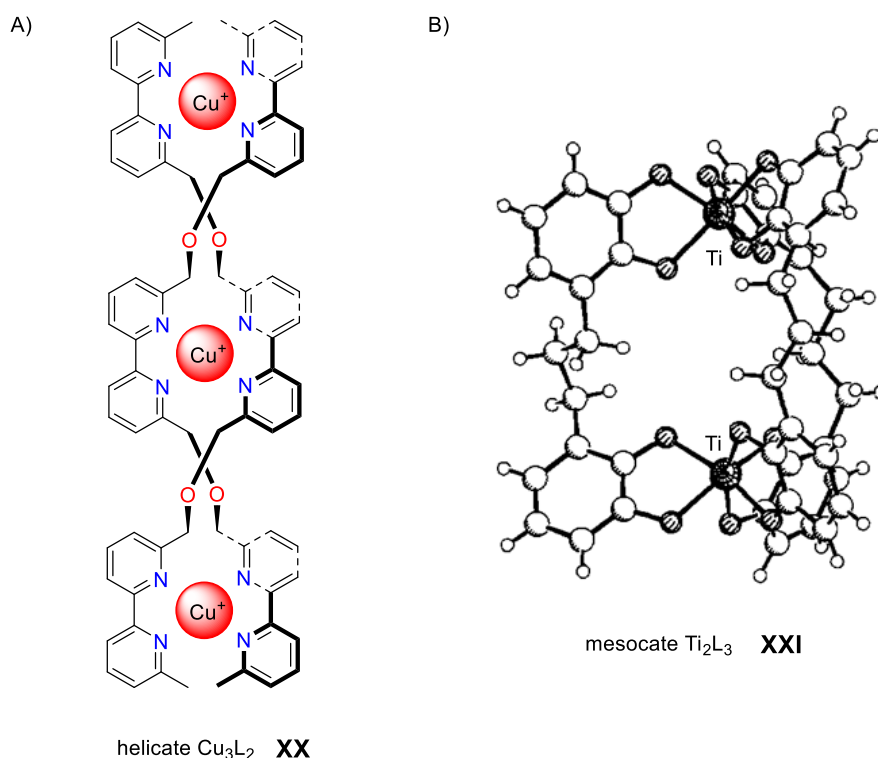


Figure 8. A) The double coordination Cu_3L_2 helicate **XX** and B) triple supramolecular coordination Ti_2L_3 mesocate **XXI**.

To understand the isomerism of dinuclear metal–organic M_2L_3 structures, it is important to remember that octahedral complexes which are formed by one metal centre and three bidentate ligands can adopt two different configurations generating Δ and Λ optical isomers (Figure 9). These Δ and Λ isomers are enantiomers of each other with non-superimposable structures between them. These two isomers have identical chemical properties and distinct absolute configurations. They are further distinguished by using the prefixes laevo ((–) or l) or dextro ((+) or d) depending whether they rotate left or right the polarised light.^[44]

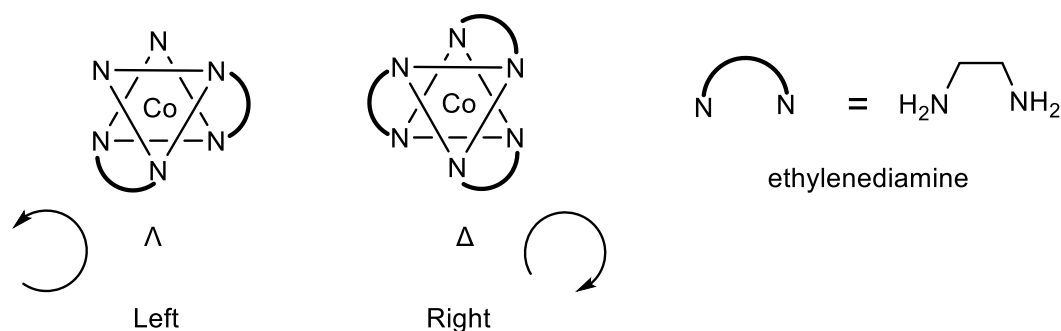


Figure 9. Absolute Δ and Λ configurations of the octahedral complex $Co(en)_3$, (en = ethylenediamine).

In M_2L_3 supramolecular metal–organic structures, which are formed from two metal ions (M^{n+}) and three bidentate ligands, two distinct types of coordination compounds can emerge, $\Lambda\Lambda$ – and $\Delta\Delta$ –helicates, which are mirror–image forms of each other. Additionally, a diastereomeric $\Delta\Lambda$ –form can also be obtained, being this form a mesocate isomer of the $\Lambda\Lambda$ – and $\Delta\Delta$ –helicates. This stereoisomer is not a mirror image of the helicates, and despite having two chiral centres, the molecule itself is achiral due to an internal plane of symmetry or/and inversion centre (Figure 10).^[45] Moreover, M ($\Lambda\Lambda$) and P ($\Delta\Delta$) configuration notation is used for naming systems that present helical chirality. P indicates a helix with a clockwise twist whereas M shows a helix with an counter–clockwise twist.^[46] This applies especially to molecules such as helicenes, supramolecular metal–organic cages M_2L_3 and certain biological macromolecules (DNA or protein helices).

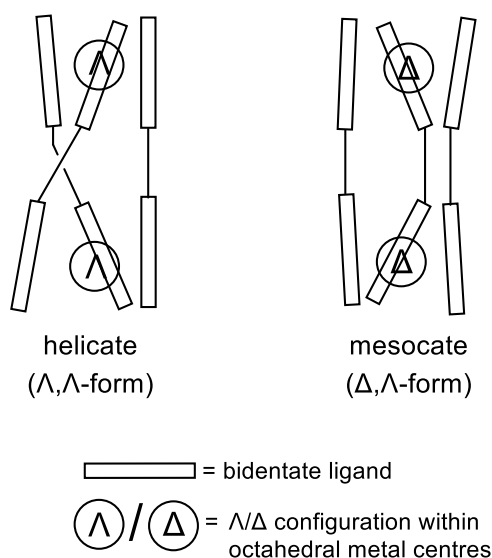


Figure 10. Comparison between M_2L_3 helicates (left) and mesocates (right) and its metal configurations.

The stabilisation of their helicate or mesocate isomeric forms, and as consequence, their cage structures, depends on different factors such as the presence of a specific guest molecule,^[47] the length and flexibility of the ligand^[48] and the charge or size of the metal ions (M^{n+}) employed.^[49] For example, Slater described a bipyridine ligand capable of forming a double helicates M_2L_3 with Cd^{2+} but with smaller metal cations such as Co^{2+} and Zn^{2+} , the mesocate M_2L_3 isomer was obtained.^[49a] Wu described a series of dinuclear triple–stranded cages Fe_2L_3 and Cu_2L_3 obtained via self–assembly of Fe^{2+} or Cu^{2+} salts with the imidazolium bromide salts of the ligand.^[47] This metal–organic system is capable of presenting different

optical isomerism depending on the anion used during the self-assembly process. In the presence of the larger tetrahedral anions such as BF_4^- , SO_4^{2-} , and ClO_4^- the mesocate cages **XXIII** are favoured whereas the smaller trigonal-planar NO_3^- or spherical Br^- anions lead to helicates **XXII** (Figure 11). They concluded that the anion encapsulation, and the ligand's conformational change play a crucial role in determining whether helicates or mesocates are formed.

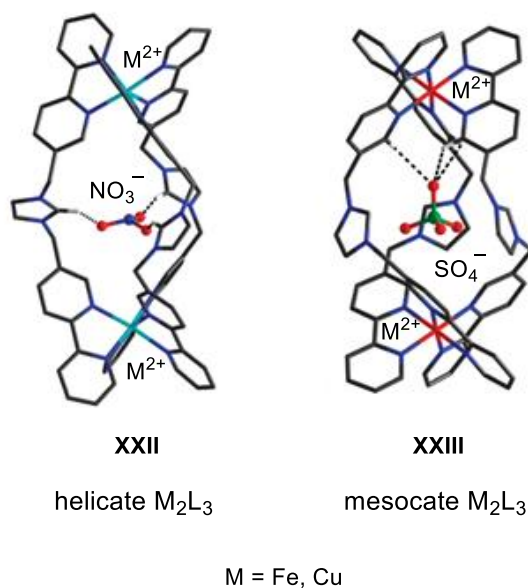


Figure 11. Helicate M_2L_3 (left) and mesocate M_2L_3 (right) cages with Fe^{2+} and Cu^{2+} .

Both M_2L_3 helicates and mesocates and their assembly process have been extensively studied in the last decades using transition metals. Several M_2L_3 metal-organic cage architectures have been obtained using metals such as Zn,^[50] Fe,^[50-51] Co,^[51c] Ni,^[50] Cu,^[47] and Ti (Figure 12).^[21a] Petitjean described a systematic study of the self-assembly of dinuclear architectures M_2L_3 **XXIV**, based on the 1,2,3-triazolylpyridine ligands and metal ions as Fe^{2+} , Zn^{2+} and Ni^{2+} . Interestingly, this study investigated the influence of the ligand's spacer group (specifically its length and flexibility) on the self-assembly process. These findings indicated that the nature of the spacer group dictated the formation of mesocates and helicates.^[50] Other interesting example of M_2L_3 cages were reported by Dolphin who established the synthesis of dinuclear octahedral poly- (dipyrromethene) assemblies **XXV**, where both triple-stranded helicates and mesocates were generated and isolated from the same reaction using Co^{3+} .^[51c] Following this, Albrecht reported a series of

catechol imine ligands for the self-assembly of triple-stranded Ti_2L_3 systems **XXVI**, obtaining helicates, mesocates or larger structures with high diastereoselectivity.^[21a]

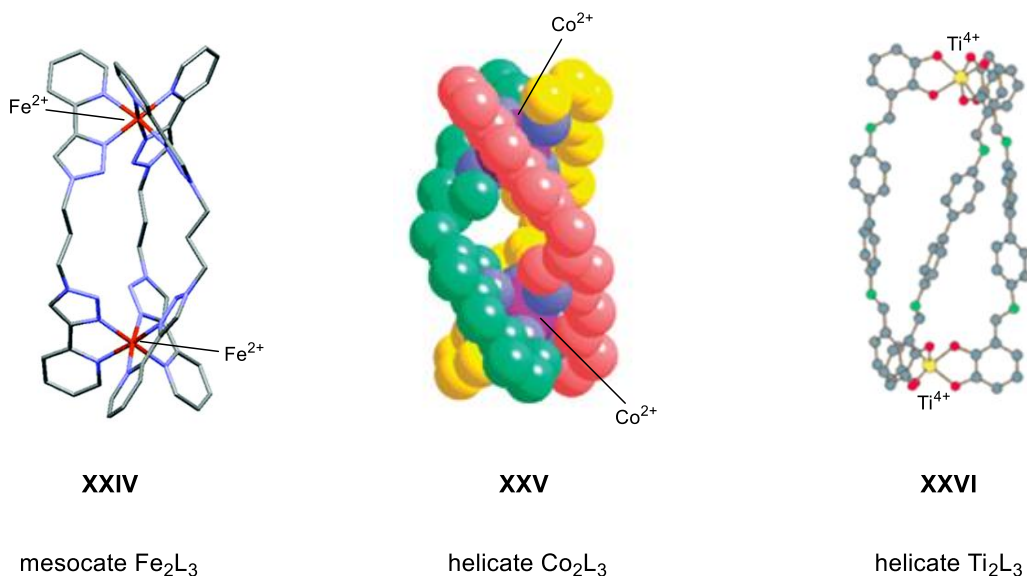


Figure 12. Transition metal-organic M_2L_3 cages: A) Mesocate Fe_2L_3 , B) Helicate Co_2L_3 and C) helicate Ti_2L_3

While most of the M_2L_3 metal-organic cages are constructed with transition metals, the use of main group metals in these supramolecular coordination compounds remain much less explored. This field is interesting to explore and study due to the multiple properties that main group metals offer. In particular group 13 metal typically exhibit predictable geometries, such as tetrahedral (Ga^{3+} halides) or octahedral ($\text{Ga}(\text{EDTA})$ and $\text{Ga}(\text{acac})_3$), making it easier to design well-defined supramolecular cages. Between these two geometries, Al^{3+} and Ga^{3+} commonly adopt robust octahedral environments, leading to the formation of highly symmetric and stable supramolecular cage structures under ambient conditions. In this context, Raymond has developed the use of main group metals such as Al^{3+} , Ga^{3+} and In^{3+} to construct multiple stable M_2L_3 ,^[52] M_4L_4 ,^[53] and M_4L_6 ^[54] supramolecular metal-organic cages. Moreover, the low cost, abundance and low toxicity of main group metals (particularly Al), make them attractive to be used as metal nodes in supramolecular coordination cages. Despite all these advantages, main group metals remain rarely studied in the context of constructing supramolecular M_2L_3 cage assemblies. In fact, only three examples of main group metals-based M_2L_3 structures, have been reported in the literature so far. Stack reported the first example of a dinuclear gallium triple helicate Ga_2L_3 **XXVII** constructed by two Ga^{3+} ions and three chiral

bis–catecholamide ligands (Figure 13A).^[55] The helical cage exhibit each Ga^{3+} within an octahedral coordination, and the protons from the amide forming intramolecular hydrogen bonds with the internal oxygens from the catechol ligands coordinated to the Ga^{3+} ions. This study showed that ligands that are enantiomerically pure and bind to multiple metal centres can strongly control the direction of the helix, creating a specific helical shape even if the ligand is relatively flexible.

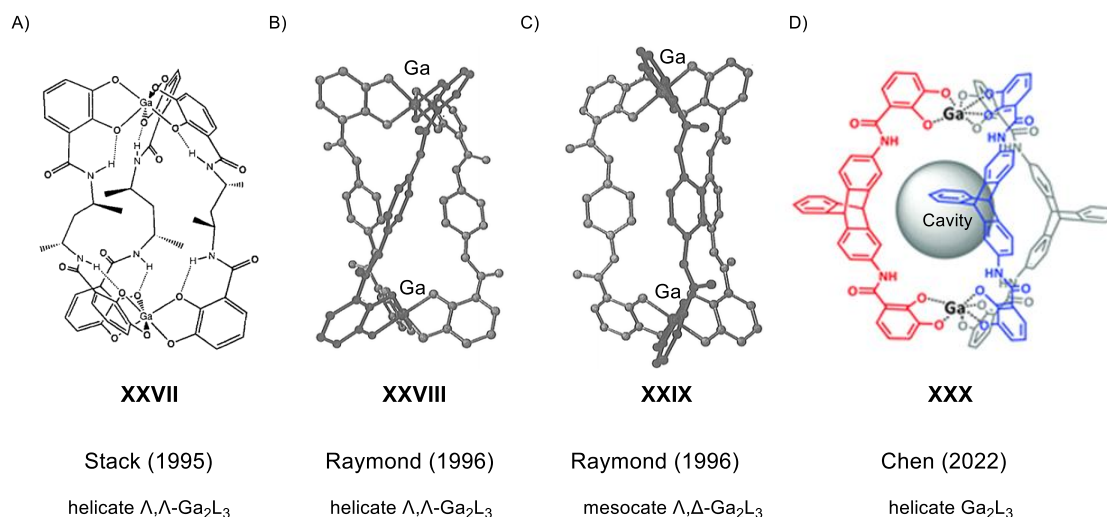


Figure 13. A) Example of Ga_2L_3 helicates and mesocates assemblies with chiral and B), C) and D) achiral biscatecholate ligands.

Secondly, Raymond described a series of dinuclear metal–organic M_2L_3 cages using bis–bidentate catecholate/amide ligands with Ga^{3+} and Fe^{3+} . These cages consist of discrete dinuclear M_2L_3 assemblies with pseudo–octahedral metal coordination centres. The helical nature of these complexes was confirmed through circular dichroism (CD) spectroscopy and X–ray crystallography. 1H NMR monitoring experiments revealed that the configuration inversion of the enantiomers is thermally induced easily in D_2O or $DMSO-d_6$. The inversion mechanism of the Ga_2L_3 helicate system, which can exist as cis and trans isomers of the helicate **XXVIII** (Figure 13B) proceeds without cis–trans isomerisation through independent trigonal twisting at each metal centre, leading to the formation of the mesocate intermediate **XXIX** (Figure 13C). This heterochiral mesocate complex **XXIX** acts as a transient kinetic intermediate in the $(\Lambda, \Lambda) \leftrightarrow (\Lambda, \Delta)$ inversion process of the helicate cage isomeric forms.^[45, 52] In a related study, Raymond was capable of forming helicates or mesocates selectively using a bis–hydroxypyridinone ligand by only changing the metal ion (M^{n+}) used. This ligand is able to form the helicate isomer Al_2L_3 when using

Al^{3+} as central node and the mesocate isomer Ga_2L_3 in the presence of Ga^{3+} ions.^[49b] showing a strong metal–metal dependence in their selective formation.

The third example reported by Chen involved the synthesis of the triple–stranded metallo–supramolecular helicate **XXX** (Figure 13D), formed through the coordination of Ga^{3+} cations with ligands derived from 2,7– and 2,6–disubstituted triptycenes. These anionic Ga_2L_3 helicates have the ability to encapsulate small cationic molecules, including Me_4N^+ and Et_4N^+ ions.^[56] In addition, in 2024, our group reported the novel triply DTE–functionalised coordination Ga_2L_3 helicate and mesocate cages in collaboration with Pischel.^[57] This was the first example of integrating DTE photoswitches with main group metals in a supramolecular metal–organic cage assembly. This Ga_2L_3 cage presents reversible photoswitching under diluted μM conditions.

1.1.2.3 Functional Applications of M_2L_3 Cages

In the field of supramolecular metal–organic cages, M_2L_3 cages represent an important category of metallo–supramolecular assemblies. These supramolecular structures are highly organised and symmetrical, exhibiting interesting internal cavities. Moreover, these cage assemblies often demonstrate chirality, as M_2L_3 helicates typically featuring a helical arrangement of ligands around the metal centres. These cage features make them play a significant role in selective guest binding and host–guest chemistry. Their internal cavities can encapsulate various guest molecules, with these cavities being tunable in terms of charge and size through ligand design. This capability allows for selective recognition of ions or small molecules. One representative example was reported by Torres, a giant Fe_2L_3 metallo–organic helicate **XXXI** (Figure 14A) based on phthalocyanine ligands as a host for electroactive molecules such as fullerene and naphthalenediimide derivatives.^[58] Furthermore, M_2L_3 cages can exhibit notable optical and electronic properties. These photophysical properties, such as luminescence or absorption, depend on the metal ions (M^{n+}) and ligands used. For example, the supramolecular helicate Eu_2L_3 **XXXII** (Figure 14B) shows luminescence and it may have applications in fields such as material science or biology.^[59] In addition, M_2L_3 supramolecular structures can exhibit dynamic behavior under different conditions. For instance, the imine–based Zn_2L_3 cage **XXXIII** (Figure 14C) shows distinct disassembly properties depending on the encapsulated guest. In the presence of small diacid guests, the cage experiment slow disassembly whereas this disassembly is fast in the presence

of larger diacid guests.^[60] This dynamic nature has potential applications for responsive materials and guest delivery systems.

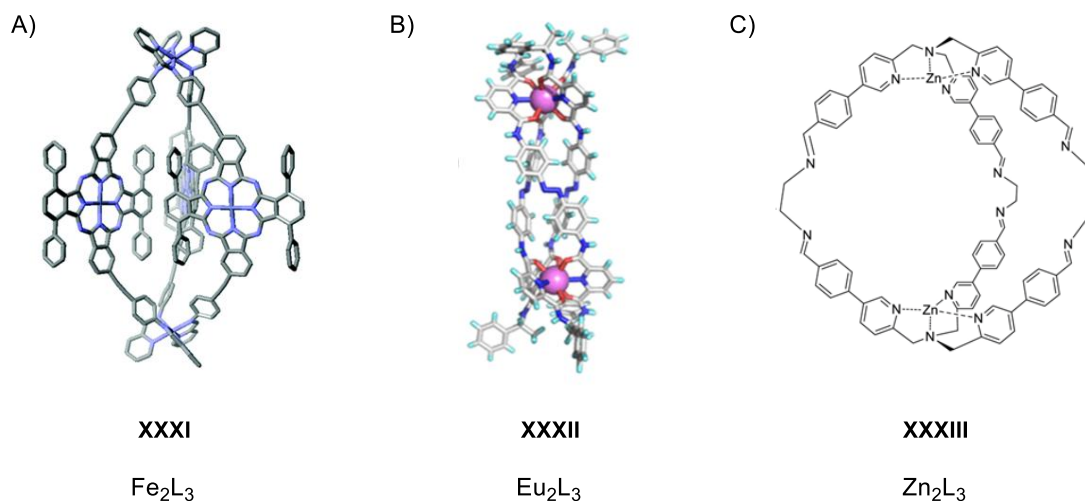


Figure 14. Examples of supramolecular coordination M_2L_3 architectures with potential applications, in : A) Selective recognition, B) Photochemistry and C) Responsive materials and guest delivery systems.

These supramolecular cages can present biological activity as well. For example, helical metal–organic M_2L_3 assemblies provide an attractive synthetic platform for non–peptidic structures capable of mimicking certain characteristics of short cationic α –helical peptides, offering adjustable charge, shape, size, and amphipathicity.^[61] Their chiral and helical structures have led to study the interaction between these supramolecular arrangements and helical biomolecules such as DNA and RNA. In fact, Fe_2L_3 ^[62] and Co_2L_3 ^[63] helicates have been studied to elucidate their capacity of interacting with DNA concluding that these helical structures are able to condense or aggregate DNA exhibiting potent and selective activities against cancer cells.^[63] This interaction between DNA and supramolecular M_2L_3 helicates have allowed to study their antimicrobial,^[64] anticancer,^[65] and anti–viral^[66] activity as well as their potential in the treatment of Alzheimer's disease.^[67] For example, the water soluble Fe_2L_3 helicates **XXXIV** and **XXXV** containing arginine–derived substituents with a particularly notable antibiotic activity against the Gram–negative strain E.coli MC4100 and a modest toxicity to C. elegans (Figure 15).^[64] Furthermore, the Fe_2L_3 helicates **XXXIV** and **XXXV**, which are stable and soluble in water, present high selectivity against colorectal cancer cells.^[65]

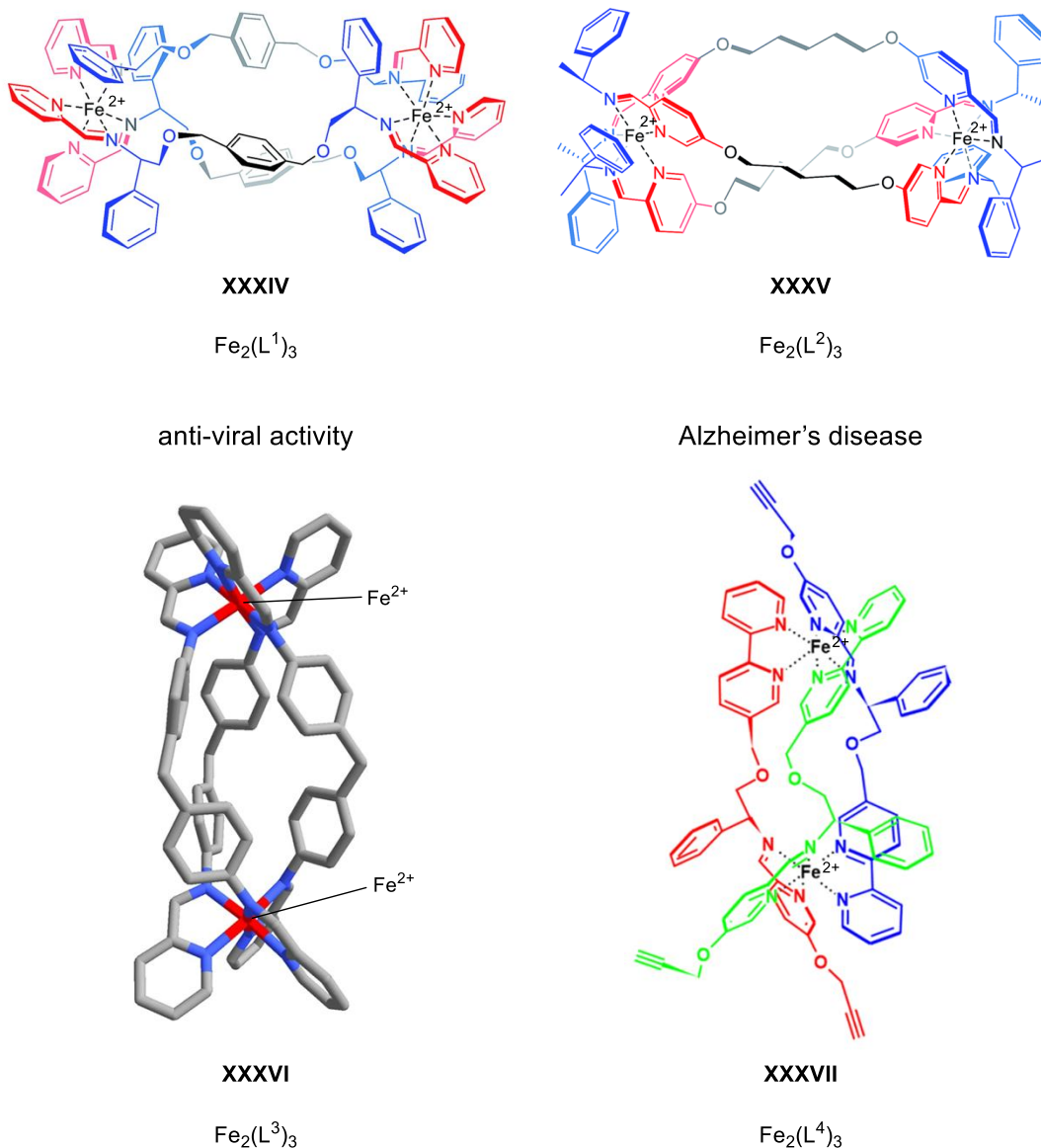


Figure 15. Examples of Fe_2L_3 helicates with biological activities.

Another relevant application of supramolecular Fe_2L_3 helicate **XXXVI** is its properties as inhibitor of Tat–TAR RNA which plays a critical role in HIV–1 transcription (Figure 15). This supramolecular helicate **XXXVI** can inhibit the Tat–TAR interaction at nanomolar concentrations by binding to TAR RNA.^[66] The metallosupramolecular Fe_2L_3 helicate **XXXVII** can act as a novel class of chiral amyloid– β inhibitors (Figure 15), representing a potential therapeutic strategy for the treatment of Alzheimer's diseases.^[67]

1.1.3 Emerging Heterometallic $(MM')_2L_3$ Cages

Most of the M_2L_3 supramolecular metal–organic cages described in the literature are homometallic in each vertex. In contrast, few examples of heterometallic supramolecular structures at each vertex have been reported up-to-date. The study of this type of supramolecular architectures remains relatively underexplored because controlling their rational synthesis into well-defined supramolecular assemblies involving two distinct metals, M^{n+} and M'^{n+} , with known composition can be challenging, limiting their preparation and study.

Albrecht studied imine-bridged and amide-bridged catecholates as ligands to form M_2L_3 helicates with Ti^{4+} and V^{4+} ions.^[21a] The use of imine-bridged ligands to construct the supramolecular structures **XXXVIII** and **XXXIX** (Figure 16A), two sodium cations (Na^+) are encapsulated in the interior of these helicates binding to the internal oxygen atoms of the catecholates. In the case of amide-bridged catecholate ligands, protons from amide groups are forming internal hydrogen bondings with the oxygen atoms of the catecholates. In this way, they obtained heterometallic $(TiNa)_2L_3$ helicates at each vertex in the solid state. The heterometallic $(TiK)_2L_3$ helicate **XL** based on enantiomerically pure ester bridged dicatecholate ligands (Figure 16B) is capable of changing its structure in the presence of different countercations by sequestering or releasing the secondary alkali metal (K^+).^[68] This helicate can present three different states, the compressed left-handed $(TiLi)_2LiL_3$ array **XLII**, the expanded right-handed potassium $(TiK)_2L_3$ topology **XL** (with carbonyl groups coordinate to K^+) and the expanded left-handed homometallic Ti_2L_3 architecture **XLI** with the carbonyl groups oriented outward (Figure 16B). They were able to change between these three states by adding [2.1.1]cryptand to trap Li^+ ions and crown ether 18-crown-6 to trap K^+ ions. The helicate structure is directly related to the presence or absence of different internal alkali ions (Li^+ , Na^+ and K^+).

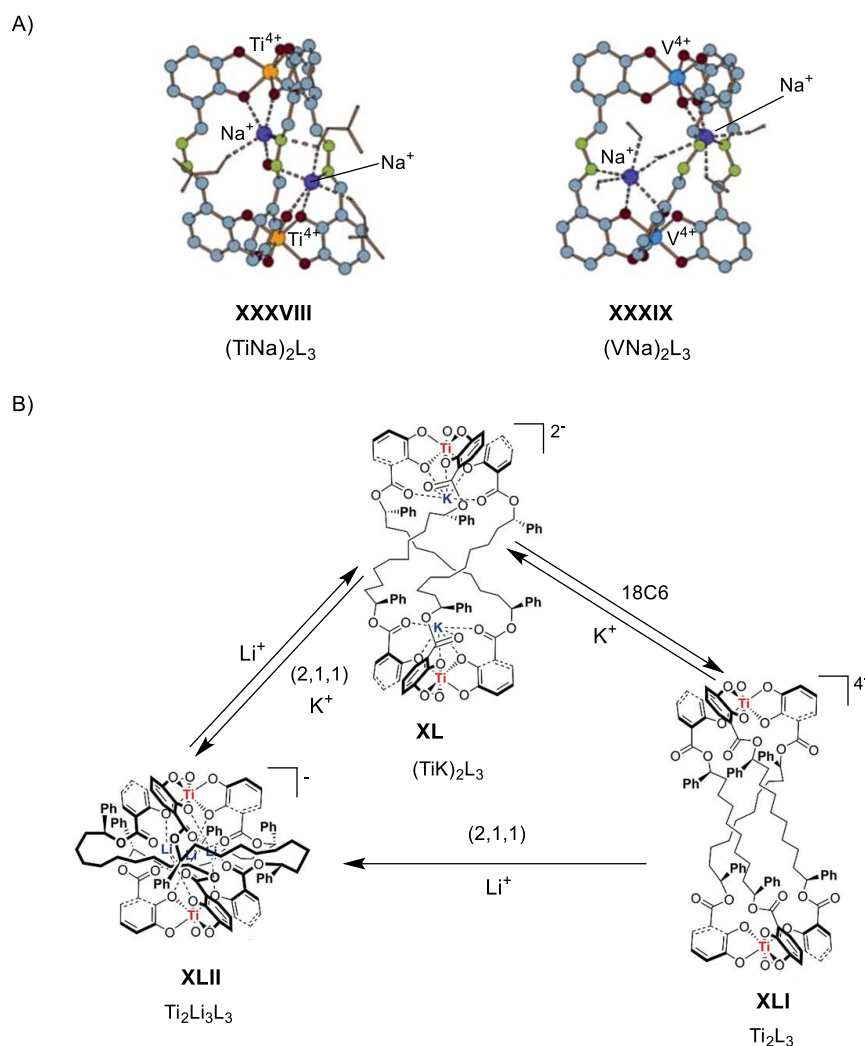


Figure 16. A) Examples of heterometallic supramolecular $(MM')_2L_3$ cage systems and B) a supramolecular heterometallic $(TiK)_2L_3$ switch.

This bimetallic character represents an excellent opportunity to obtain systems in which heterometallic (MM') vertices and the synergistic effect (combined effect of two or more metals is greater than the sum of their individual effects) between different metals may improve supramolecular capabilities in heterometallic systems of the type $(MM')_nL_m$. In addition, heterometallic structures can be really interesting in other fields such as nanomaterials, medicine and catalysis.^[69] For example, the Pd/Pt mesoporous nanoparticle which could serve as a novel drug carrier. This heterometallic nanoparticles can be utilised for the synergistic photothermal–chemotherapy of breast cancer both in vitro and in vivo.^[70]

Due to the promising synergistic effect and few examples of main–group and heterometallic supramolecular entities, we propose in this thesis a new synthetic

route to obtain heterometallic $(GaK)_2L_3$ cage structures to take advantage of using main-group metals in M_2L_3 structures. Furthermore, we will study iron heterometallic $(FeK)_2L_3$ systems as well. These metals (Ga^{3+} and Fe^{3+}) can form robust coordination bonds with catecholate-based ligands whereas K^+ provide flexibility and dynamic effect of labile coordination as shown in Ti_2L_3 architectures reported by Albretch. Moreover, heterometallic $(FeK)_2L_3$ structures are more robust than main group architectures and provide better systems to be studied using X-ray crystallography. Knowing the structural features and properties of heterometallic $(MM')_2L_3$ architectures, these systems may open new possibilities in fields such as catalysis, sensing, material science and medicine.

1.1.4 Organic Ligands in Dinuclear M_2L_n Cages

1.1.4.1 Ligands for Transition Metal M_2L_n Cages

Pyridine-based nitrogenous heterocycles are among the most prominent ligand types employed in supramolecular coordination chemistry. Pyridine and its derivatives (bipyridines, terpyridines, or bridged bis-pyridyl ligands) are extensively used because their Lewis basicity, the stability of the resulting transition metal–nitrogen bonds, the inherent rigidity conferred by their aromaticity, and their ease of functionalisation, collectively providing precise control over ligand geometry and electronic properties. This facilitates the construction of a broad range of M_2L_3 and M_2L_4 structures with transition metals in which several different pyridine-based ligands are used with different spacer and core groups for selected ligand motifs (Figure 17).^[47, 50, 71]

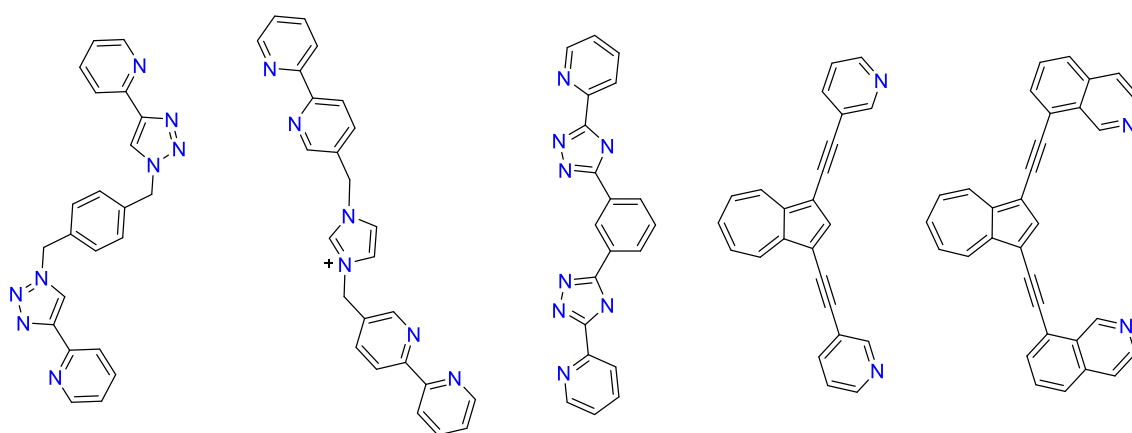


Figure 17. Examples of pyridine-based ligands used in metal–organic cage architectures.

1.1.4.2 Ligands for Main Group Metal M_2L_n Cages

Catechol represents an alternative to the pyridine metal-coordinating site, which is widely recognised in metallo-supramolecular chemistry for main-group metals. It features a chelating unit composed of two oxygen donor atoms and a double negative charge which forms stable and robust complexes with oxophilic metal ions such as Al^{3+} , Ga^{3+} and In^{3+} . Since the mid-90s, catechol derivatives have been commonly employed in the construction of supramolecular coordination architectures^[72] due to their bidentate chelating nature and the high stability of their metal complexes. The resulting five-membered catechol-metalloligand-ring are usually highly stable, a characteristic resulting from the chelate effect.

One pioneering example of supramolecular coordination M_2L_3 and M_4L_6 cages constructed catechol ligands were reported by Raymond. In particular, the M_4L_6 tetrahedral cage is capable of stabilizing reactive intermediates and accelerating chemical reactions.^[73] Moreover, several examples of M_2L_3 cage architectures have been developed using catechol-based ligands featuring amide and imine bridging groups (Figure 18).

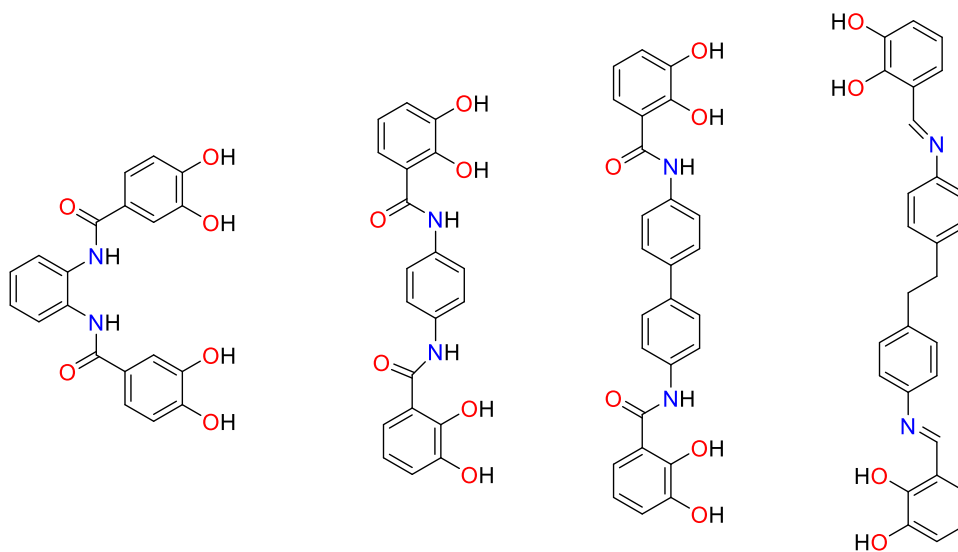


Figure 18. Catechol-based ligands used in the self-assembly of M_2L_3 cages.^[74]

1.1.4.3 1,2,3-Triazole-Based Ligands in Supramolecular Assembly

Although ligands based on catechol units have been utilised in the construction of different metal-organic supramolecular cages, the integration of this functional coordination site with 1,2,3-triazole rings to form organic ligands for building supramolecular coordination assemblies remains largely underexplored.

While catechol groups provide robust chelating sites suited for oxophilic M^{3+} centres, triazole rings exhibit remarkable versatility in participating in various non-covalent interactions, making them highly versatile building blocks for a wide range of supramolecular architectures. Their unique electronic and structural features enable them to engage in hydrogen bonding, halogen bonding, π - π stacking, metal coordination, and electrostatic interactions, often in a synergistic manner (Figure 19).^[75] In fact, new coordination motifs based on 1,2,3-triazole units display unique properties including luminescence,^[76] magnetism,^[77] and electrochemistry.^[76b, 78]

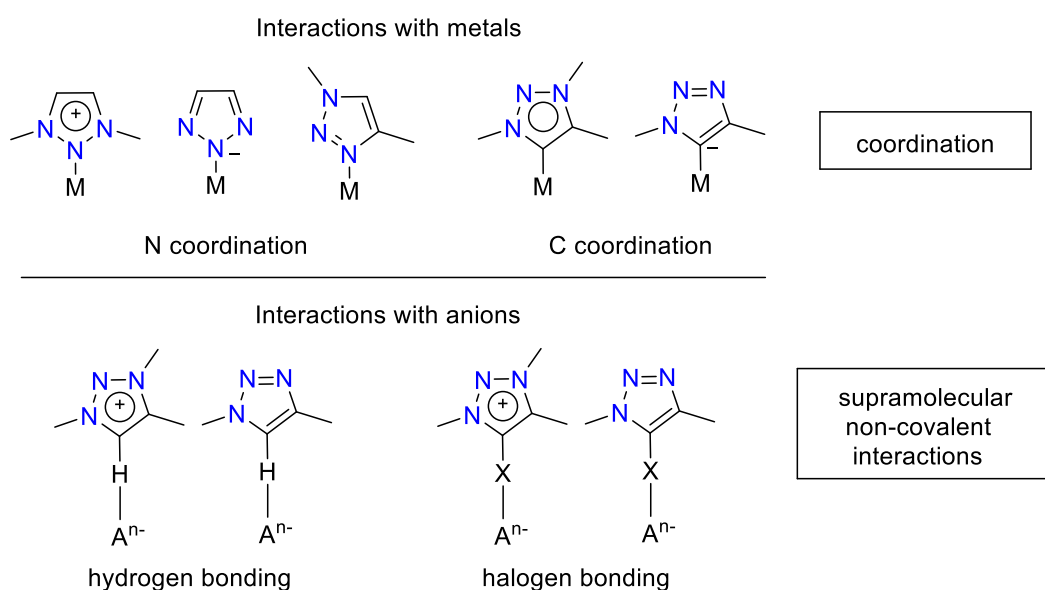
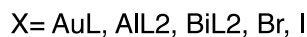
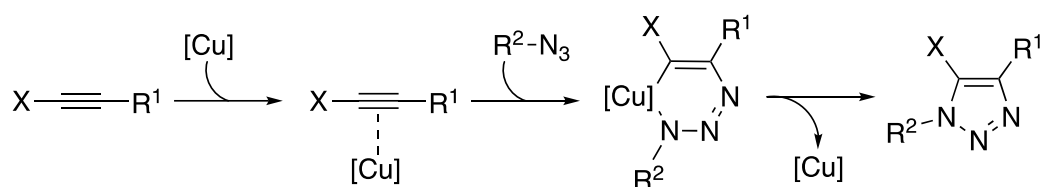


Figure 19. Covalent and non-covalent interactions from 1,2,3-triazoles.

One of the most common strategies to prepare 1,2,3-triazoles is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) (Scheme 1). CuAAC is widely employed across various fields of chemistry, including supramolecular chemistry, because it offers an efficient, regioselective, versatile, and straightforward method for synthesizing 1,4-disubstituted 1,2,3-triazoles.^[79] Since the discovery of this reaction by Meldal, Fokin, and Sharpless,^[79a] numerous mechanistic studies, both experimental and computational, have been suggested for the formation of copper alkylides and the activation of the azide group through coordination with Cu.^[80]



Scheme 1. Proposed dipolar cycloaddition mechanism between alkynes and azides using Cu catalysis (CuAAC).

Due to their multiple properties and easy preparation, the use of 1,2,3-triazoles to construct self-assembled architectures such as metal-organic cages or other supramolecular assemblies are emerging in the last years.^[81] The multiple advantages of using 1,2,3-triazole in supramolecular chemistry, encouraged us to design novel ligand frameworks combining catechol and 1,2,3-triazole groups to direct the topological self-assembly of new three-dimensional cage architectures of the type M_2L_3 -type. The inclusion of terminal catechol groups offers strong binding sites for oxophilic M^{3+} ions, while the connecting 1,2,3-triazole bridging units provide structural rigidity and conformational adaptability, alongside the potential for diverse non-covalent interactions and new coordination behaviours. Furthermore, by employing different spacer cores, we can modulate the ligand's rigidity and spatial arrangement. Consequently, this Thesis will pursue a straightforward approach to synthesise novel 1,2,3-triazole-catechol ligands capable of forming stable and robust metal-organic cages with sustainable metals such as Al^{3+} , Ga^{3+} , or Fe^{3+} .

1.2 Objectives

This chapter aims to elucidate the assembly principles of dinuclear M_2L_3 supramolecular coordination cages by bridging main-group and transition-metal chemistry, focusing on Ga^{3+} and Fe^{3+} . We will design and synthesise a family of ditopic 1,2,3-triazole-catechol and -naphthalenediol ligands via CuAAC click chemistry, in which aromatic backbones carry protected catechol groups. These scaffolds provide a rational platform to probe how donor topology and steric modifications tune solubility and cavity dimensions in the resulting M_2L_3 architectures. After deprotection, the ligands are combined with Ga^{3+} or Fe^{3+} in the presence of salts in the presence of K^+ and selected organic counter-ions (e.g., Et_4N^+) to access heterometallic cage of the general type $(\text{MK})_2\text{L}_3$. A comprehensive multi-state characterisation will be performed: In solution, $^1\text{H}/^{13}\text{C}$ NMR and DOSY NMR will delineate size, integrity, and dynamics. In the solid state, single-crystal X-ray diffraction will define geometry and clarify the role of encapsulated K^+ within the cavities. High-resolution ESI-HRMS will complement these data by identifying charged cage fragments and heterometallic compositions. Together, these methods will connect ligand design with the cage's M_2L_3 composition and unveil the key supramolecular features of the cages.

A second, complementary aim is to interrogate cage isomerism within the Ga_2L_3 and Fe_2L_3 assemblies, focusing on the balance between helicate (Δ/Λ) and mesocate ($\Delta\Lambda$) forms and on the rules that govern their selective formation. We will examine how counter-ions bias the assembly pathway and the final isomer distribution, contrasting organic ammonium salts (Et_4N^+) with alkali-metal ions (K^+), and assess the structural consequences for cavity shape/size and solution behaviour. By correlating NMR/DOSY, X-ray metrics (including the presence/position of encapsulated K^+), UV-Vis absorption spectroscopy and HRMS speciation, we will formulate counter-ion-directed assembly principles applicable across main-group metal Ga_2L_3 and transition-metal Fe_2L_3 regimes.

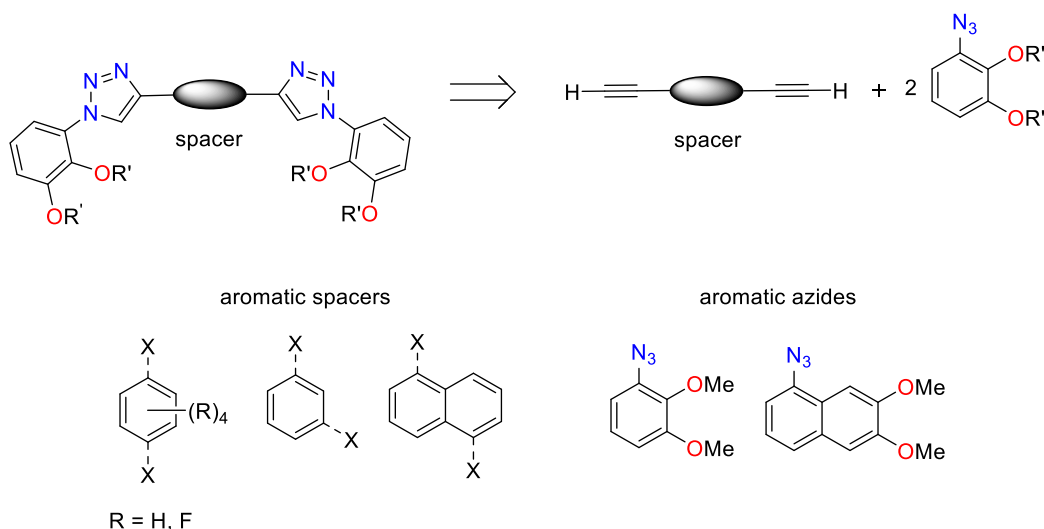
These twin objectives will connect the influence of the designed ditopic ligand scaffolds with the formation of Ga_2L_3 and Fe_2L_3 cages, and unveil their helicate/mesocate isomerism, providing a transferable framework for future host-guest chemistry, molecular recognition, drug delivery, and supramolecular catalysis based on these M_2L_3 coordination cages.

1.3 Results and Discussion

This chapter will detail various synthetic approaches for preparing novel ditopic 1,2,3-triazole–catechol ligands. These will be derived from different aromatic alkynes and catechol or naphthalenediol–based azides using the CuAAC click reaction. The terminal catechol or naphthalenediol groups in these ligands are designed for strong binding to oxophilic M^{3+} ions, while the connecting triazole units provide a balance of rigidity and flexibility, along with the possibility of diverse non-covalent interactions. Furthermore, different spacer cores allow us to tailor the ligand's rigidity and geometry of the ligand. For example, a C_6H_4 phenylene core allows for different positional isomers in the ditopic ligand (1,2–, 1,3–, or 1,4–). These 1,2,3-triazoles will then serve as ditopic ligands for self-assembly with Ga^{3+} and Fe^{3+} metal ions to yield anionic M_2L_3 supramolecular assemblies. Consequently, the results and discussion section is structured into four parts. First, the synthesis and characterisation of the new 1,2,3-triazole–catechol ligands. Second, the preparation and study of novel Ga_2L_3 metal–organic cage assemblies. And third, the preparation and study of new Fe_2L_3 cage analogues as well as the examination of their self-assembly process in the presence of various counterions, including inorganic K^+ ions and organic ammonium R_4N^+ ions.

1.3.1 Synthesis and Characterisation of Alkyne and Azide Precursors

For the preparation of ligands containing 1,2,3-triazole functions, we use a Cu-catalyzed alkyne–azide “click” reaction (CuAAC) between different alkynes and various azides (Scheme 2). To achieve this goal, a series of aromatic alkynes and azides will be prepared, including 1,4-diethynylbenzene, 1,3-diethynylbenzene, 1,5-diethynylnaphthalene, 1-azido-2,3-dimethoxybenzene and 1-azido-6,7-dimethoxynaphthalene.

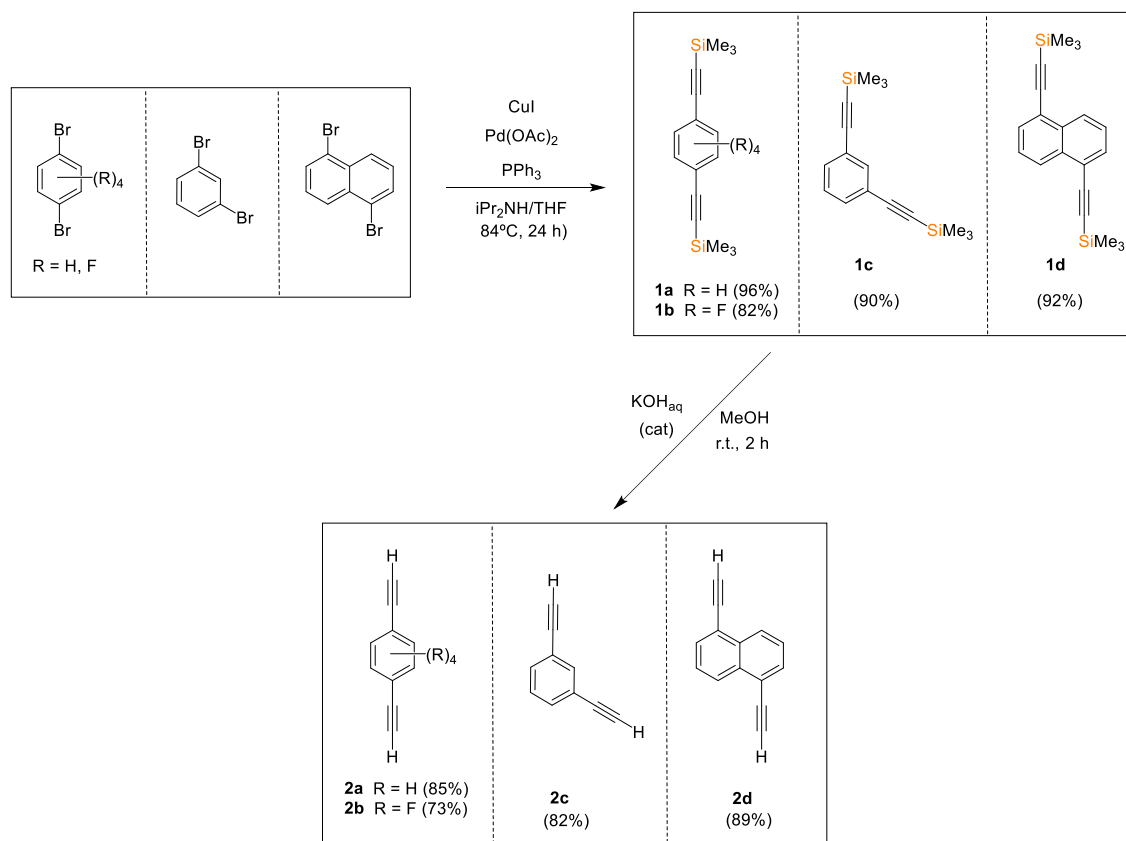


Scheme 2. Retrosynthetic analysis of ditopic ligands containing 1,2,3-triazole and catechol functional groups.

1.3.1.1 Synthesis and Characterisation of Alkynes

To obtain the alkynes **2a–d** (Scheme 3), we prepared the corresponding trimethylsilyl derivatives **1a–1d**.^[82] Specifically, the trimethylsilyl-alkynes were prepared via a Pd- and Cu-catalyzed Sonogashira cross-coupling reaction between the corresponding Bromo aromatic derivative and trimethylsilylacetylene (TMSA), followed by deprotection of the resulting trimethylsilyl product. The Pd and Cu-catalyzed Sonogashira coupling is a highly versatile method that provides high yields for the preparation of aromatic alkynes. The preparation of the starting compounds **1a–1d** was carried out through the reaction of commercial aryl bromides (1,4-dibromobenzene, 1,3-dibromobenzene and 1,5-dibromonaphthalene) and TMSA. In these reactions, a slight excess of the alkyne (2.5–3 equivalents relative to the bromo aromatic compound) was employed to optimise the yield and avoid mixtures involving homo functionalisation of the dibromo aromatic compounds. The reaction was performed in the presence of CuI (1.2 mol%), and Pd(OAc)₂ (1 mol%) and triphenylphosphine (PPh₃) in a 1:4 mixture of *i*Pr₂NH/THF. These are typical reaction conditions for Cu- and Pd-catalyzed Sonogashira couplings (Cu- and Pd-catalyzed C(sp²)-C(sp) coupling).^[83] All these coupling reactions require heating to 84°C for 24 hours. TLC monitoring of the resulting reaction crude indicated the quantitative formation the derived products **1a–1d** after this reaction time. Moreover, ¹H NMR analysis in CDCl₃, confirmed the formation of the products **1a–1d** observing a new signal between δ 0–0.5 ppm that corresponds to trimethylsilyl groups. The ¹H

NMR spectra of the products **1a–d** are consistent with the data described in the literature.^[82] After this time, the reaction mixture was filtered to remove inorganic salts (diisopropylammonium bromide), and after removing the volatiles from the reaction crude in a rotatory evaporator, products **1a–1d** were obtained in good yields (82–96%). The obtained products **1a–1d** were of sufficient purity by 1H NMR spectroscopy for their adequate use in the subsequent synthetic steps to obtain the corresponding primary alkynes **2a–2d**.



Scheme 3. Preparation of alkynes **2a–2d** via Sonogashira couplings followed by protodesilylation.

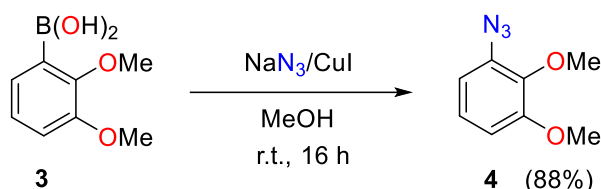
Once the alkyne trimethylsilylated derivatives **1a–1d**, were obtained, they were used for the preparation of the targeted primary alkynes **2a–2d**. The synthesis of the primary alkynes **2a–2d** was carried out via protodesilylation of **1a–1d** with KOH in $MeOH$ (Scheme 3). Although other methods for the deprotection of trimethylsilyl groups could also be used, involving weaker bases such as K_2CO_3 ^[84] or $TBAF$,^[85] the method involving KOH provides better yields under milder conditions (room temperature, short times and catalytic amounts of KOH) damping the deprotection

step. Following the conditions reported for this deprotection reaction,^[82a] a catalytic amount of KOH (aq) (1.4 mol%) was used for the protodesilylation of **1a–1d**. After 2 hours, the reaction mixtures were filtered to remove silicon salts (OHTMS), all the volatiles were removed under vacuum, and the reaction crude was purified by column chromatography with hexane on silica gel ($R_f = 0.4–0.6$), obtaining the pure products **2a–2d** in good yields (73–89%) (Scheme 3). The disappearance of the 1H NMR signal between δ 0–0.5 ppm (trimethylsilyl groups) and the appearance of a new 1H resonance between δ 3–4 ppm (alkyne's protons) confirmed their successful formation, matching the reported 1H NMR data for these compounds.^[82]

1.3.1.2 Synthesis and Characterisation of Azides

For the preparation of 1,2,3-triazole ligands, we prepared the aromatic azides 1-azido-2,3-dimethoxybenzene **4** and 1-azido-6,7-dimethoxynaphthalene **7** (Scheme 4–7).

To obtain **4**, boronic acid **3** was used as precursor (Scheme 4). The azide **4** was obtained through a cross-coupling reaction between **3** and sodium azide (NaN_3), catalyzed by CuI (10%mol) in MeOH. To prepare azide **4**, we followed the reported synthetic protocol,^[86] with a slight difference, we used CuI instead of Cu_2SO_4 as the copper source. We observed that using Cu_2SO_4 promotes the formation of a reaction mixture containing both the desired product **4** and veratrole (1,2-dimethoxybenzene), resulting from the hydrolysis of the boronic acid **3**. We observed this issue by using CuI instead. This reaction was carried out at room temperature for 16 hours, and the aromatic azide **4** was isolated as a viscous brown oil in good yield (88%) after filtering the reaction mixture and removing all the volatiles under vacuum in a rotary evaporator.

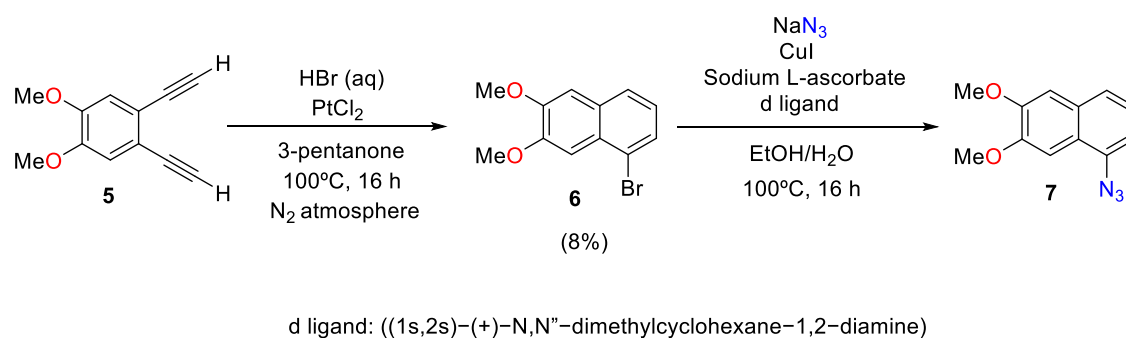


Scheme 4. Preparation of azide 1-azido-2,3-dimethoxybenzene **4**.

There are three distinct synthetic pathways that can be used to prepare azide **7**. The first route entails obtaining aryl bromide **6** and then performing a nucleophilic substitution with sodium azide (NaN_3) (Scheme 5). The second method involves

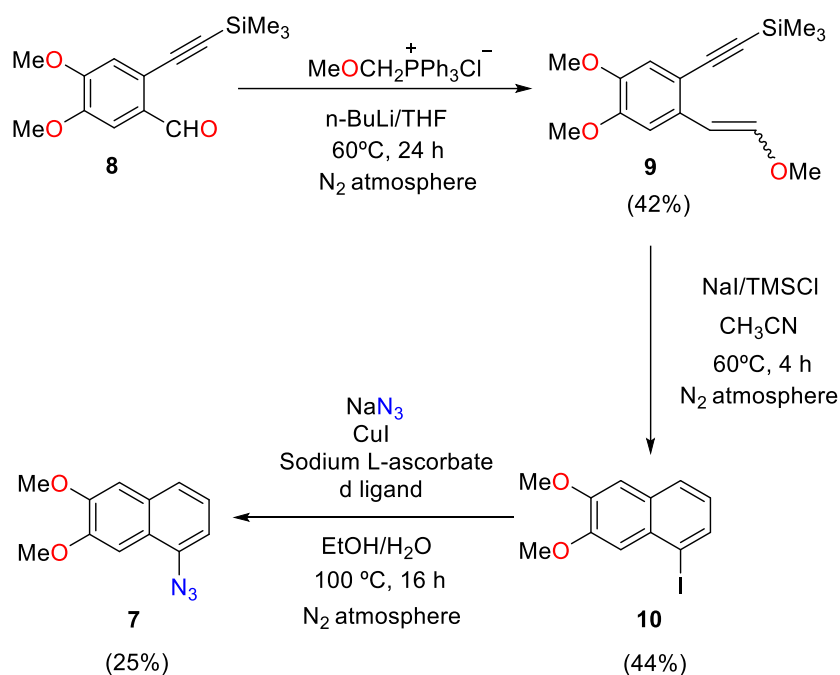
obtaining aryl iodide **10**, followed by a similar nucleophilic substitution using NaN_3 (Scheme 6). The third synthetic approach requires obtaining aryl amine **13**, which is then converted to a diazonium salt before undergoing nucleophilic substitution with NaN_3 to yield the desired azide **7** (Scheme 7).

Employing the first synthetic method, we prepared the starting material **5** via sonogashira coupling followed by protodesilylation with tetrabutylammonium fluoride (TBAF), obtaining product **5** with a yield of 95% (Scheme 5).^[87] Then, with product **5** in our hands, we performed a cyclisation of enediyne **5** using $PtCl_2$ as catalyst and HBr as nucleophile following the reported synthetic protocol.^[88] This reaction requires thermal activation at 100°C for 16 h using 3-pentanone as solvent. 1H NMR analysis and TLC monitoring confirmed the formation of a complex reaction mixture involving several unknown byproducts and a very low yield of 8% for the desired compound **6**.



Scheme 5. Pt-catalyzed cyclisation method to prepare azide 1-azido-6,7-dimethoxynaphthalene **7**.

The very poor yield of compound **6** was reproducible over several attempts and is a consequence of the formation of byproducts under the reaction conditions used. Therefore, we decided to follow the second synthetic route to prepare azide **7** (Scheme 6). For this purpose, we prepared the intermediate compounds **8–10**, following the procedure previously described for them.^[89]



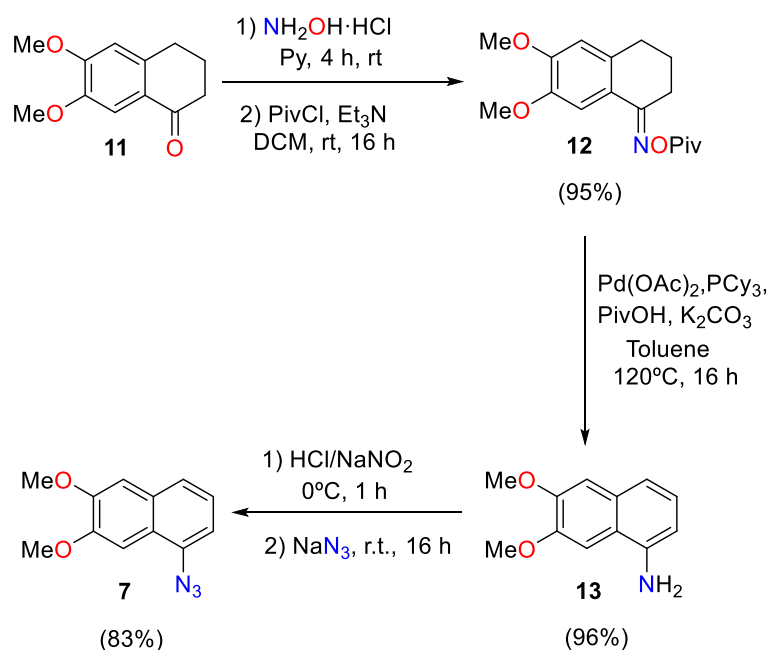
d ligand: ((1s,2s)-(+)–N,N''–dimethylcyclohexane–1,2–diamine)

Scheme 6. Metal-free iodoannulation method to prepare azide 1-azido-6,7-dimethoxynaphthalene **7**.

For the synthesis of 1-iodo-6,7-dimethoxynaphthalene **10** began with the preparation of the precursor **8** using a previously reported synthetic protocol.^[89] The synthesis of **9** was carried out through a Wittig reaction, starting with the preparation of a solution of $MeOCH_2PPh_3Cl$ in THF under nitrogen atmosphere, followed by the addition of $n-BuLi$ and subsequent combination with **8**. In this reaction, $O=PPh_3$ was formed and its separation from the desired product **9** was challenging because its similar solubility to that of **9**. To solve this issue, we used calcium bromide ($CaBr_2$) that allowed us an easy removal by precipitation of $O=PPh_3$ via coordination of $O=PPh_3$ to $CaBr_2$. The formation of the complex $[CaBr_2(O=PPh_3)_2]$ which is insoluble in THF could be removed by filtration.^[90] This approach helped us to eliminate the contamination of $O=PPh_3$ from the reaction mixture. The final yield of 42% for **9**, although moderate, is significant given the inherent difficulties of Wittig reactions and the contamination with $O=PPh_3$. To prepare the intermediate product **10** (1-iodo-6,7-dimethoxynaphthalene), NaI was left to dry under vacuum for 15 minutes and CH_3CN was added, and the resulting solution was kept at $0^\circ C$ in a J.Young's ampoule. The reaction mixture was stirred for 5 minutes at $0^\circ C$. After this time, trimethylsilyl chloride ($TMSCl$) was added dropwise with vigorous stirring.

Compound **9** was then dissolved in CH_3CN as well, and the resulting suspension was kept at $0^\circ C$ in a Schlenk flask. Once both solutions were at $0^\circ C$, the solution of **9** was added to the in-situ generated “TMS-I” solution via cannula. The resulting reaction mixture was then stirred and heated in an oil bath at $60^\circ C$ for 4 hours under a dry nitrogen gas atmosphere. After this time, the reaction mixture was filtered, and the solvent was removed under reduced pressure. Then, the residue was purified by neutral alumina column chromatography using a mixture hexane/AcOEt (7:3) as eluent to afford the iodo-annulated product **10** ($R_f = 0.7$) as a white solid (44%). 1H NMR spectroscopic data of product **10** is consistent with that previously described,^[89] observing two doublets, two singlets, and a triplet in the region between δ 7–8 ppm corresponding to aromatic protons, and two singlets (methoxy groups) between δ 4–4.1 ppm.

With product **10** in our hands, we carried out a Cu-catalyzed reaction, employing NaN_3 and the ligand **d** ((1*s*,2*s*)-(+)–N,N”-dimethylcyclohexane–1,2–diamine) in the presence of sodium ascorbate as reducing agent.^[91] We used a 7:3 EtOH/ H_2O mixture under a nitrogen atmosphere and refluxed the reaction mixture at $100^\circ C$ overnight. Despite careful monitoring by 1H NMR spectroscopy, the yield obtained for **7** was only 25%. We found this route to the aryl iodide **10** to be superior to that of the aryl bromide **6**, as it provided a higher yield. However, the subsequent nucleophilic substitution to the desired azide proceeded with only moderate yield, due to the formation of several unknown byproducts within the reaction mixture. The unsatisfactory yield of azide **7** via the synthetic route in Scheme 5 led us to choose the synthetic protocol starting from aryl amine **13** (Scheme 7) as a strategy to obtain better results.



Scheme 7. Diazotisation method of amine **13** to prepare azide 1-azido-6,7-dimethoxynaphthalene **7**.

This route involves the preparation of the pivalate oxime **12** in two steps. First, ketone **11** was mixed with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in pyridine at room temperature for 4 hours under a nitrogen atmosphere (Scheme 7). The reaction was then quenched with HCl 1M, diluted with water and extracted with Et_2O , followed by drying over Na_2SO_4 . The volatiles were removed with a rotary evaporator leading to the oxime **12** in an 88% yield. We obtained **12** with sufficient purity, measured by ^1H NMR, to use it in the next step without needing further purification. Pivalate oxime **12** was synthesised from the oxime in DCM, maintaining the reaction at 0°C . The addition of Et_3N and PivCl , followed by a period of stirring (16 h) at room temperature, constitutes an effective approach for converting the oxime into **12**. Pivalate oxime **12** ($R_f = 0.33$) was purified by column chromatography using silica gel and a mixture pentane/AcOEt (8:2) as eluent, resulting in a high yield of 95%.^[92]

A solution of **12** in dry toluene under nitrogen atmosphere was sequentially added with $\text{Pd}(\text{OAc})_2$, PCy_3 , PivOH , and K_2CO_3 . The solution was stirred overnight, heated in an oil bath at 120°C , and monitored by ^1H NMR spectroscopy. After this time, the reaction mixture was filtered using basic alumina in a filter plate, and the solvent was removed under reduced pressure. The aniline **13** was obtained as a brown solid in a high yield of 96%.^[92] ^1H NMR spectroscopic analysis confirmed the successful formation of aniline **13** observing two new doublets and one new triplet in

the aromatic region between δ 6.7–7.3 ppm and the disappearance of two triplets and one quintuplet between δ 1.8–2.9 ppm corresponding to $-CH_2$ groups from pivalate oxime group. The 1H NMR spectroscopic data is consistent with the one described in the literature.^[92]

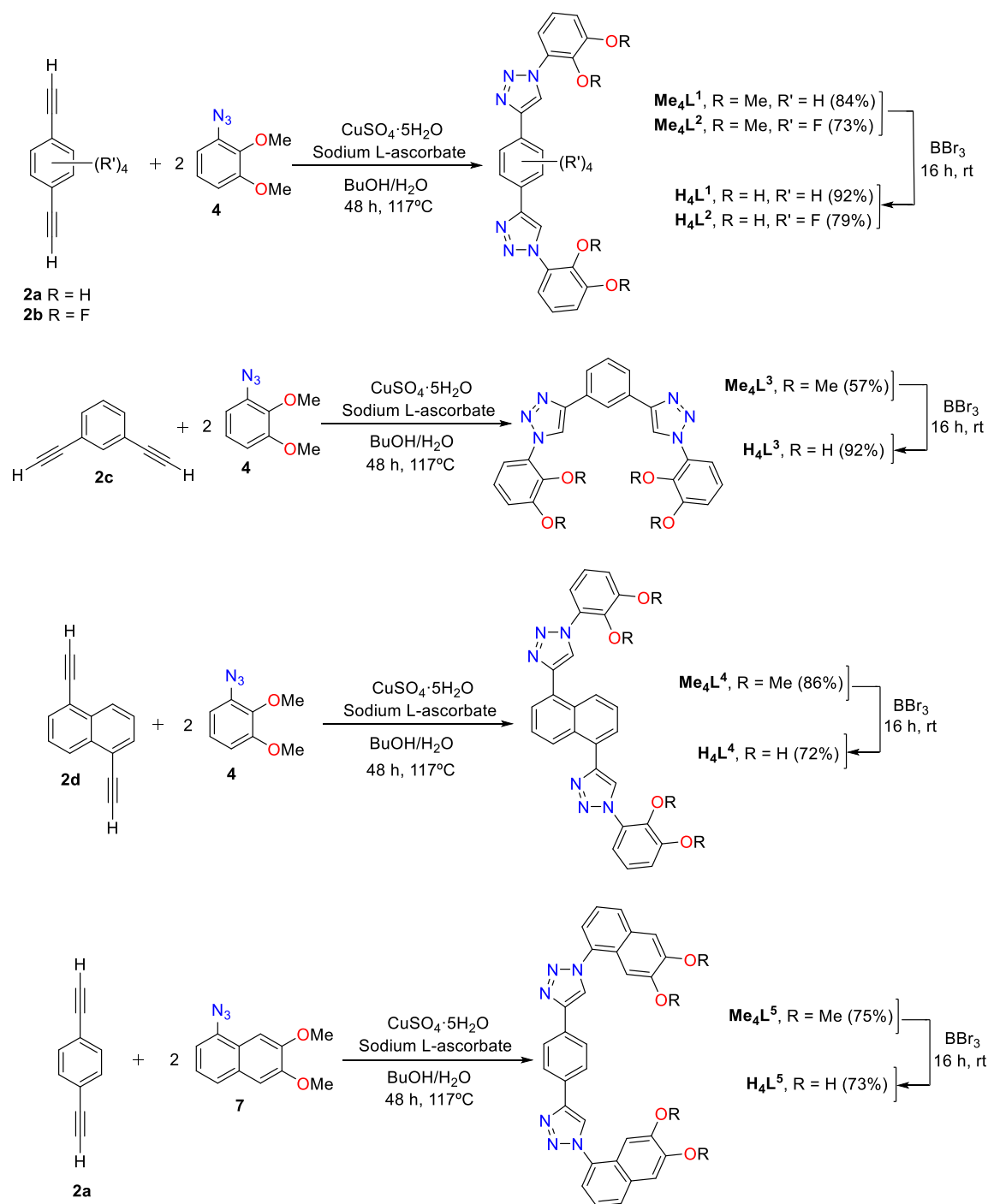
The new azide **7** was then prepared by diazotisation reaction of **13** with $NaNO_2$ at $0^\circ C$ in a 1:1 HCl/H_2O medium forming the $Ar-N_2^+Cl^-$ intermediate, followed by aromatic nucleophilic substitution with NaN_3 at room temperature.^[93] The subsequent extraction with $AcOEt$, followed by drying over Na_2SO_4 , resulted in a significantly higher yield of 83% for the naphthalene azide **7**.

In conclusion, the diazotisation method involving naphthalene amine **13** depicted in Scheme 7 proved to be the most effective synthetic route for obtaining azide **7** due to its highly reproducibility and the high yields obtained for compounds **12**, **13** and **7** (83–95%).

1.3.2 Synthesis and Characterisation of Ditopic Ligands $H_4L^1-H_4L^5$

The synthesis of the new ligands $H_4L^1-H_4L^5$ began preparing the methylated precursors $Me_4L^1-Me_4L^5$ starting from the corresponding alkynes **2a–2d** and 2 equivalents of the previously prepared aromatic azides **4** or **7** (Scheme 8).

The choice of the Cu-catalyzed coupling reaction, employing $CuSO_4 \cdot (H_2O)_5$ and sodium ascorbate as reducing reagent, proved to be an effective and selective strategy for forming bis(1,2,3-triazole) heterocycles. This reaction was performed at $117^\circ C$ in an $n-BuOH/H_2O$ mixture. The reflux process for 48 hours and subsequent extraction with $CHCl_3$, are key steps in the formation of precursors $Me_4L^1-Me_4L^5$. The yields of these reactions range 57–86%. Nevertheless, the consistency of these yields with those commonly achieved in similar reactions,^[94] suggests that the reaction conditions employed were the most suitable for these specific ditopic ligands.



Scheme 8. Preparation of ligand precursors Me_4L^1 – Me_4L^5 and ditopic ligands H_4L^1 – H_4L^5 .

To confirm the desired structure of the new 1,2,3-triazol ligands, we studied their 1H NMR spectra observing new signals between δ 8.3–8.7 ppm that corresponded to the CH triazole protons as well as the disappearance of the signal from alkynes between δ 3–4 ppm corroborating the formation of the products and providing crucial validation of the synthetic methodology for Me_4L^1 – Me_4L^5 . These

1,2,3-triazoles were obtained with sufficient purity, measured by elemental analysis, for their proper use in the next reaction step. The synthesis of ligands **H₄L¹–H₄L⁵** (Scheme 7) involved a deprotecting step of the methoxy groups of the precursors **Me₄L¹–Me₄L⁵**. This reaction was carried out under a nitrogen atmosphere using excess of boron tribromide BBr₃ in distilled DCM at –78°C and was allowed to warm to room temperature. The evaporation of DCM and subsequent neutralisation of excess BBr₃ with water, followed by refluxing the product at 100°C for 2 hours led to the precipitation of the ligands **H₄L¹–H₄L⁵** that were isolated after filtration. To perform this reaction, we followed the reported procedure, obtaining yields ranging 72–92% which are consistent with the yields obtained in similar reactions.^[54]

¹H NMR spectroscopic analysis of the isolated solids products showed the disappearance of the signals between δ 3.7–4 ppm that correspond to methoxy group (MeO) protons and the appearance of new signals between δ 9.4–10.5 ppm that correspond to protons from catechol group (C₆H₄(OH)₂), confirming the successful formation of the ditopic ligands **H₄L¹–H₄L⁵**.

Me₄L¹–Me₄L⁵ and **H₄L¹–H₄L⁵** were characterised by ESI–HRMS spectrometry. The distribution of m/z peaks indicates ion–pairing associations of **Me₄L¹–Me₄L⁴** with Na⁺ forming the cationic adducts [**Me₄L¹–Me₄L⁴** + Na]⁺ at m/z values of 507.1766 (calcd. 507.1751), 579.1301 (calcd. 579.1374), 507.1745 (calcd. 507.1751) and 557.1917 (calcd. 557.1908) respectively, whereas **Me₄L⁵** forms the protonated adduct [**Me₄L⁵** + H]⁺ at m/z values of 585.2214 (calcd. 585.2245). The ligands **H₄L¹**, **H₄L²**, **H₄L³** and **H₄L⁵** form the cationic adduct with Na⁺ ions at m/z values of 451.1132 (calcd. 451.1125), 523.0747 (calcd. 523.0748), 451.1175 (calcd. 451.1125) and 551.1438 (calcd. 551.1438), whereas **H₄L⁴** form the protonated adduct [**H₄L⁴** + H]⁺ at m/z values of 479.1493 (calcd. 479.1462). Furthermore, the observed isotope patterns matched well with the calculated isotopic distributions, confirming well resolved m/z peaks for **Me₄L¹–Me₄L⁵** and **H₄L¹–H₄L⁵**.

To further study their structures and suitability to form supramolecular arrangements, we crystallised **Me₄L¹**, **Me₄L³** and **Me₄L⁴** for single-crystal X-ray analyses. Several attempts to crystallise **H₄L¹–H₄L⁵** were unsuccessful due to their limited solubility in common organic solvents such as DCM, chloroform, AcOEt, or CH₃CN. High-quality block crystals of **Me₄L¹**, **Me₄L³** and **Me₄L⁴** were achieved using layer diffusion technique by diffusion of hexane into a chloroform solution of **Me₄L¹**, **Me₄L³** and **Me₄L⁴**.

The X-ray structure of **Me₄L¹** (Figure 20a) shows the triazole rings slightly rotated relative to the central phenylene ring C_6H_4 by a torsion angle of $13.47(17)^\circ$. The rings containing the methoxy groups $\text{C}_6\text{H}_3(\text{OMe})_2$ are rotated relative to triazole rings with a torsion angle of $38.94(15)^\circ$. In addition, the methoxy groups are positioned in a transoid conformation between the two $\text{C}_6\text{H}_3(\text{OMe})_2$ rings. This results with the triazole proton oriented towards the oxygen of the nearest methoxy group at $2.5417(19)$ Å (triazole–CH $\cdots$ OMe), allowing for a weak electrostatic interaction between them. This ligand exhibits a linear arrangement with a length of $17.98(2)$ Å, distance measured between the oxygens of the two external –OMe groups of the $\text{C}_6\text{H}_3(\text{OMe})_2$ rings. The arrangement of **Me₄L¹** provides high potential to form supramolecular structures.

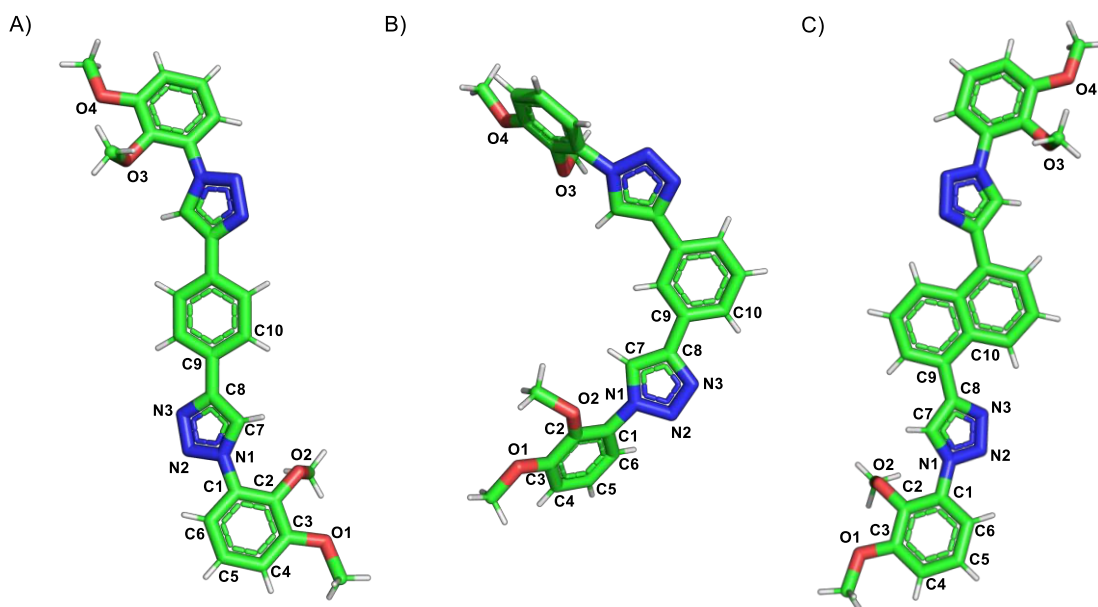


Figure 20. Molecular structure of a) **Me₄L¹**, b) **Me₄L³**, c) **Me₄L⁴**. Selected bond lengths (Å) and angles (deg): for **Me₄L¹**, O1–O4 $17.98(2)$, triazole–CH $\cdots$ OMe $2.5417(19)$; torsion angles C7–C8–C9–C10 $13.47(17)$, C7–N1–C1–C2 $38.94(15)$; for **Me₄L³**, O1–O4 $12.37(16)$, triazole–CH $\cdots$ OMe $2.8711(11)$; torsion angles C7–N1–C1–C2 $51.80(2)$, C7–C8–C9–C10 $12.60(2)$; for **Me₄L⁴**, O1–O4 $19.03(3)$, triazole–CH $\cdots$ OMe $2.6300(11)$; torsion angles C7–N1–C1–C2 $44.62(18)$, C7–C8–C9–C10 $18.90(8)$. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The ligand **Me₄L³** (Figure 20b) exhibits a significantly different geometric arrangement compared to the previous ligand **Me₄L¹**. The triazole groups are positioned in a 1,3–arrangement relative to the central phenylene C_6H_4 aromatic ring,

being are almost co-planar with the central aromatic ring, slightly rotated with a torsion angle of $12.60(2)^\circ$. Moreover, the rings containing the methoxy groups $C_6H_3(OMe)_2$ are rotated relative to triazole rings with a torsion angle of $51.80(2)^\circ$. Unlike **Me₄L¹**, triazole and $C_6H_3(OMe)_2$ rings are in a cisoid conformation. This results with the triazole proton oriented towards the oxygen of the nearest methoxy group at $2.8711(11)$ Å (triazole–CH $\cdots$ OMe), which is longer than in the ligand **Me₄L¹** (2.54 Å). Due to its angular arrangement, this ligand has a length of $12.37(16)$ Å, significantly shorter than the previous linear ligand **Me₄L¹**. This angular ligand design is interesting because it could led to the formation of a different supramolecular coordination arrays during the self-assembly process than using the linear ligand **Me₄L¹**.

In the case of **Me₄L⁴** (Figure 20c) the triazole rings are rotated relative to the central naphthylene ring $C_{10}H_6$ by a torsion angle of $18.90(8)^\circ$. This torsion can be attributed to steric hindrance between the triazole–CH protons and the $C_{10}H_6$ protons from the central naphthylene ring. The rings containing the methoxy groups $C_6H_3(OMe)_2$ are rotated relative to triazole rings with a torsion angle of $44.62(18)^\circ$. As in ligand **Me₄L¹**, the aromatic rings $C_6H_3(OMe)_2$ are positioned in a transoid conformation between them. Akin to **Me₄L¹** and **Me₄L³**, the triazole protons are oriented towards the oxygen of the nearest methoxy group at $2.6300(11)$ Å (triazole–CH $\cdots$ OMe). This ligand exhibits a linear arrangement, but it is slightly longer than **Me₄L¹** with a length of $19.03(3)$ Å and could form larger supramolecular assemblies than **Me₄L¹**.

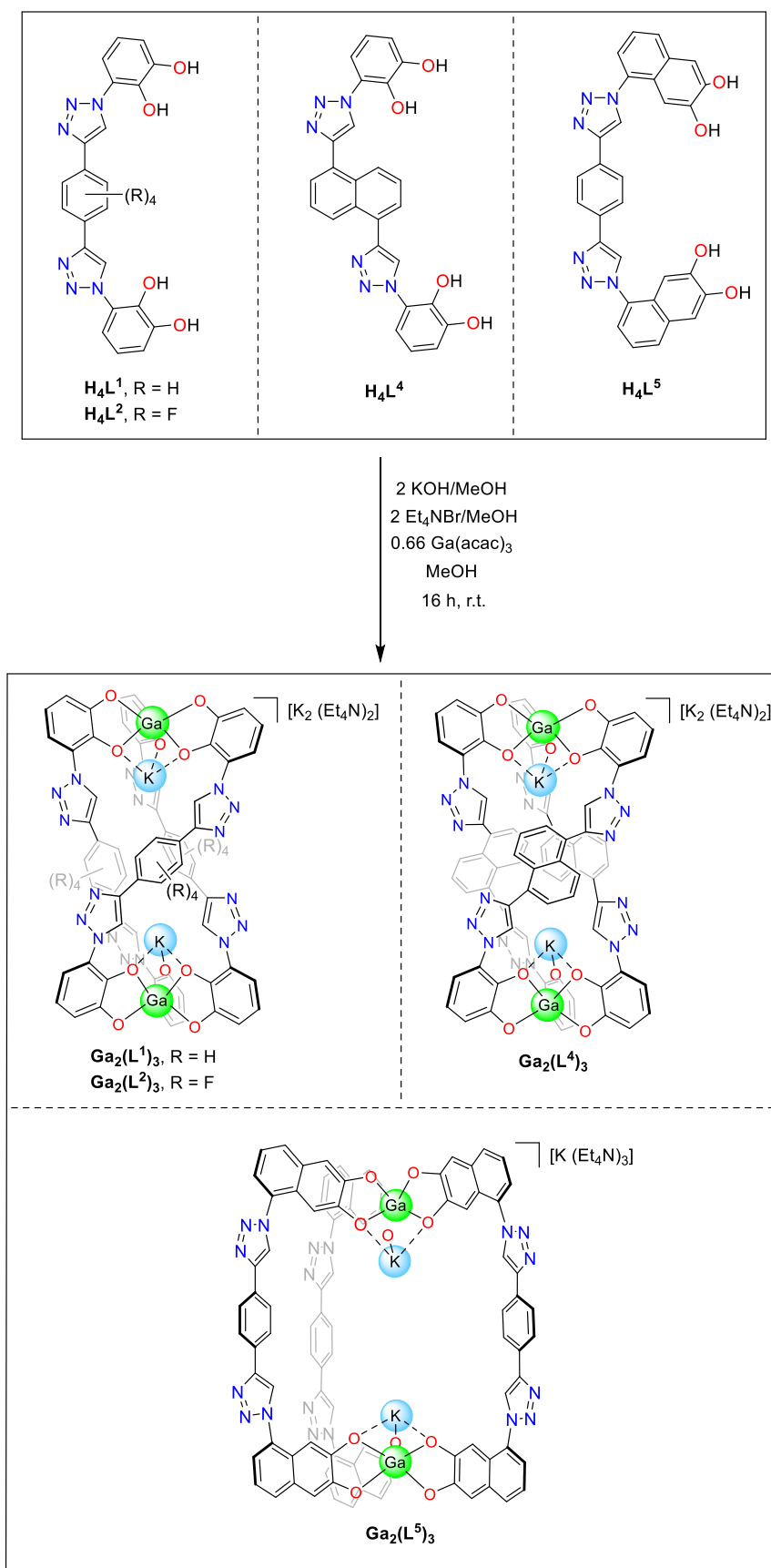
1.3.3 Supramolecular Self-Assembly of Ga_2L_3 Cages

With the successful synthesis of this family of ditopic ligands **H₄L¹**–**H₄L⁵** which are based on 1,2,3-triazoles with catechol groups that offers strong binding sites for oxophilic M^{3+} ions, in this section of the chapter, we will explore the self-assembly via coordination of **H₄L¹**–**H₄L⁵** with Ga^{3+} metal ions to form supramolecular metal-organic cages of the type M_2L_3 .

The supramolecular synthesis began preparing a suspension of the corresponding ligands **H₄L¹**–**H₄L⁵** in distilled and deoxygenated MeOH under a nitrogen atmosphere. The addition of KOH/MeOH (2 eq relative to the ligands) led to a brown solution of the deprotonated potassium salts of $(L^{1-5})^{4-}$, after 20 minutes. Then, a solution of Et_4NBr /MeOH (2 eq relative to the ligands) and $Ga(acac)_3$ (0.66 eq relative to the ligands) powder was added. The reaction was stirring

overnight at room temperature allowing the formation of the supramolecular metal–organic cages $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ (Scheme 9). Due to cages $\text{Ga}_2(\text{L}^n)_3$ are 6– charged, they precipitated as their corresponding ammonium and potassium salts. The different salts of the cages $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, $[\text{Ga}_2(\text{L}^4)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}]_3[\text{K}]_4$ were isolated by filtration obtaining in all synthesis brown solids which were dried under vacuum and isolated with a yield of 49%, 40%, 50% and 66% respectively. These yields are consistent with others reported for similar supramolecular metal–organic M_2L_3 cages.^[45b, 56] The cage $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ coprecipitated with 4 molecules of Et_4NBr whereas $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ coprecipitated with 3 molecules of Et_4NBr in the reaction mixture. $[\text{Ga}_2(\text{L}^4)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}]_3[\text{K}]_4$ were isolated without coprecipitation of Et_4NBr .

For studying the coordination self–assembly of H_4L^3 , we followed the synthetic protocol used for obtaining the cages $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$. To our disappointment, deprotonating the bis–catechol H_4L^3 with KOH in the presence of $\text{Ga}(\text{acac})_3$ failed to produce a clearly identifiable product through coordination of the catecholate groups to Ga^{3+} ions. Instead, the reaction resulted in a highly insoluble mixture, suggesting that the deprotonated ligand $(\text{L}^3)^{4-}$ underwent polymerisation by coordinating Ga^{3+} and K^+ metal ions. This outcome could be due to ligand H_4L^3 presenting a smaller distance between its catecholate groups (12.4 Å) than ligands H_4L^1 (18.0 Å) or H_4L^4 (19.0 Å) which form supramolecular Ga_2L_3 cages. In addition to this, the specific 1,3–arrangement of the ligand H_4L^3 with a torsion angle of 103° and its flexibility compared to linear ligands H_4L^1 , H_4L^2 , H_4L^4 and H_4L^5 with 1,4–disposition, make H_4L^3 a candidate to easily form polymeric coordination compounds.



Scheme 9. Self-assembly of supramolecular metal-organic cages $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$.

The following sections will outline the structural characterisation and solution behaviour of these new supramolecular metal–organic cages $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ cages. Our analyses include monodimensional NMR spectroscopy (^1H , ^{13}C , ^{19}F), two–dimensional NMR techniques (^1H – ^1H COSY, ^1H – ^{13}C HSQC, ^1H – ^{13}C HMBC, ^1H – ^1H NOESY, ^1H – ^1H ROESY), Diffusion–Ordered NMR Spectroscopy (DOSY NMR) and single crystal X–ray diffraction.

1.3.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis

The analysis of the ^1H NMR spectra of the salts of the supramolecular metal–organic cages $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, $[\text{Ga}_2(\text{L}^4)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}]_3[\text{K}]_3$ reveals important details about their structures. The high symmetry of the cage assemblies $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ were evidenced by the formation of simple ^1H NMR data which are consistent with the supramolecular cages. Notably, the disappearance of the phenolic OH proton signal between δ 9.4–10.5 ppm indicated deprotonation of the ligands H_4L^1 , H_4L^2 , H_4L^4 and H_4L^5 during self–assembly.

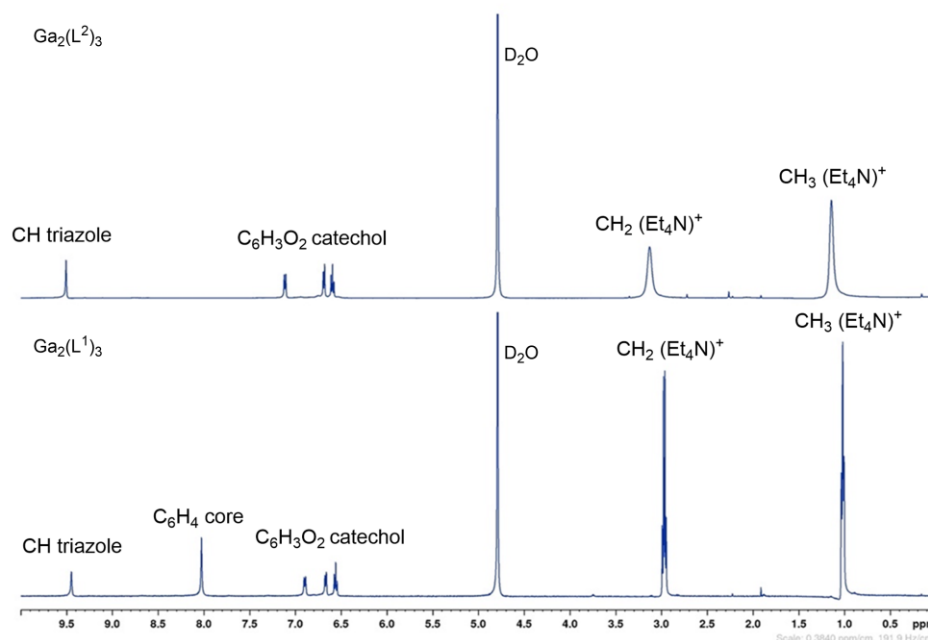


Figure 21. ^1H NMR (500 MHz, D_2O , 298 K) spectrum comparative of $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ (top) and $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ (bottom)

Additionally, the triazole protons signals exhibited significant downfield shifts compared to the free ligands H_4L^1 (δ 8.92 ppm) and H_4L^2 (δ 8.94 ppm), with supramolecular cages $\text{Ga}_2(\text{L}^1)_3$ (δ 9.44 ppm) and $\text{Ga}_2(\text{L}^2)_3$ (δ 9.50 ppm) (Figure 21). These changes in the chemical shift suggested coordination of $(\text{L}^1)^{4-}$ and $(\text{L}^2)^{4-}$ to the Ga^{3+} metal centres supporting the formation of the supramolecular cage assemblies. In the aromatic region, the signals in the range of δ 6.5–7.0 ppm reflect the complexity and symmetry of the aromatic catechol rings in the structure. Furthermore, the signal corresponding to core aromatic protons C_6H_4 (δ 8.02 ppm) in $\text{Ga}_2(\text{L}^1)_3$ disappears in the case of the cage $\text{Ga}_2(\text{L}^2)_3$, because the cage $\text{Ga}_2(\text{L}^2)_3$ presents fluor atoms in the core (C_6F_4) instead of protons (C_6H_4). For this reason, we could study the supramolecular assembly of $\text{Ga}_2(\text{L}^2)_3$ using the ^{19}F NMR. This spectrum showed a unique downfield shifted signal for $\text{Ga}_2(\text{L}^2)_3$ (δ –142.7 ppm) compared to H_4L^2 (δ –140.8 ppm), corroborating also a highly symmetric environment consistent with the formation of $\text{Ga}_2(\text{L}^2)_3$. Moreover, the signals in the range of δ 0.9–3.1 ppm correspond to protons of 2 molecules of Et_4N^+ that act as counterions as well as to protons of 4 molecules of Et_4NBr that coprecipitated with $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$ and 3 molecules of Et_4NBr that coprecipitated with $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$. In the ^{13}C NMR spectra of cages $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$ and $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$, we highlight the chemical shift observed in carbons bonded to the oxygens of the catechol groups. In both cages, $[\text{Ga}_2(\text{L}^1)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$ (δ 155.1 and 147.9 ppm) and $[\text{Ga}_2(\text{L}^2)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$ (δ 155.3 and 147.8 ppm), these carbons are downfield shifted compared to the same carbons in H_4L^1 (δ 146.6 and 138.9 ppm) and H_4L^2 (δ 146.7 and 138.8 ppm), consistent with the coordination of the oxygens to the Ga^{3+} ions.

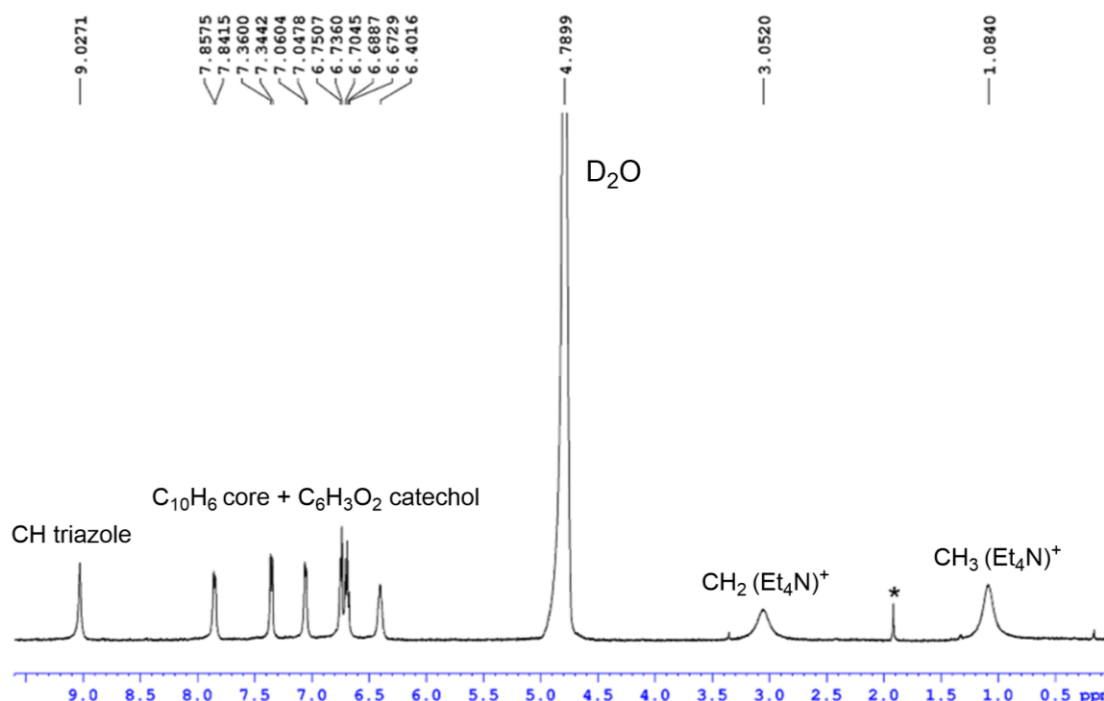


Figure 22. ^1H NMR (500 MHz, D_2O , 298 K) spectrum of $[\text{Ga}_2(\text{L}^4)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$. The symbol * denotes small residual signal from acetylacetone from isolation.

The cage $\text{Ga}_2(\text{L}^4)_3$ exhibit similar behaviour than $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$. The ^1H NMR spectrum of $[\text{Ga}_2(\text{L}^4)_3][\text{K}^+]_4[\text{Et}_4\text{N}^+]_2$ (Figure 22) shows that the triazole CH proton signal exhibit significant downfield shifts, comparing H_4L^4 (δ 8.88 ppm) with $\text{Ga}_2(\text{L}^4)_3$ (δ 9.02 ppm). This suggests coordination of $(\text{L}^4)^{4-}$ to the Ga^{3+} metal centres supporting the formation of the highly symmetric $\text{Ga}_2(\text{L}^4)_3$ assembly. The signals in the range of δ 6.3–8.0 ppm correspond to protons of the aromatic catechol rings and naphthylene core ring (C_{10}H_6). Et_4N^+ proton signals are observed at 3.05 ppm and 1.08 ppm that correspond to two molecules of Et_4N^+ that act as counterions. In the ^{13}C NMR spectrum of $[\text{Ga}_2(\text{L}^4)_3][\text{Et}_4\text{N}^+]_2[\text{K}^+]_4$, we observed a highly symmetric environment, like the one observed for $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$. The carbons bonded to the oxygens of the catechol group for $\text{Ga}_2(\text{L}^4)_3$ (δ 155.8 and 147.5 ppm) are downfield shifted compared to the same carbons in H_4L^4 (δ 146.7 and 138.9 ppm) due to the coordination of the oxygens to the metal.

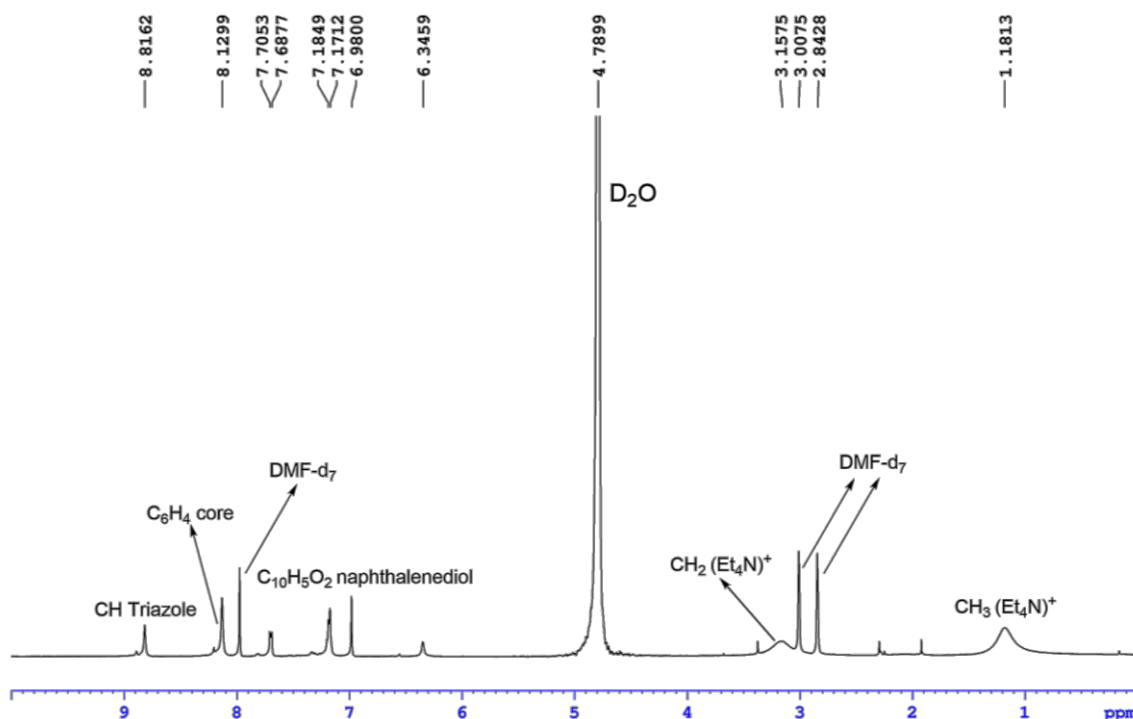


Figure 23. ^1H NMR (500 MHz, $\text{D}_2\text{O}:\text{DMF-d}_7$ (1:1), 298 K) spectrum of $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}]_3[\text{K}]_3$.

^1H NMR spectrum of $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}^+]_3[\text{K}^+]_3$ (Figure 23) was carried out in a mixture between deuterated water and deuterated DMF- d_7 due to the limited solubility of the compound $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}^+]_3[\text{K}^+]_3$ in D_2O . This spectrum revealed one set of signals suggesting the formation of a supramolecular metal–organic cage with high symmetry consistent with the cage array $\text{Ga}_2(\text{L}^5)_3$. Unlike $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$ and $\text{Ga}_2(\text{L}^4)_3$, the triazole CH proton signal exhibited significant upfield shift, compared to the free ligand H_4L^5 (δ 9.13 ppm) with $\text{Ga}_2(\text{L}^5)_3$ (δ 8.81 ppm). This effect may be due to the mixture of deuterated solvents ($\text{D}_2\text{O}:\text{DMF-d}_7$) used in the characterisation of $\text{Ga}_2(\text{L}^5)_3$ which are not comparable with neat D_2O . The signals in the range of δ 6.2–7.8 ppm correspond to protons of the aromatic naphthyldiol ($\text{C}_{10}\text{H}_5\text{O}_2$) rings. Moreover, the signal corresponding to core aromatic protons C_6H_4 appears at δ 8.12 ppm, slightly downfield shifted than the same signal for $\text{Ga}_2(\text{L}^1)_3$ (δ 8.02 ppm). The Et_4N^+ proton signals are observed at 3.15 ppm and 1.18 ppm, corresponding to 3 molecules of Et_4N^+ that act as counterions. In the ^{13}C NMR spectrum of $[\text{Ga}_2(\text{L}^5)_3][\text{Et}_4\text{N}^+]_3[\text{K}^+]_3$, we observed that the carbons bonded to the oxygens of the catechol group for $\text{Ga}_2(\text{L}^5)_3$ (δ 161.0 and 159.5 ppm) are downfield shifted compared to the

same carbons in H_4L^5 (δ 148.8 and 146.2 ppm) like in the ^{13}C NMR spectra of $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$ and $\text{Ga}_2(\text{L}^4)_3$.

1.3.3.2 Diffusion Ordered Spectroscopy (DOSY) NMR Analysis

To investigate the stability of supramolecular cage architectures $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ as well as their aggregation degree in solution, we used diffusion-ordered spectroscopy (DOSY) NMR experiments. In these experiments, single sets of signals with uniform diffusion coefficients in the DOSY spectra were observed for $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$. DOSY NMR indicated that the coordination cages M_2L_3 are stable and monodisperse in solution.

The diffusion coefficient (D) of the free ligands H_4L^1 and H_4L^2 were measured to be $3.30 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ and $3.10 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ respectively in DMF-d_7 , consistent with a similar hydrodynamic diameter (d_H) of $\sim 17 \text{ \AA}$ for both ligands, based on the Stokes–Einstein equation. Upon formation of the cages $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$, the diffusion coefficients decreased significantly to $1.80 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ in D_2O for the assembled supramolecular cages $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$ (Figure 24), reflecting the larger hydrodynamic diameter of the assembly. The calculated hydrodynamic diameters of the capsules were $\sim 19 \text{ \AA}$ which are in good agreement with the dimensions obtained from the crystal structure of $\text{Ga}_2(\text{L}^1)_3$ ($\sim 19 \text{ \AA}$) (Table 1). This data further corroborates that the supramolecular assemblies $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$ maintaining their structural cage integrity in D_2O solution.

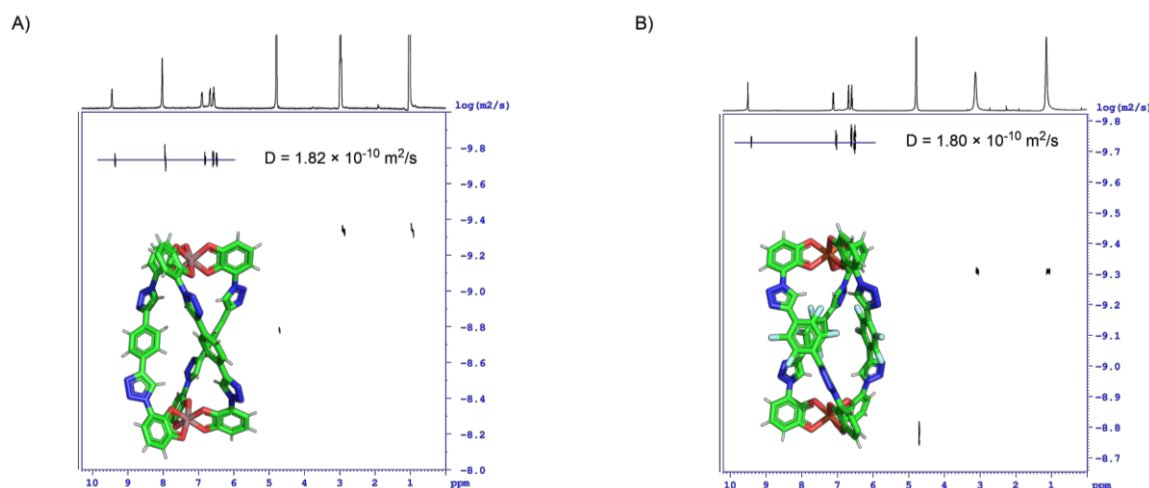


Figure 24. ^1H DOSY NMR 400 MHz (D_2O , 298 K) for $\text{Ga}_2(\text{L}^1)_3$ (left) and $\text{Ga}_2(\text{L}^2)_3$ (right).

The diffusion of the free ligand H_4L^4 in DMF-d_7 , quantified by its diffusion coefficient, was $2.80 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, a value in line with $d_{\text{H}} \sim 20 \text{ \AA}$. Upon the self-assembly of $\text{Ga}_2(\text{L}^4)_3$, the diffusion coefficient decreased noticeably to $1.80 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ in D_2O (Figure 25). This reduction means an increase in the d_{H} upon cage formation. The estimated d_{H} of the $\text{Ga}_2(\text{L}^4)_3$ cage, around $19 \text{ \AA}$, closely matched the dimensions determined from crystal structures, $19 \text{ \AA}$ (Table 1). Even though H_4L^4 is slightly larger and more rigid than H_4L^1 or H_4L^2 because of its naphthylene core, the resulting supramolecular cage exhibited a similar diffusion coefficient and size in solution to $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$. Additionally, the stability and solubility in polar solvents like water were comparable for $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$ and $\text{Ga}_2(\text{L}^4)_3$.

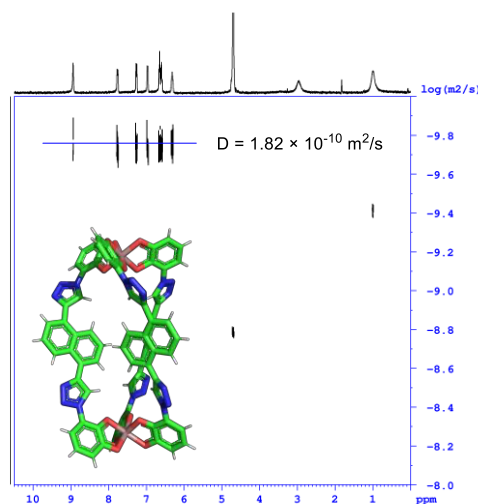


Figure 25. ^1H DOSY NMR 400 MHz (D_2O , 298 K) for $\text{Ga}_2(\text{L}^4)_3$.

Table 1. D (m^2s^{-1}) and $d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$) for $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, and $\text{Ga}_2(\text{L}^4)_3$ in D_2O at 298 K.

Species	D (m^2s^{-1})	$d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$)	$d^{\text{X-ray}}$ ($\text{\AA}$)
$\text{Ga}_2(\text{L}^1)_3$	1.82×10^{-10}	19	19
$\text{Ga}_2(\text{L}^2)_3$	1.80×10^{-10}	19	—
$\text{Ga}_2(\text{L}^4)_3$	1.82×10^{-10}	19	19

The diffusion of the free ligand H_4L^5 in DMF-d_7 , quantified by its diffusion coefficient, was $2.71 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, a value in line with $d_H \sim 20 \text{ \AA}$. Upon the self-assembly of $\text{Ga}_2(\text{L}^5)_3$, the diffusion coefficient in the deuterated solvent mixture required ($\text{D}_2\text{O}/\text{DMF-d}_7$) to dissolve the cage architecture decreased to an anomalously low value and is not comparable to the results obtained in D_2O . This result suggest that this supramolecular cage has tendency to associate in the mixture of deuterated solvents employed. This supramolecular aggregation of cages in solution has not yet been documented in the literature, representing an open area to study these features further.

1.3.3.3 High Resolution Mass Spectrometric (HRMS) Analysis

To support the studies in solution, we used ESI-HRMS to study the supramolecular assemblies in gas phase. This technique provided further evidence for the formation of the $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^2)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ cages. The distribution of m/z peaks indicates diverse ion-pairing associations with varying numbers of $[\text{Et}_4\text{N}]^+$, K^+ , Na^+ and H^+ ions during the ionisation process.

For example, for the anionic cage $\text{Ga}_2(\text{L}^1)_3$ (6 $-$), peaks at m/z values of 875.1866 (2 $-$) (calcd. 875.1878), 829.5890 (2 $-$) (calcd. 829.5897) and 783.9906 (2 $-$) (calcd. 783.9916) correspond to association of the anionic cage $\text{Ga}_2(\text{L}^1)_3$ with $2\text{Et}_4\text{N}^+/2\text{K}^+$, $1\text{Et}_4\text{N}^+/3\text{K}^+$ and 4K^+ respectively, whereas for $\text{Ga}_2(\text{L}^2)_3$ peaks at m/z values of 937.5337 (2 $-$) (calcd. 937.5331) and 891.9357 (2 $-$) (calcd. 891.9350) corresponds to association of the cage $\text{Ga}_2(\text{L}^2)_3$ with $1\text{Et}_4\text{N}^+/3\text{K}^+$ and 4K^+ respectively. Furthermore, the observed isotope patterns matched well with the calculated distributions, confirming the $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$ stoichiometry (Figure 26B). For instance, the HRMS spectrum for $\text{Ga}_2(\text{L}^1)_3$ (Figure 26A) shows two different sections. In the first section, in the range of m/z 480–600, several ions were detected from different aggregates with charge 3 $-$ resulting from association of the $\text{Ga}_2(\text{L}^1)_3$ with three cations (K^+ , Na^+ , Et_4N^+ and/or H^+) under the mass spectrometry ionisation conditions as well as aggregates from cages decomposition with charge 2 $-$. In the second section, in the range of m/z 750–900, we can observe aggregates with charge 2 $-$ resulting from association of cages with four cations ($[\text{Et}_4\text{N}]^+$, K^+ , Na^+ and/or H^+). For $\text{Ga}_2(\text{L}^2)_3$, a similar HRMS was obtained as the one for $\text{Ga}_2(\text{L}^1)_3$ (see Annexes).

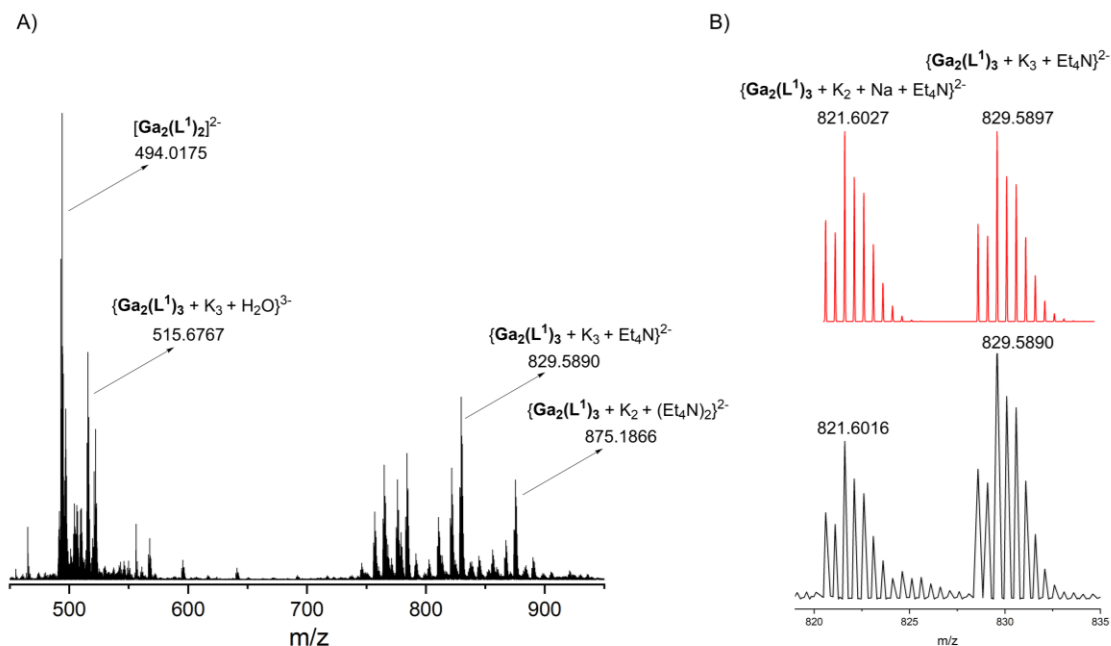


Figure 26. A) Full view for the ESI–HRMS for $\text{Ga}_2(\text{L}^1)_3$ and B) a selected section of the ESI–HRMS corresponding to the species $\text{Ga}_2(\text{L}^1)_3 + 2 \text{K}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+$ and $\text{Ga}_2(\text{L}^1)_3 + 3 \text{K}^+ + \text{Et}_4\text{N}^+$ (Red: calculated; black: experimental).

In the case of $\text{Ga}_2(\text{L}^4)_3$ cage, for example, peaks at m/z values of 904.6139 (2–) (calcd. 904.6133), 859.0160 (2–) (calcd. 859.0152) and 840.0381 (2–) (calcd. 840.0373) corresponds to association of the cage $\text{Ga}_2(\text{L}^4)_3$ with $3\text{K}^+/1\text{Et}_4\text{N}^+$, 4K^+ and $3\text{K}^+/1\text{H}^+$ respectively. The HRMS spectrum for $\text{Ga}_2(\text{L}^4)_3$ (Figure 27) shows several ions from different aggregates with charge 3– resulting from association of the $\text{Ga}_2(\text{L}^4)_3$ with three cations (K^+ , Na^+ , Et_4N^+ and/or H^+) under the mass spectrometry ionisation conditions as well as aggregates from cages decomposition with charge 3– in the range of m/z 500–650. Nevertheless, several ions were detected from different aggregates with 2– charge resulting from association of the $\text{Ga}_2(\text{L}^4)_3$ with four cations (K^+ , Na^+ , Et_4N^+ and/or H^+) in the range of m/z 800–960. In addition, cage $\text{Ga}_2(\text{L}^4)_3$ presents both 2– and 3– aggregates that are more stable than the same adducts for the cages $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^2)_3$, being these peaks much more intense for $\text{Ga}_2(\text{L}^4)_3$.

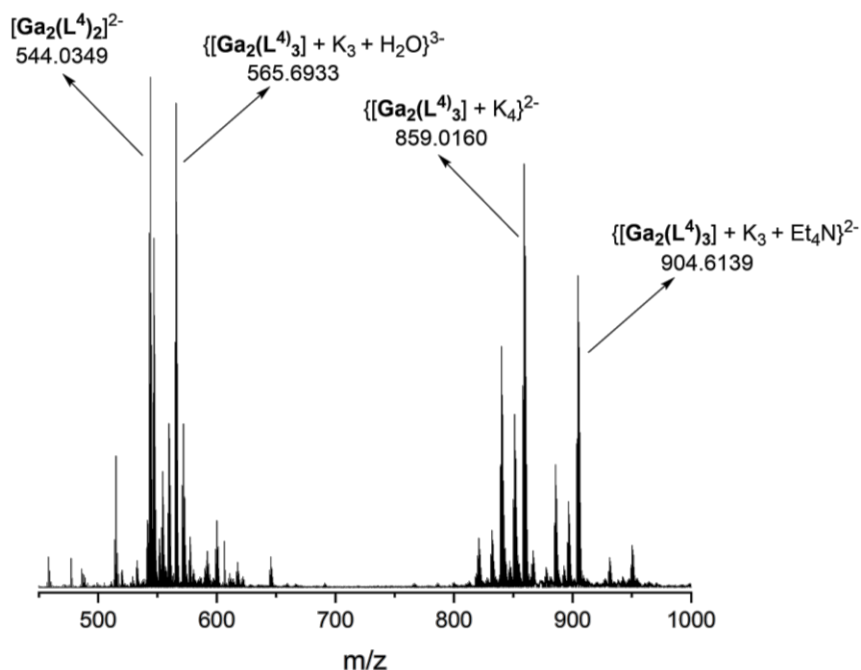


Figure 27. Full view for the ESI–HRMS spectrum for $\text{Ga}_2(\text{L}^4)_3$.

Finally, $\text{Ga}_2(\text{L}^5)_3$ mass spectrum shows multiple peaks corresponding to different degrees of ionisation of the $\text{Ga}_2(\text{L}^5)_3$ complex. The mass peaks observed at m/z 1051.8915 (2–) (calcd. 1051.8553), 1006.2929 (2–) (calcd. 1006.2572), 987.3137 (2–) (calcd. 987.2793) were assigned to the species $\text{Ga}_2(\text{L}^5)_3$ with $3\text{Et}_4\text{N}^+/\text{H}^+$, $2\text{Et}_4\text{N}^+/\text{K}^+/\text{H}^+$, $2\text{Et}_4\text{N}^+/2\text{H}^+$, respectively. The HRMS spectrum for $\text{Ga}_2(\text{L}^5)_3$ shows several ions from different adducts with 2– charge resulting from association of the $\text{Ga}_2(\text{L}^5)_3$ with four cations (K^+ , Na^+ , Et_4N^+ and/or H^+) in the range of m/z 900–1100. In addition, different aggregates with charge 3– resulting from association of the $\text{Ga}_2(\text{L}^5)_3$ with three cations (K^+ , Na^+ , Et_4N^+ and/or H^+) under the mass spectrometry ionisation conditions as well as aggregates from cages’s decomposition with charge 3– in the range of m/z 590–700.

1.3.3.4 Single-Crystal X-ray Diffraction Analysis

During our investigation on the self-assembly of M_2L_3 supramolecular coordination cages, we succeeded in growing single crystals for several Ga_2L_3 systems. These structures provided crucial insights into how the ditopic ligands self-assemble with Ga^{3+} ions in the solid state, and how these solid-state motifs correlate with the solution behaviour presented in the previous section. We successfully crystallised $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$, unfortunately repeated

crystallisation attempts for $\text{Ga}_2(\text{L}^2)_3$ cage were unsuccessful, giving amorphous solids.

We obtained high-quality crystals, suitable for X-ray analyses, for $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^4)_3$ and $\text{Ga}_2(\text{L}^5)_3$ using vapor diffusion techniques. To obtain $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$ crystals, we employed a solution of the cages in DMF and allowing the diffusion of tetrahydrofuran (THF) vapours whereas for obtaining $\text{Ga}_2(\text{L}^5)_3$ crystals we used a solution of this cage in a mixture of DMSO/ H_2O (1:1) and allowing the diffusion of acetone vapours.

The crystal structure of the cage $\text{Ga}_2(\text{L}^1)_3$ (Figure 28A) show each Ga^{3+} ion coordinated to three catechol groups derived from ligand $(\text{L}^1)^{4-}$ and separated 13.7819(18) Å (Ga–Ga distance). This structure contains a total of six negative charges, balanced by 4 K^+ ions and 2 Et_4N^+ ions. The crystalline structure pack forming a polymeric chain of $\text{Ga}_2(\text{L}^1)_3$ units supported by bridging K^+ and solvent molecules. These supramolecular cages are connected to each other in solid-state through potassium ions, which interact externally with the oxygen atoms of the catechol groups. Additionally, these potassium ions are solvated by crystallisation solvent molecules, including DMF and THF. $\text{Ga}_2(\text{L}^1)_3$ architecture shows an heterometallic, helical and chiral supramolecular structure. This $\text{Ga}_2(\text{L}^1)_3$ is featured by presenting the same octahedral configuration in both metal centres ($\Delta\Delta$ or $\Lambda\Lambda$), obtaining a racemic mixture in the synthesis and in the crystalline structure too. This metal configuration makes the ligands to adopt a helical twist in the supramolecular arrangement, resulting in a chiral structure or helicate. In this helicate $\text{Ga}_2(\text{L}^1)_3$, catechol rings are rotated relative to core aromatic and triazole rings allowing this characteristic twist of helical structures. Moreover, the core aromatic and triazole rings are sharing almost the same plane. The helicate- $\text{Ga}_2(\text{L}^1)_3$ presents triazole groups of each ligand oriented towards the cavity of $\text{Ga}_2(\text{L}^1)_3$ with a weak electrostatic interaction triazole- $\text{CH}\cdots\text{O}$ (2.253(6)–2.698(6) Å) with the oxygens of the catechol groups (triazole- $\text{CH}\cdots\text{O}-\text{Ga}$), behaviour observed in Me_4L^1 too. Moreover, triazole protons and catecholate groups are in cisoid configuration, unlike Me_4L^1 which exhibited a transoid arrangement.

This supramolecular cage array creates an internal small cavity with a volume of 38 Å³, calculated using CageCavityCalc^[95] (Figure 28). The cavity is mainly distributed around the centre and near the vertices of the Ga^{3+} atoms, presenting a negative electrostatic potential, as shown in Figure 28B. Due to its negative electrostatic potential, this cavity is of interest for hosting small cations. In fact, in the

solid state, we observe two potassium cations encapsulated within the cavity forming the host–guest complex $2\text{K}^+ \subset \text{Ga}_2(\text{L}^1)_3$. These cations (K^+) are in the regions of the cavity with the greatest volume, next to the catechol oxygen atoms (3.014(11)–3.079(10) Å), with which they interact electrostatically. (Figure 28A). Two potassium cations occupy almost the entire volume of the $\text{Ga}_2(\text{L}^1)_3$ cavity. Therefore, we could conclude that $\text{Ga}_2(\text{L}^1)_3$ cage presents an heterometallic nature at each vertex, generating the $(\text{GaK})_2(\text{L}^1)_3$ cage in solid state. This behaviour is uncommon in metal–organic cages, although a few similar examples have been reported in M_2L_3 –type supramolecular cages constructed with catechol–based ligands.^[21a, 68]

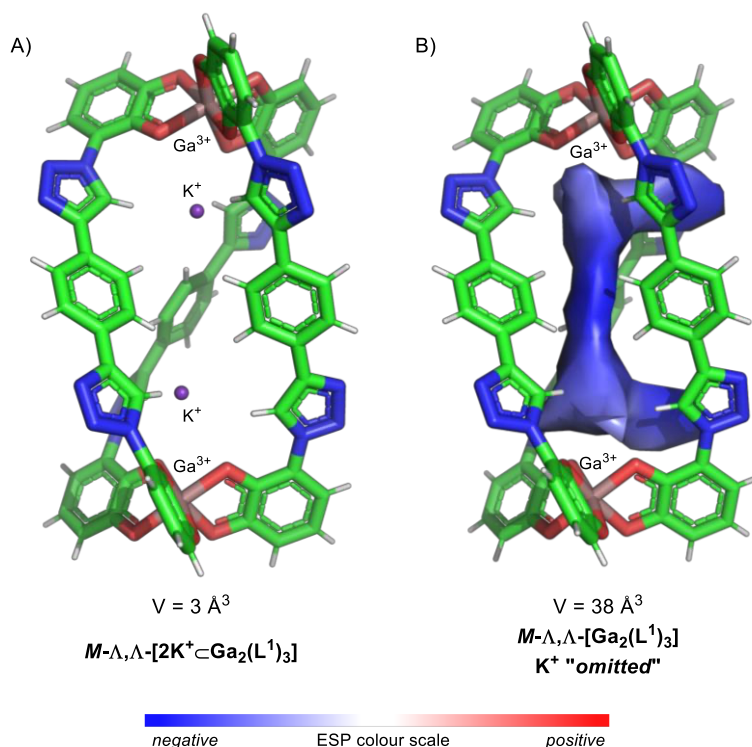


Figure 28. A) Crystal structure of the heterometallic host–guest complex $\text{M}-\Lambda, \Lambda-[2\text{K}^+ \subset \text{Ga}_2(\text{L}^1)_3]$ with two K^+ encapsulated within the cage $\text{M}-\Lambda, \Lambda-[\text{Ga}_2(\text{L}^1)_3]$ and B) crystal structure of the aggregate $\text{M}-\Lambda, \Lambda-[2\text{K}^+ \subset \text{Ga}_2(\text{L}^1)_3]$ where the encapsulated guests K^+ have been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Outer–sphere K^+ and Et_4N^+ ions and solvent molecules (DMF, THF) have been omitted for clarity. Selected bond lengths (Å): A) triazole–CH $\cdots$ O–catecholate 2.253(6)–2.698(6), $\text{K}^+ \cdots \text{O}$ –catecholate 3.014(11)–3.079(10), Ga–Ga 13.7819(18). Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The crystalline structure of $\text{Ga}_2(\text{L}^4)_3$ (Figure 29A) shows each Ga^{3+} ion coordinated to three catechol groups and separated 14.696(9) Å, distance slightly larger than in the $\text{Ga}_2(\text{L}^1)_3$ cage. Its six negative charges are balanced by 4 K^+ and 2 Et_4N^+ ions. Like $\text{Ga}_2(\text{L}^1)_3$, $\text{Ga}_2(\text{L}^4)_3$ system grows in the solid-state, as a polymeric chain of monomeric $\text{Ga}_2(\text{L}^4)_3$ units connected to each other through potassium ions which are solvated by crystallisation solvent molecules such as DMF and THF. Furthermore, $\text{Ga}_2(\text{L}^4)_3$ structure presents common features with $\text{Ga}_2(\text{L}^1)_3$ as its helical and chiral supramolecular architecture. Therefore, this helicate $\text{Ga}_2(\text{L}^4)_3$ presents the same octahedral configuration in both metal centres ($\Delta\Delta$ or $\Lambda\Lambda$) obtaining a racemic mixture in the synthesis and in the crystalline structure too. In this crystalline structure, the core aromatic (C_{10}H_6) and triazole rings are sharing almost the same plane. This reflects delocalisation across these aromatic rings via conjugation of the π -systems. The triazole groups of each ligand are oriented towards the cavity of $\text{Ga}_2(\text{L}^4)_3$ with a weak electrostatic interaction at distances of 2.608(17)–2.81(2) Å with the oxygens of the catecholate group (triazole–CH $\cdots$ O–Ga), moreover, triazole protons and catecholate rings are in cisoid configuration, behaviour observed in the helicate $\text{Ga}_2(\text{L}^1)_3$ as well.

Despite Me_4L^4 is slightly larger than Me_4L^1 , $\text{Ga}_2(\text{L}^4)_3$ system presents an internal small cavity of 38 Å³, with a cavity volume very similar to $\text{Ga}_2(\text{L}^1)_3$. Interestingly, the cavity is now distributed towards one of their metal vertices, unlike $\text{Ga}_2(\text{L}^1)_3$. This cavity shows a negative electrostatic potential, as shown in Figure 29B. Its negative electrostatic potential allows to host two potassium cations in the cavity in solid state forming the host–guest complex $2\text{K}^+ \subset \text{Ga}_2(\text{L}^4)_3$. Interestingly, in the crystalline structure of $\text{Ga}_2(\text{L}^4)_3$, these cations (K^+) are closer (2.719(19)–2.98(2) Å) to the catechol oxygen atoms than in $\text{Ga}_2(\text{L}^1)_3$ cage (3.014(11)–3.079(10) Å). Like in $\text{Ga}_2(\text{L}^1)_3$, potassium ions are interacting electrostatically with them (Figure 29A). These cations occupy almost the entire volume of the $\text{Ga}_2(\text{L}^4)_3$ cavity. Like $\text{Ga}_2(\text{L}^1)_3$, this cage presents a heterometallic nature in solid state as well, forming the $(\text{GaK})_2(\text{L}^4)_3$ system.

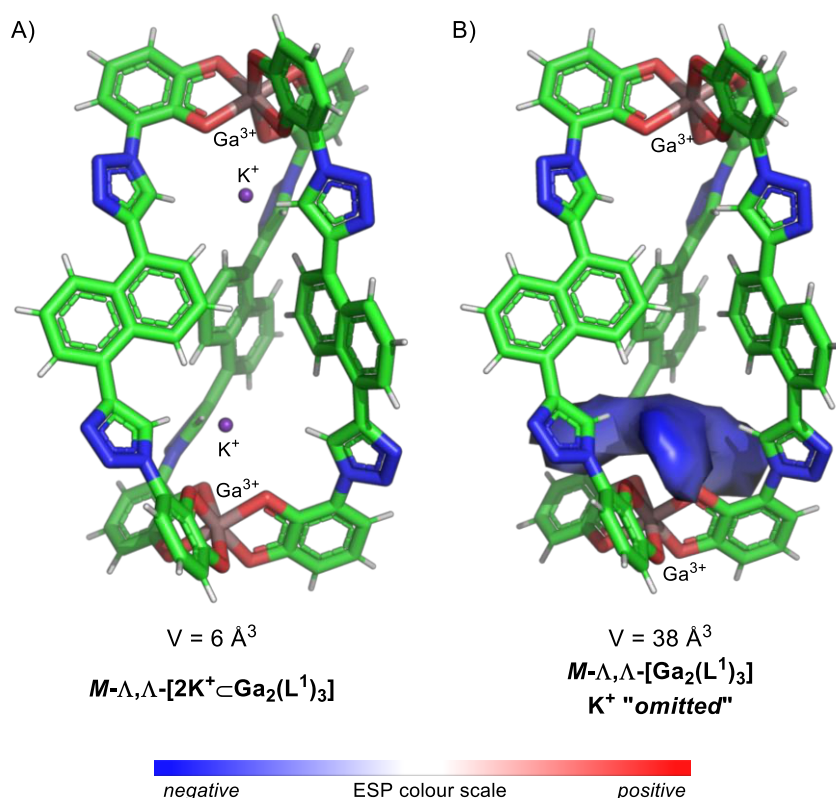


Figure 29. A) Crystal structure of the heterometallic host–guest complex $M-\Lambda, \Lambda-[2\text{K}^+ \subset \text{Ga}_2(\text{L}^4)_3]$ with two K^+ encapsulated within the cage $M-\Lambda, \Lambda-[\text{Ga}_2(\text{L}^4)_3]$ and B) crystal structure of the aggregate $M-\Lambda, \Lambda-[2\text{K}^+ \subset \text{Ga}_2(\text{L}^4)_3]$ where the encapsulated guests K^+ have been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of $0.5 \text{ \AA}$ and the EEM implemented charge model. Outer–sphere K^+ and Et_4N^+ ions and solvent molecules (DMF, THF) have been omitted for clarity. Selected bond lengths ($\text{\AA}$): A) triazole–CH $\cdots$ O–catecholate $2.608(17)$ – $2.81(2)$, $\text{K}^+ \cdots \text{O}$ –catecholate $2.719(19)$ – $2.98(2)$, Ga–Ga $14.696(9) \text{ \AA}$. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The supramolecular cage $\text{Ga}_2(\text{L}^5)_3$ (Figure 30A) contains a total of six negative charges that are balanced by 3 K^+ and 3 Et_4N^+ ions and presents and each Ga^{3+} ion separated $15.578(9) \text{ \AA}$. The different cage units $\text{Ga}_2(\text{L}^5)_3$ are pack in the solid–state through bridging K^+ ions growing as a polymeric chain, behaviour observed for $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$ too. Additionally, these K^+ ions are solvated by DMSO, H_2O and acetone (crystallisation solvent molecules). In the crystalline structure of the cage $\text{Ga}_2(\text{L}^5)_3$ (Figure 30A), the catechol groups are in cisoid configuration as in the previous helicates $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$. Nevertheless,

triazole protons are oriented outwards unlike helicates $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$ where triazole protons were oriented towards the cavity. In this structure, metal centres present different configuration ($\Delta\Delta$ or $\Lambda\Delta$). Interestingly, changing from peripheral catechol groups to naphthalenediol groups induces the self-assembly of a distinct cage isomer. The cage $\text{Ga}_2(\text{L}^5)_3$ is an achiral supramolecular coordination cage or mesocate. In the mesocate cage $\text{Ga}_2(\text{L}^5)_3$, the ligands do not adopt a helical twist as in the cages $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$, they are in a linear configuration. Therefore, this structure presents a plane and inversion centre of symmetry, being achiral. The triazole and core aromatic rings share the same plane and only naphthalenol rings are rotated relative to this plane in the crystalline structure.

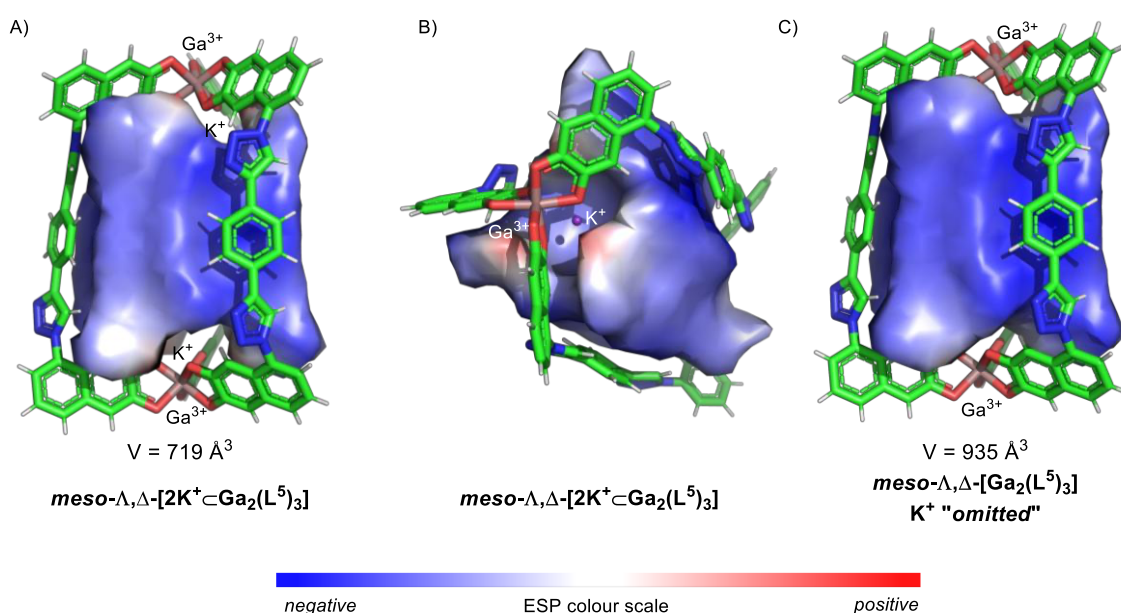


Figure 30. A) and B) Crystal structure of the heterometallic host-guest complex $\text{meso-}\Lambda,\Delta\text{-}[2\text{K}^+\subset\text{Ga}_2(\text{L}^5)_3]$ with two K^+ encapsulated within the cage $\text{meso-}\Lambda,\Delta\text{-}[\text{Ga}_2(\text{L}^5)_3]$ and C) crystal structure of the aggregate $\text{meso-}\Lambda,\Delta\text{-}[2\text{K}^+\subset\text{Ga}_2(\text{L}^5)_3]$ where the encapsulated guests K^+ have been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Outer-sphere K^+ and Et_4N^+ ions and solvent molecules (DMSO, H_2O and acetone) have been omitted for clarity. Selected bond lengths (Å): A) $\text{K}^+\cdots\text{O}$ -catecholate 2.728(16)–2.864(10), Ga–Ga 15.578(9) Å. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

In contrast to the previous helicate cages, $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$, the linear disposition and radial extension of H_4L^5 compared to H_4L^1 , makes that ligand H_4L^5 forms a mesocate structure with a large internal cavity that presents a volume of approximately $935 \text{ \AA}^3$ (Figure 30C). This cavity presents a negative electrostatic potential, being significant potential for large cations encapsulation. In solid state, we observe two K^+ cations encapsulated $2\text{K}^+ \subset \text{Ga}_2(\text{L}^5)_3$, which are close ($2.728(16)$ – $2.864(10) \text{ \AA}$) to oxygens from catechol groups (Figure 30A and 30B), like in the helicates $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$ (Figure 28 and 29). The volume of the cavity with these two encapsulated potassium cations decrease to $719 \text{ \AA}^3$ (Figure 30A). The size of the cavity generated using the naphthalene–diol H_4L^5 as ligand to construct this type of architecture is almost 25 times larger than when using the catechol ligand H_4L^1 which does not present radial elongation.

A common feature in these heterometallic cages, is the absence of hydrogen donor groups near the catechol rings prevents the formation of intramolecular hydrogen bonds with oxygens from catechol groups. Therefore, the K^+ cations can be located inside the metal–organic M_2L_3 cages, electrostatically interacting with the internal oxygens from the catechols which are coordinated to Ga^{3+} ions. This structural feature is unusual in other reported helicate M_2L_3 cages. For example, similar M_2L_3 helicates described by Raymond,^[45, 52] are assembled using ligands that present amide groups $-\text{NH}-\text{CO}-$ which are very close to catechol rings, forming intramolecular hydrogen bonds and satisfying the coordination environment of the oxygens, and these are homometallic M_2L_3 cages.

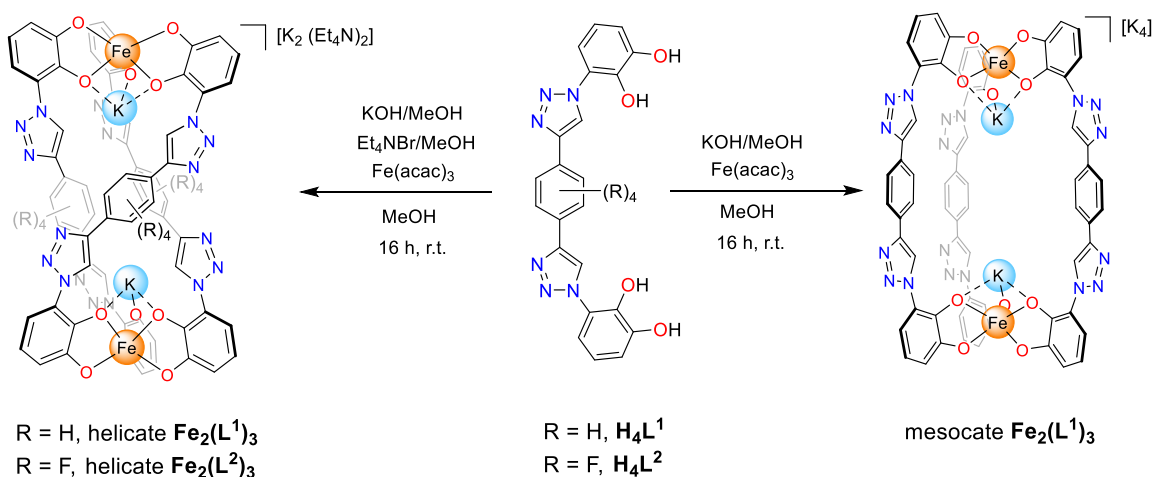
Based on these X–ray analyses, we can conclude that changes at the ligand's groups binding the metals have a significant impact on the supramolecular self–assembly, resulting in larger systems with much greater internal cavity volumes (mesocates vs helicates). In contrast, modifications within the core of the ligand, involving either electronic changes (C_6F_4) or steric changes (C_{10}H_6), do not led to major alterations in the crystalline structure and its cavity. Besides, reducing the angle between the disposition of the triazoles in the core phenylene ring from 1,4– to 1,3– prevents the formation of supramolecular cage assemblies.

1.3.4 Supramolecular Self–Assembly of Fe_2L_3 Cages

The present section is focused on the preparation and study of new Fe_2L_3 supramolecular cages. In addition to the previous sections, we will study the self–assembly process using the ligand H_4L^1 in the presence of Fe^{3+} metal ions and

either the K^+ or organic ammonium R_4N^+ ions to compare with the previous self-assembly process with Ga^{3+} .

Using the same synthetic procedure for the synthesis of Ga_2L_3 architectures, we obtained the supramolecular cages $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$. The ligand H_4L^1 was suspended in distilled and deoxygenated methanol, then, KOH/MeOH , Et_4NBr and $\text{Fe}(\text{acac})_3$ were added in a ratio 2:2:0.66 respectively. The reaction was stirred overnight at room temperature which led to the formation of $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ (Scheme 10). Product $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ precipitated in the reaction mixture whereas $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ cages were precipitated by concentrating the solution and adding Et_2O . Both cages were isolated by filtration obtaining dark red solids which were dried under vacuum and isolated with a yield of 72% and 70% respectively. Employing the same synthetic protocol used for preparing the product $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ but without adding Et_4NBr , we prepared the cage $[\text{Fe}_2(\text{L}^1)_3][\text{K}]_6$ (Scheme 10). In this synthesis, the ligand H_4L^1 was stirred overnight with KOH/MeOH and $\text{Fe}(\text{acac})_3$ at room temperature under a nitrogen atmosphere. The cage array $[\text{Fe}_2(\text{L}^1)_3][\text{K}^+]_6$ was precipitated in a concentrated solution by adding Et_2O and was purified by filtration obtaining a dark-red solid which was then dried under vacuum and isolated in 79% yield.



Scheme 10. Preparation of supramolecular metal–organic helicate $\text{Fe}_2(\text{L}^1)_3$ and mesocate $\text{Fe}_2(\text{L}^1)_3$ cages.

Because these supramolecular Fe_2L_3 cages are paramagnetic (high spin Fe^{3+}), we used UV–Vis spectroscopy to study and characterise these architectures in solution, X–ray crystallography in the solid state, and HRMS spectroscopy in gas phase.

1.3.4.1 High Resolution Mass Spectrometric (HRMS) Analysis

The formation of the supramolecular Fe_2L_3 structures, helicate $Fe_2(L^1)_3$, mesocate $Fe_2(L^1)_3$, and helicate $Fe_2(L^2)_3$ was further confirmed by ESI–HRMS analyses. Notably, helicate $Fe_2(L^1)_3$ and mesocate $Fe_2(L^1)_3$ produced identical mass peaks, which varied based on the number and type of alkali metal (K^+ , Na^+) and proton (H^+) adducts formed during the ionisation process. For instance, the helicate $Fe_2(L^1)_3$ spectrum showed peaks at m/z values of 770.0034 (2–) (calcd. 770.0012), 762.0166 (2–) (calcd. 762.0166), and 751.0242 (2–) (calcd. 751.0256) that corresponded to the association of $4K^+$, $3K^+/1Na^+$, and $3K^+/1H^+$ ions, respectively (Figure 31A). Similar peaks were observed for mesocate $Fe_2(L^1)_3$ with slightly different m/z values, 770.0037 (2–) (calcd. 770.0012), 762.0166 (2–) (calcd. 762.0166), and 751.0256 (2–) (calcd. 751.0256). Furthermore, the HRMS analysis of helicate $Fe_2(L^1)_3$ revealed adducts with tetraethylammonium ions (Et_4N^+), exemplified by the peak at m/z 815.6004 (2–) (calcd. 815.5991), indicating association with $3K^+/1Et_4N^+$. Consistent with the gallium analogue $Ga_2(L^1)_3$, the Fe_2L_3 cages displayed two distinct regions in their HRMS spectra. The lower m/z range (450–600) showed 3– charged ions of either helicate $Fe_2(L^1)_3$ or mesocate $Fe_2(L^1)_3$ complexed with three K^+ , Na^+ , H^+ , and/or Et_4N^+ ions, along with 2– charged ions resulting from the decomposition of the iron cages. The higher m/z range (700–900) exhibited 2– charged aggregates of the helicate or mesocate bound to four of these cations. Furthermore, the observed isotope patterns matched well with the calculated distributions, confirming the $Fe_2(L^1)_3$ stoichiometry (Figure 31B). For helicate $Fe_2(L^2)_3$, the mass spectrum showed peaks at m/z 923.5412 (2–) (calcd. 923.5426), 877.9440 (2–) (calcd. 877.9446), and 869.9565 (2–) (calcd. 869.9577), attributed to adducts with $3K^+/1Et_4N^+$, $4K^+$, and $3K^+/1Na^+$, respectively. Similar to the helicate $Fe_2(L^1)_3$, the HRMS of $Fe_2(L^2)_3$ helicate shows two sections: a lower m/z range (450–650) with 3– charged ions of the helicate $Fe_2(L^2)_3$ associated with three K^+ , Na^+ , H^+ , and/or Et_4N^+ ions, as well as 2– charged fragment ions, and a higher m/z range (800–1000) with 2– charged aggregates of the helicate $Fe_2(L^2)_3$ bound to four of these cations.

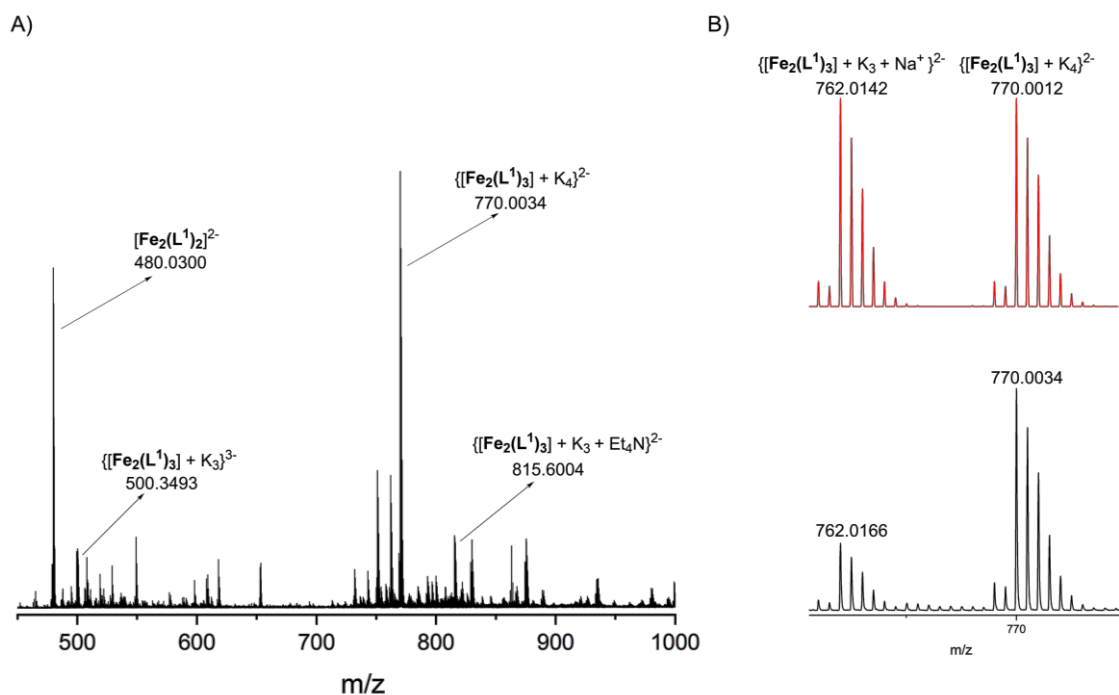


Figure 31. A) Full view for ESI–HRMS spectra for helicate $\text{Fe}_2(\text{L}^1)_3$ and B) selected section of the ESI–HRMS corresponding to the species $\text{Fe}_2(\text{L}^1)_3 + 3 \text{K}^+ + \text{Na}^+$ and $\text{Fe}_2(\text{L}^1)_3 + 4 \text{K}^+$ (Red: calculated; black: experimental).

1.3.4.2 Single-Crystal X–ray Diffraction Analysis

We obtained high–quality crystals for $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, $[\text{Fe}_2(\text{L}^1)_3][\text{K}]_6$ and $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ using the vapor diffusion technique. For $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, we employed a solution of the product in $\text{H}_2\text{O}/\text{MeOH}$ (3:7) and allowing the diffusion of a mixture of vapours of tetrahydrofuran/acetone (1:1). For $[\text{Fe}_2(\text{L}^1)_3][\text{K}]_6$ and $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, we used a solution of the cages in DMF and allowing the diffusion of vapours of tetrahydrofuran. These crystals were suitable for single–crystal X–ray studies allowing us to study their structural features and composition in the solid–state. The crystalline structure of these Fe_2L_3 supramolecular cages shows each iron ion (Fe^{3+}) coordinated to three catechol groups derived from the ligands H_4L^1 or H_4L^2 containing a total of six negative charges $[\text{Fe}_2\text{L}_3]^{6-}$. For $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ and $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, these negative charges are balanced by four K^+ ions and two Et_4N^+ ions, whereas the six negative charges of $[\text{Fe}_2(\text{L}^1)_3][\text{K}]_6$ are balanced by six K^+ ions. These K^+ metal ions are solvated by crystallisation solvent molecules, including water, DMF, methanol, THF and acetone. This solvation interaction contributes to the stability of the crystalline

structure forming polymeric chains of Fe_2L_3 cages, $(\text{Fe}_2\text{L}_3)_n$, when packing in the solid-state, akin to the same packing effects of Ga_2L_3 cages.

In the case of the crystalline structure of the cage $[\text{Fe}_2(\text{L}^1)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$ (Figure 32A), we observe a helical and chiral supramolecular structure like helicates $\text{Ga}_2(\text{L}^1)_3$ and $\text{Ga}_2(\text{L}^4)_3$. This helicate has the same configuration in both metal centres that are separated 13.879(2) Å. Moreover, ligands adopting a helical twist in the supramolecular structure resulting in a chiral structure. In this system, catecholate rings are rotated relative to core aromatic and triazole rings allowing this characteristic twist of helicates. Product $[\text{Fe}_2(\text{L}^1)_3][\text{K}]_6$ is featured by presenting different octahedral configuration in its metal centres ($\Delta\Delta$ or $\Lambda\Lambda$) like mesocate $\text{Ga}_2(\text{L}^5)_3$. In the crystalline structure of this mesocate $\text{Fe}_2(\text{L}^1)_3$ (Figure 33A), ligands do not adopt a helical twist, they are in a linear configuration leading to an achiral structure mesocate. In this architecture, only catecholate rings are rotated relative to core aromatic and triazole rings in the crystalline structure. Moreover, the helicate $\text{Fe}_2(\text{L}^1)_3$ presents triazole protons of each ligand oriented towards the cavity with a weak electrostatic interaction (triazole-CH $\cdots$ O) with the oxygens of the catecholate group (2.261(8)–2.733(8) Å), observed in H_4L^1 too. Nevertheless, in the mesocate $\text{Fe}_2(\text{L}^1)_3$ triazole and core aromatic protons of each ligand share the same plane, and they are oriented towards the other ligands within the structure, unlike the helicate $\text{Fe}_2(\text{L}^1)_3$. In both helicate $\text{Fe}_2(\text{L}^1)_3$ and mesocate $\text{Fe}_2(\text{L}^1)_3$ cages, triazole protons and catechol groups are in cisoid configuration, unlike H_4L^1 . These Fe_2L_3 cages grow as racemic crystals in the solid-state, both enantiomers ($\Delta\Delta/\Lambda\Lambda$ or $\Delta\Lambda/\Lambda\Delta$) are obtained.

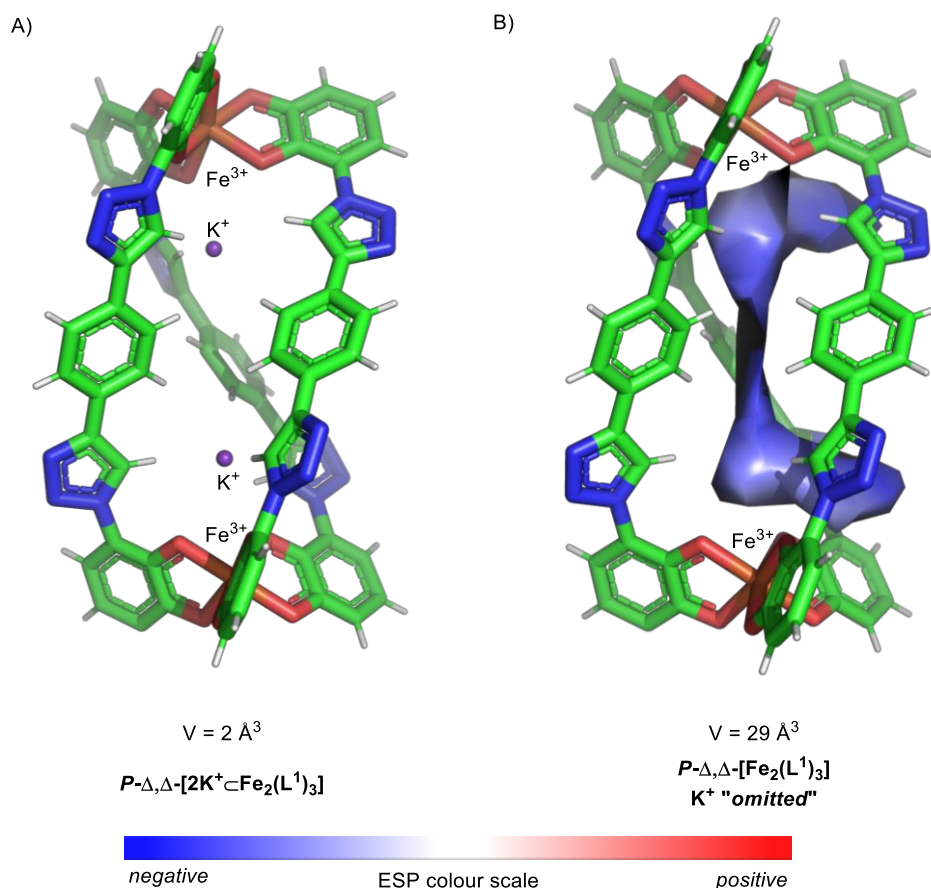


Figure 32. A) Crystal structure of the heterometallic host–guest complex $P-\Delta\Delta-[2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3]$ with two K^+ encapsulated within the cage $P-\Delta\Delta-[\text{Fe}_2(\text{L}^1)_3]$ and B) crystal structure of the aggregate $P-\Delta\Delta-[2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3]$ where the encapsulated guests K^+ have been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of $0.5 \text{ \AA}$ and the EEM implemented charge model. Outer–sphere K^+ and Et_4N^+ ions and solvent molecules (MeOH , H_2O , THF and acetone) have been omitted for clarity. Selected bond lengths ($\text{\AA}$): A) triazole– $\text{CH}\cdots\text{O}$ –catecholate $2.261(8)$ – $2.733(8)$, $\text{K}^+\cdots\text{O}$ –catecholate $2.888(13)$ – $3.154(15)$, Fe – Fe $13.879(2)$. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

Helicate $\text{Fe}_2(\text{L}^1)_3$ presents a small internal cavity with a volume of $29 \text{ \AA}^3$ (Figure 32B), slightly smaller than the cavity of helicate $\text{Ga}_2(\text{L}^1)_3$ ($38 \text{ \AA}^3$) constructed with the same ligand (H_4L^1) (Figure 28B). Like in helicate $\text{Ga}_2(\text{L}^1)_3$, the cavity is mainly distributed around the centre and near the vertices of the Fe^{3+} atoms, presenting a negative electrostatic potential, as shown in Figure 32B. Due to its negative electrostatic potential, we observed in solid state two potassium cations

encapsulated within the cavity $2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3$. These cations are in the regions of the cavity with the greatest volume, next to the oxygen atoms of the catechol group (2.888(13)–3.154(15) Å), with which they interact electrostatically (Figure 32A). These two potassium cations occupy the entire volume of the $\text{Fe}_2(\text{L}^1)_3$ cavity.

Mesocate $\text{Fe}_2(\text{L}^1)_3$ presents their metal centres (Fe^{3+}) separated by a slightly larger distance (14.6485(11) Å) and a much larger cavity than helicate $\text{Fe}_2(\text{L}^1)_3$ (29 Å³), with a volume of 174 Å³ (Figure 33). This is thanks to the linear disposition of the ligands in this supramolecular arrangement. Its cavity, with a negative electrostatic potential, is distributed homogeneously, forming a sort of cylinder cavity (Figure 33B). In the solid-state, two K^+ ions are encapsulated by the mesocate $\text{Fe}_2(\text{L}^1)_3$ forming the complex $2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3$ (Figure 33A). These cations (K^+) are quite close to the oxygen atoms of the catechol group (2.662(4)–2.951(4) Å), leaving a small cavity in the centre, next to core aromatic rings, with a volume of 38 Å³ (Figure 33A), unlike helicate $\text{Fe}_2(\text{L}^1)_3$ that no present cavity in the centre because the ligands are twisted and do not generate space in the centre of the architecture. In addition, this mesocate $\text{Fe}_2(\text{L}^1)_3$ presents a similar cavity than the one of mesocate $\text{Ga}_2(\text{L}^5)_3$ in terms of shape, electrostatic potential and distribution. Nonetheless, axial extension of the ligand H_4L^1 to give H_4L^5 , produces the formation of a larger cavity in mesocate $\text{Ga}_2(\text{L}^5)_3$ (935 Å³), being almost six times larger than the cavity of the mesocate $\text{Fe}_2(\text{L}^1)_3$ (174 Å³).

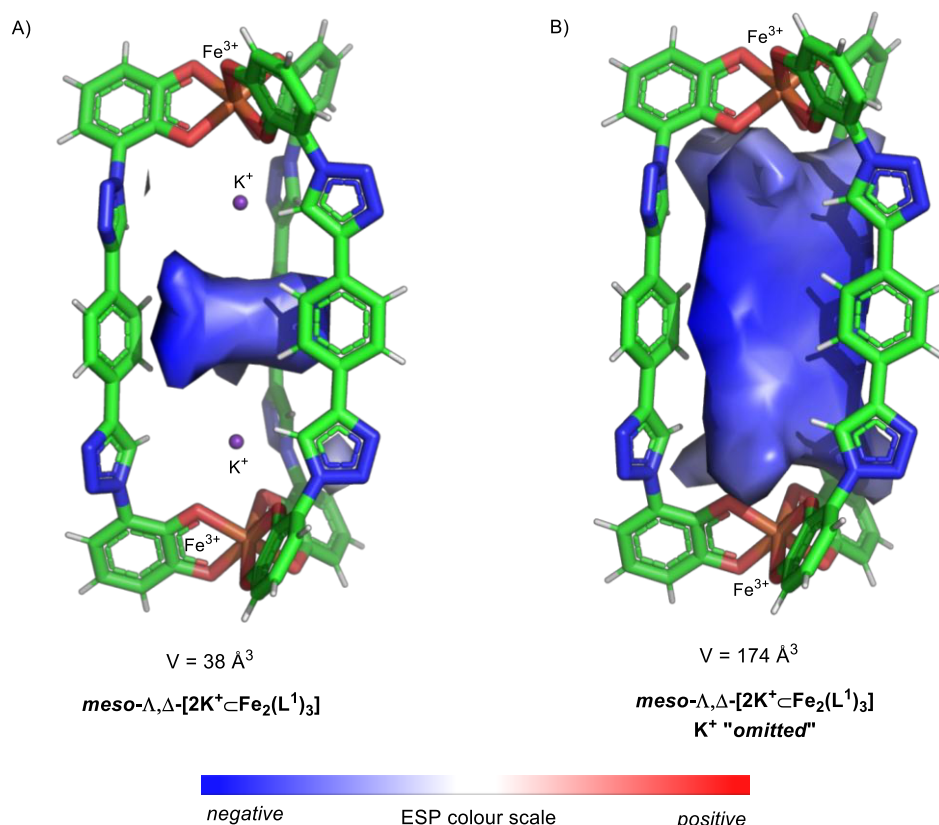


Figure 33. A) Crystal structure of the heterometallic host–guest complex $\text{meso-}\Lambda\Lambda\text{-}[2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3]$ with two K^+ encapsulated within the cage $\text{meso-}\Lambda\Lambda\text{-}[\text{Fe}_2(\text{L}^1)_3]$ and B) crystal structure of the aggregate $\text{meso-}\Lambda\Lambda\text{-}[2\text{K}^+\subset\text{Fe}_2(\text{L}^1)_3]$ where the encapsulated guests K^+ have been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of $0.5 \text{ \AA}$ and the EEM implemented charge model. Outer–sphere K^+ ions and solvent molecules (DMF, THF) have been omitted for clarity. Selected bond lengths ($\text{\AA}$): A) $\text{K}^+\cdots\text{O}$ –catecholate $2.662(4)$ – $2.951(4)$, Fe–Fe $14.6485(11)$. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

For the cage $[\text{Fe}_2(\text{L}^2)_3][\text{Et}_4\text{N}]_2[\text{K}]_4$, we obtained two different X–ray structures. The first one, $\text{M-}\Lambda\Lambda\text{-}[\text{K}^+\subset\text{Fe}_2(\text{L}^2)_3]$, presenting one K^+ ion encapsulated. This cation is very close to one of cage’s vertices interacting with the oxygens of the catechol group ($2.744(5) \text{ \AA}$). The other supramolecular structure, $\text{M-}\Lambda\Lambda\text{-}[\text{Fe}_2(\text{L}^2)_3]$, does not present potassium ions in its cavity. Both X–ray structures show helical and chiral supramolecular cage structures, helicates. Moreover, in both structures, we observe that ligands are in a cisoid configuration with triazole protons of each ligand oriented towards the cavity, allowing a weak electrostatic interaction ($\text{triazole-CH}\cdots\text{O}$) with

the oxygens of the catechol group (2.355(4)–2.798(4) Å). In addition, in $M-\Lambda, \Lambda-[K^+ \subset Fe_2(L^2)_3]$ cage (Figure 34B), fluor atoms in the ligand core are oriented towards the cavity allowing strong electrostatic interactions with the single encapsulated K^+ ion (2.807(4) Å). This interaction led to the formation of a smaller cavity than in the case of $M-\Lambda, \Lambda-[K^+ \subset Fe_2(L^2)_3]$, this space is too small to host a second K^+ ion like helicate $Fe_2(L^1)_3$ that no present this type of electrostatic interactions.

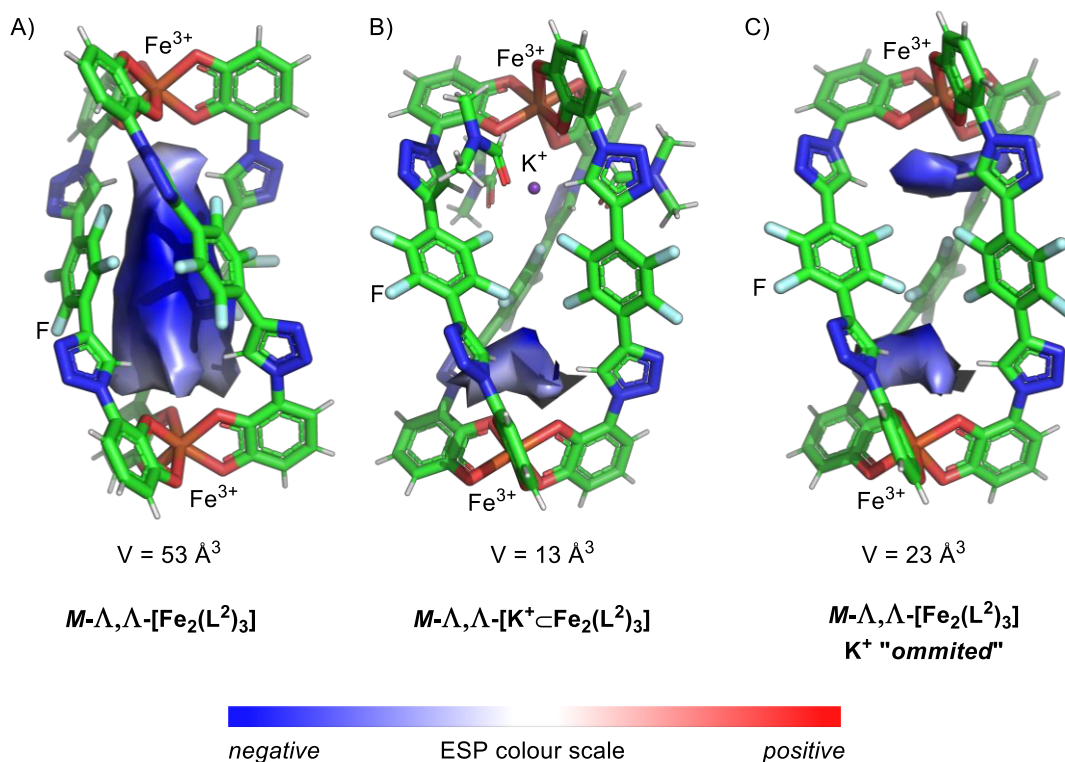


Figure 34. A) Crystal structure of $M-\Lambda, \Lambda-[Fe_2(L^2)_3]$ without K^+ ; B) Crystal structure of the heterometallic host–guest complex $M-\Lambda, \Lambda-[K^+ \subset Fe_2(L^2)_3]$ with one K^+ encapsulated within the cage $M-\Lambda, \Lambda-[Fe_2(L^2)_3]^{6-}$ and C) crystal structure of the aggregate $M-\Lambda, \Lambda-[K^+ \subset Fe_2(L^2)_3]$ where the encapsulated guest K^+ has been omitted. The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Outer–sphere K^+ and Et_4N^+ ions and solvent molecules (DMF, THF) have been omitted for clarity. Selected bond lengths (Å): B) triazole–CH $\cdots$ O–catecholate 2.355(4)–2.798(4), $K^+ \cdots$ O–catecholate 2.744(5), $K^+ \cdots$ F–C $_6$ F $_3$ 2.807(4), Fe–Fe 13.779(2). Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The small cavity of $M-\Delta, \Delta-[K^+ \subset Fe_2(L^2)_3]$ with a volume of $13 \text{ \AA}^3$ is distributed near one of its iron vertices (Figure 34B). If we omitted the encapsulated K^+ ion, this structure would present a cavity of $23 \text{ \AA}^3$ (Figure 34C), slightly smaller than the one of helicate $Fe_2(L^1)_3$ without potassium ions. $M-\Delta, \Delta-[Fe_2(L^2)_3]$ structure does not present K^+ ions in its cavity (Figure 34A), therefore, fluor atoms are not oriented towards the cavity trying to interact with K^+ ions. This structure without encapsulated K^+ cations presents a larger cavity with a volume of $53 \text{ \AA}^3$ and is mainly distributed around the centre and near the iron vertices.

1.3.4.3 UV–Vis Absorption Spectroscopic Analysis

To study the nature of the supramolecular architectures helicate $Fe_2(L^1)_3$, mesocate $Fe_2(L^1)_3$, and helicate $Fe_2(L^2)_3$ in solution, we used UV–Vis spectroscopy. Therefore, we measured the UV/Vis absorption spectrum of Me_4L^1 , Me_4L^2 , H_4L^1 , H_4L^2 , helicate $Fe_2(L^1)_3$, mesocate $Fe_2(L^1)_3$, and helicate $Fe_2(L^2)_3$ which helped us to characterise them in solution and ensure they feature distinct UV–Vis features akin to their different helicate and mesocate cage assemblies.

The UV/Vis absorption spectrum of Me_4L^1 presents a main band of 300 nm and Me_4L^2 of 280 nm associated with triazole and aromatic rings absorptions. However, the UV/Vis absorption spectrum of H_4L^1 and H_4L^2 exhibit different bands at 360 nm. The bands at 300 nm are associated with triazole and aromatic rings absorptions as for Me_4L^1 and Me_4L^2 whereas bands at 360 nm are derived from the absorption of the catechol groups. The appearance of bands at 360 nm corroborates the deprotection of the methyl groups to give hydroxyl groups (Figure 35).

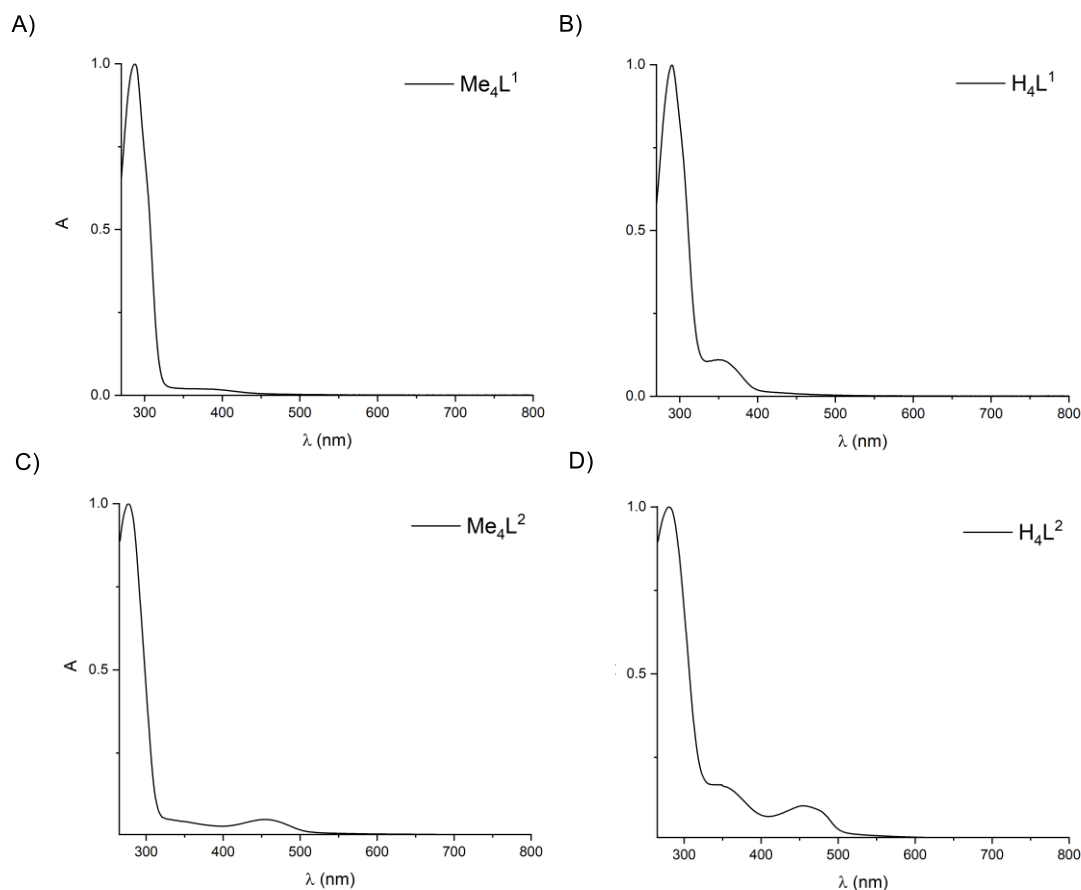


Figure 35. Normalised UV/vis absorption spectra of A) Me_4L^1 , B) H_4L^1 , C) Me_4L^2 and D) H_4L^2 .

The UV/Vis absorption spectra of helicate $\text{Fe}_2(\text{L}^1)_3$ and mesocate $\text{Fe}_2(\text{L}^1)_3$ cages show two different absorption bands, the band at 300 nm associated to the absorption of the organic part of ligand H_4L^1 , and a second band associated to Fe–O bonds absorptions at 490–520 nm. This second band appears about 490 nm for the helicate $\text{Fe}_2(\text{L}^1)_3$ and about 520 nm for the mesocate $\text{Fe}_2(\text{L}^1)_3$. Comparing the UV/Vis absorption spectrum of both iron cages with the one of H_4L^1 (Figure 36), we observe that for supramolecular Fe_2L_3 cages, the band derived from catechol groups disappears at 360 nm and a new band associated with the absorption of metal–ligand bonds appears at 490–520 nm. This suggests coordination of $(\text{L}^1)^{4-}$ to the Fe^{3+} metal centres supporting the formation of Fe_2L_3 cages. This demonstrates the robustness and stability of these supramolecular coordination structures in solution.

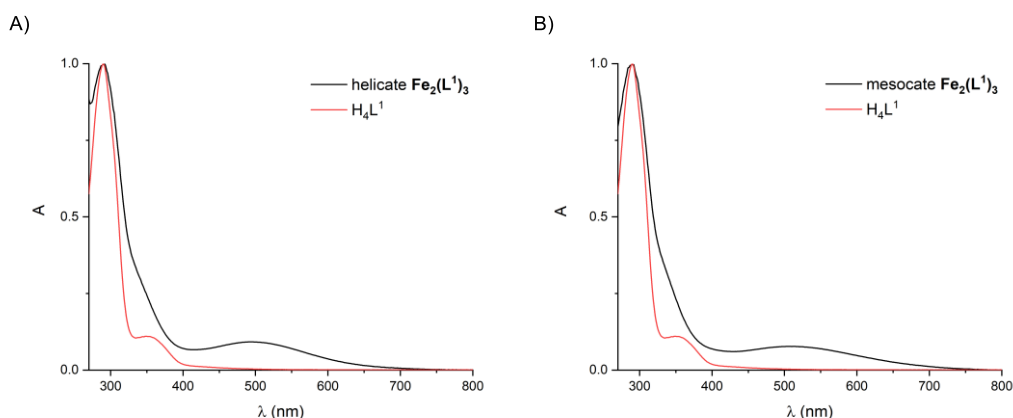


Figure 36. Normalised UV/vis absorption spectra comparison between A) the helicate $Fe_2(L^1)_3$ and H_4L^1 , and B) between the mesocate $Fe_2(L^1)_3$ and H_4L^1 .

The UV/vis spectrum for these Fe_2L_3 cage arrays are slightly different (Figure 37), suggesting that we have different cages in solution, which is consistent with the results observed in the solid-state. The different absorption bands associated with iron–ligand bonds suggest that the coordination environment of Fe^{3+} atoms is slightly different in each cage. The mesocate $Fe_2(L^1)_3$, achiral, presents two metal centres with opposite configuration ($\Delta\Delta$ or $\Lambda\Lambda$) whereas the helicate $Fe_2(L^1)_3$, which is chiral, besides belong a racemic mixture, it has the same configuration in both metal centres ($\Delta\Delta$ or $\Lambda\Lambda$). This different metal configuration and coordination environment explains that the mesocate $Fe_2(L^1)_3$ absorbs at a longer wavelength (520 nm) than the helicate $Fe_2(L^1)_3$ (490 nm) suggesting lower energy and, consequently, greater stability of the mesocate $Fe_2(L^1)_3$ compared to the helicate $Fe_2(L^1)_3$.

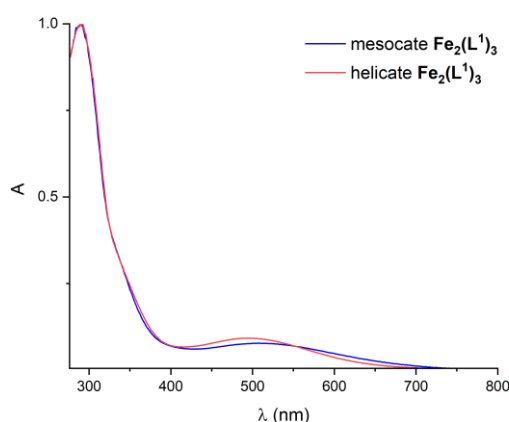


Figure 37. Normalised UV/vis absorption spectra comparison between helicate $Fe_2(L^1)_3$ and mesocate $Fe_2(L^1)_3$.

With this data, we can conclude that in the presence of Et_4N^+ ions, the helicate $Fe_2(L^1)_3$ is favoured whereas without this ammonium ion, in the exclusive presence of K^+ ions we obtain the mesocate $Fe_2(L^1)_3$. Therefore, we studied if helicate $Fe_2(L^1)_3$ and mesocate $Fe_2(L^1)_3$ structures were interconvertible between them in solution in presence of K^+ or Et_4N^+ ions. For this purpose, we measured the UV/Vis absorption spectrum for the mesocate $Fe_2(L^1)_3$, before and after the addition of an excess of Et_4N^+ ions and for the mesocate $Fe_2(L^1)_3$ cage before and after the addition of an excess of K^+ ions. Comparing this UV/Visible spectral data, we observed no changes after addition of Et_4N^+ or potassium ions was observed. Therefore, both iron architectures are not interconvertible among themselves in the presence of Et_4N^+ or potassium ions, therefore, are highly robust unique cage assemblies.

The UV/Vis absorption spectrum of helicate $Fe_2(L^2)_3$ shows two different absorption bands (Figure 38). Like its analogue $Fe_2(L^1)_3$, the band about 300 nm is associated with the absorption of the organic part of ligand H_4L^2 and a second band about 490 nm associated with Fe–O bonds absorptions. Comparing the UV/Vis spectrum of helicate $Fe_2(L^2)_3$ cage with the one of the free ligand H_4L^2 , we observe that the band derived from catechol groups disappears at 360 nm, and a new band at 490 nm, associated with the absorption of iron–ligand bonds appears. This suggests coordination of $(L^2)^{4-}$ to the Fe^{3+} metal centres supporting the formation of this supramolecular Fe_2L_3 cage and demonstrating its robustness and stability in solution.

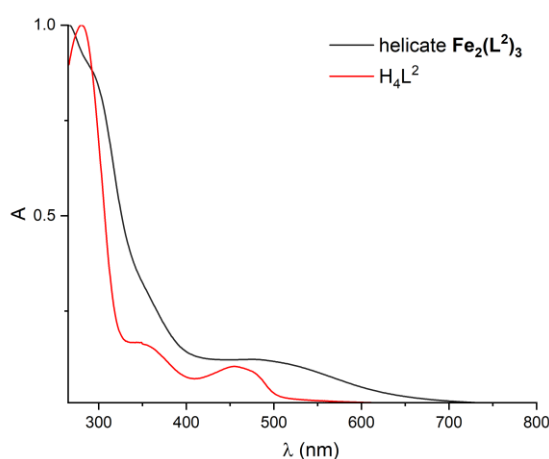


Figure 38. Normalised UV/vis absorption spectra comparison between helicate $Fe_2(L^2)_3$ and the free ligand H_4L^2 .

These results suggest that the presence of Et_4N^+ ions induce the formation of helicates structures during the self-assembly process. This induction may be due to electrostatic non-covalent interactions between Et_4N^+ cations and the anionic organic ligands L^{4-} during the self-assembly process of these Fe_2L_3 metal-organic cages. These supramolecular interactions seem to stabilise helical structures and favour their formation instead of mesocate's formation. This induction in the selective formation of helicates or mesocates for the Fe_2L_3 cages, depending on the presence or absence of Et_4N^+ , was not observed in the Ga_2L_3 cages. Therefore, the selective self-assembly process also depends on the metal cation used (Ga^{3+} vs Fe^{3+}).

1.4 Conclusions

In this chapter we have established a rational ligand-to-cage design for dinuclear M_2L_3 supramolecular coordination cages by developing a new family of ditopic 1,2,3-triazole-catechol and -naphthalenediol ligands (H_4L^1 – H_4L^5) via CuAAC click chemistry. The controlled self-assembly of these donors with Ga^{3+} and Fe^{3+} under basic conditions furnished a robust family of cages $(\text{MK})_2\text{L}_3$ in which catecholate O,O'-coordination templates these cage architectures. Across the M_2L_3 series, solution NMR ($^1\text{H}/^{13}\text{C}$) and DOSY evidences single and well-defined cage assemblies whose hydrodynamic diameters are consistent with the single-crystal X-ray dimensions. ESI-HRMS corroborates the cage composition and different charge states, and their heterometallic compositions within K^+ ions. In the solid state, single-crystal X-ray crystallography reveals the encapsulation of K^+ metal ions within their internal cavities, giving rise to heterometallic $(\text{MK})_2\text{L}_3$ cages in which encapsulated K^+ ions are proximal to the $\text{Ga}^3/\text{Fe}^{3+}$ metal nodes through interactions with either the catecholate or naphthalenediolate oxygens. This feature is a distinction with respect to analogous transition-metal M_2L_3 cages.

Importantly, the ligand scaffolds control emerges as a key handle. Electronic and, especially, axial/steric modifications (catechol vs naphthalenediol) tune the M_2L_3 cage solubility, geometry and cavity metrics, enabling access to larger internal voids and subtly altered metal-ligand topologies. For Ga_2L_3 , the platform delivers helicate cages that are structurally persistent. In contrast, for Fe_2L_3 , we uncovered a clean helicate/mesocate dichotomy, where the counter-ion (K^+ vs Et_4N^+) identity exerts decisive control over the cages' isomerism. The ionic K^+ ion and the absence of organic Et_4N^+ cations delivers mesocate Fe_2L_3 , whereas the presence of Et_4N^+ selectively stabilises helicate Fe_2L_3 . This counter-ion-directed isomer selection is metal selective (not observed for Ga_2L_3), highlighting counter ions can act as powerful, yet underexplored tools, in main-group metal coordination self-assembly.

Thus, this *Chapter* provides transferable design criteria (ligand topology/metal choice/ionic environment) apply directly to the self-assembly process and host-guest recognition for future applications in molecular switching and supramolecular catalysis, thereby widening the scope of main-group metal M_2L_3 coordination cages.

1.5 Experimental Methods

Herein, a representative synthetic procedure and characterisation for selected ligands Me₄Lⁿ, H₄Lⁿ, and cages Ga₂L₃ and Fe₂L₃ are provided. Complete synthetic protocols, characterisation details, and reactivity studies, for all precursors, ligands and Ga₂L₃ and Fe₂L₃ cages discussed in this Chapter, including full spectroscopic and crystallographic data, are included as electronic Annexes on the USB device accompanying this Thesis.

1.5.1 Materials

Experiments were carried out under a nitrogen inert atmosphere using either a glove box (MBraun, LabMaster SP) or standard Schlenk techniques. Methanol was dried over Mg for two hours and then distilled under nitrogen, after this, it was deoxygenated with nitrogen and stored under an atmosphere of nitrogen gas over molecular sieves (3 Å). Dichloromethane (DCM) was taken from SPS system and stored under an atmosphere of nitrogen gas. Deuterated chloroform (CDCl₃), deuterium oxide (D₂O), deuterated dimethyl sulfoxide (DMSO-*d*₆) and deuterated dimethyl formamide (DMF-*d*₇) were purchased from Cambridge Isotopes or Merck. 1,4-dibromobenzene, 1,4-dibromo-2,3,5,6-tetrafluorobenzene, 1,3-dibromobenzene, 1,5-dibromonaphthalene, (TMSA), CuI, Pd(OAc)₂, PPh₃, iPr₂NH, KOH, NaN₃, 2,3-dimethoxyphenylboronic acid, CuSO₄, L-ascorbic acid, *n*-BuOH, EtOH, THF, BBr₃, 6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one, hydroxylammonium chloride, pyridine, pivaloyl chloride, Et₃N, acetonitrile, pivalic acid, K₂CO₃, toluene, tricyclohexylphosphine, NaNO₂, HCl, Et₄NBr, NaI, TMSCl, *n*-BuLi, MeOCH₂PPh₃Cl, HBr, PtCl₂, 3-pentanone, Ga(acac)₃ and Fe(acac)₃ (acac = acetyl acetate) were purchased from Merck and used as received. 1,4-diethynylbenzene, 1,4-diethynyl-2,3,5,6-tetrafluorobenzene, 1,3-diethynylbenzene, 1,5-diethynylnaphthalene,^[82] 6,7-dimethoxynaphthalen-1-amine^[92], 1-iodo-6,7-dimethoxynaphthalene^[89], 2,3-dimethoxyphenyl azide^[86] and 1-bromo-6,7-dimethoxynaphthalene^[88] were prepared according to reported procedures. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified.

NMR experiments were conducted 5 mm NMR tubes. Multinuclear NMR spectra were collected on either a Bruker AVIIIHD 400 nanobay (equipped with a 9.4

tesla magnet) or Bruker AVIII 500 (equipped with 11.7 tesla magnet and a Prodigy cryoprobe) spectrometer. Assignments of NMR resonance signals in the 1H and $^{13}C\{^1H\}$ NMR spectra were made with the help of two-dimensional NMR experiments ($^1H, ^1H$ -COSY, $^1H, ^{13}C$ -HSQC, $^1H, ^{13}C$ -HMBC). For NOESY and ROESY (phase sensitive) experiments, standard pulse sequences were used consisting of 256 transients with 32 scans in the f_1 domain using an optimised 300 ms mixing time and 2 sec relaxation delay. Chemical shifts (δ) are reported in parts per million (ppm) and referenced the residual solvent resonances. Coupling constants (J) are given in Hertz (Hz). Signal multiplicities are abbreviated as follows: s (singlet), d (doublet), sept (septet), m (multiplet) and br (broad).

Electrospray ionisation high resolution mass spectrometry (ESI-HRMS) was carried out using a Bruker Compact QToF. Typical acquisition parameters were used (sample flow rate: $3\ \mu L\ min^{-1}$, nebuliser gas pressure: 0.3 bar, drying gas: nitrogen at $200^\circ C$ flowing at $3\ L\ min^{-1}$, capillary voltage: 3.5 kV, exit voltage: 0.5 kV). The spectrometer was calibrated in negative ion mode using an ESI-L low concentration tuning mix (Agilent) ranging m/z from 112 until 2833 in a mixture of acetonitrile (HPLC grade) and DI (deionised, HPLC grade) H_2O (95:5 mixture). Samples were diluted to a concentration of *ca.* $< 1 \times 10^{-6}\ M$ in an appropriate solvent using 1.5 mL glass vials capped with appropriate septum and then sampled by direct infusion using a 500 μL gas tight syringe.

CHN elemental microanalysis were carried out at the elemental analysis services from the Metropolitan University of London using a ThermoFlash 2000 Elemental Analyzer.

Infrared (IR) spectra were obtained using Nujol mulls between KBr discs inside a nitrogen glove box on a Bruker Alpha FT-IR spectrometer.

The photochemical measurements were carried out at room temperature ($25^\circ C$) with air-equilibrated solutions contained in quartz cuvettes with 1 cm optical pathlength. Dimethylformamide (DMF) was the solvent used for these measurements and is commercially available on Sigma-Aldrich with highest purity level. For the UV/vis absorption measurements was used a CARY 5000 UV/Vis spectrophotometer (Agilent).

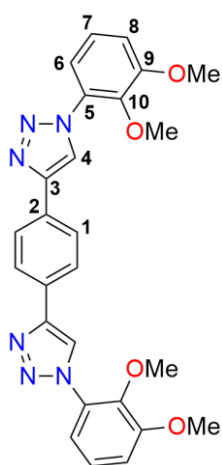
Single-crystal X-ray diffraction data was collected under a stream of nitrogen gas using an Oxford Cryostream 1000 unit at the given temperature with a Bruker D8 Quest Eco diffractometer (micro-focus sealed X-ray tube, Mo- $K\alpha$, $\lambda = 0.71073$

Å) equipped with a Photon II 7. Raw frame data were reduced using APEX3. The structures were solved using SHELXT and refined using full-matrix least squares refinement on all F²data using the SHELXL. Unless otherwise stated, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and allowed to ride on their parent atoms. Disorder was treated by introducing a split site model and restraining geometries and displacement parameters. Distances and angles were calculated using the full covariance matrix. Selected crystallographic data is summarised in the text. Full details are given in the supplementary deposited CIF files (Anexes).

The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3)^[95] package with a grid size of 0.5 Å and the EEM implemented charge model.

1.5.2 Synthesis and Characterisation of Me_4L^n and H_4L^n

1.5.2.1 Synthesis and Characterisation of Me_4L^1



1,4-diethynylbenzene (0.282 g, 2.23 mmol) and 1-azido-2,3-dimethoxybenzene (0.8 g, 4.46 mmol) were dissolved in 26 mL of a mixture of n-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.087 g, 0.44 mmol, 20 mol%) and $CuSO_4 \cdot 5H_2O$ (0.055 g, 0.22 mmol, 10 mol%) were added. Stirring was continued overnight until TLC showed the completion of the reaction. n-Butanol was removed under reduced pressure, and the viscous residue was extracted with $CHCl_3$ (3 x 20 mL). The combined

organic extractions were treated with saturated brine and anhydrous Na_2SO_4 and then organic extractions were filtered and $CHCl_3$ was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.903 g, 84% yield).

1H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.41 (s, 2H, H4), 8.02 (s, 4H, H1), 7.44 (d, 2H, H8, $^3J_{H8-H7} = 8.0$ Hz), 7.22 (t, 2H, H7, $^3J_{H7-H8} = ^3J_{H7-H6} = 8.0$ Hz), 7.04 (d, 2H, H6, $^3J_{H6-H7} = 8.0$ Hz), 3.96 (s, 6H, C9-OMe), 3.77 (s, 6H, C10-OMe).

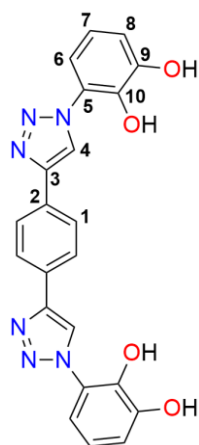
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K): δ 153.7 (C9), 147.3 (C2), 141.4 (C10), 131.3 (C5), 130.4 (C3), 126.4 (CH1), 124.7 (CH7), 121.6 (CH4), 117.0 (CH8), 112.9 (CH6), 61.4 (C10-OMe), 56.3 (C9-OMe).

IR (KBr/Nujol, cm^{-1}): $\nu(C=N, C=C)$ 1598, 1491.

Elemental analysis calculated for $C_{26.25}H_{24.5}N_6O_4$ ($C_{26}H_{24}N_6O_4 + (CH_2Cl_2)_{0.25}$): C, 62.34; H, 4.88; N, 16.62 Found: C, 63.07; H, 4.78; N, 15.81.

HRMS (ESI) m/z found (calculated) for $C_{26}H_{24}N_6O_4$ [M]: $[M + Na]^+$, 507.1766 (507.1751).

1.5.2.2 Synthesis and Characterisation of H_4L^1



BBr_3 (2.86 ml, 30 mmol) was added by syringe to a solution of 1,4-bis(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)benzene (0.9 g, 1.86 mmol) in CH_2Cl_2 (60 ml) under nitrogen at $-78^\circ C$. The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed under vacuum, and the remaining brown residue was stirred in water for 2 h at $100^\circ C$. The white precipitate was collected by filtration and dried under vacuum at $70^\circ C$ for 6 h (0.735 g, 92% yield).

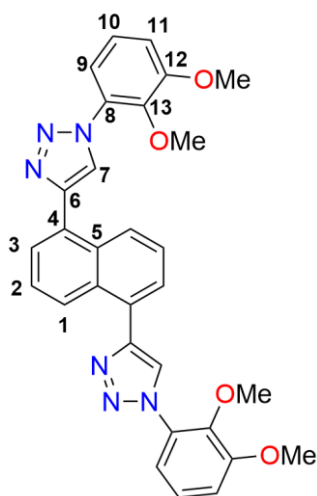
1H NMR (400 MHz, $DMSO-d_6$, 298 K): δ 10.02 (br s, 2H, OH), 9.46 (br s, 2H, OH), 8.92 (s, 2H, H4), 8.04 (s, 4H, H1), 7.07 (d, 2H, H6, $^3J_{H6-H7} = 8.0$ Hz), 6.97 (d, 2H, H8, $^3J_{H8-H7} = 8.0$ Hz), 6.84 (t, 2H, H7, $^3J_{H7-H8} = ^3J_{H7-H6} = 8.0$ Hz)

$^{13}C\{^1H\}$ NMR (101 MHz, $DMSO-d_6$, 298 K): δ 146.6 (C9), 145.6 (C2), 138.9 (C10), 130.0 (C3), 125.7 (CH1), 125.3 (C5), 123.1 (CH4), 119.0 (CH7), 115.8 (CH8), 115.6 (CH6).

IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ 3638 (br); $\nu(C=N, C=C)$ 1657, 1612, 1520, 1488

Elemental analysis calculated for $C_{22}H_{22}N_6O_7$ ($C_{22}H_{16}N_6O_4 + (H_2O)_3$): C, 54.77; H, 4.60; N, 17.42 Found: C, 55.22; H, 4.38; N, 16.80.

HRMS (ESI) m/z found (calculated) for $C_{22}H_{16}N_6O_4$ [M]: $[M + Na]^+$, 451.1132 (451.1125).

1.5.2.3 Synthesis and Characterisation of Me_4L^4 

1,5-diethynylnaphthalene (0.15 g, 0.851 mmol) and 1-azido-2,3-dimethoxybenzene (0.305 g, 1.70 mmol) were dissolved in 18 mL of a mixture of *n*-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.034 g, 0.170 mmol, 20 mol%) and $CuSO_4 \cdot 5H_2O$ (0.021 g, 0.085 mmol, 10 mol%) were added. Stirring was continued overnight until TLC showed the completion of the reaction. *n*-Butanol was removed under reduced pressure, and the viscous residue was extracted with $CHCl_3$ (3 x 20 mL). The combined

organic extractions were treated with saturated brine and anhydrous Na_2SO_4 and then organic extractions were filtered and $CHCl_3$ was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.392 g, 86% yield).

1H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.55 (d, 2H, H1 or H3, $^3J = 8.0$ Hz), 8.51 (s, 2H, H7), 7.88 (d, 2H, H3 or H1, $^3J = 8.0$ Hz), 7.63 (t, 2H, H2, $^3J_{H2-H3} = ^3J_{H2-H1} = 8.0$ Hz), 7.55 (d, 2H, H9, $^3J_{H9-H10} = 8.0$ Hz), 7.26 (t, 2H, H10, $^3J_{H10-H11} = ^3J_{H10-H9} = 8.0$ Hz), 7.06 (d, 2H, H11, $^3J_{H11-H10} = 8.0$ Hz), 3.97 (s, 6H, C12- OCH_3), 3.81 (s, 6H, C13- OCH_3).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K): δ 153.8 (C12), 141.4 (C13), 131.9 (C4 or C5), 131.4 (C8), 128.6 (C6), 127.8 (CH1 or CH3), 126.5 (CH3 or CH1), 126.3 (CH2), 124.8 (CH10), 117.0 (CH9), 112.9 (CH11), 61.4 (C13- OCH_3), 56.3 (C12- OCH_3).

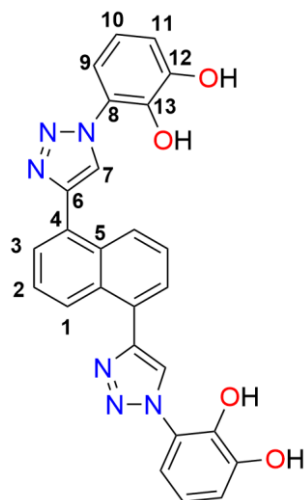
IR (KBr/Nujol, cm^{-1}): $\nu(C=N, C=C)$ 1595, 1491.

Elemental analysis calculated for $C_{30.25}H_{26.5}N_6O_4Cl_{0.5}$ ($C_{30}H_{26}N_6O_4 + (CH_2Cl_2)_{0.25}$): C, 65.37 ; H, 4.81; N, 15.12 Found: C, 66.24; H, 4.39; N, 14.23.

HRMS (ESI) m/z found (calculated) for $C_{30}H_{26}N_6O_4$ [M]: $[M + Na]^+$, 557.1917 (557.1908).

1.5.2.4 Synthesis and Characterisation of H_4L^4

BBr_3 (1.22 ml, 12.6 mmol) was added by syringe to a solution of 1,5-bis(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)naphthalene (0.211 g, 0.394 mmol) in dry $CHCl_3$ (40 ml) under nitrogen at $-78^\circ C$.



The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed under vacuum, and the remaining brown residue was stirred in water for 2 h at $100^\circ C$. The brown precipitate was collected by filtration and dried under vacuum at $70^\circ C$ for 6 h (0.135 g, 72% yield).

1H NMR (400 MHz, $DMSO-d_6$, 298 K): δ 10.04 (br s, 2H, OH), 9.51 (br s, 2H, OH), 8.88 (s, 2H, H7), 8.62 (d, 2H, H3, $^3J_{H3-H2} = 8.0$ Hz), 7.88 (d, 2H, H1, $^3J_{H1-H2} = 8.3$ Hz), 7.69 (t,

2H, H2, $^3J_{H2-H1} = ^3J_{H2-H3} = 8.0$ Hz), 7.17 (d, 2H, H9, $^3J_{H9-H10} = 8.0$ Hz), 6.99 (d, 2H, H11, $^3J_{H11-H10} = 8.0$ Hz), 6.88 (t, 3H, H10, $^3J_{H10-H11} = ^3J_{H10-H9} = 8.0$ Hz).

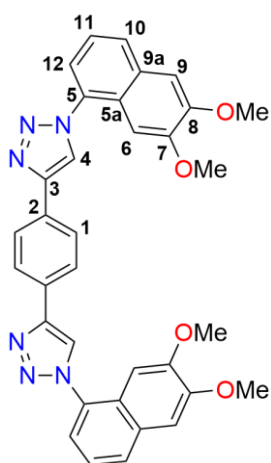
$^{13}C\{^1H\}$ NMR (101 MHz, $DMSO-d_6$, 298 K): δ 146.7 (C12), 145.4 (C4), 138.9 (C13), 131.0 (C5), 128.3 (C6), 127.4 (CH1), 126.2 (CH2), 126.2 (CH3), 125.8 (CH7), 125.4 (C8), 119.2 (CH10), 115.8 (CH11), 115.7 (CH9).

IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ 3346 (br); $\nu(C=N, C=C)$ 1617, 1524, 1488.

Elemental analysis calculated for $C_{26}H_{18}N_6O_4$: Found: C, 58.77; H, 3.47; N, 13.62.

HRMS (ESI) m/z found (calculated) for $C_{26}H_{18}N_6O_4$ [M]: $[M + H]^+$, 479.1493 (479.1462).

1.5.2.5 Synthesis and Characterisation of Me_4L^5



1,4-diethynylbenzene (0.1 g, 0.79 mmol) and 1-azido-6,7-dimethoxynaphthalene (0.545 g, 2.37 mmol) were dissolved in 24 mL of a mixture of *n*-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.1 g, 0.5 mmol, 20 mol%) and $CuSO_4 \cdot 5H_2O$ (0.064 g, 0.25 mmol, 10 mol%) were added. Stirring was continued overnight until TLC showed the completion of the reaction. *n*-Butanol was removed under reduced pressure, and the viscous residue was extracted with $CHCl_3$ (3 x 20 mL). The combined organic extractions were

treated with saturated brine and anhydrous Na_2SO_4 and then organic extractions

were filtered and $CHCl_3$ was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.347 g, 75% yield).

1H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.20 (s, 2H, H4), 8.09 (s, 4H, H1), 7.82 (dd, 2H, H10 or H12, $^3J = 7.0$ Hz, $J^4 = 1.7$ Hz), 7.44 (m, 4H, H12 or H10 and H11), 7.23 (s, 2H, H6 or H9), 7.05 (s, 2H, H9 or H6), 4.03 (s, 6H, C-OMe), 3.87 (s, 6H, C-OMe).

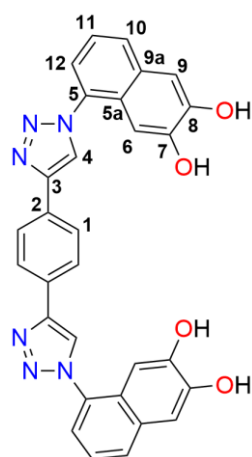
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K): δ 151.3 (C7 or C8), 150.5 (C8 or C7), 147.4 (C2 or C3), 132.6 (Cq naphthylene), 130.7 (Cq naphthylene), 130.5 (C3 or C2), 128.8 (C10 or C12), 126.6 (CH1), 124.6 (Cq naphthylene), 123.5 (C10 or C11 or C12), 122.3 (CH4), 121.7 (C10 or C11 or C12), 106.7 (CH9 or CH6), 101.3 (CH6 or CH9), 56.1 (2 $\times$ C-OMe, overlapped).

IR (KBr/Nujol, cm^{-1}): $\nu(C=N, C=C)$ 1629, 1603, 1583.

Elemental analysis calculated for $C_{34}H_{28}N_6O_4$: C, 69.85; H, 4.83; N, 14.38 Found: C, 70.09; H, 4.73; N, 14.10.

HRMS (ESI) m/z found (calculated) for $C_{34}H_{28}N_6O_4$ [M]: $[M + H]^+$, 585.2214 (585.2245).

1.5.2.6 Synthesis and Characterisation of H_4L^5



BBr_3 (1.36 ml, 14.24 mmol) was added by syringe to a solution of (0.52 g, 0.89 mmol) in CH_2Cl_2 (37 ml) under nitrogen at $-78^\circ C$. The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed under vacuum, and the remaining brown residue was stirred in water for 2 h at $100^\circ C$. The white precipitate was collected by filtration and dried under vacuum at $70^\circ C$ for 6 h (0.34 g, 72% yield).

1H NMR (400 MHz, $DMSO-d_6$, 298 K): δ 9.95 (br s, 4H, OH), 9.13 (s, 2H, H4), 8.15 (s, 4H, H1), 7.86 (d, 2H, H10 or H12, $^3J = 8.0$ Hz), 7.48 (d, 2H, H12 or H10, $^3J = 8.0$ Hz), 7.41 (t, 2H, H11, $^3J = 8.0$ Hz), 7.31 (s, 2H, H6 or H9), 6.83 (s, 2H, H9 or H6).

$^{13}C\{^1H\}$ NMR (101 MHz, $DMSO-d_6$, 298 K): δ 148.8 (C7 or C8), 147.9 (C8 or C7), 146.2 (C2 or C3), 131.6 (Cq naphthylene), 130.2 (C3 or C2), 129.8 (Cq naphthylene), 128.0 (CH10 or CH12), 126.0 (CH1), 124.2 (CH4), 123.9 (Cq naphthylene), 122.2 (CH11), 120.8 (CH12 or CH10), 110.2 (CH9 or CH6), 104.0 (CH6 or CH9).

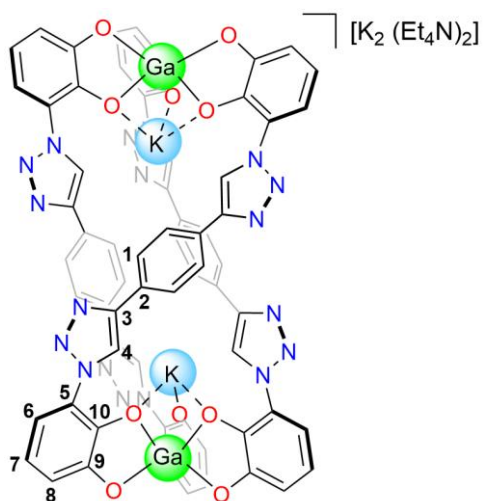
IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ 3136 (br); $\nu(C=N, C=C)$ 1610, 1529.

Elemental analysis calculated for $C_{30}H_{24}N_6O_6$ ($C_{30}H_{20}N_6O_4 + 2 H_2O$): C, 63.83; H, 4.29; N, 14.89 Found: C, 64.05; H, 4.02; N, 14.61.

HRMS (ESI) m/z found (calculated) for $\text{C}_{30}\text{H}_{20}\text{N}_6\text{O}_4$ [M]: $[\text{M} + \text{Na}]^+$, 551.1438 (551.1438).

1.5.3 Synthesis and Characterisation of Ga_2L_3

1.5.3.1 Synthesis and Characterisation of $\text{Ga}_2(\text{L}^1)_3$



The ligand H_4L^1 (0.2 g, 0.467 mmol) was suspended under oxygen-free conditions in distilled MeOH (60 mL). A 0.5 M solution of KOH in MeOH (1.87 mL, 0.933 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which $\text{Et}_4\text{NBr/MeOH}$ (3.33 mL, 0.933 mmol) solution and $\text{Ga}(\text{acac})_3$ (0.114 g, 0.311 mmol) was then added to the mixture reaction. The solution was stirred at room temperature

overnight. Then, the solid was collected by filtration and dried under high vacuum (0.138 g, 0.0754 mmol, 49%).

^1H NMR (500 MHz, D_2O , 298 K): δ 9.44 (s, 6H, H4), 8.02 (s, 12H, H1), 6.89 (d, 6H, H6, $^3J_{\text{H6-H7}} = 8.0$ Hz), 6.66 (d, 6H, H8, $^3J_{\text{H8-H7}} = 8.0$ Hz), 6.56 (t, 6H, H7, $^3J_{\text{H7-H8}} = 8.0$ Hz), 2.96 (q, 48H, $\text{CH}_2(2\text{Et}_4\text{N}^+ + 4\text{Et}_4\text{NBr})$), 1.01 (t, 72H, $\text{CH}_3(2\text{Et}_4\text{N}^+ + 4\text{Et}_4\text{NBr})$).

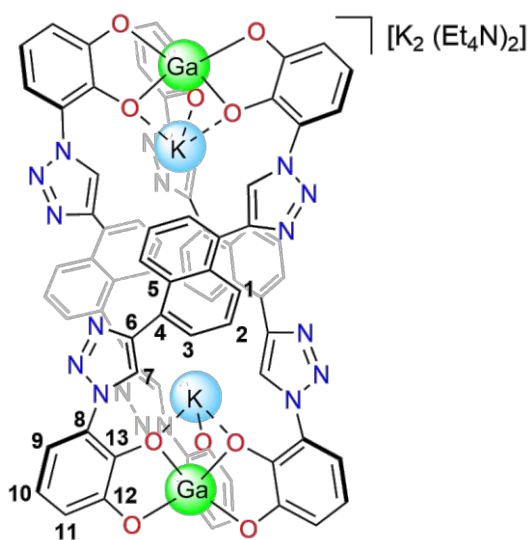
$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, D_2O , 298 K): δ 155.1 (C9), 147.9 (C10), 145.7 (C2), 130.2 (C3), 126.1 (CH1), 123.6 (CH4), 121.8 (C5), 114.4 (CH7), 112.4 (CH6), 110.2 (CH8), 51.7 [$\text{CH}_2-(2\text{Et}_4\text{N}^+ + 4\text{Et}_4\text{NBr})$], 6.3 [$\text{CH}_3-(2\text{Et}_4\text{N}^+ + 4\text{Et}_4\text{NBr})$].

IR (KBr/Nujol, cm^{-1}): $\nu(\text{O-H})$ 3395 (v br); $\nu(\text{C=N}, \text{C=C})$ 1638, 1565.

HRMS-ESI (negative-ion detection, $\text{H}_2\text{O} : \text{DMF}$ (1:1)) $\square^{6-} = [\text{Ga}_2(\text{L}^1)_3]^{6-}$: m/z found (calc.), $[\square^{6-} + 2\text{K}^+ + \text{H}^+]^{3-} = 497.0199$ (497.0214); $[\square^{6-} + 2\text{K}^+ + \text{Na}^+]^{3-} = 504.3486$ (504.3487); $[\square^{6-} + 3\text{K}^+ + \text{H}_2\text{O}]^{3-} = 515.6767$ (515.6769); $[\square^{6-} + 2\text{K}^+ + 2\text{H}^+]^{2-} = 746.0336$ (746.0358); $[\square^{6-} + 2\text{K}^+ + \text{H}^+ + \text{Na}^+]^{2-} = 757.0249$ (757.0267); $[\square^{6-} + 3\text{K}^+ + \text{H}^+]^{2-} = 765.0120$ (765.0137); $[\square^{6-} + 3\text{K}^+ + \text{Na}^+]^{2-} = 776.0038$ (776.0016); $[\square^{6-} + 4\text{K}^+]^{2-} = 783.9906$ (783.9916); $[\square^{6-} + \text{K}^+ + 2\text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 791.6322$ (791.6339); $[\square^{6-} + \text{K}^+ + \text{H}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{2-} = 802.6223$ (802.6248); $[\square^{6-} + 2\text{K}^+ + \text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 810.6096$ (810.6118); $[\square^{6-} + 2\text{K}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{2-} = 821.6016$ (821.6027); $[\square^{6-} + 3\text{K}^+ + \text{Et}_4\text{N}^+]^{2-} = 829.5890$ (829.5897); $[\square^{6-} + \text{K}^+ + \text{H}^+ + 2\text{Et}_4\text{N}^+]^{2-} = 856.2080$ (856.2099);

$[\square^{6-} + \text{K}^+ + \text{Na}^+ + 2 \text{Et}_4\text{N}^+]^{2-} = 867.1995$ (867.2008); $[\square^{6-} + 2 \text{K}^+ + 2 \text{Et}_4\text{N}^+]^{2-} = 875.1866$ (875.1878).

1.5.3.2 Synthesis and Characterisation of $\text{Ga}_2(\text{L}^4)_3$



The linker H_4L^4 (0.090 g, 0.188 mmol) was suspended under oxygen-free conditions in distilled MeOH (25 mL). A 0.5 M solution of KOH in MeOH (0.75 mL, 0.376 mmol) was added by syringe. The linker dissolved after about 20 min with stirring, after that, $\text{Et}_4\text{NBr/MeOH}$ (1.34 mL, 0.376 mmol) solution and $\text{Ga}(\text{acac})_3$ (0.046 g, 0.124 mmol) were then added to the mixture reaction. The solution was stirred at room temperature overnight. Then, the

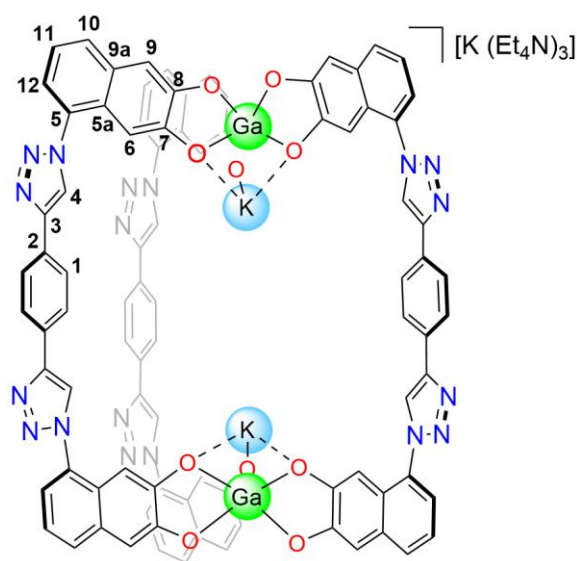
solid was collected by filtration and dried under vacuum (0.060 g, 0.031 mmol, 50%).

^1H NMR (500 MHz, D_2O , 298 K): δ 9.02 (s, 6H, H7), 7.85 (d, 6H, H3, $^3J_{\text{H}3-\text{H}2} = 8.0$ Hz), 7.34 (d, 6H, H9, $^3J_{\text{H}9-\text{H}10} = 8.0$ Hz), 7.03 (d, 6H, H1, $^3J_{\text{H}1-\text{H}2} = 8.0$ Hz), 6.74 (d, 6H, H11, $^3J_{\text{H}11-\text{H}10} = 8.0$ Hz), 6.68 (t, 6H, H10, $^3J_{\text{H}10-\text{H}9} = ^3J_{\text{H}10-\text{H}11} = 8.0$ Hz), 6.40 (t, 6H, H2, $^3J_{\text{H}2-\text{H}3} = ^3J_{\text{H}2-\text{H}1} = 8.0$ Hz), 2.97 (br s, 16H, CH_2 (2 Et_4N^+)), 1.00 (br s, 24H, CH_3 (2 Et_4N^+)).

$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, D_2O , 298 K): δ 155.8 (C12), 147.5 (C13), 144.2 (C4), 130.5 (C5), 127.1 (C6), 126.5 (CH3), 126.0 (CH7), 125.3 (CH2), 124.7 (CH1), 121.8 (C8), 114.6 (CH10), 111.8 (CH9), 108.4 (CH11), 51.7 [$\text{CH}_2-(\text{Et}_4\text{N}^+)$], 6.3 [$\text{CH}_3-(\text{Et}_4\text{N}^+)$].

IR (KBr/Nujol, cm^{-1}): $\nu(\text{C}=\text{N}, \text{C}=\text{C})$ 1634, 1574.

HRMS-ESI (negative-ion detection, $\text{H}_2\text{O} : \text{DMF}$ (1:1)) $\square^{6-} = [\text{Ga}_2(\text{L}^4)_3]^{6-}$: m/z found (calc.), $[\square^{6-} + 2 \text{K}^+ + \text{H}^+]^{3-} = 547.0379$ (547.0372); $[\square^{6-} + 2 \text{K}^+ + \text{Na}^+]^{3-} = 554.3654$ (554.3645); $[\square^{6-} + 3 \text{K}^+]^{3-} = 559.6918$ (559.6891); $[\square^{6-} + 3 \text{K}^+ + \text{H}_2\text{O}]^{3-} = 565.6933$ (565.6926); $[\square^{6-} + \text{K}^+ + \text{H}^+ + \text{Et}_4\text{N}^+]^{3-} = 577.4365$ (577.4359); $[\square^{6-} + 2 \text{K}^+ + 2 \text{H}^+]^{2-} = 821.0597$ (821.0594); $[\square^{6-} + 2 \text{K}^+ + \text{H}^+ + \text{Na}^+]^{2-} = 832.0508$ (832.0504); $[\square^{6-} + 3 \text{K}^+ + \text{H}^+]^{2-} = 840.0381$ (840.0373); $[\square^{6-} + 3 \text{K}^+ + \text{Na}^+]^{2-} = 851.0290$ (851.0283); $[\square^{6-} + 4 \text{K}^+]^{2-} = 859.0160$ (859.0152); $[\square^{6-} + \text{K}^+ + 2 \text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 866.6578$ (866.6575); $[\square^{6-} + 2 \text{K}^+ + \text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 885.6360$ (885.6354); $[\square^{6-} + 2 \text{K}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{2-} = 896.6268$ (896.6264); $[\square^{6-} + 3 \text{K}^+ + \text{Et}_4\text{N}^+]^{2-} = 904.6139$ (904.6133); $[\square^{6-} + \text{K}^+ + \text{H}^+ + 2 \text{Et}_4\text{N}^+]^{2-} = 931.2337$ (931.2335); $[\square^{6-} + 2 \text{K}^+ + 2 \text{Et}_4\text{N}^+]^{2-} = 950.2116$ (950.2114).

1.5.3.3 Synthesis and Characterisation of $\text{Ga}_2(\text{L}^5)_3$ 

The ligand H_4L^5 (0.08 g, 0.151 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (0.61 mL, 0.302 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which $\text{Et}_4\text{NBr/MeOH}$ (1.08 mL, 0.302 mmol) solution and $\text{Ga}(\text{acac})_3$ (0.037 g, 0.099 mmol) was then added to the mixture reaction. The solution was stirred at room

temperature overnight. Then, the solid was collected by filtration and dried under high vacuum (0.9 g, 0.0405 mmol, 80%).

^1H NMR (500 MHz, $\text{D}_2\text{O/DMF-d}_7$ (1:1), 298 K): δ 8.81 (s, 6H, H4), 8.13 (s, 12H, H1), 7.69 (d, 6H, H12 or H10, $^3J = 8.0$ Hz), 7.18 (m, 12H, H11 and H10 or H12), 6.98 (s, 6H, H6 or H9), 6.34 (s, 6H, H9 or H6), 3.15 (m, 24H, CH_2 ($3\text{Et}_4\text{N}^+$), 1.18 (m, 38H, CH_3 ($3\text{Et}_4\text{N}^+$)).

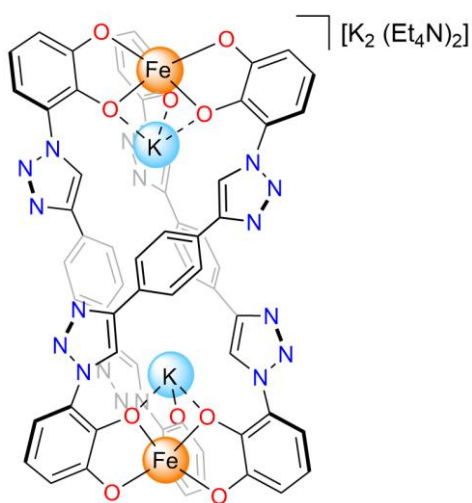
$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{D}_2\text{O/DMF-d}_7$ (1:1), 298 K): δ 157.9 (C7 or C8), 156.4 (C8 or C7), 145.5 (C2 or C3), 129.0 (Cq), 128.7 (Cq), 125.9 (CH11 or CH10 or CH12), 125.2 (Cq), 125.2 (CH1), 123.6 (CH4), 122.7 (Cq), 118.1 (CH11 or CH10 or CH12), 117.3 (CH10 or CH12), 104.0 (CH9 or CH6), 96.8 (CH6 or CH9), 50.7 [CH_2 -($3\text{Et}_4\text{N}^+$)], 5.5 [CH_3 -($3\text{Et}_4\text{N}^+$)].

IR (KBr/Nujol, cm^{-1}): $\nu(\text{O-H})$ 3607 (v br); $\nu(\text{C=N, C=C})$ 1562.

HRMS-ESI (negative-ion detection, H_2O) $[\square^{6-} = [\text{Ga}_2(\text{L}^5)_3]^{6-}]$: m/z found (calc.), $[\square^{6-} + \text{K}^+ + \text{H}^+ + \text{Et}_4\text{N}^+]^{3-} = 627.4743$ (627.4517); $[\square^{6-} + 2\text{K}^+ + \text{Et}_4\text{N}^+]^{3-} = 640.1285$ (640.10366); $[\square^{6-} + 3\text{K}^+ + \text{H}^+]^{2-} = 915.0942$ (915.0610); $[\square^{6-} + \text{K}^+ + 2\text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 941.7142$ (941.6812); $[\square^{6-} + \text{K}^+ + \text{H}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{2-} = 952.7049$ (952.6722), $[\square^{6-} + 2\text{K}^+ + \text{H}^+ + \text{Et}_4\text{N}^+]^{2-} = 960.6934$ (960.6591); $[\square^{6-} + 2\text{H}^+ + 2\text{Et}_4\text{N}^+]^{2-} = 987.3137$ (987.2793); $[\square^{6-} + \text{Na}^+ + \text{H}^+ + 2\text{Et}_4\text{N}^+]^{2-} = 998.3040$ (998.2703); $[\square^{6-} + \text{K}^+ + \text{H}^+ + 2\text{Et}_4\text{N}^+]^{2-} = 1006.2929$ (1006.2572); $[\square^{6-} + 2\text{K}^+ + 2\text{Et}_4\text{N}^+]^{2-} = 1025.2738$ (1025.2351); $[\square^{6-} + \text{H}^+ + 3\text{Et}_4\text{N}^+]^{2-} = 1051.8915$ (1051.8553); $[\square^{6-} + \text{K}^+ + 3\text{Et}_4\text{N}^+]^{2-} = 1070.8722$ (1070.8332).

1.5.4 Synthesis and Characterisation of Fe_2L_3

1.5.4.1 Synthesis and Characterisation of Helicate $Fe_2(L^1)_3$



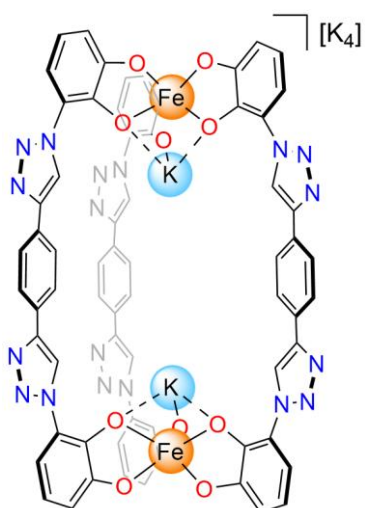
To a suspension of the ligand H_4L^1 (0.1 g, 0.233 mmol) in deoxygenated MeOH (30 mL) under an atmosphere of nitrogen gas, KOH was added (0.932 mL from a 0.5 M solution in MeOH, 0.466 mmol) via syringe, after which, a solution 0.28 M of Et_4NBr in MeOH (1.66 mL, 0.466 mmol) was added. After 5 min of stirring, a solution was obtained to which $Fe(acac)_3$ (0.054 g, 0.154 mmol) was then added under nitrogen gas. The reaction mixture was then

stirred at room temperature for 16 hours. Then, a dark-red silky suspension was filtered and the solid was dried under high vacuum for 6 hours to give $[Fe_2(L^1)_3]$ $[Et_4N]_2[K]_4$ as a dark-red solid (0.1 g, 0.0554 mmol, 72% yield).

IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ 3151 (v br); $\nu(C=N, C=C)$ 1635, 1564, 1522.

HRMS-ESI (negative-ion detection, $H_2O : DMF$ (1:1)) $\square^{6-} = [Fe_2(L^1)_3]^{6-}$: m/z found (calc.), $[\square^{6-} + 3 K^+ + Et_4N^+]^{2-} = 815.6004$ (815.5991); $[\square^{6-} + 2 K^+ + Na^+ + Et_4N^+]^{2-} = 807.6132$ (807.6122); $[\square^{6-} + 2 K^+ + H^+ + Et_4N^+]^{2-} = 796.6221$ (796.6212); $[\square^{6-} + 4 K^+]^{2-} = 770.0034$ (770.0012); $[\square^{6-} + 3 K^+ + Na^+]^{2-} = 762.0166$ (762.0142); $[\square^{6-} + 3 K^+ + H^+]^{2-} = 751.0242$ (751.0232); $[\square^{6-} + 2 K^+ + Na^+ + H^+]^{2-} = 743.0366$ (743.0362); $[\square^{6-} + 2 K^+ + 2 H^+]^{2-} = 732.0471$ (732.0453).

1.5.4.2 Synthesis and Characterisation of Mesocate $Fe_2(L^1)_3$



To a suspension of the ligand H_4L^1 (0.1 g, 0.233 mmol) in deoxygenated MeOH (30 mL) under an atmosphere of nitrogen gas, KOH was added (0.932 mL from a 0.5 M solution in MeOH, 0.466 mmol) via syringe. After 5 min of stirring, a solution was obtained to which $Fe(acac)_3$ (0.054 g, 0.154 mmol) was then added under nitrogen gas. The reaction mixture was then stirred at room temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure (5 mL) and then Et_2O (10 mL) was added to give a

dark-red silky suspension. The solid was filtered and dried under high vacuum for 6 hours to give $[Fe_2(L^1)_3][K]_6$ as a dark red solid (0.105 g, 0.0607 mmol, 79% yield).

IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ 3162; $\nu(C=N, C=C)$ 1632, 1562, 1520.

HRMS-ESI (negative-ion detection, $H_2O : DMF$ (1:1)) $\square^{6-} = [Fe_2(L^1)_3]^{6-}$: m/z found (calc.), $[\square^{6-} + 4 K^+]^{2-} = 770.0037$ (770.0012); $[\square^{6-} + 3 K^+ + Na^+]^{2-} = 762.0166$ (762.0142); $[\square^{6-} + 3 K^+ + H^+]^{2-} = 751.0256$ (751.0232); $[\square^{6-} + 2 K^+ + Na^+ + H^+]^{2-} = 743.0376$ (743.0362); $[\square^{6-} + 2 K^+ + 2 H^+]^{2-} = 732.0469$ (732.0453).

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CHAPTER II:

Self-Assembly, Structures and Host–Guest Chemistry of Tetrahedral Coordination Cages Al_4L_4 and Ga_4L_4

2.1 Introduction

2.1.1 Historical Development of Supramolecular Metal–Organic M_4L_m , M_6L_m and $M_{6n}L_m$ Cages

In 1988, Saalfrank unexpectedly discovered the first self-assembled tetrahedral metal–organic cage **I** (Figure 1).^[1] While attempting to synthesise allene compounds, instead, a magnesium–malonate structure resulted from condensing diethyl malonate with oxalyl chloride in the presence of methylmagnesium iodide as the base. Analysis using NMR and X–ray diffraction revealed a highly symmetrical ammonium salt of a tetramagnesium supramolecular Mg_4L_6 assembly. This novel anionic structure Mg_4L_6 cage featured a tetrahedral framework with four Mg^{2+} nodes and six bis–bidentate organic ditopic ligands. Although this assembly was serendipitously obtained, this discovery marked the beginning of a new effervescent research area into discrete metal–organic supramolecular cage assemblies.

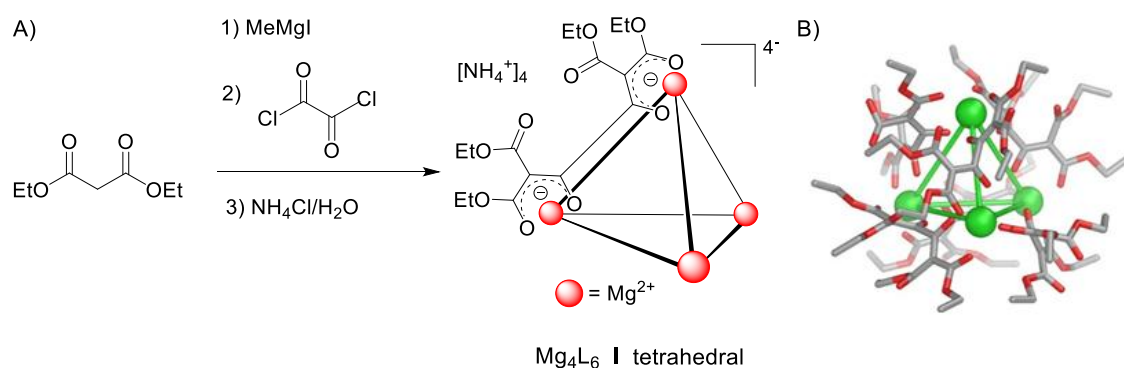


Figure 1. A) Development of the first self-assembled tetrahedral metal–organic cage Mg_4L_6 **I** and B) its crystal structure.

Following this pioneering work, Fujita demonstrated in 1995 that reacting $[Pd(en)]^{2+}$ (en = ethylenediamine) units with the tritopic ligand 1,3,5–tris(4–pyridyl)triazine ligands in a 6:4 ratio led to the formation of a water–soluble octahedral Pd_6L_4 cage **II** with a sufficiently large central cavity to host small guest molecules such as adamantane, adamantanol and tri–tert–butylbenzene (Figure 2).^[2] The cage structure, Pd_6L_4 , composed of ten components, was confirmed through X–ray crystallography. In this supramolecular structure, four triazine tritopic panels are connected by six Pd^{2+} centers, forming a shape that can be described as a truncated tetrahedron or, more appropriately, a molecular octahedron with

alternating closed and open faces. Interestingly, contrary to the anionic Saalfrank's Mg_4L_6 cage, Fujita's Pd_6L_4 is a cationic cage.

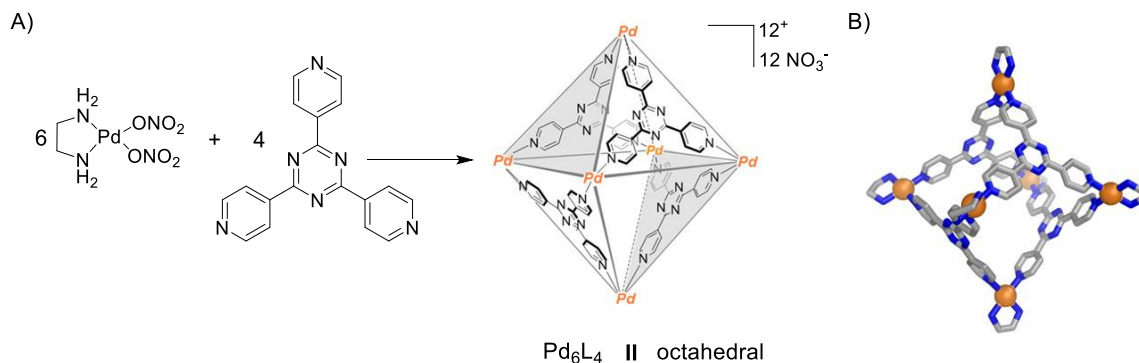


Figure 2. A) Synthesis of the water-soluble octahedral Pd_6L_4 cage II discovered by Fujita in 1995 and B) its crystal structure.

In this context, Raymond made significant advances in the field of metal-organic cages with encapsulating properties. He developed a new type of anionic metal-organic M_4L_6 tetrahedral cages in 1998 (Figure 3),^[3] akin to the Mg_4L_6 cage reported by Saalfrank. The geometry of the bis-catechol ditopic ligand 1,5-bis(2,3-dihydroxybenzoylamino)-naphthalene was specifically designed to prevent the formation of M_2L_3 helicates while promoting the self-assembly of an M_4L_6 tetrahedron. The rigidity of the naphthalene spacer and the presence of amide groups caused the two catechol binding units to be offset from one another, preventing helicate formation and guiding the system to form the cage III. This metal-organic cage presents interesting encapsulation properties, being able to host small guest molecules as the Et_4N^+ cation (Figure 3B).

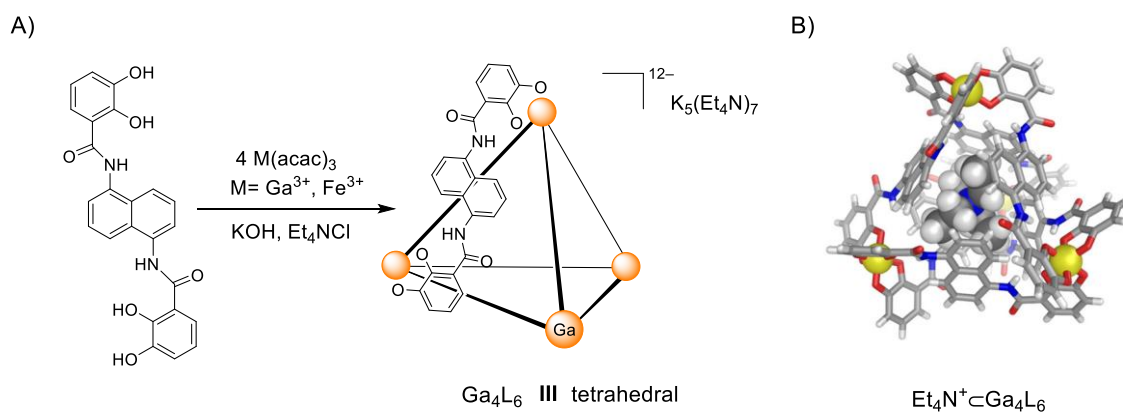


Figure 3. A) Synthesis of the metal-organic M_4L_6 tetrahedral cage III reported by Raymond and B) its crystal structure encapsulating Et_4N^+ giving $Et_4N^+@Ga_4L_6$.

During the same year, Harrison incorporated carboxylate coordinating groups into the design of metal–organic cages. They observed that a water–soluble Co_4L_2 **IV**, based on a resorcinarene ligand functionalized with iminodiacetate chelating groups (Figure 4). This cage is self–assembled when the ligand is treated with $Ba(OH)_2$ in the presence of K_2CO_3 ($pH \approx 6$) and $CoCl_2$.^[4] Crystallographic analysis revealed that the Co_4L_2 cage consists of two cup–shaped resorcinarene motifs held together by four pseudooctahedral Co^{2+} ions, each coordinated to two doubly deprotonated iminodiacetate groups. The octaanionic cage's charge was balanced by Ba^{2+} and Co^{2+} counterions.

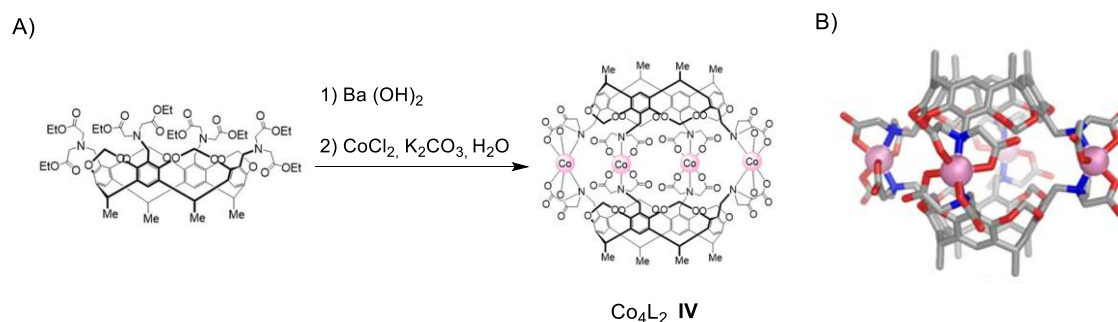


Figure 4. A) Synthesis of the cage Co_4L_2 **IV** and B) its X-ray structure showing the four Co^{2+} ions around the cage's periphery.

By applying the fundamental concepts in the construction of supramolecular metal–organic cage–structures, different types of cages have been successfully developed following these landmark discoveries (**I–IV**), with different metal/ligand stoichiometries, resulting in different cavity sizes, geometries and applications in chemical transformations.^[5] These supramolecular cages can encapsulate guest compounds ranging from small molecular sizes to nanoparticles,^[6] or even protein–sized molecules.^[7]

2.1.2 Geometries of M_4L_m , M_6L_m and $M_{6n}L_m$ Cages

Key factors such as metal M^{n+} ion coordination preferences,^[8] ligand design,^[9] and the principles of self–assembly and thermodynamic factors,^[10] influence the geometry of the M_nL_m cage assemblies. For example, transition metals typically exhibit specific coordination numbers and geometries, such as tetrahedral or octahedral coordination at the cage's vertex. M^{n+} coordination preferences play a crucial role in determining the overall shape and geometry of the M_nL_m cage. The topology of the ligand, referring to the number of donor sites, along with their spatial

orientation, also governs the directionality and connectivity of the cage assembly. Additionally, during the self-assembly process, the formation of reversible metal-ligand bonds, allows the formation of the most thermodynamically stable cage configuration. Together, these factors contribute to the precise design and stability of metal-organic cages, generating supramolecular coordination assemblies with different geometries. Some of the most common geometries in metal-organic cages are tetrahedral,^[5c, 11] octahedral,^[2, 12] and Archimedean (M_nL_{2n}),^[13] which will be further discussed in the following sections.

2.1.2.1 Tetrahedral M_4L_m Cages

There are different combinations of organic ligands and metal ions M^{n+} that self-assemble into this cage's geometry, the two most common stoichiometries are M_4L_6 and M_4L_4 which will be discussed as follows.

M_4L_6 cages are typically composed of four metal M^{n+} centres and six bridging ligands (L), resulting in a highly symmetric tetrahedral topological geometry. The assembly is driven by the directional coordination preferences of the metal ions M^{n+} and the geometric restriction imposed by the ligands, following the principles of coordination-driven self-assembly.^[14] In a typical M_4L_6 cage, the metal ions are usually octahedral transition metals such as Fe^{2+} ,^[11a, 11b, 15] Co^{2+} ,^[15b, 16] Ni^{2+} ,^[17] Zn^{2+} ,^[16d, 18] Ti^{4+} ,^[19] and Cd^{2+} ,^[16d, 20] or main group metals such as Al^{3+} or Ga^{3+} ,^[21] which coordinate to bidentate ligands that bridge the edges of the tetrahedral cage.^[5c] These ligands often contain coordinating sites, such as imine, pyridine, or catecholate groups, positioned at specific angles to enforce the tetrahedral topology during their self-assembly.

For example, Nitschke developed Fe_4L_6 **V** tetrahedral cages (Figure 5) that are water soluble using this self-assembly strategy.^[11a] These structures were assembled using a subcomponent self-assembly approach. In this method, metal-ligand coordination bonds and covalent imine bonds (C=N) form simultaneously, allowing the pyridyl-imine chelating ligands to be generated directly within the reaction mixture and organised around the M^{n+} ions, which act as structural metal templates. Cage Fe_4L_6 **V** consists entirely of low-spin Fe^{2+} ions, as evidenced by its diamagnetic NMR spectrum and intense metal-to-ligand charge transfer transitions, which give it a deep purple color. Its X-ray structure (Figure 5B) confirms the formation of an anionic tetrahedral assembly with four Fe^{2+} vertices and six bis-bidentate ligand edges. The sulfonate groups in Fe_4L_6 **V** are symmetrically

oriented outward, providing it with high water solubility. The cage **V** remains stable in solution due to the strong binding interactions and mutual stabilisation between Fe^{2+} and the ligand's imine groups. Thanks to its water solubility and hydrophobic internal cavity ($141 \text{ \AA}^3$), the cage Fe_4L_6 can encapsulate a series of guest molecules such as cyclohexane and cyclopentane. This methodology has proven useful for constructing many different water-soluble tetrahedral Fe_4L_6 cages incorporating varying numbers ($n = 0-3$) of oligo-*p*-xylene spacers and chiral amines.^[11b, 11c]

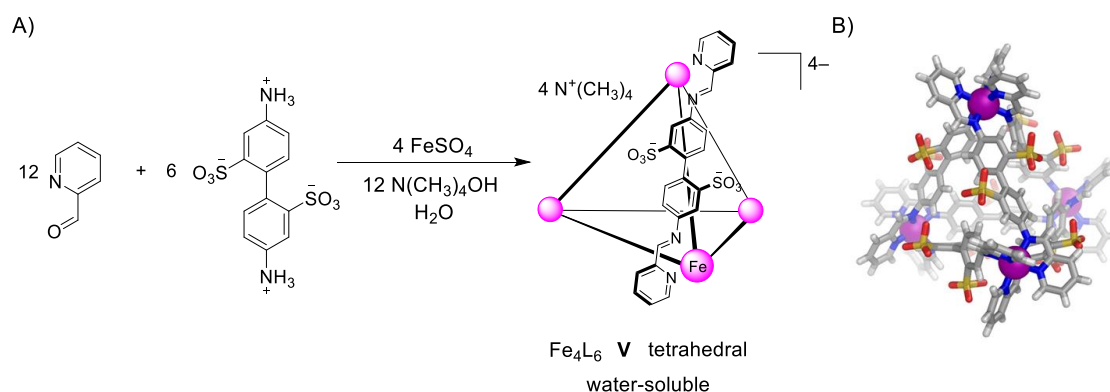


Figure 5. A) Water-soluble Fe_4L_6 tetrahedral cage **V** designed by Nitschke and B) its crystal structure.

The use of catechol-amide ligands, which share the same structure as the previously described for the cage Ga_4L_6 **III**,^[3] was further developed by Raymond. Cages **VI** M_4L_6 (Figure 6) exhibit greater kinetic stability because they incorporate tetravalent metal ions (M^{4+}) at the vertices.^[19] These cages **VI** (Figure 6) required elevated temperatures, longer reaction times and the use of guest templates to form, reflecting the lower exchange rates of M^{4+} -catecholate bonds.^[22] Ligand exchange experiments using mononuclear Ga^{3+} and Ge^{4+} models of the cage vertices provided evidence for notable differences in the lability of catecholate complexes, being cage Ga_4L_6 **III** more labile than cages **VI**. However, while the substitution of Ga^{3+} with a tetravalent metal improved kinetic stability, it also resulted in reduced water solubility, likely due to the lower overall negative charge of the cage structure.

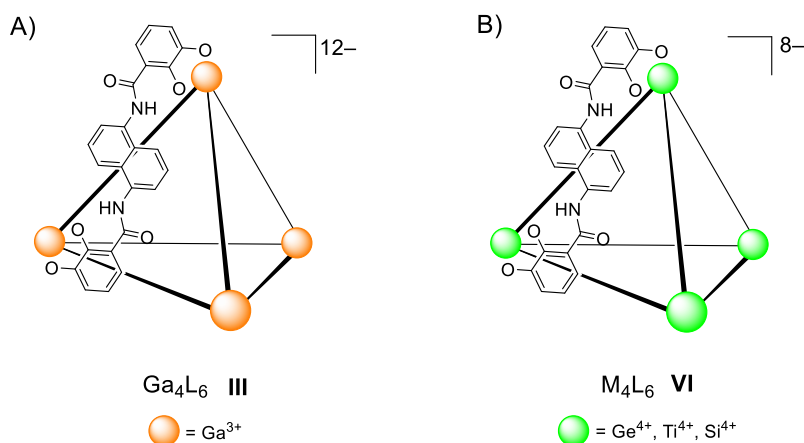


Figure 6. Ga_4L_6 tetrahedron and its more robust congeners M_4L_6 ($M = Ge^{4+}$, Ti^{4+} , Si^{4+}).

M_4L_4 cages are a class of discrete supramolecular metal–organic assemblies formed through the self–assembly of four metal M^{n+} ions and four bridging ligands (L). These structures typically adopt pseudo–tetrahedral or square–shaped topologies, depending on the coordination preferences of the M^{n+} centres and the geometry the ligands involved. Unlike the more common M_4L_6 tetrahedral cages, which rely on six ditopic ligands to bridge four metal M^{n+} centres, M_4L_4 cages use fewer tritopic ligands, often resulting in more open or flexible cage assemblies. As in M_4L_6 systems, in M_4L_4 architectures, the metal M^{n+} ions are usually octahedral transition metals such as Fe^{2+} ,^[23] Ti^{4+} ,^[21a] Zn^{2+} ,^[24] Ni^{2+} , Cd^{2+} , and Co^{2+} ,^[25] main group metals such as Al^{3+} or Ga^{3+} ,^[21a, 26] or even lanthanide ions as Ce^{3+} ,^[27] or Eu^{3+} .^[28] The ligands often contain coordinating sites, such as imine, pyridine, or catecholate groups depending on the nature of the M^{n+} ion. In M_4L_4 systems, unlike M_4L_6 cages, ligands are usually tris–bidentate and are positioned on the faces of the tetrahedron at specific angles forming the tetrahedral M_4L_4 topology.

For instance, using the same method to prepare the water–soluble Fe_4L_6 system **V** (Figure 5),^[11a] a wide range of Fe_4L_4 cage derivatives were developed using pyridyl–imine chelating ligands and different core groups (*N*–heterotriangulene, triazatruxene).^[23d, 29] Furthermore, cages with heterometallic vertices of the type $(MM')_4L_4$ have also been developed.^[30] The vertices of these structures are built from 2–formyl–6–diphenylphosphinopyridine, a subcomponent that generates ligands capable of efficiently bridging two metal ions (M and M'), thereby promoting the creation of bimetallic coordination sites within the heterometallic $(MM')_4L_4$ cages. Using this phosphino–pyridine ligand is possible to assemble octanuclear $(CdCu)_4L_4$

tetrahedral cages **VII** (Figure 7), which stand as one of the first examples of self-assembled cages featuring well-defined heterobimetallic vertices.

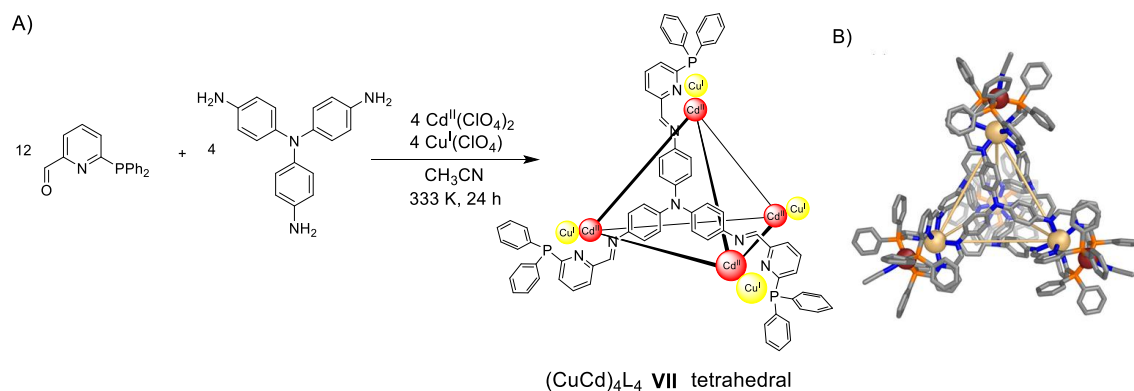


Figure 7. A) Synthesis of a heterometallic (CdCu)₄L₄ tetrahedral cage **VII** and B) its crystal structure.

Following the strategy to prepare Ga_4L_6 systems using ditopic ligands, Raymond prepared a series of M_4L_4 ($M = Al^{3+}$, Ga^{3+} , In^{3+}) cages based on tritopic catecholamide ligands (Figure 8).^[21a, 31] They observed that these M_4L_4 cages **VIII** show significant distinctions in their behavior compared to previously reported M_4L_6 cages **III** and **IV** in terms of self-assembly, guest selectivity and host stability.

The M_4L_4 tetrahedral cages are anticipated to exhibit greater stability compared to M_4L_6 cage assemblies. This enhanced stability is primarily attributed to the higher denticity of the ligand within the M_4L_4 assembly and a reduced entropic penalty associated with its self-assembly. The increased denticity of the tritopic ligands in M_4L_4 cages contributes significantly to their robustness, requiring M_4L_4 assemblies only four ligands for their self-assembly and incurring a lower entropic cost than that for M_4L_6 structures, which need six ligands. This decreased free energy penalty is a key determinant of the M_4L_4 cage's superior stability. Additionally, the use of symmetric tris-bidentate ligands in the M_4L_4 system prevents the formation of alternative, lower-stoichiometry structures, such as the M_2L_3 helicate, which could compete with the desired M_4L_6 tetrahedron.

M_4L_4 and M_4L_6 tetrahedral cages exhibit three key structural differences in terms of cavity size, shape, and accessibility of the cavity. The M_4L_4 cages **VIII** possess a smaller internal cavity than their M_4L_6 cage analogues **III** and **VI**. For example, M_4L_4 cages **VIII** with a 19 Å metal-to-metal distance has an estimated maximum cavity volume of approximately 450 Å³, significantly less than the 2400 Å³

found in a hypothetical M_4L_6 cage analogue with the same metal-to-metal separation. This indicates that the M_4L_4 design is not optimal for achieving the largest possible cavity.

Beyond size, cavity shape is another distinguishing factor. The M_4L_4 cages features an almost perfectly tetrahedral cavity, while the M_4L_6 cages form a cavity that more closely approximates a cubic shape. This geometric difference impacts the types and shapes of guest molecules each structure can accommodate. For instance, M_4L_4 cages **VIII** encapsulate tetrahedrally shaped such as Et_4N^+ and Et_4P^+ cations, but they are unable to host cylindrically shaped bis(cyclopentadienyl)–cobaltocenium ions (volume = $190 \text{ \AA}^3$), despite their smaller volume. Conversely, the M_4L_6 naphthalene–based cages **III** and **IV**, while possessing a similar volume to M_4L_4 cages **VIII**, features a cubic-shaped cavity. This cubelike architecture successfully encapsulates both bis(cyclopentadienyl)–cobaltocenium and the considerably larger bis(decamethylcyclopentadienyl)–cobaltocenium ions (volume = $450 \text{ \AA}^3$), highlighting the dominant role of cavity shape over volume in guest encapsulation.

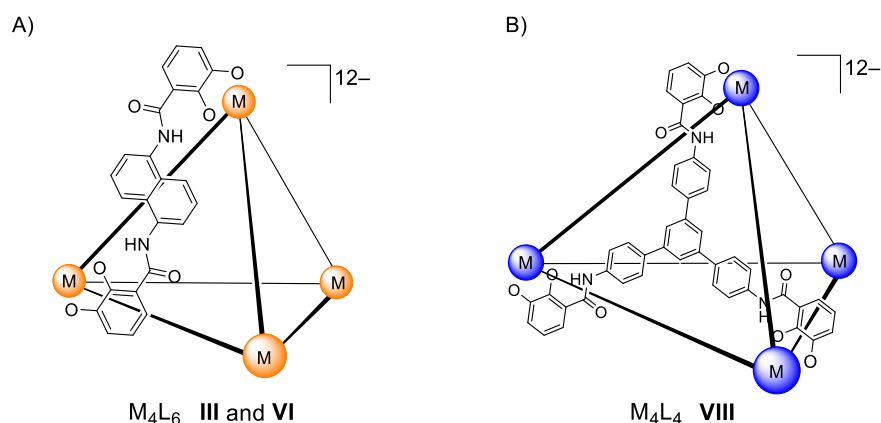


Figure 8. M_4L_6 tetrahedron and its analogues M_4L_4 ($\text{M} = \text{Al}^{3+}$, Ga^{3+} , In^{3+} and Ti^{4+}).

Finally, M_4L_4 tetrahedral assemblies **VIII** possess more accessible cavities than M_4L_6 cages of similar volume, an important distinction that influences guest exchange kinetics. This enhanced accessibility facilitates faster guest exchange, which is hypothesised to occur via a non-dissociative mechanism involving a concerted distortion and enlargement of the cage's inherent openings. This is supported by experimental observations, for instance, the absence of an encapsulated NMe_4^+ signal in the ^1H NMR spectrum of M_4L_4 cages **VIII** contrasts with the observation of a broadened signal of encapsulated NMe_4^+ in the M_4L_6 assemblies

III and **VI**. Such data suggest a more rapid guest exchange rate for the M_4L_4 cage architectures **VIII**, aligning with computational studies that demonstrate its superior cavity accessibility compared to M_4L_6 cages **III** and **IV**.

2.1.2.2 Octahedral M_6L_m Cages

There are different combinations of organic ligands and metal M^{n+} ions that self-assemble into this octahedral cage topology. The two most common stoichiometries are M_6L_4 and M_6L_8 , which will be discussed in this section.

Octahedral metal–organic cages represent an intriguing class of coordination–driven assemblies, where usually six metal M^{n+} ions are coordinated to four or eight organic ligands to form octahedral or close to octahedral cage topologies depending on the metal–ligand coordination environment. The metal M^{n+} centers in octahedral cages are typically Pd^{2+} ,^[12b, 32] Pt^{2+} ,^[12a] Zn^{2+} ,^[24c] Cu^{2+} ,^[33] Fe^{3+} ,^[34] Ga^{3+} ,^[34–35] or even lanthanide ions such as Lu, Yb and Eu,^[36] for their ability to form stable coordination bonds with monodentate, bidentate or multidentate ligands. These ligands often contain functional groups, such as pyridine, amine, carboxylate, or imine, which allow them to bind multiple metal ions, creating these octahedral cage frameworks during self-assembly.

Fujita reported the family of Pd_6L_4 metal–organic cages **IX–XI** employing different metal sources with two accessible cis-oriented coordination sites.^[32a, 37] These include $[(tmeda)Pd]^{2+}$ ($tmeda = N,N,N',N'$ -tetramethylethylenediamine), chiral $[(EtCyhex)Pd]^{2+}$ ($EtCyhex = cis-(1R,2R)-N,N'$ -diethyl-1,2-diaminocyclohexane), and $[(bipy)Pd]^{2+}$ ($bipy = 2,2'$ -bipyridine) derivatives (Figure 9A). These cages are analogues to Pd_6L_4 cage **II** and present the same shape, size, and binding capabilities.^[2] Moreover, Fujita described the specific conditions necessary to achieve the self-assembly of tritopic pyridine-based ligands to form robust coordination Pt_6L_4 cages. The resulting Pt–pyridine bonds are more stable and stay mostly fixed at room temperature. To facilitate this assembly, they applied heat to increase the lability of the Pt–N coordination bonds and used appropriate large templates (sodium adamantanecarboxylate), enabling the quantitative formation of the cage Pt_6L_4 .^[12a] This cage assembly is isostructural to the octahedral Pd_6L_4 cage,^[2] but it offers enhanced kinetic stability due to the robust nature of the Pt^{2+} –ligand interactions. In addition to these examples, Su developed novel heterometallic octahedral cages composed of Pd^{2+} and Ru^{2+} centres, constructed using a carefully designed C_3 -symmetric Ru^{2+} metalloligand.^[12b] This triangular metallo–ligand,

featuring three phenanthroline units for metal coordination and three free pyridine groups, self-assembled with Pd^{2+} ions at 80 °C to form the desired cage **XII** (Figure 9B). Binding studies using NMR spectroscopy confirmed that the $Pd_6Ru_8L_8$ cage **XII** can encapsulate varying amounts of aromatic guests such as phenanthrene, pyrene, and anthracene, with the encapsulation driven primarily by hydrophobic interactions. Notably, the design of this heterometallic cage **XII** allows it to shield light-sensitive molecules such as 2,2-dimethoxy-2-phenylacetophenone (DMPA), 1-hydroxycyclohexyl phenyl ketone (HCPK), and 2-hydroxy-2-methylpropiophenone (HMPP) within its cavity, as the surrounding ligand framework can effectively absorb UV and visible light, offering protection to the encapsulated guests.

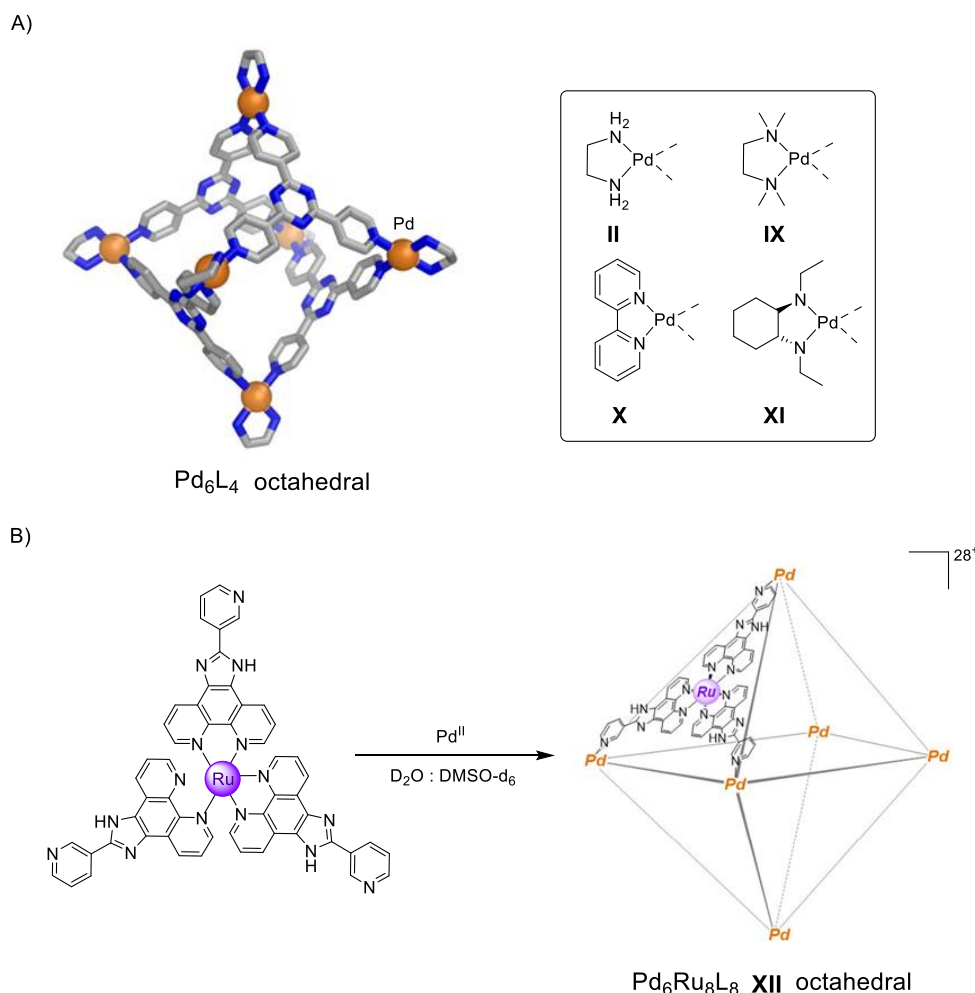


Figure 9. A) Octahedral Pd_6L_4 cages prepared using different cis-capped metallic corners in place of the $[(en)Pd]^{2+}$ units and B) self-assembly of a heterometallic $Pd_6Ru_8L_8$ cage **XII**.

2.1.2.3 Archimedean $M_{6n}L_m$ Cages

Archimedean polyhedra are convex polyhedra with equal-length edges, composed of regular polygons arranged identically at each vertex, though not necessarily all the same type (M_nL_{2n}). The design of these cages often involves linear or angular ligands, such as pyridine derivatives, that link metal M^{n+} centers positioned at the vertices. For instance, Pd^{2+} or Pt^{2+} ions, which prefer square-planar coordination, are commonly used to occupy the vertices, while ligands with appropriate binding angles bridge the metals along the edges. A notable example is the landmark work from Fujita, who successfully created large M_nL_{2n} ($n = 6, 12, 24, 30$, or 60) cages **XIII–XVII** using Pd^{2+} centres and linear bidentate ligands (Figure 10),^[5b, 38] producing assemblies with cavities large enough to encapsulate multiple guest molecules simultaneously.

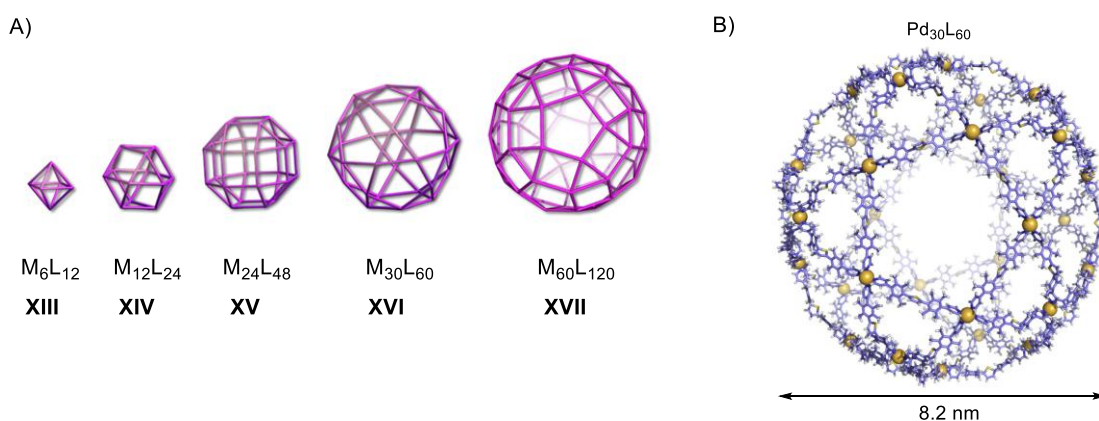


Figure 10. A) Family of different Archimedean Pd_nL_{2n} cages and B) the crystal structure of $Pd_{30}L_{60}$ polyhedra.

Inside Archimedean cages M_nL_{2n} , the large size, well-defined geometry, and spontaneous formation of $M_{12}L_{24}$ cages from twenty-four identical ligands make them highly suitable platforms for exploring the functionalisation of artificial cage architectures. Peripheral modification at the convex site of the ligand backbone (Figure 11A) leads to the formation of $M_{12}L_{24}$ assembly **XVIII** bearing twenty-four identical functional groups oriented toward the exterior of the cage. This strategy was initially demonstrated through the modification of $M_{12}L_{24}$ spheres with either twenty-four zinc porphyrin units or twenty-four fullerene moieties as a proof-of-concept.^[38a] Alternatively, modification at the concave site of the ligand scaffold led to cage $M_{12}L_{24}$ **XIX** (Figure 11B). This modification enables the tuning of

the internal cavity environment. This approach allows for the generation of structurally well-defined, discrete interior phases within the cage features that are inaccessible under conventional conditions. Using this methodology, spherical self-assembled inverse dendrimers have been successfully synthesised.^[39]

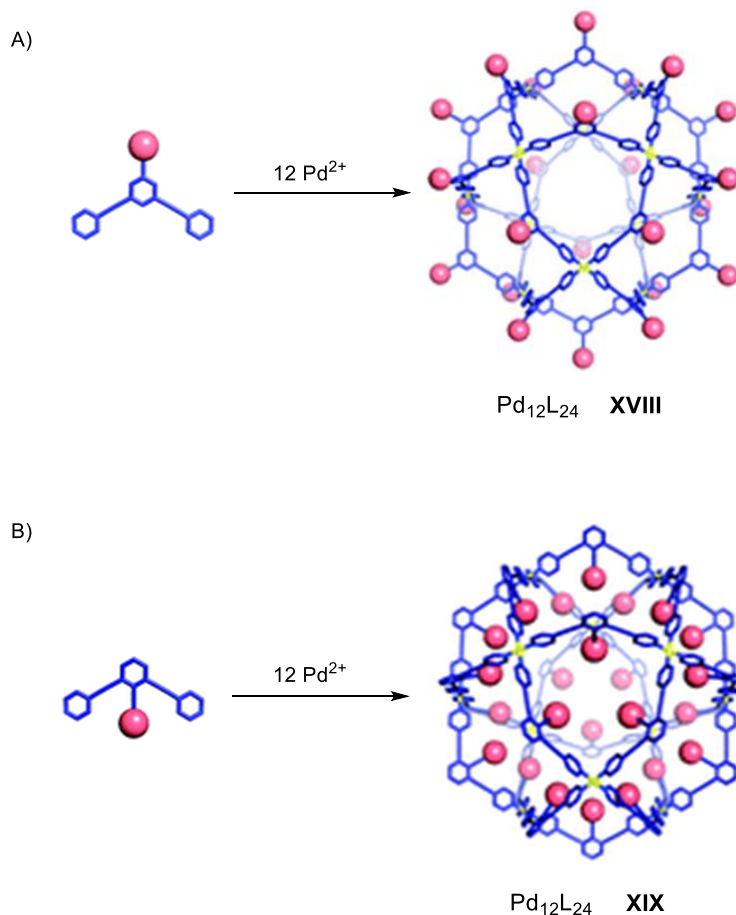


Figure 11. Modification of the bis(pyridine) ligand for A) exohedral and B) endohedral functionalisation of $M_{12}L_{24}$ spherical cages.

The installation of twenty-four functional groups on the outer surface of the $M_{12}L_{24}$ spherical framework via exohedral functionalisation (Figure 11A) can lead to a cooperative enhancement of weak intermolecular interactions. By carefully selecting the nature of the peripheral functional groups, these spherical assemblies can be tailored to exhibit strong and selective binding affinities toward a broad range of target substrates. As a demonstration of this strategy, a series of saccharide-functionalised $M_{12}L_{24}$ molecular spheres was synthesised using angular bis(pyridine) ligands bearing covalently bonded sugar moieties.

Through endohedral functionalisation (Figure 11B), multiple discrete and structurally well-defined microenvironments have been created within the interior of

the $M_{12}L_{24}$ framework. These confined internal phases enable the selective encapsulation of guest molecules within the spherical cavity. In contrast to previous systems, such as micelles,^[40] that exhibit structural heterogeneity, this approach offers a uniform and precisely engineered nanoscale environment. A series of functionalised $M_{12}L_{24}$ cages was synthesised using curved bis(pyridine) ligands containing poly(ethylene oxide) groups,^[41] perfluoroalkyl^[42] and alkyl chains,^[43] azobenzene^[44] and coronene^[45] units and peptide fragments.^[46] In this way, Archimedean cages Pd_nL_{2n} provide a platform for hierarchical self-assembly, where smaller polyhedral units assemble into even larger architectures, expanding the possibilities for nanomaterial design and host-guest chemistry.

2.1.3 Applications of M_4L_m , M_6L_m and $M_{6n}L_m$ Cages

2.1.3.1 Confined Reactivity and Catalysis

Supramolecular coordination M_nL_m cages have the ability to accelerate reactions in a way that mimics enzymatic catalysis.^[47] Like Nature's catalysts, they form hydrophobic pockets isolated from the surrounding media and enhance reaction rates and selectivity by stabilizing certain transition states^[48] that are not accessible through conventional catalytic pathways. Since the initial studies on guest binding by supramolecular metal-organic cages, researchers have recognised that their confined, hydrophobic cavities could potentially replicate the functions of enzyme active sites.^[49] Significant progress has been made toward this objective, though there is still room for improving their catalytic efficiency.^[50] In some cases, supramolecular metal-organic cages M_nL_m can regulate substrate access through secondary non-covalent interactions like hydrogen bonding, π -contacts or ionic forces akin to enzymes. Nevertheless, it is much more usual that substrate specificity is primarily dictated by the size and shape of the cavity.

Transition metals-based metal-organic cages have been widely used as supramolecular catalyst to perform distinct chemical reactions.^[12b, 18b, 51] One representative example is Rh-catalyzed hydroformylation reaction that increased its enantioselectivity toward branched aldehydes when they took place inside the supramolecular cage **XX** (Figure 12).^[51d] The supramolecular cage aggregate consists of a chiral phosphoramidate coordinated with Rh, which in turn binds to a Zn^{2+} -mixed porphyrin, forming the guest catalyst within the host coordination framework composed of four Pd^{2+} metal centres coordinated by triamine ligands yielding the cage $Pd_4L_4L'_2$ (Figure 12A). This system can catalyze the

hydroformylation of alkenes with enantiomeric excesses (e.e.) of up to 71%, significantly surpassing the free Rh–phosphoramidate catalyst (Figure 12B).

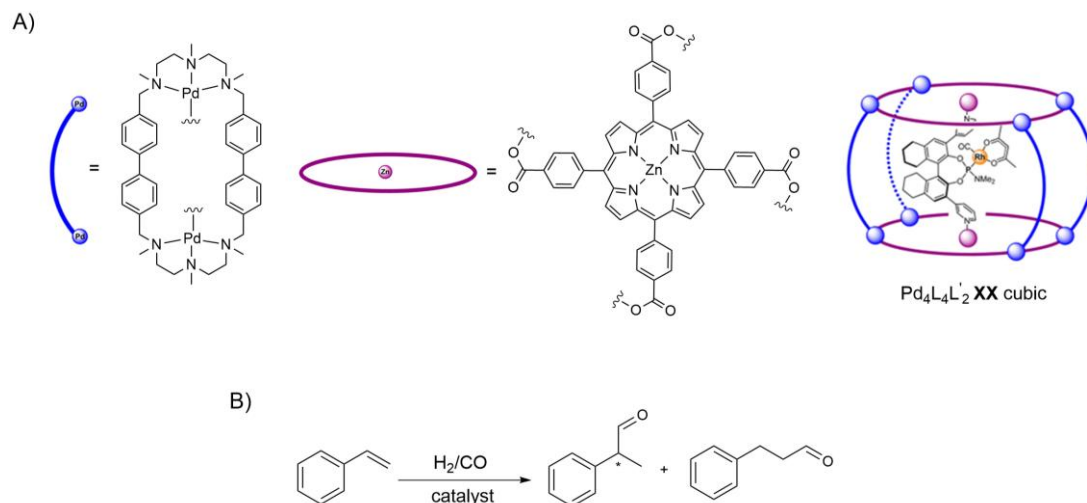


Figure 12. A) Supramolecular encapsulation of a Rh complex within the cage $Pd_4L_4L'_2$ **XIII** and B) hydroformylation reaction catalyzed by the encapsulated Rh complex within the cage **XX**.

In this thesis we will focus on main-group-based metal–organic cages that can act as supramolecular catalyst or stabilise reactive species. For instance, the supramolecular tetrahedral cage Ga_4L_6 **III** has proven to be very versatile in catalyzing various types of organic reactions. For instance, this cage is capable of catalyzing Aza–Cope–type reactions involving the unimolecular carbon–carbon bond-forming rearrangement of enammonium cations (Figure 13).^[52] It was observed that the use of the supramolecular cage **III** had an accelerating effect on the reaction by encapsulation of enammonium cations, in this way, a wide range of enammonium substrates with different size, shape, and substitution pattern were explored. For instance, the isopropyl substituted ($R_1 = H$, $R_2 = iPr$, $R_3 = H$) enammonium cation resulted in a rate increase by a factor of 854. The good results obtained also for other enammonium substrates demonstrated the scope and versatility of this supramolecular catalytic system.^[53]

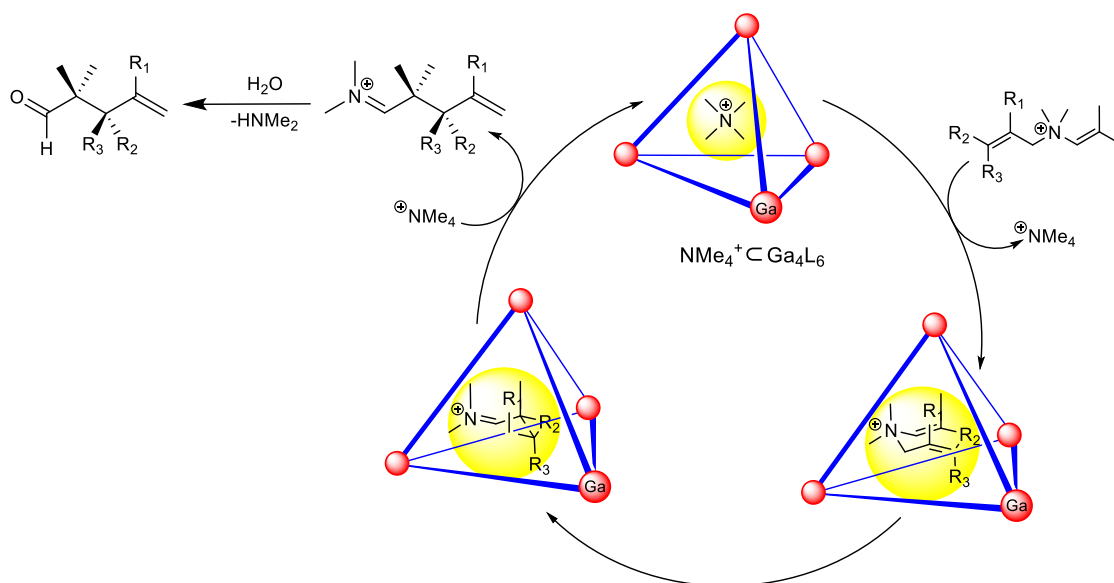


Figure 13. Aza-Cope-type reaction catalyzed by the supramolecular Ga_4L_6 cage **III**.

The same tetrahedral supramolecular cage Ga_4L_6 **III** exhibits a pronounced affinity for cationic guests, a property that can be strategically leveraged through the protonation of neutral or basic species. This protonation facilitates encapsulation, thereby enhancing the reactivity of the resulting charged intermediates. This approach was first demonstrated in the context of supramolecular confined catalysis of orthoester hydrolysis (Figure 14).^[53] Under normal conditions, orthoformate remains stable in aqueous solutions of neutral or basic pH; however, upon encapsulation within the Ga_4L_6 **III** cage, protonation of the oxygen atom is induced, which activates the substrate towards hydrolysis. This process proceeds catalytically, with a remarkable rate acceleration ($k_{cat}/k_{uncat} = 3900$), highlighting the potential of the cage **III** as an efficient platform for promoting transformations of otherwise inert substrates.^[54]

Additionally, the cage Ga_4L_6 **III** supramolecular cage has proven to be an effective catalyst in a variety of chemical transformations, including the hydrolysis of acetals.^[55] The kinetic analysis of the rate constants of the catalyzed and uncatalyzed reactions showed the cage Ga_4L_6 **III** is able to efficiently catalyze the hydrolysis of a variety of acetals, with rate accelerations of up to 10^3 . The acceleration rate is promoted by encapsulation of the neutral acetals which is driven by the hydrophobic effect. Another chemical transformation catalyzed by cage Ga_4L_6 **III** is Nazarov cyclisation.^[56] The cage **III** is capable of catalyzing the Nazarov cyclisation of 1,4-pentadien-3-ols by encapsulation of these substrates in water and mixed

water/DMSO. The rate of the catalyzed reaction is up to 2 100 000 times larger than that of the uncatalyzed reaction, representing the first instance of supramolecular catalysis that achieves rate enhancements comparable in size to those seen in enzymatic systems. Furthermore, the metal–organic cage **III** has enabled to accelerate intramolecular Prins reactions between alkenes and aldehydes or ketones, achieve selective monoterpene–like cyclisation reactions and retain the absolute configuration in nucleophilic substitutions.^[57]

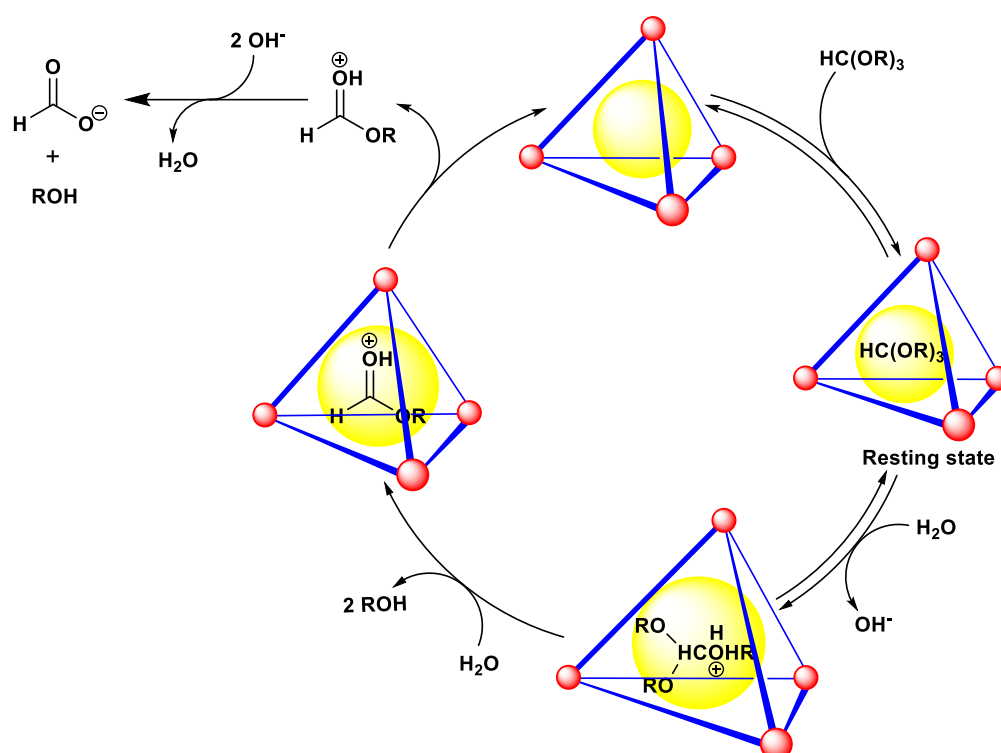


Figure 14. Hydrolysis reaction of orthoformates catalyzed by the supramolecular Ga_4L_6 cage **III**.

In organometallic transformations, the encapsulation effect of organometallic catalysts allows the stabilisation of positively charged catalytic intermediates that would be inaccessible in conventional catalytic conditions. This phenomenon enables the acceleration of organometallic catalytic reactions, and many of these concepts have been demonstrated using the Ga_4L_6 **III** tetrahedral cage.^[58] For example, the cage **III** catalyzes the reductive elimination of iodide from dimethyl monophosphine of Au^{3+} , generating ethane with a rate acceleration of 1.9×10^{-7} (Figure 15A).^[59] This rate acceleration is due to the stability of the positively charged transition state that occurs during supramolecular encapsulation.^[60] Similarly, the

rate of reductive elimination of an encapsulated Pt⁴⁺ complex increases by 2.6×10^{-4} (Figure 15B). Furthermore, the Cage **III** can promote the reaction between the Pt complex and Me₄Sn, resulting in the sp³–sp³ coupling of a tin alkyl and an alkyl halide (Figure 15C). In this transformation, the reductive elimination step of the catalytic cycle is accelerated by supramolecular encapsulation.^[61]

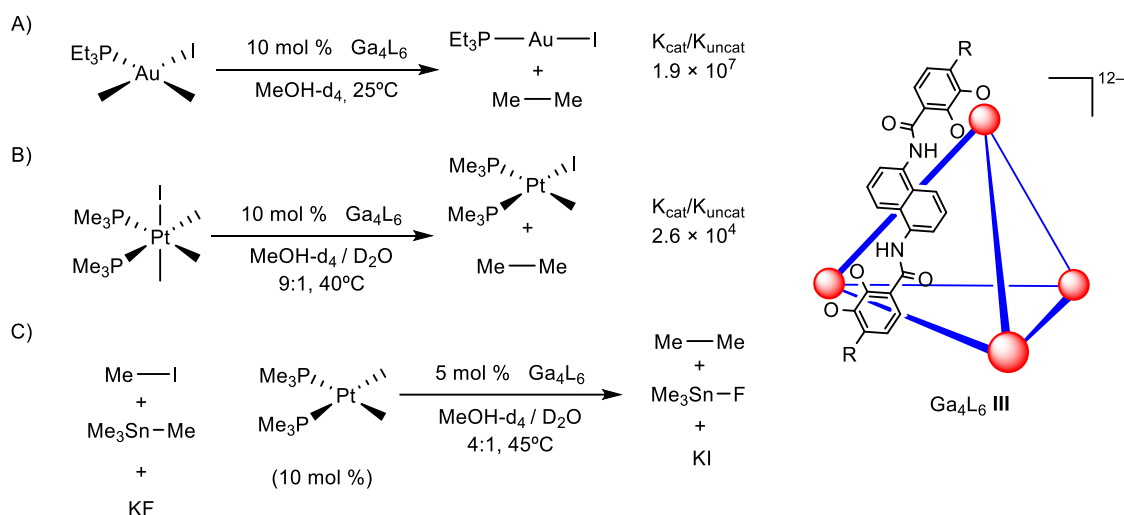


Figure 15. Examples of encapsulation and reactivity of encapsulated organometallic compounds within the Ga₄L₆ cage: A) Au complex, B) Pt complex, and C) intermolecular reactivity between Sn and Pt organometallic species.

These studies demonstrate that oxidative additions occur exclusively within the confines of the cage host, as the organometallic complexes are either poorly reactive or follow decomposition pathways in the absence of the supramolecular cage. On the other hand, the selectivity of catalytic transformations is also influenced by the nature of the microenvironment within the cavity of the supramolecular cage **III**.

2.1.3.2 Encapsulation of Reactive Organic Species

The design of supramolecular metal–organic M_nL_m cages is intrinsically dependent on the size of the guest compound to be encapsulated. In this context, supramolecular M_nL_m cages possess the ability to modulate the chemical equilibria involving the encapsulated species. For example, the tetrahedral cage Ga₄L₆ **III** can shift the equilibrium position between iminium cations (Figure 16A), amines (Figure 16B), and the corresponding carbonyl compound in aqueous solution.^[62] Iminium ions play a significant role in both biology and chemistry as key

intermediates in a range of enzyme-catalyzed processes and synthetic transformations. Methods to efficiently generate these reactive species in situ typically require acidic conditions and/or organic solvents. Moreover, in aqueous solution, iminium ions exist only transiently due to their high reactivity toward hydrolysis. Nevertheless, the cage Ga₄L₆ **III** can stabilise these species by encapsulation at room temperature in aqueous solution.

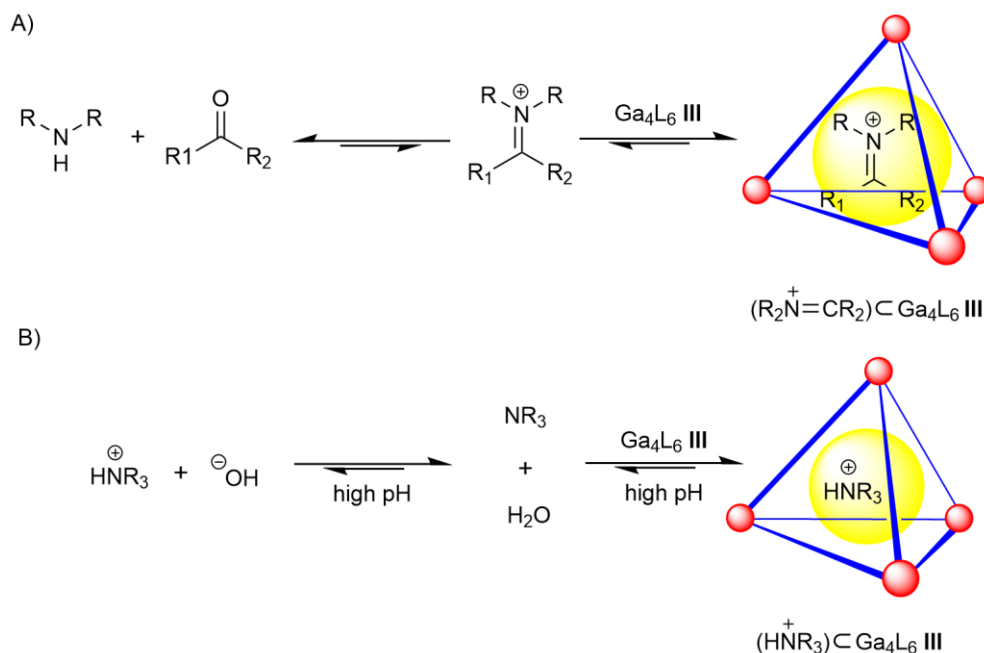


Figure 16. A) Stabilisation of iminium cation binding through encapsulation and B) enhancement of amine basicity through encapsulation.

The unfavourable equilibrium toward the generation of the iminium cation (Figure 16A) is due to the tendency of the iminium cation to undergo hydrolysis in aqueous solution. However, this effect is prevented through the encapsulation of this cation within the Ga₄L₆ cage **III**. A similar phenomenon can be observed between amines and their conjugate acids, such that this equilibrium is disturbed by the encapsulation of the ammonium salt (Figure 16B) in Ga₄L₆ cage.^[63] The negatively charged [Ga₄L₆]¹²⁻ cavity exhibits a strong preference for ammonium (R₄N⁺) cations, promoting protonation. Another interesting effect is that the basicity of the compounds to be encapsulated (their protonation) increases upon encapsulation compared to non-encapsulated substrates.^[64]

2.1.3.3 Gas Storage and Separation

Supramolecular metal-organic cages M_nL_m have gained significant attention for their potential in gas storage and separation applications. These cage structures,

characterised by their well-defined hydrophobic cavities, can selectively encapsulate gas molecules, facilitating efficient storage and separation processes. As a remarkable example, the truxene-faced Zn_4L_4 tetrahedral cage **XXI**, is able to bind small hydrocarbons in solution by hydrophobic effect (Figure 17A).^[65] By strategically introducing inward-facing ethyl groups on the truxene faces, the resulting lipophilic cavity was designed to encapsulate methane, ethane, and ethene through hydrophobic effect and van der Waals interactions at atmospheric pressure in acetonitrile, as well as in the amorphous solid state. Notably, gas capture exhibited different selectivity patterns in solution compared to the solid state. This selective binding behavior could be valuable in developing new methods for purifying methane and ethane for use as feedstocks in chemical synthesis.

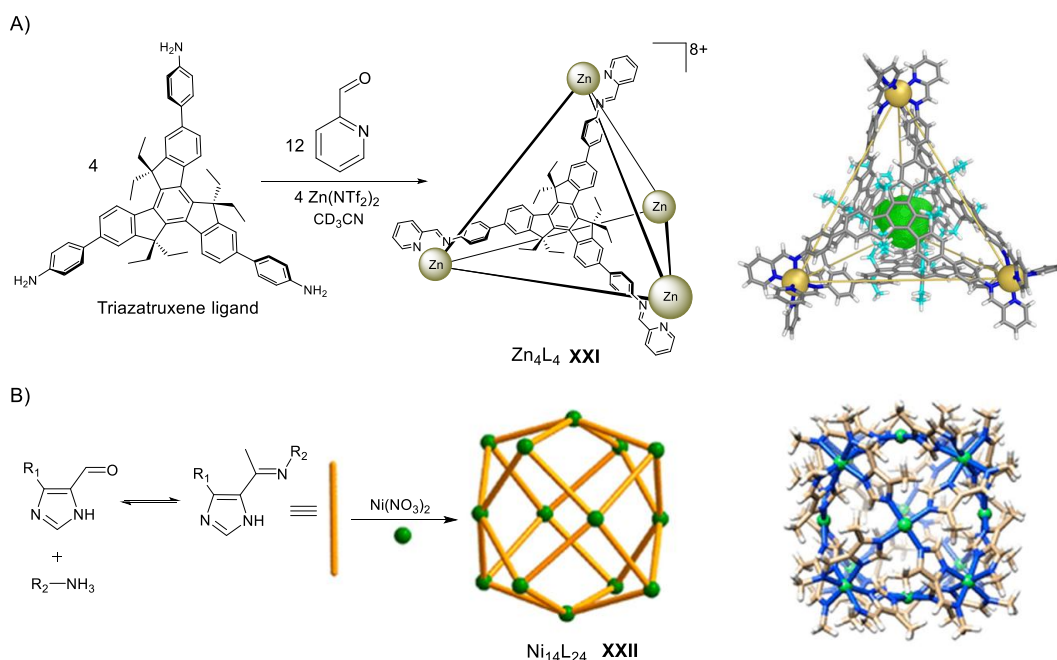


Figure 17. A) Subcomponent self-assembly of the tetrahedral Zn_4L_4 cage **XXI** and its crystal structure and B) self-assembly of the rhombic dodecahedral $Ni_{14}L_{24}$ cage **XXII** and its crystal structure.

In other studies, supramolecular metal-organic cages capable of encapsulating gases like CO_2 have been reported. For instance, a series of rhombic dodecahedral Ni-imidazolate cages $Ni_{14}L_{24}$ **XXII** have been synthesised with precisely controlled apertures for CO_2 capture (Figure 17B).^[66] Much like the breathing function of alveoli, CO_2 can pass through the dynamic aperture into the cages under a pressure of 2.0–3.0 bar in a methanol solution and is gradually released as the pressure decreases. In the solid state, CO_2 remains trapped within

cages under high pressures of 15.0–30.0 bar or under supercritical conditions. However, when the square-coordinated Ni²⁺ is replaced with Cu²⁺, the resulting Ni–Cu heteronuclear cage loses its ability to physically encapsulate CO₂, despite only a slight change in aperture size.

2.1.3.4 Biomedical Applications

Recent efforts have explored the use of coordination cages for biomedical applications.^[67] To achieve these applications, it has been essential to regulate the uptake and release of guest molecules through external stimuli.^[68] In aqueous environments, the simplest method for cargo release involves either partial or complete disassembly of the cage. Alternatively, strategies such as pH modulation or introducing competing guests have been employed to trigger guest release without compromising the integrity of the cage.

In drug delivery, Lippard developed a cisplatin Cl₂Pt(NH₃)₂ delivery system utilizing an octahedral cage Pt₆L₄ **XXIII** and Pt⁴⁺ prodrugs (Figure 18).^[69] The Pt₆L₄ octahedral structure **XXIII**, previously reported by Fujita,^[12a] served as the transport vehicle. This Pt²⁺–based cage is capable of encapsulating four equivalents of the adamantyl–appended Pt⁴⁺ prodrug, forming the corresponding host–guest complex (G)₄⊂Pt₆L₄. While Pt⁴⁺ prodrug has low water solubility (<500 mM) but becomes readily soluble when encapsulated. The mechanism for cisplatin release from the host–guest complex undergoes via reduction with ascorbic acid under neutral pH conditions, leading to the release of cisplatin Cl₂Pt(NH₃)₂, 1–adamantylamine, and succinic acid (Figure 18).

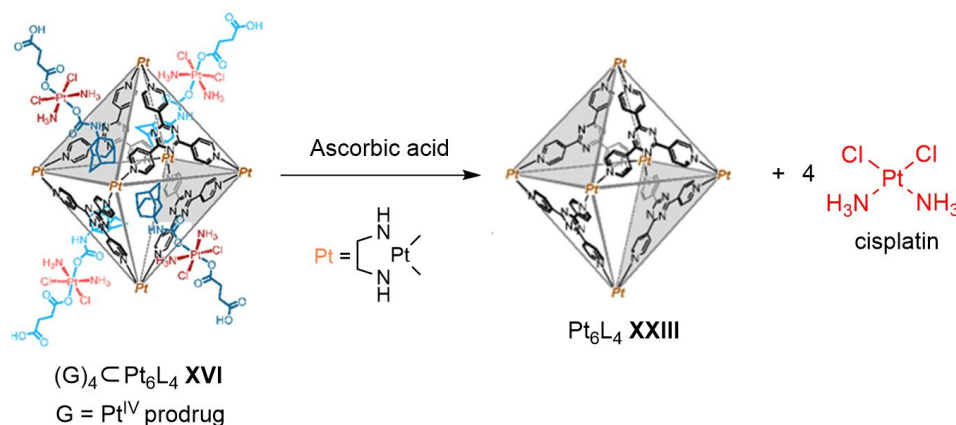


Figure 18. Release of cisplatin Cl₂Pt(NH₃)₂ upon reduction of the cage (G)₄⊂Pt₆L₄ **XXIII** by ascorbic acid.

The host–guest assembly $(G)_4\subset Pt_6L_4$ **XXIII** was tested for its anticancer activity across a range of human cancer cell lines. It showed μM potency against all evaluated cell lines, displaying effectiveness like cisplatin and outperforming both the prodrug and the cage individually. The action mechanism of the Pt host–guest array involves inducing programmed cell death through the intracellular release of cisplatin. The strong cytotoxicity of Pt host–guest system was linked to the enhanced cellular uptake of the cationic cage. Both Pt–cage and Pt–host–guest architecture showed a tenfold higher uptake compared to cisplatin or the Pt^{4+} prodrug.

In imaging, Lusby demonstrated that the kinetically stable cage Co_4L_6 **XXIV** can effectively encapsulate the γ -emitting $^{99m}TcO_4^-$ anion (Figure 19), a radioisotope of ^{99}Tc which is metastable, and it is in a higher energy state than regular ^{99}Tc emitting gamma radiation as it decays. This radioisotope is commonly used as precursor in clinical nuclear diagnostic imaging, under conditions suitable for in vivo administration.^[70] In vivo experiments in mice showed that $^{99m}TcO_4^- \subset Co_4L_6$ resulted in reduced thyroid and stomach uptake, and increased liver uptake (Figure 19) showing both the robustness of the cage Co_4L_6 **XXIV** in vivo and that binding the $[^{99m}Tc]TcO_4^-$ anion significantly affects its biodistribution. Consequently, this or similar systems could act as a universal platform for multiple imaging modalities and be expanded to the delivery of radiotherapeutic isotopes.

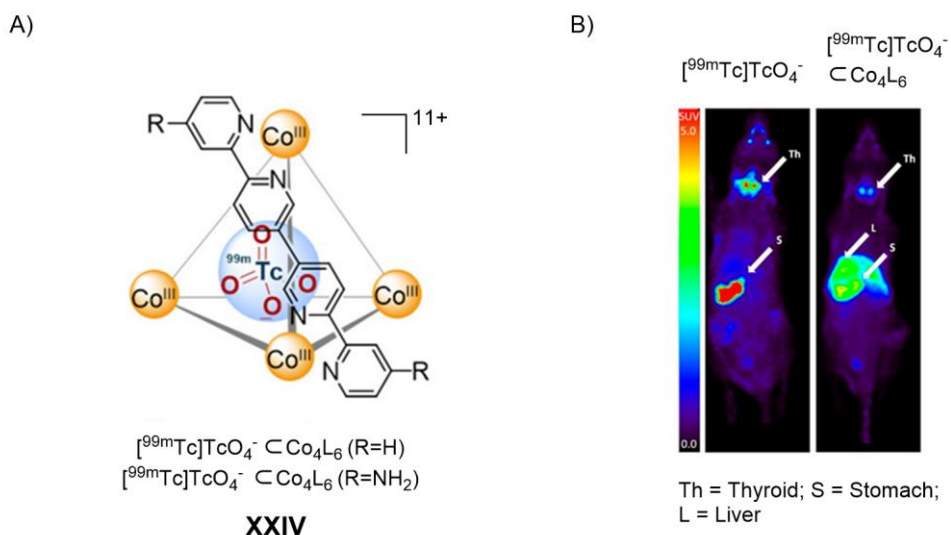


Figure 19. A) Chemical structure of $^{99m}TcO_4^- \subset Co_4L_6$ complexes and (B) comparison of $^{99m}TcO_4^-$ uptake in mice (left) vs $^{99m}TcO_4^- \subset Co_4L_6$ (right).

In the field of recognition and detection of biomolecules, metal–organic cages M_nL_m can bind a diverse array of biologically and medically active molecules. To

advance their use in applications such as highly sensitive analytical devices, these cages must exhibit a level of selectivity and affinity for specific substrates that closely resemble the precision and discrimination of protein receptors. In this context, Fujita showed that the internal cavities of supramolecular coordination cages can selectively recognise and encapsulate peptides of up to nine residues in aqueous environments, influencing their conformation (Figure 20). For example, inside a porphyrin-based water-soluble coordination cage $Pd_{12}L_{24}$ **XXV**, water interference in hydrogen-bond formation is minimised, allowing for the stabilisation of intrapeptide hydrogen bonds and promoting distinct folding patterns.^[71] Encapsulating larger biomolecules presents a greater challenge. However, leveraging the modular nature of self-assembly, successful encapsulation of a small protein was achieved, within synthetic $Pd_{12}L_{24}$ coordination nanocage in aqueous media. The process involved attaching the protein to a ditopic ligand, and upon introducing additional ligands and $Pd(NO_3)_2$ in D_2O/CD_3CN , the host structures spontaneously self-assembled around the protein (Figure 17).^[7a]

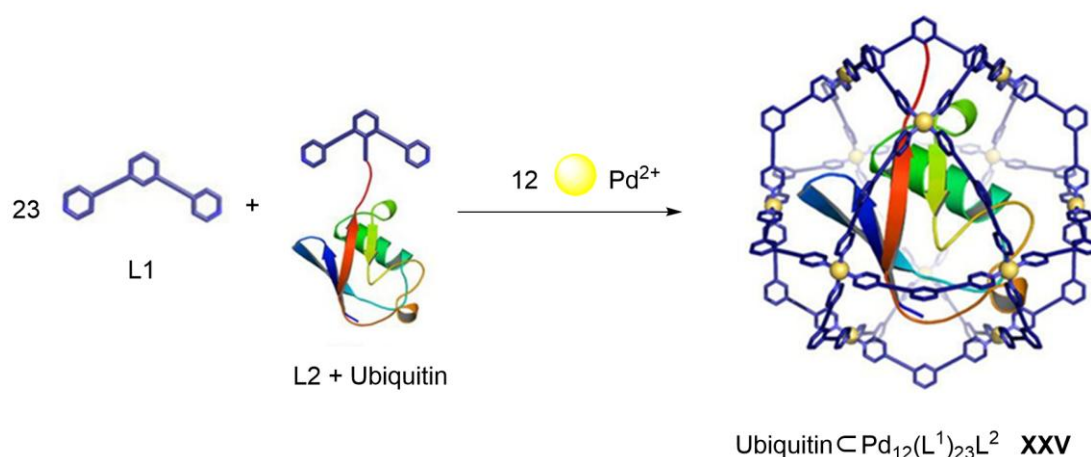


Figure 20. Aqueous self-assembly of ubiquitin-containing cage $Pd_{12}(L^1)_{23}L^2$ **XXV**.

The $Pd_{12}L_{24}$ cage featured nanometer-scale cavities that could be expanded up to 7.3 nm in diameter simply by extending the ligand arms. Due to the well-defined structure of this host framework, the protein-encapsulated complex was successfully analyzed using NMR spectroscopy, and X-ray crystallography. In this case, the covalent and irreversible attachment of ubiquitin to the interior of the $Pd_{12}L_{24}$ cage prevents its release or exchange. These synthetic self-assembled cages have the potential to modulate biomolecule properties and influence their resistance to enzymatic degradation.

Building on the successful synthesis of M_2L_3 cages employing ditopic 1,2,3-triazole–catechol ligands described in Chapter 1, and motivated by the promising catalytic potential of tetrahedral main–group–based cages as well as the limited number of reported examples of these cages featuring well–defined internal cavities, this Chapter explores a systematic approach toward the synthesis of tritopic 1,2,3-triazole–catechol ligands which incorporate spacer cores with varying rigidity and electronic characteristics to construct new tetrahedral main–group–based cages utilizing Al^{3+} and Ga^{3+} ions, with an emphasis on tuning host–guest properties.

2.2 Objectives

This Chapter aims to define general design rules for the self-assembly of tetrahedral M₄L₄ coordination cages assembled from main-group nodes (Al³⁺ and Ga³⁺) and tritopic 1,2,3-triazole-catechol and -naphthalenediol ligands. We will design and synthesise a family of new tritopic ligands **H₆L⁶–H₆L¹⁰** via CuAAC click chemistry from tris-alkyne and aromatic azide (catechol and naphthalenediol) precursors, enabling systematic modulation of donor topology and radial/steric bulk in the derived Al₄L₄ Ga₄L₄ cages. Following deprotection of catechol functions, controlled self-assembly with Al³⁺ and Ga³⁺ (M(acac)₃) under basic conditions (KOH) will target anionic cages [M₄L₄]¹²⁻. We will also probe the influence of K⁺ vs R₄N⁺ counter ions during self-assembly to assess the heterometallic cavity organisation in (MK)₄L₄ cages (e.g., K⁺ encapsulation). Characterisation will be pursued in solution through ¹H/¹³C NMR and DOSY NMR to establish cage size, integrity, and dynamics. In the solid state, single-crystal X-ray diffraction to determine the cages' geometries and counter ion encapsulation, and in the gas phase, high-resolution ESI-HRMS to define charge states and cage M_nL_m compositions. Where informative, computational structural modelling will be used to rationalise cage dimensions and “breathing” through solvent-dependent expansion/contraction.

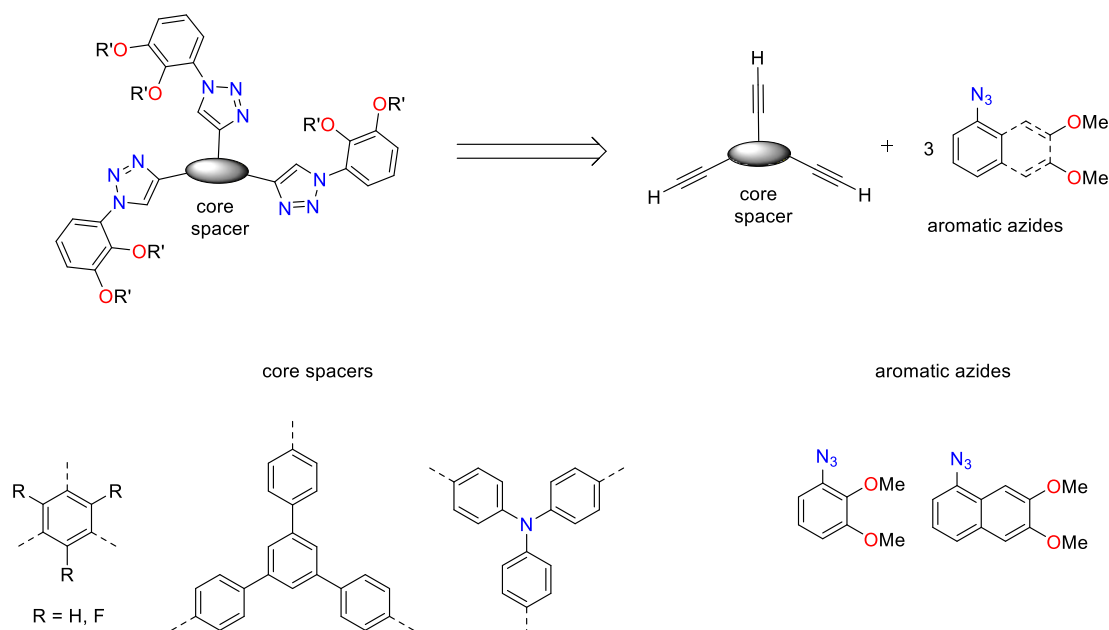
A second main objective is to quantify host-guest recognition in water across the M₄L₄ series and correlate cavity metrics with binding performance. We will examine the encapsulation of ammonium guests R₄N⁺ of increasing size (Me₄N⁺, Et₄N⁺, Pr₄N⁺, Bu₄N⁺) using NMR (¹H, NOESY, DOSY) and isothermal titration calorimetry (ITC). Particular attention will be paid to cavity size/shape tailored by the ligands **H₆L⁶–H₆L¹⁰**, binding stoichiometries and affinities (*K_a*), and the driving forces (Δ*H*, TΔ*S* and Δ*G*) behind the encapsulation processes. We will further compare the cages Al₄L₄ and Ga₄L₄ to test for potential metal-dependent selectivity in host-guest chemistry and to delineate the limits of encapsulation across the R₄N⁺ size series.

This *Chapter II* will deliver a proof-of-principle for the efficient, selective self-assembly of new tritopic 1,2,3-triazole-catechol and -naphthalene-diol ligands into main-group metal Al₄L₄ and Ga₄L₄ cages, together with a coherent characterisation across solution/solid/gas phases and a quantitative framework linking cavity engineering and metal identity to host-guest thermodynamics. These principles aim to underpin future applications in supramolecular encapsulation and catalysis.

2.3 Results and Discussion

This Chapter II outlines the synthetic strategies employed to prepare a series of novel tritopic 1,2,3-triazole–catechol ligands. These ligands are synthesised using various simple aromatic alkynes and azides as precursors. The terminal catechol groups are introduced to enable strong coordination with oxophilic M^{3+} ions (Al^{3+} and Ga^{3+}) while the triazole units contribute both rigidity and conformational adaptability, as well as offering potential for diverse non-covalent interactions. Variation in the central spacer cores allows for precise tuning of the overall geometry and flexibility of these tritopic ligands. These tris(1,2,3-triazoles) ligands are subsequently utilised in the self-assembly of anionic tetrahedral M_4L_4 -type supramolecular cages with Al^{3+} and Ga^{3+} ions. The discussion of the results is organised into three main sections. First, the synthesis and full characterisation of the new tritopic 1,2,3-triazole–catechol ligands. Then, the synthesis, characterisation and structural analysis of Al_4L_4 and Ga_4L_4 cage assemblies using ligands with varying spacer lengths and flexibilities. Finally, the investigation of host–guest properties of selected M_4L_4 cages using tetraalkylammonium (R_4N^+) ions of different sizes as model guest probes, with binding behaviour analyzed by NMR spectroscopy and isothermal titration calorimetry (ITC).

For the preparation of the tritopic 1,2,3-triazole ligands, we have used the same synthetic strategy employed in Chapter I but employing a three-fold copper-catalyzed cycloaddition (CuAAC) reaction between azides and alkynes (Scheme 1). To achieve this core goal, a series of different simple alkynes and organic azides have been prepared using adaptations or modifications of previously reported methods, described in the following sections.



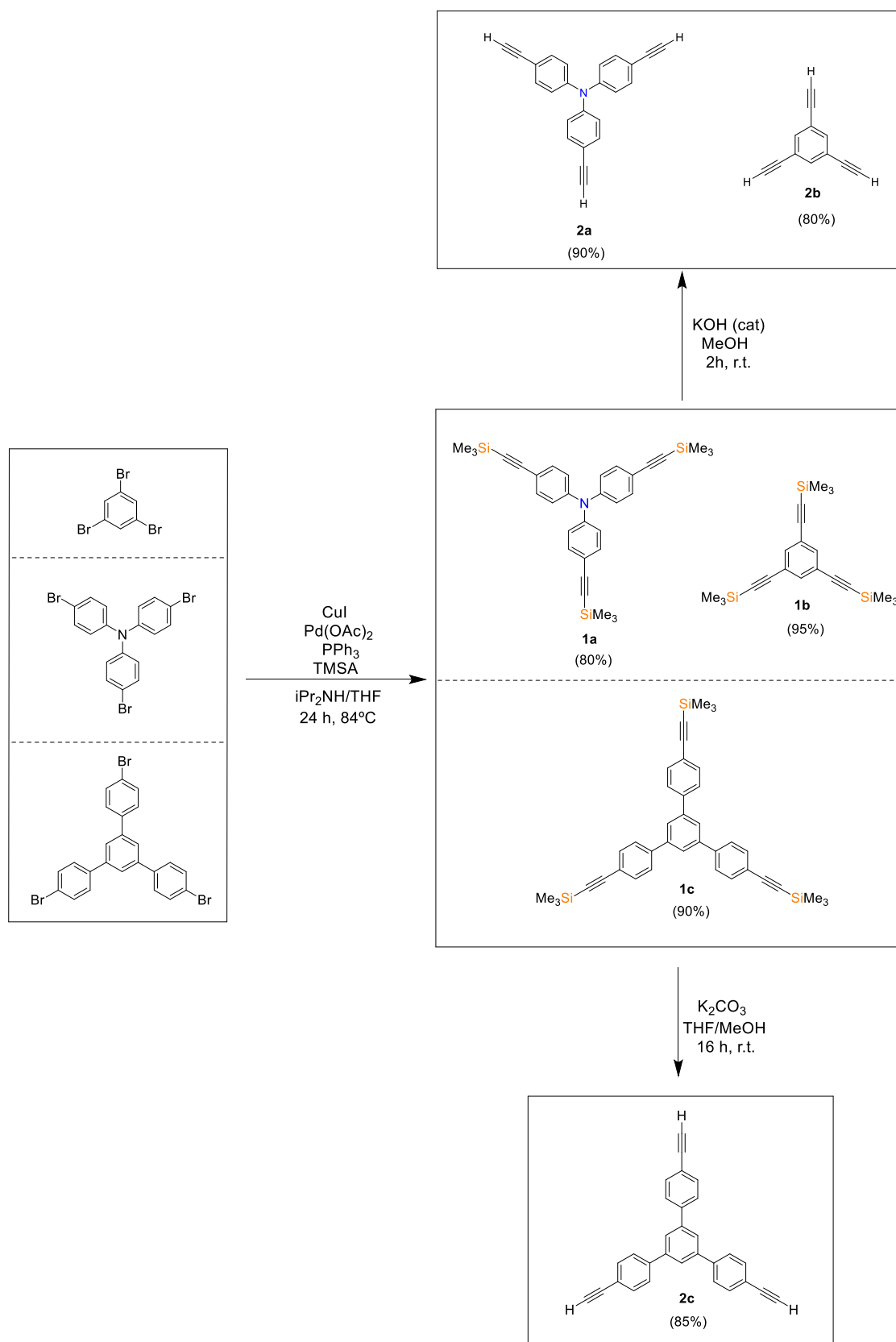
Scheme 1. Retrosynthetic analysis for the preparation of tritopic 1,2,3-triazole ligands.

2.3.1 Synthesis and Characterisation of Tris-Alkyne Precursors

To obtain the terminal alkynes **2a–2c** (Scheme 2), we first synthesised the starting materials **1a–1c**. The alkynes **2a–2c** were prepared following a three-fold Pd- and Cu-catalyzed Sonogashira cross-coupling reaction between the corresponding tri-bromo aromatic core and the alkyne trimethylsilylacetylene, followed by deprotection of the trimethylsilyl group. The synthesis of products **1a–1c** was carried out through the reaction of the commercial aryl bromides 1,3,5-tribromobenzene, tris(4-bromophenyl)amine and 4,4''-dibromo-5'-(4-bromophenyl)-1,1':3',1''-terphenyl and trimethylsilylacetylene. In these reactions, a slight excess of the alkyne (4 equivalents relative to the brominated arene) was used to optimise the yield and avoid mixtures. Reactions were performed at 84°C for 24 hours in the presence of the catalysts CuI (1.2 mol%) and Pd(OAc)₂ (1 mol%) and triphenylphosphine (PPh₃) in a 1:4 mixture of iPr₂NH/THF. A TLC monitoring of the resulting reaction mixtures indicated the quantitative formation of products **1a–1c**. Moreover, ¹H NMR analysis, confirmed the formation of these products observing a new signal between δ 0–0.6 ppm that correspond to trimethylsilyl groups. The reaction mixtures were filtered to remove inorganic salts (isopropylammonium bromide), and after removing the volatiles from the crudes, products **1a–1c** were obtained in good yields (80–95%).

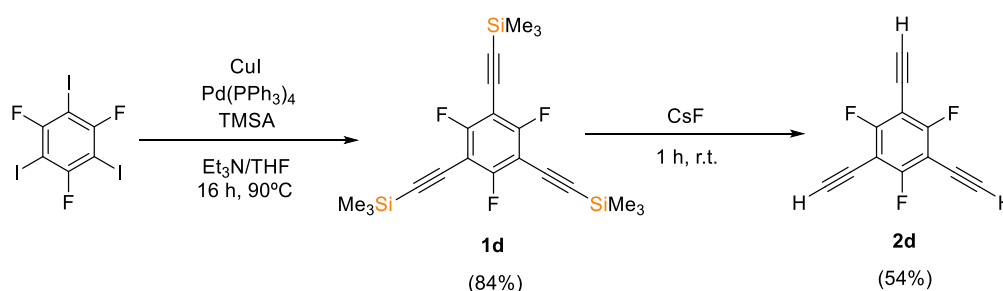
The products obtained **1a–1c** were of sufficient purity by ¹H NMR for their proper use in the subsequent synthetic step to obtain the primary alkynes **2b–2c**. The ¹H NMR of the products **1a–1c** are consistent with those previously reported.^[72]

Once the trimethylsilylated derivatives of the alkynes **1a–1c** were prepared, they were used for the preparation of the primary alkynes **2a–2c** using different conditions that will be discussed in the present section. The synthesis of products **2a** and **2b** were carried out via protodesilylation of **1a** and **1b** with KOH in MeOH (Scheme 2). A catalytic amount of KOH (1.4 mol%) was used in these reactions. After 2 hours, the reaction mixtures were filtered, and all the volatiles were removed under vacuum. The preparation of product **2c** was performed via protodesilylation of **1c** with K₂CO₃ (7 eq) in a mixture MeOH/THF (4:1) (Scheme 2) following the synthetic protocol.^[72] After 16 hours, DCM was added and the organic phase was washed with water, separated, the organic layer dried over Na₂SO₄, filtered and concentrated. Product **2a** was purified by column chromatography on silica gel using a mixture hexane/DCM (9:1) yielding **2a** (R_f = 0.3) in 90% yield after removing all volatiles. **2b** was purified in a similar manner by column chromatography on silica gel using hexane as eluent (R_f = 0.6) with a yield of 80%. Finally, product **2c** (R_f = 0.66) was purified by column chromatography using as eluent a mixture hexane/DCM (10:3) with a yield of 85%. ¹H NMR analysis confirmed the formation of the products **2a–2c** observing the disappearance of the signals between δ 0–0.6 ppm (trimethylsilyl groups) and the appearance of a new signal between δ 3–4 ppm that correspond to the protons of alkyne groups. The ¹H NMR of the products **2a–2c** are consistent with those reported.^[72]



Scheme 2. Preparation of alkynes **2a–2c** via Sonogashira couplings following and subsequent protodesilylation.

However, because the fluorinated aryl halide is deactivated by an inductive effect in the Sonogashira reaction, it was necessary to use the iodinated derivative instead of the brominated derivative in this reaction. Moreover, specific conditions such as a different palladium catalyst (Pd(PPh₃)₄ or a large excess of TMSA (1:6 stoichiometry) were chosen to promote this reaction.^[72d] Therefore, the synthesis of compound **1d** (Scheme 3) was carried out through the reaction of the aryl iodide (1,3,5-trifluoro-2,4,6-triiodobenzene) with trimethylsilylacetylene (**6** eq). The reaction, catalyzed by CuI and Pd(PPh₃)₄ (10 mol%), was conducted under a nitrogen atmosphere in a 1:1 mixture of Et₃N/THF, which is commonly used in Cu- and Pd-catalyzed Sonogashira coupling reactions. This reaction that requires thermal activation, was maintained at 90°C for 16 hours. ¹H and ¹⁹F NMR analysis confirmed the successful formation of product **1d** observing a new signal between δ 0–0.6 ppm in ¹H NMR that corresponds to trimethylsilyl groups. The inorganic salts (Et₃NHI) present in the reaction mixture were removed by filtration and compound **1d** was purified through column chromatography using n-hexane as the eluent (R_f = 0.6). Finally, after removing the volatiles from the crude product, product **1d** was obtained as a very pale-yellow solid with a yield of 84%. The reaction presented a particular challenge due to the electron-withdrawing nature of the fluorine groups on the benzene ring, which obstructs the Sonogashira coupling. Generally, electron-rich rings facilitate this type of coupling. However, the electron-withdrawing effect of the fluorinated groups leads to a redistribution of electron density in the benzene ring, causing a deactivating effect on the Sonogashira reaction.



Scheme 3. Preparation of alkyne **2d** via Sonogashira coupling and subsequent protodesilylation.

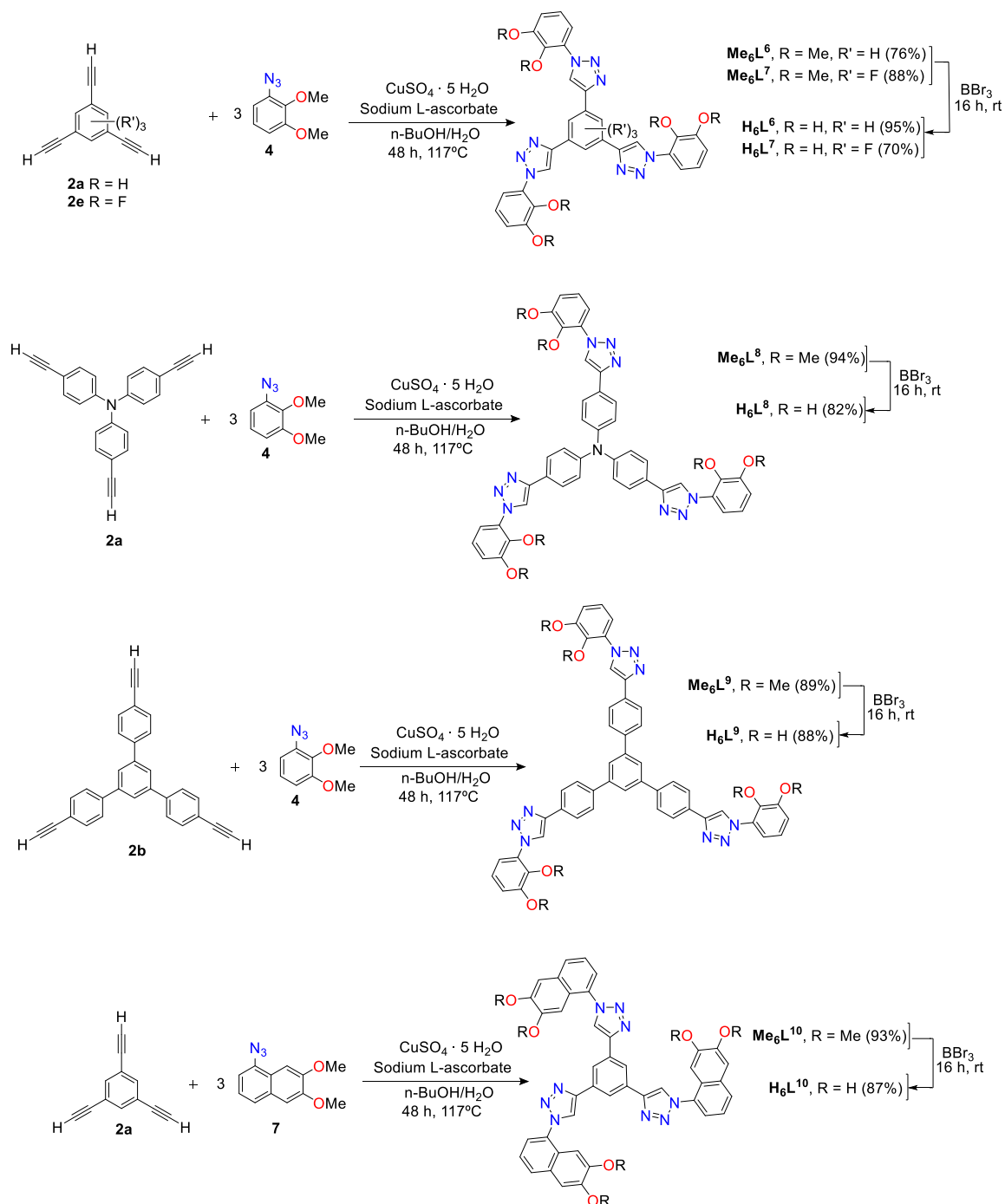
Product **2d** was obtained by deprotecting the TMS group in the presence of CsF (3.1 eq) and a THF/EtOH solvent mixture, at room temperature under a nitrogen atmosphere (Scheme 3). After 1 hour, the volatiles were removed under vacuum,

and product **2d** ($R_f = 0.3$) was purified through column chromatography using *n*-hexane as the eluent. Once chromatography was completed and the volatiles were removed, compound **2d** was obtained as a white solid with a yield of 54%. The ¹H NMR of the product **2d** is consistent with that reported.^[72d]

2.3.2 Synthesis and Characterisation of Tritopic Ligands H₆L⁶–H₆L¹⁰

The synthesis of the new tritopic ligands H₆L⁶–H₆L¹⁰ began preparing the methylated precursors Me₆L⁶–Me₆L¹⁰. For this purpose, we started with the corresponding alkynes **2a–2d**, and 3 equivalents of the aromatic azides **4** and **7** previously described in Chapter I. For the preparation of Me₆L⁶–Me₆L¹⁰, we chose the Cu-catalyzed coupling reaction, employing CuSO₄·(H₂O)₅ and sodium ascorbate at 117°C in an *n*-BuOH/H₂O mixture. The reflux was maintained for 48 hours, followed by confirmation of reaction completion via TLC and subsequent extraction with CHCl₃, led to the formation of ligands Me₆L⁶–Me₆L¹⁰ with yields between 76–94% (Scheme 4). To confirm the structure of Me₆L⁶–Me₆L¹⁰, we studied their ¹H NMR spectrum observing new signals between δ 8–9 ppm that corresponded to triazole protons as well as the disappearance of the signal of alkynes between δ 3–4 ppm corroborating the formation of the products Me₆L⁶–Me₆L¹⁰. These 1,2,3-triazoles were obtained with sufficient purity, measured by elemental analysis and ¹H NMR, for their proper use in the next reaction.

The synthesis of ligands H₆L⁶–H₆L¹⁰ (Scheme 4) involved the step of deprotecting the methoxy groups of the precursors Me₆L⁶–Me₆L¹⁰. This reaction was carried out under a nitrogen atmosphere using boron tribromide BBr₃ in distilled DCM at –78°C and was allowed to warm to room temperature. The evaporation of DCM and subsequent neutralisation of excess BBr₃ with water, followed by refluxing the product at 100°C for 2 hours led to the precipitation of compounds H₆L⁶–H₆L¹⁰ that were isolated by filtration. To perform these reactions, we followed the same synthetic procedures employed in the previous Chapters to deprotect methoxy groups, obtaining yields ranging from 70 to 95%. ¹H NMR analysis of the ligands H₆L⁶–H₆L¹⁰ products showed the disappearance of the signals between δ 3.7–4 ppm that correspond to methoxy group protons and the appearance of new signals between δ 9.4–10–5 ppm that correspond to catechol protons, confirming the successful formation of H₆L⁶–H₆L¹⁰.



Scheme 4. Preparation of compounds **Me₆L⁶–Me₆L¹⁰** and ligands **H₆L⁶–H₆L¹⁰**.

ESI–HRMS of **Me₆L⁶–Me₆L¹⁰** and **H₆L⁶–H₆L¹⁰** corroborate their successful synthesis as well. The distribution of m/z peaks indicates ion–pairing associations of **Me₆L⁷** and **Me₆L⁸** with 1 Na^+ ion forming the corresponding cationic adducts at m/z values of 764.2146 (calcd. 764.2163) and 877.3157 (calcd. 877.3181) respectively. However, **Me₆L⁶**, **Me₆L⁹** and **Me₆L¹⁰** form the corresponding cationic adducts with 1 H^+ at m/z values of 688.2630 (calcd. 688.2627), 916.3576 (calcd. 916.3566) and

838.3098 (calcd. 838.3096) respectively. **H₆L⁶** and **H₆L⁹** form cationic adducts with 1 H⁺ at m/z values of 604.1692 (calcd 604.1688) and 832.2602 (calcd 832.2627) respectively, whereas **H₆L⁷**, **H₆L⁸** and **H₆L¹⁰** form adducts with 1 Na⁺ ion at m/z values of 680.1247 (calcd. 680.1224), 793.2246 (calcd. 793.2242) and 776.1939 (calcd. 776.1977) respectively. Moreover, the observed isotope patterns matched well with the calculated distributions, confirming both **Me₆L⁶–Me₆L¹⁰** and **H₆L⁶–H₆L¹⁰** composition.

To further study their structures and suitability to form supramolecular architectures, we obtained crystals of **Me₆L⁶** and **Me₆L⁹** for X-ray analyses. Several attempts to crystallise **Me₆L⁷**, **Me₆L⁸**, **Me₆L¹⁰** and **H₆L⁶–H₆L¹⁰** were unsuccessful. High-quality block crystals of **Me₆L⁶** were obtained by slow evaporation of a concentrated solution of **Me₆L⁶** in AcOEt. Nevertheless, **Me₆L⁹** crystals were achieved by layering of hexane into a concentrated DCM solution of **Me₆L⁹**.

The X-ray structure of **Me₆L⁶** (Figure 21A) shows the triazole rings almost coplanar with respect to the central phenylene ring C₆H₃, with torsion angles nearly 180° (163.98(16)–178.58(19)°). The rings containing the methoxy groups C₆H₃(OMe)₂ are rotated relative to this aromatic core plane with torsion angles of 47.9(2)–66.73(19)°. In addition, the triazole CH groups are oriented towards the oxygen of the nearest methoxy group at distances of 2.7931(12)–3.1251(13) Å (triazole–CH···OMe), allowing for weak electrostatic interactions between them. This ligand exhibits a triangular arrangement with terminal catechols at distances of 12.5321(17)–18.1290(16) Å, these distances were measured between the oxygens of the two external –OMe groups of the C₆H₃(OMe)₂ rings. The arrangement of **Me₆L⁶** is ideally spaced for coordination metal nodes.

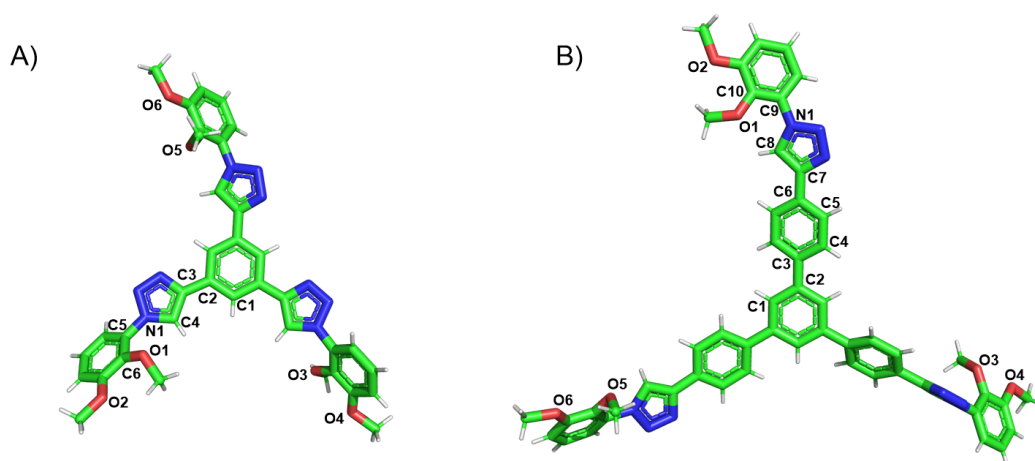


Figure 21. Molecular structure of A) **Me₆L⁶** and B) **Me₆L⁹**. Selected bond lengths (Å) and angles (°): for **Me₆L⁶**, O2–O4 12.5321(17), O4–O6 18.1290(16), triazole–CH···OMe 2.7931(12)–3.1251(13); torsion angles C1–C2–C3–C4 163.98(16)–178.58(19), C4–N1–C5–C6 47.9(2)–66.73(19); for **Me₆L⁹**, O2–O6 18.140(6), O2–O4 24.180(5), triazole–CH···OMe 2.574(3)–2.927(3); torsion angles C1–C2–C3–C4 139.1(3)–166.0(3), C5–C6–C7–C8 146.4(3)–170.4(3), C8–N1–C9–C10 39.3(5)–56.8(5). Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The ligand **Me₆L⁹** (Figure 21B) exhibit phenylene rings C_6H_4 with torsion angles of 139.1(3)–166.0(3)° with respect to the central aromatic C_6H_3 ring. Moreover, the triazole rings are twisted with respect to the phenylene rings C_6H_4 with torsion angles of 146.4(3)–170.4(3)° as well as the rings containing the methoxy groups $C_6H_3(OMe)_2$ are rotated relative to triazole rings with torsion angles of 39.3(5)–56.8(5)°. Like in **Me₆L⁶**, weak electrostatic interactions between the triazole CH groups and the oxygen of the nearest methoxy group (triazole–CH···OMe) were observed at distances of 2.574(3)–2.927(3) Å. Akin to **Me₆L⁶**, this ligand shows a triangular arrangement but with larger distances between its terminal catechols (18.140(6)–24.180(5) Å). The arrangement and size of **Me₆L⁹** provides high potential to form large metal–organic cages.

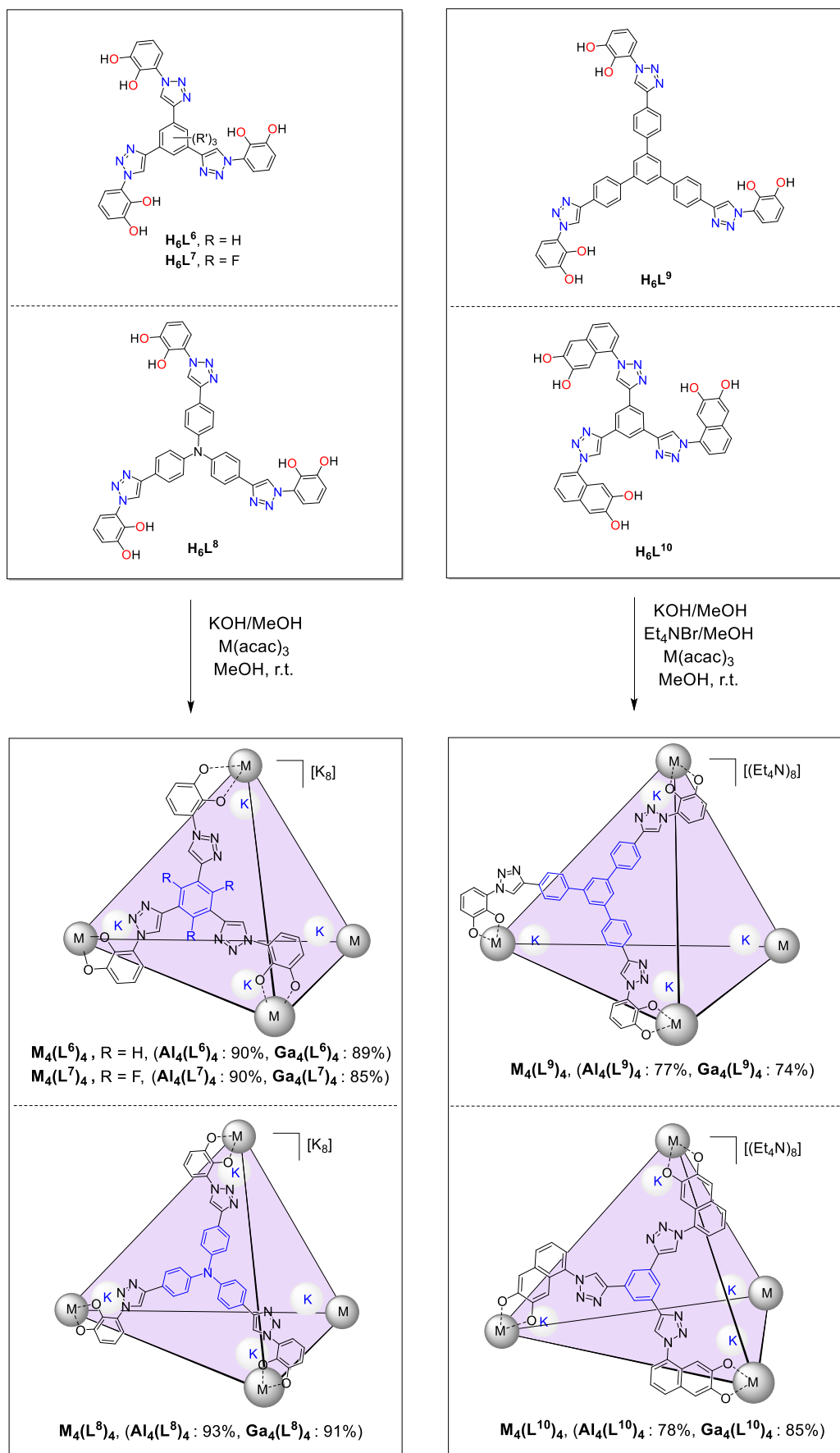
2.3.3 Supramolecular Self–Assembly of Tetrahedral M_4L_4 Cages

With the successful synthesis of tritopic ligands **H₆L⁶**–**H₆L¹⁰** which are based on 1,2,3–triazoles with catechol groups that offer strong binding sites for oxophilic M^{3+} ions, in this section of the Chapter, we will explore the coordination chemistry of

$H_6L^6-H_6L^{10}$ with Al^{3+} and Ga^{3+} metal ions with the aim to form novel supramolecular cage architectures.

The supramolecular self-assembly of tetranuclear cages $M_4(L^6)_4$, $M_4(L^7)_4$ and $M_4(L^8)_4$ began preparing a suspension of the corresponding ligands in distilled and deoxygenated MeOH under a nitrogen atmosphere (Scheme 5). The addition of KOH/MeOH led to a brown solution of deprotonated ligand after 20 minutes, then, $M(acac)_3$ ($M = Al, Ga$) powder was added. The reaction was then stirred overnight at room temperature allowing the formation of the cages $M_4(L^6)_4$, $M_4(L^7)_4$ and $M_4(L^8)_4$. The coordination cage $Ga_4(L^6)_4$ precipitated as a brown solid in the reaction mixture, whereas $Al_4(L^6)_4$, $M_4(L^7)_4$ and $M_4(L^8)_4$, were precipitated as brown silky solids concentrating their solutions under reduced pressure and adding then Et_2O to aid precipitation of the solids. The cages were isolated as potassium salts $[M_4(L^6)_4][K]_{12}$, $[M_4(L^7)_4][K]_{12}$ and $[M_4(L^8)_4][K]_{12}$ after filtration, and dried under vacuum, with high yields between 85% and 93%.

For the synthesis of $M_4(L^9)_4$ and $M_4(L^{10})_4$ (Scheme 5), we prepared a suspension of the corresponding ligands H_6L^n in distilled and deoxygenated MeOH under a nitrogen gas atmosphere. The addition of KOH/MeOH led to a brown solution of $(L^n)^{6-}$ after 20 minutes, then, a solution of $Et_4NBr/MeOH$ and $M(acac)_3$ powder was added. After 16 hours, the cages $M_4(L^9)_4$ and $M_4(L^{10})_4$ precipitated in the reaction mixture as their corresponding ammonium and potassium salts. Cages $[M_4(L^9)_4][Et_4N]_8[K]_4$ and $[M_4(L^{10})_4][Et_4N]_8[K]_4$ were isolated by filtration and dried under vacuum with high yields of 78% and 93% respectively. Cages $M_4(L^9)_4$ and $M_4(L^{10})_4$ need the presence of Et_4N^+ ions in addition to K^+ ions to aid precipitation. Therefore, the addition of a solution of $Et_4NBr/MeOH$ allowed the precipitation and efficient isolation of the cages $M_4(L^9)_4$ and $M_4(L^{10})_4$ as their potassium salts are highly soluble, in contrast to the other cage derivatives discussed above. The yields obtained for these tetranuclear M_4L_4 cages are consistent with others reported in the literature for similar supramolecular M_4L_4 arrangements (54%–94%).^[31]

Scheme 5. Self-assembly of supramolecular coordination cages $M_4(L^{6-10})_4$.

The following sections will outline the structural characterisation and solution behaviour of these new supramolecular coordination $\text{M}_4(\text{L}^{6-10})_4$ cages. Our analyses include monodimensional NMR spectroscopy (^1H , ^{13}C , ^{19}F), two-dimensional NMR techniques (^1H – ^1H COSY, ^1H – ^{13}C HSQC, ^1H – ^{13}C HMBC, ^1H – ^1H NOESY, ^1H – ^1H ROESY), Diffusion–Ordered NMR Spectroscopy (DOSY NMR), single crystal X–ray diffraction, HRMS, TGA and isothermal titration calorimetry (ITC).

2.3.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis

The analysis of the ^1H NMR spectrum of the supramolecular tetranuclear cages $[\text{M}_4(\text{L}^6)_4][\text{K}]_{12}$, $[\text{M}_4(\text{L}^7)_4][\text{K}]_{12}$, $[\text{M}_4(\text{L}^8)_4][\text{K}]_{12}$, $[\text{M}_4(\text{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ and $[\text{M}_4(\text{L}^{10})_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ reveals important features about their structures. The high symmetry of these $\text{M}_4(\text{L}^{6-10})_4$ assemblies was evidenced by their simple ^1H NMR spectra which are consistent with highly–symmetric supramolecular structures. Notably, the disappearance of the phenolic OH proton signals (δ 9–11 ppm) is indicative of deprotonation of the ligands $\text{H}_6\text{L}^{6-10}$.

For the $\text{M}_4(\text{L}^6)_4$ assemblies, the triazole–CH signal exhibit significant downfield shifts in the ^1H NMR spectra, comparing H_6L^6 (δ 9.08 ppm) with both $\text{Al}_4(\text{L}^6)_4$ and $\text{Ga}_4(\text{L}^6)_4$ cages at δ 9.25 and 9.26 ppm, respectively. The core C_6H_4 phenylene protons appeared upfield with respect to the free ligands, from δ 8.52 ppm for H_6L^6 to δ 7.15 and 7.11 ppm for $\text{Al}_4(\text{L}^6)_4$ and $\text{Ga}_4(\text{L}^6)_4$, respectively. The resonances in the range δ 6.6–7.6 ppm correspond to the protons of the aromatic catechol rings (Figure 22). This strongly suggests coordination of the deprotonated ligand $(\text{L}^6)^{6-}$ to the Al^{3+} and Ga^{3+} metal centres supporting the formation of these cage assemblies. In the ^{13}C NMR spectra, carbons bonded to the oxygens of the catechol (δ 156.3 and 148.2 ppm) for $\text{Al}_4(\text{L}^6)_4$ and (δ 155.1 and 147.5 ppm) for $\text{Ga}_4(\text{L}^6)_4$ are downfield shifted compared to those of the free ligand H_6L^6 (δ 146.7 and 138.8 ppm), confirming the successful coordination of the ligand $(\text{L}^6)^{6-}$ to the metal centres. Both cages present a highly symmetric ^1H NMR and ^{13}C NMR consistent with tetrahedral cage assemblies as we will discuss in their X–ray structural characterisation.

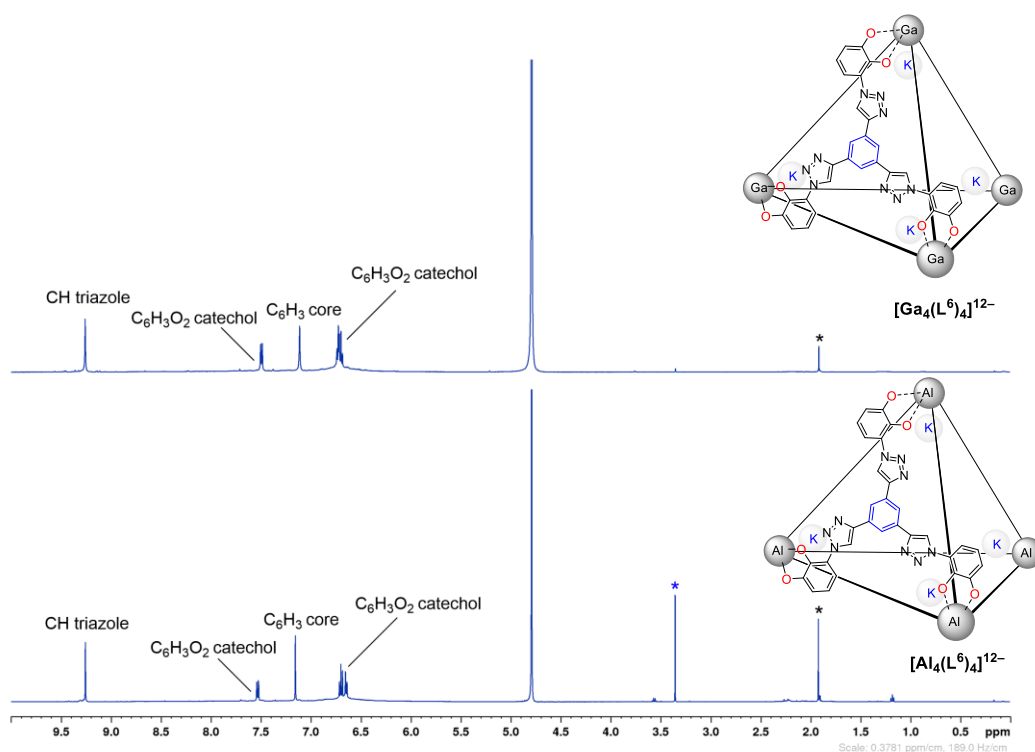


Figure 22. ^1H NMR (500 MHz, D_2O , 298 K) spectrum of $[\text{Al}_4(\text{L}^6)_4][\text{K}]_{12}$ (bottom) and $[\text{Ga}_4(\text{L}^6)_4][\text{K}]_{12}$ (top). The black symbol * denotes residual signal for acetylacetone and blue symbol * denotes residual signal for methanol from precipitation.

The $\text{M}_4(\text{L}^7)_4$ ($\text{M} = \text{Al}, \text{Ga}$) cages exhibit similar behaviour than $\text{M}_4(\text{L}^6)_4$ assemblies. The ^1H NMR spectra of $\text{M}_4(\text{L}^7)_4$ (Figure 23) show that the triazole–CH proton signals experiment significant downfield shifts, comparing H_6L^7 (δ 8.87 ppm) with both $\text{Al}_4(\text{L}^7)_4$ and $\text{Ga}_4(\text{L}^7)_4$ cages, from δ 9.29 and 9.25 ppm, respectively. The signals in the range δ 6.6–7.5 ppm correspond to protons of the aromatic catechol rings. Furthermore, the signal corresponding to core aromatic phenylene protons (C_6H_3) in $\text{M}_4(\text{L}^6)_4$ disappears in the case of the cages $\text{M}_4(\text{L}^7)_4$, because these compounds present fluor atoms in the core (C_6F_3) instead of protons (C_6H_3). The ^{19}F spectrum of $\text{M}_4(\text{L}^7)_4$ shows a unique upfield shifted signal for $\text{M}_4(\text{L}^7)_4$ cages (δ –111.3 ppm) compared to free H_6L^7 ligand (δ –109.2 ppm). This shielding of the fluorine atoms could be due to the accumulation of π –electron density within the cage assemblies. An analogous effect is observed for the core aromatic phenylene protons (C_6H_3) in cages $\text{M}_4(\text{L}^6)_4$. In the ^{13}C NMR spectra, carbons bonded to the oxygens of the catechol (δ 156.1 and 148.3 ppm) for $\text{Al}_4(\text{L}^7)_4$ and (δ 155.1 and 147.6 ppm) for $\text{Ga}_4(\text{L}^7)_4$ are downfield shifted compared to those of the free ligand H_6L^7 .

(δ 146.7 and 138.7 ppm). ^1H NMR, ^{13}C NMR and ^{19}F NMR confirm the successful coordination of the ligand (L^7) $^{6-}$ to the Al and Ga centres, being consistent with highly symmetric cage structures. $\text{M}_4(\text{L}^7)_4$ systems present similar solubility in water than $\text{M}_4(\text{L}^6)_4$ architectures.

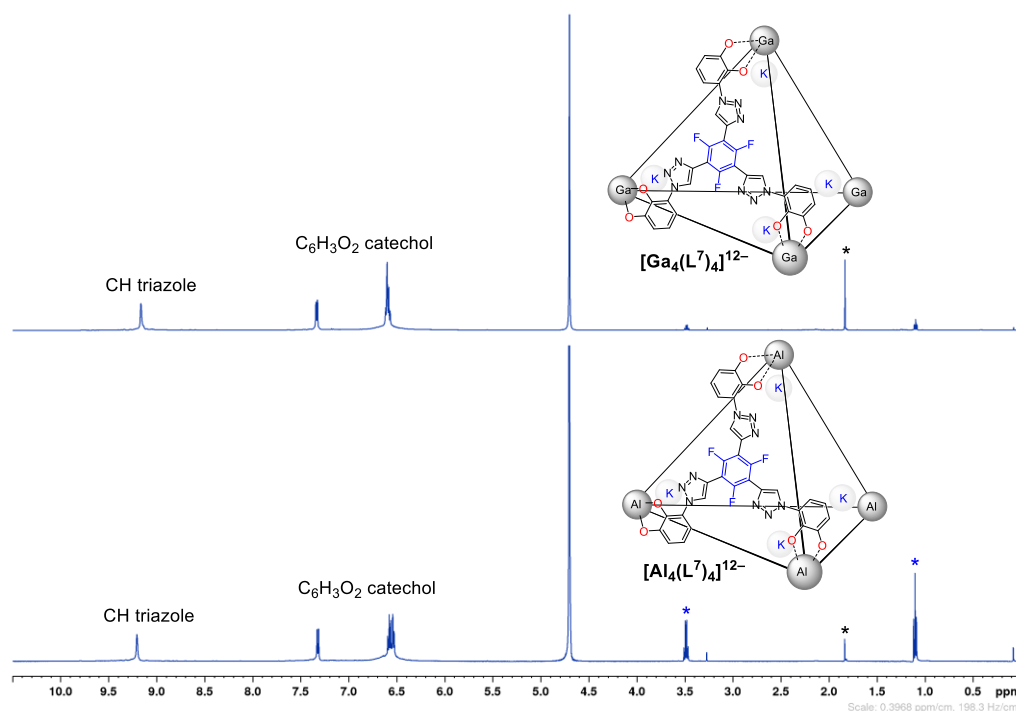


Figure 23. ^1H NMR (500 MHz, D_2O , 298 K) spectrum of $[\text{Al}_4(\text{L}^7)_4][\text{K}]_{12}$ (bottom) and $[\text{Ga}_4(\text{L}^7)_4][\text{K}]_{12}$ (top). The black symbol * denotes residual signal for acetylacetone and blue symbol * denotes residual signal for Et_2O from precipitation.

The $\text{M}_4(\text{L}^8)_4$ assemblies follow similar NMR spectroscopic features than $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$. The triazole–CH proton resonances exhibit notable downfield shifts relative to the free ligand H_6L^8 , shifting from δ 8.81 ppm to δ 9.86 ppm for $\text{Al}_4(\text{L}^8)_4$ and δ 9.76 ppm for $\text{Ga}_4(\text{L}^8)_4$. Conversely, the $\text{N}(\text{Ph})_3$ proton signals show upfield shifts, moving from δ 7.90 and 7.19 ppm in H_6L^8 to δ 7.71 and 6.75 ppm for $\text{Al}_4(\text{L}^8)_4$, and δ 7.75 and 6.77 ppm for $\text{Ga}_4(\text{L}^8)_4$, respectively. This shielding of the core aromatic signals could be due to the accumulation of π –electron density within the cage arrangement. This behaviour was observed in cages $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ as well. Signals corresponding to the aromatic protons of the catechol rings are observed within the δ 6.4–7.0 ppm range (Figure 24). In the ^{13}C NMR spectra, the carbons bonded to the catechol oxygen atoms show significant downfield shifts upon

coordination as seen before, appearing at δ 158.3 and 150.4 ppm for $\text{Al}_4(\text{L}^8)_4$ and δ 156.9 and 149.5 ppm for $\text{Ga}_4(\text{L}^8)_4$, compared to δ 146.7 and 138.9 ppm in the free ligand. These $\text{M}_4(\text{L}^8)_4$ cages exhibit markedly lower water solubility compared to their $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ architectures. This may be due to the presence of greater number of hydrophobic aromatic rings in the core of $\text{M}_4(\text{L}^8)_4$ cages, decreasing their solubility in solvents as water. Consequently, dissolution requires a 1:1 mixture of DMF and water.

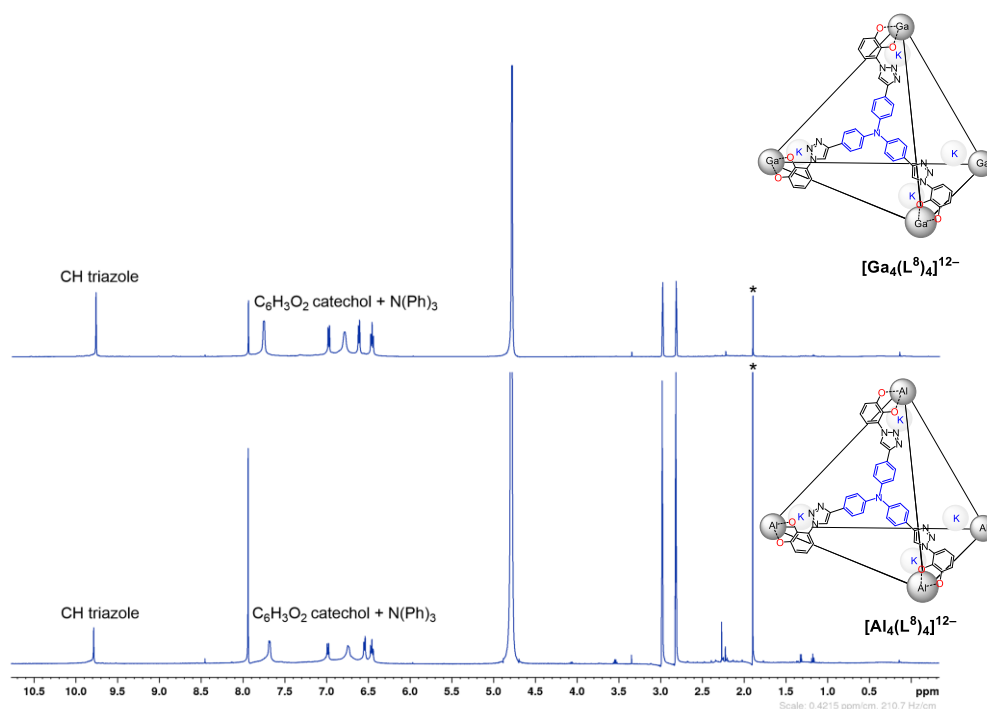


Figure 24. ^1H NMR (500 MHz, $\text{D}_2\text{O}/\text{DMF-d}_7$ (1:1), 298 K) spectrum of $[\text{Al}_4(\text{L}^8)_4][\text{K}]_{12}$ (bottom) and $[\text{Ga}_4(\text{L}^8)_4][\text{K}]_{12}$ (top). The symbol * denotes residual signal for acetylacetone from precipitation.

In the $\text{M}_4(\text{L}^9)_4$ supramolecular assemblies, the triazole–CH proton signals exhibit significant downfield shifts compared to the free ligand H_6L^9 , moving from δ 8.97 ppm to δ 10.50 ppm for $\text{Al}_4(\text{L}^9)_4$ and δ 10.51 ppm for $\text{Ga}_4(\text{L}^9)_4$. The aromatic protons of the $\text{C}_6\text{H}_3(\text{Ph})_3$ moiety in the free ligand appear as two doublets and one singlet in the δ 8.03–8.09 ppm range. Upon coordination, one of the doublets shifts downfield to δ 8.44 ppm for $\text{Al}_4(\text{L}^9)_4$ and δ 8.52 ppm for $\text{Ga}_4(\text{L}^9)_4$, while the remaining doublet and the singlet shift upfield to δ 7.50 (d) and 7.27 (s) ppm for $\text{Al}_4(\text{L}^9)_4$ and δ 7.57 (d) and 7.33 (s) ppm for $\text{Ga}_4(\text{L}^9)_4$. Signals corresponding to the aromatic protons of the catechol units are observed between δ 6.4 and 7.2 ppm (Figure 25).

Additionally, resonances at δ 1.26 and 3.24 ppm are assigned to the ethyl and methylene protons of eight tetraethylammonium cations which act as counterions in the isolated $[\mathbf{M}_4(\mathbf{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ salts. The ^{13}C NMR spectra further support metal–coordination, with the carbon atoms bonded to the catechol oxygen atoms exhibiting marked downfield shifts: δ 155.4 and 147.1 ppm for $\mathbf{Al}_4(\mathbf{L}^9)_4$ and δ 154.3 and 146.4 ppm for $\mathbf{Ga}_4(\mathbf{L}^9)_4$ compared to δ 146.7 and 139.0 ppm in the free ligand. Furthermore, resonances at δ 1.25 and 3.23 ppm correspond to the ethyl and methylene protons of eight tetraethylammonium cations, which serve as counterions in the isolated $[\mathbf{M}_4(\mathbf{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ salts. The poor water solubility of the $[\mathbf{M}_4(\mathbf{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ salts can be attributed to both the hydrophobic character of the ligands used in the self-assembly process and the presence of organic cations such as Et_4N^+ . Therefore, these assemblies require a 1:1 DMF/water solvent mixture for effective dissolution.

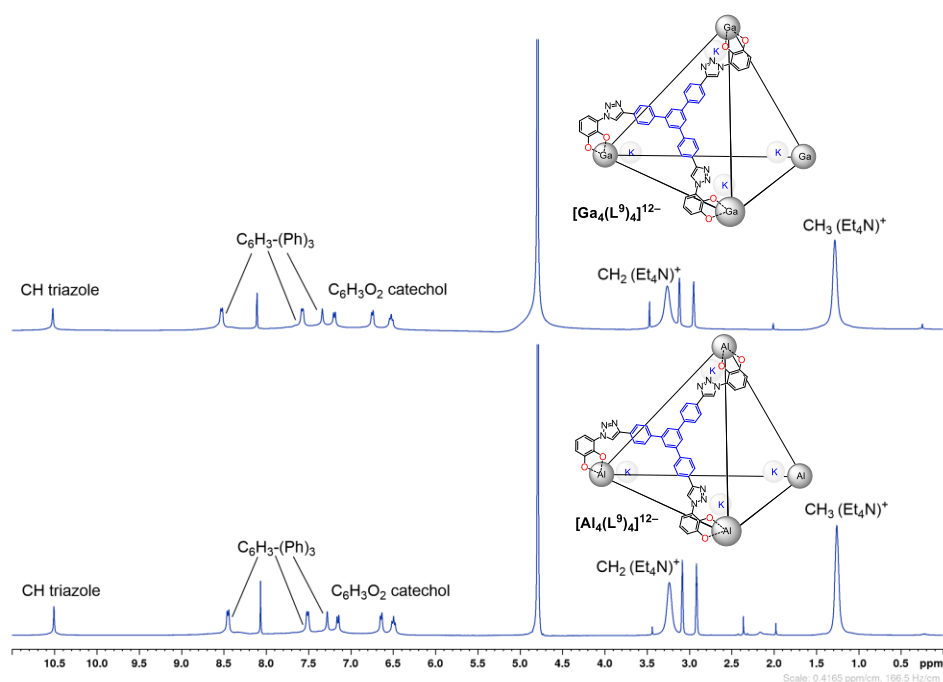


Figure 25. ^1H NMR (500 MHz, $\text{D}_2\text{O}/\text{DMF}-d_7$ (1:1), 298 K) spectrum of $[\text{Al}_4(\text{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ (bottom) and $[\text{Ga}_4(\text{L}^9)_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ (top).

In the naphthalene-derived $\mathbf{M}_4(\mathbf{L}^{10})_4$ assemblies, the triazole–CH proton resonances exhibit slight upfield shifts when comparing the free ligand $\mathbf{H}_6\mathbf{L}^{10}$ (δ 9.23 ppm) with the corresponding $\mathbf{Al}_4(\mathbf{L}^{10})_4$ and $\mathbf{Ga}_4(\mathbf{L}^{10})_4$ cages (δ 9.02 and 9.04 ppm, respectively) unlike their analogues $\mathbf{M}_4(\mathbf{L}^6)_4$. The protons of the central aromatic

(C_6H_3) core experience moderate downfield shifts, from δ 8.68 ppm in H_6L^{10} to δ 8.76 and 8.77 ppm for the Al^{3+} and Ga^{3+} assemblies, respectively. The signals observed in the δ 6.5–7.8 ppm region are attributed to the aromatic protons of the naphthalenediol moieties (Figure 26). Additionally, resonances at δ 1.18 and 3.17 ppm correspond to the ethyl and methylene protons of eight tetraethylammonium counterions in the isolated $[\text{M}_4(\text{L}^{10})_4][\text{Et}_4\text{N}]_8[\text{K}]_4$ salts. The corresponding ^{13}C NMR spectra further support the formation of highly symmetric carbon frameworks within these naphthalene cage assemblies.

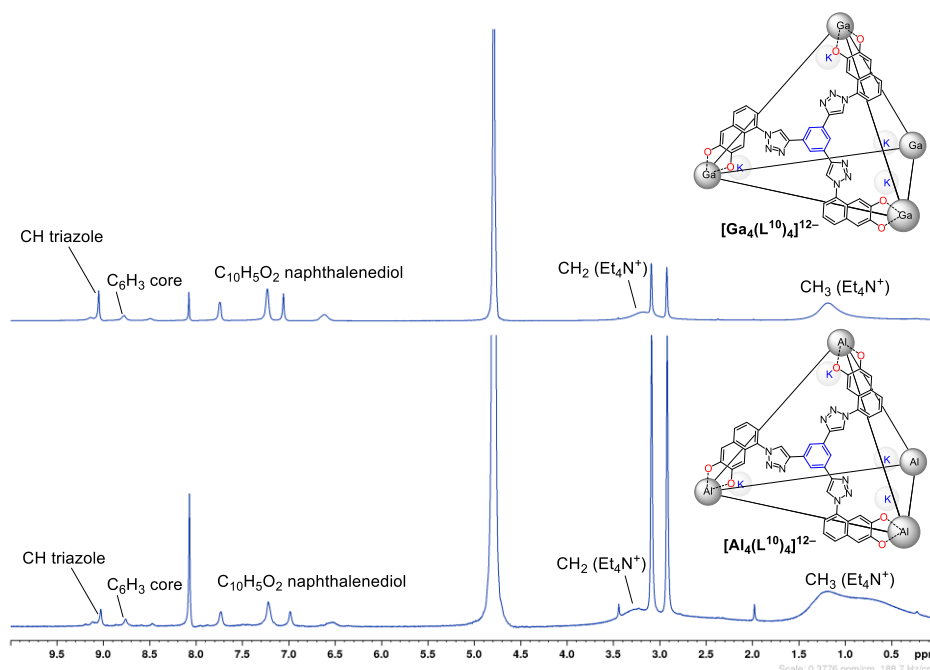


Figure 26. ^1H NMR (500 MHz, $\text{D}_2\text{O}/\text{DMF}-d_7$ (1:1), 298 K) spectrum of $[\text{Al}_4(\text{L}^{10})_4][\text{K}]_{12}$ (bottom) and $[\text{Ga}_4(\text{L}^{10})_4][\text{K}]_{12}$ (top).

2.3.3.2 Diffusion-Ordered Spectroscopy (DOSY) NMR Analysis

To investigate the stability of supramolecular architectures $\text{M}_4(\text{L}^{6-10})_4$ as well as their aggregation state in solution, we carried out DOSY NMR experiments. In these experiments, single sets of signals with uniform diffusion coefficients in the DOSY spectra were observed for the series of $\text{M}_4(\text{L}^{6-10})_4$ cages. We observed that the free ligands $\text{H}_6\text{L}^{6-10}$ have an intrinsic tendency for self-association in polar solvents like DMF or methanol. In fact, DOSY NMR studies corroborates a significant aggregation of $\text{H}_6\text{L}^{6-10}$ in $\text{DMF}-d_7$. The measured diffusion coefficients (D) of $\text{H}_6\text{L}^{6-10}$ correspond to hydrodynamic diameter of approximately two associates

molecules of $\text{H}_6\text{L}^{6-10}$ in this solvent. Moreover, DOSY NMR experiments in D_2O reveal a significant dimeric pre-organisation of $\text{Na}_6\text{L}^{6-10}$ akin to $\text{H}_6\text{L}^{6-10}$. Approximately, the hydrodynamic diameter is twice the monomeric dimensions suggesting predominant dimer aggregation for the free and protonated ligands in solution. This ligand pre-organisation in polar solvents is probably induced by the hydrophobic effect, which is a key driving force for cage formation in polar media like methanol, the solvent employed during synthesis. This phenomenon enhances ligand aggregation and supports their metal-directed self-assembly into supramolecular coordination cages. Additionally, pre-organisation is expected to minimise the entropic cost associated with cage formation.

To study the behaviour of the water-soluble systems $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$, we measured the diffusion coefficient (D) of the free ligands H_6L^6 and H_6L^7 , obtaining values of $2.60 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ and $2.50 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ respectively in DMF-d_7 . These values match with a similar hydrodynamic diameter of $\sim 21 \text{ \AA}$ for both ligands, based on the Stokes-Einstein equation. This hydrodynamic diameter corresponds to two molecules of H_6L^6 or H_6L^7 associated in DMF-d_7 , suggesting dimeric pre-organisation of H_6L^6 and H_6L^7 . Upon formation of the cages $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$, the diffusion coefficients decreased significantly to $1.30 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ for $\text{Al}_4(\text{L}^{6-7})_4$ and to $1.40 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ for $\text{Ga}_4(\text{L}^{6-7})_4$ in D_2O (Figure 27), reflecting the larger hydrodynamic diameter ($26 \text{ \AA}$) of these assemblies (Table 1).

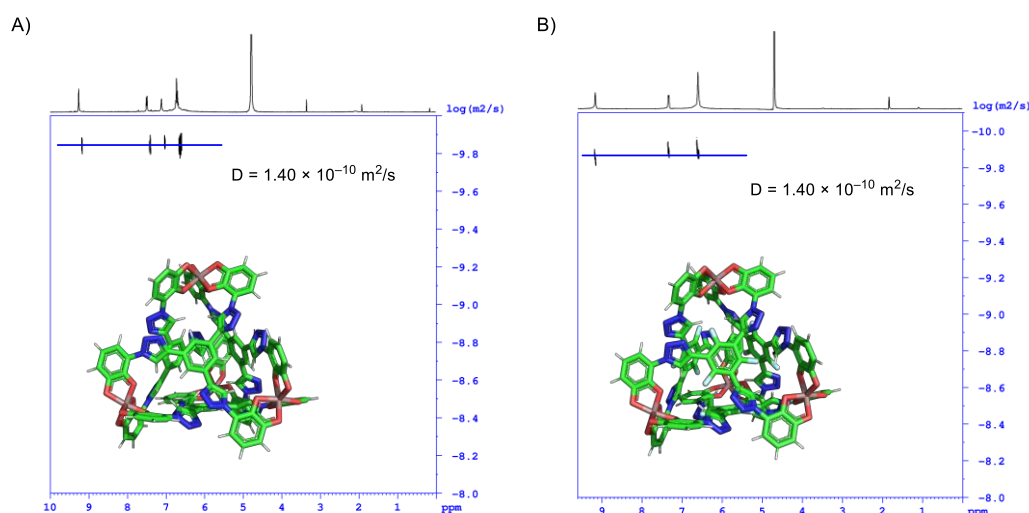
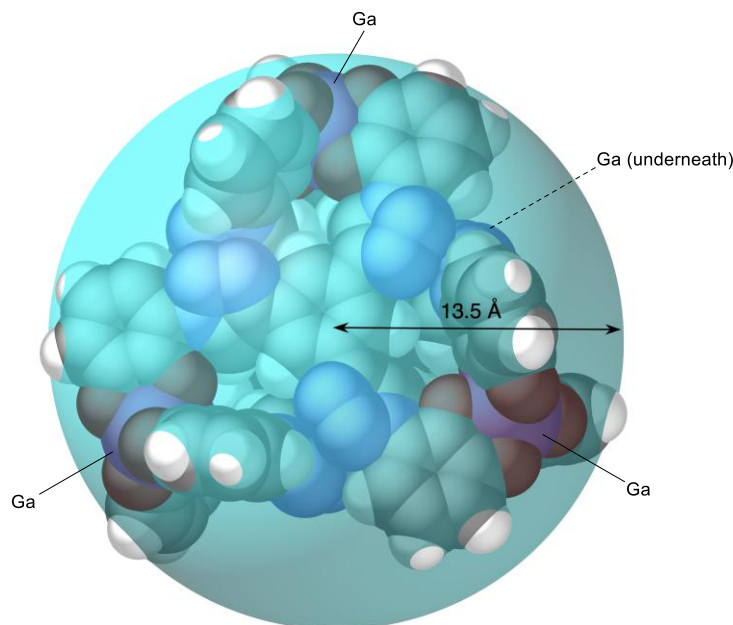


Figure 27. A) ^1H DOSY NMR spectrum (400 MHz, 298 K, D_2O) for the cages $\text{Ga}_4(\text{L}^6)_4$ and B) for $\text{Ga}_4(\text{L}^7)_4$.

Table 1. D (m^2s^{-1}) and $d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$) for the cages $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ in D_2O at 298 K.

Species	D (m^2s^{-1})	$d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$)	d^{DFT} ($\text{\AA}$)
$\text{Al}_4(\text{L}^6)_4$	1.30×10^{-10}	27	–
$\text{Ga}_4(\text{L}^6)_4$	1.40×10^{-10}	25	27
$\text{Al}_4(\text{L}^7)_4$	1.30×10^{-10}	27	–
$\text{Ga}_4(\text{L}^7)_4$	1.40×10^{-10}	25	27

The calculated hydrodynamic diameter of the tetrahedral cages $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ are approximately 26 $\text{\AA}$, which aligns well with the dimensions derived from the optimised geometry for $\text{Ga}_4(\text{L}^6)_4$ in water (27 $\text{\AA}$, Figure 28). This consistent metrics supports the conclusion that the $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ ($\text{M} = \text{Ga}, \text{Al}$) assemblies feature comparable sizes, retaining their structural integrity as monodisperse species in solution.

**Figure 28.** Estimated hydrodynamic radius ($d_{\text{H}}/2$) of the optimised $\text{Ga}_4(\text{L}^6)_4$ optimised geometry using van der Waals model.

Because of the poor solubility of systems $\text{M}_4(\text{L}^8)_4$, $\text{M}_4(\text{L}^9)_4$ and $\text{M}_4(\text{L}^{10})_4$ in D_2O , we used a mixture $\text{D}_2\text{O}/\text{DMF}-d_7$ to dissolve them and study their behaviour in

solution. The diffusion coefficient of the larger ligands **H₆L⁸**, **H₆L⁹** and **H₆L¹⁰** was found to be $2.30 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, $2.05 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ and $2.41 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ respectively in DMF-d₇, matching with molecular sizes of 24, 26 and 23 Å respectively, suggesting dimeric aggregation in this polar solvent. Upon formation of the cages, the diffusion coefficients in D₂O/DMF-d₇ decreased to an anomalously low value and is not comparable to the results obtained in D₂O. These results suggest that these supramolecular cages have tendency to associate in the mixture of deuterated solvents employed, forming short oligomeric associations ($n \geq 10$), behaviour observed as well for ligands **H₆L⁶⁻¹⁰** in DMF-d₇. This supramolecular aggregation of cages in solution has not yet been documented in the literature, representing an open area to study these features further. These are only preliminary results requiring further investigation.

2.3.3.3 High-Resolution Mass Spectrometric (HRMS) Analysis

To support the studies in solution, we employed ESI-HRMS to provide further evidence of cage formation. The distribution of m/z peaks indicates diverse ion-pairing associations during the ionisation process, with varying numbers of K⁺, Na⁺ and H⁺ ions and in the cases of **M₄(L⁹)₃** and **M₄(L¹⁰)₄** cages with additional Et₄N⁺ ions. Moreover, the observed isotopic patterns matched well with the calculated distributions, confirming the **M₄(L⁶⁻¹⁰)₄** stoichiometries.

For cages **M₄(L⁶)₄** (12-), peaks with charge 3- at m/z values of 949.6883 (calcd. 949.6873), 937.0355 (calcd. 937.0355) and 931.7137 (calcd. 931.7109) were observed for cage **Al₄(L⁶)₄** with 9K⁺, 8K⁺/1H⁺ and 7K⁺/1Na⁺/1H⁺ respectively. Similarly, for the cage **Ga₄(L⁶)₄**, peaks at m/z values of 1006.9475 (calcd. 1006.9456), 1001.2917 (calcd. 1001.2879) and 993.9633 (calcd. 993.9606) were detected for cage **Ga₄(L⁶)₄** with 9K⁺/H₂O, 9K⁺ and 8K⁺/1Na⁺ respectively. For instance, the HRMS spectrum for **Ga₄(L⁶)₄** (Figure 29) shows two different parts. In the first section, in the range of m/z 700–800, several ions were detected from different aggregates with charge 4- resulting from association of the **Ga₄(L⁶)₄** with eight cations (K⁺, Na⁺ and/or H⁺) under the mass spectrometry ionisation conditions, as well as aggregates from cage decomposition. In the second section, in the range of m/z 950–1150, we observed aggregates with charge 3- resulting from association of **Ga₄(L⁶)₄** with nine cations. According to HRMS for both cages, in gas phase, **Ga₄(L⁶)₄** seems to be more stable than **Al₄(L⁶)₄**, because for **Ga₄(L⁶)₄** system, we detected more peaks and with a major intensity that corresponded to associations of

Mass spectrum showing relative intensity versus m/z (ranging from 700 to 1100). The spectrum displays several peaks, with two main regions highlighted by blue dashed boxes:

- Left Region (Cage Decomposition):** A cluster of peaks between m/z 700 and 800. A peak is labeled $\{[\text{Ga}_4(\text{L}^6)_4] + \text{K}_8 + \text{H}_2\text{O}\}^{4-}$ at m/z 749.9763. Another peak is labeled $4-$ at m/z 1006.9475.
- Right Region (Cluster Ions):** A cluster of peaks between m/z 1000 and 1100. A peak is labeled $\{[\text{Ga}_4(\text{L}^6)_4] + \text{K}_9\}^{3-}$ at m/z 1006.9475. Another peak is labeled $\{[\text{Ga}_4(\text{L}^6)_4] + \text{K}_9 + \text{H}_2\text{O}\}^{3-}$ at m/z 1012.9533.

The x-axis is labeled m/z and ranges from 700 to 1100. The y-axis represents relative intensity.

For cage assemblies $\mathbf{M}_4(\mathbf{L}^7)_4$ (12–), the peak with charge 3– was observed at m/z value of 1021.6500 (calcd. 1021.6497) corresponding to association of the cage $\mathbf{Al}_4(\mathbf{L}^7)_4$ with 9K^+ whereas peaks with the same charge (3–) were detected at 1078.9082 (calcd. 1078.9079) and 1073.5860 (calcd. 1070.5833) for the cage $\mathbf{Ga}_4(\mathbf{L}^7)_4$ with 9K^+ and $8\text{K}^+/1\text{Na}^+$. $\mathbf{Ga}_4(\mathbf{L}^7)_4$ seems to exhibit greater gas-phase stability compared to its aluminum analogue, behaviour observed for $\mathbf{M}_4(\mathbf{L}^6)_4$ as well. This is supported by the increased extent of fragmentation observed in the mass spectrum of the $\mathbf{Al}_4(\mathbf{L}^7)_4$ cage under identical ionisation conditions. In addition, both cages appear to be more labile under ionisation conditions than their non-fluorinated analogues $\mathbf{M}_4(\mathbf{L}^6)_4$. Probably, the electrostatic repulsion between fluorine atoms in the cages $\mathbf{M}_4(\mathbf{L}^7)_4$ destabilise them and for this reason many peaks from cage decomposition were observed in their HRMS spectra. In fact, multiple peaks that correspond to M_3L_3 -type adducts (cage fragmentation) with different cations (K^+ , Na^+ , H^+) in the region between 700 and 850 were detected. For example, peaks with

charge 3[−] at m/z values of 761.3170 (calcd. 761.3176) and 773.9692 (calcd. 773.9695) correspond to association of $\text{Ga}_3(\text{L}^7)_3$ with $3\text{K}^+/3\text{H}^+$ and $4\text{K}^+/2\text{H}^+$ whereas peaks at m/z values of 718.3750 (calcd. 718.3741) and 731.0269 (calcd. 731.0261) correspond to association of $\text{Al}_3(\text{L}^7)_3$ with $3\text{K}^+/3\text{H}^+$ and $4\text{K}^+/2\text{H}^+$.

For the $\text{M}_4(\text{L}^8)_4$ (12[−]) cage architectures, mass spectrometric analysis of the $\text{Al}_4(\text{L}^8)_4$ complex revealed peaks at m/z 1172.7893 (3[−]) (calcd. 1172.7861), 869.5992 (4[−]) (calcd. 869.5985), and 865.6056 (4[−]) (calcd. 865.6051), corresponding to species with 5K^+ , 4K^+ , and a combination of $3\text{K}^+/1\text{Na}^+$ respectively. Similarly, for the $\text{Ga}_4(\text{L}^8)_4$ cage, peaks at m/z values of 1229.7150 (3[−]) (calcd. 1229.7109), 912.5455 (4[−]) (calcd. 912.5424) and 908.5520 (4[−]) (calcd. 908.5489) were detected corresponding to analogous species. For example, the HRMS spectrum for $\text{Ga}_4(\text{L}^8)_4$ (Figure 30) shows three different parts. The first section, in the range of m/z 550–700, ions from $\text{Ga}_4(\text{L}^8)_4$ decomposition were observed. In the second section, between 850–1000, several aggregates with charge 4[−] were detected resulting from association of the $\text{Ga}_4(\text{L}^8)_4$ with eight cations under the mass spectrometry ionisation conditions. In the third section, in the range of m/z 1200–1300, we could observe aggregates with charge 3[−] resulting from association of $\text{Ga}_4(\text{L}^8)_4$ with nine cations.

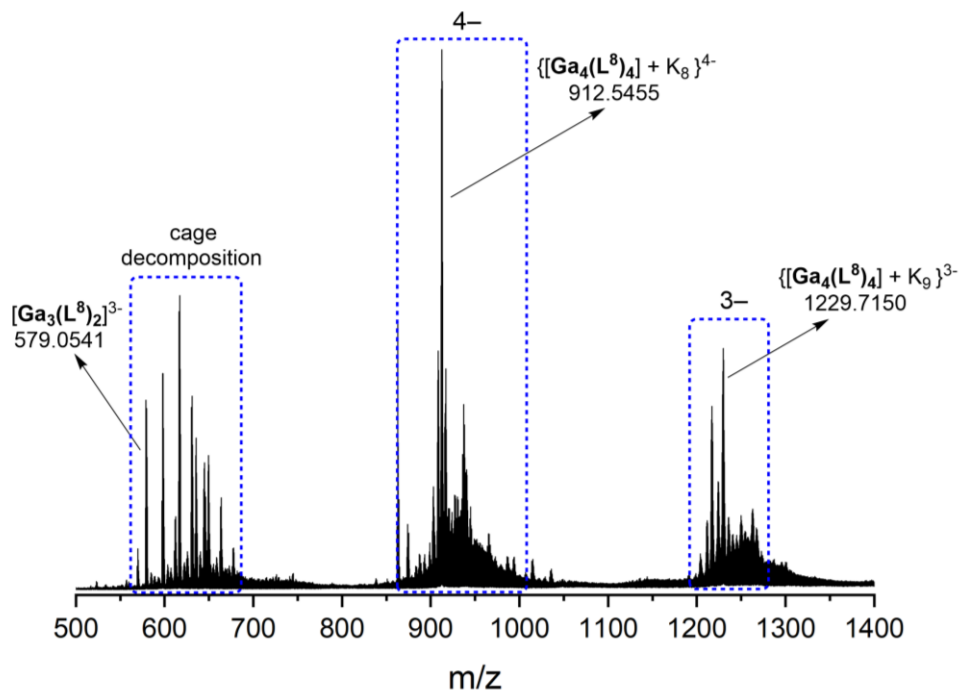


Figure 30. ESI–HRMS spectrum (negative mode) of the cage $\text{Ga}_4(\text{L}^8)_4$ in $\text{H}_2\text{O}/\text{DMF}$ (1:1).

The observed isotope patterns matched well with the calculated distributions, confirming the $\text{M}_4(\text{L}^8)_4$ stoichiometry (Figure 31). Major presence and stability of aggregates with 4– charge was observed comparing with 3– charge adducts. Similar HRMS was obtained for $\text{Al}_4(\text{L}^8)_4$ cage, with a major presence and stability of aggregates with 4– charge. As in the previous $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ assemblies, the peaks observed in the mass spectrum of $\text{Ga}_4(\text{L}^8)_4$ cage are more intense, suggesting that gallium cage is more stable than its aluminum analogue. Moreover, $\text{M}_4(\text{L}^8)_4$ architectures appear significantly more stable in the gas phase compared to the $\text{M}_4(\text{L}^6)_4$ and $\text{M}_4(\text{L}^7)_4$ cages, as evidenced by the increased abundance and persistence of M_4L_4 adducts. This enhanced stability is likely associated with the higher number of aromatic rings in the $\text{M}_4(\text{L}^8)_4$ cages, which may promote additional stabilisation through π – π stacking interactions.

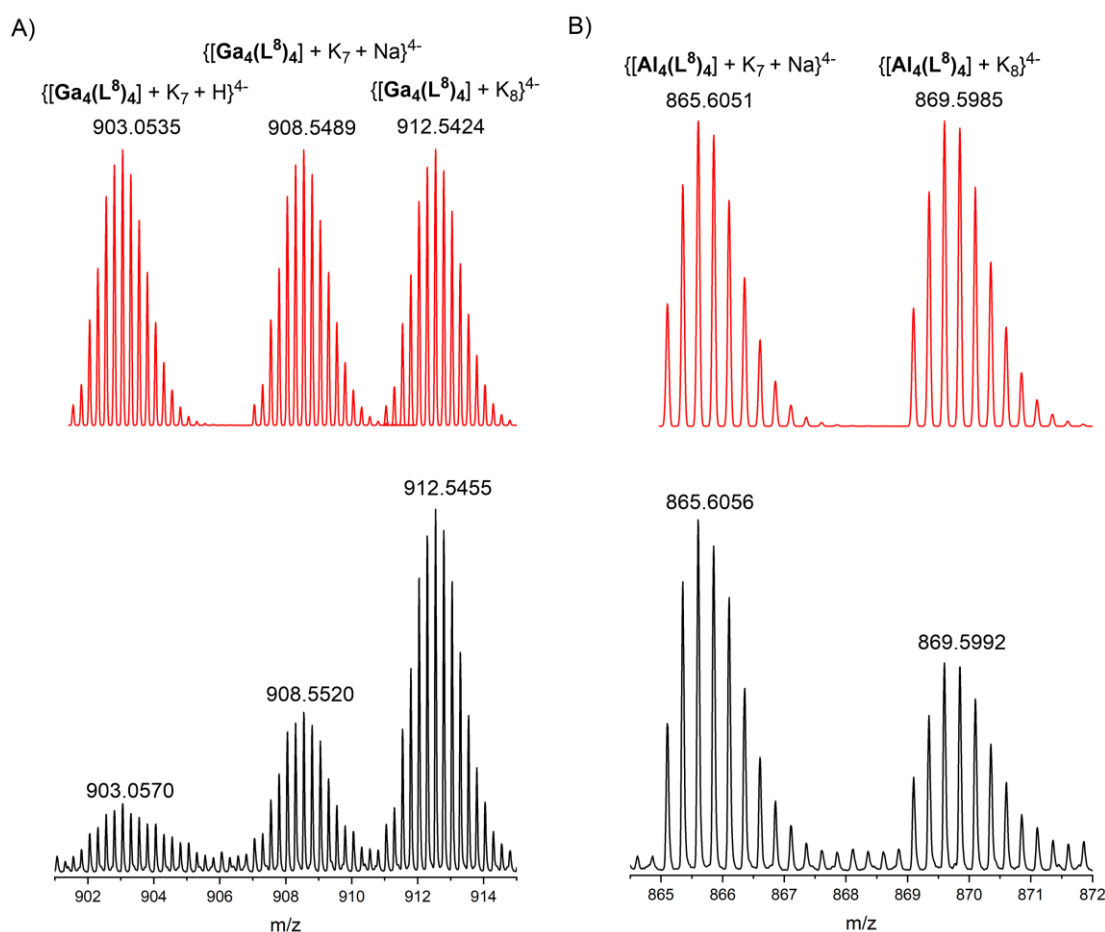


Figure 31. A) Selected section of ESI–HRMS spectrum (negative mode) of cages $\text{Ga}_4(\text{L}^8)_4$ and B) $\text{Al}_4(\text{L}^8)_4$ in $\text{H}_2\text{O}/\text{DMF}$ (1:1).

For cage assemblies $\text{M}_4(\text{L}^9)_4$, we observed that the incorporation of Et_4N^+ as counterion of the cages resulted in enhanced stabilisation of their gas–phase

adducts, with a marked abundance of M_4L_4 -type cage adducts and reduced fragmentation relative to previously synthesised cages containing only K^+ as counterion. This stabilisation could be due to supramolecular interactions between the organic chains of Et_4N^+ ions and the ligands which form the cages. Their HRMS spectrum presents, in the range of m/z 700–850, several aggregates with 5– charge resulting from association of the $\text{M}_4(\text{L}^9)_4$ (12–) with seven cations (K^+ , Na^+ , H^+ and/or Et_4N^+). These aggregates with 5– charge have not been observed in other M_4L_4 cage architectures described in this Chapter. Probably, this is due to the presence of Et_4N^+ ions which can stabilise these adducts under the ionisation conditions. In the second section, in the range of m/z 900–1100, we observed aggregates with charge 4– that correspond with association of $\text{M}_4(\text{L}^9)_4$ with eight cations, and in the first section, between 1300–1450 m/z , adducts with 3– charge corresponding to association of $\text{M}_4(\text{L}^9)_4$ with nine cations were detected. Aggregates with a 4– charge state exhibit the highest stability and relative abundance, followed by species with a 5– charge state, whereas those with a 3– charge state are observed to be the least stable and least abundant under the experimental conditions, behaviour observed with the previous cages as well. In the case of the cages $\text{M}_4(\text{L}^9)_4$ (12–), peaks at m/z values of 1345.0151 (3–) (calcd. 1345.0092), 976.4745 (4–) (calcd. 976.4675) and 747.3576 (5–) (calcd. 747.3507) were observed for $\text{Al}_4(\text{L}^9)_4$ with $6\text{K}^+/3\text{Et}_4\text{N}^+$, $6\text{K}^+/2\text{Et}_4\text{N}^+$ and $5\text{K}^+/\text{H}^+/\text{Et}_4\text{N}^+$ respectively, whereas peaks at m/z of 1402.2559 (3–) (calcd. 1402.2503), 1019.1539 (4–) (calcd. 1019.1611) and 781.7006 (5–) (calcd. 781.7059) were detected for $\text{Ga}_4(\text{L}^9)_4$ corresponding to analogous species.

Despite Et_4N^+ was incorporated as a counterion in the cages $\text{M}_4(\text{L}^{10})_4$ (12–), only a limited number of peaks corresponding to species with a 3– charge was observed in both systems. For example, the cage $\text{Al}_4(\text{L}^{10})_4$ exhibited peaks at m/z 1169.5064 (calcd. 1169.4999), 1174.8309 (calcd. 1174.8245) and 1180.4915 (calcd. 1169.4999), corresponding to species with $6\text{K}^+/2\text{Na}^+/1\text{Et}_4\text{N}^+$, $7\text{K}^+/1\text{Na}^+/1\text{Et}_4\text{N}^+$ and $8\text{K}^+/1\text{Et}_4\text{N}^+$, respectively. Similarly, $\text{Ga}_4(\text{L}^{10})_4$ showed peaks at m/z 1226.7555 (calcd. 1226.7584), 1232.0813 (calcd. 1232.0830) and 1237.7424 (calcd. 1237.7410), which can be assigned to analogous species.

2.3.4 Single-Crystal X-ray Diffraction and Computational Structural Analysis

During our investigations on the supramolecular coordination cages M_4L_4 , we succeeded in growing single crystals for several M_4L_4 systems. These structures

provided crucial insights into how the tritopic ligands self-assemble with Al^{3+} and Ga^{3+} ions in solid state, consolidating their previously suspected tetrahedral geometries.

We successfully crystallised single crystals of the $M_4(L^8)_4$ and $M_4(L^{10})_4$ cages suitable for X-ray analyses. High-quality block crystals of $Al_4(L^8)_4$ were obtained by diffusion of a mixture THF/acetone (1:1) into a concentrated solution of $Al_4(L^8)_4$ in a mixture DMF/ H_2O (4:1). The naphthalene-derived $Ga_4(L^{10})_4$ cage was crystallised by diffusion of acetone into a concentrated solution of the cages in a mixture DMF/ H_2O (4:2). Repeated crystallisation attempts for $M_4(L^6)_4$, $M_4(L^7)_4$ and $M_4(L^9)_4$ cages were unsuccessful, giving amorphous solids. Consequently, $Ga_4(L^6)_4$, $Ga_4(L^7)_4$ and $Ga_4(L^9)_4$ geometries were optimised by Ujaque's group from Universidad Aut3noma de Barcelona using DFT methods. The Gaussian 16 software package was used for computational analysis. Geometry optimisations were carried out at the DFT level using the B3LYP functional including dispersion corrections (D3) with the 6-31G(d) basis set for the main group elements and the scalar relativistic Stuttgart–Dresden (SDD) pseudopotential complemented with a set of d polarisation functions for the gallium ions. The solvent effects were considered with the SMD continuum solvent model with water as the solvent. All M_4L_4 cages were optimised in an aqueous environment without explicitly solvent molecules within their internal cavities (microsolvation). This approach favours the formation of more compact structures with smaller cavity volumes than those present in solution are generated, thereby maximizing supramolecular interactions in the implicit solvent model.

The optimised structure of $Ga_4(L^6)_4$ (Figure 32) reveals that the triazole rings exhibit a slight torsional deviation from the core C_6H_3 aromatic ring, with a torsion angle of 37.8 – 39.0° . Similarly, the catecholate rings are rotated relative to the triazole rings, with a torsion angle 36.0 – 37.6° . The triazole–CH groups are directed toward the interior of the cavity, suggesting the presence of weak intramolecular hydrogen bonding with the catecholate oxygen atoms (triazole–CH $\cdots$ O–catecholate), at 2.41 – 2.45 Å. Furthermore, the triazole rings are oriented toward adjacent triazole moieties, indicating potential π – π stacking interactions between triazole rings at 3.51 – 3.53 Å. The triazole CH groups within each ligand adopt alternate orientations. The gallium centres defining the vertices of the supramolecular tetrahedral cage are separated by 13.40 – 13.47 Å. The optimised $Ga_4(L^6)_4$ cage results in a cavity of ~ 86 Å³ (Figure 32A), calculated with CageCavityCalc–C3,^[73] that is distributed in the centre of the tetrahedron. Additionally, the $Ga_4(L^6)_4$ cage was also subjected to

classical molecular dynamics simulations, explicitly including solvent molecules within the cavity. On average, three water molecules were present inside the cavity during the simulation, yielding structural models with cavity sizes more representative of the solvated state in solution. Using molecular dynamics the **Ga₄(L⁶)₄** cage presents a cavity with a volume of $\sim 503 \text{ \AA}^3$ (Figure 32B). Interestingly, this expansion of the cage tetrahedral geometry is closer to the real structure of the cage in solution as we will see in the encapsulation experiments in section 1.3.7. In solution, the cage can expand and contract depending on the solution media, which is well-known as breathing effect.^[74] Thanks to this effect, supramolecular cages can present different cavity volumes depending on the size of the guest and the solvents used. Therefore, large guests generate much bigger cavities than small guests and polar solvents tend to compress cage architectures reducing cavity size due to hydrophobic effect. This behaviour is attributed to the inherent flexibility of the ligands **L⁶**, which translates into a dynamic cage capable of reversible structural changes. Such flexibility allows modulation of both the cavity size and the dimensions of the windows through which guest species may enter the cavity. This dynamic nature is particularly noteworthy, as it suggests the potential to encapsulate cations significantly larger than the cavity observed in the compressed structure, potentially ranging from ~ 86 – $503 \text{ \AA}^3$.

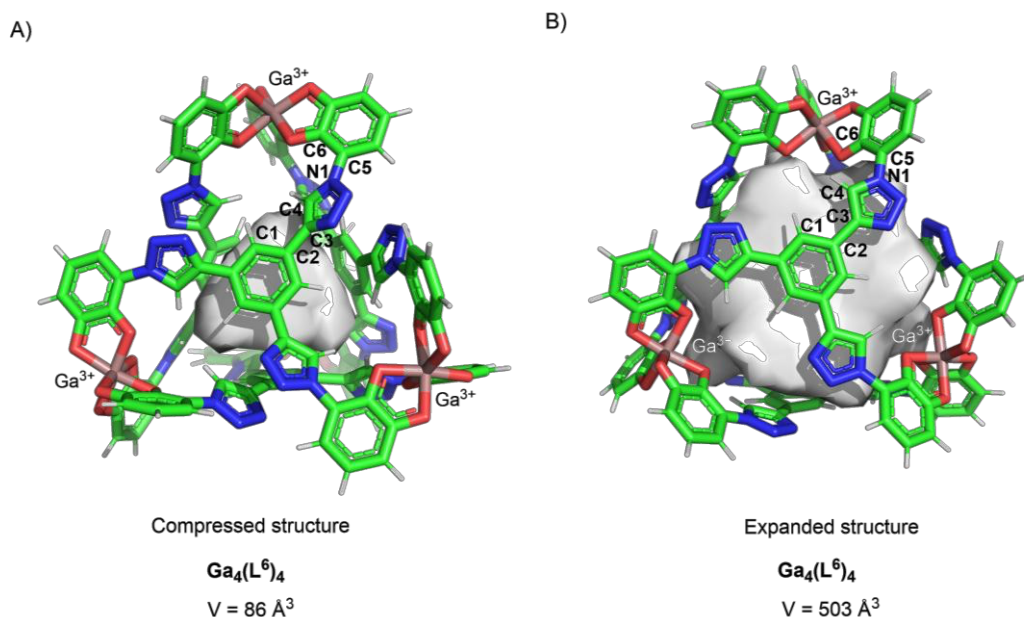


Figure 32. A) Optimised geometry of cage $\Delta,\Delta,\Delta,\Delta$ - $[\text{Ga}_4(\text{L}^6)_4]$ and B) Optimised geometry of cage $\Delta,\Delta,\Delta,\Delta$ - $[\text{Ga}_4(\text{L}^6)_4]$ using classical molecular dynamic. The computed cage cavity volumes of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of $0.5 \text{ \AA}$ and the EEM implemented charge model.

Selected bond lengths ($\text{\AA}$) and angles ($^\circ$): triazole-CH $\cdots$ O-catecholate 2.41 – 2.45 , triazole ring (cent) $\cdots$ triazole ring (cent) 3.51 – 3.53 , Ga–Ga 13.40 – 13.47 , torsion angles C1–C2–C3–C4 37.8 – 39.0 , C4–N1–C5–C6 36.0 – 37.6 .

The optimised geometry of the $\text{Ga}_4(\text{L}^7)_4$ cage (Figure 33) is very similar to its non-fluorinated analogue, $\text{Ga}_4(\text{L}^6)_4$. In this cage, the triazole rings exhibit a modest torsional offset relative to the central aromatic core, with torsion angles ranging from 40.2° to 43.4° . This torsion angle is slightly larger than the one for $\text{Ga}_4(\text{L}^6)_4$ (37.8 – 39.0°), suggesting that the presence of bulkier fluorine atoms (C_6F_3) in the ligand core led to larger torsion angles in $\text{Ga}_4(\text{L}^7)_4$ cage. The catecholate rings are likewise rotated with respect to the triazole rings, displaying torsion angles of 36.2 – 38.0° , similar to $\text{Ga}_4(\text{L}^6)_4$ cage (36.0 – 37.6°). The triazole-CH groups are oriented toward the cavity, indicative of weak intramolecular hydrogen bonding interactions with the catecholate oxygen atoms (triazole-CH $\cdots$ O-catecholate), with distances of 2.40 – $2.44 \text{ \AA}$, akin to $\text{Ga}_4(\text{L}^6)_4$ cage (2.41 – $2.45 \text{ \AA}$). Additionally, the triazole rings are directed toward adjacent triazole units, suggesting the possibility of π – π stacking interactions between them at an interplanar distance of about 3.55 – $3.59 \text{ \AA}$, behaviour observed in $\text{Ga}_4(\text{L}^6)_4$ as well. The gallium centers that define the tetrahedral framework are separated by 13.20 – $13.28 \text{ \AA}$, dimensions very similar

to those for $\text{Ga}_4(\text{L}^6)_4$ (13.40–13.47 Å). Nevertheless, if we compare the optimised geometry of $\text{Ga}_4(\text{L}^7)_4$ cage with $\text{Ga}_4(\text{L}^6)_4$, we observed that $\text{Ga}_4(\text{L}^7)_4$ presents a slightly larger cavity with a volume of 111 Å³ (Figure 33). Both cavities are distributed toward the centre of tetrahedrons, however, the presence of fluorine atoms in the central aromatic ring of $\text{Ga}_4(\text{L}^7)_4$ affects the cages optimised geometry increasing the cavity volume. The internal cavity of $\text{Ga}_4(\text{L}^6)_4$ featuring hydrogen atoms in the phenylene core is therefore smaller (86 Å³). In addition, the presence of highly electronegative fluorine atoms in the core induces electrostatic repulsion between the ligands that forming the cage, causing the structure presents less compression compared to its non-fluorinated analogue $\text{Ga}_4(\text{L}^6)_4$. This results in a larger cavity in $\text{Ga}_4(\text{L}^7)_4$, as observed from the analysis of their optimised geometries.

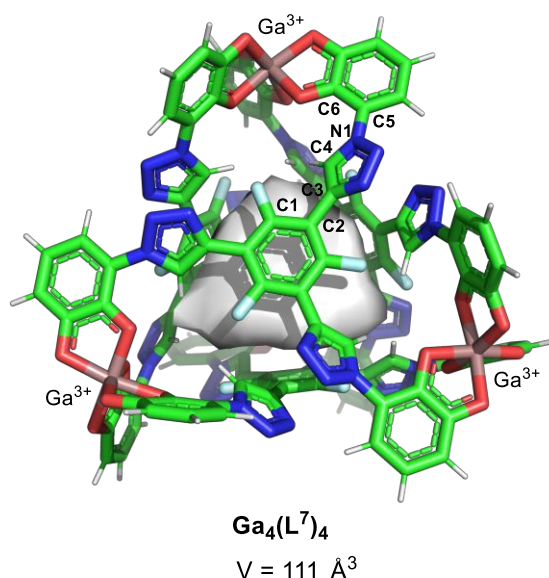


Figure 33. Optimised geometry of the cage $\Delta,\Delta,\Delta,\Delta$ -[$\text{Ga}_4(\text{L}^7)_4$]. The computed cage cavity volume of the system was calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Selected bond lengths (Å) and angles (°): triazole–CH····O–catecholate 2.40–2.44, triazole ring (cent)····triazole ring (cent) 3.55–3.59, Ga–Ga 13.20–13.28, torsion angles C1–C2–C3–C4 40.2–43.6, C4–N1–C5–C6 36.2–38.0°.

In the crystalline structure of $\text{Al}_4(\text{L}^8)_4$ (Figure 34A), the aromatic $[(\text{C}_6\text{H}_4)_3\text{N}]$ core is almost coplanar with the triazole ring plane with torsion angles of 176.7(3) –177.1(3)°, indicating delocalisation through conjugation of their π – π systems. Moreover, the $\text{Al}_4(\text{L}^8)_4$ cage shows that core aromatic C_6H_4 rings are twisted relative to the central nitrogen atom with a bond angle of 116.6(2)–126.6(3)°. Nevertheless, the optimised geometry of $\text{Ga}_4(\text{L}^9)_4$ cage (Figure 34B) shows that

phenylene rings of 1,3,5-triphenylbenzene core of the ligand **L**⁹, are twisted with respect to the central aromatic ring plane, with torsion angles of 16.6–36.0° as well as triazole rings are twisted with respect to phenylene rings with torsion angles of 159.2–179.3°. Both cages present catecholate rings with a rotational displacement, with torsion angles of 18.48(17)–44.30(18)° relative to the [(C₆H₄)₃N] core plane for **Al**₄(**L**⁸)₄ and of 20.7–39.9° with respect to triazole rings plane for **Ga**₄(**L**⁹)₄. Like in the previous cage examples, the triazole–CH groups of each ligand are oriented toward the internal cavities of **Al**₄(**L**⁸)₄ and **Ga**₄(**L**⁹)₄ cages, positioned at distances of 2.4204(16)–2.6485(16) Å for **Al**₄(**L**⁸)₄ and 2.19–2.56 Å for **Ga**₄(**L**⁹)₄ from the oxygen atoms of the catecholate groups, suggesting weak electrostatic interactions (triazole–CH····O–catecholate). Additionally, the triazole–CH units of both cages adopt opposing orientations within each ligand, alternating between them. Unlike **Al**₄(**L**⁸)₄ cage, the optimised geometry of **Ga**₄(**L**⁹)₄ reflects that the aromatic rings of 1,3,5-triphenylbenzene core are directed toward adjacent 1,3,5-triphenylbenzene units, highlighting the presence of weak CH····π interactions at a distance ranging between 2.75–3.44 Å. **Al**₄(**L**⁸)₄ crystalised with four K⁺ in its cavity, similar behaviour observed for cages M₂L₃ in Chapter 1. These cations (K⁺) are in the cavity next to the catechol oxygen atoms, with which they interact electrostatically (K⁺ have been omitted in figure 34A for clarity).

The spatial separation between metal ions constituting these supramolecular tetrahedral architectures ranging between 17.2048(16)–17.2156(11) Å for **Al**₄(**L**⁸)₄ and 19.28–20.14 Å for **Ga**₄(**L**⁹)₄. Despite **H**₆**L**⁸ and **H**₆**L**⁹ forming larger tetrahedral structures than the ligands **H**₆**L**⁶ and **H**₆**L**⁷, with Ga–Ga distances of ~13 Å for both **M**₄(**L**⁶)₄ and **M**₄(**L**⁷)₄ cages, the **M**₄(**L**⁸)₄ and **M**₄(**L**⁹)₄ (M = Ga, Al) systems present very small internal cavities of less than 25 Å³ (Figure 34) in both Al and Ga systems. These **M**₄(**L**⁸)₄ and **M**₄(**L**⁹)₄ cavities are much smaller than in the **M**₄(**L**⁶)₄ and **M**₄(**L**⁷)₄ cages (86–111 Å³). This is attributed to the combination of triazole and catechol moieties within the ligands, which promotes twisting and helicity at each vertex of the tetrahedron, similar to the behaviour observed in the helicates M₂L₃ discussed in Chapter 1. Moreover, the intrinsic nature and the greater aromatic character of the ligands **H**₆**L**⁸ and **H**₆**L**⁹, compared to the ligands **H**₆**L**⁶ and **H**₆**L**⁷, as well as the hydrophobic effect, favour that the ligands **H**₆**L**⁸ and **H**₆**L**⁹ are compressed toward the cavity, maximizing electrostatic interactions between ligands in the cages **M**₄(**L**⁸)₄ and **M**₄(**L**⁹)₄, leaving minimal volume for the internal cavity. The axial extension of the

ligands H_6L^8 and H_6L^9 , which consists of an elongation of the ligands from their centre, amplifies this effect, comparing with the ligands H_6L^6 and H_6L^7 .

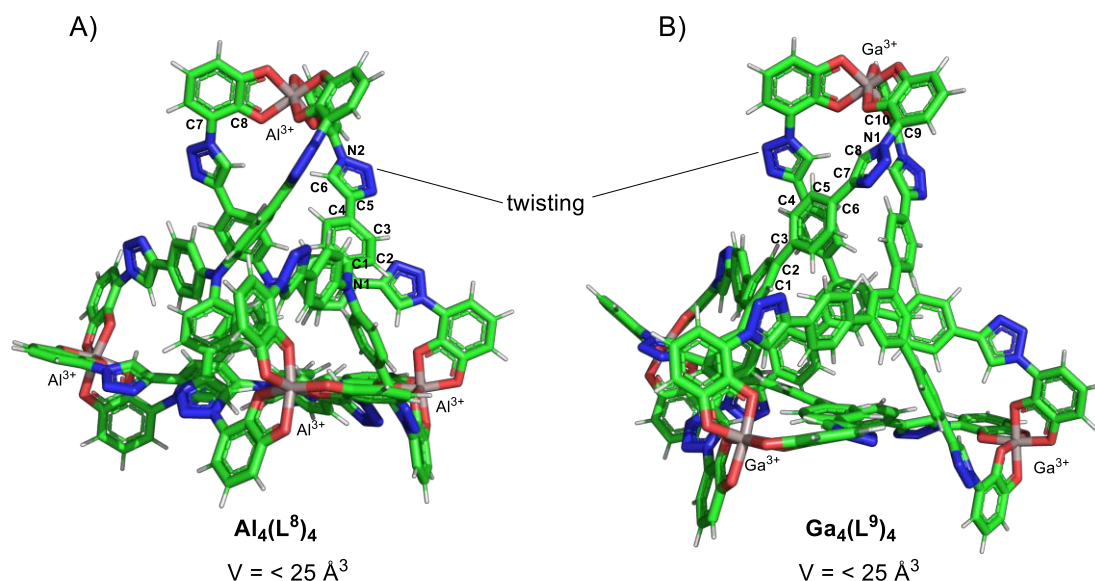


Figure 34. A) Crystalline structure of the cage $\Delta, \Delta, \Delta, \Delta$ -[$\text{Al}_4(\text{L}^8)_4$]. Both enantiomers $\Delta, \Delta, \Delta, \Delta$ -[$\text{Al}_4(\text{L}^8)_4$] and $\Lambda, \Lambda, \Lambda, \Lambda$ -[$\text{Al}_4(\text{L}^8)_4$] crystallised together but only one enantiomer is shown; B) Optimised geometry of the cage $\Delta, \Delta, \Delta, \Delta$ -[$\text{Ga}_4(\text{L}^9)_4$]. The computed cage cavity volumes of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Disordered K^+ counterions and solvent molecules (DMF, H_2O , THF and acetone) from crystallisation are omitted for clarity. The core cage is fully ordered and unaffected by the solvent disorder. Selected bond lengths (Å) and angles ($^\circ$): A) triazole-CH $\cdots$ O-catecholate 2.4204(16)–2.6485(16), Al–Al 17.2048(16)–17.2156(11), bond angles N1–C1–C2 116.6(2)–126.6(3), torsion angles C3–C4–C5–C6 176.7(3)–177.1(3), C6–N2–C7–C8 18.48(17)–44.30(18); B), triazole-CH $\cdots$ O-catecholate 2.19–2.56, Ga–Ga 19.28–20.14, phenylene-CH $\cdots$ π -phenylene (cent) 2.75–3.44, torsion angles C1–C2–C3–C4 16.6–36.0, C5–C6–C7–C8 159.2–179.3, C8–N1–C9–C10 20.7–39.9. Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

The crystalline structure of the naphthalene-derived $\text{Ga}_4(\text{L}^{10})_4$ cage (Figure 35) shows different structural features than the catechol-derived cages for L^{6-10} ligands. The triazole and central phenylene C_6H_3 rings are slightly twisted between them with torsion angles of 155.5(6)–179.8(6) $^\circ$, indicating potential π -system conjugation and electron delocalisation across these aromatic units. In contrast, the

naphthalenediol moieties largely deviate from this plane, displaying a torsion angle of $108.0(16)$ – $127.9(15)^\circ$, which disrupts the ligand's planarity. Unlike $Ga_4(L^6)_4$ cage, the triazole–CH groups are positioned between $4.457(10)$ – $4.924(5)$ Å away from the nearest oxygen atoms, inhibiting any significant electrostatic interaction (CH $\cdots$ O–catecholate contacts) due to the extended geometry imposed by naphthalene–dioxy units. Additionally, the spatial arrangement of the naphthalene–dioxy units leads to a larger separation between ligands, preventing the formation of stabilizing supramolecular interactions. As observed in previous tetrahedral cages containing catecholate ligands L^{6-9} , the triazole–CH groups within each ligand adopt antiparallel orientations. Akin to $Al_4(L^8)_4$ cage, $Ga_4(L^6)_4$ crystalised with four K^+ in its cavity. These cations (K^+) are in the cavity close to the catechol oxygen atoms, with which they interact electrostatically (K^+ have been omitted in figure 35 for clarity).

The increased intermetallic separation of $13.784(2)$ – $14.2226(14)$ Å between gallium centres in $Ga_4(L^{10})_4$ is slightly larger relative to its analogue $Ga_4(L^6)_4$ (~ 13 Å) reflects the influence of the larger ligand framework on the overall cage dimensions. Interestingly, the radial elongation by the naphthalene group within the ligand H_6L^{10} suppresses the torsional flexibility typically observed at the vertices of the previous catechol–derived tetrahedral cages. This geometric constraint induces an outward displacement of the ligands, resulting in a global expansion of the supramolecular architecture $Ga_4(L^{10})_4$. Therefore, a substantial central void is generated, producing a nearly spherical cavity of ~ 1148 Å³ (Figure 35) whose volume is distributed throughout the interior of the tetrahedral framework. This cavity is significantly larger than those observed in any of the other catechol–derived tetrahedral cages discussed in this Chapter, highlighting the importance of this radial elongation of the ligand H_6L^{10} .

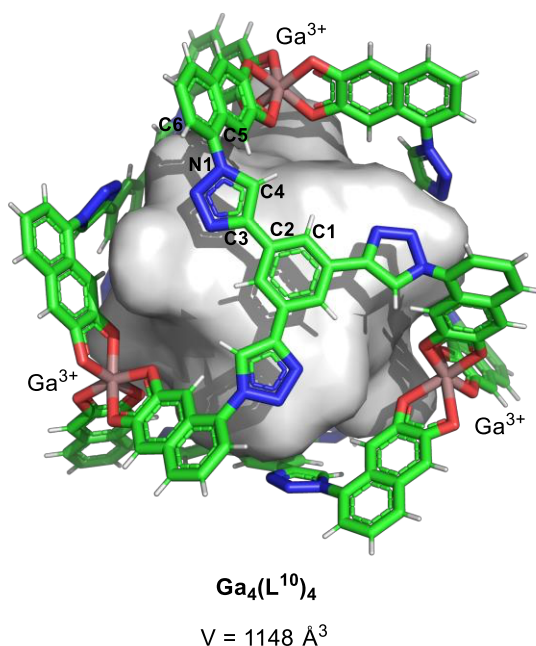


Figure 35. Crystalline structure of the naphthalene-expanded cage $\Delta,\Delta,\Delta,\Delta\text{-Ga}_4(\text{L}^{10})_4$. The computed cage cavity volume of the system was calculated using the CageCavityCalc (C3) package with a grid size of 1.5 Å and the EEM implemented charge model. Disordered K^+ and Et_4N^+ counterions and solvent molecules (DMF, H_2O , and acetone) from crystallisation are omitted for clarity. The core cage is fully ordered and unaffected by the solvent disorder. Selected bond lengths (Å) and angles (°): triazole-CH $\cdots$ O-catecholate 4.457(10)–4.924(5), Ga–Ga 13.784(2)–14.2226(14), torsion angles C1–C2–C3–C4 155.5(6)–179.8(6), C4–N1–C5–C6 108.0(16)–127.9(15). Thermal ellipsoid plots at 50% probability are given in the Annexes to this Chapter.

Such an increase in internal volume has potential implications for host–guest chemistry due to the expanded cavity in $\text{Ga}_4(\text{L}^{10})_4$ may accommodate larger or more structurally complex guest molecules, enhance guest exchange dynamics, or allowing for the encapsulation of multiple smaller guests simultaneously. Furthermore, the increased spatial separation between ligands may reduce steric hindrance at entry points, potentially improving guest accessibility and diffusion. These cage properties suggest that $\text{M}_4(\text{L}^6)_4$, $\text{M}_4(\text{L}^7)_4$ and $\text{M}_4(\text{L}^{10})_4$ systems could serve as promising platforms for molecular recognition, selective encapsulation, or catalytic transformations within confined environments. These cage features remain open for further investigations.

2.3.5 Host–Guest Encapsulation Studies of Ammonium Ions (R_4N^+)

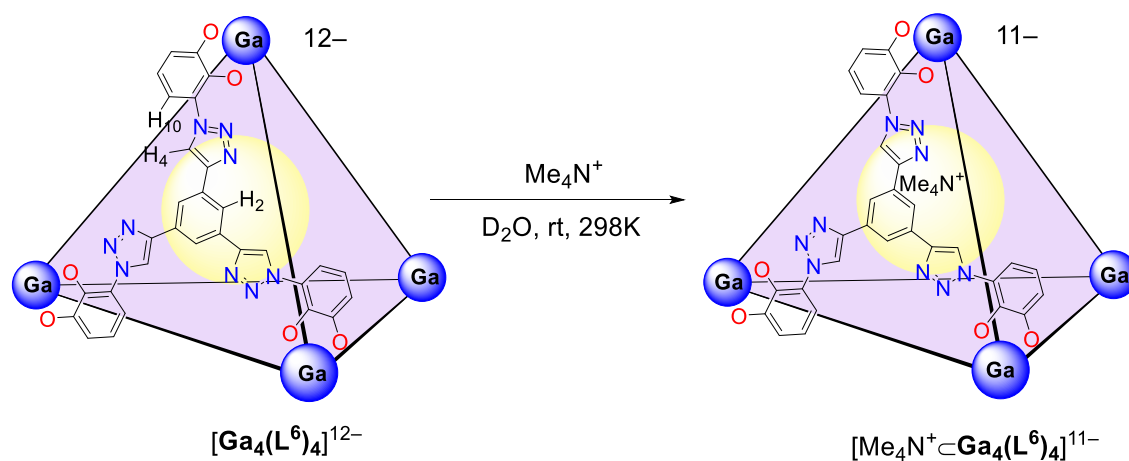
In this section, we study the host–guest chemistry of the tetrahedral cages $Al_4(L^6)_4$ and $Ga_4(L^6)_4$, presenting these cage assemblies suitable cavity sizes and adequate electrostatic potentials to accommodate small cationic molecules. Nevertheless, larger cages such as $M_4(L^8)_4$ and $M_4(L^9)_4$ are more compact and present small cavities which cannot host small organic cations. In fact, encapsulation experiments using cages $M_4(L^8)_4$ and $M_4(L^9)_4$ as hosts and Me_4N^+ , Et_4N^+ and Pr_4N^+ ions as model guests were unsuccessful. Cage architectures $M_4(L^7)_4$ and $M_4(L^{10})_4$ present adequate cavity volumes for encapsulating cations, the study of their host–guest properties requires further investigation, representing an open area to study in the future.

For studying the encapsulation properties of cages $Al_4(L^6)_4$ and $Ga_4(L^6)_4$, we employed different ammonium cations (R_4N^+) as model guests. Concerning the negative electrostatic potential of the cavity of $M_4(L^6)_4$ assemblies, the series Me_4N^+ , Et_4N^+ , Pr_4N^+ and Bu_4N^+ were chosen as potential guest organic cations. The encapsulation process of these cations was studied in-situ by NMR and ITC techniques, allowing us to understand the host–guest properties of the cages $Al_4(L^6)_4$ and $Ga_4(L^6)_4$ in D_2O . These experiments were conducted in a highly polar solvent, water, in which the cages are soluble. This solvent environment favours the encapsulation of the organic cations due to the hydrophobic effect. This effect refers to the tendency of hydrophobic molecules or groups to aggregate in aqueous environments to minimise their disruptive effect on the hydrogen–bonded network of water molecules. In host–guest chemistry, many guests are often expelled from water and are encapsulated by the host cavity, which is more hydrophobic, due to this effect. This reduces the overall system's free energy, making encapsulation thermodynamically favourable.

Me_4N^+ , Et_4N^+ , Pr_4N^+ and Bu_4N^+ cations are quite different in terms of size, which was of particular interest for our study, allowing us to know the cages's ability to “breathe” and adapt its cavity to host different guests. All these cations have a tetrahedral and single positively charged nitrogen atom, being compatible with the cavity features and sizes, as discussed in section 1.3.6.

In accordance with Rebek's rule,^[75] optimal binding with $[Al_4(L^6)_4]^{12-}$ and $[Ga_4(L^6)_4]^{12-}$ would correspond to a guest molecule with a volume of approximately 45–55% of their cavity volume. Me_4N^+ , Et_4N^+ , Pr_4N^+ occupy approximately 49%,

56%, and 63% of the total cavity volume of [Al₄(L⁶)₄]¹²⁻ and [Ga₄(L⁶)₄]¹²⁻, respectively, thus complying with Rebek's rule. In contrast, Bu₄N⁺ occupies around 76%, exceeding the upper limit defined by Rebek's rule. According to NMR experiments, Me₄N⁺, Et₄N⁺, Pr₄N⁺ can bind inside the cavity of [Al₄(L⁶)₄]¹²⁻ and [Ga₄(L⁶)₄]¹²⁻ cages. For example, by adding Me₄N⁺ as guest into a solution of cage [Ga₄(L⁶)₄]¹²⁻ (Scheme 6), we observed a progressive disappearance of the signals for [Ga₄(L⁶)₄]¹²⁻ with each Me₄N⁺ addition and the appearance of a new specie that correspond with [Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻ (triangles) culminating in a complete signal loss for [Ga₄(L⁶)₄]¹²⁻ upon reaching 3 equivalents of Me₄NBr (Figure 37). [Ga₄(L⁶)₄]¹²⁻ and [Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻ species are in dynamic equilibrium during the titration, and the equilibrium can be completely shifted toward [Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻ formation by the addition of 3 equivalents. The protons H4, H10, and H2 of the cages are most notably affected by the encapsulation of Me₄N⁺, with a slight downfield shielding observed for H4 and H10, H4 from δ 9.24 ppm [Ga₄(L⁶)₄]¹²⁻ to δ 9.18 ppm ([Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻) and H10 from δ 7.48 ppm ([Ga₄(L⁶)₄]¹²⁻) to δ 7.39 ppm ([Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻) whereas a significant upfield shielding for H2 was observed, shifting from δ 7.10 ppm ([Ga₄(L⁶)₄]¹²⁻) to δ 7.71 ppm ([Me₄N⁺⊂Ga₄(L⁶)₄]¹¹⁻). Additionally, a pronounced shielding of 2 ppm is observed for the signal corresponding to the encapsulated tetramethylammonium, shifting from δ 3.05 ppm for free Me₄N⁺ (circle) to δ 1.05 ppm for encapsulated Me₄N⁺ (square). A similar behaviour was observed for NMR titrations of Al₄(L⁶)₄ system with Me₄N⁺ as guest. The upfield shielding of the guest signals is attributed to the accumulation of π-electron density within the host cavity, resulting from the high aromatic character of the ligands that form the host structure. This electron-rich environment generates magnetic fields, which induce local shielding effects on the encapsulated guest, particularly on protons positioned close to the aromatic rings. Consequently, the chemical shifts in the NMR spectrum move upfield, providing further evidence of guest encapsulation within an aromatic and hydrophobic cavity. Nevertheless, downfield shifts in the host's NMR signals are observed due to noncovalent interactions with the guest that generate changes in the local electronic environment, further deshielding nearby protons.



Scheme 6. Encapsulation of Me_4N^+ with $[\text{Ga}_4(\text{L}^6)_4]^{12-}$.

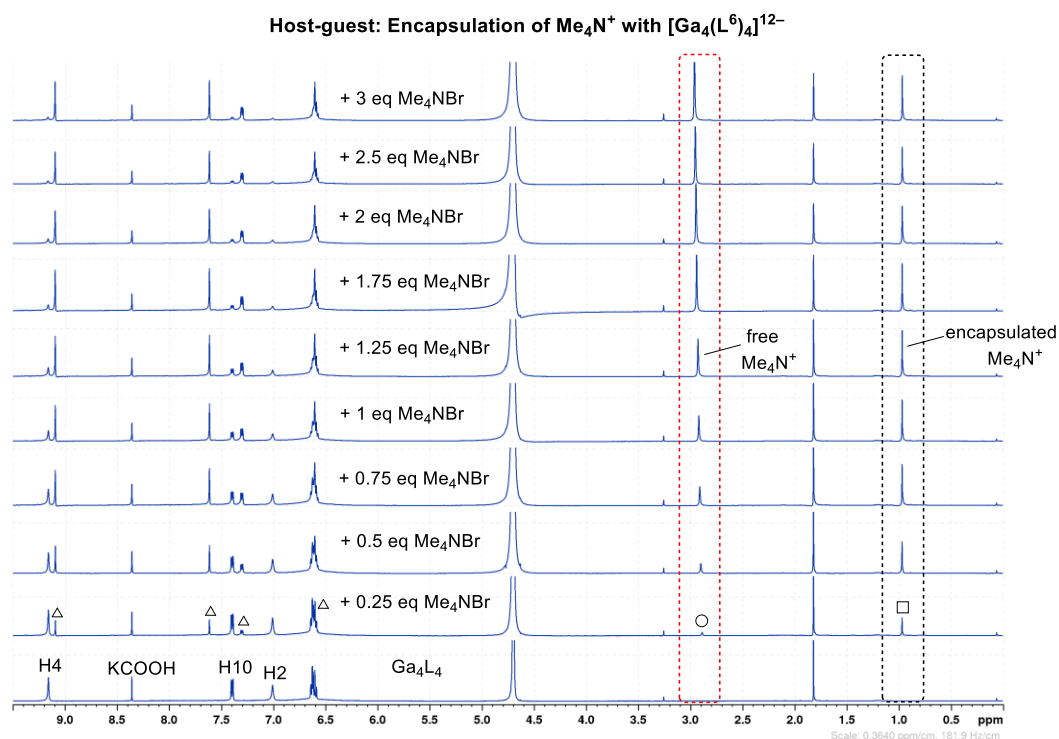


Figure 36. ^1H NMR (500 MHz, D_2O , 298 K) titrations of Me_4NBr (1 Mm) into $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ (826 μM). The new complex $[\text{Me}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$ is indicated by triangles, circle indicates external Me_4N^+ ions and square indicates Me_4N^+ as guest. KCOOH (potassium formate) is the internal standard.

The encapsulation process of Me_4N^+ , Et_4N^+ and Pr_4N^+ by the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cages was studied using DOSY NMR and Nuclear Overhauser effect

spectroscopy as well. For instance, NOESY experiment of the complex $[\text{Me}_4\text{N}^+\text{cGa}_4(\text{L}^6)_4]^{11-}$ show cross peaks (blue box) between the bound guest signal and the triazole signal (H4) and core aromatic signal (H2) of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage (Figure 38A). Moreover, DOSY NMR of $[\text{Me}_4\text{N}^+\text{cGa}_4(\text{L}^6)_4]^{11-}$ (Figure 38B) indicated that the signals of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and the bound Me_4N^+ diffuse with a very similar rate, being the diffusion coefficient $1.40 \times 10^{-10} \text{ m}^2/\text{s}$ for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and $1.50 \times 10^{-10} \text{ m}^2/\text{s}$ for the bound Me_4N^+ . This fact corroborates that Me_4N^+ is diffusing with the cage $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ due to Me_4N^+ is in the internal cavity of $[\text{Ga}_4(\text{L}^6)_4]^{12-}$. The diffusion coefficient for the host–guest complex $[\text{Me}_4\text{N}^+\text{cGa}_4(\text{L}^6)_4]^{11-}$ match with the diffusion coefficient for the empty cage $[\text{Ga}_4(\text{L}^6)_4]^{12-}$. A similar behaviour was observed for $[\text{Al}_4(\text{L}^6)_4]^{12-}$ system in the NMR titrations with Me_4N^+ .

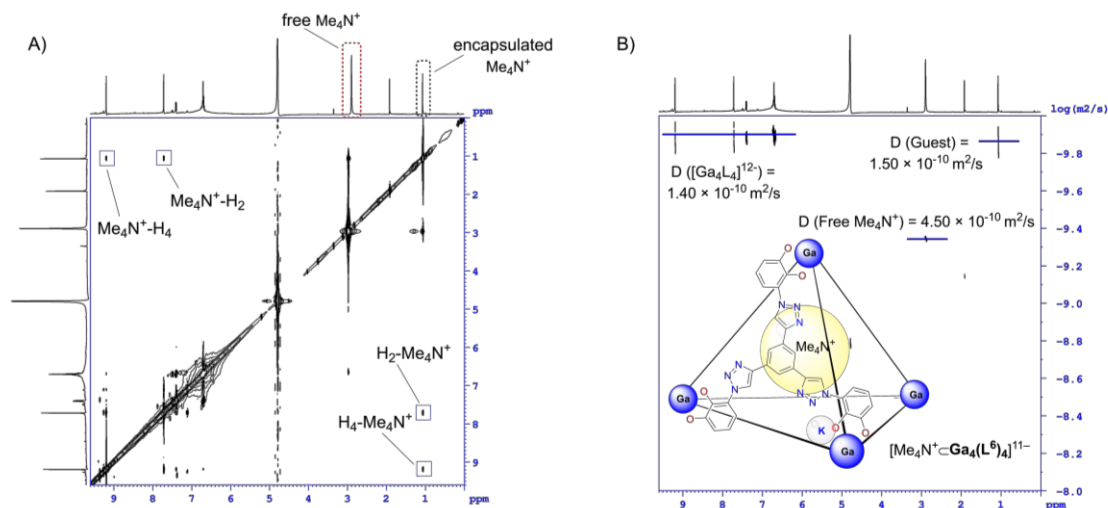


Figure 37. A) ^1H - ^1H NOESY (500 MHz, D_2O , 298 K) spectrum and B) DOSY NMR (400 MHz, D_2O , 298 K) of the complex $[\text{Me}_4\text{N}^+\text{cGa}_4(\text{L}^6)_4]^{11-}$.

To determine the thermodynamic driving forces that govern the encapsulation of these ammonium cations (R_4N^+), we employed isothermal titration calorimetry (ITC). Since accurate determination of the thermodynamics parameters of the encapsulation reactions requires concentrations to be precisely known, the effective molecular weight of $[\text{Al}_4(\text{L}^6)_4][\text{K}]_{12}$ and $[\text{Ga}_4(\text{L}^6)_4][\text{K}]_{12}$ were determined via thermogravimetric analyses (TGA). The first decreased observed in the TGA curve (up to 130 $^\circ\text{C}$) accounts for the adsorbed residual solvent that amounts to 8–10% of the total height weight. The concentration of the hygroscopic R_4NBr ($\text{R} = \text{Me}, \text{Et}, \text{Pr}$ and Bu) was obtained indirectly by determining the bromide concentration according

to the Mohr procedure. ITC experiments show that $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cages exhibit similar Gibbs free energy changes ($\Delta G = -22$ kJ/mol) for the encapsulation of Me_4N^+ in water, indicating that the driving force for encapsulation is comparable. However, the enthalpy (ΔH) and entropy ($T\Delta S$) contributions differ. The $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage has a lower enthalpy change ($\Delta H = 35$ kJ/mol) compared to the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage ($\Delta H = 42$ kJ/mol), suggesting a slightly more endothermic binding in the Ga cage. Nevertheless, the entropy change ($T\Delta S$) is higher for the Ga cage (63 kJ/mol) than for the Al cage (57 kJ/mol). Equilibrium constants (K_a) extracted from the isotherms for the complexations of the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage with Me_4N^+ were thus determined to be $8.5 \times 10^3 \text{ M}^{-1}$ and $6.1 \times 10^3 \text{ M}^{-1}$ respectively (Figure 39), suggesting a slightly higher affinity of Me_4N^+ for the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage compared to the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage. These thermodynamic data indicate that this encapsulation process is endothermic and predominantly driven by entropy. The positive enthalpy suggests that energy is required to disrupt existing interactions, such as the strong solvation shell surrounding the ammonium cation and potential electrostatic interactions within the anionic cage. Additionally, structural rearrangements of the host necessary to accommodate the guest may contribute to the enthalpic cost. Conversely, the favourable entropic contribution is likely due to the release of ordered solvent molecules from both the host cavity and the cation's solvation shell upon complex formation. This desolvation leads to an overall increase in the degrees of freedom of the system, reflecting a gain in disorder. Therefore, despite the enthalpic penalty, the gain in entropy provides the main thermodynamic driving force for the encapsulation process.

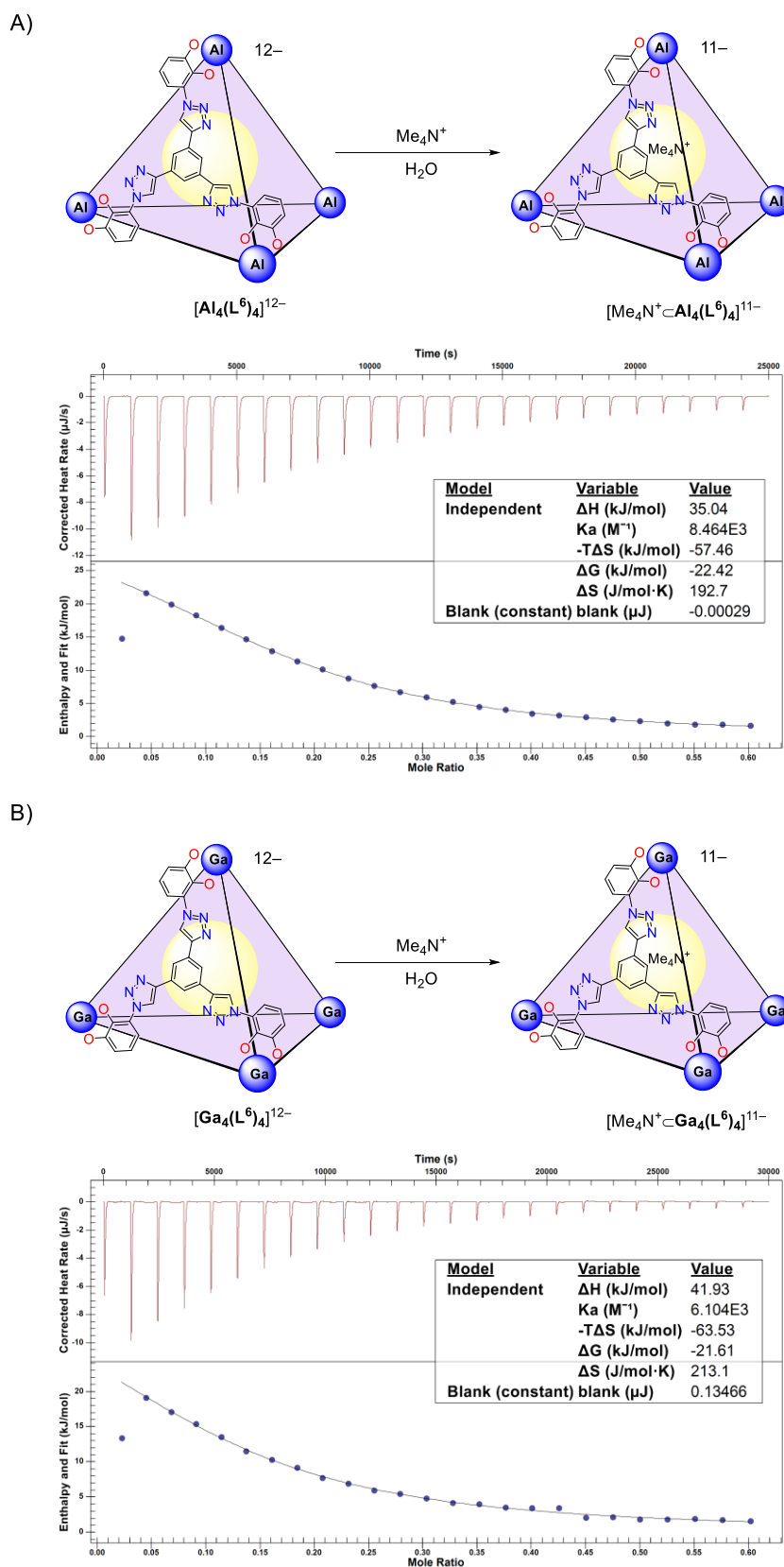
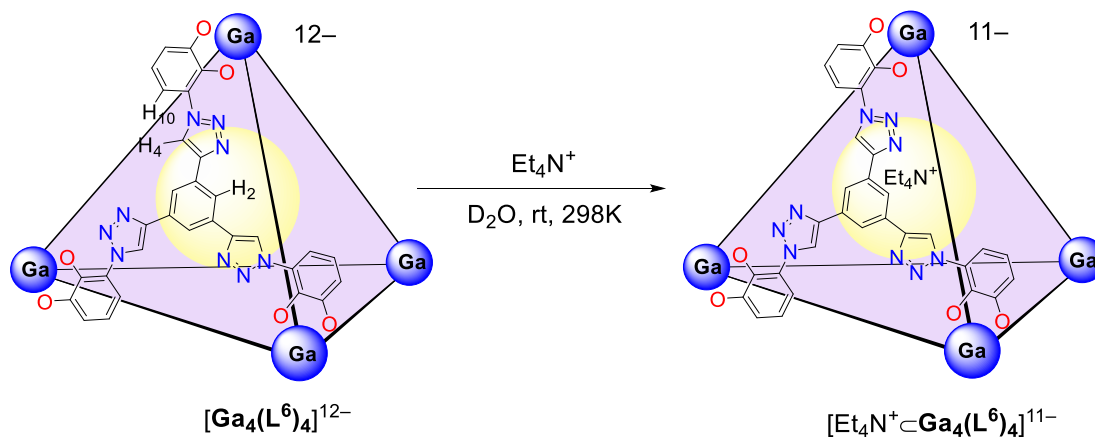


Figure 38. ITC titration plot and fitted curve obtained through titrations of Me_4NBr (6.6 Mm) into A) $[\text{Al}_4(\text{L}^6)_4]^{12-}$ (1.5 mM) and B) $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ (1.5 Mm) in water.

To study the encapsulation of Et_4N^+ by both supramolecular systems, a similar titration procedure like the one used for Me_4N^+ was employed. For instance, for $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage (Scheme 7), a progressive disappearance of the signals for $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ with each Et_4N^+ addition was observed whereas a new specie corresponding to $[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$ appeared (triangles), culminating in a complete signal loss for $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ upon reaching 2.5 equivalents of Et_4NBr (Figure 40). The equilibrium can be completely shifted toward $[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$ formation by the addition of 2.5 equivalents. Like in the titrations with Me_4N^+ , protons H4, H10, and H2 of the cages are the most significantly influenced by the encapsulation of Et_4N^+ . H4 and H10 experiment a downfield shifted, H4 from δ 9.24 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 9.10 ppm ($[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$) and H10 from δ 7.48 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 7.40 ppm ($[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$) whereas H2 show an upfield shifted from δ 7.10 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 7.78 ppm ($[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$). Additionally, a pronounced shielding is observed for the signal corresponding to the encapsulated Et_4N^+ , shifting from δ 3.01 ppm ($\text{CH}_2\text{--N}$ of free Et_4N^+) to δ 1.17 ppm ($\text{CH}_2\text{--N}$ of encapsulated Et_4N^+) and from δ 1.04 ppm (--CH_3 of free Et_4N^+) to δ -0.25 ppm (--CH_3 of encapsulated Et_4N^+). Like in Me_4N^+ titration, the upfield shielding of the guest (Et_4N^+) signals is attributed to the accumulation of π -electron density within the host cavity, resulting from the high aromatic character of the ligands that form the host structure. A similar behaviour was observed for $[\text{Al}_4(\text{L}^6)_4]^{12-}$ system in the NMR titrations with Et_4N^+ .



Scheme 7. Encapsulation of Et_4N^+ with $[\text{Ga}_4(\text{L}^6)_4]^{12-}$.

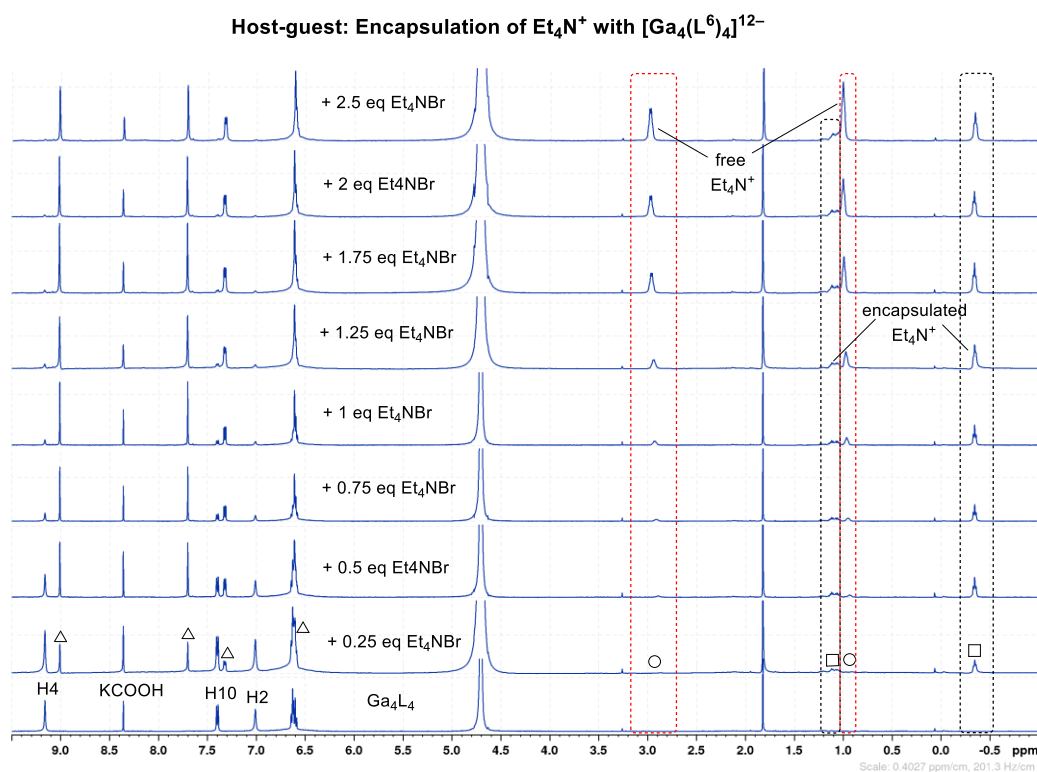


Figure 39. ^1H NMR (500 MHz, D_2O , 298 K) titrations of Et_4NBr (1 Mm) into $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ (454 μM). The new complex $[\text{Et}_4\text{N}^+\subset\text{Ga}_4(\text{L}^6)_4]^{11-}$ is indicated by triangles, circle indicates external Et_4N^+ ions and square indicates Et_4N^+ as guest. KCOOH (potassium formate) is the internal standard.

NOESY experiment of the host–guest complex $[\text{Et}_4\text{N}^+\subset\text{Ga}_4(\text{L}^6)_4]^{11-}$ show cross peaks (blue box) between the bound guest signal and the triazole signal (H4) and core aromatic signal (H2) of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage (Figure 41A). Furthermore, DOSY NMR of the complex $[\text{Et}_4\text{N}^+\subset\text{Ga}_4(\text{L}^6)_4]^{11-}$ (Figure 41B) suggest that the signals from the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and the bound Et_4N^+ diffuse with similar rate, being the diffusion coefficient $1.40 \times 10^{-10} \text{ m}^2/\text{s}$ for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and $1.50 \times 10^{-10} \text{ m}^2/\text{s}$ for the bound Et_4N^+ which means Et_4N^+ is in the cavity of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage. Like the complex $[\text{Me}_4\text{N}^+\subset\text{Ga}_4(\text{L}^6)_4]^{11-}$, the diffusion coefficient for the host–guest complex $[\text{Et}_4\text{N}^+\subset\text{Ga}_4(\text{L}^6)_4]^{11-}$ match with the diffusion coefficient for the empty cage $[\text{Ga}_4(\text{L}^6)_4]^{12-}$.

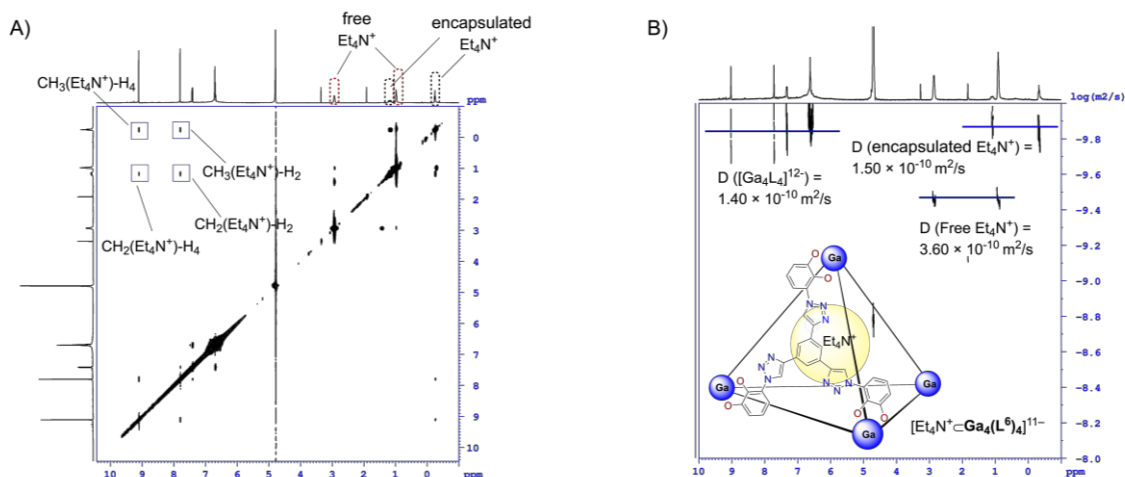


Figure 40. A) ^1H - ^1H NOESY (500 MHz, D_2O , 298 K) spectrum and B) DOSY NMR (400 MHz, D_2O , 298 K) of the complex $[\text{Et}_4\text{N}^+ \cdot \text{Ga}_4(\text{L}^6)_4]^{11-}$.

Equilibrium constants (K_a) extracted from the isotherms for the complexations of the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage with Et_4N^+ were thus determined to be $1.3 \times 10^4 \text{ M}^{-1}$ and $3.5 \times 10^4 \text{ M}^{-1}$ respectively (Figure 41), suggesting a slightly higher affinity of Et_4N^+ for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage. For this guest (Et_4N^+), both cages $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ show comparable Gibbs free energy change for the encapsulation process ($[\text{Al}_4(\text{L}^6)_4]^{12-}$: $\Delta G = -24 \text{ kJ/mol}$; $[\text{Ga}_4(\text{L}^6)_4]^{12-}$: $\Delta G = -26 \text{ kJ/mol}$). The enthalpy change is higher for the Al cage ($\Delta H = 58 \text{ kJ/mol}$) than for the Ga cage ($\Delta H = 44 \text{ kJ/mol}$), while the entropy change ($T\Delta S$) is more significant for the Al cage (82 kJ/mol) compared to the Ga cage (70 kJ/mol). Both cages exhibit higher affinities for the Et_4N^+ than for Me_4N^+ . The higher affinity of tetraethylammonium (Et_4N^+) for both cages is largely due to complementary shape and size. Et_4N^+ cation fits well into the cavity of the cages, allowing for optimal non-covalent interactions such as electrostatic and van der Waals interactions. This shape and size complementarity stabilises the complex, resulting in a higher binding constant (K_a) and a more negative Gibbs free energy (ΔG), indicating a more favourable and spontaneous binding process. Notably, both Me_4N^+ and Et_4N^+ encapsulation process are entropically driven, as the higher entropy contributions ($T\Delta S$) compared to the enthalpy changes (ΔH). This indicates a specific and strong interaction between the host cages and guests, leading to stable host-guest complex formation.

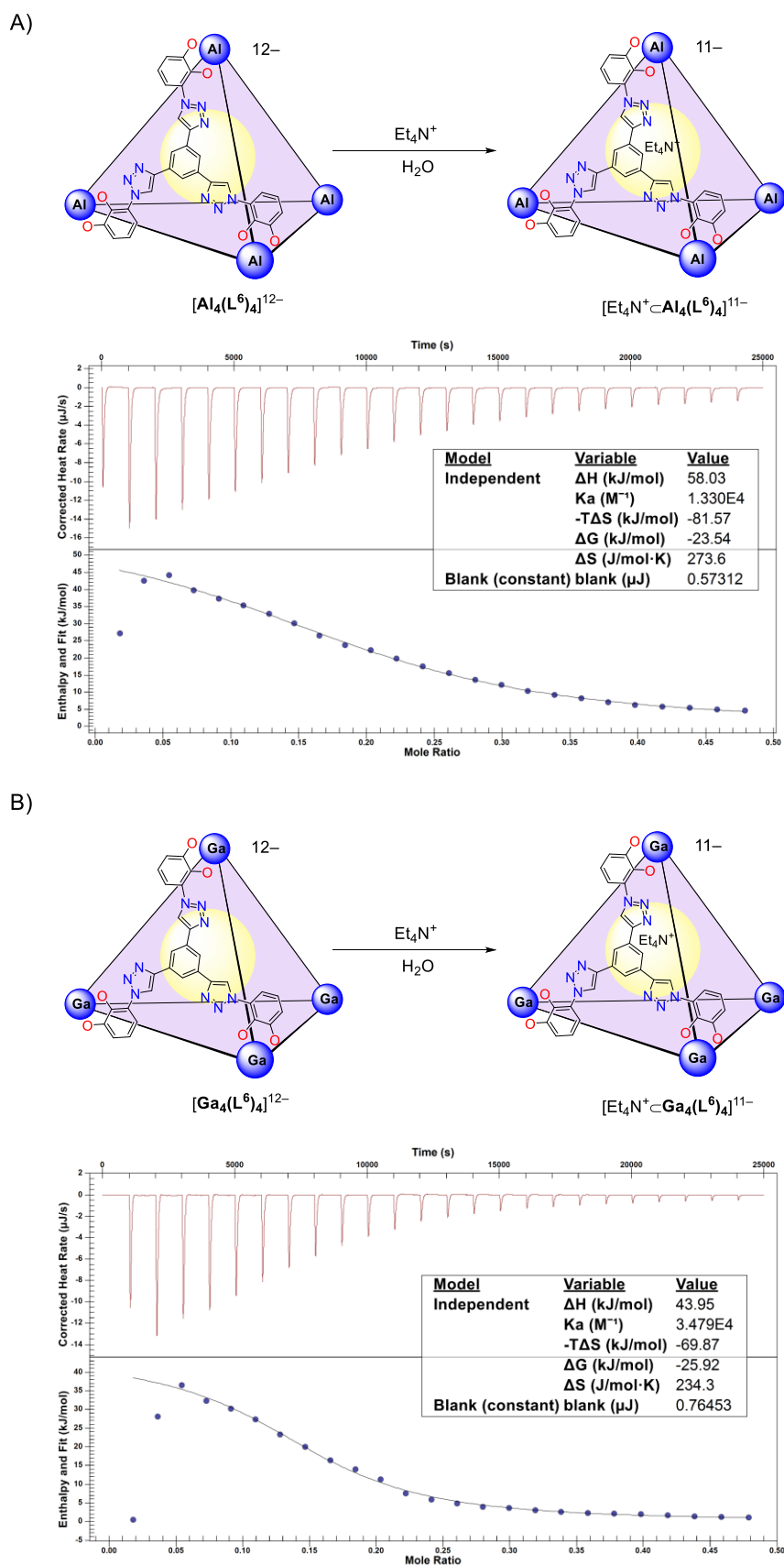
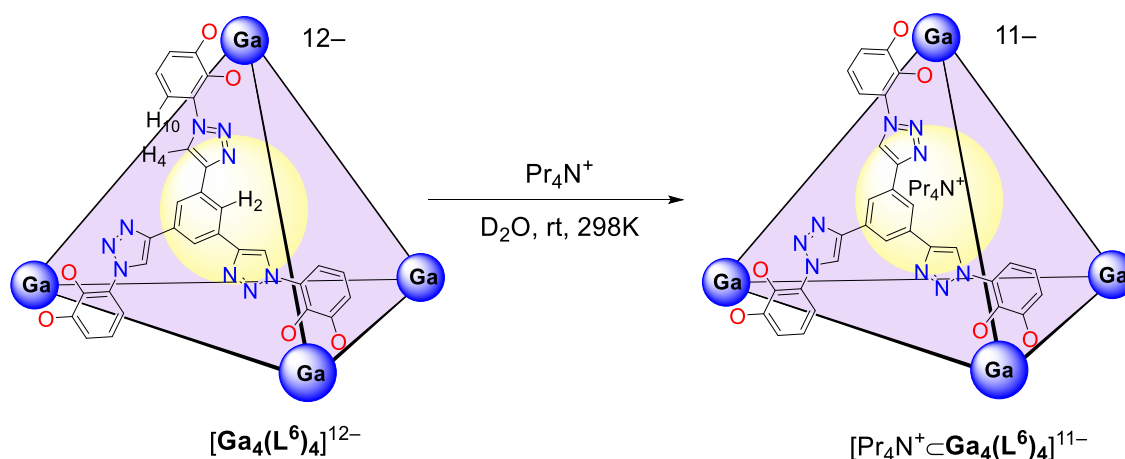


Figure 41. ITC titration plot and fitted curve obtained through titrations of Et_4NBr (5.25 Mm) into A) $[\text{Al}_4(\text{L}^6)_4]^{12-}$ (1.5 mM) and B) $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ (1.5 mM) in water.

NMR titrations show that the encapsulation process for the Pr_4N^+ guest appears to be at the frontier in terms of size, requiring high saturation. Besides, the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage exhibits lower affinity for Pr_4N^+ requiring higher saturation level (26 equivalents of the Pr_4N^+ guest) to shift the equilibrium completely toward $[\text{Pr}_4\text{N}^+ \subset \text{Al}_4(\text{L}^6)_4]^{11-}$ formation whereas the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage needs 12 equivalents of the Pr_4N^+ guest to shift the equilibrium completely toward $[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$ formation. Qualitative analysis suggests that the Al cage has a lower affinity for the Pr_4N^+ guest than the Ga cage. For instance, for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage titration with Pr_4N^+ (Figure 43), H4 and H10 experiment a downfield shifted, H4 from δ 9.24 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 9.13 ppm ($[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$) and H10 from δ 7.48 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 7.38 ppm ($[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$) whereas H2 show an upfield shifted from δ 7.10 ppm ($[\text{Ga}_4(\text{L}^6)_4]^{12-}$) to δ 7.90 ppm ($[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$). A pronounced shielding was observed for the signal corresponding to the encapsulated Pr_4N^+ , shifting from δ 2.93 ppm ($\text{CH}_2\text{--N}$ of free Pr_4N^+) to δ 1.20/1.09 ppm ($\text{CH}_2\text{--N}$ of encapsulated Pr_4N^+), from δ 1.49 ppm ($\text{--CH}_2\text{--}$ of free Pr_4N^+) to δ 0.11 ppm ($\text{--CH}_2\text{--}$ of encapsulated Pr_4N^+) and from δ 0.78 ppm (--CH_3 of free Pr_4N^+) to δ 0.22 ppm (--CH_3 of encapsulated Pr_4N^+). In the encapsulated Pr_4N^+ , we observe that the two protons of the $\text{--CH}_2\text{--}$ group bonded to the quaternary nitrogen are not equivalent inside the cages, with two distinct signals (δ 1.20/1.09 ppm) corresponding to diastereotopic protons. This phenomenon may be because the Pr_4N^+ fitting very tightly within the cavity of the cage, thus preventing the free rotation of the four propyl groups and making them non-equivalent inside the cage, effectively generating a chiral quaternary centre at the nitrogen of Pr_4N^+ . Like in Me_4N^+ and Et_4N^+ titration, the upfield shielding of the guest (Pr_4N^+) signals is attributed to the accumulation of π -electron density within the host cavity, resulting from the high aromatic character of the ligands that form the host structure.



Scheme 8. Encapsulation of Pr_4N^+ with $[\text{Ga}_4(\text{L}^6)_4]^{12-}$.

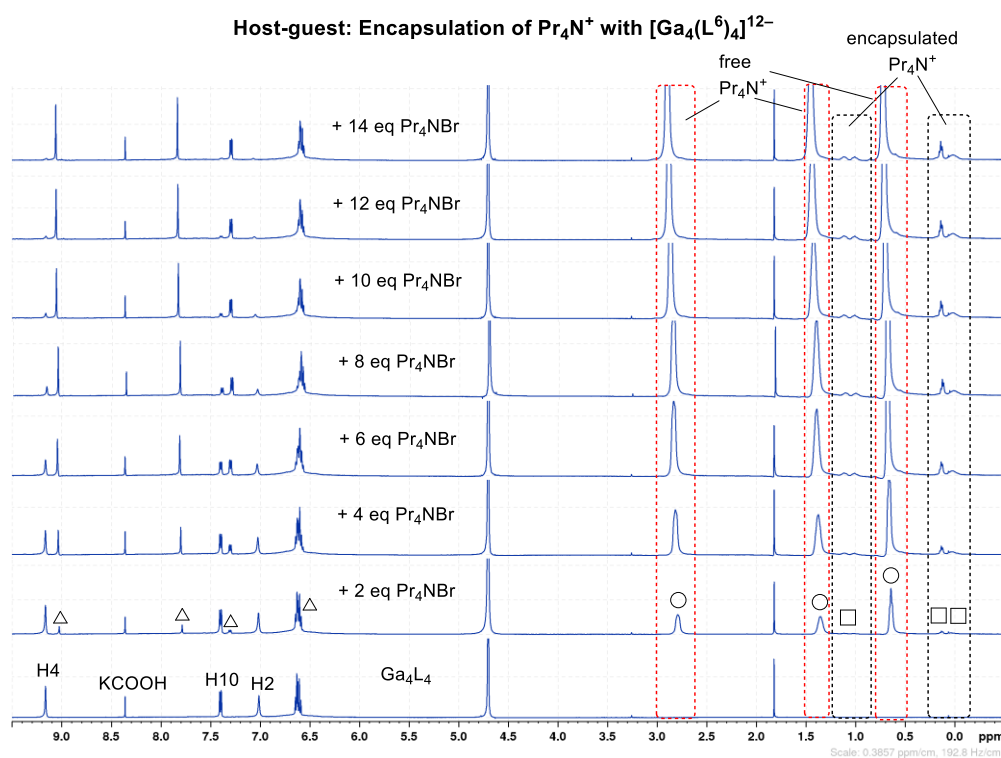


Figure 42. ^1H NMR (500 MHz, D_2O , 298 K) titrations of Pr_4NBr (25 mM) into $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ (1.43 mM). The new complex $[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$ is indicated by triangles, circle indicates external Pr_4N^+ ions and square indicates Pr_4N^+ as guest. KCOOH (potassium formate) is the internal standard.

NOESY experiment of the complex $[\text{Pr}_4\text{N}^+ \subset \text{Ga}_4(\text{L}^6)_4]^{11-}$ show cross peaks (blue box) between the bound guest signal and the triazole signal (H4) and core aromatic signal (H2) of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage (Figure 44A). Furthermore, DOSY NMR

of the complex $[\text{Pr}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$ (Figure 44B) suggest that the signals from the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and the bound Pr_4N^+ diffuse with similar rate, being the diffusion coefficient $1.40 \times 10^{-10} \text{ m}^2/\text{s}$ for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage and $1.50 \times 10^{-10} \text{ m}^2/\text{s}$ for the bound Pr_4N^+ which means Pr_4N^+ is in the cavity of the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage. Like the complexes $[\text{Me}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$ and $[\text{Et}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$, the diffusion coefficient for the host-guest complex $[\text{Pr}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$ match with the diffusion coefficient for the empty cage $[\text{Ga}_4(\text{L}^6)_4]^{12-}$.

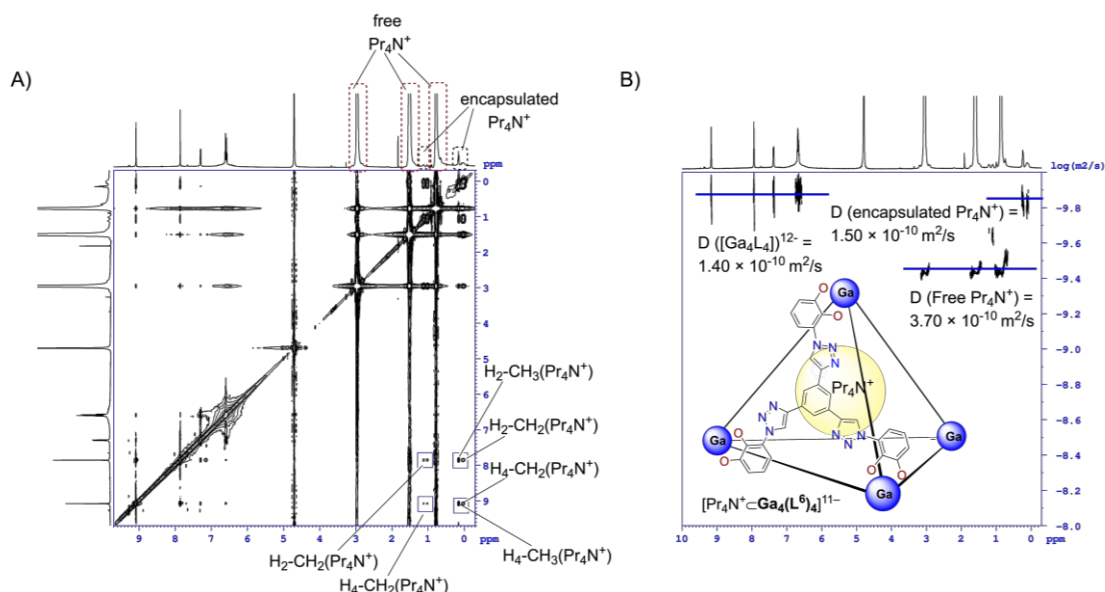


Figure 43. A) ^1H - ^1H NOESY (500 MHz, D_2O , 298 K) spectrum and B) DOSY NMR (400 MHz, D_2O , 298 K) of the complex $[\text{Pr}_4\text{N}^+\text{Ga}_4(\text{L}^6)_4]^{11-}$.

Unlike the Me_4N^+ and Et_4N^+ guests, the study of encapsulation process for the Pr_4N^+ guest by ITC was not possible due to the low binding constant (K_{aff} approximately $<10^3 \text{ M}^{-1}$) for this cation was lower than the detection limit of the calorimeter equipment. Interestingly, the Bu_4N^+ cation is not encapsulated by either the Al or Ga cage, as observed from NMR titrations, even at high saturation levels of the guest (20 equivalents). Observations showed no changes of the signals for both $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cages with Bu_4NBr additions. In the case of $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ titration with Bu_4N^+ , a progressive disappearance of the signals for the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage was observed due to the precipitation of the complex $[\text{Ga}_4(\text{L}^6)_4] [\text{K}]_x [\text{Bu}_4\text{N}]_y$ ($X = 1-12$, $Y = 12-X$). This suggests that the steric hindrance or size of the Bu_4N^+ guest prevents its effective encapsulation within the cages.

In conclusion, NMR and ITC data show that $[\text{Al}_4(\text{L}^6)_4]^{12-}$ and $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cages present distinct behaviour in terms of guest cation encapsulation, with

differences in thermodynamic parameters and binding affinities. The $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage tends to have more affinity for small guests as Me_4N^+ , presenting a higher binding constant (K_a) and a more favourable ΔG than the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage for this encapsulation process, nevertheless, the $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage needs a higher saturation level for Pr_4N^+ , reflecting a lower affinity for larger guests. Conversely, the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage presents more affinity for large guests such as Et_4N^+ and Pr_4N^+ , showing a higher binding constant for Et_4N^+ and a lower saturation level needed for Pr_4N^+ encapsulation compared to $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage.

Although metal–organic cages constructed with Ga^{3+} and Al^{3+} may share identical structural architectures, they exhibit markedly different affinities for the same guest molecules. This variation arises primarily from differences in the electronic and structural properties of the metal centres. Ga^{3+} possesses filled 3d orbitals and a larger ionic radius than Al^{3+} , resulting in distinct Lewis acidity, geometry and size of the internal cavity, and the overall rigidity or flexibility of the cage. These factors influence host–guest interactions, including binding strength, cavity polarity, and conformational adaptability. Probably, the $[\text{Ga}_4(\text{L}^6)_4]^{12-}$ cage presents a slightly larger and more flexible cavity than $[\text{Al}_4(\text{L}^6)_4]^{12-}$ cage, allowing to host large guests with high affinities. As a result, the metal ion plays a critical role in modulating the recognition and binding behaviour of the cage toward specific guest species. Moreover, the challenges observed with Pr_4N^+ and Bu_4N^+ highlight the importance of considering guest size and steric effects in the design and application of these molecular cages.

2.4 Conclusions

In this Chapter, we have developed a new series of tritopic 1,2,3-triazole-based ligands bearing catechol and naphthalenediol motifs via CuAAC click chemistry, thereby extending the toolbox of catechol-functionalised donors for supramolecular assembly. Under basic conditions, controlled self-assembly with Al³⁺ and Ga³⁺ furnished a robust family of tetrahedral M₄L₄ anionic cages. Across the ligand set **H₆L⁶**–**H₆L¹⁰**, systematic electronic and radial/steric modifications proved to be decisive in tuning the M₄L₄ cages' solubility, geometry, and cavity dimensions, enabling access to both small-void (86 Å) and large-void (1148 Å) hosts. In the solid state, single-crystal X-ray diffraction consistently revealed K⁺ encapsulated within the internal cavities, establishing a heterometallic cavity organisations (MK)₄L₄ that are maintained across compositions. Characterisation confirmed the integrity of these assemblies in solution, the solid-state and gas phase. In solution, ¹H/¹³C NMR and DOSY evidenced single, well-defined cages with hydrodynamic sizes that align with the crystallographic dimensions, while computational structural studies rationalised cavity “breathing” as a solvent-dependent expansion/contraction of the M₄L₄ cages. In the gas phase, high-resolution ESI-HRMS corroborated the expected charge states and M₄L₄ formulations. TGA provided complementary solid-state confirmation.

The host-guest behaviour in water was quantified using R₄N⁺ guests (Me₄N⁺, Et₄N⁺, Pr₄N⁺, Bu₄N⁺). NMR (¹H, NOESY, DOSY) and ITC calorimetry established 1:1 encapsulation stoichiometry with cage size-dependent affinities ($K_a \sim 10^3$ – 10^4 M⁻¹) that are predominantly entropy-driven ($\Delta H > 0$, $T\Delta S > 0$, $\Delta G < 0$), consistent with desolvation-led binding and optimal cavity occupancy. Notably, the Al₄L₄ cages prefer smaller guests (Me₄N⁺), whereas the Ga₄L₄ cages tolerate bulkier guests (Et₄N⁺ and Pr₄N⁺), with Bu₄N⁺ exceeding the encapsulation thresholds.

These results establish the new designed tritopic ligands **H₆L⁶**–**H₆L¹⁰** as suitable scaffolds for assembling main-group metal tetrahedral Al₄L₄ and Ga₄L₄ cages with a validation of their heterometallic K⁺-containing cavities in the solid state and a clear map of their cavity-affinity correlations that couple ligand design and metal choice to host-guest thermodynamics. Beyond broadening the synthetic repertoire of tetrahedral M₄L₄ cages, this work provides transferable design principles for molecular recognition, supramolecular encapsulation for future applications in catalysis in water using these newly designed main-group metal M₄L₄ cages.

2.5 Experimental Methods

Herein, a representative synthetic procedure and characterisation for selected Me₆Lⁿ, H₆Lⁿ, Ga₄L₄ and Al₄L₄ cage architectures are provided. Complete synthetic protocols, characterisation details, and reactivity studies, for all for all precursors, ligands and Ga₄L₄ and Al₄L₄ cages discussed in this Chapter, including full spectroscopic and crystallographic data, are included as electronic Annexes on the USB device accompanying this Thesis.

2.5.1 Materials

Experiments were carried out under a nitrogen inert atmosphere using either a glove box (MBraun, LabMaster SP) or standard Schlenk techniques. Methanol was dried over Mg for two hours and then distilled under nitrogen, after this, it was deoxygenated with nitrogen and stored under an atmosphere of nitrogen gas over molecular sieves (3 Å). Dichloromethane (DCM) was taken from SPS system and stored under an atmosphere of nitrogen gas. Deuterated chloroform (CDCl₃), deuterium oxide (D₂O), deuterated dimethyl sulfoxide (DMSO-*d*₆) and deuterated dimethyl formamide (DMF-*d*₇) were purchased from Cambridge Isotopes or Merck. Tris(4-bromophenyl)amine, 4,4''-dibromo-5'-(4-bromophenyl)-1,1':3',1''-terphenyl, (TMSA), CuI, Pd(OAc)₂, Pd(PPh₃)₄, PPh₃, iPr₂NH, KOH, NaN₃, 2,3-dimethoxyphenylboronic acid, CuSO₄, L-ascorbic acid, *n*-BuOH, EtOH, MeOH, DCM, THF, BBr₃, Et₃N, K₂CO₃, CsF, Ga(acac)₃ and Al(acac)₃ (acac = acetyl acetonate) were purchased from Merck and used as received. Tris(4-ethynylphenyl)amine^[76] and 4,4''-diethynyl-5'-(4-ethynylphenyl)-1,1':3',1''-terphenyl,^[72f] were prepared according to reported procedures. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified.

NMR experiments were conducted 5 mm NMR tubes. Multinuclear NMR spectra were collected on either a Bruker AVIIIHD 400 nanobay (equipped with a 9.4 tesla magnet) or Bruker AVIII 500 (equipped with 11.7 tesla magnet and a Prodigy cryoprobe) spectrometer. Assignments of NMR resonance signals in the ¹H and ¹³C{¹H} NMR spectra were made with the help of two-dimensional NMR experiments (¹H,¹H-COSY, ¹H,¹³C-HSQC, ¹H,¹³C-HMBC). For NOESY and ROESY (phase sensitive) experiments, standard pulse sequences were used consisting of 256 transients with 32 scans in the f1 domain using an optimised 300 ms mixing time and

2 sec relaxation delay. Chemical shifts (δ) are reported in parts per million (ppm) and referenced the residual solvent resonances. Coupling constants (J) are given in Hertz (Hz). Signal multiplicities are abbreviated as follows: s (singlet), d (doublet), sept (septet), m (multiplet) and br (broad).

Electrospray ionisation high resolution mass spectrometry (ESI–HRMS) was carried out using a Bruker Compact QToF. Typical acquisition parameters were used (sample flow rate: $3\ \mu\text{L min}^{-1}$, nebuliser gas pressure: 0.3 bar, drying gas: nitrogen at 200°C flowing at $3\ \text{L min}^{-1}$, capillary voltage: 3.5 kV, exit voltage: 0.5 kV). The spectrometer was calibrated in negative ion mode using an ESI–L low concentration tuning mix (Agilent) ranging m/z from 112 until 2833 in a mixture of acetonitrile (HPLC grade) and DI (deionised, HPLC grade) H_2O (95:5 mixture). Samples were diluted to a concentration of *ca.* $< 1 \times 10^{-6}\ \text{M}$ in an appropriate solvent using 1.5 mL glass vials capped with appropriate septum and then sampled by direct infusion using a 500 μL gas tight syringe.

CHN elemental microanalysis were carried out at the elemental analysis services from the Metropolitan University of London using a ThermoFlash 2000 Elemental Analyzer.

Infrared (IR) spectra were obtained using Nujol mulls between KBr discs inside a nitrogen glove box on a Bruker Alpha FT–IR spectrometer.

Single–crystal X–ray diffraction data was collected under a stream of nitrogen gas using an Oxford Cryostream 1000 unit at the given temperature with a Bruker D8 Quest Eco diffractometer (micro–focus sealed X–ray tube, Mo– $K\alpha$, $\lambda = 0.71073\ \text{\AA}$) equipped with a Photon II 7. Raw frame data were reduced using APEX3. The structures were solved using SHELXT and refined using full–matrix least squares refinement on all F^2 data using the SHELXL. Unless otherwise stated, all non–hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and allowed to ride on their parent atoms. Disorder was treated by introducing a split site model and restraining geometries and displacement parameters. Distances and angles were calculated using the full covariance matrix. Selected crystallographic data is summarised in the text. Full details are given in the supplementary deposited CIF files (Annexes).

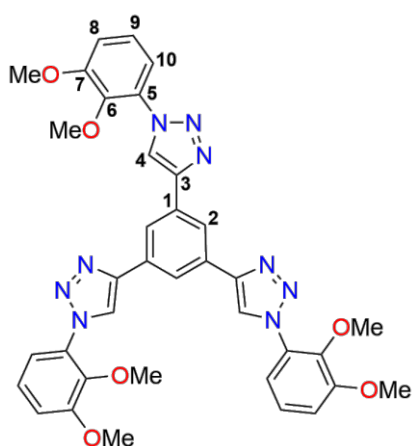
Isothermal Titration Calorimetry (ITC) experiments were performed on Nano ITC (TA Instruments) calorimeter equipped with a cylindrical inert sample cell of

standard volume (1 mL). Prior to analysis, solutions underwent thorough degassing by stirring under vacuum using a dedicated degassing station.

The computed cage cavity volumes of the different systems were calculated using the CageCavityCalc (C3)^[73] package with a grid size of 0.5 Å and the EEM implemented charge model.

2.5.2 Synthesis and Characterisation of Me₆Lⁿ and H₆Lⁿ

2.5.2.1 Synthesis and Characterisation of Me₆L⁶



To a solution of 1,3,5-triethynylbenzene (0.15 g, 1 mmol) and 1-azido-2,3-dimethoxybenzene (0.536 g, 3 mmol) in a 1:1 mixture of *n*-butanol:water (15 mL) in a 100 mL round-bottom flask, L-ascorbic acid (0.040 g, 0.2 mmol, 20 mol%) and CuSO₄·5H₂O (0.025 g, 0.1 mmol, 10 mol%) were added. The reaction mixture was stirred at 117°C until TLC showed the completion of the reaction (72 hours). Then, *n*-butanol was removed under

reduced pressure, and the viscous residue was extracted with CHCl₃ (3 × 20 mL). The combined organic extractions were treated with saturated brine and anhydrous Na₂SO₄ and then organic extractions were filtered and CHCl₃ was removed under reduced pressure in a rotary evaporator to afford Me₆L⁶ as a light-brown solid (0.525 g, 0.764 mmol, 76% yield). Crystals suitable for an X-ray diffraction crystallographic study were obtained by layering a solution of Me₆L⁶ in ethyl acetate with *n*-hexane.

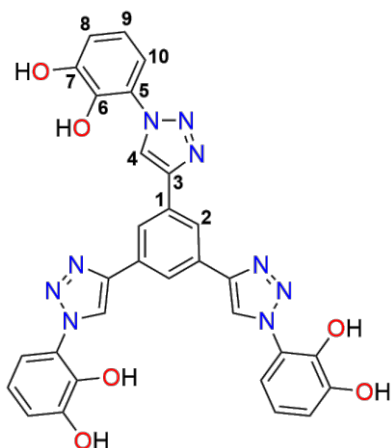
¹H NMR (400 MHz, CDCl₃, 298 K): δ 8.57 (s, 3H, H₄), 8.51 (s, 3H, H₂), 7.45 (d, 3H, H₈, ³J_{H8-H9} = 8.0 Hz), 7.22 (t, 3H, H₉, ³J_{H9-H8} = J_{H9-H10} = 8.0 Hz), 7.04 (d, 3H, H₁₀, ³J_{H10-H9} = 8.0 Hz), 3.96 (s, 9H, C7–OCH₃), 3.80 (s, 9H, C6–OCH₃).

¹³C{¹H} NMR (100.6 MHz, CDCl₃, 298 K): δ 153.8 (C₇), 147.1 (C₁ or C₃), 141.6 (C₆), 132.0 (C₁ or C₃), 131.2 (C₅), 124.5 (CH₉), 122.9 (CH₂), 122.3 (CH₄), 117.1 (CH₈), 113.1 (CH₁₀), 61.4 (C₇–OCH₃), 56.3 (C₆–OCH₃).

IR (KBr/Nujol, cm⁻¹): ν(C=N, C=C) 1612, 1595, 1488.

Elemental analysis found (calculated): C₃₆H₃₅N₉O₇ (C₃₆H₃₃N₉O₆·H₂O); C, 61.43 (61.27); H, 4.84 (5.00); N, 17.66 (17.86).

HRMS (ESI) *m/z* found (calculated) for C₃₆H₃₃N₉O₆ [M]: [M + Na]⁺, 710.2452 (710.2446); [M + H]⁺, 688.2630 (688.2627).

2.5.2.2 Synthesis and Characterisation of H₆L⁶

To a solution of 1,3,5-tris(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)benzene (0.500 g, 0.73 mmol) in CH₂Cl₂ (35 mL) under an atmosphere of nitrogen gas in a cold acetone bath at -78 °C, BBr₃ (1.12 mL, 11.6 mmol) was added via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. All volatiles were removed under vacuum, and the resulting brown residue was stirred in water at 100°C for 2 hours. The resulting

light-brown precipitate was collected by filtration and dried under vacuum at 70°C for 6 hours (0.420 g, 0.696 mmol, 95% yield).

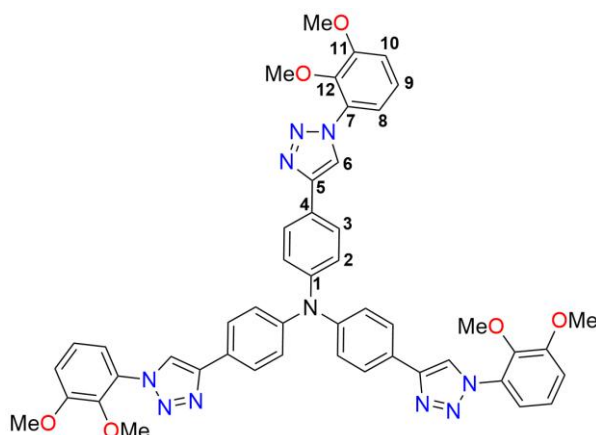
¹H NMR (400 MHz, DMSO-*d*₆, 298 K): δ 10.05 (s, 3H, OH), 9.52 (s, 3H, OH), 9.08 (s, 3H, H₄), 8.52 (s, 3H, H₂), 7.12 (d, 3H, H₈, ³J_{H₈-H₉} = 7.9 Hz), 6.99 (d, 3H, H₁₀, ³J_{H₁₀-H₉} = 7.9 Hz), 6.86 (t, 3H, H₉, ³J_{H₉-H₈} = J_{H₉-H₁₀} = 7.9 Hz).

¹³C{¹H} NMR (100.6 MHz, DMSO-*d*₆, 298 K): δ 146.7 (C₇), 145.6 (C₃), 138.8 (C₆), 132.0 (C₁), 125.4 (C₅), 123.6 (CH₄), 121.5 (CH₂), 119.1 (CH₉), 115.8 (CH₁₀), 115.6 (CH₈).

IR (KBr/Nujol, cm⁻¹): ν (O-H) 3498 (br); ν (C=N, C=C) 1620, 1520, 1491.

Elemental analysis found (calculated): C₃₀H₂₈N₉O_{9.5} (C₃₀H₂₁N₉O₆ + (H₂O)_{3.5}); C, 54.25 (54.05); H, 4.00 (4.23); N, 18.68 (18.91).

HRMS (ESI) *m/z* found (calculated) for C₃₀H₂₁N₉O₆ [M]: [M + H]⁺, 604.1692 (604.1688).

2.5.2.3 Synthesis and Characterisation of Me₆L⁸

Tris(4-ethynylphenyl)amine (0.123 g, 0.387 mmol) and 1-azido-2,3-dimethoxybenzene (0.208 g, 1.16 mmol) were dissolved in 14 mL of a mixture of *n*-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.015 g, 0.078 mmol, 20 mol%) and CuSO₄·5H₂O (0.009 g,

0.039 mmol, 10 mol %) were added. Stirring was continued overnight until TLC showed the completion of the reaction. n-butanol was removed under reduced pressure, and the viscous residue was extracted with DCM (3 x 20 mL). The combined organic extractions were treated with saturated brine and anhydrous Na₂SO₄ and then organic extractions were filtered, and dichloromethane was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.311 g, 94% yield).

¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ 8.33 (s, 3H, H₆), 7.84 (d, 6H, H₃, ³J_{H₃-H₂} = 8.3 Hz), 7.38 (d, 3H, H₈, ³J_{H₈-H₉} = 8.2 Hz), 7.25 (d, 6H, H₂, ³J_{H₂-H₃} = 8.3 Hz), 7.20 (t, 3H, H₉, ³J_{H₉-H₈} = ³J_{H₉-H₁₀} = 8.2 Hz), 7.04 (d, 3H, H₁₀, ³J_{H₁₀-H₉} = 8.2 Hz), 3.92 (s, 9H, C₁₁-OCH₃), 3.74 (s, 9H, C₁₂-OCH₃).

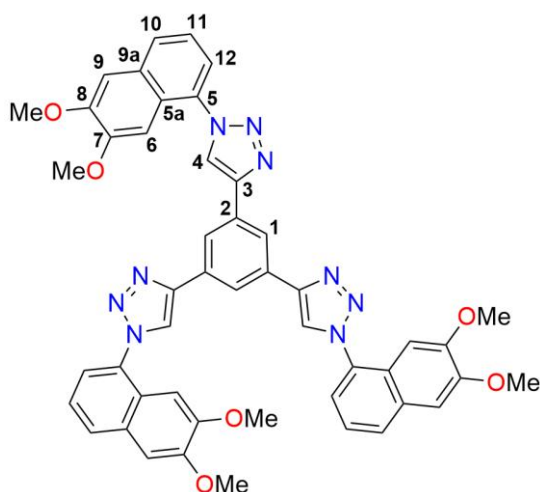
¹³C{¹H} NMR (101 MHz, CD₂Cl₂, 298 K): δ 154.1 (C₁₁), 147.6 (C₁), 147.4 (C₄), 141.8 (C₁₂), 131.5 (C₇), 127.1 (CH₂), 125.9 (C₅), 124.8 (CH₃), 124.7 (CH₉), 121.4 (CH₆), 117.0 (CH₁₀), 113.2 (CH₈), 61.4 (C₁₂-OCH₃), 56.5 (C₁₁-OCH₃).

IR (KBr/Nujol, cm⁻¹): ν(C=N, C=C) 1596, 1557.

Elemental analysis calculated for C₄₈H₄₂N₁₀O₆: C, 67.44; H, 4.95; N, 16.38 Found: C, 67.59; H, 5.29; N, 16.10.

HRMS (ESI) m/z found (calculated) for C₄₈H₄₂N₁₀O₆ [M]: [M + Na]⁺, 877.3157 (877.3181).

2.5.2.4 Synthesis and Characterisation of Me₆L¹⁰



1,3,5-Triethynylbenzene (0.1 g, 0.665 mmol) and 1-azido-6,7-dimethoxynaphthalene (0.457 g, 1.997 mmol) were dissolved in 24 mL of a mixture of n-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.084 g, 0.426 mmol) and CuSO₄·5H₂O (0.053 g, 0.213 mmol) were added. Stirring was continued overnight until TLC showed

the completion of the reaction. n-Butanol was removed under reduced pressure, and the viscous residue was extracted with CHCl₃ (3 x 20 mL). The combined organic extractions were treated with saturated brine and anhydrous Na₂SO₄ and then

organic extractions were filtered, and chloroform was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.521 g, 93% yield).

¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ 8.62 (s, 3H, H1 or H4), 8.43 (s, 3H, H4 or H1), 7.90 (d, 3H, H10), 7.48 (m, 6H, H11 and H12, overlapped), 7.27 (s, 3H, H9), 7.04 (s, 3H, H6), 4.00 (s, 9H, C8–OMe), 3.83 (s, 9H, C7–OMe).

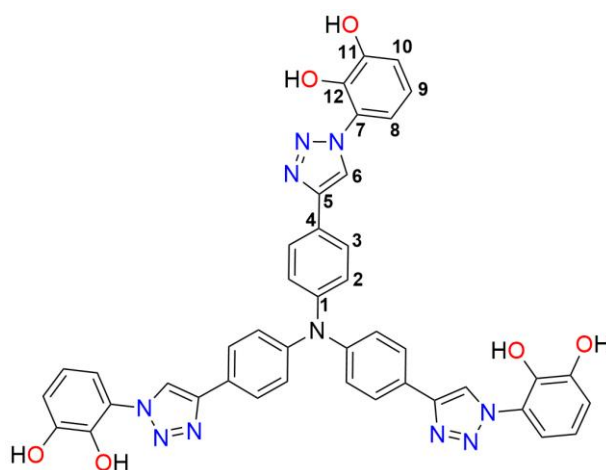
¹³C{¹H} NMR (101 MHz, CD₂Cl₂, 298 K): δ 151.6 (C7), 150.9 (C8), 147.2 (C3 or C2), 132.8 (C9a or C5), 132.4 (C2 or C3), 130.8 (C5 or C9a), 128.9 (CH10), 124.6 (C5a), 123.7 (CH12 or CH11), 123.3 (CH4 or CH1), 123.0 (CH1 or CH4), 121.9 (CH11 or CH12), 106.9 (CH9), 101.3 (CH6), 56.1 (2 × C–OMe, overlapped).

IR (KBr/Nujol, cm^{−1}): ν(C=N, C=C) 1627, 1605, 1584.

Elemental analysis calculated for C₄₈H₃₉N₉O₆: C, 68.81; H, 4.69; N, 15.05 Found: C, 69.05; H, 4.98; N, 14.80.

HRMS (ESI) m/z found (calculated) for C₄₈H₃₉N₉O₆ [M]: [M + H]⁺, 838.3098 (838.3096).

2.5.2.5 Synthesis and Characterisation of H₆L⁸



BBr₃ (0.55 ml, 5.67 mmol) was added by syringe to a solution of tris(4-(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)phenyl)amine (0.303 g, 0.354 mmol) in CH₂Cl₂ (24 ml) under nitrogen at −78°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were

removed under vacuum, and the remaining brown residue was stirred in water for 2 h at 100°C. The light-brown precipitate was collected by filtration and dried under vacuum at 70°C for 6 h (0.225 g, 82% yield).

¹H NMR (400 MHz, DMSO-*d*₆, 298 K): δ 10.06 (br s, 3H, OH), 9.46 (br s, 3H, OH), 8.81 (s, 3H, H6), 7.90 (d, 6H, H3, ³J_{H3–H2} = 8.3 Hz), 7.19 (d, 6H, H2, ³J_{H2–H3} = 8.3 Hz), 7.07 (d, 3H, H10, ³J_{H10–H9} = 8.0 Hz), 6.96 (d, 3H, H8, ³J_{H8–H9} = 8.0 Hz), 6.83 (t, 3H, H9, ³J_{H9–H10} = ³J_{H9–H8} = 8.0 Hz).

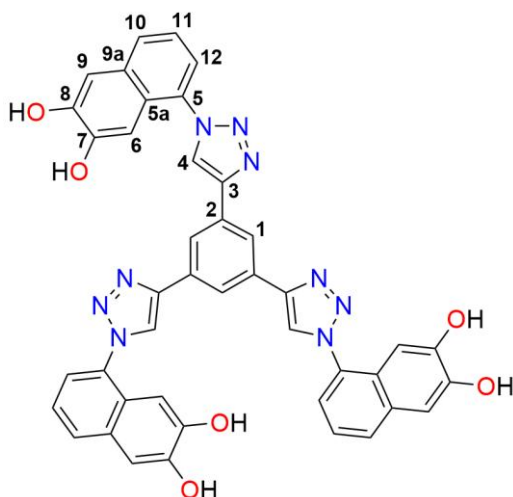
¹³C{¹H} NMR (101 MHz, DMSO-*d*₆, 298 K): δ 146.7 (C11), 146.5 (C1), 145.8 (C4), 138.9 (C12), 126.7 (CH3), 125.5 (C7), 125.4 (C5), 124.2 (CH2), 122.6 (CH6), 119.2 (CH9), 115.8 (CH8), 115.6 (CH10).

IR (KBr/Nujol, cm⁻¹): $\nu(\text{O-H})$ 3489, 3166 (br); $\nu(\text{C=N, C=C})$ 1609, 1560.

Elemental analysis calculated for C₄₂H₃₀N₁₀O₆: C, 65.45; H, 3.92; N, 18.17 Found: C, 65.73; H, 4.09; N, 17.83.

HRMS (ESI) *m/z* found (calculated) for C₄₂H₃₀N₁₀O₆ [M]: [M + H]⁺, 771.2423 (771.2423); [M + Na]⁺, 793.2246 (793.2242).

2.5.2.6 Synthesis and Characterisation of H₆L¹⁰



BBr₃ (0.184 ml, 1.91 mmol) was added by syringe to a solution of 1,3,5-tris(1-(6,7-dimethoxynaphthalen-1-yl)-1H-1,2,3-triazol-4-yl)benzene (0.1 g, 0.119 mmol) in CH₂Cl₂ (26 ml) under nitrogen at -78°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed under vacuum, and the remaining brown residue was stirred in water for 2 h at 100°C. The light-brown

precipitate was collected by filtration and dried under vacuum at 70°C for 6 h (0.078 g, 87% yield).

¹H NMR (400 MHz, DMSO-d₆, 298 K): δ 10.00 (br s, 6H, OH), 9.23 (s, 3H, H₄), 8.68 (s, 3H, H₁), 7.87 (d, 3H, H₁₀, ³J_{H₁₀-H₁₁ = 7.6 Hz), 7.51 (d, 3H, H₁₂, ³J_{H₁₂-H₁₁ = 7.6 Hz), 7.40 (t, 3H, H₁₁, ³J_{H₁₁-H₁₀ = ³J_{H₁₁-H₁₂ = 7.6 Hz), 7.32 (s, 3H, H₉), 6.90 (s, 3H, H₆).}}}}

¹³C{¹H} NMR (101 MHz, DMSO-d₆, 298 K): δ 148.8 (C₇), 147.9 (C₈), 146.0 (C₃ or C₂), 132.0 (C₂ or C₃), 131.5 (C₅ or C_{9a}), 129.8 (C_{9a} or C₅), 128.0 (CH₁₀), 124.6 (CH₄), 123.7 (C_{5a}), 122.2 (CH₁₁), 121.9 (CH₁), 120.7 (CH₁₂), 110.1 (CH₉), 103.9 (CH₆).

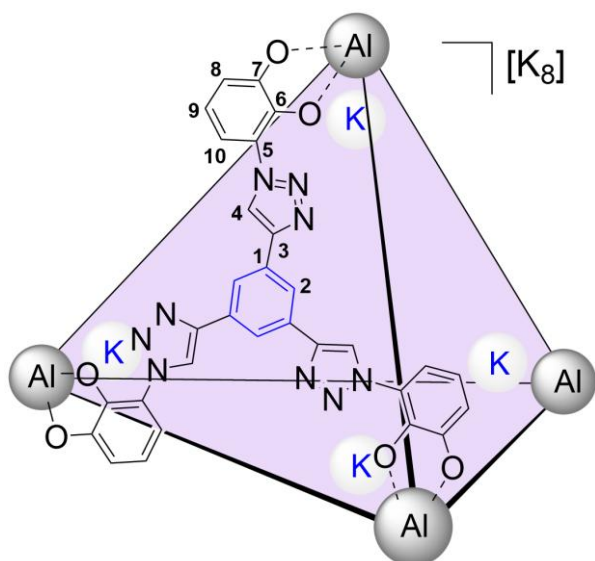
IR (KBr/Nujol, cm⁻¹): $\nu(\text{O-H})$ 3137 (br); $\nu(\text{C=N, C=C})$ 1634, 1612, 1530.

Elemental analysis calculated for C₄₂H₃₁N₉O₈ (C₄₂H₂₇N₉O₆ + 2H₂O): C, 63.87; H, 3.96; N, 15.96 Found: C, 64.13; H, 4.19; N, 15.53.

HRMS (ESI) *m/z* found (calculated) for C₄₂H₂₇N₉O₆ [M]: [M + Na]⁺, 776.1939 (776.1977).

2.5.3 Synthesis and Characterisation of M₄L₄

2.5.3.1 Synthesis and Characterisation of Al₄(L⁶)₄



The ligand **H₆L⁶** (0.080 g, 0.132 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (1.06 mL, 0.53 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which [Al(acac)₃] (0.034 g, 0.106 mmol) was then added to the solution as a powder. The reaction mixture was stirred at room temperature overnight.

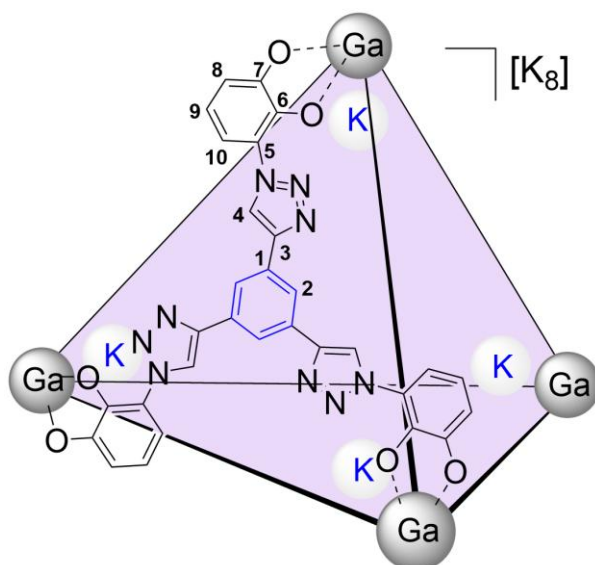
Then, the reaction mixture was concentrated to 5 mL and then 20 mL of Et₂O was added to precipitate a brown silky solid. This was isolated by filtration and dried under vacuum (0.07 g, 0.0235 mmol, 90%).

¹H NMR (500 MHz, D₂O, 298 K): δ 9.25 (s, 12H, H₄), 7.53 (dd, 12H, H₁₀, ³J_{H₁₀-H₉} = 8.0 Hz, ⁴J_{H₁₀-H₈} = 1.2 Hz), 7.15 (s, 12H, H₂), 6.69 (t, 12H, H₉, ³J_{H₉-H₈} = ³J_{H₉-H₁₀} = 8.0 Hz), 6.64 (dd, 12H, H₈, ³J_{H₈-H₉} = 8.0 Hz, ⁴J_{H₈-H₁₀} = 1.2 Hz).

¹³C{¹H} NMR (125.6 MHz, D₂O, 298 K): δ 156.3 (C₇), 148.2 (C₆), 145.2 (C₁), 131.7 (C₃), 125.1 (CH₂), 121.4 (C₅), 121.2 (CH₄), 114.4 (CH₉), 111.3 (CH₈), 108.9 (CH₁₀).

IR (KBr/Nujol, cm⁻¹): ν (C=N, C=C) 1613, 1575, 1530.

HRMS (ESI) (negative-ion detection, H₂O, $[\square^{12-} = [\text{Al}_4(\text{L}^6)_4]^{12-}]$): m/z found (calc.), $[\square^{12-} + 9 \text{ K}^+]^{3-} = 949.6883$ (949.6873); $[\square^{12-} + 8 \text{ K}^+ + 1 \text{ H}^+]^{3-} = 937.0342$ (937.0355); $[\square^{12-} + 7 \text{ K}^+ + 1 \text{ H}^+ + 1 \text{ Na}^+]^{3-} = 931.7137$ (931.7109); $[\square^{12-} + 7 \text{ K}^+ + 2 \text{ H}^+]^{3-} = 924.0490$ (924.0501); $[\square^{12-} + 8 \text{ K}^+ + 1 \text{ H}_2\text{O}]^{4-} = 707.0322$ (707.0274); $[\square^{12-} + 7 \text{ K}^+ + 1 \text{ H}^+]^{4-} = 693.0382$ (693.0359).

2.5.3.2 Synthesis and Characterisation of $Ga_4(L^6)_4$ 

The ligand H_6L^6 (0.080 g, 0.132 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (1.06 mL, 0.53 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which $[Ga(acac)_3]$ (0.039 g, 0.106 mmol) was then added to the solution as a powder. The reaction mixture was stirred at

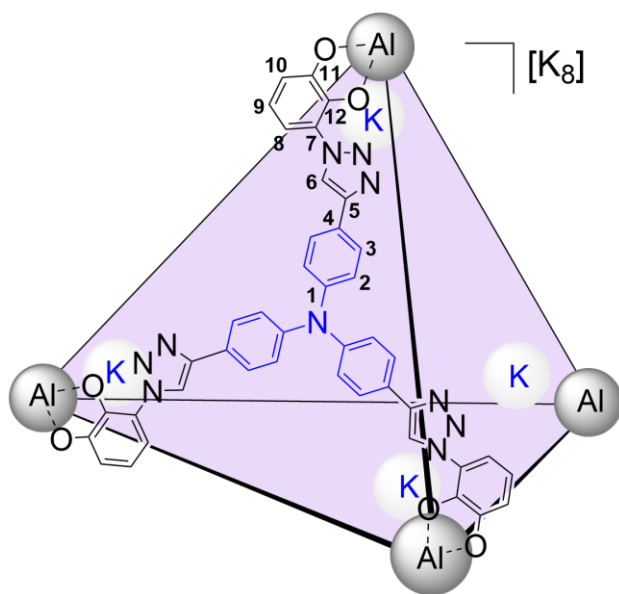
room temperature overnight. Then, a brown silky solid precipitated. This solid was isolated by filtration and dried under vacuum (0.074 g, 0.0284 mmol, 89%).

1H NMR (500 MHz, D_2O , 298 K): δ 9.26 (s, 12H, H4), 7.49 (dd, 12H, H10, $^3J_{H10-H9} = 8.0$ Hz, $^4J_{H10-H8} = 1.2$ Hz), 7.11 (s, 12H, H2), 6.73 (dd, 12H, H8, $^3J_{H8-H9} = 8.0$ Hz, $^4J_{H8-H10} = 1.2$ Hz), 6.70 (t, 12H, H9, $^3J_{H9-H8} = ^3J_{H9-H10} = 8.0$ Hz).

$^{13}C\{^1H\}$ NMR (125.6 MHz, D_2O , 298 K): δ 155.1 (C7), 147.5 (C6), 145.1 (C1), 131.6 (C3), 124.7 (CH2), 122.1 (C5), 120.8 (CH4), 114.4 (CH9), 112.2 (CH8), 109.8 (CH10).

IR (KBr/Nujol, cm^{-1}): $\nu(C=N, C=C)$ 1644, 1614, 1574.

HRMS (ESI) (negative-ion detection, H_2O : DMF (1:1), $\square^{12-} = [Ga_4(L^6)_4]^{12-}$): m/z found (calc.), $[\square^{12-} + 9 K^+ + 1 H_2O]^{3-} = 1012.9533$ (1012.9491); $[\square^{12-} + 9 K^+]^{3-} = 1006.9475$ (1006.9456); $[\square^{12-} + 8 K^+ + 1 Na^+]^{3-} = 1001.6210$ (1001.6241); $[\square^{12-} + 8 K^+ + 1 H^+]^{3-} = 993.9606$ (993.9633); $[\square^{12-} + 8 K^+ + 1 H_2O]^{4-} = 749.9763$ (749.9711).

2.5.3.3 Synthesis and Characterisation of Al₄(L⁸)₄

The ligand **H₆L⁸** (0.08 g, 0.103 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (0.83 mL, 0.415 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which [Al(acac)₃] (0.027 g, 0.083 mmol) was then added to the solution as a powder. The reaction mixture was stirred at room temperature overnight. Then,

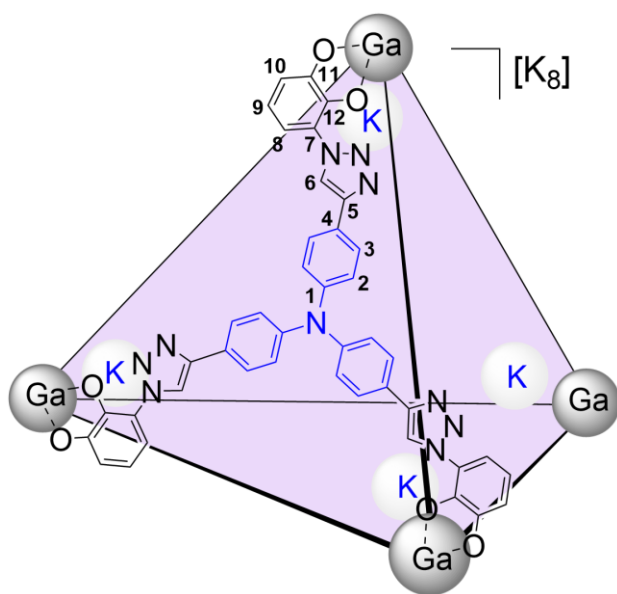
the reaction mixture was concentrated to 5 mL and then 20 mL of Et₂O was added to precipitate a brown silky solid. This solid was isolated by filtration and dried under vacuum (0.07 g, 0.01867 mmol, 93%).

¹H NMR (500 MHz, DMF-d₇/D₂O (1:4), 298 K): δ 9.86 (s, 12H, H₆), 7.72 (d, 24H, H₃, ³J_{H₃-H₂} = 8.0 Hz), 7.00 (d, 12H, H₈ or H₁₀, ³J = 8.0 Hz), 6.75 (d, 24H, H₂, ³J_{H₂-H₃} = 8.0 Hz), 6.55 (d, 12H, H₁₀ or H₈, ³J = 8.0 Hz), 6.44 (t, 12H, H₉, ³J_{H₉-H₁₀} = ³J_{H₉-H₈} = 8.0 Hz).

¹³C{¹H} NMR (125 MHz, DMF-d₇/D₂O (1:4), 298 K): δ 158.3 (C₁₁), 150.4 (C₁₂), 147.0 (C₁), 146.5 (C₄), 127.1 (CH₃), 126.2 (C₅), 124.4 (CH₂), 122.8 (CH₆), 121.9 (C₇), 114.7 (CH₉), 111.7 (CH₁₀), 108.9 (CH₈).

IR (KBr/Nujol, cm⁻¹): ν(O-H) 3612, 3340 (br); ν(C=N, C=C) 1609, 1577.

HRMS (ESI) (negative-ion detection, H₂O: DMF (1:1), □¹²⁻ = [Al₄(L⁸)₄]¹²⁻): m/z found (calc.), [□¹²⁻ + 6 K⁺ + 1 Na⁺ + 1 H⁺]⁴⁻ = 856.1154 (856.1162); [□¹²⁻ + 5 K⁺ + 3 Na⁺]⁴⁻ = 857.6189 (857.6182); [□¹²⁻ + 7 K⁺ + 1 H⁺]⁴⁻ = 860.1095 (860.1096); [□¹²⁻ + 6 K⁺ + 2 Na⁺]⁴⁻ = 861.6122 (861.6117); [□¹²⁻ + 7 K⁺ + 1 Na⁺]⁴⁻ = 865.6056 (865.6051); [□¹²⁻ + 8 K⁺]⁴⁻ = 869.5992 (869.5985); [□¹²⁻ + 6 K⁺ + 2 Na⁺ + 1 H⁺]³⁻ = 1149.1507 (1149.1513); [□¹²⁻ + 7 K⁺ + 1 Na⁺ + 1 H⁺]³⁻ = 1154.4756 (1154.4759); [□¹²⁻ + 8 K⁺ + 1 H⁺]³⁻ = 1159.8027 (1159.8005); [□¹²⁻ + 7 K⁺ + 2 Na⁺]³⁻ = 1161.8033 (1161.8032); [□¹²⁻ + 8 K⁺ + 1 Na⁺]³⁻ = 1167.1272 (1167.1278); [□¹²⁻ + 9 K⁺]³⁻ = 1172.4531 (1172.4524).

2.5.3.4 Synthesis and Characterisation of $Ga_4(L^8)_4$ 

The ligand H_6L^8 (0.06 g, 0.0778 mmol) was suspended under oxygen-free conditions in distilled MeOH (18 mL). A 0.5 M solution of KOH in MeOH (0.62 mL, 0.311 mmol) was added by syringe. The ligand dissolved after about 20 min with stirring, after which $[Ga(acac)_3]$ (0.023 g, 0.0622 mmol) was then added to the solution as a powder. The reaction mixture was stirred at room temperature overnight. Then,

the reaction mixture was concentrated to 5 mL and then 20 mL of Et_2O was added to precipitate a brown silky solid. This solid was isolated by filtration and dried under vacuum (0.054 g, 0.0141 mmol, 91%).

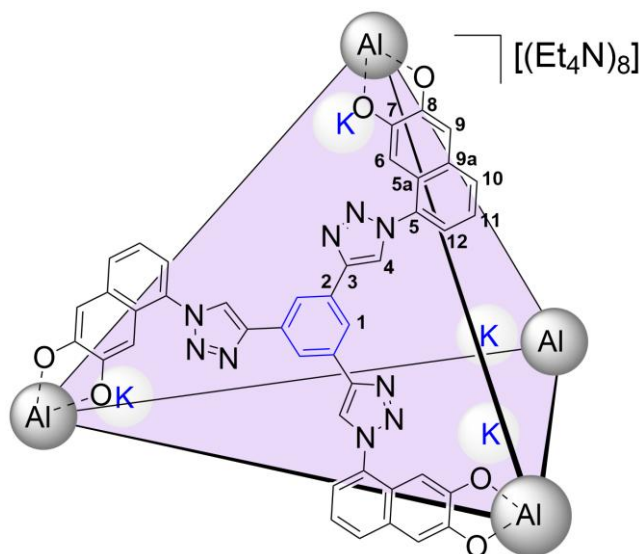
1H NMR (500 MHz, $DMF-d_7/D_2O$ (1:4), 298 K): δ 9.76 (s, 12H, H6), 7.75 (d, 24H, H3, $^3J_{H3-H2} = 7.0$ Hz), 6.98 (d, 12H, H8, $^3J_{H8-H9} = 8.0$ Hz), 6.77 (d, 24H, H2, $^3J_{H2-H3} = 7.0$ Hz), 6.61 (d, 12H, H10, $^3J_{H10-H9} = 8.0$ Hz), 6.46 (t, 12H, H9, $^3J_{H9-H10} = ^3J_{H9-H8} = 8.0$ Hz).

$^{13}C\{^1H\}$ NMR (125 MHz, $DMF-d_7/D_2O$ (1:4), 298 K): 156.9 (C11), 149.5 (C12), 147.0 (C1), 146.5 (C4), 126.9 (CH3), 126.1 (C5), 124.3 (CH2), 123.1 (CH6), 122.5 (C7), 114.6 (CH9), 112.6 (CH10), 109.6 (CH8).

IR (KBr/Nujol, cm^{-1}): $\nu(O-H)$ (br) 3589, 3337; $\nu(C=N, C=C)$ 1609, 1545.

HRMS (ESI) (negative-ion detection, $H_2O: DMF$ (1:1), $\square^{12-} = [Ga_4(L^8)_4]^{12-}$): m/z found (calc.), $[\square^{12-} + 7 K^+ + 1 H^+]^{4-} = 903.0570$ (903.0535); $[\square^{12-} + 7 K^+ + 1 Na^+]^{4-} = 908.5520$ (908.5489); $[\square^{12-} + 8 K^+]^{4-} = 912.5455$ (912.5424); $[\square^{12-} + 7 K^+ + 1 Na^+ + 1 H^+]^{3-} = 1211.7370$ (1211.7343); $[\square^{12-} + 8 K^+ + 1 H^+]^{3-} = 1217.0614$ (1217.0689); $[\square^{12-} + 8 K^+ + 1 Na^+]^{3-} = 1224.3904$ (1224.3863); $[\square^{12-} + 9 K^+]^{3-} = 1229.7150$ (1229.7109).

2.5.3.5 Synthesis and Characterisation of $\text{Al}_4(\text{L}^{10})_4$



The linker **H₆L¹⁰** (0.08 g, 0.106 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (0.85 mL, 0.424 mmol) was added by syringe followed by the addition of a 0.28 M solution of Et₄NBr/MeOH (1.13 mL, 0.318 mmol). The linker dissolved after about 20 min with stirring, after which [Al(acac)₃]

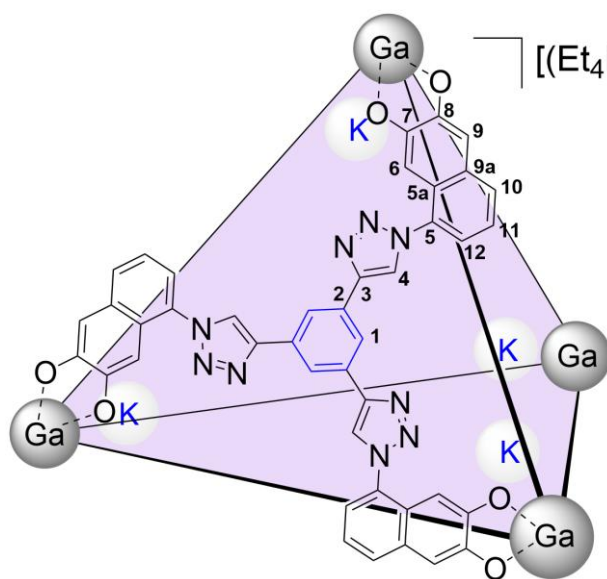
(0.027 g, 0.084 mmol) was then added to the solution as a powder. The reaction mixture was stirred at room temperature overnight. The brown solid that formed was subsequently collected via filtration and dried under vacuum (0.070 g, 0.0163 mmol, 78%).

¹H NMR (500 MHz, DMF-d₇/D₂O (1:1), 298 K): δ 9.02 (s, 12H, H₄), 8.75 (s, 12H, H₁), 7.73 (br s, 12H, H naphthalene), 7.21 (br s, 24H, H naphthalene), 6.98 (br s, 12H, H naphthalene), 6.52 (m, 12H, H naphthalene), 3.22 (br s, 64H, CH₂ (8Et₄N⁺)), 1.23 (br s, 96H, CH₃ (8Et₄N⁺)).

¹³C{¹H} NMR (125.6 MHz, DMF-d₇/D₂O (1:1), 298 K): δ 159.4 (Cq), 158.2 (Cq), 145.1 (Cq), 131.0 (Cq), 129.9 (Cq), 129.2 (Cq), 126.0 (CH naphthalene), 123.4 (CH₄), 122.2 (Cq), 120.4 (Cq), 117.9 (CH naphthalene), 116.8 (CH naphthalene), 103.5 (CH naphthalene), 97.1 (CH naphthalene), 50.9 (CH₂ (Et₄N⁺)), 5.7 (CH₃ (Et₄N⁺)).

IR (KBr/Nujol, cm^{-1}): $\nu(\text{C}=\text{N}, \text{C}=\text{C})$ 1603, 1570.

HRMS (ESI) (negative-ion detection, H₂O: DMF (1:1), $\square^{12-} = [\text{Al}_4(\text{L}^{10})_4]^{12-}$): m/z found (calc.), $[\square^{12-} + 5 \text{ K}^+ + 3 \text{ Na}^+ + \text{Et}_4\text{N}^+]^{3-} = 1164.1818$ (1164.1753); $[\square^{12-} + 6 \text{ K}^+ + 2 \text{ Na}^+ + \text{Et}_4\text{N}^+]^{3-} = 1169.5064$ (1169.4999); $[\square^{12-} + 7 \text{ K}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{3-} = 1174.8309$ (1174.8245); $[\square^{12-} + 8 \text{ K}^+ + \text{Et}_4\text{N}^+]^{3-} = 1180.1599$ (1180.1491).

2.5.3.6 Synthesis and Characterisation of $\text{Ga}_4(\text{L}^{10})_4$ 

The linker H_6L^{10} (0.08 g, 0.106 mmol) was suspended under oxygen-free conditions in distilled MeOH (20 mL). A 0.5 M solution of KOH in MeOH (0.85 mL, 0.424 mmol) was added by syringe followed by the addition of a 0.28 M solution of $\text{Et}_4\text{NBr/MeOH}$ (1.13 mL, 0.318 mmol). The linker dissolved after about 20 min with stirring, after which $[\text{Ga}(\text{acac})_3]$ (0.031 g,

0.084 mmol) was then added to the solution as a powder. The reaction mixture was stirred at room temperature overnight. The brown solid that formed was subsequently collected via filtration and dried under vacuum (0.079 g, 0.0178 mmol, 85%).

^1H NMR (500 MHz, $\text{DMF-d}_7/\text{D}_2\text{O}$ (1:1), 298 K): δ 9.04 (s, 12H, H4), 8.77 (s, 12H, H1), 7.74 (br s, 12H, H naphthalene), 7.23 (br s, 24H, H naphthalene), 7.05 (br s, 12H, H naphthalene), 6.61 (m, 12H, H naphthalene), 3.17 (br s, 64H, CH_2 ($8\text{Et}_4\text{N}^+$)), 1.18 (br s, 96H, CH_3 ($8\text{Et}_4\text{N}^+$)).

$^{13}\text{C}\{^1\text{H}\}$ NMR (125.6 MHz, $\text{DMF-d}_7/\text{D}_2\text{O}$ (1:1), 298 K): δ 158.5 (Cq), 157.2 (Cq), 145.1 (Cq), 131.0 (Cq), 129.6 (Cq), 129.2 (Cq), 125.9 (CH naphthalene), 123.2 (CH4), 122.3 (Cq), 120.3 (Cq), 118.0 (CH naphthalene), 116.9 (CH naphthalene), 104.1 (CH naphthalene), 97.7 (CH naphthalene), 50.9 (CH_2 (Et_4N^+)), 5.7 (CH_3 (Et_4N^+)).

IR (KBr/Nujol, cm^{-1}): $\nu(\text{C}=\text{N}, \text{C}=\text{C})$ 1603, 1567.

HRMS (ESI) (negative-ion detection, $\text{H}_2\text{O}:\text{DMF}$ (1:1), $[\square^{12-} = [\text{Ga}_4(\text{L}^{10})_4]^{12-}]$: m/z found (calc.), $[\square^{12-} + 7 \text{K}^+ + \text{Na}^+ + \text{H}_2\text{O}]^{3-} = 896.0206$ (896.0250); $[\square^{12-} + 6 \text{K}^+ + 2 \text{Na}^+ + \text{Et}_4\text{N}^+]^{3-} = 1226.7555$ (1226.7584); $[\square^{12-} + 7 \text{K}^+ + \text{Na}^+ + \text{Et}_4\text{N}^+]^{3-} = 1232.0813$ (1232.0830); $[\square^{12-} + 8 \text{K}^+ + \text{Et}_4\text{N}^+]^{3-} = 1237.4086$ (1237.4076); $[\square^{12-} + 8 \text{K}^+ + \text{Et}_4\text{N}^+ + \text{H}_2\text{O}]^{3-} = 1243.4117$ (1243.4111).

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CHAPTER III:

Cooperative Reversible Assembly of Triply Interlocked Coordination Cages Al_6L_4 and Ga_6L_4

3.1 Introduction

Mechanically interlocked molecules, particularly catenanes,^[1] rotaxanes,^[2] molecular shuttles,^[3] and interlocked cages^[4] represent a new and active research area in the field of mechanically interlocked materials (MIMs).^[5] What makes them unique is that their interconnection is achieved through mechanical bonds,^[6] connections between molecular entities that are interlocked in space (like links in a chain), without relying on covalent or traditional non-covalent interactions. This means that to separate the components that form these interlocked entities, a chemical bond must be broken, implying that the interlocked structure functions as a single molecular entity.^[7] Mechanical bonds play a crucial role in mechanically interlocked structures, as they provide unique properties to supramolecular architectures, including enhanced structural stability,^[8] porous architectures,^[4a] and dynamic responsiveness to external stimuli.^[9] Interlocking can lead to distinct pore types, cavity shapes, and sizes, resulting in a porous network.^[10] This means that the internal space is not a single cavity, but a complex system of interconnected cavities.

Although the formation of mechanical bonds between monomeric species to give dimeric species is entropically unfavourable, because of the decrease in entropy or molecular disorder, the resulting interlocked structures gain enhanced stability due to electrostatic and van der Waals interactions between their components. These include π – π stacking, hydrophobic effects, metal–metal contacts, metal–ligand covalent bond formation and ion–ion interactions.^[11] Moreover, MIMs exhibit dynamic responses to external stimuli, such as shape-switching,^[4a, 10] high-affinity guest binding,^[12] and artificial-muscle-like actuation.^[13] This adaptability is essential for functional applications such as elastomeric materials.^[13] Notably, reduced mobility in highly interlocked systems such as 4-fold [2]catenanes^[4a, 10] or 5-fold [2]catenanes^[14] have been observed to enhance structural stability while preserving dynamic responsiveness. These structures allow for the emergence of localised and favourable electrostatic interactions, enabling properties such as selective ion binding,^[10] magnetic behaviour,^[12] electronic conductivity, and photothermal characteristics.^[13]

The formation of interlocked supramolecular structures can generally be interpreted through both enthalpic and entropic considerations.^[9, 15] Enthalpically, host–guest interactions and electrostatic forces such as π – π stacking between aromatic rings, metal–metal contacts, and aromatic–aromatic interactions, play key

roles in stabilizing the interlocked architecture. Entropically, however, the process is unfavourable, as it results in a decrease in overall disorder. Nonetheless, the self-assembly of interlocked systems can be entropically compensated by the release of ordered guest and structured solvent molecules initially confined within the cavities of monomeric precursors.^[4a] Some parameters that influence the interlocking process include the templating effect of small anionic guests, π – π interactions, host–guest dynamics, temperature, and ligand functionalisation. Despite recent progress, the factors that govern mechanical interlocking and their stabilisation remain not well understood, yet. Examples of interlocked cage motifs are observed across various fields of chemistry, including interlocked organic [2]catenanes, interlocked metal–organic frameworks (MOFs), and interlocked coordination cages (Figure 1).

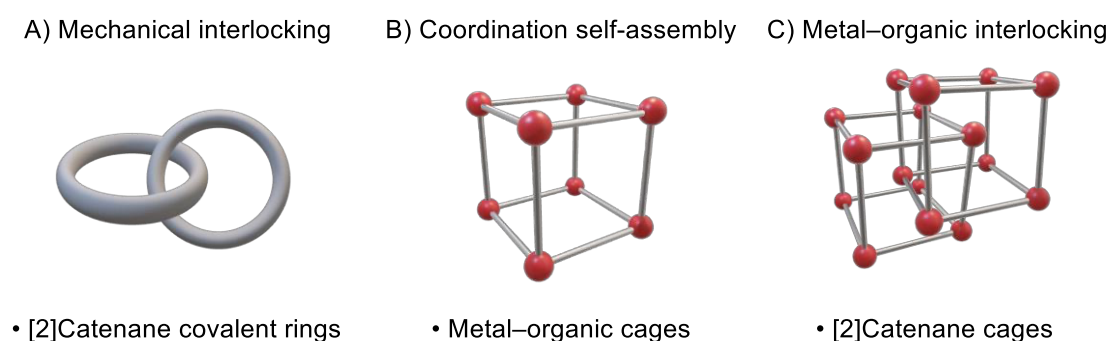


Figure 1. From covalent to metal–organic interlocking.

3.1.1 Organic Mechanically Interlocked Cages

Examples of organic interlocked [2]catenane cages are scarce. This is mainly due to the difficulty in predicting their formation and the challenges in their characterisation. An important example of this type of structure was presented by Mastalerz.^[7] They successfully synthesised the cage I (Figure 2) via a one-pot condensation reaction involving 48 units of a benzene (tris–boronic acid) and triptycene tetraol building blocks with attached alkyl groups. This cage dimerised during the crystallisation process forming a [2]catenane cage. It is important to note that the formation of this [2]catenated cage was only observed in the solid state after crystallisation. In solution, the interlocked structure disassembled, reverting to its individual monomeric cages. This was attributed to the increase of entropy because of the formation of two monomeric cages from one [2]catenane cage in solution. The driving force for the dimer formation in the solid state was attractive dispersion

interactions. Specifically, these interactions occurred between the alkyl chains of one cage and the aromatic planes of the triptycene units of the other monomeric cage. Attaching shorter alkyl groups to the backbone inhibited interpenetration, probably due to the lack of these attractive forces, demonstrating the influence of these interactions.

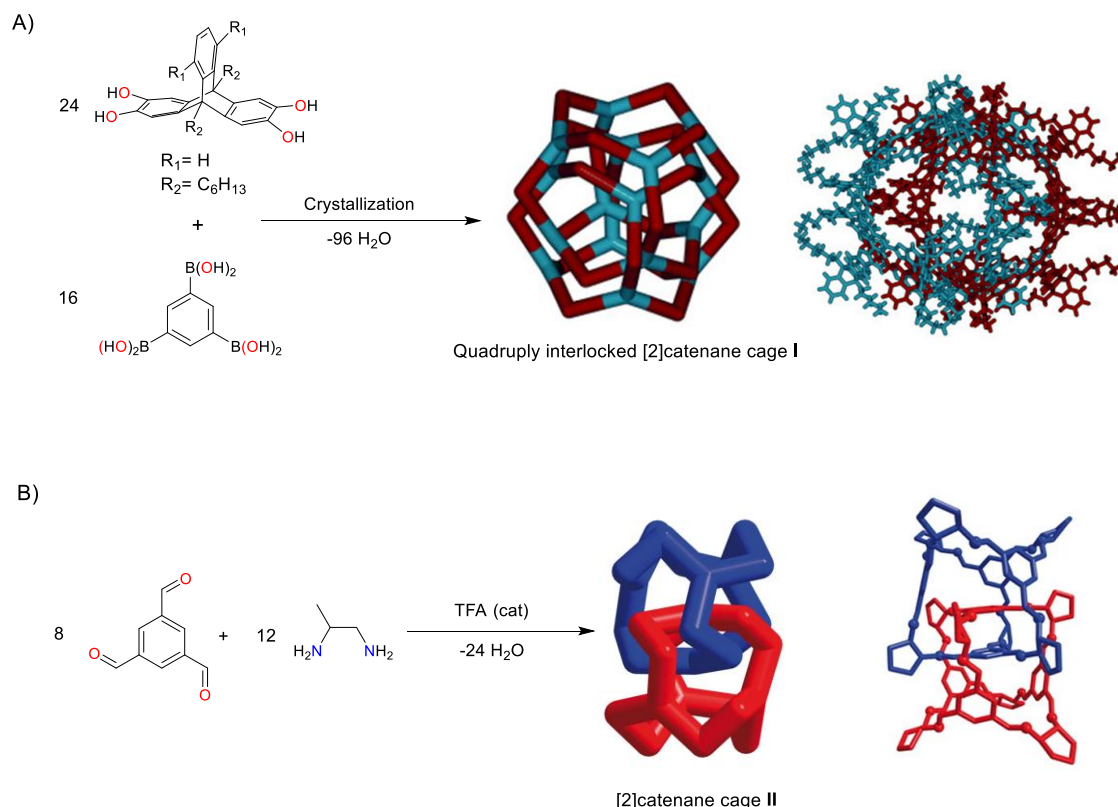


Figure 2. A) Synthesis of the organic interlocked system I and B) Synthesis of the organic interlocked cage II.

Another interesting example is the triply interlocked covalent organic cage II. This cage II is synthesised in a single step using a cycloamination reaction involving a trialdehyde and various diamines in acetonitrile (Figure 2).^[16] The formation of these dimeric cages was observed when trifluoroacetic acid (TFA) was present in the solution. Nonetheless, in the absence of TFA, only tetrahedral monomeric cages were formed. This indicates that TFA acts as a templating molecule, guiding the dimerisation process. When these monomeric cages are dissolved in a solution of dichloromethane and p-xylene, they exhibit a slow dimerisation process, taking approximately 50 days. This occurs due to the reversible nature of the imine bonds within the tetrahedral monomeric cages. The main attractive forces that stabilise the dimer formation are attributed to the π - π stacking between the two aryl rings located inside the dimer. Furthermore, aryl-hydrogen $\cdots$ imine interactions between the two

inner arene rings and the six bis(imine) strands that penetrate them also play a crucial role in stabilizing the structure.

In contrast to the previously discussed examples, which relied on relatively unstable mechanical bonds, Zhang successfully demonstrated the creation of the interlocked cage **III**, that is permanently interlocked (Figure 3).^[17] These interlocked cages were constructed in solution through an alkyne metathesis reaction, utilizing substituted 1,3,5-tris(phenyl)benzene units and building blocks containing carbazole. This [2]catenane cage structure exhibits exceptional stability due to its robust ethynylene linkages, and it forms as the thermodynamically preferred product. The primary force driving this dimerisation process is described to be the attractive π – π stacking interactions between the aromatic groups of the cage's walls, which are crucial for neutralizing the loss of entropy associated with the dimerisation (unfavourable process).

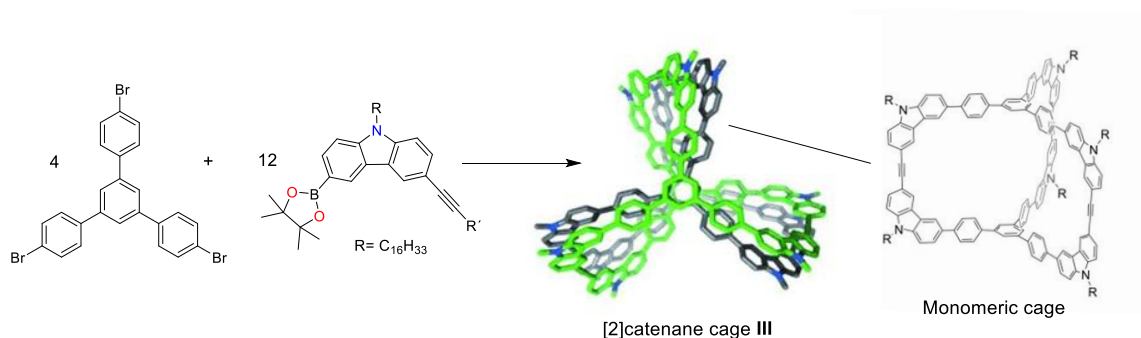


Figure 3. Synthesis of the interlocked [2]catenane cage **III**.

3.1.2 Mechanically Interlocked Coordination M_nL_n Cages

Metal–organic cages are well-known systems in supramolecular chemistry and, their self-assembly process rarely leads to the interpenetration of these cages. The self-assembly of interlocked SCCs is a challenging process. Covalent synthetic routes offer exact connectivity but lack error correction, whereas purely non-covalent methods typically compromise directional precision.^[18] In contrast, metal-directed self-assembly is a powerful tool, combining predictable coordination geometries, thermodynamic error correction, and tunable lability of metal–ligand bonds.^[19] In this section, some representative examples of transition–metal–based interlocked cages will be discussed.

Fujita was the first to demonstrate, in 1999, that metal–organic cages could be joined through mechanical bonding, resulting in the creation of interlocked cages

Pd_6L_4 and Pt_6L_4 .^[9] These interlocked cages were constructed from two different types of trispyridine ligands and six square-planar metal cations (M^{n+}), which could be either Pd^{2+} or Pt^{2+} with cis-coordinated ethylenediamine units. When all these building blocks were heated together at 100°C in D_2O , the kinetic intermediate monomeric cages Pd_3L_2 and Pt_3L_2 were formed. However, in three days, this mixture gradually transformed into a single, more thermodynamically stable assembly, the interlocked structure **IV** (Figure 4). These interlocked cages were characterised by NMR spectroscopic techniques, ESI mass spectrometry and crystallographic analysis. When Pt^{2+} cations are employed, the formation of the interlocked [2]catenane cages is much slower. Probably, this is because the platinum–pyridine bond is stronger than palladium–pyridine bond. The dimeric structure forms because it is the most thermodynamically stable product. This is due to electrostatic and van der Waals interactions between their components that leading to its stabilisation. In fact, face-to-face π – π stacking interactions occurring between the aromatic rings of the individual monomeric units which are close between them in the Pd_6L_4 and Pt_6L_4 metal–organic cages, stabilizing their structures. Furthermore, the release of solvent molecules and anions from inside the monomers contributes to the increase of entropy favouring the formation of the interlocked Pd_6L_4 and Pt_6L_4 cages.

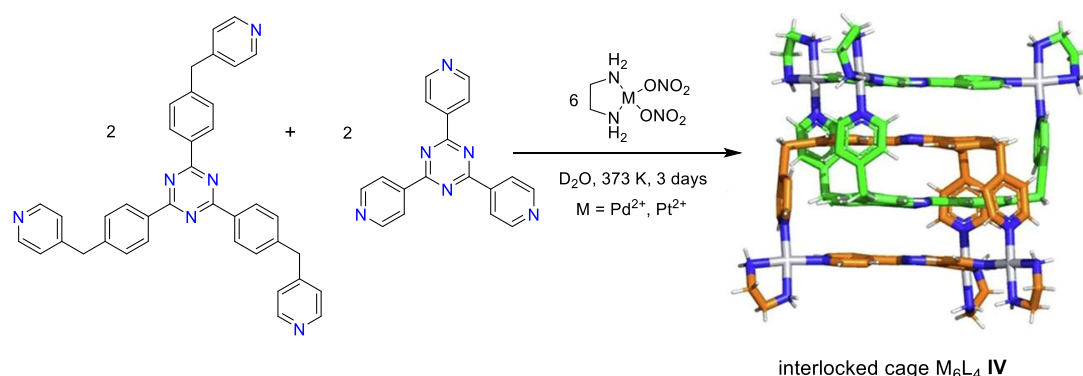


Figure 4. First example of an interlocked [2]catenane coordination cage **IV**.

Almost 10 years later, Fujita described the synthesis of a new interlocked coordination cage **V** (Figure 5).^[4c] This interlocked cage was obtained by combining four triazine and six trans-1,2-bis-pyridylethene building blocks and twelve $Pd(en)(NO_3)_2$ in the presence of triphenylene in D_2O . The mixture was heated at 100°C for three hours. It was observed that three aromatic guest molecules (triphenylene) arranged themselves in stacks between the triazine building blocks. These guest molecules act as templates, guiding the formation of the dimeric

structure and providing stability through π – π stacking interactions. These interactions occur specifically between the electron–poor triazine ligands and the electron–rich triphenylene groups. When longer pillars were used in the synthesis, this results in double or even triple aromatic stacks of triphenylene molecules inside the central cavity of the [2]catenane cage.

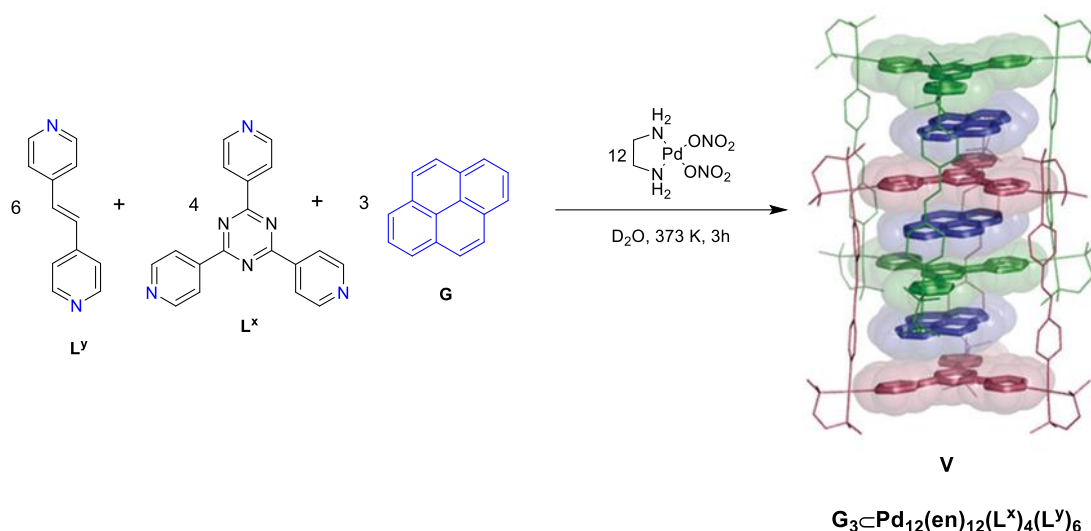


Figure 5. Synthesis of the interlocked [2]catenane **V**.

Hardie demonstrated the formation of the interlocked [2]catenane cage **VI** (Figure 6), using two bowl-shaped tris-bidentate ligands, derived from cyclotrimeratrylene, combine with three octahedrally coordinated metal ions, either Zn^{2+} or Co^{2+} in a DMSO solution, to create a single trigonal bipyramidal cage monomer M_3L_2 ($\text{M} = \text{Zn}^{2+}$ or Co^{2+}).^[4b] Each metal ion has six octahedral coordination sites, with two of these sites occupied by a chelating nitrate anion. These individual monomers then come together to form the larger interlocked cage M_6L_4 **VI**. Unlike some other examples of dimerisation, the primary force driving the formation of this [2]catenane cage cannot be attributed to face-to-face π – π stacking. This is because the distance between the aromatic rings is too great (4.77 Å) for such interactions to be significant. Instead, the attractive forces within the [2]catenane cage are thought to arise from two distinct types of weak hydrogen bonds. One type of hydrogen bond occurs between the CH protons of the bipyridine part of one cage and the OMe groups located on the inner ligand backbone of the second cage. The second type of hydrogen bond forms between the OMe group of the bipyridine residues and the non-coordinating oxygen atoms of the chelating nitrates.

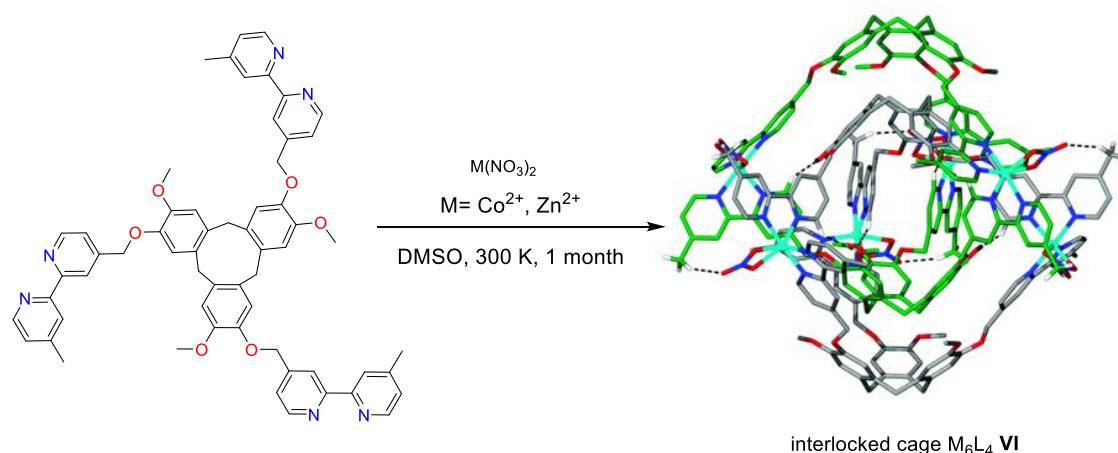


Figure 6. Synthesis of the interlocked [2]catenane cage **VI**.

Clever synthesised the new interlocked system Pd_4L_8 **VII** (Figure 7) by using a simple bis-monodentate pyridyl ligand and Pd^{2+} ions.^[10] First, bis-monodentate pyridyl ligand and Pd^{2+} ions self-assemble to form the kinetic product, the monomeric cage Pd_2L_4 . Upon prolonged heating, at $45^\circ C$ for 24 h, the monomeric cage forms the interlocked structure in the thermodynamic phase. This interlocked structure presents three different cavities that can host three BF_4^- anions. The centrally located BF_4^- is strongly retained within the core cavity, whereas the two peripheral anions are weaker associated and can be displaced by halide ions through an allosteric binding mechanism involving a concerted structural rearrangement. Notably, Cl^- exhibits particularly strong binding affinity. They proposed that both enthalpic factors, such as $\pi-\pi$ interactions between ligands and Coulombic attractions between Pd^{2+} centres and BF_4^- anions as well as entropic contributions derived from solvent release upon dimerisation, contribute to the [2]catenane cage, being the thermodynamically preferred product.

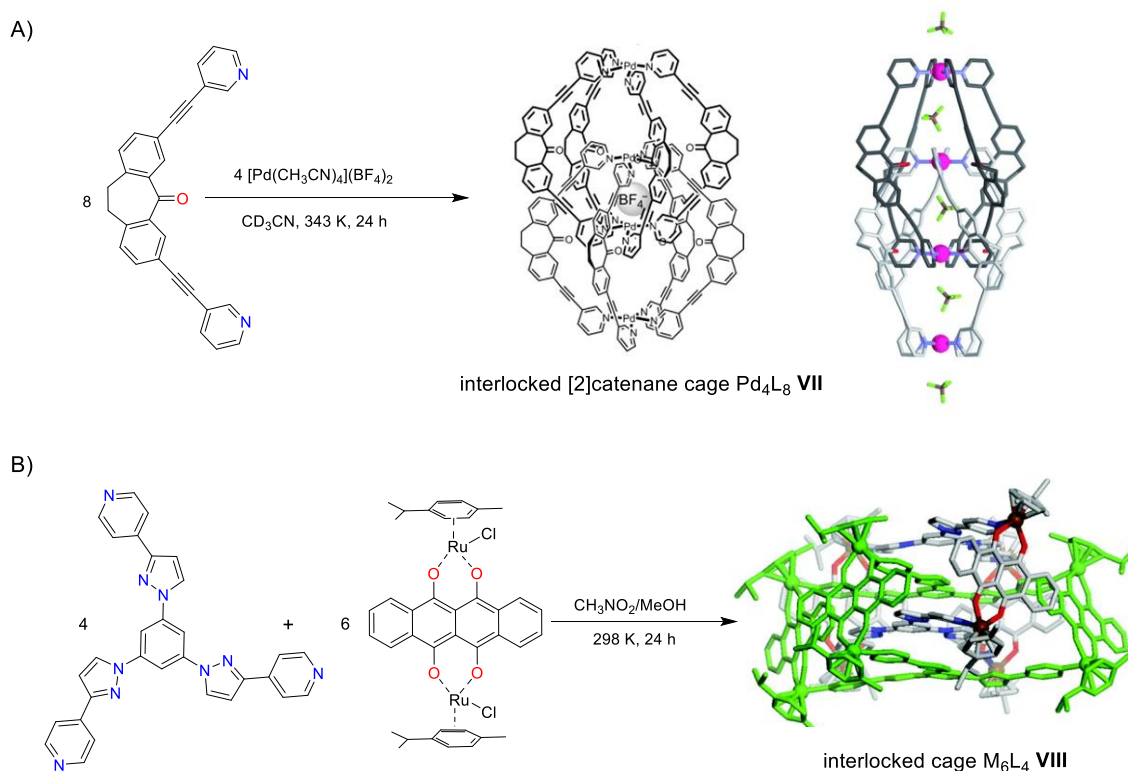


Figure 7. Synthesis of the interlocked [2]catenane cage **VII** Pd_4L_8 and B) Synthesis of the interlocked cage **VIII**.

Stang also described an important example of a interlocked [2]catenane cage. In this work, he synthesised interlocked metal–organic cages employing a tridentate ligand, specifically, 1,3,5–tris(3–(pyridine–4–yl)–1H–pyrazol–1–yl)benzene which coordinates with the ruthenium–containing dinuclear clips to produce the dimeric cage Ru_6L_4 **VIII** (Figure 7).^[11] X–ray crystallography and NMR spectroscopy revealed that efficient π – π interactions between the panels and the trispyridine ligand at a distance of 3.4 Å are crucial for the formation of the interlocked architecture **VIII**. The tetracene component maximises stronger π – π interactions and the formation of the interlocked structure. In contrast, when the linking clips do not present aromatic units, the cages do not mechanically interlock, and instead, monomeric SCCs are formed. Adjusting the aromatic properties of these clips, they could direct the synthesis towards either interlocked [2]catenane cage Ru_6L_4 or individual monomeric metal–organic cages Ru_3L_2 .

Duan demonstrated a metal–ion templated synthesis of [2]catenanes, employing Zn^{2+} ions in a synergistic approach that integrated multicomponent self–assembly with a template–directed strategy.^[20] Their method involved the

formation of the interlocked cage Zn_8L_8 **IX** (Figure 8). This [2]catenane cage was constructed through the self-assembly of tris(4-aminophenyl)amine groups, extended with a 2,2'-bipyridine-5-carbaldehyde chelator, and $Zn(BF_4)_2$. He observed that the formation of the interlocked architecture **IX** was contingent upon the templating anion effect. The formation of the interlocking structure was studied for BF_4^- , PF_6^- , $CF_3SO_3^-$ and ClO_4^- anions. NMR results revealed that the catenane formed better with ClO_4^- anions whereas with $CF_3SO_3^-$ anion the non-interlocked tetrahedral cage **X** was obtained. A notable consequence of the SCCs' interlocking was the generation of a void structure, attributed to the substantial internal volume of the monomeric cage. This unique architecture facilitated the inclusion of anions as Br^- in its cavity promoting the dehalogenation reaction of 3-bromo-cyclohexene.

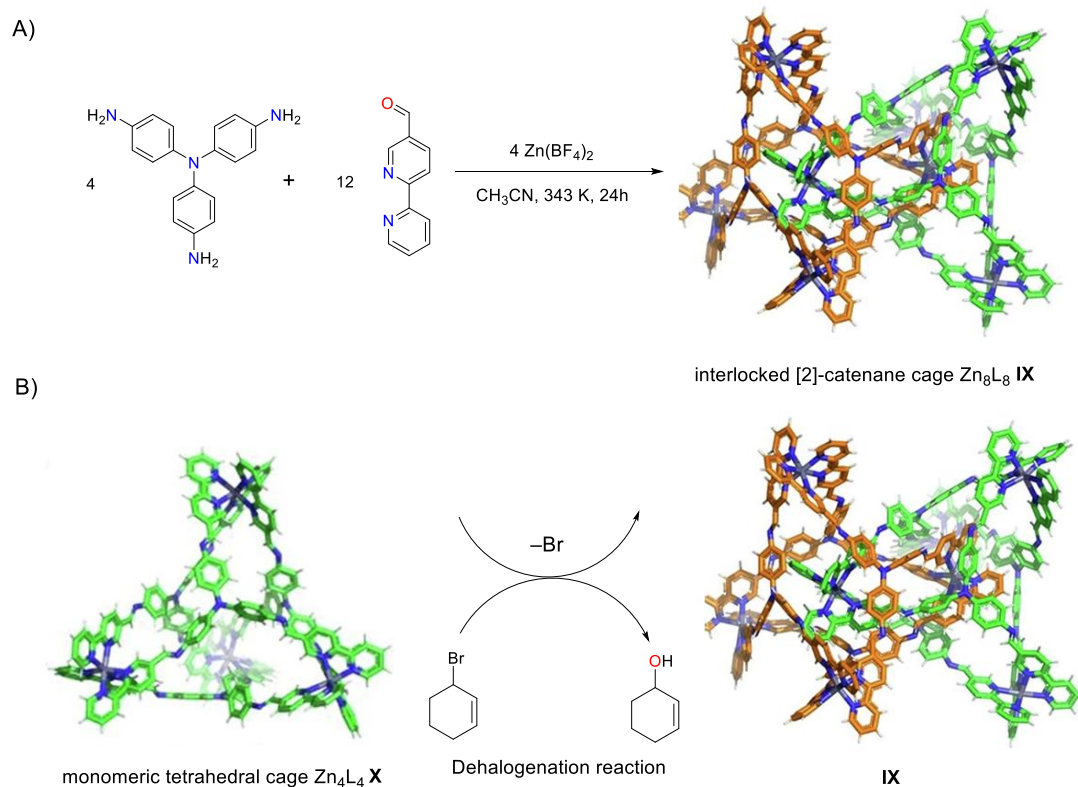


Figure 8. A) Synthesis of the interlocked [2]catenane cage **IX** and B) Dehalogenation reactions exploit the pockets generated upon interlocking.

In contrast to the previously discussed examples, which are based on nitrogen-metal bonds, Han taking advantage of ligand design, presented the effective synthesis of the triply interlocked cage Ag_6L_4 **XI** (Figure 9).^[21] In this interlocked cage, Ag^+ ions exclusively bond to nitrogen-heterocyclic carbene (NHC) units. They also described their subsequent conversion to the corresponding Au^+

analogues through transmetalation. These formation and conversion processes occur under mild conditions. These new interlocked [2]catenane cages were characterised by a wide range of techniques, including multinuclear NMR spectroscopy, ESI–MS, and single–crystal X–ray diffraction, to verify the formation and structure of these three–dimensional triply interlocked architectures. The crystal structure of **XI** definitively shows the presence of a [2]catenane M_6L_4 , composed of two identical, mechanically linked trinuclear hexacarbene cage units M_3L_2 . The interlocking of these two metal–organic cages to form a [2]catenane is driven by the efficient π – π stacking of triazine–triazine stacks with cooperative interactions between imidazo–pyridine subunits.

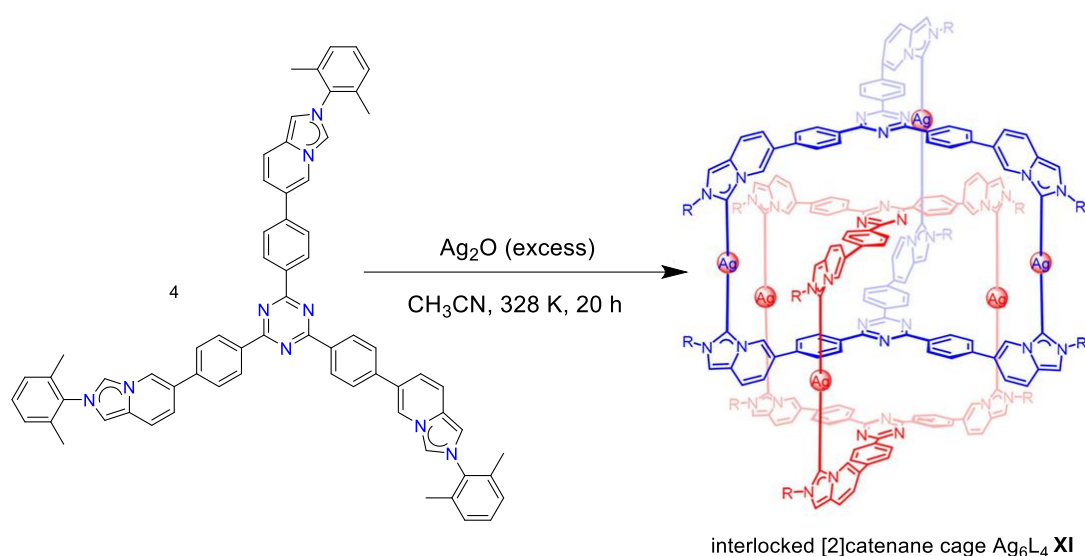


Figure 9. Synthesis of the interlocked [2]catenane cage **XI**.

3.1.3 Oligomeric and Polymeric Interlocked $(M_nL_m)_z$ Cages

Notably, all the structures reported to date involve two interlocked [2]catenane SCCs, which can be made with identical or different monomeric cages. However, to the best of our knowledge, only two examples of structures featuring three concatenated SCCs such linked SCCs (considering non–polymeric n values) have been reported.

Some examples of interlocked polymeric cage structures have been described in solution or in gas phase by Dehnen,^[22] and Lu.^[23] The first example reported involves a 2,4,6–tris(4–pyridyl)pyridine ligand coordinated to Zn^{2+} centres to form icosahedral coordination metal–organic cages **XII** presenting an internal cavity with a volume of more than 2700 Å³, suitable for encapsulation of guest

molecules (Figure 10). Interpenetration occurs through two vertices, enabling face-to-face π - π interactions between the ligand aromatic cores. The oligomeric interlocked cages **XII** form a linear arrangement, a chain-like structure composed of interlocked assemblies.

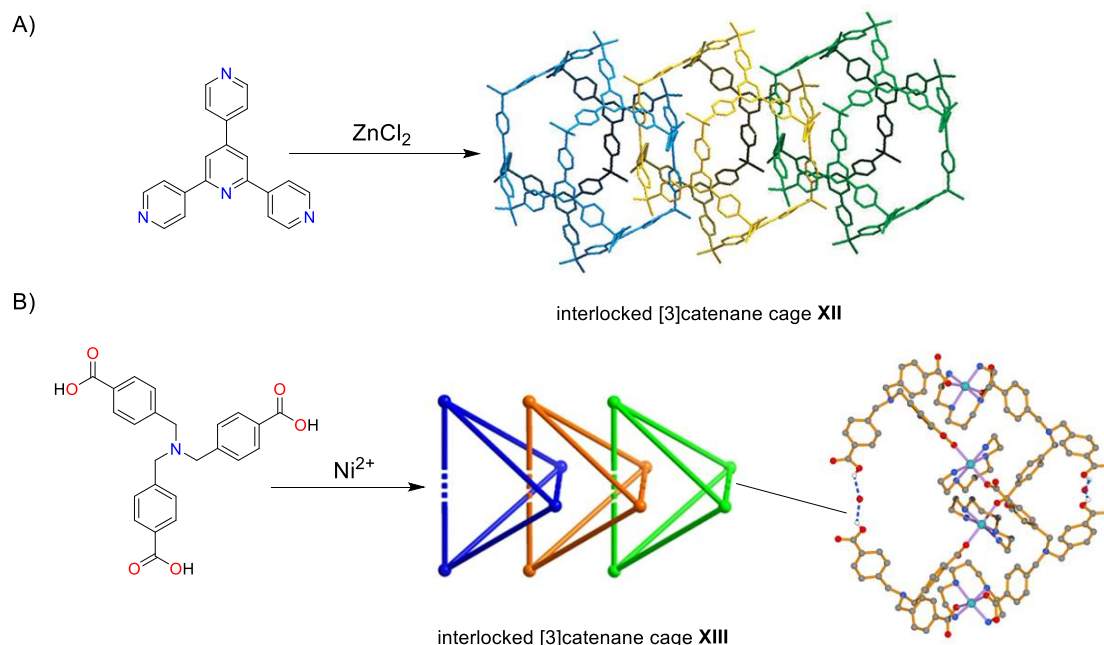


Figure 10. A) Synthesis of interlocked [3]catenane **XII** and B) Interlocked [3]catenane **XIII**.

Lu reported another example of interconnected, chain-like cages based on three separate tetrahedral metal-organic cages together. Each individual cage is assembled from a protonated ligand bonded to protected Ni^{2+} nodes (Figure 12).^[23] The four ligands occupy the four corners of the tetrahedral cage, while six Ni^{2+} cations are positioned along the six edges. Interpenetration happens between one tetrahedral cage and the adjacent one through all the four corners, resulting in the three-dimensional polycatenane structure **XIII**, where many metal-organic cages are linked together. When chloride is used as the counter anion, this leads to the formation of one-dimensional infinite chains of these interpenetrating cages.

Numerous examples of interlocked metal-organic cages have been developed exclusively using transition metals. Nevertheless, mechanical interlocking involving main-group metals remains completely unexplored. Consequently, this chapter will pursue a straightforward approach to synthesise the first interlocked metal-organic cages using main-group metals such as Al^{3+} and Ga^{3+} .

3.2 Objectives

This *Chapter* aims to uncover the assembly of mechanically interlocked coordination cages based on main-group metals by using tritopic 1,2,3-triazole-catechol ligands to promote interlocking with Al^{3+} and Ga^{3+} . We will prepare a set of tritopic ligands via CuAAC click chemistry from tris-alkyne/aromatic-azide precursors and deploy them under controlled stoichiometric conditions to access interlocked Al_6L_4 and Ga_6L_4 cages. The ligands will be rationally varied in steric and electronic features to bias interlocking. A comprehensive, multi-state characterisation will be undertaken. In solution, $^1\text{H}/^{13}\text{C}$ NMR, NOESY, and DOSY will define composition, topology, and hydrodynamic size. In the solid state, single-crystal X-ray diffraction will determine the interlocking topology (number and nature of mechanical links), connectivity, and cavity architecture. In the gas phase, high-resolution ESI-HRMS will corroborate charged fragments and M:L stoichiometry within the interlocked cages.

A second objective is to quantify and rationalise the reversibility of these main-group interlocked M_6L_4 cages and their responsiveness to external stimuli in water. We will probe acid-base cycles by time-resolved ^1H /NOESY/DOSY to monitor unlocking and re-catenation and explicitly test whether monomeric M_3L_2 species mediate the interlocking process (as often found in d-block systems). Complementary isothermal titration calorimetry (ITC) will deliver thermodynamic parameters for both disassembly and re-assembly, enabling comparison of the energy landscapes for Al vs Ga interlocked M_6L_4 cages. These quantitative trends will be used to establish metal-dependent stability tendencies and the non-covalent driving forces that underpin triply interlocked M_6L_4 topologies under mild, aqueous conditions.

By meeting these objectives, this chapter will elucidate the interlocking mechanism governing these new mechanically interwoven M_6L_4 cages and provide design rules for stimuli-responsive host systems, molecular switches, and adaptive supramolecular materials based on main-group metal interlocking.

3.3 Results and Discussion

The discussion of results is organised into two main sections. The first section is focused on the synthesis, characterisation and structural analysis of interlocked metal–organic cages using different tritopic ligands with varying spacer lengths and flexibilities; and the second section is centred on the investigation of reversible assembly of triply interlocked [2]catenanes Al₆L₄ and Ga₆L₄ cages via NMR spectroscopy and isothermal titration calorimetry (ITC).

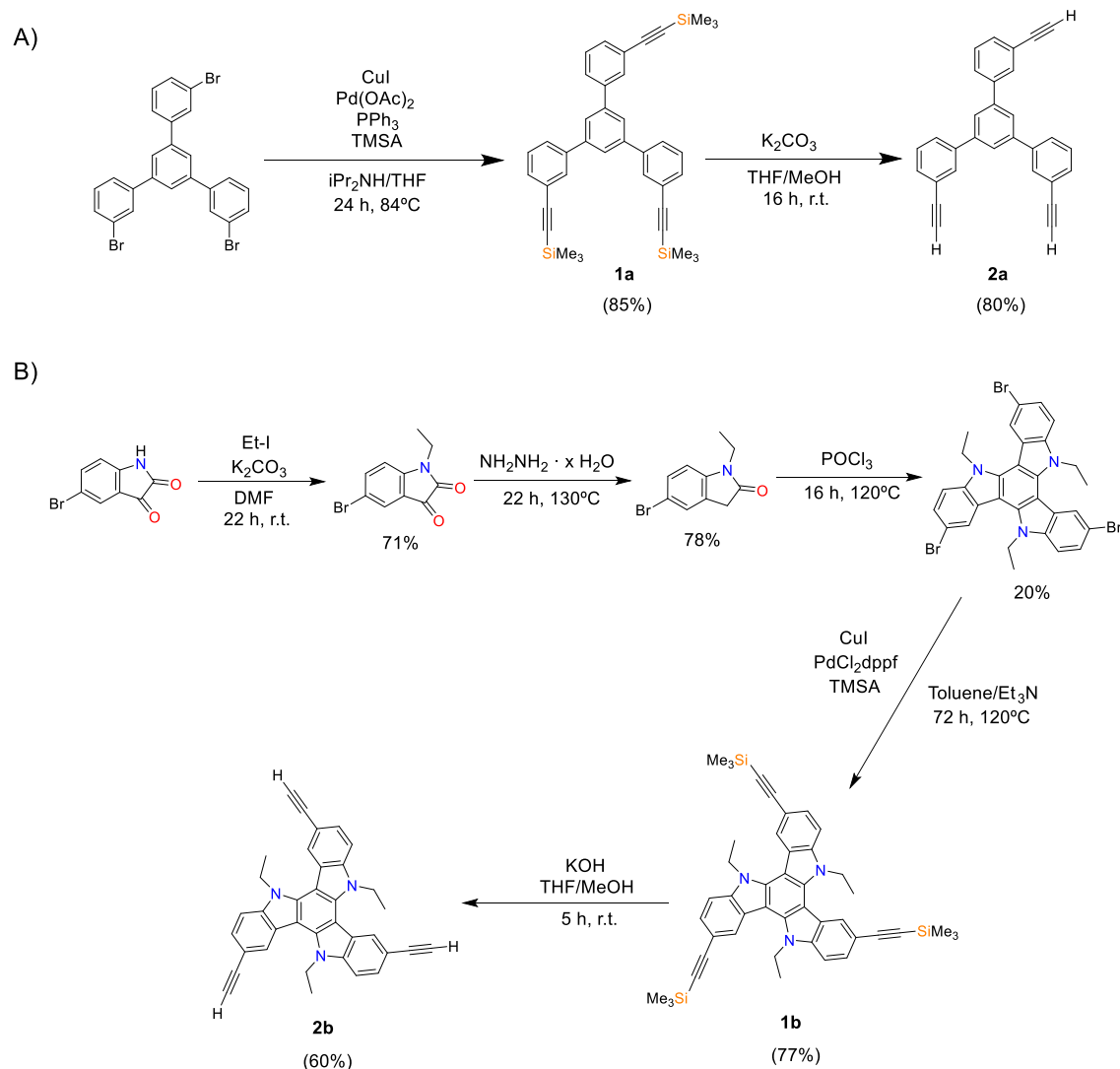
3.3.1 Synthesis and Characterisation of Tris–Alkyne Precursors

For the preparation of the tritopic 1,2,3–triazole ligands described in this chapter, we have used the same synthetic strategy employed in Chapter 2, (CuAAC) reaction between azide **4** that was previously described in Chapter 1 and various triple alkynes. To achieve this goal, a series of different alkynes have been prepared.

To obtain the products **2a** and **2b**, it was necessary to prepare the starting materials **1a** and **1b**. The alkyne **2a** was prepared following a Pd– and Cu–catalyzed Sonogashira cross–coupling reaction between the corresponding aromatic compound and the alkyne trimethylsilylacetylene, followed by deprotection of the trimethylsilyl group. The preparation of product **1a** (Scheme 1A) was carried out through the reaction of the commercial aryl bromide (3,3'–dibromo–5'–(4–bromophenyl)–1,1':3',1'–terphenyl) and trimethylsilylacetylene. In this reaction, a slight excess of the alkyne (4 equivalents relative to the brominated derivative) was used to optimise the yield and avoid mixtures. The reaction was performed at 84°C for 24 hours in the presence of the catalysts CuI (1.2 mol%) and Pd(OAc)₂ (1 mol%) and triphenylphosphine (PPh₃) in a 1:4 mixture of iPr₂NH/THF. A TLC monitoring of the resulting reaction crude indicated the quantitative formation of product **1a**. Moreover, ¹H NMR analysis, confirmed the formation of this product observing a new signal between δ 0–0.6 ppm that corresponds to trimethylsilyl groups. The reaction mixture was filtered to remove inorganic salts (isopropylammonium bromide), and after removing the volatiles from the reaction crude, product **1a** was obtained in 85% yield. The ¹H NMR of product **1a** is consistent with that reported.^[24]

Once the trimethylsilylated derivative of the alkyne **1a** was prepared, it was used for the preparation of the primary alkyne **2a**. The preparation of product **2a** was performed via protodesilylation of **1a** with K₂CO₃ (7 eq) in a mixture MeOH/THF (4:1)

(Scheme 1A). After 16 hours, DCM was added and the organic phase was washed with water, separated, dried over Na₂SO₄, filtered and concentrated. Product **2a** (*R_f* = 0.33) was purified by column chromatography using as eluent a mixture hexane/DCM (10:3) obtaining product **2a** with a yield of 80%.



Scheme 1. Preparation of alkynes **2a** and **2b** via Sonogashira couplings following by protodesilylation.

However, to obtain product **1b**, it was necessary to prepare its brominated precursor (3,8,13-tribromo-5,10,15-triethyl-triazatruxene). For this purpose, a mixture of 5-bromoisatin, potassium carbonate, C₂H₅I was dissolved in DMF and was stirred at room temperature for 22 h under a nitrogen atmosphere. After, the reaction mixture was poured into water, and extracted with dichloromethane, the combined organic layers were dried with anhydrous Na₂SO₄, filtered and evaporated to dryness, to give 5-bromo-1-ethylindoline-2,3-dione with a yield of 71%. Then, this

product was mixed with hydrazine hydrate (80%) and stirred at 130°C (reflux) for 22 h under nitrogen protection. The reaction mixture was allowed to cool to room temperature and was extracted with dichloromethane, the combined organic layers were dried with anhydrous Na₂SO₄, filtered and evaporated to dryness obtaining the yellow product 5-Bromo-N-ethyloxindole with a yield of 78%. Finally, a mixture of 5-Bromo-N-ethyloxindole and POCl₃ was heated at 120 °C (reflux) for 16 h. Then, the reaction mixture was poured into ice and neutralised carefully with KOH until pH 7–8. After neutralisation, the precipitate was filtered to give the crude product as a brown solid. The crude product was purified by flash chromatography (n-hexane/DCM 8:2), and the resulting yellow solid was recrystallised in DCM at –33°C to give pure 3,8,13-tribromo-5,10,15-triethyl-triazatruxene as a white solid (20%). The preparation of product **1b** (Scheme 1B) was carried out through the reaction of the aryl bromide (3,8,13-tribromo-5,10,15-triethyl-triazatruxene) and trimethylsilylacetylene under a nitrogen atmosphere. In this reaction, a large excess of the alkyne (37 equivalents relative to the brominated derivative) was used to optimise the yield and avoid mixtures. The reaction was performed at 120°C for 72 hours in the presence of CuI (0.21 eq) and PdCl₂dppf (0.36 eq) in a 1:1 mixture of toluene/Et₃N. A TLC monitoring of the resulting reaction crude indicated the quantitative formation of product **1b**. Then, the reaction mixture was extracted with DCM, the organic phase was washed with distilled water, dried with anhydrous Na₂SO₄ and filtered to remove inorganic salts (triethylammonium bromide). After removing the volatiles from the reaction crude, product **1b** (R_f = 0.25) was purified by column chromatography (n-hexane/DCM 8:2) obtaining this white product with a yield of 77%. The ¹H NMR of product **1b** is consistent with the one reported.^[25] Once the trimethylsilylated derivative of the alkyne **1b** was prepared, it was used for the preparation of the primary alkynes **2b**. For this purpose, product **1b** was dissolved in a 1:1 mixture of THF and MeOH. Then, a large excess of KOH (17 eq) was added. The mixture was stirred for 5 h under a nitrogen atmosphere at room temperature. After this time, the reaction was quenched by evaporating most of the solvent and aqueous NH₄Cl solution to adjust the pH value below 7 was added. The mixture was then extracted with DCM, and the DCM layer was washed with distilled water, dried with anhydrous Na₂SO₄ and filtered. The volatiles were removed under reduced pressure in a rotavapor, obtaining the product **2b** with a yield of 60%.

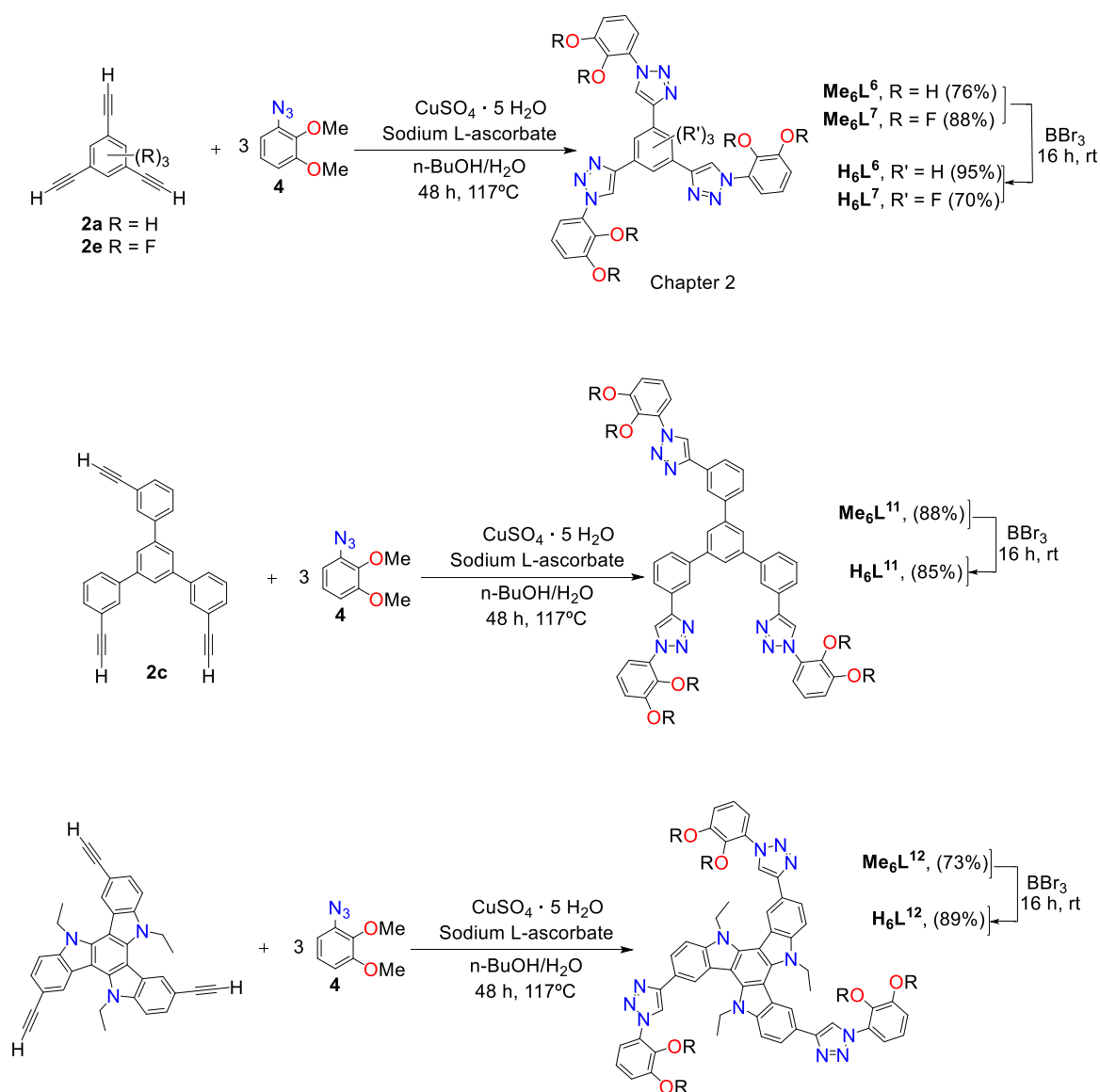
¹H NMR analysis confirmed the formation of the products **2a** and **2b** observing the disappearance of the signal between δ 0–0.6 ppm (trimethylsilyl groups) and the

appearance of a new signal between δ 3–4 ppm that correspond to protons of alkynes. The 1H NMR of the products **2a** and **2b** are consistent with those reported.^[24-25]

3.3.2 Synthesis and Characterisation of Ligands H_6L^{11} and H_6L^{12}

The preparation of ligands H_6L^6 and H_6L^7 , which will be used in this chapter for constructing interlocked cages, was described in Chapter 2. Therefore, in this chapter, we will describe the preparation of the new tritopic ligands H_6L^{11} and H_6L^{12} . This synthesis began with the preparation of their methylated precursors Me_6L^{11} and Me_6L^{12} . These were obtained via a copper-catalyzed azide-alkyne cycloaddition (CuAAC) between the corresponding terminal alkynes (**2a–2b**) and three equivalents of the aromatic azide **4**, previously described in Chapter 1. The reaction was performed using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as the catalytic system in an *n*-butanol/water solvent mixture at 117 °C under reflux for 72 hours. Completion of the reaction was monitored by thin-layer chromatography (TLC), and the products were subsequently extracted with chloroform to afford the precursors Me_6L^{11} and Me_6L^{12} in yields ranging from 73% to 88%. The formation of the 1,2,3-triazole rings was confirmed by 1H NMR spectroscopy, which showed the appearance of characteristic triazole signal between δ 8.2 and 9.1 ppm and the disappearance of the terminal alkyne group signal between δ 3.0 and 4.0 ppm. The compounds were obtained with sufficient purity, as confirmed by 1H NMR and elemental analysis, for using in subsequent synthetic steps.

To obtain the ligands H_6L^{11} and H_6L^{12} (Scheme 2), the methoxy protecting groups of the precursors Me_6L^{11} and Me_6L^{12} were removed. This demethylation was performed under an inert nitrogen atmosphere using boron tribromide (BBr_3) in dry dichloromethane at -78 °C, followed by gradual warming to room temperature. After solvent evaporation, the reaction mixture was quenched with water to neutralise excess BBr_3 , and the crude product was refluxed at 100 °C for 2 hours to promote precipitation. The resulting ligands H_6L^{11} and H_6L^{12} were isolated by filtration in yields of 85–89%. 1H NMR analysis of H_6L^{11} and H_6L^{12} confirmed successful deprotection, evidenced by the disappearance of methoxy proton signals (δ 3.7–4.0 ppm) and the appearance of new resonances corresponding to catechol protons (δ 9.4–10.5 ppm).



Scheme 2. Preparation of precursors **Me₆L¹¹–Me₆L¹²** and ligands **H₆L¹¹–H₆L¹²**.

ESI–HRMS further confirmed the successful synthesis of the ligands **Me₆L¹¹–Me₆L¹²** and **H₆L¹¹–H₆L¹²**. **Me₆L¹¹** and **Me₆L¹²** exhibited protonated molecular ions forming the corresponding cationic adducts [**Me₆L¹¹** + H]⁺ and [**Me₆L¹²** + H]⁺ at *m/z* values of 916.3575 (calcd. 916.3566) and 1039.4411 (calcd. 1039.4362) respectively. Regarding the demethylated ligands, **H₆L¹¹** primarily formed protonated species [**H₆L¹¹** + H]⁺ at *m/z* values of 832.2626 (calcd. 832.2627), whereas **H₆L¹²** showed adduct formation with K⁺ ions, forming [**H₆L¹²** + K]⁺ at *m/z* values of 993.3059 (calcd. 993.2982). Moreover, the experimental isotopic distributions closely matched the theoretical patterns, further validating the molecular composition and successful synthesis of the **Me₆L¹¹–Me₆L¹²** and **H₆L¹¹–H₆L¹²** series.

To gain further insight into the molecular structures and study their potential for forming metal–organic architectures, single crystals of **Me₆L**¹² were successfully obtained for X–ray analyses. Despite multiple crystallisation attempts, suitable crystals of **Me₆L**¹¹, **H₆L**¹¹ and **H₆L**¹² were unsuccessful. High–quality block crystals of **Me₆L**¹² were achieved by layering of hexane into a concentrated DCM solution of the respective compound.

The X–ray structure of **Me₆L**¹² (Figure 11) shows the triazole rings slightly rotated respect to the central triazatruxene plane, with torsion angles of 5.7(4)–42.6(4)°. Moreover, the rings containing the methoxy groups $C_6H_3(OMe)_2$ are twisted relative to triazole rings plane with torsion angles of 27.3(4)–47.7(4)°. The triazole CH groups are oriented towards the oxygen of the nearest methoxy group at distances ranging between 2.6686(17)–2.7899(16) Å (triazole–CH···OMe), allowing for weak electrostatic interactions between them. This ligand exhibits a triangular arrangement with terminal catechols at distances of 19.667(3)–20.045(4) Å, these distances were measured between the oxygens of the two external –OMe groups of the $C_6H_3(OMe)_2$ rings. The arrangement of **Me₆L**¹² is ideally spaced for coordination metal nodes.

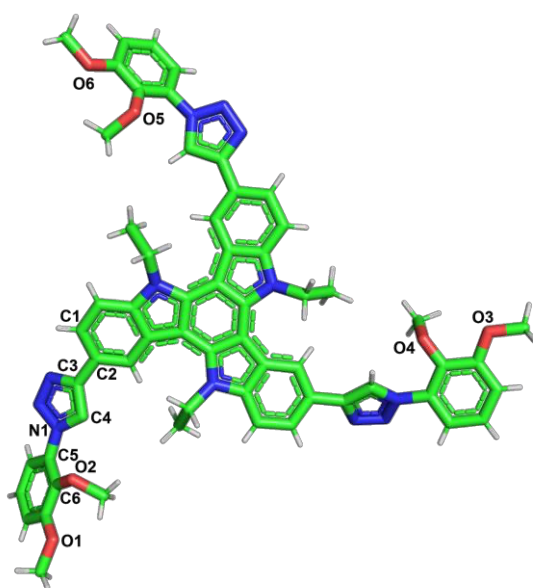
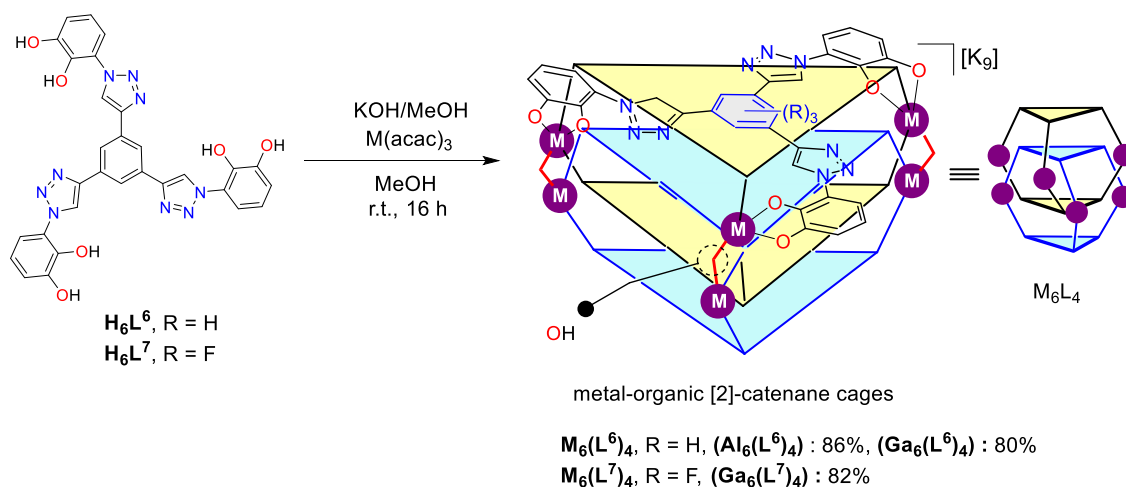


Figure 11. Molecular structure of **Me₆L**¹². Selected bond lengths (Å) and angles (°): O1–O6 19.667(3), O1–O3 20.045(4), triazole–CH···OMe 2.6686(17)–2.7899(16); torsion angles C1–C2–C3–C4 5.7(4)–42.6(4), C4–N1–C5–C6 27.3(4)–47.7(4). Thermal ellipsoid plots at 50% probability are given in the annexes to this Chapter.

3.3.3 Supramolecular Triply Interlocking of Al_6L_4 and Ga_6L_4 Cages

With the synthesised ligands H_6L^6 and H_6L^7 in Chapter 2 and the successful synthesis of the new tritopic ligands H_6L^{11} and H_6L^{12} , we will explore the coordination chemistry of these ligands with Al^{3+} and Ga^{3+} metal ions to form interlocked metal–organic cages, distinct from tetrahedral M_4L_4 cages described in Chapter 2.

With the aim of synthesizing novel interlocked metal–organic cages, we used a similar synthetic procedure that those employed in chapter 2 for obtaining tetrahedral M_4L_4 cages but using a different ratio M:L (M = metal, L = ligand). Self-assembly of H_6L^6 and H_6L^7 with $\text{Al}(\text{acac})_3$ and $\text{Ga}(\text{acac})_3$ (acac = acetylacetonate), and KOH in a ratio 4:6:9 in MeOH, selectively produced the triply interlocked cages $\text{Al}_6(\text{L}^6)_4$, $\text{Ga}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ within 16 hours at room temperature (Scheme 3). The use of an excess of metal relative to the ligand is extremely important to avoid the formation of M_4L_4 cages and selectively obtain interlocked metal–organic cages M_6L_4 . $\text{Al}_6(\text{L}^6)_4$, $\text{Ga}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ interlocked cages were isolated as their corresponding potassium salts in high yields, ranging between 80% and 86%, by simple ether trituration. In the case of the self-assembly of H_6L^7 with Al^{3+} ions, the formation of the interlocked metal–organic cage $\text{Al}_6(\text{L}^7)_4(\text{OH})_3$ was observed. However, due to the lower stability of the aluminum acetylacetonate complexes and the presence of fluorine atoms in the core of the ligand used, which weaken the π – π stacking in the resulting interlocked structure, the assembly proceeded with limited purity. As a result, the isolation of the target interlocked cage $[\text{Al}_6(\text{L}^7)_4(\text{OH})_3][\text{K}]_9$ was not achieved. $\text{Al}_6(\text{L}^6)_4$, $\text{Ga}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ represent the first examples of main-group-based interlocked cages.



Scheme 3. Preparation of the triply interlocked metal–organic cages $\text{M}_6(\text{L}^{6-7})_4$.

The self-assembly of the tritopic ligands H_6L^{11} and H_6L^{12} with $Al(acac)_3$ and $Ga(acac)_3$ ($acac$ = acetylacetonate) in the presence of KOH and Et_4NBr in $MeOH$, resulted in the formation of complexes mixtures corresponding to asymmetric metal-organic architectures. The stoichiometries of these metal-organic assemblies will be elucidated and discussed in the HRMS section 1.3.5.

3.3.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis

The analysis of the 1H NMR spectrum of the interlocked coordination cages $Al_6(L^6)_4$, $Ga_6(L^6)_4$ and $Ga_6(L^7)_4$ reveals important details about their complex structure. Disappearance of the catechol OH signals between δ 9.4–10.5 ppm indicated deprotonation of the ligands H_6L^6 and H_6L^7 confirming metal-catecholate coordination (Figure 12). Notably, each interlocked cage displays two sets of sharp resonances in D_2O at 298 K, reflecting two chemically inequivalent ligand environments. This spectral duplication evidences the mechanical interpenetration of two cage monomeric units, $Al_3(L^6)_2$, $Ga_3(L^6)_2$ or $Ga_3(L^7)_2$, within each dimeric assembly. The triazole protons $H^b/H^{b'}$ shift downfield ($Al_6(L^6)_4$: δ 9.28/9.42 ppm; $Ga_6(L^6)_4$: δ 9.26/9.36 ppm; $Ga_6(L^7)_4$: δ = 9.25/9.65 ppm) relative to H_6L^6 (δ 9.08 ppm) and H_6L^7 (δ = 8.87 ppm), consistent with a peripheral cage location. In contrast, the phenylene C_6H_3 core protons $H^a/H^{a'}$ are strongly shielded ($Al_6(L^6)_4$: δ 7.70/7.36 ppm; $Ga_6(L^6)_4$: δ 7.71/7.38 ppm) vs. H_6L^6 : δ 8.52 ppm) owing to the π -stacking within the cage interior. In addition, $Ga_6(L^7)_4$ architecture was studied using the ^{19}F NMR due to the presence of fluor atoms in the H_6L^7 core (C_6F_3). This spectrum showed two downfield shifted signals for $Ga_6(L^7)_4$ (δ = -101.9/-105.8 ppm) compared to H_6L^7 (δ = -109.2 ppm). This effect may result from a combination of metal-ligand coordination and π - π stacking interactions between the fluorinated ligands within the interlocked cage $Ga_6(L^7)_4$, which act to withdraw electron density from the fluorinated aromatic rings C_6F_3 . Signals corresponding to the aromatic protons of the catechol rings are observed within the δ 6.3–7.0 ppm range. $^{13}C\{^1H\}$ NMR data in D_2O also shows duplicated sets at 298 K, confirming ligand interpenetration.

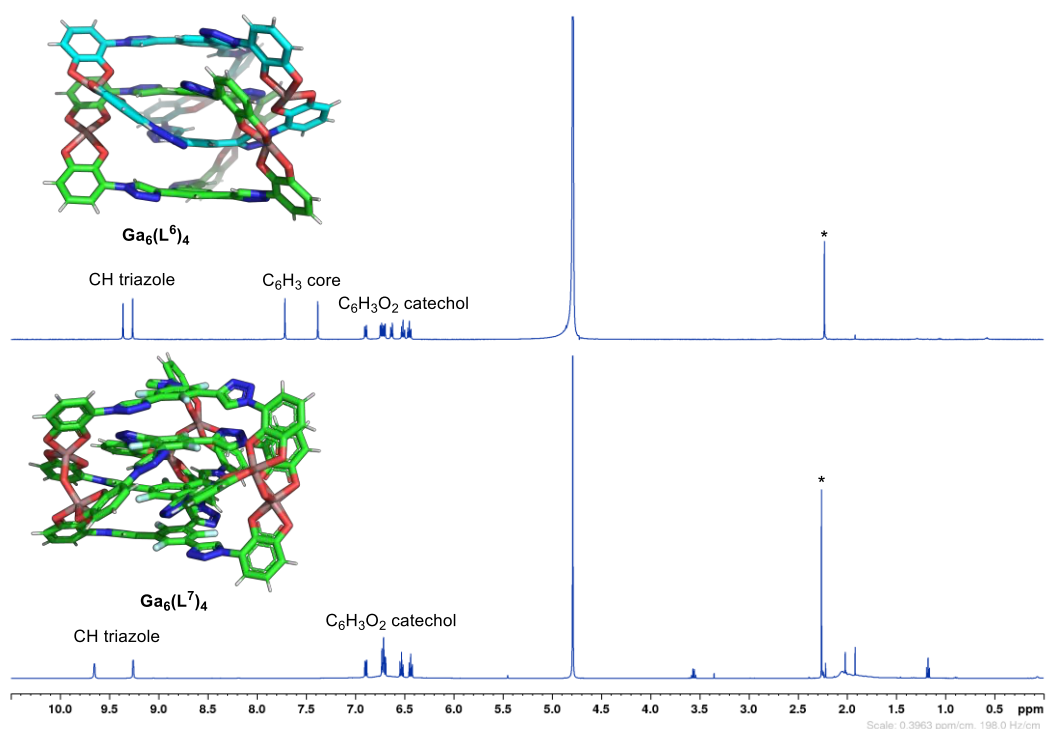


Figure 12. ^1H NMR (500 MHz, D_2O , 298 K) spectrum comparative of $\text{Ga}_6(\text{L}^6)_4$ (top) and $\text{Ga}_6(\text{L}^7)_4$ (bottom). The symbol * denotes residual signal for acetylacetone.

Detailed NOESY NMR analyses of $\text{M}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ permitted precise assignment of internal and external ligand environments. For interlocked cages $\text{M}_6(\text{L}^6)_4$, explicit NOE correlations between internal ligand aromatic C_6H_3 core protons and adjacent triazole protons from external ligand layers confirmed their close spatial proximity (Figure 13). For interlocked cage $\text{Ga}_6(\text{L}^7)_4$, only NOE correlations between ligand triazole protons from external and internal layers were observed due to the presence of fluorine atoms in the H_6L^7 core. Furthermore, these distinct NOE couplings between adjacent ligands reinforced retention of the π – π stacking motifs in solution for $\text{M}_6(\text{L}^6)_4$ and $\text{M}_6(\text{L}^7)_4$, directly supporting the [2]catenane interlocked cage formation.

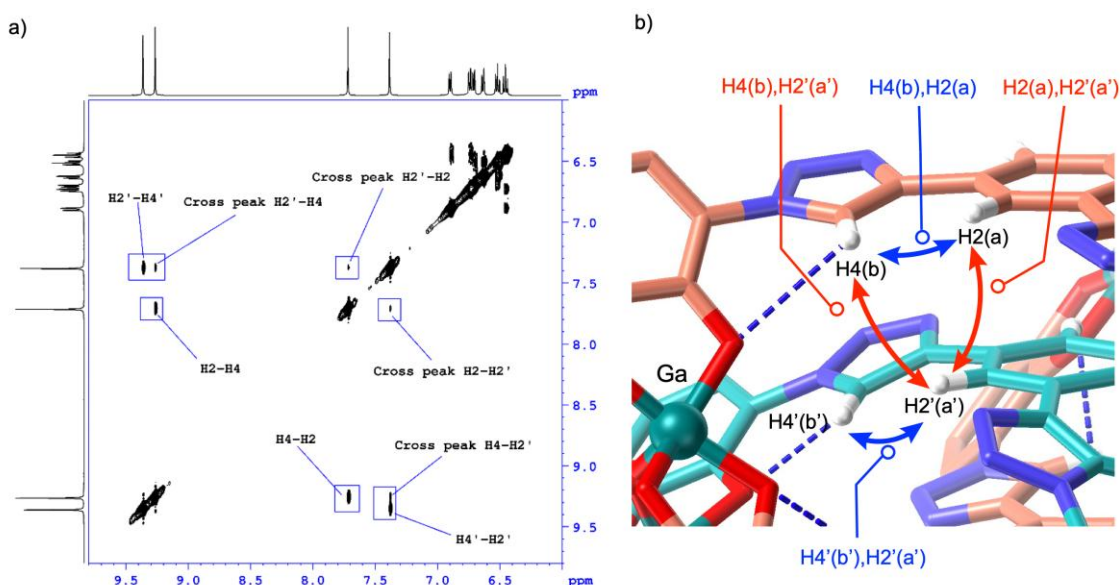


Figure 13. a) $^1\text{H}, ^1\text{H}$ -NOESY spectrum (500 MHz, D_2O , 298 K) of $\text{Ga}_6(\text{L}^6)_4$. NOE couplings are highlighted with a blue box. The highlighted cross peaks $\text{H4(b)}\text{--H2'(a')}$ and $\text{H2(a)}\text{--H2'(a')}/\text{H2'(a')}\text{--H2(a)}$ indicate ^1H atoms that are close between the inner and outer ligand decks (ie. they do not belong to the same ligand system) within the supramolecular molecular geometry of $\text{Ga}_6(\text{L}^6)_4$. b) Illustration of NOE interactions in the crystalline structure of $\text{Ga}_6(\text{L}^6)_4$.

The self-assembly of ligands H_6L^{11} and H_6L^{12} with Al^{3+} and Ga^{3+} exhibited complex ^1H NMR spectra. These complex ^1H NMR spectra are consistent with the formation of different asymmetric isomers of metal-organic assemblies. The observed spectral complexity can be attributed to the presence of two distinct metal coordination modes (Δ or Δ) and the two possible helical orientations (clockwise and anticlockwise) for the triazatruxene-based ligand H_6L^{12} within the supramolecular framework. These structural variables give rise to multiple diastereomeric asymmetric metal-organic assemblies, consistent with the NMR observations. The stoichiometry of these coordination architectures will be discussed in the HRMS section 1.3.5. The flexibility of the ligands, along with the intrinsic structural features of H_6L^{11} and H_6L^{12} favoured the formation of metal-organic assemblies with lower stoichiometry compared to those formed with H_6L^6 and H_6L^7 . This behaviour aligns with a well-established principle of supramolecular self-assembly, wherein entropy favours assemblies with a larger number of smaller units. The conformational adaptability of H_6L^{11} and H_6L^{12} enables multiple chelation sites to bind a single metal centre simultaneously, facilitating the formation of such lower-stoichiometry species.

In contrast, the rigid geometries of H_6L^6 and H_6L^7 impose steric constraints that inhibit the formation of lower-order architectures and favouring the formation of interlocked cages M_6L_4 .

3.3.3.2 Diffusion-Ordered Spectroscopy (DOSY) NMR Analysis

To investigate the stability of the interlocked supramolecular coordination cages $\text{M}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ as well as their aggregation degree in solution, we carried out diffusion-ordered spectroscopy NMR experiments of these compounds. In these experiments, single sets of signals with uniform diffusion coefficients in the DOSY spectra were observed indicating that the coordination compounds M_6L_6 are stable and discrete entities in solution.

As we saw in Chapter 2, the diffusion coefficient (D) of the free ligands H_6L^6 and H_6L^7 were measured to be $2.60 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ and $2.50 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ respectively in DMF-d_7 , consistent with a similar hydrodynamic diameter of $\sim 20\text{--}22 \text{ \AA}$ for both ligands. This diameter, approximately double the crystallographic monomer size ($11 \text{ \AA}$) of Me_6L^6 , suggesting predominantly dimeric aggregation, stabilised by $\pi\text{--}\pi$ stacking and hydrogen-bonding interactions. This pre-organisation is expected to reduce the entropic cost of cage assemblies using H_6L^6 and H_6L^7 . Upon formation of the interlocked cages $\text{M}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ the diffusion coefficients decreased significantly to $1.4\text{--}1.5 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ in D_2O for the interlocked metal-organic cages (Figure 14), reflecting the larger hydrodynamic diameter of the assembly.

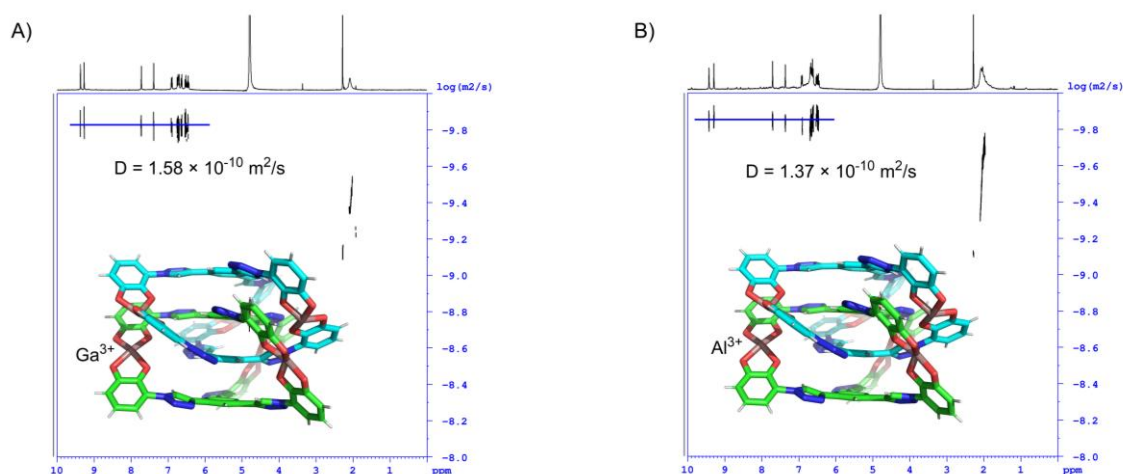


Figure 14. A) DOSY NMR spectrum of the interlocked cage structure $\text{Ga}_6(\text{L}^6)_4$ and B) $\text{Al}_6(\text{L}^7)_4$.

Table 1. D (m^2s^{-1}) and $d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$) for $\text{Al}_6(\text{L}^6)_4$, $\text{Ga}_6(\text{L}^6)_4$, and $\text{Ga}_6(\text{L}^7)_4$ in D_2O at 298 K.

Species	D (m^2s^{-1})	$d_{\text{H}}^{\text{DOSY}}$ ($\text{\AA}$)	$d^{\text{X-Ray}}$ ($\text{\AA}$)
$\text{Al}_6(\text{L}^6)_4$	1.37×10^{-10}	24	—
$\text{Ga}_6(\text{L}^6)_4$	1.58×10^{-10}	22	27
$\text{Ga}_6(\text{L}^7)_4$	1.42×10^{-10}	24	27

The calculated hydrodynamic diameters ($d_{\text{H}}^{\text{DOSY}}$) of the interlocked cages were ~ 22 – 24 $\text{\AA}$ which are in good agreement with the dimensions obtained from the crystal structure of $\text{Ga}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ (27 $\text{\AA}$) (Table 1). This further corroborates that the supramolecular assemblies $\text{Ga}_6(\text{L}^1)_4$ and $\text{Ga}_6(\text{L}^2)_4$ maintain their interlocked topology in water.

3.3.3.3 High-Resolution Mass Spectrometric (HRMS) Analysis

Time of flight mass spectrometry confirmed the integrity and composition of cages $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$. Isotopically resolved m/z peaks for intact anionic cage species $\text{M}_6(\text{L}^6)_4$ and $\text{Ga}_6(\text{L}^7)_4$ were observed in multiple charge states ($n = 2-$, $3-$ and $4-$), primarily via ion-pairing with K^+ , Na^+ and/or H^+ counterions. Notably, additional peaks, predominantly through pairing with three hydroxo (OH^-) ions were detected for $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ cages. HRMS analysis of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ ($9-$) revealed peaks at m/z 763.4597 ($4-$) (calcd. 763.4604), 1030.9327 ($3-$) (calcd. 1030.9348), and 1565.8804 ($2-$) (calcd. 1565.8838), corresponding to adducts associated with five, six, and seven K^+ ions, respectively. Similarly, the spectra of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ ($9-$) and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ ($9-$) displayed analogous species. For $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$, peaks were observed at m/z 945.7075 ($3-$) (calcd. 945.7143), and 1438.0436 ($2-$) (calcd. 1438.0529), while $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ exhibited signals at m/z 1102.8977 ($3-$) (calcd. 1102.8971) and 1673.8275 ($2-$) (calcd. 1673.8272), each corresponding to complexes incorporating increasing numbers of K^+ cations. Moreover, the observed isotope patterns matched well with the calculated distributions, confirming the $\text{M}_6\text{L}_4(\text{OH})_3$ stoichiometry (Figure 15). Furthermore, partial monomerisation into monomeric cage subunits was observed at m/z peaks of 425.0574 (calcd. 425.0584) for $\text{Al}_3(\text{L}^6)_2$ ($3-$), 467.6689

(calcd. 467.6691) for $\text{Ga}_3(\text{L}^6)_2$ (3–) and 503.6516 (calcd. 503.6503) for $\text{Ga}_3(\text{L}^7)_2$ (3–), reflecting unlocking of $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ under ionisation conditions. These HRMS data suggest that the interlocked cage $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ exhibits greater gas-phase stability compared to its analogues $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$. This conclusion is supported by the predominance and higher relative intensities of ion adducts corresponding to $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$, indicating a more favourable association with various cations under the mass spectrometric conditions.

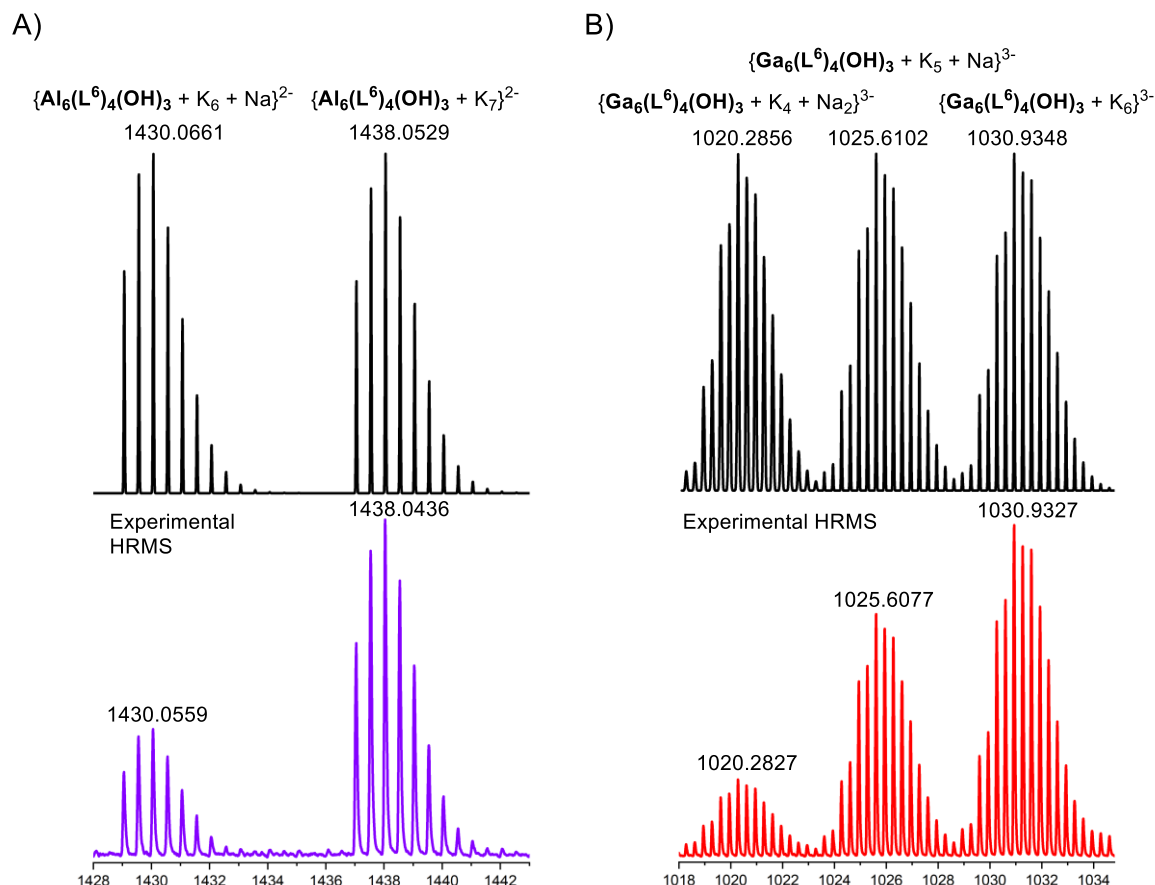


Figure 15. A) A selected section of the ESI–HRMS corresponding to the species $\text{Al}_6(\text{L}^6)_4(\text{OH})_3 + 6 \text{K}^+ + \text{Na}^+$ and $\text{Al}_6(\text{L}^6)_4(\text{OH})_3 + 7 \text{K}^+$ and B) selected section of the ESI–HRMS corresponding to the species $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3 + 4 \text{K}^+ + 2 \text{Na}^+$, $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3 + 5 \text{K}^+ + \text{Na}^+$, $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3 + 6 \text{K}^+$.

For $\text{M}_2(\text{L}^{11})_2$ architectures, ESI–HRMS revealed distinct peaks corresponding to various cationic adducts. In the case of $\text{Al}_2(\text{L}^{11})_2$ (6–) assembly, peaks at m/z of 589.4479 (3–) (calcd. 589.4486), 594.7728 (3–) (calcd. 594.7733), and 938.2594 (2–) (calcd. 938.2615) were assigned to species incorporating $1\text{K}^+/1\text{Na}^+/1\text{H}^+$, $2\text{K}^+/1\text{H}^+$, and $1\text{K}^+/2\text{H}^+/1\text{Et}_4\text{N}^+$, respectively. For $\text{Ga}_2(\text{L}^{11})_2$ architectures, peaks at m/z of 623.0791 (3–) (calcd. 623.0687), 635.7326 (3–) (calcd. 635.7206), 973.0784 (2–)

(calcd. 973.0624), and 1018.6769 (2[−]) (calcd. 1018.6605) were observed for aggregates containing $2\text{K}^+/\text{H}^+$, 3K^+ , 4K^+ , and $3\text{K}^+/\text{Et}_4\text{N}^+$, respectively. The ESI–HRMS spectrum of $\text{Ga}_2(\text{L}^3)_2$ (Figure 16) shows ions with a 3[−] charge in the m/z range of 590–670, attributed to the association of the $\text{Ga}_2(\text{L}^{11})_2$ core with three cations (K^+ , Na^+ , H^+ , and/or Et_4N^+) whereas in the higher m/z range of 925–1025, multiple 2[−] charged species were observed, corresponding to adducts formed through the association of four cations under the ionisation conditions of the mass spectrometry experiment.

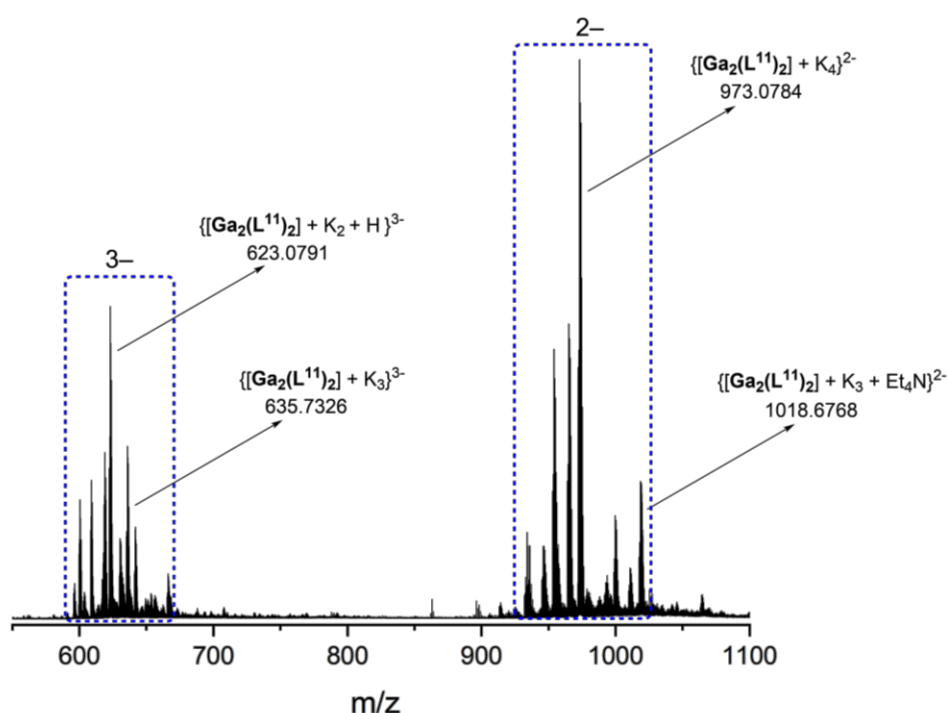


Figure 16. Full view for ESI–HRMS for $\text{Ga}_2(\text{L}^{11})_2$.

Finally, for $\text{M}_3(\text{L}^{12})_3$ (9[−]) architectures, peaks at m/z values of 752.1969 (4[−]) (calcd. 752.1918), 774.9960 (4[−]) (calcd. 774.9908) and 1046.3135 (3[−]) (calcd. 1046.3088) were observed for compound $\text{Al}_3(\text{L}^{12})_3$ with $2\text{K}^+/\text{H}^+$, $1\text{K}^+/\text{H}^+/\text{Et}_4\text{N}^+$ and $2\text{K}^+/\text{H}^+/\text{Et}_4\text{N}^+$ respectively. The ESI–HRMS spectrum of $\text{Ga}_3(\text{L}^{12})_3$ (Figure 17), peaks at m/z values of 784.1715 (4[−]) (calcd. 784.1494), 806.9705 (4[−]) (calcd. 806.9485) and 1088.9463 (3[−]) (calcd. 1088.9190) were detected corresponding to analogous species. Their ESI–HRMS spectrum shows, in the first section (m/z 750–850), several ions from different aggregates with charge 4[−] resulting from association of $\text{M}_3(\text{L}^{12})_3$ with five cations (K^+ , Na^+ , H^+ , and/or Et_4N^+) whereas in the second section (m/z 1040–1150), we could observe aggregates with charge 3[−] resulting from association of $\text{M}_3(\text{L}^{12})_3$ with six cations. According to these

HRMS results, in gas phase, $\text{Al}_3(\text{L}^{12})_3$ seems to be more stable than $\text{Ga}_3(\text{L}^{12})_3$, because for $\text{Al}_3(\text{L}^{12})_3$ system, we detected more peaks and with a major intensity that corresponded to associations of $\text{Al}_3(\text{L}^{12})_3$ with diverse ions.

Further investigation is required to elucidate and fully comprehend the structural characteristics of both $\text{M}_2(\text{L}^{11})_2$ and $\text{M}_3(\text{L}^{12})_3$ metal–organic assemblies.

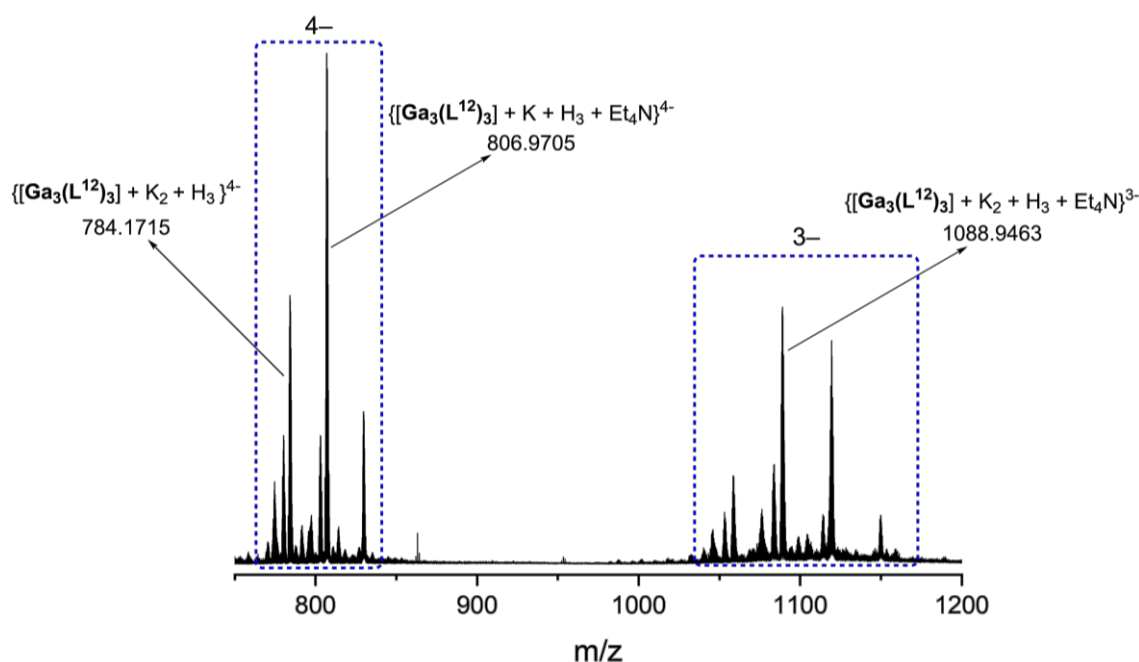


Figure 17. Full view for ESI–HRMS for $\text{Ga}_3(\text{L}^{12})_3$.

3.3.3.4 Single–Crystal X–ray Diffraction Structural Analysis

During our investigation on interlocked supramolecular coordination cages, we succeeded in growing single crystals for $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ systems. Single–crystal X–ray diffraction confirmed the anticipated triply interlocked [2]–catenane topology of M_6L_4 architectures, crystallised as their potassium salts $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3][\text{K}]_9$ and $[\text{Ga}_6(\text{L}^7)_4(\text{OH})_3][\text{K}]_9$. High–quality block crystals of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ were obtained using layer diffusion technique by diffusion of acetone into a concentrated solution of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ or $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ in a mixture MeOH/ H_2O (1:1). Repeated crystallisation attempts for $\text{M}_2(\text{L}^{11})_2$ and $\text{M}_3(\text{L}^{12})_3$ compounds were unsuccessful, giving amorphous solids.

Molecular structure of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ (Figure 18) reveals two mechanically threaded monomeric units $\text{Ga}_3(\text{L}^6)_2$ which are connected by six Ga–catecholate chelate nodes (Ga–O 1.8926(18)–1.9544(19) Å). At each of the three crossing nodes

a μ -OH bridge spans a Ga_2 unit (Ga-OH 1.890(2)–1.928(2) Å), rendering every Ga^{3+} centre five-coordinate within the anionic $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$ framework. Each $\text{Ga}_3(\text{L}^6)_2$ cage encloses a prolate cavity with 6.8180(18) and 6.7422(19) Å inter-deck spacings and voids of 83 and 107 Å³ (calculated using CageCavityCalc-C3),^[26] ideally sized to host the tris(triazole)phenylene hub of its interpenetrating $\text{Ga}_3(\text{L}^6)_2$ partner (Figure 18B). Four ligand decks form an eclipsed π -stack (inter-deck phenylene centroid⋯centroid: 3.3691(17), 3.3753(19) and 3.4493(18) Å). These decks are successively rotated by 17.28(3)–29.16(3)°, generating P/M helices that crystallise as a racemate in $P-1$ space group (P -helix is shown, Fig. 18C). An additional π -staircase array of contacts between triazoles (3.5120(19)–4.044(2) Å), supported by directional internal $\text{CH}\cdots\text{O}$ interactions (2.266(2)–2.782(2) Å), further consolidate this quadruple-decker. When interlocked, three tris(triazole)-phenylene cores remain planar (Fig. 18A: decks 1, 3 and 4), whereas one bends (deck 2) to accommodate the interlocked array $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$, underscoring the adaptive flexibility of the ligand $(\text{L}^6)^{6-}$ framework. In addition, these discrete anionic interlocked $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$ cages pack into a three-dimensional lattice via outer-sphere K^+ bridges and solvent channels. The four ligands are crystallographically non-equivalent in $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$, partitioning into two inner and two outer decks. This solid-state asymmetry rationalises the inner/outer twofold NMR splitting observed D_2O solution.

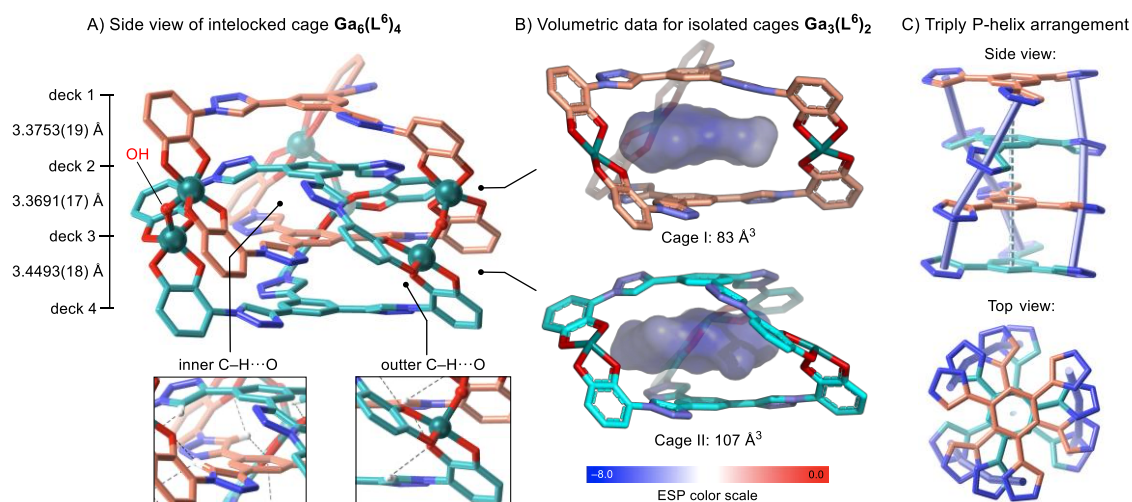


Figure 18. Crystal structure of the triply interlocked $\text{Ga}_6(\text{L}^6)_4$ cage in its anionic form $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$. A) Side view of the quadruple-decker assembly, $\text{CH}\cdots\text{O}$ contacts shown as dashed lines and B) P-helical arrangement of the four ligands decks (side and top views). The computed cage cavity volumes and the ESP partial charge mapped on the van der Waals sphere of the different systems were calculated using the CageCavityCalc (C3) package with a grid size of 0.5 Å and the EEM implemented charge model. Disordered K^+ counterions and solvent molecules (H_2O , methanol and acetone) from crystallisation are omitted for clarity. The core cage is fully ordered and unaffected by the solvent disorder. Selected bond lengths (Å): triazole– $\text{CH}\cdots\text{O}$ –catecholate 2.266(2)–2.782(2), triazole (cent) $\cdots$ (cent) triazole 3.5120(19)–4.044(2), Ga–O 1.8926(18)–1.9544(19), Ga–OH 1.890(2)–1.928(2), phenylene (cent) $\cdots$ (cent) phenylene 3.3691(17)–3.4493(18). Thermal ellipsoid plots at 50% probability are given in the annexes to this Chapter.

Similarly, the molecular structure of $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ (Figure 19) features six Ga–catecholate chelate nodes, with Ga–O bond lengths ranging from 1.881(13) to 1.955(9) Å, and three bridging hydroxo ($\mu\text{-OH}$) ligands exhibiting Ga–OH distances of $\sim 1.874(9)$ – $1.902(9)$ Å. Each $\text{Ga}_3(\text{L}^7)_2$ unit encloses a prolate cavity with inter-deck spacings of 6.885(5) and 6.870(5) Å, which are slightly larger than those observed in $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$. As in the structure of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$, the four ligand decks form an eclipsed π -stack (inter-deck phenylene centroid $\cdots$ centroid distances: 3.428(5), 3.464(5), and 3.427(5) Å), along with a π -staircase array of contacts between triazole groups (3.392(6)–4.311(6) Å). These interactions are further supported by directional internal $\text{CH}\cdots\text{O}$ hydrogen bonds (2.222(6)–2.637(7) Å), which collectively stabilise this fluorinated quadruple-decker architecture.

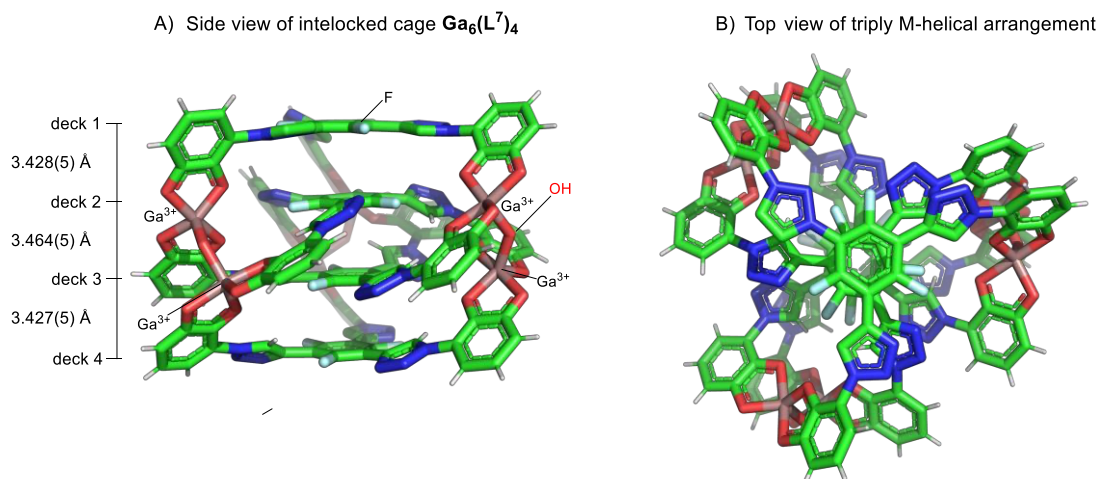


Figure 19. Crystal structure of the fluorinated interlocked $\text{Ga}_6(\text{L}^7)_4$ cage in its anionic form $[\text{Ga}_6(\text{L}^7)_4(\text{OH})_3]^{9-}$. A) Side view of the quadruple-decker assembly and B) M-helical arrangement of the four ligand decks (top view). Disordered K^+ counterions and solvent molecules (H_2O , methanol and acetone) from crystallisation are omitted for clarity. The core cage is fully ordered and unaffected by the solvent disorder. Selected bond lengths (Å): triazole-CH $\cdots$ O-catecholate 2.222(6)–2.637(7), triazole (cent) $\cdots$ (cent) triazole 3.392(6)–4.311(6), Ga–O 1.881(13)–1.955(9), Ga–OH 1.874(9)–1.902(9), phenylene (cent) $\cdots$ (cent) phenylene 3.427(5)–3.464(5). Thermal ellipsoid plots at 50% probability are given in the annexes to this Chapter.

3.3.4 Reversible Interlocking of Al_6L_4 and Ga_6L_4 via Acid–Base Cycles

3.3.4.1 NMR Studies of the Reversible Interlocking of $\text{M}_6(\text{L}^6)_4$

Motivated by the unique topological features and the presence of stabilizing $\mu\text{-OH}$ bridges, we examined the response of the cages $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ to protonation. Titration of solutions of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ with incremental additions of deuterio-hydrochloric acid (DCl) in D_2O were monitored by ^1H NMR (Figure 20). Cage $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ underwent rapid structural disruption upon addition of one equivalent of acid as evidenced by progressive disappearance and broadening of the cage resonances after four equivalents. By contrast, cage $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ remains intact until the third equivalent of acid, underscoring its higher kinetic and thermodynamic robustness (Figure 20). Remarkably, subsequent neutralisation with sodium deuterioxide (NaOD , 1–4 equiv) fully restores the diagnostic spectra of each interlocked cage $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$. While $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ re-catenates after 3–4 equivalents of base, $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ readily interlocks after one equivalent. Identical spectral changes

were obtained across the window 1–5 mM, the highest range permitted by the solubility of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$, demonstrating a fully reversible unlocking/re-catenation process. The absence of resonances attributable to monomeric cages $\text{Al}_3(\text{L}^6)_2$ or $\text{Ga}_3(\text{L}^6)_2$ further supports a highly cooperative and effectively direct assembly pathway under these conditions.

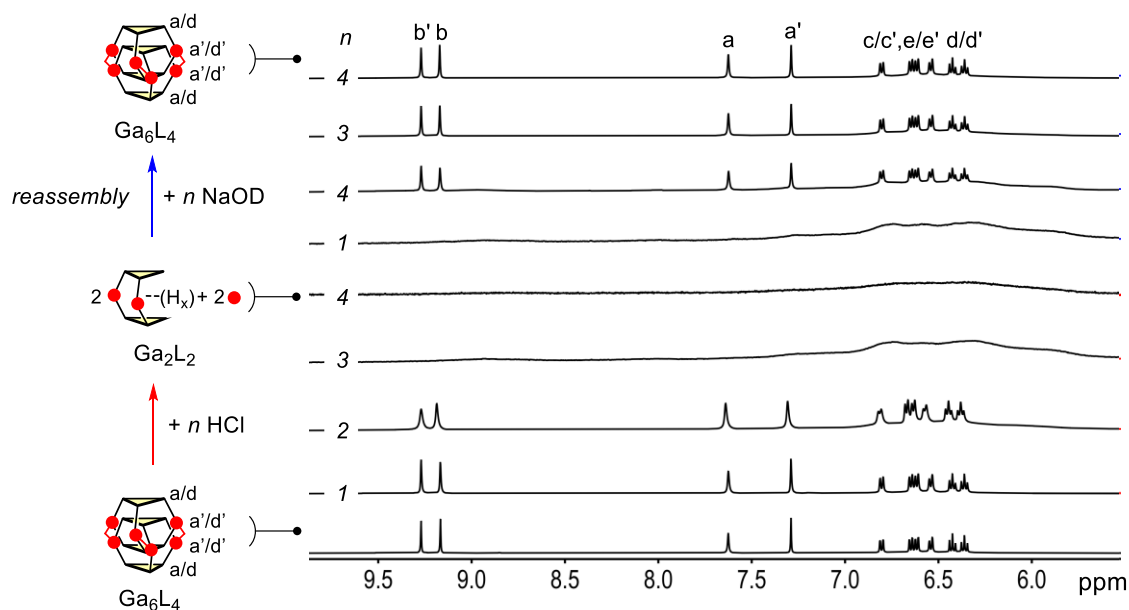


Figure 20. ^1H NMR monitoring of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ in D_2O (500 MHz, 298 K) upon sequential addition of DCl (1–4 equiv) and back-titration with NaOD (1–4 equiv).

To map the direct interlocking pathway, we conducted *in-situ* NMR monitoring starting from the fully protonated ligand H_6L^6 . Titration of H_6L^6 with incremental additions of NaOD (1–6 equiv) in D_2O generates the hexaanionic ligand species, $(\text{L}^6)^{6-}$, in its sodium form Na_6L^6 . DOSY NMR analysis reveals a significant dimeric pre-organisation of Na_6L^6 in solution ($D = 2.08 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$, $r_H = 9 \text{ \AA}$), akin to Me_6L^6 and H_6L^6 . Addition of two equivalents of AlCl_3 and GaCl_3 as water soluble sources of Al^{3+} and Ga^{3+} ions, immediately produced the duplicated ligand ^1H NMR resonances of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ (Figure 21). Although partial replacement of the bridging $\mu\text{-OH}$ groups for $\mu\text{-Cl}$ and outer-sphere exchange of K^+ for Na^+ cannot be excluded under these conditions, the formation of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ is essentially instantaneous ($< 2 \text{ min}$), underscoring the high kinetic facility of this unusual main-group interlocking process. The rapid assembly is consistent with cooperative metal-catecholate chelation together with a hydrophobic/solvophobic contribution that further strengthens π -stacking and

releases structured solvent molecules and counterions from the cavity regions during the assembly of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$. This essentially direct main-group interlocking pathway, occurring without detectable formation of monomeric cage intermediates M_3L_2 , $\text{Al}_3(\text{L}^6)_2$ or $\text{Ga}_3(\text{L}^6)_2$, contrasts markedly with the established monomer-to-dimer interlocking pathways typical for transition-metal-mediated cage assemblies.^[4a, 10, 20]

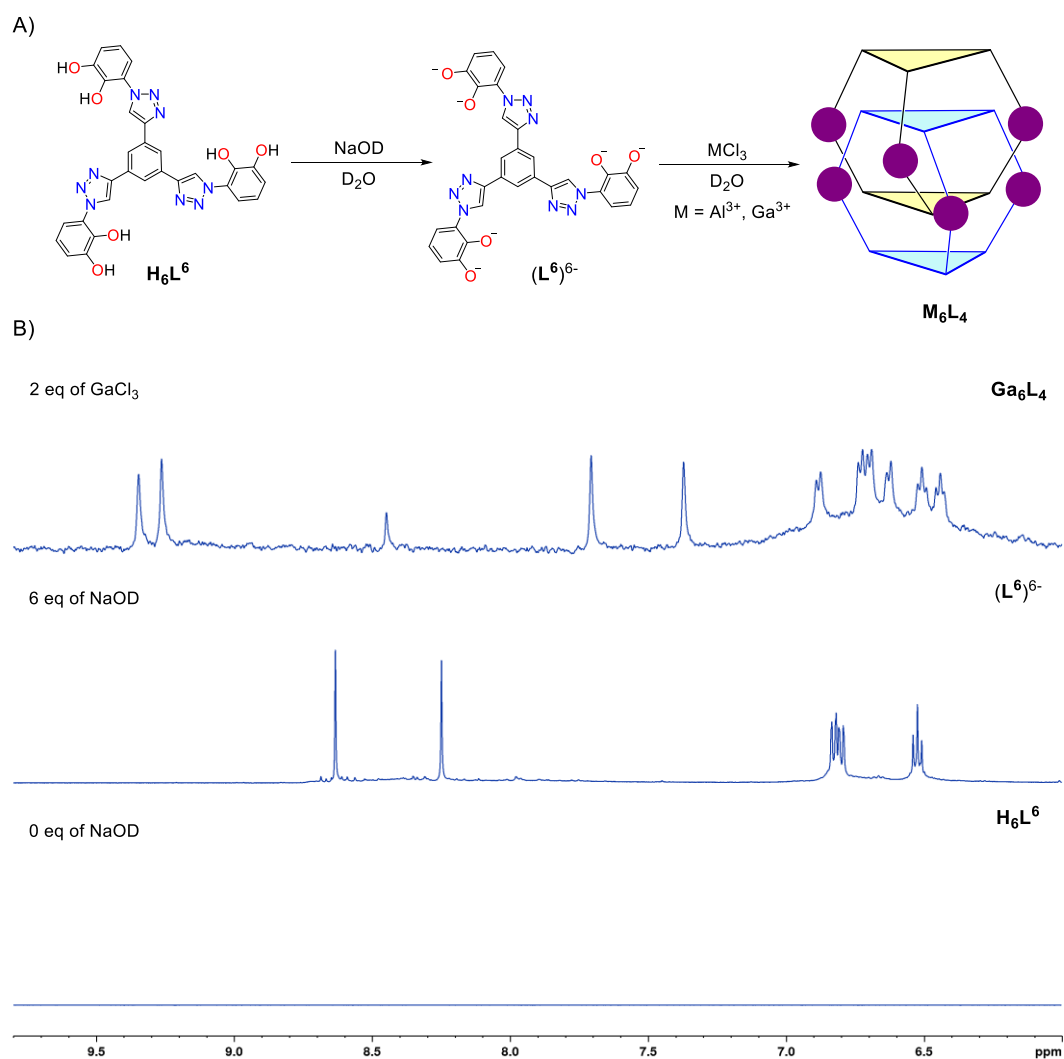


Figure 21. A) Reactions involved in the self-assembly of $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$ and B) Stacked ^1H NMR (500 MHz, D_2O , 298 K) spectra illustrating the self-assembly of $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$ via titration with GaCl_3 (2 equiv) of $(\text{L}^6)^{6-}$.

Quantitative formation of both cages occurred without resonances attributable to monomeric cage intermediates (M_3L_2) throughout the entire titration sequence, strongly implying a highly cooperative interlocking mechanism. Although partial substitution of bridging OH^- groups by Cl^- anions cannot be excluded under these

assembly conditions, the appearance of clear cage-specific resonances demonstrate structurally selective cage interlocking processes for both aluminium $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and gallium $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ systems.

3.3.4.2 NMR Studies of the Reversible Interlocking of $\text{Ga}_6(\text{L}^7)_4$

The fluorinated interlocked cage $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ shows greater lability compared to the $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ assemblies. The incorporation of fluorine atoms in the $\text{M}_6(\text{L}^7)_4(\text{OH})_3$ architecture weakens the π - π stacking interactions facilitating unlocking of this [2]catenane (Figure 22). In fact, the fluorinated interlocked cage $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ undergoes rapid structural disruption upon the addition of two equivalents of acid, as evidenced by the progressive broadening and eventual disappearance of the characteristic cage resonances after four equivalents. Remarkably, subsequent neutralisation with 1–4 equivalents of sodium deuteroxide (NaOD) fully restores the diagnostic NMR signals of $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$, indicating reversible self-assembly as well. While $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ requires 3–4 equivalents of base to induce disassembly, the fluorinated analogue disassembles more readily after only 2–3 equivalents. These observations clearly indicate that $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ exhibits greater lability than $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ under identical conditions. This increased sensitivity may be attributed to the presence of electron-withdrawing fluorine atoms in the ligand core, which weaken π - π interactions between ligand decks, thereby destabilizing the interlocked structure and reducing its overall thermodynamic robustness (Figure 22). Similar to the behavior of interlocked cages $\text{M}_6(\text{L}^6)_4(\text{OH})_3$, the addition of two equivalents of GaCl_3 leads to the immediate appearance of duplicated ^1H NMR resonances corresponding to $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$. Notably, as with $\text{M}_6(\text{L}^6)_4(\text{OH})_3$, the reassembly occurs without detectable formation of monomeric $\text{Ga}_3(\text{L}^7)_2$ intermediates, suggesting a concerted or cooperative interlocking pathway as well. ^{19}F NMR monitoring is consistent with ^1H NMR results, showing progressive broadening and eventual disappearance of the characteristic cage ^{19}F NMR signals after four equivalents of DCI and fully restores of these resonances after addition of four equivalents of NaOD .

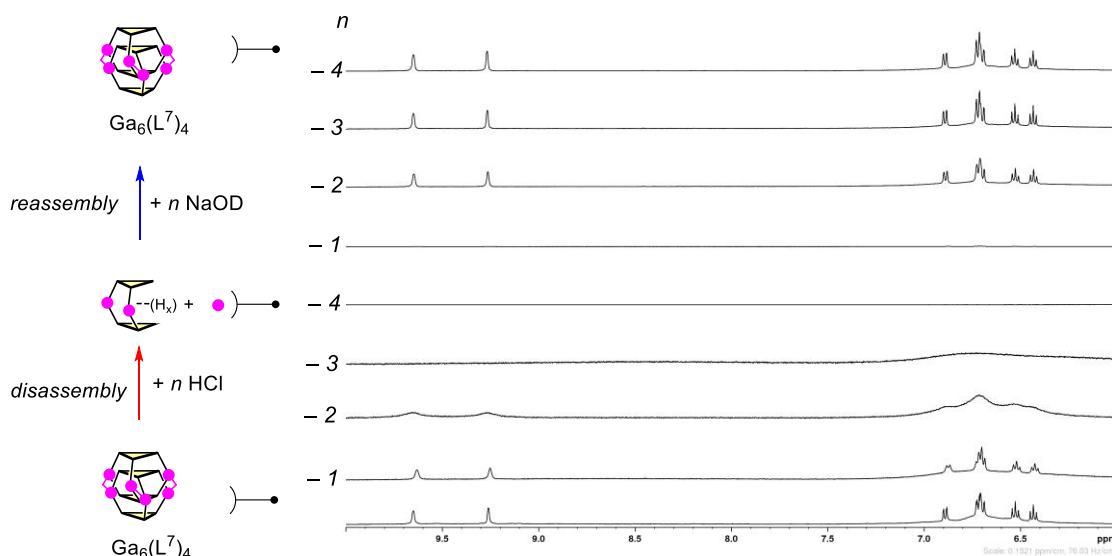


Figure 22. ^1H NMR monitoring of $\text{Ga}_6(\text{L}^7)_4(\text{OH})_3$ in D_2O (500 MHz, 298 K) upon sequential addition of DCl (1–4 equiv) and back-titration with NaOD (1–4 equiv).

3.3.4.3 ITC Studies of the Reversible Interlocking of $\text{M}_6(\text{L}^6)_4$

To quantify the thermodynamic driving forces underlying the reversible assembly of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$, isothermal titration calorimetry (ITC) was carried out under the same acid–base NMR cycling regimes at 1 mM concentrations. The ITC isotherms captured single cooperative transition equilibria for both the disassembly and reassembly of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ (Figure 23), therefore, data were fitted to one-set-of-sites models (independent-sites/Wiseman). Hence, the overall macroscopic equilibria returned N (acid/base titrant equivalents per cage at the transition) and apparent macroscopic equilibrium constants K (M^{-1}) for the overall disassembly ($\text{cage} + n \text{H}^+ \rightleftharpoons \text{disassembled state}$) and reassembly ($\text{disassembled state} + n \text{OH}^- \rightleftharpoons \text{cage}$) modelled steps at the specific transition N equivalents. Acid-induced disassembly is entropy-driven ($T\Delta S > 0$, Figure 24) for both cages $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ ($T\Delta S = 32.9 \text{ kJ}\cdot\text{mol}^{-1}$) and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ ($T\Delta S = 19.1 \text{ kJ}\cdot\text{mol}^{-1}$), consistent with the gain in translational/rotational and conformational freedom upon releasing ligands and metal ions. The modest exothermicity ($\text{Al}_6(\text{L}^6)_4(\text{OH})_3$: $\Delta H = -16.0 \text{ kJ}\cdot\text{mol}^{-1}$; $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$: $\Delta H = -15.2 \text{ kJ}\cdot\text{mol}^{-1}$) is attributed to protonation of $\mu\text{-OH}$ bridges and catecholate groups. Overall, unlocking is easier for $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ ($\Delta G = -48.9 \text{ kJ}\cdot\text{mol}^{-1}$) than for $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ ($\Delta G = -34.3 \text{ kJ}\cdot\text{mol}^{-1}$), consistent with the higher intrinsic stability of

the Ga_6L_4 cage **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** . Consistently, the ITC stoichiometries indicate $N = 1.06 \pm 0.03$ acid equivalent per cage for **$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** and $N = 3.12 \pm 0.11$ for **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** during disassembly, matching the macroscopic equivalence points seen by ^1H NMR titrations. Re-assembly on base addition is strongly enthalpy-driven (**$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** : $\Delta H = -42.1 \text{ kJ}\cdot\text{mol}^{-1}$; **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** : $\Delta H = -42.7 \text{ kJ}\cdot\text{mol}^{-1}$, Figure 24). This reflects the formation of twelve M–O chelate bonds and three $\mu\text{--OH}$ bridges, reinforced by dense $\pi\cdots\pi$ and $\text{C--H}\cdots\text{O}$ contacts within the quadruple-decker stacks, providing a large exothermic gain that outweighs the desolvation costs. The re-assembly entropy terms diverge. **$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** pays a small entropic penalty ($T\Delta S = -15.3 \text{ kJ}\cdot\text{mol}^{-1}$), whereas **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** incurs essentially none ($T\Delta S = -0.3 \text{ kJ}\cdot\text{mol}^{-1}$). This reflects the balance between ordering penalties and the favourable hydrophobic/solvophobic release of structured solvent molecules and counterions from catecholate solvation shells and π -rich cavities during interlocking. We ascribe the minimal entropic term in **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** to a more extensive π -stacking and stronger Ga–O chelation, which together favour a more pre-organised unlocked ensemble and better compensates ordering in water compared to **$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** . The resulting re-assembly free energies (**$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** : $\Delta G = -26.8 \text{ kJ}\cdot\text{mol}^{-1}$; **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** : $\Delta G = -42.4 \text{ kJ}\cdot\text{mol}^{-1}$) confirm the greater thermodynamic stability of the Ga_6L_4 cage **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** . In line with this, re-catenation proceeds with $N = 3.62 \pm 0.04$ base equivalents per cage for **$\text{Al}_6(\text{L}^6)_4(\text{OH})_3$** vs $N = 0.92 \pm 0.01$ for **$\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$** , again consistent with the ^1H NMR titrations. The obtained thermodynamic magnitudes are consistent with other metal-organic cages, where guest capture/assembly is generally exothermic and enthalpy-driven (typically $\Delta H \sim -20$ to $-60 \text{ kJ}\cdot\text{mol}^{-1}$; $T\Delta S \sim -15$ to $25 \text{ kJ}\cdot\text{mol}^{-1}$), while release/exchange commonly shows favourable entropy ($T\Delta S > 10 \text{ kJ}\cdot\text{mol}^{-1}$).

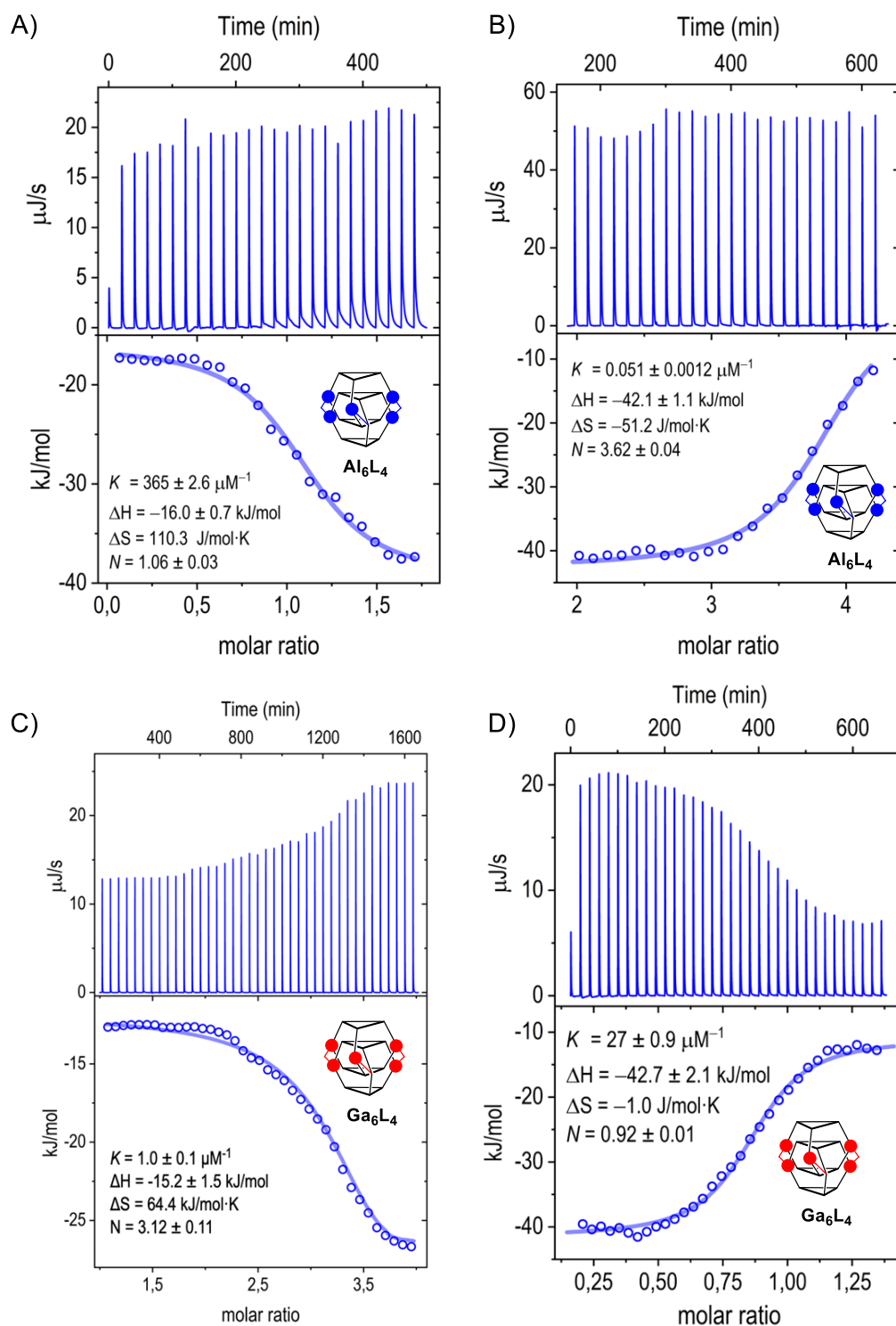


Figure 23. ITC traces for sequential disassembly and reassembly of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ with DCl and NaOD (298K, D_2O), with thermodynamic data.

At 298 K, the re-catenation free energies are $\Delta G = -26.8 \text{ kJ}\cdot\text{mol}^{-1}$ ($K = 5.1 \times 10^4 \text{ M}^{-1}$) for $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\Delta G = -42.4 \text{ kJ}\cdot\text{mol}^{-1}$ ($K = 2.7 \times 10^7 \text{ M}^{-1}$) for $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$. For unlocking, ΔG is $-48.9 \text{ kJ}\cdot\text{mol}^{-1}$ for $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ ($K = 3.7 \times 10^8 \text{ M}^{-1}$) and $-34.3 \text{ kJ}\cdot\text{mol}^{-1}$ ($K = 1.0 \times 10^6 \text{ M}^{-1}$) for $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$.

The resulting $\Delta\Delta G (\text{Ga}_6(\text{L}^6)_4(\text{OH})_3 - \text{Al}_6(\text{L}^6)_4(\text{OH})_3) = -15.6 \text{ kJ/mol}$ for re-catenation, corresponds to a ~ 500 -fold greater thermodynamic preference for the Ga_6L_4 cage $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ over the Al_6L_4 cage $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$. This metal dependence is consistent with the generally higher affinity of Ga–O chelation relative to Al–O (e.g., phenolate chelates exhibit $\log K \sim 31$ for Ga vs 22 for Al in water), reinforcing that stronger Ga–catecholate binding together with more extensive π -stacking, stabilises the triply interlocked Ga_6L_4 $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ topology.

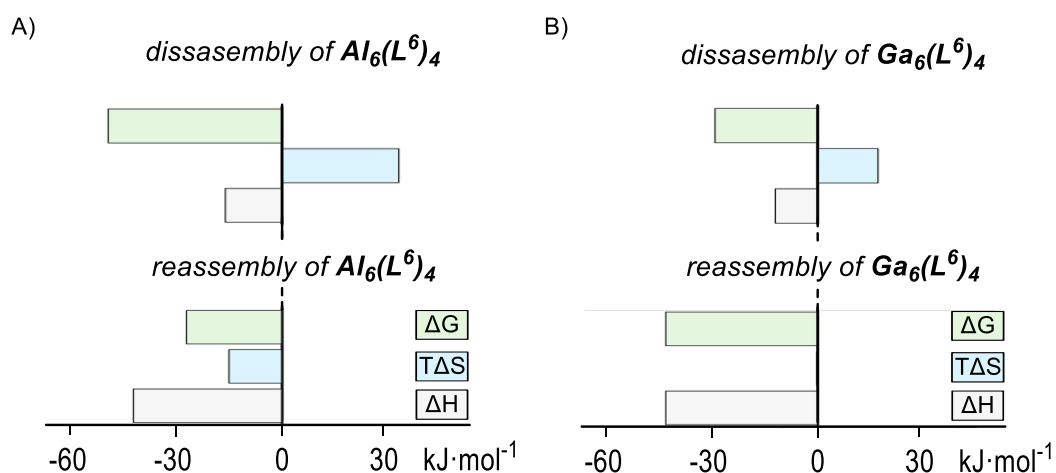


Figure 24. Thermodynamic ITC data for the acid–base disassembly–reassembly of $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$.

Isothermal titration calorimetry studies of the disassembly–reassembly process of the fluorinated interlocked cages $\text{M}_6(\text{L}^7)_4(\text{OH})_3$ were not performed because of their greater lability compared to the $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ assemblies. As we saw in the section 1.3.7.2., the incorporation of fluorine atoms in the $\text{M}_6(\text{L}^7)_4(\text{OH})_3$ architecture weakens the π – π stacking interactions between ligands that stabilise the interlocked cage structure.

3.3.4.4 Lyophilisation Studies of Disassembled $\text{M}_6(\text{L}^6)_4$

Lyophilisation of the acidified solutions allowed us to analyze the unlocked intermediates resulting from disassembling both cages, $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$. ESI–TOF mass analysis revealed the formation of partially protonated entities $[\text{Al}_2(\text{H}_x\text{L}^6)_2]^{n-}$ and $[\text{Ga}_2(\text{H}_x\text{L}^6)_2]^{n-}$ (Figure 25). For example, for aluminum intermediate species, peaks at m/z values of 626.1121 (2–) (calcd. 626.1123) and 645.0904 (2–) (calcd. 645.0902) were observed for $\text{Al}_2(\text{L}^6)_2$

with 4H^+ and $1\text{K}^+/3\text{H}^+$ respectively. Similarly, for $\text{Ga}_2(\text{L}^6)_2$, peaks at m/z values of 669.0500 (2 $-$) (calcd. 669.0564) and 688.0300 (2 $-$) (calcd. 688.0343) were detected corresponding to analogous species. The absence of higher-mass ions suggests that protonation lowers the net charge, favouring H-bonded " $\text{M}_2(\text{H}_x\text{L}^6)_2$ " species that exchange rapidly in D_2O solution and thus broaden the ^1H NMR signals during disassembly. Notably, under these partially acidified conditions (4 equiv), the dominant $[\text{M}_2(\text{H}_x\text{L}^6)_2]^{n-}$ ions do not contain OH^- groups, in contrast to the intact cage $[\text{M}_6(\text{L}^6)_4(\text{OH})_3]^{9-}$ ions, where $\mu\text{-OH}$ bridging is implicit. This indicates protonation/disruption of the $\mu\text{-OH}$ bridges during unlocking; conversely, re-appearance of the $\text{Al}_6(\text{L}^6)_4(\text{OH})_3$ and $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$ resonances upon basification correlates with re-formation of these bridges. IR spectroscopy showed a broad $\nu(\text{OH})$ at 3500 cm^{-1} and ^1H NMR in $\text{DMSO}-d_6$ confirming partial catechol reprotonation. Together, these observations indicate that full deprotonation of H_6L^6 and intact $\mu\text{-OH}$ bridges are pre-requisites for cage assembly. Unlike $\text{M}_6(\text{L}^6)_4(\text{OH})_3$ cages, lyophilisation studies of the disassembled species of fluorinated interlocked cages $\text{M}_6(\text{L}^7)_4(\text{OH})_3$, remain an open area for further investigation.

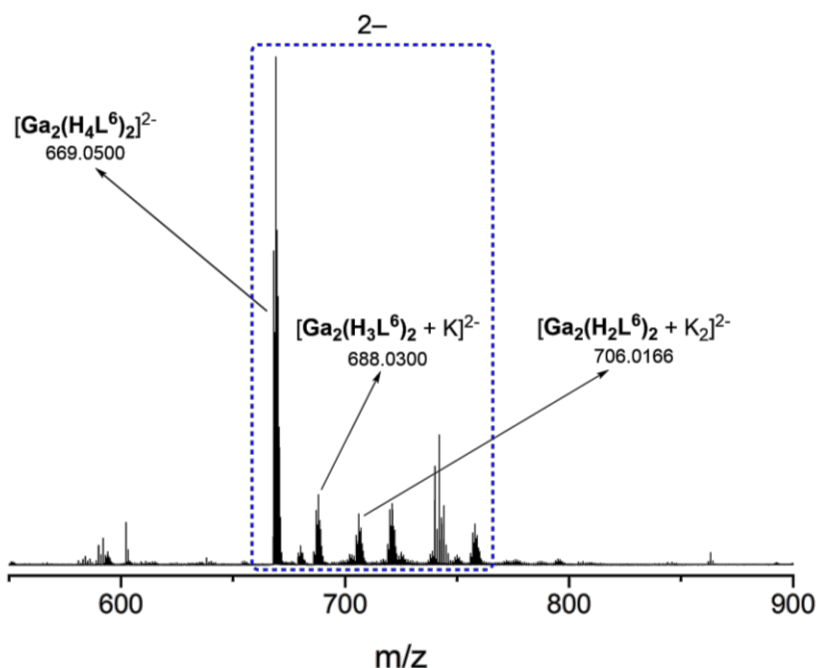


Figure 25. Full view for ESI-HRMS corresponding to lyophilised disassembled species from $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$.

3.4 Conclusions

In this *Chapter* we have established a main-group platform for mechanically interlocked coordination cages, delivering triply interlocked M_6L_4 [2]catenanes with Al^{3+} and Ga^{3+} from tritopic 1,2,3-triazole-catechol ligands. Under basic, aqueous conditions, the controlled self-assembly of these donors afforded a family of anionic interlocked M_6L_4 cages exemplified as K^+ salts of $[M_6(L^n)_4(OH)_3]^{9-}$, in which μ -OH bridges and metal-catecholate O,O'-coordination deliver quadruple-decker triply interlocked M_6L_4 topologies with intrinsic helical chirality. Characterisation through $^1H/^{13}C$ /NOESY/DOSY NMR, single-crystal X-ray diffraction crystallography, and high-resolution ESI-HRMS unequivocally confirmed their composition, topology, and connectivity, with hydrodynamic sizes from DOSY in excellent accord with the crystallographic dimensions.

Mechanistic studies establish that these interlocked [2]catenanes Al_6L_4 and Ga_6L_4 cages are reversible by switching pH in water. Acid triggers unlocking (disassembly) whereas base restores selectively the fully interlocked M_6L_4 state (re-assembly). Time-resolved NMR shows direct, highly cooperative formation of the M_6L_4 catenanes without observable M_3L_2 monomeric intermediates, in stark contrast to typical d-block routes. Calorimetric measurements (ITC) quantify the thermodynamic profiles of these processes, revealing an entropy-dominated disassembly and a strongly enthalpy-driven re-assembly. Importantly, a marked metal dependence is observed, the interlocked Ga_6L_4 cages are ~500 times more robust than their Al_6L_4 analogues ($\Delta\Delta G \sim -15.6 \text{ kJ}\cdot\text{mol}^{-1}$ for re-catenation), which we ascribe to stronger Ga-O coordination and more extensive $\pi\cdots\pi$ stabilisation within the interlocked Ga_6L_4 frameworks.

These results, beyond broadening the synthetic toolbox for mechanically interlocked M_nL_m architectures, provide a new cooperative reversible pathway for developing new stimuli-responsive hosts, molecular switches, and adaptive supramolecular materials based on main-group metal coordination chemistry, alternative to the d-block metals.

3.5 Experimental Methods

Herein, a representative synthetic procedure and characterisation for selected Me₆Lⁿ, H₆Lⁿ, M₆(Lⁿ)₄(OH)₃ architectures are provided. Complete synthetic protocols, characterisation details, and reactivity studies, for all precursors, ligands and M₆(Lⁿ)₄(OH)₃ cages discussed in this Chapter, including full spectroscopic and crystallographic data, are included as electronic Annexes on the USB device accompanying this Thesis.

3.5.1 Materials

Experiments were carried out under a nitrogen inert atmosphere using either a glove box (MBraun, LabMaster SP) or standard Schlenk techniques. Methanol was dried over Mg for two hours and then distilled under nitrogen, after this, it was deoxygenated with nitrogen and stored under an atmosphere of nitrogen gas over molecular sieves (3 Å). Dichloromethane (DCM) was taken from SPS system and stored under an atmosphere of nitrogen gas. Deuterated chloroform (CDCl₃), deuterium oxide (D₂O), deuterated dimethyl sulfoxide (DMSO-*d*₆) and deuterated dimethyl formamide (DMF-*d*₇) were purchased from Cambridge Isotopes or Merck. 1,3,5-tribromobenzene, 1,3,5-tribromo-2,4,6-trifluorobenzene, 3,3"-dibromo-5'-(3-bromophenyl)-1,1':3',1"-terphenyl, 5-bromoindoline-2,3-dione, (TMSA), CuI, Pd(OAc)₂, PPh₃, iPr₂NH, Pd(PPh₃)₄, K₂CO₃, KOH, CuSO₄, L-ascorbic acid, CsF, *n*-BuOH, MeOH, EtOH, THF, toluene, DMF, Et-I, BBr₃, Et₃N, POCl₃, hydrazine hydrate, Et₄NBr, PdCl₂dppf, Al(acac)₃ and Ga(acac)₃ (acac = acetyl acetonate) were purchased from Merck and used as received. 1,3,5-triethynylbenzene, 1,3,5-triethynyl-2,4,6-trifluorobenzene, 3,3"-diethynyl-5'-(3-ethynylphenyl)-1,1':3',1"-terphenyl, 5,10,15-triethyl-3,8,13-triethynyl-10,15-dihydro-5H-diindolo[3,2-*a*:3',2'-*c*]carbazole were prepared according to reported procedures.^[24-25, 27] All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified.

NMR experiments were conducted with 5 mm NMR tubes. Multinuclear NMR spectra were collected on either a Bruker AVIIIHD 400 nanobay (equipped with a 9.4 tesla magnet) or Bruker AVIII 500 (equipped with 11.7 tesla magnet and a Prodigy cryoprobe) spectrometer. Assignments of NMR resonance signals in the ¹H and ¹³C{¹H} NMR spectra were made with the help of two-dimensional NMR experiments

(¹H,¹H–COSY, ¹H,¹³C–HSQC, ¹H,¹³C–HMBC). For NOESY and ROESY (phase sensitive) experiments, standard pulse sequences were used consisting of 256 transients with 32 scans in the f1 domain using an optimised 300 ms mixing time and 2 sec relaxation delay. Chemical shifts (δ) are reported in parts per million (ppm) and referenced the residual solvent resonances. Coupling constants (*J*) are given in Hertz (Hz). Signal multiplicities are abbreviated as follows: s (singlet), d (doublet), sept (septet), m (multiplet) and br (broad).

Electrospray ionisation high resolution mass spectrometry (ESI–HRMS) was carried out using a Bruker Compact QToF. Typical acquisition parameters were used (sample flow rate: 3 μ L min^{−1}, nebuliser gas pressure: 0.3 bar, drying gas: nitrogen at 200°C flowing at 3 L min^{−1}, capillary voltage: 3.5 kV, exit voltage: 0.5 kV). The spectrometer was calibrated in negative ion mode using an ESI–L low concentration tuning mix (Agilent) ranging *m/z* from 112 until 2833 in a mixture of acetonitrile (HPLC grade) and DI (deionised, HPLC grade) H₂O (95:5 mixture). Samples were diluted to a concentration of *ca.* < 1 $\times$ 10^{−6} M in an appropriate solvent using 1.5 mL glass vials capped with appropriate septum and then sampled by direct infusion using a 500 μ L gas tight syringe.

CHN elemental microanalysis was carried out at the elemental analysis services from the Metropolitan University of London using a ThermoFlash 2000 Elemental Analyzer.

Infrared (IR) spectra were obtained using Nujol mulls between KBr discs inside a nitrogen glove box on a Bruker Alpha FT–IR spectrometer.

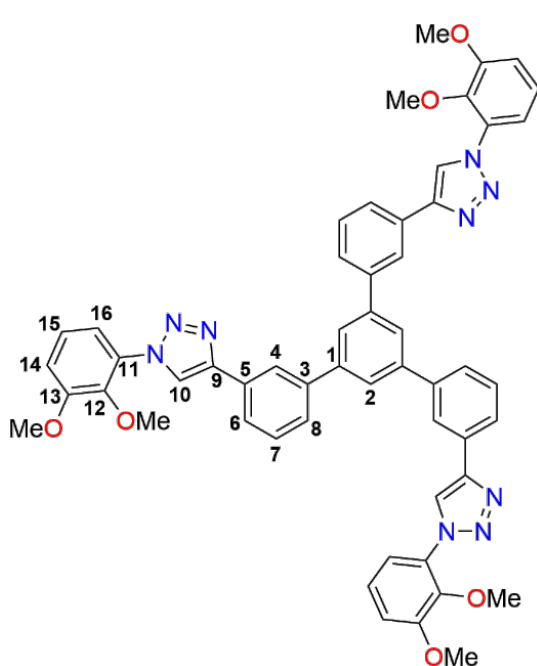
Single–crystal X–ray diffraction data was collected under a stream of nitrogen gas using an Oxford Cryostream 1000 unit at the given temperature with a Bruker D8 Quest Eco diffractometer (micro–focus sealed X–ray tube, Mo–K α , λ = 0.71073 Å) equipped with a Photon II 7. Raw frame data were reduced using APEX3. The structures were solved using SHELXT and refined using full–matrix least squares refinement on all F²data using the SHELXL. Unless otherwise stated, all non–hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and allowed to ride on their parent atoms. Disorder was treated by introducing a split site model and restraining geometries and displacement parameters. Distances and angles were calculated using the full covariance matrix. Selected crystallographic data is summarised in the text. Full details are given in the supplementary deposited CIF files (Annexes).

Isothermal Titration Calorimetry (ITC) experiments were performed on Nano ITC (TA Instruments) calorimeter equipped with a cylindrical inert sample cell of standard volume (1 mL). Prior to analysis, solutions underwent thorough degassing by stirring under vacuum using a dedicated degassing station.

The computed cage cavity volumes of the different systems were calculated using the CageCavityCalc (C3)^[26] package with a grid size of 0.5 Å and the EEM implemented charge model.

3.5.2 Synthesis and Characterisation of Me₆Lⁿ and H₆Lⁿ

3.5.2.1 Synthesis and Characterisation of Me₆L¹¹



3,3"-diethynyl-5'-(3-ethynylphenyl)-1,1':3',1"-terphenyl (0.2 g, 0.528 mmol) and 1-azido-2,3-dimethoxybenzene (0.284 g, 1.58 mmol) were dissolved in 16 mL of a mixture of n-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.021 g, 0.105 mmol, 20 mol %) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.013 g, 0.0528 mmol, 10 mol %) were added. Stirring continued overnight until TLC showed the completion of the reaction. n-

Butanol was removed under reduced pressure, and the viscous residue was extracted with CHCl_3 (3 x 40 mL). The combined organic extractions were treated with saturated brine and anhydrous Na_2SO_4 and then organic extractions were filtered and CHCl_3 was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.43 g, 89% yield).

¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ 8.46 (s, 3H, H₁₀), 8.31 (s, 3 H, H₄), 8.01 (s, 3 H, H₂), 7.95 (d, 3 H, H₆, ³J_{H₆-H₇} = 7.50 Hz), 7.77 (d, 3 H, H₈, ³J_{H₈-H₇} = 7.50 Hz), 7.60 (t, 3 H, H₇, ³J_{H₇-H₆} = ³J_{H₇-H₈} = 7.50 Hz), 7.38 (d, 3 H, H₁₆, ³J_{H₁₆-H₁₅} = 8.00 Hz), 7.20 (t, 3 H, H₁₅, ³J_{H₁₅-H₁₄} = ³J_{H₁₅-H₁₆} = 8.00 Hz), 7.04 (d, 3 H, H₁₄, ³J_{H₁₄-H₁₅} = 8.00 Hz), 3.91 (s, 9 H, C₁₃-OMe), 3.75 (s, 9 H, C₁₂-OMe).

$^{13}\text{C}\{^1\text{H}\}$ NMR (125.6 MHz, CD_2Cl_2 , 298 K): δ 154.1 (C13), 147.5 (C9), 142.5 (C1), 142.0 (C3), 141.9 (C12), 131.7 (C5), 131.5 (C11), 129.8 (CH7), 127.6 (CH8), 125.8

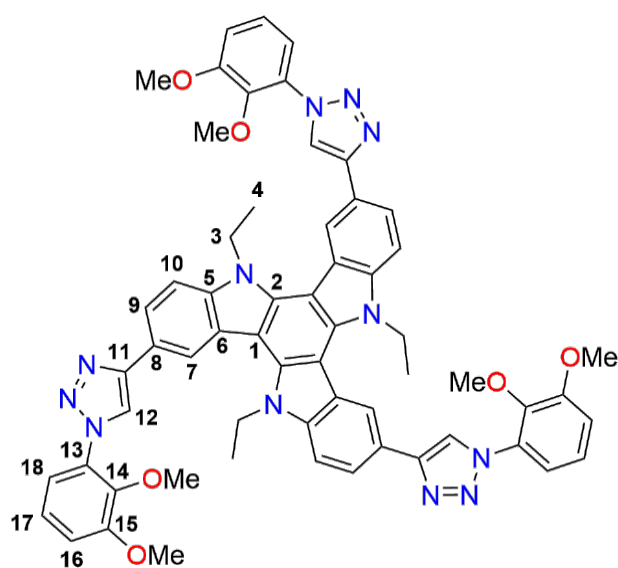
(CH₂), 125.4 (CH₆), 125.0 (CH₄), 124.7 (CH₁₅), 122.2 (CH₁₀), 117.1 (CH₁₆), 113.3 (CH₁₄), 61.5 (C₁₂–OMe), 56.5 (C₁₃–OMe).

IR (KBr/Nujol, cm⁻¹): ν (C=N, C=C) 1594, 1522.

Elemental analysis found (calculated): C₅₄H₄₅N₉O₆; C, 71.05 (70.81); H, 4.83 (4.95); N, 13.45 (13.76).

HRMS (ESI) *m/z* found (calculated) for C₅₄H₄₅N₉O₆ [M]: [M + H]⁺: 916.3575 (916.3566).

3.5.2.2 Synthesis and Characterisation of Me₆L¹²



5,10,15-triethyl-3,8,13-triethynyl-10,15-dihydro-5H-diindolo[3,2-*a*:3',2'-*c*]carbazole (0.15 g, 0.299 mmol) and 1-azido-2,3-dimethoxybenzene (0.16 g, 0.897 mmol) were dissolved in 10 mL of a mixture of *n*-butanol and deionised water (1:1) in a 100 mL round-bottom flask. To the stirred solution L-ascorbate acid (0.012 g, 0.060 mmol, 20 mol %) and

CuSO₄·5H₂O (0.008 g, 0.03 mmol, 10 mol %) were added. Stirring continued overnight until TLC showed the completion of the reaction. *n*-Butanol was removed under reduced pressure, and the viscous residue was extracted with CHCl₃ (3 x 40 mL). The combined organic extractions were treated with saturated brine and anhydrous Na₂SO₄ and then organic extractions were filtered and CHCl₃ was removed under reduced pressure to afford the triazole as a light-brown amorphous solid (0.218 g, 70% yield).

¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ 9.04 (s, 3H, H₇), 8.50 (s, 3 H, H₁₂), 8.00 (d, 3 H, H₉, ³J_{H₉–H₁₀} = 8.10 Hz), 7.79 (d, 3 H, H₁₀, ³J_{H₁₀–H₉} = 8.10 Hz), 7.48 (d, 3 H, H₁₈, ³J_{H₁₈–H₁₇} = 8.00 Hz), 7.27 (t, 3 H, H₁₇, ³J_{H₁₇–H₁₆} = ³J_{H₁₇–H₁₈} = 8.00 Hz), 7.10 (d, 3 H, H₁₆, ³J_{H₁₆–H₁₇} = 8.00 Hz), 5.13 (q, 6 H, H₃), 3.98 (s, 9 H, C₁₅–OMe), 3.83 (s, 9 H, C₁₄–OMe), 1.83 (t, 9H, H₄).

¹³C{¹H} NMR (125.6 MHz, CD₂Cl₂, 298 K): δ 154.2 (C₁₅), 149.0 (C₁₁), 141.7 (C₁₄), 141.2 (C₅), 139.5 (C₂); 131.7 (C₁₃), 124.8 (CH₁₇), 123.9 (C₈ or C₆), 123.0 (C₈ or C₆), 121.5 (CH₉), 121.1 (CH₁₂), 119.3 (CH₇), 117.0 (CH₁₈), 113.0 (CH₁₆), 111.0

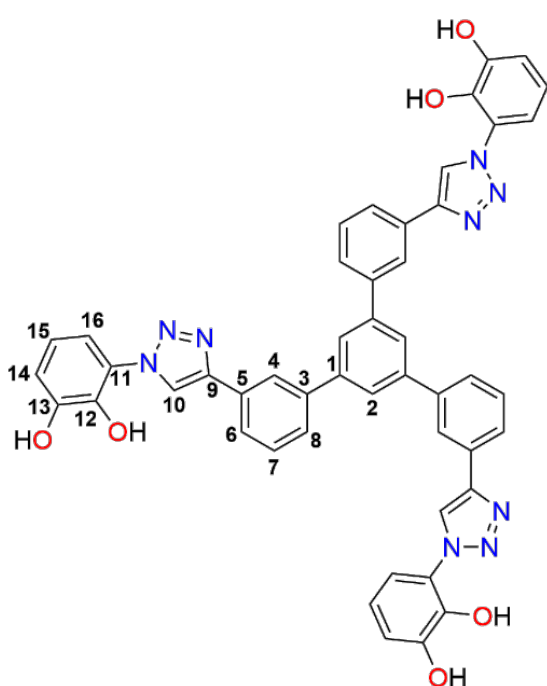
(CH10), 103.7 (C1), 61.5 (C14–OMe), 56.5 (C15–OMe), 42.5 (CH₂ (N–Et)), 16.1 (CH₃ (N–Et)).

IR (KBr/Nujol, cm^{−1}): ν (C=N, C=C) 1595.

Elemental analysis found (calculated): C₆₀H₅₄N₁₂O₆; C, 69.80 (69.35); H, 5.05 (5.24); N, 15.90 (16.17).

HRMS (ESI) *m/z* found (calculated) for C₆₀H₅₄N₁₂O₆ [M]: [M + H]⁺: 1039.4411 (1039.4362).

3.5.2.3 Synthesis and Characterisation of H₆L¹¹



To a solution of 4,4'-(5'-(3-(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)phenyl)-[1,1':3,1''-terphenyl]-3,3''-diyl)bis(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazole) (0.438 g, 0.478 mmol) in CH₂Cl₂ (35 mL) under an atmosphere of nitrogen gas in a cold acetone bath at −78 °C, BBr₃ (0.74 mL, 7.65 mmol) was added via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. All volatiles were removed under vacuum, and the resulting brown residue was stirred in water at 100°C for 2 hours. The

resulting light-brown precipitate was collected by filtration and dried under vacuum at 70°C for 6 hours (0.380 g, 0.456 mmol, 95% yield).

¹H NMR (400 MHz, DMSO-*d*₆, 298 K): δ 10.02(s, 3H, OH), 9.42 (s, 3H, OH), 9.09 (s, 3H, H10), 8.39 (s, 3H, H4), 8.10 (s, 3H, H2), 8.05 (d, 3H, H6 ³J_{H6–H7} = 7.2 Hz), 7.92 d, 3H, H8, ³J_{H8–H7} = 7.2 Hz), 7.65 (t, 3H, H7, ³J_{H7–H8} = ³J_{H7–H6} = 7.2 Hz), 7.06 (d, 3H, H14 or H16, ³J_{H–H15} = 7.5 Hz), 6.97 (d, 3H, H14 or H16, ³J_{H–H15} = 7.5 Hz), 6.84 (t, 3H, H15, ³J_{H15–H16} = ³J_{H15–H14} = 7.5 Hz).

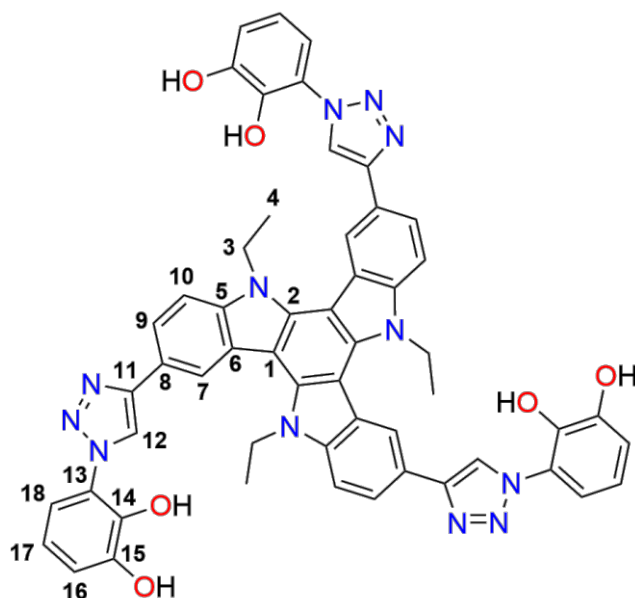
¹³C{¹H} NMR (100.6 MHz, DMSO-*d*₆, 298 K): δ 146.6 (C13), 145.9 (C9), 141.5 (C1), 140.9 (C3), 139.0 (C12), 131.3 (C5), 129.6 (CH7), 126.9 (CH8), 125.4 (C11), 125.0 (CH2), 124.5 (CH6), 124.1 (CH4), 123.6 (CH10), 119.1 (CH15), 115.8 (CH14 and CH16).

IR (KBr/Nujol, cm^{−1}): ν (O–H) 3498 (br); ν (C=N, C=C) 1611, 1551, 1519.

Elemental analysis found (calculated): C₄₈H₃₃N₉O₆; C, 69.64 (69.31); H, 3.80 (4.00); N, 15.04 (15.15).

HRMS (ESI) *m/z* found (calculated) for C₄₈H₃₃N₉O₆ [M]: [M + H]⁺, 832.2626 (832.2627).

3.5.2.4 Synthesis and Characterisation of H₆L¹²



To a solution of 3,8,13-tris(1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)-5,10,15-triethyl-10,15-dihydro-5H-diindolo[3,2-a:3',2'-c]carbazole (0.4 g, 0.384 mmol) in CH₂Cl₂ (32 mL) under an atmosphere of nitrogen gas in a cold acetone bath at -78 °C, BBr₃ (0.6 mL, 6.15 mmol) was added via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 16

hours. All volatiles were removed under vacuum, and the resulting brown residue was stirred in water at 100°C for 2 hours. The resulting light-brown precipitate was collected by filtration and dried under vacuum at 70°C for 6 hours (0.330 g, 0.346 mmol, 90% yield).

¹H NMR (400 MHz, DMSO-*d*₆, 298 K): δ 10.03 (s, 3H, OH), 9.49 (s, 3H, OH), 9.04 (s, 3H, H7), 8.94 (s, 3H, H12), 8.03 (d, 3H, H9, ³J_{H9-H10} = 7.5 Hz), 7.97 (d, 3H, H10, ³J_{H10-H9} = 7.5 Hz), 7.14 (d, 3H, H16 or H18, ³J_{H-H17} = 7.0 Hz), 6.99 (d, 3H, H16 or H18, ³J_{H-H17} = 7.0 Hz), 6.87 (t, 3H, H17, ³J_{H17-H16} = ³J_{H17-H18} = 7.0 Hz).

¹³C{¹H} NMR (100.6 MHz, DMSO-*d*₆, 298 K): δ 147.3 (C11 or C8), 146.7 (C15), 140.1 (C5), 138.9 (C14), 138.3 (C2), 125.6 (C13), 122.8 (C11 or C8), 122.7 (C6), 122.2 (CH12), 121.3 (CH9), 119.1 (CH17), 118.1 (CH7), 115.7 (CH16 or CH18), 115.7 (CH16 or CH18), 111.2 (CH10), 102.7 (C1), 41.6 (CH2 (N-Et), 15.7 (CH3 (N-Et)).

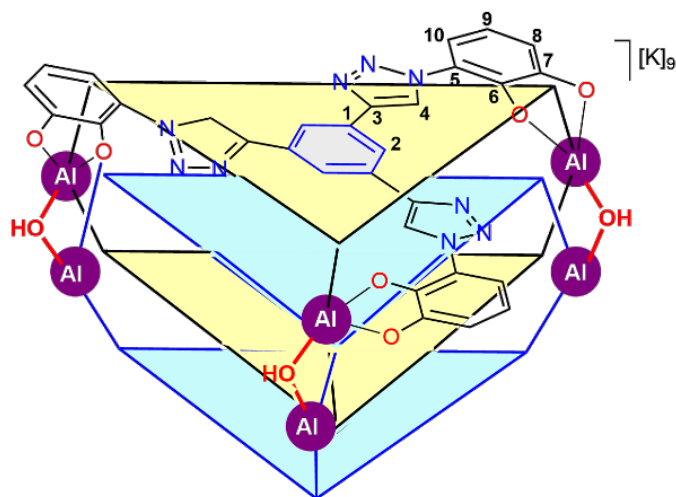
IR (KBr/Nujol, cm⁻¹): ν(O-H) 3149 (br); ν(C=N, C=C) 1612, 1569, 1518.

Elemental analysis found (calculated): C₅₄H₄₂N₁₂O₆; C, 68.24 (67.92); H, 4.02 (4.43); N, 17.31 (17.60).

HRMS (ESI) *m/z* found (calculated) for C₅₄H₄₂N₁₂O₆ [M]: [M + K]⁺, 993.3059 (993.2982).

3.5.3 Synthesis and Characterisation of M₆(Lⁿ)₄(OH)₃ systems

3.5.3.1 Synthesis and Characterisation of Al₆(L⁶)₄(OH)₃



To a suspension of 3,3',3''-(benzene-1,3,5-triyltris(1H-1,2,3-triazole-4,1-diyl))tris(benzene-1,2-diol) (0.1 g, 0.166 mmol) in deoxygenated MeOH (25 mL) under an atmosphere of nitrogen gas, KOH was added (0.75 mL from a 0.5 M solution in MeOH, 0.373 mmol) was added via syringe.

After 5 min of stirring a solution was obtained to which Al(acac)₃ (0.081 g, 0.249 mmol) was then added under nitrogen gas. The reaction mixture was then stirred at room temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure (5 mL) and then Et₂O (10 mL) was added to give a brown silky suspension. The solid was filtered and dried under high vacuum (< 1 × 10⁻² mbar) for 6 hours to give [Al₆(L⁶)₄(OH)₃]K₉ as a light brown solid (0.106 g, 0.0358 mmol, 86% yield). Due to its highly hygroscopic nature, [Al₆(L⁶)₄(OH)₃]K₉ was stored in a glove box under dry nitrogen gas to prevent hydration of the solid.

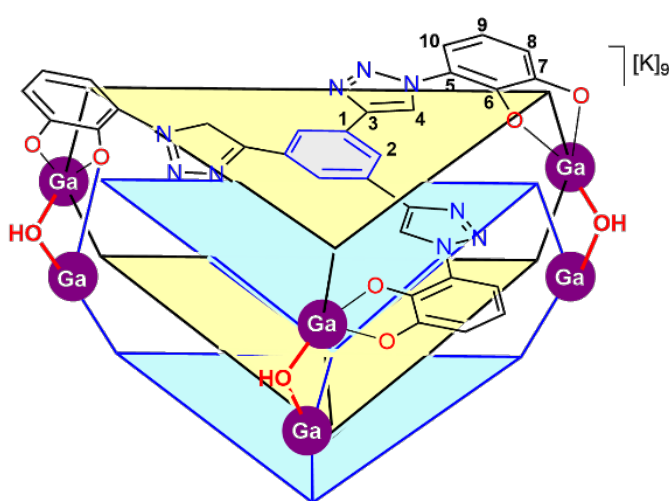
¹H NMR (500 MHz, D₂O, 298 K): δ 9.42 (s, 6H, H4'), 9.28 (s, 6H, H4), 7.70 (s, 6H, H2), 7.35 (s, 6H, H2'), 6.91 (dd, 6H, H8 or H10, H8' or H10', ³J_{H-H} = 8.0 Hz, ⁴J_{H-H} = 1.2 Hz), 6.67 (dd, 6H, H8 or H10, H8' or H10', ³J_{H-H} = 8.0 Hz, ⁴J_{H-H} = 1.2 Hz), 6.62 ("t", 12H, H8 or H10, H8' or H10', ³J_{H-H} = 8.0 Hz), 6.50 (t, 6H, H9 or H9', ³J_{H-H} = 8.0 Hz), 6.46 (t, 6H, H9 or H9', ³J_{H-H} = 8.0 Hz).

¹³C{¹H} NMR (125.6 MHz, D₂O, 298 K): δ 155.0 (C7 or C7'), 153.9 (C7 or C7'), 146.6 (C6 or C6'), 146.2 (C6 or C6'), 145.9 (C1), 144.3 (C1'), 131.1 (C3 or C3'), 130.7 (C3 or C3'), 123.6 (CH4), 122.5 (CH2), 122.0 (C5 or C5'), 121.6 (CH4'), 121.4 (C5 or C5'), 121.2 (CH2'), 115.5 (CH9 or CH9'), 115.2 (CH9 or CH9'), 111.7 (CH8 or CH8', C10H10 or CH10'), 111.5 (CH8 or CH8', CH10 or CH10'), 110.9 (CH8 or CH8', CH10 or CH10'), 110.3 (CH8 or CH8', CH10 or CH10').

IR (KBr/Nujol, cm^{-1}): $\nu(\text{O-H})$ 3386 (v br); $\nu(\text{C=N, C=C})$ 1585 (br), 1532.

ESI-HRMS (negative-ion detection, H_2O , $[\text{L}^6]^{6-} = [\text{Al}_6(\text{L}^6)_4]^{6-}$, $[\text{L}^6]^{3-} = [\text{Al}_3(\text{L}^6)_2]^{3-}$): m/z found (calc.), $[\text{L}^6]^{3-} = 425.0564$ (425.0584); $[\text{L}^6]^{3-} + \text{K}^+ = 657.0654$ (657.0692); $[\text{L}^6]^{3-} + \text{OH}^- + \text{K}^+ = 685.0490$ (685.0525); $[\text{L}^6]^{3-} + 4 \text{OH}^- + \text{K}^+ + 3 \text{Na}^+ + \text{H}^+ = 726.0689$ (726.0633); $[\text{L}^6]^{6-} + 3 \text{OH}^- + 5 \text{K}^+ + 1 \text{Na}^+ = 940.0548$ (940.0561); $[\text{L}^6]^{6-} + 3 \text{OH}^- + 6 \text{K}^+ = 945.7085$ (945.7143); $[\text{L}^6]^{6-} + 3 \text{OH}^- + 6 \text{K}^+ + 1 \text{Na}^+ = 1430.0573$ (1430.0661); $[\text{L}^6]^{6-} + 3 \text{OH}^- + 7 \text{K}^+ = 1438.0436$ (1438.0529).

3.5.3.2 Synthesis and Characterisation of $\text{Ga}_6(\text{L}^6)_4(\text{OH})_3$



To a suspension of 3,3',3''-(benzene-1,3,5-triyltris(1H-1,2,3-triazole-4,1-diyl))tris(benzene-1,2-diol) (0.1 g, 0.166 mmol) in deoxygenated MeOH (25 mL) under an atmosphere of nitrogen gas, KOH was added (0.75 mL from a 0.5 M solution in MeOH, 0.373 mmol) was

added via syringe. After 5 min of stirring a solution was obtained to which $\text{Ga}(\text{acac})_3$ (0.091 g, 0.249 mmol) was then added under nitrogen gas. The reaction mixture was then stirred at room temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure (5 mL) and then Et_2O (10 mL) was added to give a brown silky suspension. The solid was filtered and dried under high vacuum ($< 1 \times 10^{-2}$ mbar) for 6 hours to give $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]\text{K}_9$ as a light brown solid (107 mg, 0.0332 mmol, 80% yield). Due to its highly hygroscopic nature, $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]\text{K}_9$ was stored in a glove box under dry nitrogen gas to prevent hydration of the solid. Crystals suitable for an X-ray diffraction crystallographic study were obtained by vapor diffusion of a solution of $[\text{Ga}_6(\text{L}^6)_4(\text{OH})_3]\text{K}_9$ in a 1:1 mixture of water and methanol with acetone.

^1H NMR (500 MHz, D_2O , 298 K): δ 9.36 (s, 6H, $\text{H}4'$), 9.26 (s, 6H, $\text{H}4$), 7.71 (s, 6H, $\text{H}2$), 7.38 (s, 6H, $\text{H}2'$), 6.89 (dd, 6H, $\text{H}8$ or $\text{H}10$, $\text{H}8'$ or $\text{H}10'$, $^3J_{\text{H-H}} = 8.0$ Hz, $^4J_{\text{H-H}} = 1.2$ Hz), 6.73 (dd, 6H, $\text{H}8$ or $\text{H}10$, $\text{H}8'$ or $\text{H}10'$, $^3J_{\text{H-H}} = 8.0$ Hz, $^4J_{\text{H-H}} = 1.2$ Hz), 6.70 (dd, 6H, $\text{H}8$ or $\text{H}10$, $\text{H}8'$ or $\text{H}10'$, $^3J_{\text{H-H}} = 8.0$ Hz, $^4J_{\text{H-H}} = 1.2$ Hz), 6.63 (dd, 6H, $\text{H}8$ or

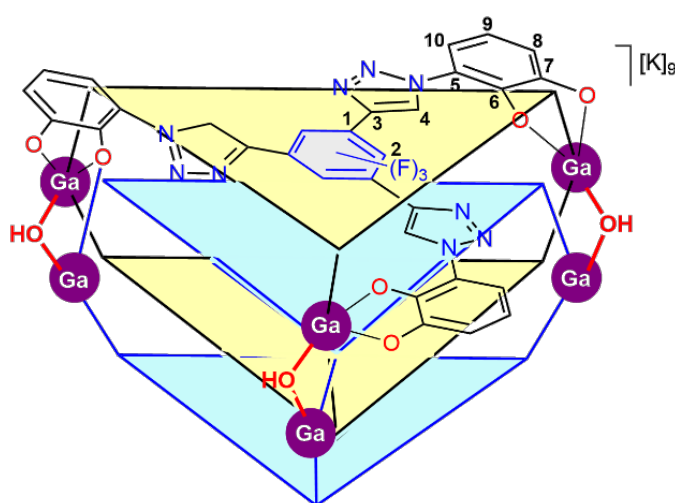
H10, H8' or H10', $^3J_{\text{H-H}} = 8.0$ Hz, $^4J_{\text{H-H}} = 1.2$ Hz), 6.51 (t, 6H, H9 or H9', $^3J_{\text{H-H}} = 8.0$ Hz), 6.40 (t, 6H, H9 or H9', $^3J_{\text{H-H}} = 8.0$ Hz).

$^{13}\text{C}\{^1\text{H}\}$ NMR (125.6 MHz, D₂O, 298 K): δ 153.4 (C7 or C7'), 152.6 (C7 or C7'), 145.8 (C1), 145.6 (C6 or C6'), 145.6 (C6 or C6'), 144.3 (C1'), 131.0 (C3), 130.7 (C3'), 123.7 (CH4), 122.4 (C5 or C5'), 122.3 (CH2), 121.8 (C5 or C5'), 121.7 (CH4'), 121.1 (CH2'), 115.2 (CH9 or CH9'), 114.9 (CH9 or CH9'), 112.0 (CH8 or CH8', CH10 or CH10'), 111.9 (CH8 or CH8', CH10 or CH10'), 111.5 (CH8 or CH8', CH10 or CH10'), 110.7 (CH8 or CH8', CH10 or CH10').

IR (KBr/Nujol, cm⁻¹): $\nu(\text{O-H})$ 3357 (v br); $\nu(\text{C=N, C=C})$ 1576 (br), 1529.

ESI-HRMS (negative-ion detection, H₂O, $[\text{Ga}_6(\text{L}^6)_4]^{6-}$, $[\text{Ga}_3(\text{L}^6)_2]^{3-}$): m/z found (calc.), $[\text{Ga}_6(\text{L}^6)_4]^{6-} = 467.6689$ (467.6691); $[\text{Ga}_3(\text{L}^6)_2]^{3-} = 486.3246$ (486.3246); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + 2 \text{K}^+ + 2 \text{OH}^- = 504.9808$ (504.9800); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + 3 \text{K}^+ + 3 \text{OH}^- = 523.6358$ (523.6355); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + \text{K}^+ = 720.9847$ (720.9852); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 4 \text{K}^+ + 2 \text{OH}^- = 749.9661$ (749.9685); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + 2 \text{K}^+ + \text{OH}^- = 748.9681$ (748.9684); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 5 \text{K}^+ + 2 \text{OH}^- + \text{H}^- = 759.4660$ (759.4669); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 5 \text{K}^+ + 2 \text{OH}^- + \text{H}^- = 763.4597$ (759.4604); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + 3 \text{K}^+ + 2 \text{OH}^- = 776.9530$ (776.9516); $[\text{Ga}_3(\text{L}^6)_2]^{3-} + 4 \text{K}^+ + 3 \text{OH}^- = 804.9348$ (804.9381); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 4 \text{K}^+ + 3 \text{OH}^- + 2 \text{Na}^+ = 1020.2828$ (1020.2856); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 5 \text{K}^+ + 3 \text{OH}^- + 1 \text{Na}^+ = 1025.6077$ (1025.6102); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 6 \text{K}^+ + 3 \text{OH}^- = 1030.9328$ (1030.9328); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 5 \text{K}^+ + 3 \text{OH}^- + 2 \text{Na}^+ = 1549.9055$ (1549.9099); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 6 \text{K}^+ + 3 \text{OH}^- + 1 \text{Na}^+ = 1557.8929$ (1557.8969); $[\text{Ga}_6(\text{L}^6)_4]^{6-} + 7 \text{K}^+ + 3 \text{OH}^- = 1562.8806$ (1557.8838).

3.5.3.3 Synthesis and Characterisation of Ga₆(L⁷)₄(OH)₃



To a suspension of 3,3',3''-((2,4,6-trifluorobenzene-1,3,5-triyl)tris(1H-1,2,3-triazole-4,1-diyl))tris(benzene-1,2-diol) (0.080 g, 0.121 mmol) in deoxygenated MeOH (25 mL) under an atmosphere of nitrogen gas, KOH was added (0.55 mL from a 0.5 M solution

in MeOH, 0.273 mmol) was added via syringe. After 5 min of stirring a solution was obtained to which Ga(acac)₃ (0.067 g, 0.182 mmol) was then added under nitrogen gas. The reaction mixture was then stirred at room temperature for 16 hours. Then,

the reaction mixture was concentrated under reduced pressure (5 mL) and then Et₂O (10 mL) was added to give a brown silky suspension. The solid was filtered and dried under high vacuum ($< 1 \times 10^{-2}$ mbar) for 6 hours to give [Ga₆(L⁷)₄(OH)₃]K₉ as a light brown solid (0.085 g, 0.02474 mmol, 82% yield). Due to its highly hygroscopic nature, [Ga₆(L⁷)₄(OH)₃]K₉ was stored in a glove box under dry nitrogen gas to prevent hydration of the solid.

¹H NMR (500 MHz, D₂O, 298 K): δ 9.65 (s, 6 H, H4 or H4'), 9.25 (s, 6 H, H4 or H4'), 6.89 (d, 6 H, H8 or H10, H8' or H10' ³J_{H-H} = 7.6 Hz), 6.71 (m, 12 H, H8 or H10, H8' or H10', ³J_{H-H} = 7.6 Hz), 6.52 (t, 6 H, H9 or H9', ³J_{H-H} = 7.6 Hz), 6.43 (t, 6 H, H9 or H9', ³J_{H-H} = 7.6 Hz).

¹³C{¹H} NMR (125.6 MHz, D₂O, 298 K): δ 155.7 (dt, CF-2 or CF-2', ¹J_{CF} = 320 Hz, ²J_{CF} = 15 Hz), 154.3 (dt, CF-2 or CF-2', ¹J_{CF} = 320 Hz, ²J_{CF} = 15 Hz), 154.1 (C7 or C7'), 153.1 (C7 or C7'), 145.7 (C6 or C6'), 145.6 (C6 or C6'), 134.5 (C3 or C3'), 133.1 (C3 or C3'), 127.1 (C5 or C5'), 126.9 (C5 or C5'), 121.9 (CH4 or CH4'), 121.5 (CH4 or CH4'), 115.2 (CH9 or CH9'), 115.1 (CH9 or CH9'), 112.1 (CH10 or CH10'), 111.8 (CH10 or CH10'), 111.5 (CH8 or CH8'), 110.5 (CH8 or CH8'), 106.6 (t, CF-1, ²J_{CF} = 15 Hz), 105.8 (t, CF-1, ²J_{CF} = 15 Hz).

¹⁹F{¹H} NMR (476.2 MHz, D₂O, 298 K): δ -101.91 (s), -105.84 (s).

IR (KBr/Nujol, cm⁻¹): ν (O-H) 3606 (v br); ν (C=N, C=C) 1574, 1526.

ESI-HRMS (negative-ion detection, H₂O : MeOH (1:1), [Ga₆(L⁷)₄]⁶⁻ = [Ga₆(L⁷)₄]⁶⁻, [Ga₃(L⁷)₂]³⁻): m/z found (calc.), [Ga₃(L⁷)₂]³⁻ = 503.6516 (503.6503); [Ga₃(L⁷)₂]³⁻ + K⁺ + OH⁻]³⁻ = 522.3072 (522.3057); [Ga₃(L⁷)₂]³⁻ + 2 K⁺ + 2 OH⁻]³⁻ = 540.9629 (540.9612); [Ga₃(L⁷)₂]³⁻ + K⁺]²⁻ = 774.9589 (774.9570); [Ga₃(L⁷)₂]³⁻ + 2 K⁺ + OH⁻]²⁻ = 802.9423 (802.9402); [Ga₃(L⁷)₂]³⁻ + 3 K⁺ + 2 OH⁻]²⁻ = 830.9260 (830.9234); [Ga₆(L⁷)₄]⁶⁻ + 4 K⁺ + 2 Na⁺ + 3 OH⁻]³⁻ = 1092.2486 (1092.2479); [Ga₆(L⁷)₄]⁶⁻ + 5 K⁺ + Na⁺ + 3 OH⁻]³⁻ = 1097.5729 (1097.5725); [Ga₆(L⁷)₄]⁶⁻ + 6 K⁺ + 3 OH⁻]³⁻ = 1102.8977 (1102.8971); [Ga₆(L⁷)₄]⁶⁻ + 5 K⁺ + 2 Na⁺ + 3 OH⁻]²⁻ = 1657.8508 (1657.8534); [Ga₆(L⁷)₄]⁶⁻ + 6 K⁺ + Na⁺ + 3 OH⁻]²⁻ = 1665.8393 (1665.8403); [Ga₆(L⁷)₄]⁶⁻ + 7 K⁺ + 3 OH⁻]²⁻ = 1673.8275 (1673.8272).

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Conclusiones

Conclusiones

Esta *Tesis Doctoral* establece principios de diseño generales, verificados experimentalmente, para el desarrollo de cajas supramoleculares de coordinación (SSC) construidas a partir de ligandos ditópicos y tritópicos 1,2,3-triazol–catecol y –naftalendiol y centros metálicos de elementos de los grupos principales Al^{3+} and Ga^{3+} , junto con Fe^{3+} como metal de transición de referencia, en medio acuoso. A lo largo de los tres capítulos se detallan desde cajas dinucleares M_2L_3 (Ga^{3+} , Fe^{3+}) de tipo helicato y mesocato, a cajas tetraédricas M_4L_4 (Al^{3+} , Ga^{3+}), y finalmente a cajas triplemente interconectadas M_6L_4 de tipo [2]catenano (Al^{3+} , Ga^{3+}). Se demuestra así cómo la topología del ligando, la naturaleza del metal, los contraiones, la estequiometría metal:ligando y las condiciones de disolución determinan de forma conjunta el tipo de caja M_nL_m que se forma, su cavidad, su isomería, sus propiedades encapsulantes de tipo anfitrión–huésped, y su respuesta a estímulos externos. A continuación se resumen las conclusiones y hallazgos principales.

- **Desde el Ligando a la Caja: Ligandos Triazol–Catecol/Naftalendiol**

Ligandos ditópicos y tritópicos de tipo triazol–catecol/naftalendiol, obtenidos mediante protocolos sintéticos de química “click” CuAAC, permiten el autoensamblaje predecible de cajas $\text{Ga}_2\text{L}_3/\text{Fe}_2\text{L}_3$ de tipo helicato y mesocato, cajas tetraédricas $\text{Al}_4\text{L}_4/\text{Ga}_4\text{L}_4$, y cajas triplemente interconectadas de tipo [2]catenano $\text{Al}_6\text{L}_4/\text{Ga}_6\text{L}_4$. Modificaciones de tipo electrónicas, y en particular, las de tipo radiales/estéricas (expansion catecol vs naftalendiol) proporcionan un método de controlar la solubilidad, la geometría metal–ligando y el tamaño/forma de las cavidades generadas, estableciéndose así, las condiciones del autoensamblaje de las nuevas cajas M_nL_m basadas en metales de los grupos principales.

- **Topología Dirigida por Estequiometría (Tetraédricas vs Interconectadas)**

En la serie de ligandos triópicos para los metales Al^{3+} y Ga^{3+} , la proporción M:L dicta la topología de la caja M_nL_m resultante del proceso de autoensamblaje. En condiciones básicas acuosas, una proporción M:L $\sim 1:1$ conduce a cajas tetraédricas M_4L_4 (p. ej., $[\text{M}_4\text{L}_4]^{12-}$ en el *Capítulo 2*), mientras que aumentar el metal hasta M:L $\sim 3:2$ favorece la formación selectiva de cajas interconectadas de tipo [2]catenano M_6L_4 (dos subunidades M_3L_2 se catenan de forma triple en el *Capítulo 3*). Esta selectividad y selección topológica durante el proceso de

autoensamblaje de los ligandos de tipo tritópico con los metales Al^{3+} y Ga^{3+} es un distintivo de las cajas M_nL_m con metales de los grupos principales.

- **Influencia de los contraiones y cavidades heterometálicas**

En las cajas Fe_2L_3 , la isomería helicato/mesocato está dirigida por la naturaleza del contraión, la presencia de K^+ y ausencia de cationes amonio Et_4N^+ dicta que se formen cajas de tipo mesocato Fe_2L_3 , mientras que la presencia de Et_4N^+ estabiliza de forma selectiva la formación de cajas helicato Fe_2L_3 . Las cajas análogas Ga_2L_3 son menos sensibles a esta selectividad durante su formación y permanecen en forma de cajas helicato en presencia de K^+ y/o Et_4N^+ . En estado sólido, las cajas dinucleares M_2L_3 muestran cavidades heterometálicas a través de la encapsulación de iones K^+ dando lugar a topologías del tipo $(\text{MK})_2\text{L}_3$, una característica que también está presente en las cajas tetraédricas $\text{M}_4\text{L}_4 \rightarrow (\text{MK})_4\text{L}_4$ que son desarrolladas posteriormente.

- **Geometría y Control de la Cavity en Cajas Tetrahédricas M_4L_4**

Empleando los ligandos tritópicos ($\text{H}_6\text{L}^6\text{--H}_6\text{L}^{10}$) con Al^{3+} y Ga^{3+} se consigue el autoensamblaje de cajas tetrahédricas M_4L_4 en condiciones de estequiometría $\text{M:L} \sim 1:1$, que muestran procesos de expansión/contracción o “*breathing*” en agua, con ventanas de entrada y salida de huéspedes y cavidades de volúmenes modulables. Las cajas $\text{M}_4(\text{L}^8)_4$ and $\text{M}_4(\text{L}^9)_4$ contienen cavidades pequeñas $< 25 \text{ \AA}^3$, mientras que los procesos de expansión dependientes del disolvente proporcionan un rango de cavidades de mayor tamaño para $\text{M}_4(\text{L}^6)_4 \sim 85 \rightarrow 503 \text{ \AA}^3$, y cavidades de gran tamaño a través de la expansión con la caja de tipo naftalendiolato $\text{Ga}_4(\text{L}^{10})_4 \sim 1148 \text{ \AA}^3$. Los tamaños hidrodinámicos por DOSY NMR concuerdan con los tamaños cristalográficos, y el análisis estructural computacional concluye la existencia de una pronunciada expansión/contracción dependiente del disolvente. Estos resultados definen una relación estructura–cavidad que permite vincular la modificación radial resultante del empleo de ligandos naftalenodiol hacia la formación de cajas con cavidades de mayor tamaño. Además, en estado sólido, estas cajas forman también cavidades heterometálicas $(\text{MK})_4\text{L}_4$ mediante la encapsulación de iones K^+ .

- **Encapsulación Anfitrión–Huésped en Cajas Tetrahédricas M_4L_4 en Agua**

Estudios sistemáticos de encapsulación huésped–anfitrión con huéspedes amonio R_4N^+ de diversos tamaños ($\text{Me}_4\text{N}^+ < \text{Et}_4\text{N}^+ < \text{Pr}_4\text{N}^+ < \text{Bu}_4\text{N}^+$) demuestran procesos de encapsulación 1:1 anfitrión:huésped y afinidades dependientes del

tamaño ($K_a \sim 10^3\text{--}10^4 \text{ M}^{-1}$). La encapsulación está fuertemente dominada por la contribución entrópica del proceso ($\Delta H > 0$, $T\Delta S > 0$, $\Delta G < 0$) que es coherente con la desolvatación de la caja y el huésped, y la ocupación cavidad–huésped confirma la regla de Rebek (45-65%). Además, se pone de manifiesto la dependencia del metal en los procesos de encapsulación. Mientras que las cajas Al_4L_4 prefieren huéspedes pequeños (Me_4N^+), las cajas Ga_4L_4 son más afines por huéspedes más voluminosos (Et_4N^+ y Pr_4N^+). Estos resultados establecen una serie de tendencias y reglas entre cavidad–afinidad que permiten relacionar de forma directa el diseño y geometría de los ligandos (elongaciones axiales vs radiales), naturaleza del metal empleado (Al vs Ga) con la predicción de las propiedades encapsulantes de las cajas tetraédricas M_nL_m resultantes.

- **Cajas M_6L_4 Mecánicamente Interconectadas**

Los ligandos tritópicos H_6L^6 (no fluorado) y H_6L^7 (fluorado) se autoensamblan en forma de cajas de tipo [2]catenano Al_6L_4 and Ga_6L_4 con puentes $\mu\text{-OH}$ y mediante coordinación de tipo O,O' metal–catecolato en condiciones de estequiometría M:L $\sim 3:2$. Estas entidades supramoleculares forman topologías apiladas cuádruples con quiralidad de tipo helicoidal. Estas cajas Al_6L_4 and Ga_6L_4 son los primeros ejemplos conocidos de cajas interconectadas basadas en metales de los grupos principales.

- **Ensamblaje Reversible y Cooperativo en Agua Mediante Ciclos Ácido–Base**

Las cajas interconectadas Al_6L_4 and Ga_6L_4 se forman a través de procesos de autoensamblaje reversibles, selectivos y cooperativos. En condiciones ácidas se desensamblan y condiciones básicas inducen su re–ensamblaje. El seguimiento de estas transformaciones mediante RMN/ITC demuestra proceso de ensamblaje directos y altamente cooperativos en agua sin la detección cajas M_3L_2 monoméricas, que son intermedios típicamente observables en los procesos de catenación de cajas interconectadas con metales del bloque d. Los datos termodinámicos permiten concluir que se trata de procesos de desensamblaje dirigidos entrópicamente y re–catenaciones fuertemente dependientes de la contribución entálpica. Además, una marcada dependencia del metal es evidente con la caja interconectada Ga_6L_4 ~ 500 veces más estable que la análoga Al_6L_4 ($\Delta\Delta G \sim -15.6 \text{ kJ}\cdot\text{mol}^{-1}$ durante la recatenación), atribuible a la formación de enlaces Ga–O más fuertes e interacciones $\pi\cdots\pi$ más pronunciadas.

- **Relevancia y Perspectivas Futuras**

Esta *Tesis* ofrece una lógica para el diseño de ligandos (geometría, perfil axial/estérico), elección del metal ($\text{Ga}^{3+}/\text{Al}^{3+}/\text{Fe}^{3+}$) e influencia del entorno iónico (K^+ vs R_4N^+) y la estequiometría M:L, como variables ortogonales que dirigen el autoensamblaje de cajas M_nL_m (helicato vs mesocato, tetraédricas, interconectadas) y sus funciones (expansión/contracción, encapsulación selectiva de huéspedes, formación reversible). Estos principios sobre el proceso de autoensamblaje de estos sistemas son de aplicabilidad y utilidad en el diseño de nuevos sistemas anfitrión que muestren una respuesta a estímulos externos y cajas supramoleculares M_nL_m encapsulantes para catálisis en agua, abriendo así nuevas vías más allá de sistemas con metales del bloque d, hacia el desarrollo de nuevos materiales y sistemas con aplicaciones en reconocimiento molecular con metales de los grupos principales.

Conclusions

Conclusions

This *Doctoral Dissertation* establishes general, experimentally verified design principles for developing supramolecular coordination cages (SSC) constructed from ditopic and tritopic 1,2,3-triazole–catechol and –naphthalenediol ligands and main-group metal nodes Al^{3+} and Ga^{3+} , alongside Fe^{3+} as transition metal benchmark, in aqueous media. Across the three *Chapters*, we progress from dinuclear helicate/mesocate M_2L_3 cages (Ga^{3+} , Fe^{3+}) to tetrahedral M_4L_4 cages (Al^{3+} , Ga^{3+}), and finally to triply interlocked [2]catenane M_6L_4 cages (Al^{3+} , Ga^{3+}), revealing how ligand topology, metal identity, counterions, ligand:metal stoichiometries and solution conditions co-determine the architecture, cavity metrics, isomerism, host–guest encapsulation properties and stimulus responsiveness of these new M_nL_m cages. Key conclusions and findings are summarised below.

- **Ligand-to-Cage Design with Triazole–Catechol/Naphthalenediol Scaffolds**

Ditopic and tritopic triazole–catechol/–naphthalene–diol ligands, accessed by CuAAC click chemistry, enable predictable self-assembly into $\text{Ga}_2\text{L}_3/\text{Fe}_2\text{L}_3$ helicate and mesocate cages, tetrahedral $\text{Al}_4\text{L}_4/\text{Ga}_4\text{L}_4$ cages, and triply interlocked $\text{Al}_6\text{L}_4/\text{Ga}_6\text{L}_4$ cages. Electronic and, especially, radial/steric modifications (catechol vs naphthalenediol expansion) provide fine control over solubility, metal–ligand geometry and cavity size/shape, establishing new self-assembly rules for main-group M_nL_m cages.

- **Stoichiometry-Directed Topology Selection (Tetrahedral vs Interlocked)**

Across the tritopic ligand series, the global M:L ratio dictates the resulting self-assembled M_nL_m topology. Under basic aqueous conditions, M:L $\sim$ 1:1 yields tetrahedral M_4L_4 cages (e.g., $[\text{M}_4\text{L}_4]^{12-}$ in *Chapter 2*), whereas increasing the metal to M:L $\sim$ 3:2 favours triply interlocked [2]catenane M_6L_4 cages (two M_3L_2 cage subunits catenating together in *Chapter 3*). This stoichiometry-driven topology selection during self-assembly is a distinctive feature of these main-group M_nL_m cage systems.

- **Counter-Ion Influence and Heterometallic Cages**

In Fe_2L_3 cages, the helicate/mesocate isomerism is directed by the nature of the counterions, where the presence of K^+ and absence of ammonium Et_4N^+ biases the formation of mesocate Fe_2L_3 cages, whereas the presence of Et_4N^+ selectively stabilises helicate Fe_2L_3 cages. The analogues Ga_2L_3 cages are less sensitive and

remain helicate in the presence of K^+ and or Et_4N^+ . The developed helicate and mesocate M_2L_3 cages are found to be heterometallic in the solid state via K^+ encapsulation within their internal voids, yielding $(MK)_2L_3$ cages, mirroring observations later seen for tetrahedral $(MK)_4L_4$ cages.

- **Geometry and Cavity Control in Tetrahedral M_4L_4 Cages**

The tritopic ligands (H_6L^6 – H_6L^{10}) assemble with Al^{3+} and Ga^{3+} into tetrahedral M_4L_4 cages under $M:L \sim 1:1$ stoichiometric conditions, displaying cavity “breathing” features in water and a tuneable volume windows from small-void hosts, cavities $< 25 \text{ \AA}^3$ for $M_4(L^8)_4$ and $M_4(L^9)_4$, through solvent-expandable cages $M_4(L^6)_4$ with cavities of $\sim 85 \rightarrow 503 \text{ \AA}^3$, to large-voids withing the cage naphthalenediolate expanded $Ga_4(L^{10})_4$ featuring a cavity of $\sim 1148 \text{ \AA}^3$. DOSY NMR hydrodynamic sizes align with the crystallographic cages dimensions, and structural computational analysis rationalises their solvent-dependent expansion/contraction behaviour. These results define a structure–cavity relationship linking radial naphthalenediol functionalisation to increased cavity metrics. In the solid state, these tetrahedral hosts also form heterometallic $(MK)_4L_4$ cages via K^+ encapsulation.

- **Host–Guest Encapsulation of Tetrahedral M_4L_4 Cages in Water**

Systematic host–guest encapsulation studies with ammonium guests R_4N^+ of increasing size ($Me_4N^+ < Et_4N^+ < Pr_4N^+ < Bu_4N^+$) reveal 1:1 host:guest encapsulation and size-dependent affinities ($K_a \sim 10^3$ – 10^4 M^{-1}). Binding is entropy-driven ($\Delta H > 0$, $T\Delta S > 0$, $\Delta G < 0$) consistent with cage and guest desolvation and optimal occupancies follow Rebek’s rule (45-65%). A clear metal effect is evident with the Al_4L_4 cages preferring smaller guests (Me_4N^+), whereas the Ga_4L_4 accommodate bulkier guests (Et_4N^+ and Pr_4N^+). These results define a set of cavity–affinity correlations that couple ligand design (axial vs radial elongations) and metal identity (Al vs Ga) to recognition and encapsulation performances.

- **Mechanically Interlocked M_6L_4 Cages**

The tritopic ligands H_6L^6 (non-fluorinated) and H_6L^7 (fluorinated) yields triply interlocked [2]catenane cages Al_6L_4 and Ga_6L_4 featuring μ -OH bridges and metal–catecholate O,O'-coordination, under $M:L \sim 3:2$ stoichiometric conditions. These interwoven assemblies form quadruple-decker topologies of intrinsic helical

chirality. These main-group metal interlocked Al_6L_4 and Ga_6L_4 topologies are the first examples based exclusively on main-group metals.

- **Reversible Cooperative Assembly in Water via Acid–Base Cycles**

The interlocked Al_6L_4 and Ga_6L_4 cages are formed via a reversible process driven by acid–base cycles. Acid unlocks and base induces re-catenation of their interwoven topologies. NMR/ITC monitoring demonstrates a direct, highly cooperative interlocking process in water without observable M_3L_2 monomeric intermediates, contrasting typical d-block routes. Thermodynamics reveal entropy-driven disassembly and strongly enthalpy-driven re-assembly. A pronounced metal dependence is quantified with the interlocked Ga_6L_4 cages ~ 500 times more robust than its Al_6L_4 analogues ($\Delta\Delta G \sim -15.6 \text{ kJ}\cdot\text{mol}^{-1}$ for re-catenation), attributed to stronger Ga–O bonding and more extensive $\pi\cdots\pi$ stabilisation.

- **Significance and Outlook**

This *Thesis* delivers a coherent cage-design logic: ligand topology (donor geometry, axial/steric profile), metal choice ($\text{Ga}^{3+}/\text{Al}^{3+}/\text{Fe}^{3+}$), ionic environment (K^+ vs R_4N^+) and the M:L stoichiometries, acting as orthogonal handles to direct M_nL_m architectures (helicate vs mesocate, tetrahedral, interlocked) and functions (cavity breathing, selective guest binding, acid–base assembly reversibility). These principles are immediately transferable to future research in developing stimuli-responsive hosts, molecular switches, and supramolecular M_nL_m hosts for confined catalysis in water, opening routes to adaptive materials and recognition platforms that leverage main-group metal coordination chemistry well beyond traditional d-block paradigms.

Publications and Conference Contributions

4.1 Introduction

This section includes the scientific publications and contributions resulting from the research conducted during the development of this *Doctoral Thesis*. Some of these contributions were obtained in parallel to the main research project described herein. Additionally, conference presentations derived from this doctoral work are also included.

Publications

I. Izquierdo, L. Martínez-Castro, G. Ujaque, A. J. Martínez-Martínez, *Chem. Sci.* **2025**. DOI: 10.1039/D5SC05441A.

A. Carbonell, **I. Izquierdo**, D. B. Guzmán Ríos, G. Norjmaa, G. Ujaque, A. J. Martínez-Martínez, U. Pischel, *Inorg. Chem.* **2024**, 63, 19872-19884. DOI: 10.1021/acs.inorgchem.4c03279.

Conference Contributions

Poster Communications:

1) Ignacio Izquierdo, Antonio Martínez-Martínez. Encapsulation of amino Rh(I) organometallic complexes inside a supramolecular gallium metallocage. Symposium RSEQ, Spain 2021(online).

2) Ignacio Izquierdo, Antonio Martínez-Martínez Encapsulation of a cyclopentadienyl Co(III) organometallic complex inside a supramolecular gallium metallocage. 2nd Geqonovel Simposio de Investigadores Jóvenes del Grupo Especializado de Química Organometálica, Spain (online) 2021.

3) Ignacio Izquierdo, Antonio Martínez-Martínez. Constructing coordination supramolecular cages using bis-and tris-1,2,3-triazole linkers. XL GEQO, Barcelona, Spain 2022.

4) Ignacio Izquierdo, Antonio Martínez-Martínez. Constructing different coordination supramolecular structures from a single tripodal linker. Reunión Bienal de la Sociedad Española de Química, Granada, Spain 2022.

5) Ignacio Izquierdo, Antonio Martínez-Martínez. Reversible assembly of Quadruple-Decker gallium coordination structures. EuCOMC XXV, Alcalá de Henares, Spain 2023.

6) Ignacio Izquierdo, Antonio Martínez-Martínez. Reversible assembly of Quadruple-Decker Ga_6L_4 complex. XLII GEQO, Seville, Spain 2024.

Oral Communications:

1) Ignacio Izquierdo, Antonio Martínez-Martínez. *Constructing different bimetallic coordination supramolecular cages*. Reunión Bienal de la Sociedad Española de Química, Zaragoza, Spain 2023.

4.2 Cooperative reversible assembly in triply interlocked Al₆L₄ and Ga₆L₄ cages

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Cite this: DOI: 10.1039/d5sc05441a

All publication charges for this article have been paid for by the Royal Society of Chemistry

Cooperative reversible assembly in triply interlocked Al₆L₄ and Ga₆L₄ cages

Ignacio Izquierdo,^a Laura Martínez-Castro,^b Gregori Ujaque^b and Antonio J. Martínez-Martínez^{a*}

Understanding and controlling the assembly of mechanically interlocked molecules remains a significant challenge. Formation of mechanically interlocked metal–organic cages has, to date, relied exclusively on transition metals due to their predictable coordination geometries and robust bonding. Here, we report, for the first time, the reversible assembly of mechanically interlocked cages based on main-group metals, Al₆L₄ and Ga₆L₄. Structural and computational analyses reveal helical [2]catenane quadruple-decker cage topologies stabilized by six metal–ligand nodes, bridging μ-OH groups, extensive π-stacking, and directional CH⋯O interactions. Remarkably, simple acid–base cycling triggers fully reversible cage unlocking–recatenation processes in water at room temperature. Unlike transition-metal-mediated cage interlocking, they assemble instantaneously and selectively via an unprecedented cooperative main-group interlocking pathway, without detectable monomeric cage intermediates. Thermodynamic analyses reveal metal-dependent switching, involving entropy-driven disassembly coupled to strongly enthalpy-driven reassembly, with the Ga₆L₄ cage ~500-fold more stable than Al₆L₄. These findings provide fundamental understanding of new assembly dynamics beyond conventional transition metals.

Received 21st July 2025
Accepted 23rd September 2025

DOI: 10.1039/d5sc05441a
rsc.li/chemical-science

Introduction

Mechanically interlocked molecules, including catenanes,^{1–7} rotaxanes,^{8–13} clippanes¹⁴ and molecular knots,^{15–23} enable unique controlled molecular motion, gated transport and stimulus-responsive behaviour.^{24,25} Because their mechanical bonds can only be disrupted by covalent cleavage, these topologically complex architectures underpin emerging technologies from molecular machines,^{26,27} stimulus-gated catalysis^{28,29} to adaptive materials and soft robotics.^{30–34} However, precisely controlling their assembly remains a fundamental challenge. Covalent synthetic routes offer exact connectivity but lack error correction, whereas purely non-covalent methods typically compromise directional precision.³⁵ In contrast, metal-directed self-assembly is a powerful tool, combining predictable coordination geometries, thermodynamic error correction, and tunable lability of metal–ligand bonds.^{36,37} These features enable the formation of mechanically interlocked metal–organic architectures (Fig. 1) whose cavity size, shape, and charge can be encoded during self-assembly.

Since Fujita's seminal report of the first mechanically interlocked metal–organic cage, a triply interwoven [2]catenane M₆L₄

structure assembled using Pd or Pt,³⁸ the field has expanded rapidly. Numerous examples have been developed exclusively using transition metals, including Co,³⁹ Cu,⁴⁰ Zn,^{39,41} Ru,^{42,43} Rh,^{44–46} Pd,^{47–56} Ag⁵⁷ and Pt.^{58,59} These cage assemblies exhibit diverse stimulus-responsive functionalities, such as shape-switching,^{48,50,54,56} high-affinity guest binding,⁵¹ and artificial-muscle-like actuation.⁴⁴ However, reversible mechanical interlocking switching under mild conditions, essential for programmable and responsive supramolecular function, remains rare.^{60,61} Main-group metals offer an orthogonal and unexplored toolkit for switchable mechanical interlocking. Although some examples of discrete monomeric main-group metal–organic cages have been developed,^{62–74} mechanical interlocking involving such metals remains completely unexplored.

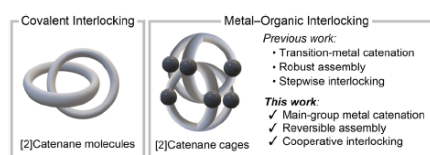


Fig. 1 From covalent to metal–organic interlocking: transition-metal vs. main-group metal-mediated catenation (this work).

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Here we introduce first examples of mechanically interlocked metal-organic cages assembled from main-group metals, Al_6L_4 IC1 and Ga_6L_4 IC2. Through a simple tritopic ligand, H_6L , we demonstrate fully reversible acid-base-triggered disassembly and reassembly of their triply interwoven helical [2] catenane topologies in water at room temperature. In contrast to transition-metal cage interlocking assembly, which typically proceeds through dimerization of monomeric cage intermediates, they assemble instantaneously *via* an unprecedented cooperative main-group pathway, without detectable monomeric M_3L_2 cage intermediates. Thermodynamic analyses reveal a distinctive metal-dependent switching dynamics, driven by entropy during disassembly and enthalpy during reassembly, with the Ga_6L_4 cage exhibiting ~ 500 -fold higher stability than its Al_6L_4 analogue.

Results and discussion

The tritopic ligand H_6L was obtained in two steps (Scheme 1a). A Cu-catalyzed three-fold alkyne-azide “click” reaction (CuAAC)^{75,76} between 1,3,5-triethynylbenzene and 1-azido-2,3-dimethoxybenzene afforded the tris(1,2,3-triazole) precursor Me_6L (76%). Subsequent demethylation with BBr_3 gave H_6L quantitatively (95%). The terminal catechol groups offer robust chelation for oxophilic M^{3+} ions, while the rigid C_{3v} phenylene C_6H_3 core pre-arranges three metal binding sites within a trigonal array. Furthermore, the bridging triazole units add conformational adaptability and promote $\pi\cdots\pi/\text{CH}\cdots\pi$ stackings. Self-assembly of H_6L with $\text{Al}(\text{acac})_3$ or $\text{Ga}(\text{acac})_3$ (acac = acetylacetonate), and KOH in a ratio 4 : 6 : 9 in MeOH, selectively produced the triply interlocked cages Al_6L_4 IC1 and Ga_6L_4 IC2 within 16 hours at room temperature (Scheme 1b). This click-demethylation-assembly sequence provided IC1 and IC2 in 86% and 80% yield, respectively, after simple trituration with diethyl ether. Notably, IC1 and IC2 represent the first examples

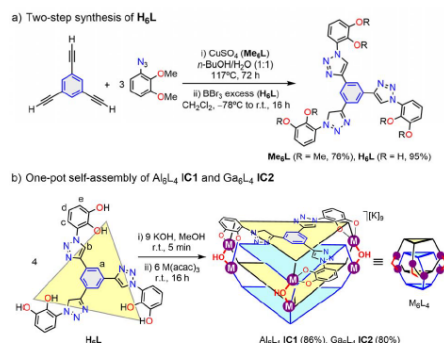
of mechanically interlocked metal-organic cages constructed exclusively from main-group metals.⁹⁰

Disappearance of the catechol OH signals of H_6L (δ 10.05 and 9.52 ppm) in the ^1H NMR spectra of IC1 and IC2 confirms metal-catecholate coordination (Fig. 2a–d). Each interlocked cage displays two sets of sharp resonances in D_2O at 298 K, reflecting two chemically inequivalent ligand environments. This spectral duplication evidences the mechanical interpenetration of two cage monomeric units, Al_3L_2 C1 or Ga_3L_2 C2, within each dimeric assembly. The triazole protons $\text{H}^b/\text{H}^{b'}$ shift downfield (IC1: δ 9.28/9.42 ppm; IC2: δ 9.26/9.36 ppm) relative to H_6L (δ 9.08 ppm), consistent with a peripheral cage location. In contrast, the phenylene C_6H_3 core protons $\text{H}^a/\text{H}^{a'}$ are strongly shielded (IC1: δ 7.70/7.36 ppm; IC2: δ 7.71/7.38 ppm; vs. H_6L : δ 8.52) owing to the π -stacking within the cage interior. ^{13}C NMR data in D_2O also shows duplicated sets at 298 K, confirming ligand interpenetration (Fig. S18 and S35, SI).

Complementary ^1H NMR in CD_3OD shows that the duplicated ligand resonances visible in D_2O coalesce into single broadened sets at 298 K. $\text{H}^b/\text{H}^{b'}$ appear as averaged and broad singlets at δ 9.12 (IC1) and 9.14 (IC2) ppm, and $\text{H}^a/\text{H}^{a'}$ at δ 8.43 (IC1) and 8.34 (IC2) ppm (Fig. S16 and S33, SI). This solvent-dependent modulation reflects the weaker hydrophobic/solvophobic driving force in CD_3OD relative to D_2O , which attenuates π -stacking in IC1 and IC2, thereby reducing inner/outer chemical-shift differences ($\Delta\delta$) and averaging them on the NMR timescale at 298 K. Variable-temperature ^1H NMR in CD_3OD (318–238 K) progressively resolves these resonances as exchange slows upon cooling to 238 K. At 238 K, the ligand resonances desymmetrize, $\text{H}^b/\text{H}^{b'}$ resolve into five (IC1) and four (IC2) partially overlapping broad singlets spanning δ 9.04–9.31 ppm and δ 9.31–9.60 ppm, respectively. Likewise, $\text{H}^a/\text{H}^{a'}$ split into five (IC1) and three (IC2) overlapping broad singlets δ 8.38–8.80 ppm and δ 8.29–8.37 ppm, respectively; with the catecholate $\text{H}^c/\text{H}^d/\text{H}^e$ showing analogous behavior (Fig. S55 and S56, SI). Warming up to 298 K restores the initial state. These low-temperature spectra are consistent with freezing of the interlocked topologies IC1 and IC2, where four ligands are arranged in a non-equivalent fashion (*vide infra*).

High-resolution ESI-TOF MS (negative mode) confirmed the M_6L_4 formulation for IC1 and IC2. Each spectrum displays isotopically resolved series of peaks for intact anions $[\text{Al}_6\text{L}_4]^{n-}$ (for IC1) and $[\text{Ga}_6\text{L}_4]^{n-}$ (for IC2) in charge states 4–, 3–, and 2–, detected as Na^+/K^+ adducts drawn from the ionization medium (Fig. 2e and f). A second family of peaks reveals that each cage retains three hydroxide OH^- groups. IC1 gives representative peaks at m/z 940.0542 (3–) and 1438.0436 (2–) for $[\text{Al}_6\text{L}_4(\text{OH})_3 + x\text{A}]^{n-}$, whereas IC2 furnishes an analogous series at m/z 763.4597 (4–), 1030.9328 (3–) and 1549.9055 (2–) for $[\text{Ga}_6\text{L}_4(\text{OH})_3 + x\text{A}]^{n-}$ ($\text{A} = \text{Na}^+, \text{K}^+$). In addition, in-source collisional activation cleaves each interlocked assembly into units $[\text{Al}_3\text{L}_2]^{3-}$ C1 (m/z 425.0564) and $[\text{Ga}_3\text{L}_2]^{3-}$ C2 (m/z 467.6689), evidencing mechanical unlocking of IC1 and IC2 during ionization.

Single crystals of Me_6L suitable for X-ray diffraction were obtained by slow evaporation of a concentrated EtOAc solution (50 mM, 0.5 mL) at room temperature over 24 h. The crystal



Scheme 1 (a) Synthesis of ligands Me_6L and H_6L . (b) Self-assembly of triply interlocked quadruple-decker cages Al_6L_4 IC1 and Ga_6L_4 IC2. Isolated yields are shown in parenthesis.

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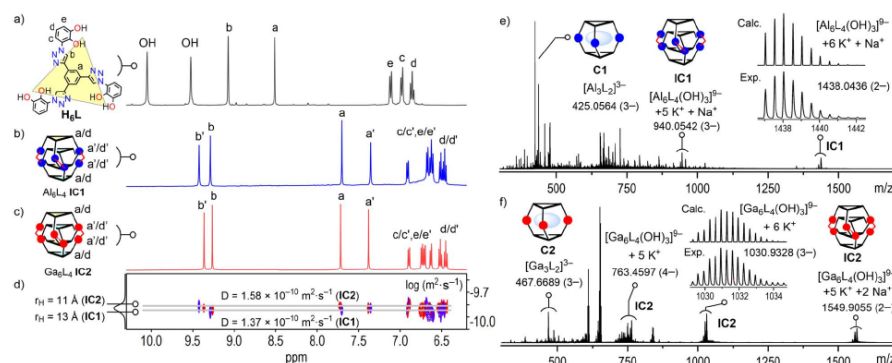


Fig. 2 (a) ^1H NMR spectra (400 MHz, 298 K) of ligand H_6L in $\text{DMSO}-d_6$. (b) cage Al_6L_4 IC1 (blue) and (c) Ga_6L_4 IC2 (red) in D_2O ; duplicated ligand environments are labelled with a/d and a'/d'. (d) Overlay of DOSY NMR (400 MHz, 298 K) for IC1 and IC2 in D_2O . (e) ESI-TOF HR mass spectra (negative mode) of IC1 and (f) IC2, showing selected peaks for interlocked cages $[\text{Me}_6\text{L}]^{n-}$ and $[\text{M}_3\text{L}_2]^{n-}$ C1 and C2 units.

structure of Me_6L reveals a planar 1,3,5-phenylene C_6H_3 core flanked by three peripheral 1,2,3-triazoles, promoting extended ligand conjugation (Fig. 3a). The catechol termini are pre-organized at distances of ~ 15.1 Å, ideal for chelating remote M^{3+} nodes. Packing is governed by $\pi\cdots\pi$ contacts (centroid-centroid 3.7483(9) Å) supplemented by $\text{C}-\text{H}\cdots\pi/\text{Me}\cdots\pi/\text{C}-\text{H}\cdots\text{N}$ interactions (Fig. 3b and c), underscoring the intrinsic propensity of this ligand framework for stacking. DOSY NMR studies corroborate a significant aggregation of both Me_6L and H_6L in solution. The measured diffusion coefficients (D) of $3.10 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for Me_6L and $2.60 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for H_6L correspond to Stokes-Einstein hydrodynamic radii (r_h) of 9 and 11 Å (Fig. S57 and S58, SI), respectively, roughly twice the estimated monomer size (6 Å) and consistent with predominant dimer aggregation. This pre-organization is expected to reduce the entropic cost of cage assembly using H_6L .

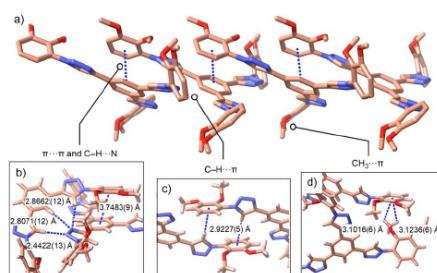


Fig. 3 Crystal packing of Me_6L highlighting key non-covalent interactions: (a) side-on view of a slipped stack showing π -overlap, (b) close-up of $\pi\cdots\pi$ and $\text{C}-\text{H}\cdots\text{N}$ contacts, (c) representative $\text{CH}\cdots\pi$ contacts and (d) $\text{Me}\cdots\pi$ interactions.

Single crystals of the cage Ga_6L_4 IC2 suitable for X-ray diffraction, as its potassium salt form $\text{K}_9[\text{Ga}_6\text{L}_4(\text{OH})_3]_3$, were grown by vapor diffusion of acetone (2 mL) into a 1 : 1 $\text{H}_2\text{O}/\text{MeOH}$ solution of the cage (10 mM, 0.5 mL) at room temperature over one week. These crystals confirm the anticipated triply interlocked [2]catenane topology (Fig. 4). Two mechanically threaded monomeric units Ga_3L_2 C2 (cage I and cage II) are connected by six Ga-catecholate chelate nodes ($\text{Ga}-\text{O}$ 1.8926(18)–1.9544(19) Å). At each of the three crossing nodes a μ -OH bridge spans a Ga_2 unit ($\text{Ga}-\text{OH}$ 1.890(2)–1.928(2) Å), rendering every Ga^{3+} center five-coordinate within the anionic $[\text{Ga}_6\text{L}_4(\text{OH})_3]^{9-}$ framework. Each Ga_3L_2 C2 cage encloses a prolate cavity with 6.8180(18) and 6.7422(19) Å inter-deck spacings and voids of 83 and 107 Å³ (calculated using CageCavityCalc-C3),⁷⁷ ideally sized to host the tris(triazole)phenylene hub of its interpenetrating Ga_3L_2 partner (Fig. 4b). ESP mapping shows a uniformly negative potential inside each cavity, reflecting the π -rich ligand walls in each formal Ga_3L_2 C2 unit, suggesting that dispersion, π -stacking and Ga–O coordination likely drive interlocking.

Additional NCI analyses of DFT-optimized (B3LYP-D3/6-31g*) structures of IC1 and IC2 provided deeper insights into the non-covalent forces underpinning these assemblies. The presence of diffuse attractive isosurfaces highlights extensive π -stacking between ligand layers in both interlocked assemblies IC1 and IC2 (Fig. S97 and S98, SI). The distinct interaction maps, despite similar, suggest greater stability of the cage IC2 compared to IC1 through enhanced π -stacking (slightly larger and greener surfaces).

Four ligand decks form an eclipsed π -stack (inter-deck phenylene centroid-centroid: 3.3691(17), 3.3753(19) and 3.4493(18) Å). These decks are successively rotated by 17.28(3)–29.16(3)°, generating P/M helices that crystallize as a racemate in $P\bar{1}$ space group (P-helix is shown, Fig. 4c). An additional π -staircase array of contacts between triazoles (3.5120(19)–



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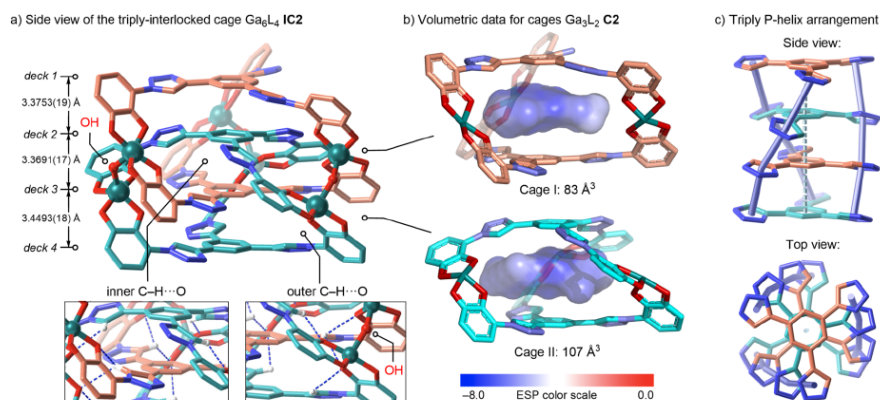
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Fig. 4 Crystal structure of the triply-interlocked cage Ga_6L_4 IC2 (anionic form $[\text{Ga}_6\text{L}_4(\text{OH})_3]^{9-}$). (a) Side view of the quadruple-decker assembly; μ -OH bridges and Ga atoms are shown ball-and-sticks, and key $\text{CH}\cdots\text{O}$ contacts as dashed lines. (b) Isolated Ga_3L_2 C2 units (cage I and cage II) rendered with internal voids as ESP isosurfaces calculated using CageCavityCalc-C3 (grid size 0.7 Å, eem charge model). (c) P-Helical arrangement of the four ligand decks (side and top). H atoms (except those in $\text{CH}\cdots\text{O}$ contacts), K^+ ions, and solvent are omitted; C beige/cyan, N blue, O red, Ga teal.

4.044(2) Å), supported by directional internal $\text{CH}\cdots\text{O}$ interactions (2.266(2)–2.782(2) Å), further consolidate this quadruple-decker. When interlocked, three tris(triazole)-phenylene cores remain planar (Fig. 4a: decks 1, 3 and 4), whereas one bends (deck 2) to accommodate the interlocked array IC2, underscoring the adaptive flexibility of the ligand L^{6-} framework. In addition, these discrete anionic interlocked $[\text{Ga}_6\text{L}_4(\text{OH})_3]^{9-}$ cages pack into a three-dimensional lattice *via* outer-sphere K^+ bridges and solvent channels (Fig. S95, SI).

The four ligands are crystallographically non-equivalent in IC2, partitioning into two inner and two outer decks. This solid-state asymmetry rationalizes the inner/outer twofold NMR splitting observed in D_2O solution and the further desymmetrisation observed in CD_3OD at 238 K. Moreover, ^1H , ^1H -NOESY cross-peaks between inner phenylene H^a and outer triazole H^b confirm face-edge proximity required for the quadruple-decker helix (Fig. S22 and S39, SI). Additional inter-deck H^a/H^b NOESY contacts between neighboring phenylene C_6H_3 cores confirm retention of the π -stacking motif of IC1 and IC2 in solution. DOSY experiments further supports intact cage architectures in D_2O solution (IC1: $D = 1.37 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$; IC2: $D = 1.58 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, both in D_2O , Fig. 2d), yielding r_H of 13 and 11 Å, respectively, demonstrating retention of the interlocked topologies in water (estimated crystallographic radii of 13 Å for IC2, see SI). Additional DOSY results in CD_3OD solution (IC1: $D = 2.75 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, $r_H = 13$ Å; IC2: $D = 2.90 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, $r_H = 12$ Å) closely matching the structural cage dimensions, confirming intact interlocked topologies in both D_2O and CD_3OD .

Motivated by the unique topological features and the presence of stabilizing μ -OH bridges, we examined the response of the cages IC1 and IC2 to protonation. Titration of solutions of

IC1 and IC2 with incremental additions of deuterio-hydrochloric acid (DCl) in D_2O were monitored by ^1H NMR (Fig. 5). Cage IC1 underwent rapid structural disruption upon addition of one equivalent of acid as evidenced by progressive disappearance and broadening of the cage resonances after four equivalents (Fig. S64, SI). By contrast, cage IC2 remains intact until the third equivalent of acid, underscoring its higher kinetic and thermodynamic robustness (Fig. 5a). Remarkably, subsequent neutralization with sodium deuterioxide (NaOD , 1–4 equiv.) fully restores the diagnostic spectra of each interlocked cage IC1 and IC2. While IC1 recatenates after 3–4 equivalents of base, IC2 readily interlocks after one equivalent. Identical spectral changes were obtained across the window 1–5 mM, the highest range permitted by the solubility of IC1 and IC2, demonstrating a fully reversible unlocking/recatenation process. The absence of resonances attributable to monomeric M_3L_2 cages C1 or C2 further supports a highly cooperative and effectively direct assembly pathway under these conditions.

Lyophilization of the acidified solutions allowed us to analyze the unlocked intermediates resulting from disassembling both cages, IC1 and IC2. ESI-TOF mass analysis reveal dominant ions at m/z 626.1121 (2–) and 669.0500 (2–) corresponding to partially protonated species $[\text{Al}_2(\text{H}_x\text{L})_2]^{2-}$ and $[\text{Ga}_2(\text{H}_x\text{L})_2]^{2-}$ (Fig. S74 and S85, SI). The absence of higher-mass ions suggests that protonation lowers the net charge, favoring H-bonded “ $\text{M}_2(\text{H}_x\text{L})_2$ ” species that exchange rapidly in D_2O solution and thus broaden the ^1H NMR signals during disassembly. Notably, under these partially acidified conditions (4 equiv.), the dominant $[\text{M}_2(\text{H}_x\text{L})_2]^{2-}$ ions do not contain OH^- groups, in contrast to the intact cage $[\text{M}_6\text{L}_4(\text{OH})_3]^{9-}$ ions, where μ -OH bridging is implicit. This indicates protonation/disruption of the μ -OH bridges during unlocking; conversely,

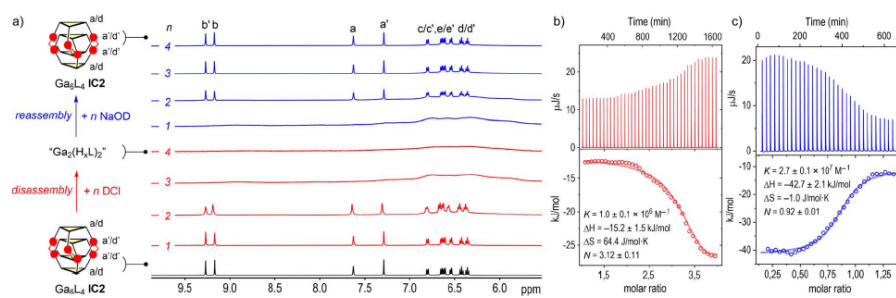


Fig. 5 Reversible acid–base switching of the interlocked cage Ga_6L_4 IC2: (a) ^1H NMR (500 MHz, 298 K, 4 mM) stack for Ga_6L_4 IC2 during titration with DCI (1–4 equiv., red) and back-titration with NaOD (1–4 equiv., blue) in D_2O (identical spectra are obtained in the 1–5 mM range). ITC traces: (b) disassembly (1–4 equiv. of DCI) and (c) reassembly (0–1.5 equiv. of NaOD) of IC2 in D_2O (1 mM) at 298 K.

reappearance of the IC1 and IC2 resonances upon neutralization with base correlates with re-formation of these bridges. IR spectroscopy showed a broad $\nu(\text{OH})$ at 3500 cm^{-1} and ^1H NMR in $\text{DMSO}-d_6$ confirming partial catechol reprotonation (Fig. S81–S84, SI). Together, these observations indicate that full deprotonation of H_6L and intact $\mu\text{-OH}$ bridges are pre-requisites for cage assembly.

While controlled addition of acid (1–4 equiv.) resulted in partial protonated “ $\text{M}_2(\text{H}_4\text{L})_2$ ” species, addition of a large excess of acid (30 equiv.) fully protonated the system, regenerating back the neutral ligand H_6L . To map the direct interlocking pathway, we conducted *in situ* NMR monitoring starting from the fully protonated ligand H_6L . Titration of H_6L with incremental additions of NaOD (1–6 equiv.) in D_2O generates the hexaanionic ligand species, L^{6-} , in its sodium form Na_6L (Fig. S68–S70, SI). DOSY NMR analysis reveals a significant dimeric pre-organization of Na_6L in solution ($D = 2.08 \times 10^{-10}\text{ m}^2\text{ s}^{-1}$, $r_{\text{H}} = 9\text{ \AA}$), akin to Me_6L and H_6L . Addition of two equivalents of AlCl_3 and GaCl_3 as water soluble sources of Al^{3+} and Ga^{3+} ions, immediately produced the duplicated ligand ^1H NMR resonances of IC1 and IC2. Although partial replacement of the bridging $\mu\text{-OH}$ groups for $\mu\text{-Cl}$ and outer-sphere exchange of K^+ for Na^+ cannot be excluded under these conditions, the formation of IC1 and IC2 is essentially instantaneous (<2 min), underscoring the high kinetic facility of this unusual main-group interlocking process. The rapid assembly is consistent with cooperative metal–catecholate chelation together with a hydrophobic/solvophobic contribution that further strengthens π -stacking and releases structured solvent molecules and counterions from the cavity regions during the assembly of IC1 and IC2. This essentially direct main-group interlocking pathway, occurring without detectable formation of monomeric cage intermediates M_3L_2 C1 or C2, contrasts markedly with the established monomer-to-dimer interlocking pathways typical for transition-metal-mediated cage assemblies.^{41,48,50,52,54,55,78}

To quantify the thermodynamic driving forces underlying the reversible assembly of IC1 and IC2, isothermal titration

calorimetry (ITC) was carried out under the same acid–base NMR cycling regimes at 1 mM concentrations (Fig. 5b, c and S72, SI). The ITC isotherms captured single cooperative transition equilibria for both the disassembly and reassembly of IC1 and IC2, therefore, data were fitted to one-set-of-sites models (independent-sites/Wiseman). Hence, the overall macroscopic equilibria returned N (acid/base titrant equivalents per cage at the transition) and apparent macroscopic equilibrium constants K (M^{-1}) for the overall disassembly (cage + $n\text{H}^+ \rightleftharpoons$ disassembled state) and reassembly (disassembled state + $n\text{OH}^- \rightleftharpoons$ cage) modelled steps at the specific transition N equivalents. Acid-induced disassembly is entropy-driven ($T\Delta S > 0$, Fig. 6) for both cages IC1 ($T\Delta S = 32.9\text{ kJ mol}^{-1}$) and IC2 ($T\Delta S = 19.1\text{ kJ mol}^{-1}$), consistent with the gain in translational/rotational and conformational freedom upon releasing ligands and metal ions. The modest exothermicity (IC1: $\Delta H = -16.0\text{ kJ mol}^{-1}$; IC2: $\Delta H = -15.2\text{ kJ mol}^{-1}$) is attributed to protonation of $\mu\text{-OH}$ bridges and catecholate groups. Overall, unlocking is easier for IC1 ($\Delta G = -48.9\text{ kJ mol}^{-1}$) than for IC2 ($\Delta G = -34.3\text{ kJ mol}^{-1}$), consistent with the higher intrinsic stability of the Ga_6L_4 cage IC2. Consistently, the ITC stoichiometries indicate $N = 1.06 \pm 0.03$ acid equivalent per cage for IC1 and $N = 3.12 \pm 0.11$ for IC2 during disassembly, matching the macroscopic equivalence points seen by ^1H NMR titrations. Reassembly on base addition is strongly enthalpy-driven (IC1: $\Delta H = -42.1\text{ kJ mol}^{-1}$; IC2: $\Delta H = -42.7\text{ kJ mol}^{-1}$). This reflects

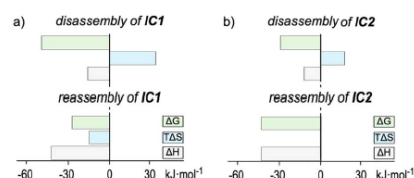


Fig. 6 Thermodynamic ITC data (ΔG , $T\Delta S$ and ΔH) for acid-induced disassembly and base-induced reassembly: (a) Al_6L_4 IC1 and (b) Ga_6L_4 IC2.



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the formation of twelve M–O chelate bonds and three μ -OH bridges, reinforced by dense $\pi \cdots \pi$ and C–H $\cdots$ O contacts within the quadruple-decker stacks, providing a large exothermic gain that outweighs the desolvation costs. The reassembly entropy terms diverge. IC1 pays a small entropic penalty ($T\Delta S = -15.3 \text{ kJ mol}^{-1}$), whereas IC2 incurs essentially none ($T\Delta S = -0.3 \text{ kJ mol}^{-1}$). This reflects the balance between ordering penalties and the favorable hydrophobic/solvophobic release of structured solvent molecules and counterions from catecholate solvation shells and π -rich cavities during interlocking. We ascribe the minimal entropic term in IC2 to a more extensive π -stacking and stronger Ga–O chelation, which together favor a more pre-organized unlocked ensemble and better compensates ordering in water compared to IC1. The resulting reassembly free energies (IC1: $\Delta G = -26.8 \text{ kJ mol}^{-1}$; IC2: $\Delta G = -42.4 \text{ kJ mol}^{-1}$) confirm the greater thermodynamic stability of the Ga_6L_4 cage IC2. In line with this, recatenation proceeds with $N = 3.62 \pm 0.04$ base equivalents per cage for IC1 vs. $N = 0.92 \pm 0.01$ for IC2, again consistent with the ^1H NMR titrations. The obtained thermodynamic magnitudes are consistent with other metal–organic cages, where guest capture/assembly is generally exothermic and enthalpy-driven (typically $\Delta H \sim -20$ to -60 kJ mol^{-1} ; $T\Delta S \sim -15$ to 25 kJ mol^{-1}), while release/exchange commonly shows favorable entropy ($T\Delta S > 10 \text{ kJ mol}^{-1}$).^{79–81}

At 298 K, the recatenation free energies are $\Delta G = -26.8 \text{ kJ mol}^{-1}$ ($K = 5.1 \times 10^4 \text{ M}^{-1}$) for IC1 and $\Delta G = -42.4 \text{ kJ mol}^{-1}$ ($K = 2.7 \times 10^7 \text{ M}^{-1}$) for IC2. For unlocking, ΔG is $-48.9 \text{ kJ mol}^{-1}$ for IC1 ($K = 3.7 \times 10^8 \text{ M}^{-1}$) and $-34.3 \text{ kJ mol}^{-1}$ ($K = 1.0 \times 10^6 \text{ M}^{-1}$) for IC2. The resulting $\Delta\Delta G(\text{IC2–IC1}) = -15.6 \text{ kJ mol}^{-1}$ for recatenation, corresponds to a ~ 500 -fold greater thermodynamic preference for the Ga_6L_4 cage IC2 over the Al_6L_4 cage IC1. This metal dependence is consistent with the generally higher affinity of Ga–O chelation relative to Al–O (e.g., phenolate chelates exhibit $\log K \sim 31$ for Ga vs. 22 for Al in water),⁸² reinforcing that stronger Ga–catecholate binding together with more extensive π -stacking, seen by NCI, stabilizes the triply interlocked Ga_6L_4 IC2 topology.

Conclusions

We have demonstrated an unprecedented reversible assembly of the first examples of mechanically interlocked metal–organic cages involving main-group metals, Al_6L_4 and Ga_6L_4 . A simple tritopic ligand, H_6L , directly folds each metal into helical, triply interwoven [2]catenane quadruple-decker topologies. Structural and computational studies confirm cage stabilization *via* six metal–ligand nodes, bridging μ -OH groups, extensive π -stacking and directional CH $\cdots$ O interactions. Remarkably, simple acid–base cycling induces fully reversible cage disassembly–reassembly in water at room temperature. Unlike transition-metal-mediated cage interlocking, which typically assemble through detectable monomeric cages, this main-group metal assembly proceeds rapidly through an unusual cooperative pathway without observable monomeric M_3L_2 cage intermediates. Thermodynamic analyses reveal a metal-dependent switching behavior through entropy-driven unlocking coupled

with strongly enthalpy-driven recatenation. The Ga_6L_4 cage exhibits ~ 500 -fold higher stability than Al_6L_4 ($\Delta G = -42.4$ vs. $-26.8 \text{ kJ mol}^{-1}$), reflecting enhanced Ga–ligand affinity and π -stacking. These results provide new fundamental insights into main-group metal-driven interlocking, thereby opening opportunities for novel stimuli-responsive supramolecular materials beyond conventional transition-metal systems.

Author contributions

I. I. conducted all experiments, synthesis, characterisation, NMR and ITC assembly studies. L. M. C. and G. U. performed electronic structure calculations of molecular models. A. J. M. M.: conceived the idea, project supervision, wrote the manuscript and conducted X-ray crystallography. All authors provided comments and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The datasets supporting this article have been uploaded as part of the Supplementary Information (SI). Supplementary information: experimental procedures, characterisation data, selected figures, crystallographic and computational details. See DOI: <https://doi.org/10.1039/d5sc05441a>.

CCDC 2467878 and 2467879 contain the supplementary crystallographic data for this paper.^{†3a,b}

Acknowledgements

Dedicated to Prof. Pedro J. Pérez on the occasion of his 60th birthday. We thank the Spanish Ministerio de Ciencia, Innovación y Universidades MICIN/AEI/10.13039/501100011033 (grant PID2023-150881NB-I00 for G. U. and PID2022-142270OB-I00 for A. J. M. M.), MICIN/NextGenerationEU/PRTR (CNS2022-136087), the European Research and Development Fund (ERDF) and the University of Huelva (EPTT1442023). I. I. acknowledges the AEI Research State Agency for an FPI Research Contract (PRE2020-094250). L. M.-C. acknowledges the support of the Generalitat de Catalunya (2021 FISDU 00034). Funding for open access was provided by the University of Huelva (CBUA).

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