ChemPlusChem | doi.org/10.1002/cplu.202000254



# Self-Assembly, Adaptive Response, and *in,out*-Stereoisomerism of Large Orthoformate Cryptands

Henrik Löw,[a] Elena Mena-Osteritz,[a] Kathleen M. Mullen,[b] Christof M. Jäger,*[c] and Max von Delius*[a]

*Dedicated to Prof. John A. Gladysz*

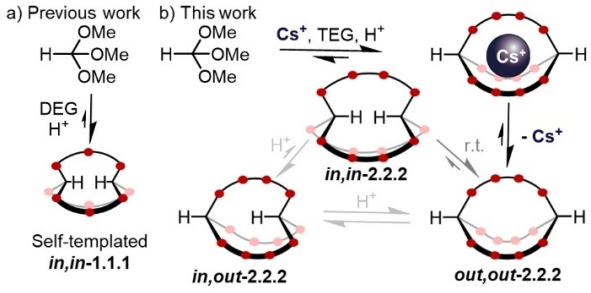
We report on triethylene glycol-based orthoformate cryptands, which adapt their bridgehead configurations in response to metal templates and intramolecular hydrogen bonding in a complex manner. In contrast to smaller **1.1.1**-orthoformate cryptands, the inversion from ***out,out*-2.2.2** to ***in,in*-2.2.2** occurs spontaneously by thermal homeomorphic isomerization, i.e., without bond breakage. The global thermodynamic minimum of the entire network, which includes an unprecedented third isomer (***in,out*-2.2.2**), could only be reached under conditions that facilitate dynamic covalent exchange. Both inversion processes were studied in detail, including DFT calculations and MD simulations, which were particularly helpful for explaining differences between equilibrium compositions in solvents chloroform and acetonitrile. Unexpectedly, the system could be driven to the ***in,out*-2.2.2** state by using a metal template with a size mismatch with respect to the ***out,out*-2.2.2** cage.

Certain macrocycles and macrobicycles (e.g. cryptands[1]) are subject to a type of stereoisomerism that results from different orientations of a substituent or lone pair at bridgehead atoms.[2] Many large macrocycles can, for instance, invert between *out,out*- and *in,in*-isomers *via* homeomorphic isomerization.[2a,3] In this process, the configuration at both bridgehead atoms is inverted by pulling one chain through the macrocycle defined by the other two chains.[4] Further examples for *in,out*-isomerization are based on protonation/deprotonation of Brønsted basic bridgehead atoms[4d,5] or pyramidal inversion of one bridgehead atom.[6] A case of bridgehead inversion by dynamic covalent chemistry (DCvC) was recently demonstrated by our own group in a study on small orthoformate *in,in*- and *out,out*-cryptands (Scheme 1a).[7]

We have recently utilized the dynamic covalent reaction[8] between orthoesters and diols[9] for the template synthesis of monometallic cryptates.[10] Most recently, we reported inherently dynamic architectures based on the acidic $NH_4^+$ template[11] and a "self-templated" orthoformate cryptand, which is stabilized by intramolecular hydrogen bonds (Scheme 1a).[7] This *in,in*-cryptand was found to undergo bridgehead inversion only *via* dynamic orthoester exchange.

Herein, we describe larger orthoformate cryptands that equilibrate between *out,out*-, *in,in*- and *in,out*-configurations by either homeomorphic isomerization or DCvC inversion (Scheme 1b).

Following up on our preliminary studies on orthoformate ***o*-$(H_{in})_2$-1.1.1** and ***o*-$(H_{out})_2$-1.1.1** cryptands and their bridgehead inversion by dynamic covalent exchange,[7] we aimed at exploring the potential *in,out*-isomerism of larger orthoformate **2.2.2**-cryptands. To this end, trimethoxy orthoformate and triethylene glycol (TEG) as ligand for cation binding were subjected to previously optimized conditions for orthoester exchange.[10a] By employing the large cesium template (CsBArF, see Figure S1 for $K_a$ determination), the desired cryptate [**$Cs^+\subset$*o*-$(H_{out})_2$-2.2.2**] was obtained in an isolated yield of 95%




**Scheme 1.** a) Previous work on self-templated cryptand ***o*-$(H_{in})_2$-1.1.1**.[7] b) Synthesis and adaptive response of larger orthoformate **2.2.2**-cryptands: *out,out*-, *in,in*- and *in,out*-cryptands.

[a] H. Löw, Dr. E. Mena-Osteritz, Prof. Dr. M. von Delius
Institute of Organic Chemistry
University of Ulm
Albert-Einstein-Allee 11, 89081 Ulm (Germany)
E-mail: max.vondelius@uni-ulm.de
[b] Dr. K. M. Mullen
School of Chemistry and Physics
Queensland University of Technology
Brisbane, Queensland, 4001 (Australia)
[c] Dr. C. M. Jäger
Department of Chemical and Environmental Engineering
University of Nottingham
University Park, Nottingham, NG7 2RD (United Kingdom)
E-mail: christof.jaeger@nottingham.ac.uk

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cplu.202000254

*This article is part of a Special Collection on "Supramolecular Chemistry: Young Talents and their Mentors". More articles can be found under https://onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)2192-6506.Supramolecular-Chemistry.*



(Figure 1a, **I**). To our initial surprise, the removal of $Cs^+$ by treatment with anion exchange resin (Cl form, for further details, see Supporting Information) did not lead to the formation of a single empty host, but to a mixture of two isomers. Structure elucidation efforts (NMR, HRMS, HPLC-MS, see Supporting Information) confirmed the presence of stereoisomers ***o*-($H_{out}$)$_2$-2.2.2** and ***o*-($H_{in}$)$_2$-2.2.2** (Figure 1a and b, **II**).

This finding can be rationalized by homeomorphic isomerization of the initially formed ***o*-($H_{out}$)$_2$-2.2.2**. Indeed, we were able to determine the $k_{obs}$ ($2.5\times10^{-5}$ $s^{-1}$ at r.t., $\triangle^{\neq}G^{\circ}=99$ kJ $mol^{-1}$, see Supporting Information) for this process by HPLC-MS monitoring of pristine ***o*-($H_{out}$)$_2$-2.2.2** (isolated by preparative HPLC).

In stark contrast to previously reported orthoformate **1.1.1**-cryptands and trithioformate cages,[7,12] the ring is sufficiently large to enable this isomerization[2a,3] and ***o*-($H_{out}$)$_2$-2.2.2** is thermodynamically favored over ***o*-($H_{in}$)$_2$-2.2.2** (2:1 molar ratio in $CD_3CN$, Figure 1c, **II**). In less polar solvent chloroform we observed an equimolar mixture of ***o*-($H_{out}$)$_2$-2.2.2** and ***o*-($H_{in}$)$_2$-2.2.2** (1:1 molar ratio in $CDCl_3$, see Supporting Information), which can be rationalized by a less effective completion of the solvent with the intramolecular hydrogen bonds. Addition of one equivalent of the $Cs^+$ template inverts ***o*-($H_{in}$)$_2$-2.2.2** quantitatively back to [$Cs^+\subset$***o*-($H_{out}$)$_2$-2.2.2**] within one day ($k_{obs}$ derived from NMR monitoring: $2.6\times10^{-5}$ $s^{-1}$, $\triangle^{\neq}G^{\circ}=99$ kJ $mol^{-1}$, see Supporting Information).

Subjecting the mixture of ***o*-($H_{out}$)$_2$-2.2.2** and ***o*-($H_{in}$)$_2$-2.2.2** to conditions of dynamic orthoester exchange (addition of 10 mol% TFA in $CH_3CN$) led to the formation of two additional signals in the NMR spectrum after two days (Figure 1b, **III**). Based on (2D-)NMR evidence, we suggest that this observation is due to the dynamic covalent inversion of one bridgehead atom from either ***o*-($H_{out}$)$_2$-2.2.2** or ***o*-($H_{in}$)$_2$-2.2.2**, giving a third isomer, namely ***o*-($H_{in}H_{out}$)-2.2.2**. Because under these conditions both homeomorphic and DCvC inversion are possible, we believe that this mixture corresponds to the global thermodynamic equilibrium of the network (molar ratio *out,out-*, *in,in-*, and *in,out-cryptand* ca. 2:1:2 in $CD_3CN$). In agreement with this reasoning, the reaction of trimethoxy orthoformate with triethylene glycol without metal template in $CHCl_3$ leads to the same mixture of *out,out-*, *in,in-*, and *in,out*-cryptands, albeit accompanied by a large fraction of oligomeric side products[13] (see Supporting Information).

Quantum chemical (QM) calculations and molecular-dynamics (MD) simulations were used to shed further light onto the stabilities and thermodynamic equilibrium of the different species in solution. While initial density functional theory (DFT) calculations *in vacuo* showed that cryptands ***o*-($H_{in}$)$_2$-2.2.2** and ***o*-($H_{in}H_{out}$)-2.2.2** are both enthalpically more stable than ***o*-($H_{out}$)$_2$-2.2.2** due to favorable intramolecular dispersion interactions (see Supporting Information), MD simulations revealed significant differences for the conformers in the two investigated solvent systems (Figure 2 and Table S7).

In $CHCl_3$, all structures lacking a stabilizing $Cs^+$ guest show significant structural flexibility. In case of $CH_3CN$, however, the *out,out*-isomer ***o*-($H_{out}$)$_2$-2.2.2** appears to be significantly more rigid (Figure 2a and b). The reason for this intriguing observation seems to be a well-defined structure that features association of the solvent into all three faces of the cryptands (see radial solvent distribution in Figure 2c and structure in Figure S5). This strong association is also reflected by high interaction energies between the cryptand and the $CH_3CN$ (42% higher than for ***o*-($H_{in}$)$_2$-2.2.2**) which leads to further enthalpic stabilization and shifts the equilibrium towards the ***o*-($H_{out}$)$_2$-2.2.2** in this solvent.

Christof Jäger is an assistant professor at the University of Nottingham working on computational chemistry in the field of enzyme design, biotechnology, supramolecular chemistry, and catalysis. Following his PhD in supramolecular computational chemistry at the Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg in Germany in 2010 and postdoctoral research on the design of organic electronic devices he moved to Nottingham in 2014. Since 2015 he worked as a Marie Curie COFUND and Nottingham Advanced Research Fellow on computational strategies for predictive enzyme engineering, before being promoted to his current position in 2018.

Max von Delius is a full professor at Ulm University in Southern Germany. His research interests include supramolecular chemistry, dynamic covalent reaction networks, and functional organic materials. He obtained his PhD in 2011 at the University of Edinburgh (Prof. David A. Leigh) and was a Leopoldina Postdoctoral Fellow at the University of Toronto (Prof. Vy M. Dong). In 2013 he returned to Germany (FAU Erlangen-Nürnberg) as an Emmy Noether junior research group leader and in 2016 he was appointed as an associate professor in Ulm. He was made full professor in 2019.

Both corresponding authors pursued their undergraduate studies at FAU Erlangen-Nürnberg, where Prof. John A. Gladysz taught, with great passion, the introductory lectures on organic chemistry and in 2004 organized a memorable trip to the ISHC-14 meeting in Munich. Our collaboration was born at a scientific meeting 12 years later (ICPOC, Sydney) and this special issue contribution builds on previous research by Prof. Gladysz, to whom we dedicate this work.

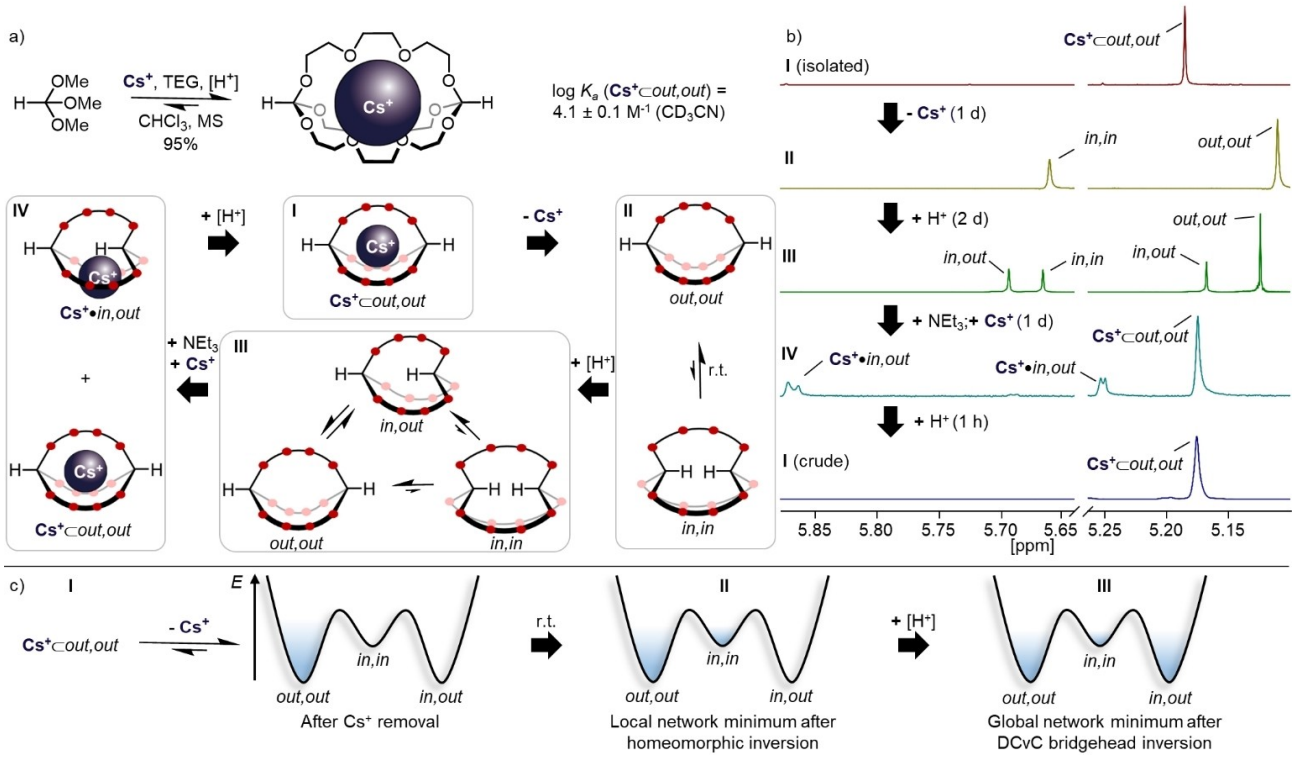



**Figure 1.** a) Synthesis and adaptive response of triethylene glycol-based orthoformate cryptands. Solvent: $CHCl_3$ for self-assembly, $CHCl_3$ or $CH_3CN$ for adaptive response reactions. $Cs^+$ = Cesium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (CsBArF), TEG = triethylene glycol, $H^+$ = 10% TFA, MS = 5 Å molecular sieves, $NEt_3$ = triethylamine. See Figure S1 for $K_a$ determination. b) Partial $^1$H NMR stack plot (500 MHz, 298 K, $CD_3CN$). c) Schematic energy diagrams for interconversion of orthoformate cryptands (based on $^1$H NMR integration, solvent: $CD_3CN$). For further details, see Supporting Information.

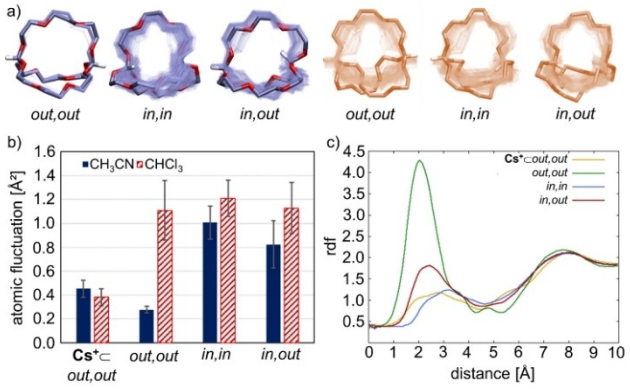



**Figure 2.** 1 μs long MD simulations (*out,out-*, *in,in-*, *in,out*-cryptand) reveal differences in flexibility and solvent association around cryptands. a) Representative structures and flexibilities (transparent structures) of cryptands in $CH_3CN$ (left) and $CHCl_3$ (right). b) Atomic fluctuations. c) Radial distribution function of $CH_3CN$ around cryptands.

To further explore the thermodynamic landscape that governs this remarkable dynamic network (Figure 1c), we quenched the mixture of ***o*-($H_{out}$)$_2$-2.2.2**, ***o*-($H_{in}$)$_2$-2.2.2** and ***o*-($H_{in}H_{out}$)-2.2.2** by addition of base and added $Cs^+$ ions to provide a thermodynamic driving force for the inversion from the *in,in-* to the *out,out*-isomer. As anticipated, after one day the $^1$H NMR spectrum revealed full conversion of ***o*-($H_{out}$)$_2$-2.2.2** and ***o*-($H_{in}$)$_2$-2.2.2** to [**$Cs^+$⊂*o*-($H_{out}$)$_2$-2.2.2**]. However, since inversion from the *in,out-* to the *out,out*-cryptand would require acid catalyst, the original portion of *in,out*-cryptand ***o*-($H_{in}H_{out}$)-2.2.2** remained unchanged, with the observed $^1$H NMR shifts suggesting the formation of the *exo* complex [**$Cs^+$•*o*-($H_{in}H_{out}$)-2.2.2**] (Figure 1b, **IV**). After acid was added to this mixture, we observed the quantitative formation of [**$Cs^+$⊂*o*-($H_{out}$)$_2$-2.2.2**] within one hour (Figure 1b, **I** (crude); for further details, see Supporting Information), which provides solid support for the full reversibility of all the complexation and inversion processes studied herein.

When $Na^+$ ions were used as metal template, the outcome of the self-assembly was different from the reaction with $Cs^+$. The smaller ionic radius of $Na^+$ favors the formation of the unsymmetric complex [**$Na^+$•*o*-($H_{in}H_{out}$)-2.2.2**] over [**$Na^+$⊂*o*-($H_{out}$)$_2$-2.2.2**] (Figure 3a, **I**, ratio 2:1 in $CD_3CN$). Removal of the metal ion from the mixture leads to a kinetically trapped mixture of the three isomers ***o*-($H_{out}$)$_2$-2.2.2**, ***o*-($H_{in}$)$_2$-2.2.2** and ***o*-($H_{in}H_{out}$)-2.2.2** (Figure 3a and b, **II**, ratio 3:1:10). Addition of acid catalyst to this mixture opens a pathway to the overall thermodynamic equilibrium between isomers ***o*-($H_{out}$)$_2$-2.2.2**, ***o*-($H_{in}$)$_2$-2.2.2** and ***o*-($H_{in}H_{out}$)-2.2.2** (Figure 3a and b, **III**, ratio 2:1:2). DFT calculations *in vacuo* at the ωB97XD[14]/aug-cc-pVTZ[15] level of theory (details in Supporting Information) indicate that the symmetric *endo* complex [**$Na^+$⊂*o*-($H_{out}$)$_2$-2.2.2**] is more stable than the less symmetric [**$Na^+$•*o*-($H_{in}H_{out}$)-2.2.2**] complex (see Table S8). The calculations also reveal multiple stable associations of $Na^+$ to ***o*-($H_{in}H_{out}$)-2.2.2** based on

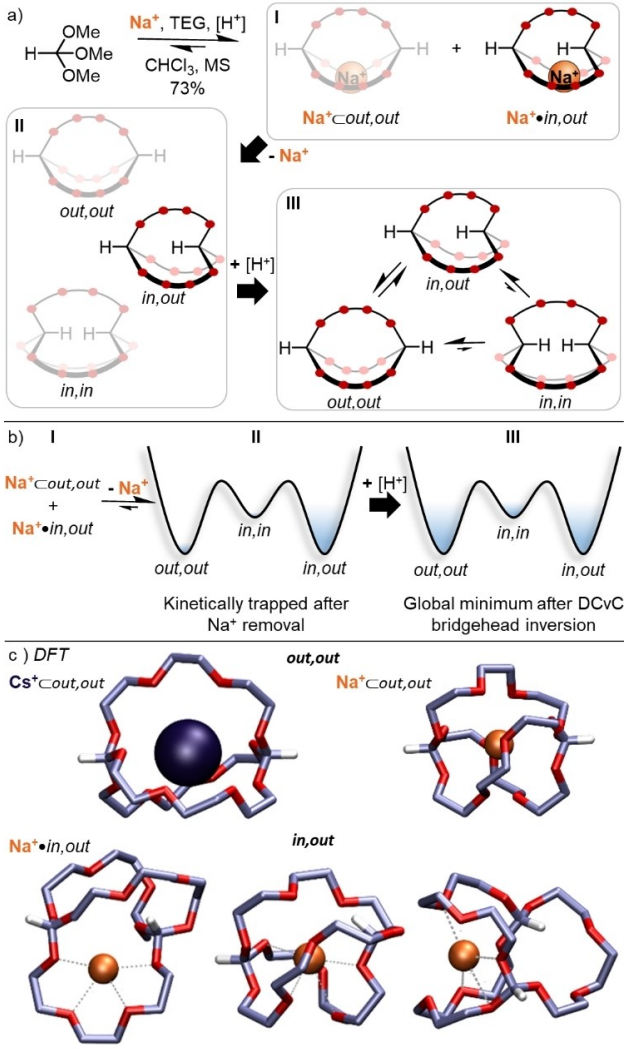



**Figure 3.** a) Synthesis and adaptive response of triethylene glycol-based orthoformate cryptands with $Na^+$ as metal template. Solvent: $CHCl_3$ for self-assembly, $CHCl_3$ or $CH_3CN$ for adaptive response reactions. $Na^+$ = Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF), TEG = triethylene glycol, $H^+$ = 10% TFA, MS = 5 Å molecular sieves. b) Schematic energy diagrams for interconversion of orthoformate cryptands (based on $^1$H NMR integration, solvent: $CD_3CN$). For further details, see Supporting Information. c) DFT-optimized structures of $Cs^+$ and $Na^+$ bound to ***o*-($H_{out}$)$_2$-2.2.2** and ***o*-($H_{in}H_{out}$)-2.2.2**.

interactions of the metal ion with either one or two TEG chains and additional hydrogen bonds between the methine hydrogen atom and ether oxygen atoms (Figure 3c). These asymmetric associations also show stability in MD simulations. Moreover, the symmetric [**$Na^+$⊂*o*-($H_{out}$)$_2$-2.2.2**] complex displays a significant contraction of the cryptand with a high coordination number for $Na^+$ which might be unfavorable in solution. The multitude of possible [**$Na^+$•*o*-($H_{in}H_{out}$)-2.2.2**] association complexes thus might explain their favored formation over [**$Na^+$⊂*o*-($H_{out}$)$_2$-2.2.2**].

To obtain structural insights into the triethylene glycol-based orthoformate cryptands, we grew single crystals of [**$Cs^+$⊂*o*-($H_{out}$)$_2$-2.2.2**]$BArF^-$ by slow diffusion of hexane into chloroform solutions (Figure 4). The cryptate features the

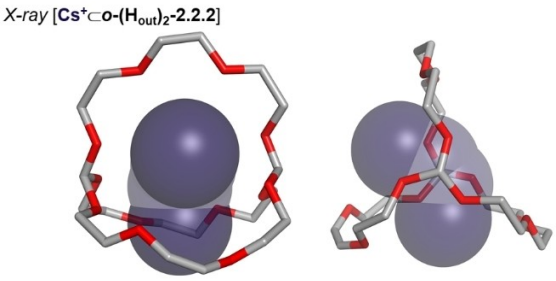



**Figure 4.** Solid-state structure of [**$Cs^+$⊂*o*-($H_{out}$)$_2$-2.2.2**]. Single crystals were obtained by the layering method (hexane/chloroform). Hydrogen atoms, anions and solvent are omitted for clarity. Metal ions are displayed with 2×40% and 2×10% chemical occupancy and at 100% of effective ionic radius.[17] CCDC 1875501 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

encapsulation of one cesium ion at four positions (with an occupancy of 2×40% and 2×10%). In the two positions with 40% occupancy, the binding geometry for cesium resembles the one found in large crown ethers[16] (seven Cs–O bonds, 3.01-3.59 Å), but overall we would nevertheless classify the observed structure as an *endo* complex. These structural characteristics are also remarkably well resembled in MD simulations (Figure S6) showing comparable flexible and slightly asymmetric binding of $Cs^+$ in the cavity.

Similar to the previously reported solid-state structure of [**$Cs^+$⊂*o*-($CH_3$)$_2$-2.2.1**],[10c] Cs–F bonds (3.53 Å) between the metal ion and the BArF counter-anion lead to the formation of a helical coordination polymer in the solid state (Figure S7). Additionally, the average torsion angle (H–C–O–$Cs^+$ dihedrals) of 155° supports our previously described hypothesis[6] that orthoformate cryptates tend to adopt a distorted geometry (Graph S9) compared to the corresponding orthoacetate cryptates, in which this angle is typically very close to 180°. In other words, orthoformate cryptands have smaller cavities than all other orthoester cryptands prepared to date,[10a] which needs to be considered, when predicting effective host-guest pairs (Table S1).

In conclusion, we were able to make use of the antagonism between metal template binding and intramolecular hydrogen bonding to generate different dynamic mixtures of *out,out*-, *in,in*- and *in,out*-cryptands. Both key processes, the homeomorphic inversion without bond breakage and the bridgehead inversion by DCvC were studied in different solvents and understood in detail.

## Acknowledgements

*This work was supported by the European Union (ERCstg 802428 "SUPRANET"), the Deutsche Forschungsgemeinschaft (Emmy-Noether grant DE1830/2-1) and the Deutscher Akademischer Austauschdienst DAAD (mobility grant to HL). CMJ gratefully acknowledges support and access to the University of Nottingham High Performance Computing Facility.*

## Conflict of Interest

*The authors declare no conflict of interest.*

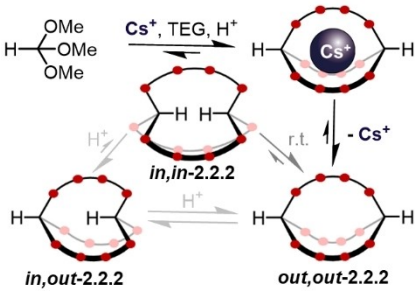
**Keywords:** dynamic covalent chemistry · host-guest chemistry · molecular-dynamics · self-assembly · stereoisomerism

[1] M. Kołodziejski, A. R. Stefankiewicz, J. M. Lehn, *Chem. Sci.* **2019**, *10*, 1836–1843.
[2] a) R. W. Alder, S. P. East, *Chem. Rev.* **1996**, *96*, 2097–2111; b) R. W. Alder, *Tetrahedron* **1990**, *46*, 683–713.
[3] C. H. Park, H. E. Simmons, *J. Am. Chem. Soc.* **1968**, *90*, 2429–2431.
[4] a) M. Stollenz, N. Bhuvanesh, J. H. Reibenspies, J. A. Gladysz, *Organometallics* **2011**, *30*, 6510–6513; b) S. Kharel, H. Joshi, S. Bierschenk, M. Stollenz, D. Taher, N. Bhuvanesh, J. A. Gladysz, *J. Am. Chem. Soc.* **2017**, *139*, 2172–2175; c) M. Stollenz, M. Barbasiewicz, A. J. Nawara-Hultzsch, T. Fiedler, R. M. Laddusaw, N. Bhuvanesh, J. A. Gladysz, *Angew. Chem. Int. Ed.* **2011**, *50*, 6647–6651; *Angew. Chem.* **2011**, *123*, 6777–6781; d) A. H. Haines, P. Karntiang, *J. Chem. Soc. Perkin Trans. 1* **1979**, 2577–2587; e) M. Saunders, N. Krause, *J. Am. Chem. Soc.* **1990**, *112*, 1791–1795; f) R. S. Wareham, J. D. Kilburn, D. L. Turner, N. H. Rees, D. S. Holmes, *Angew. Chem. Int. Ed.* **1995**, *34*, 2660–2662; *Angew. Chem.* **1995**, *107*, 2902–2904.
[5] a) R. W. Alder, D. Read, *Angew. Chem. Int. Ed.* **2000**, *39*, 2879–2882; *Angew. Chem.* **2000**, *112*, 3001–3004; b) J.-M. Lehn, *Angew. Chem. Int. Ed.* **1988**, *27*, 89–112; *Angew. Chem.* **1988**, *100*, 91–116; c) R. A. Bell, G. G. Christoph, F. R. Fronczek, R. E. Marsh, *Science* **1975**, *190*, 151–152; d) C. H. Park, H. E. Simmons, *J. Am. Chem. Soc.* **1968**, *90*, 2431–2432; e) R. W. Alder, *J. Chem. Soc. Perkin Trans. 2* **2001**, 288–295; f) L. R. MacGillivray, J. L. Atwood, *Angew. Chem. Int. Ed.* **1996**, *35*, 1828–1830; *Angew. Chem.* **1996**, *108*, 1937–1939; g) L. R. MacGillivray, J. L. Atwood, *J. Org. Chem.* **1995**, *60*, 4972–4973; h) S. O. Kang, J. M. Llinares, V. W. Day, K. Bowman-James, *Chem. Soc. Rev.* **2010**, *39*, 3980–4003; i) P. Morehouse, M. A. Hossain, J. M. Llinares, D. Powell, K. Bowman-James, *Inorg. Chem.* **2003**, *42*, 8131–8133; j) B. Pool, S. Balalaie, A. Kunze, G. Schilling, P. Bischof, R. Gleiter, *Eur. J. Org. Chem.* **2004**, 2812–2817; k) L. Bonnot, J. C. Chambron, E. Espinosa, K. Bernauer, U. Scholten, R. Graff, *J. Org. Chem.* **2008**, *73*, 7871–7881; l) P. B. Smith, J. L. Dye, J. Cheney, J.-M. Lehn, *J. Am. Chem. Soc.* **1981**, *103*, 6044–6048.
[6] a) M. Stollenz, D. Taher, N. Bhuvanesh, J. H. Reibenspies, Z. Baranová, J. A. Gladysz, *Chem. Commun.* **2015**, *51*, 16053–16056; b) S. Kharel, T. Jia, N. Bhuvanesh, J. H. Reibenspies, J. Blümel, J. A. Gladysz, *Chem. Asian J.* **2018**, *13*, 2632–2640; c) R. W. Alder, E. Honegger, A. B. Mcewen, R. E. Moss, E. Olefirowicz, P. A. Petillo, R. B. Sessions, G. R. Weisman, J. M. White, Z. Yang, *J. Am. Chem. Soc.* **1993**, *115*, 6580–6591.
[7] H. Löw, E. Mena-Osteritz, M. von Delius, *Chem. Commun.* **2019**, *55*, 11434–11437.
[8] a) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711; b) J. Li, P. Nowak, S. Otto, *J. Am. Chem. Soc.* **2013**, *135*, 9222–9239; c) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *Curr. Opin. Chem. Biol.* **2002**, *6*, 321–327; d) R.-C. Brachvogel, M. von Delius, *Eur. J. Org. Chem.* **2016**, *2016*, 3662–3670; e) Q. Ji, R. C. Lirag, O. Š. Miljanić, *Chem. Soc. Rev.* **2014**, *43*, 1873–1884; f) A. Herrmann, *Chem. Soc. Rev.* **2014**, *43*, 1899–1933; g) A. Wilson, G. Gasparini, S. Matile, *Chem. Soc. Rev.* **2014**, *43*, 1948–1962; h) F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211–2221; i) S. L. Diemer, M. Kristensen, B. Rasmussen, S. R. Beeren, M. Pittelkow, *Int. J. Mol. Sci.* **2015**, *16*, 21858–21872.
[9] R.-C. Brachvogel, M. von Delius, *Chem. Sci.* **2015**, *6*, 1399–1403.
[10] a) H. Löw, E. Mena-Osteritz, M. von Delius, *Chem. Sci.* **2018**, *9*, 4785–4793; b) R.-C. Brachvogel, F. Hampel, M. von Delius, *Nat. Commun.* **2015**, *6*, 7129; c) O. Shyshov, R. C. Brachvogel, T. Bachmann, R. Srikantharajah, D. Segets, F. Hampel, R. Puchta, M. von Delius, *Angew. Chem. Int. Ed.* **2017**, *56*, 776–781; *Angew. Chem.* **2017**, *129*, 794–799.
[11] X. Wang, O. Shyshov, M. Hanzevacki, C. M. Jäger, M. von Delius, *J. Am. Chem. Soc.* **2019**, *141*, 8868–8876.
[12] M. S. Collins, T. A. Shear, E. K. Smith, S. M. Strain, L. N. Zakharov, D. W. Johnson, *Chem. Eur. J.* **2019**, *25*, 13290–13293.
[13] We note that the formation of oligomers is only observed during self-assembly (i.e. starting from trimethyl orthoformate), but not during adaptive response (i.e. starting from cryptand) experiments. We believe this could be due to a combination of three differences in the reaction conditions: (i) methanol is generated during self-assembly experiments; (ii) oligomer formation is favoured in chloroform (self-assembly) and suppressed in acetonitrile (adaptive response), which is in agreement with our DFT studies (Figure 2); (iii) for practical reasons, self-assembly reactions were performed at higher concentration than adaptive response studies.
[14] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[15] R. A. Kendall, T. H. Dunning, R. J. Harrison, *J. Chem. Phys.* **1992**, *96*, 6796–6806.
[16] a) T. G. Levitskaia, J. C. Bryan, R. A. Sachleben, J. D. Lamb, B. A. Moyer, *J. Am. Chem. Soc.* **2000**, *122*, 554–562; b) J. C. Bryan, B. P. Hay, *Struct. Chem.* **2001**, *12*, 283–290.
[17] R. D. Shannon, *Acta Crystallogr.* **1976**, *A32*, 751–767.

Manuscript received: March 31, 2020
Revised manuscript received: April 16, 2020
Accepted manuscript online: April 19, 2020

# COMMUNICATIONS

**Shake it all about**: Large orthoester cryptands have been shown to be dynamic on three different levels: they can spontaneously turn themselves inside-out in a process called homeomorphic isomerization; they interconvert in the presence of acid by dynamic covalent orthoester exchange, which furnishes an unusual *in,out*-stereoisomer; they bind metal ions, and this host–guest chemistry has a strong impact on both homeomorphic and dynamic covalent bridgehead inversion.




*H. Löw, Dr. E. Mena-Osteritz, Dr. K. M. Mullen, Dr. C. M. Jäger*, Prof. Dr. M. von Delius**