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Adaptive Behavior of Dynamic Orthoester Cryptands

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Abstract: *The integration of dynamic covalent bonds into macrocycles has been a tremendously successful strategy for investigating noncovalent interactions and identifying effective host–guest pairs. While numerous studies have focused on the dynamic responses of macrocycles and larger cages to various guests, the corresponding constitutionally dynamic chemistry of cryptands remains unexplored. Reported here is that cryptands based on orthoester bridgeheads offer an elegant entry to experiments in which a metal ion selects its preferred host from a dynamic mixture of competing subcomponents. In such dynamic mixtures, the alkali metal ions Li*$^+$*, Na*$^+$*, K*$^+$*, Rb*$^+$*, and Cs*$^+$ *exhibit pronounced preferences for the formation of cryptands of certain sizes and donor numbers, and the selection is rationalized by DFT calculations. Reported is also the first self-assembly of a chiral orthoester cryptate and a preliminary study on the use of stereoisomers as subcomponents.*

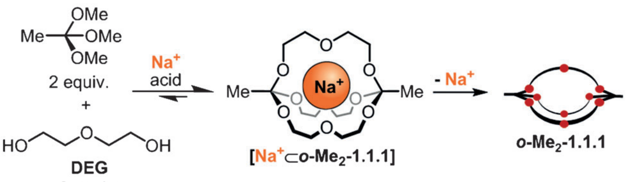
The unique feature of dynamic covalent bonds, their stability or dynamics depending on the reaction conditions, has led to diverse applications in chemistry and adjacent disciplines.[1] In supramolecular host–guest chemistry, the integration of dynamic covalent bonds into macrocycles,[2] their combination with metal–ligand interactions,[3] and the structural response of macrocyclic systems to (ionic) guests have recently attracted considerable interest.[4]

The majority of constitutionally dynamic metal-ligand cages are rigid and positively charged, a property which makes them an ideal platform for the binding and recognition of anions. The groups of Nitschke,[5] Clever,[6] and others[7] have recently reported impressive examples of adaptive cage transformations in response to different anions. Besides metal-ligand cages, there have been numerous studies on the adaptive behavior of dynamic combinatorial macrocycles in response to guests.[1f,8] However, in most examples reported to date, the selection occurs between oligomeric species, for example, dimeric and trimeric species compete for guest binding. Studies in which adaptive behavior is based on subcomponent selection and subtle architectural differences between competing organic hosts are rare.[2c,9]

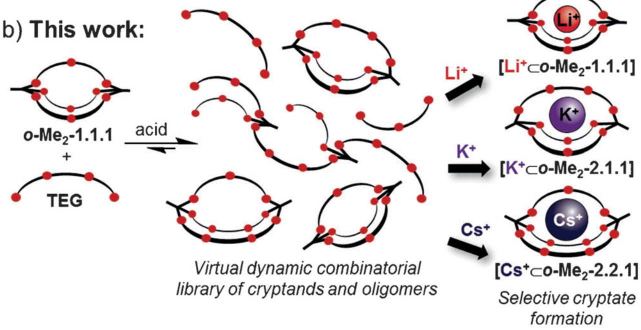
As the smallest three-dimensional hosts, dynamic cryptands represent an attractive, yet practically unexplored[10] area of chemical (host–guest) space. We have recently reported the first dynamic covalent self-assembly of a monometallic cryptate[11] (**[Na$^+\subset$*o*-Me$_2$-1.1.1]**), which was based on the reversible, acid-catalyzed reaction of a simple orthoester with diethylene glycol (Scheme 1 a).[12] Herein, we report the adaptive behavior of orthoester cryptands in response to cationic guests (Scheme 1 b).

In a first series of experiments, we tested whether the orthoester cyptand ***o*-Me$_2$-1.1.1** would respond to the addition of mismatched metal guests by either a dynamic covalent shrinkage or expansion event (Scheme 2 a). The combination of one equivalent of LiTPFPB (lithium tetrakis(pentafluorophenyl)borate), ethylene glycol, and acid catalyst, for instance, should lead to the formation of the shrunken cryptate **[Li$^+\subset$*o*-Me$_2$-1.1.0]**, if this host-guest pair repre-

a) **Self-assembly of an orthoester cryptate[11]:**



b) **This work:**



Scheme 1. a) Sodium-templated self-assembly of the orthoester cryptate **[Na$^+\subset$*o*-Me$_2$-1.1.1]** and subsequent preparation of cryptand ***o*-Me$_2$-1.1.1**. b) Adaptive behavior of ***o*-Me$_2$-1.1.1** in the presence of triethylene glycol (TEG), catalytic acid, and selected guest ions. DEG = diethylene glycol.

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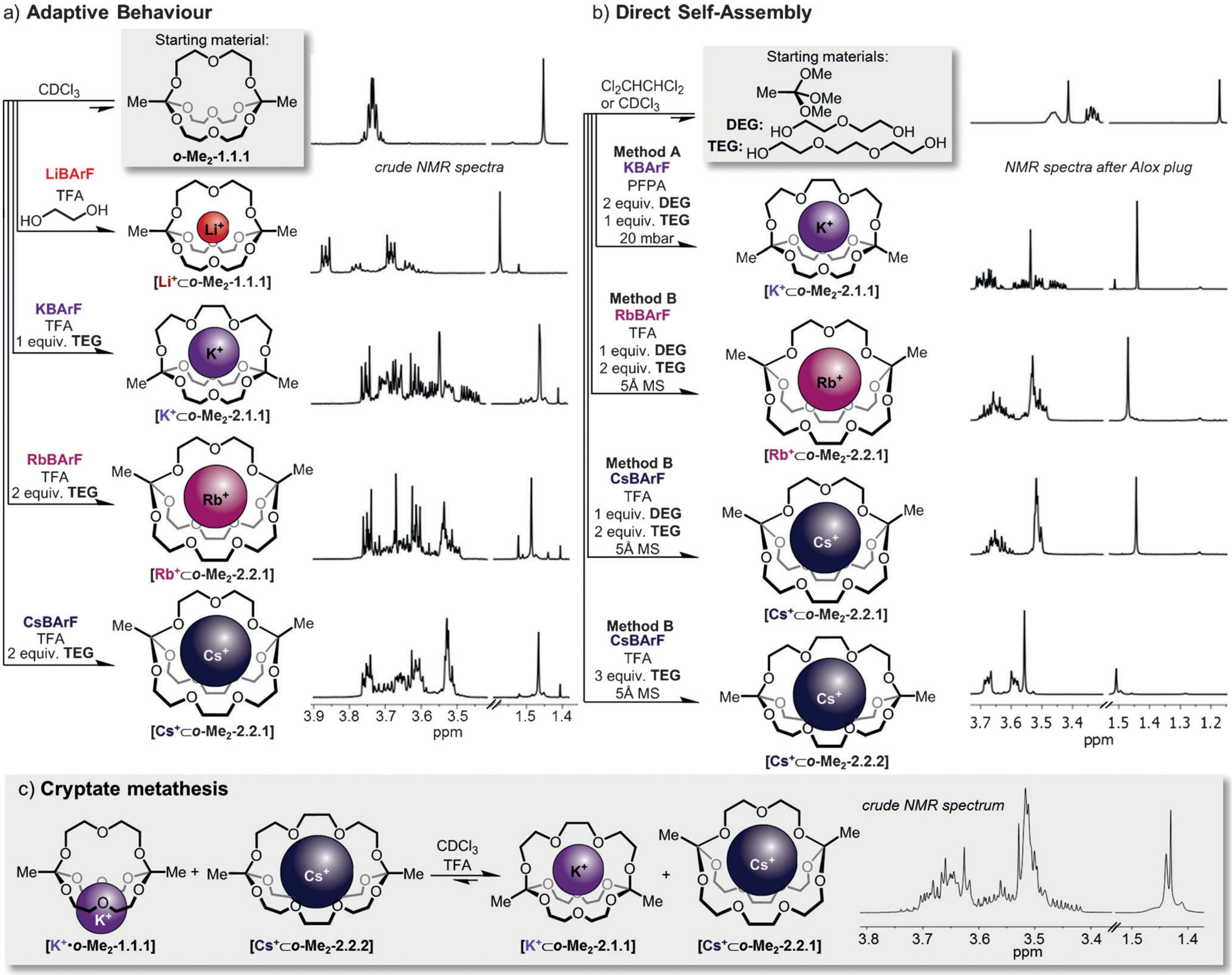


Scheme 2. a) Adaptive behavior of **o-Me$_2$-1.1.1** in the presence of different diols and metal ions. Reaction conditions: 5 mmol **o-Me$_2$-1.1.1**, 5 mmol metal salt, 5–10 mmol **TEG**, and 0.5 mmol TFA in CDCl$_3$; equilibration time: 3–6 hours, yields (NMR) 20–83% (for further experiments see Supporting Information). b) Direct self-assembly of the different orthoester cryptates. Method A: 5 mmol metal salt, 5–10 mmol **TEG**, 5–10 mmol DEG, 1.5 mmol PFPA, 1,1,2,2-tetrachloroethane, 20 mbar, yield (isolated) 39–55%. Method B: 5 mmol metal salt, 0–5 mmol TEG, 10–15 mmol DEG, 1.5 mmol TFA, 1.5 mL CDCl$_3$, 5 Å M.S. (ca. 0.5 g), yield (isolated) 27–49%. BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, DEG = diethylene glycol, PFPA = perfluoropentanoic acid, TEG = triethylene glycol, TFA = trifluoroacetic acid.

sented the thermodynamic minimum. In the corresponding experiment, we found that the dynamic system remained mainly at the **[Li$^+$⊂*o*-Me$_2$-1.1.1]** state, thus indicating that the cryptand ***o*-Me$_2$-1.1.0** is either too small to accommodate Li$^+$ or that binding to a host with one additional oxygen donor atom outweighs a possible preference for the smaller host. It is worth noting that **[Li$^+$⊂*o*-Me$_2$-1.1.1]** does not only outcompete the alternative host ***o*-Me$_2$-1.1.0**, but also five-membered ring products derived from an addition of both alcohol functions in ethylene glycol to the orthoester.[12a]

When we studied larger alkali metal ions in combination with longer diol triethylene glycol (TEG), we observed that these metals exhibit pronounced preferences for the formation of certain orthoester hosts. The selectivity becomes evident by the appearance of only one predominant signal in the methyl region of the ^{1}H NMR spectra of the crude mixture in each of these experiments (Scheme 2a). For example, potassium directs the dynamic system almost exclusively towards the formation of the cryptand ***o*-Me$_2$-2.1.1**, whereas both rubidium and cesium direct towards ***o*-Me$_2$-2.2.1**. All these experiments were independently conducted with zero, one, two, and three equivalents of TEG, because the quantity of this subcomponent represents a bias for the formation of certain species. Throughout these experiments we found preferences for the same cryptates, even in cases where the amount of TEG should favor other reaction products (see the Supporting Information for all experiments).

These template-based desymmetrization reactions are also remarkable from a synthetic perspective, because conventional unsymmetric cryptands require multistep syntheses.[13] However, having to synthesize a symmetric cryptand en route to an unsymmetric one, does not meet the requirements of any modern metric of synthesis efficiency.[14]

As a result, we focused our efforts on the direct self-assembly of unsymmetric orthoester cryptates. To achieve this, we needed to identify reaction conditions under which methanol could be slowly removed from equilibrium, while no source of sodium ions [e.g. 4 Å molecular sieves (M.S.)] is present, because the latter would lead to the formation of the symmetric cryptate **[Na$^+$$\subset$*o*-Me$_2$-1.1.1]**.[11] As shown in Scheme 2b, two such methods, based on either reduced pressure or 5 Å M.S. (containing Ca^{2+} ions) could be identified, thus leading to the preparation of the desired unsymmetric cryptates in yields of 27–55 %.

In light of possible applications it is worth noting that all cryptands can conveniently be prepared in quantitative yield from the corresponding cryptates by treatment with ion-exchange resin (see the Supporting Information). We were also able to prepare the symmetric cryptate **[Cs$^+$$\subset$*o*-Me$_2$-2.2.2]**, which interestingly, was not observed in previous experiments, where this compound would have been a possible product. The preference of Cs^+ for the cryptand ***o*-Me$_2$-2.2.1** was confirmed by a shrinkage experiment, in which **[Cs$^+$$\subset$*o*-Me$_2$-2.2.2]**, under reaction conditions for orthoester exchange was treated with DEG, and **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]** was observed as predominant product (see the Supporting Information).[16]

Adaptive behavior at a higher level of complexity was observed in the multi-metal/multi-cryptand exchange experiment illustrated in Scheme 2c. The symmetric cryptands ***o*-Me$_2$-1.1.1** and ***o*-Me$_2$-2.2.2** were combined with mismatched[17] metal ions K^+ and Cs^+, and orthoester exchange was initiated by addition of acid. The NMR spectrum of the crude mixtures after equilibration and the ESI$^+$ mass spectrum after work-up (see the Supporting Information) clearly demonstrate that a 1:1 mixture of the unsymmetric cryptates **[K$^+$$\subset$*o*-Me$_2$-2.1.1]** and **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]** was formed. Even though we cannot deduce from our data which one of the two host–guest pairs provides the main thermodynamic driving force, this cryptate metathesis is nevertheless a remarkable case of adaptive behavior.

To shed further light on the underlying noncovalent interactions, we grew single crystals from all cryptates which represented preferred species in self-assembly experiments. The resulting X-ray structures are depicted in Figure 1a, along with the structure of previously reported **[Na$^+$$\subset$*o*-Me$_2$-1.1.1]**. Relatively symmetric coordination geometries are adopted in the cryptates **[K$^+$$\subset$*o*-Me$_2$-2.1.1]**, **[Rb$^+$$\subset$*o*-Me$_2$-2.2.1]**, and **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]**, while the unique combination of orthoester bridgeheads with glycol side chains results in the formation of up to eleven metal–oxygen bonds. An apparent limit for binding is reached with the cryptand ***o*-Me$_2$-2.2.2**, which only forms eleven out of twelve possible Cs–O bonds. This observation might explain why **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]** is the preferred species in experiments where ***o*-Me$_2$-2.2.1** and ***o*-Me$_2$-2.2.2** compete for Cs^+. An unusual type of anisotropic long-range order was observed in the crystal structure of **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]**: the presence of Cs–F bonds between counteranion and cryptates results in the formation of a helical coordination polymer (see the Supporting Information for the packing diagram).

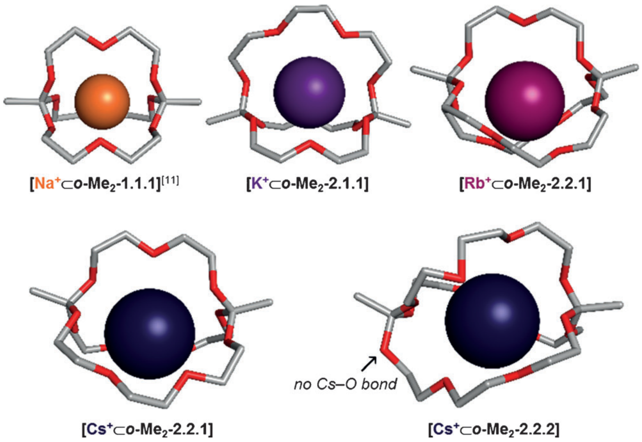


Figure 1. a) Solid-state structures of five orthoester cryptates.[21] The structure of **[Na$^+$$\subset$*o*-Me$_2$-1.1.1]** was reported previously[11] and is shown for comparison. Single crystals of **[K$^+$$\subset$*o*-Me$_2$-2.1.1]** were obtained by the vapor diffusion method (cyclopentane/ chloroform). Single crystals of **[Rb$^+$$\subset$*o*-Me$_2$-2.2.1]**, **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]**, and **[Cs$^+$$\subset$*o*-Me$_2$-2.2.2]** were obtained by the layering method (*n*-heptane/ chloroform). Hydrogen atoms, anions, solvent, and disorder (where applicable) are omitted for clarity. Metal ions are displayed at 100% of effective ionic radius.[15] Selected bond length ranges: Na–O: 2.5–2.6 Å; K–O: 2.8–3.0 Å; Rb–O: 3.0–3.3 Å; Cs–O: 3.2–3.3 Å in **[Cs$^+$$\subset$*o*-Me$_2$-2.2.1]**; Cs–O: 3.1–3.7 Å (binding) and 4.4 Å (nonbinding) in **[Cs$^+$$\subset$*o*-Me$_2$-2.2.2]**.

Because some of our experiments represent a stoichiometrically unbiased[18] competition between two dynamic cryptands for a metal ion, we wanted to test, whether the observed trends could be rationalized by theory. In a first set of DFT-based (B3LYP/LANL2DZp) model equations (see the Supporting Information for details), we determined complexation energies for the combination of the cryptands ***o*-Me$_2$-1.1.0**, ***o*-Me$_2$-1.1.1**, ***o*-Me$_2$-2.1.1**, ***o*-Me$_2$-2.2.1**, and ***o*-Me$_2$-2.2.2** with five alkali metal ions.[19] We also carried out NMR titrations for all 20 host-guest combinations, as well as one representative isothermal titration calorimetry (ITC) study, which revealed that sodium binding to ***o*-Me$_2$-1.1.1** is driven both enthalpically and entropically (see the Supporting Information).

With the exception of two outliers (**[Li$^+$$\subset$*o*-Me$_2$-1.1.1]** and **[Rb$^+$$\cdot$*o*-Me$_2$-1.1.1]**), we observed good agreement between the trends in experiment (Figure 2a) and theory (Figure 2b). More importantly, the relative binding energies do indeed allow rationalizing our findings on adaptive behavior. For instance, K^+ represents a clear minimum for ***o*-Me$_2$-2.1.1** (Figure 2a and 2b), thus explaining the predominant formation of **[K$^+$$\subset$*o*-Me$_2$-2.1.1]** in the experiment shown in Scheme 2a. It is also evident from the data that binding of Rb^+ and Cs^+ only becomes favorable for the larger cryptands ***o*-Me$_2$-2.2.1** and ***o*-Me$_2$-2.2.2**. The flat line observed in the computational binding energies for ***o*-Me$_2$-1.1.0** (Figure 2b) suggests that no alkali-metal ion fits into this host, and would explain why not even the small Li^+ template led to its formation.

A second set of model equations was designed to more adequately mimic the competition of two cryptands for cation binding. For each metal ion, these calculations revealed

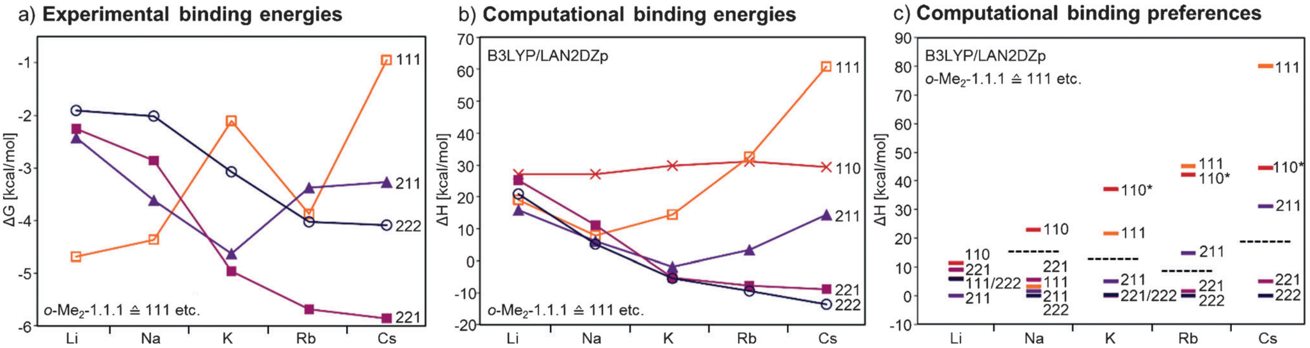
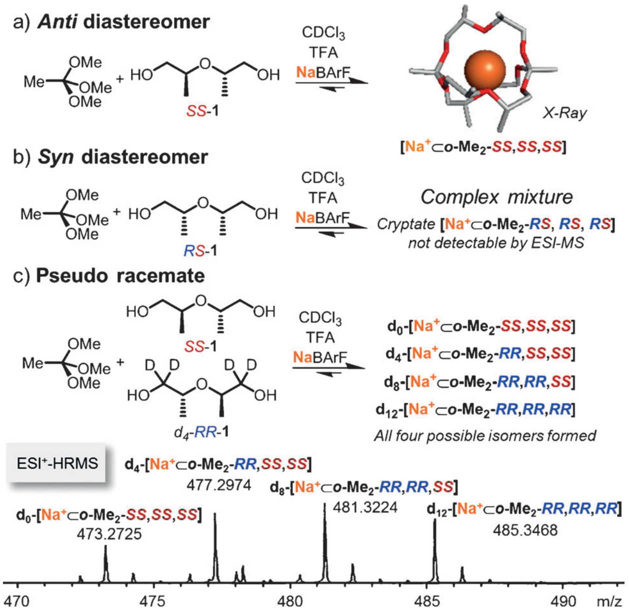


Figure 2. a) Experimental binding energies determined by ^{1}H NMR titrations and data fitting ([D$_3$]acetonitrile, 298 K). b) Computational binding enthalpies (B3LYP/LANL2DZp; gas phase) based on a model equation that mimics the transfer of a metal ion from sixfold water coordination to the orthoester cryptand. c) Computational binding enthalpies (B3LYP/LANL2DZp; gas phase) based on a model equation that mimics the transfer of a metal ion from one orthoester cryptand to another. *: metal was expelled from cage as a result of DFT calculation. See the Supporting Information for experimental/computational details and a discussion of the limitations of the DFT calculations.

energy differences between five host-guest species (Figure 2c). Although these calculations fail to correctly predict all experimental outcomes (for example, ***o*-Me$_2$-2.1.1** should represent the minimum in the case of K$^+$), they do reveal relatively large energy cutoffs above which a metal ion seemingly is too large to fit into the cavity of the host (highlighted by dashed lines).

Finally, we turned our attention to more complex subcomponents, from which stereochemical insights could be gained.[20] When enantiopure diol *SS*-**1** was subjected to standard self-assembly conditions, the corresponding homochiral cryptate **[Na$^+$$\subset$*o*-Me$_2$-*SS*,*SS*,*SS*]** formed as the predominant product (Scheme 3a). Interestingly, the corresponding *meso* diastereomer *RS*-**1** failed to produce detectable quantities of the corresponding cryptate under identical reaction conditions (Scheme 3b). A complex mixture of species formed instead (see the Supporting Information), thus indicating that the self-assembly is highly sensitive to conformational differences between diastereomers.

To study a racemic mixture of diols, we prepared the deuterated compound d$_4$-*RR*-**1**, which was subsequently mixed (1:1) with *SS*-**1** to form a pseudo-racemate (Scheme 3c). Because orthoester cryptands comprise an uneven number of diol building blocks, we wondered whether only the homochiral cryptates would form or if opposite enantiomers could be incorporated into the bicyclic structure. Analysis of the reaction outcome by NMR spectroscopy and mass spectrometry revealed that the latter is the case: all four possible cryptate species were formed in roughly statistical mixture.



Scheme 3. a) Self-assembly of a chiral cryptate based on diol *SS*-**1**. Solid-state structure of **[Na$^+$$\subset$*o*-Me$_2$-*SS*,*SS*,*SS*]**.[21] Single crystals were obtained by the vapor diffusion method (CDCl$_3$/ cyclopentane). Hydrogen atoms, anions, and solvent are omitted for clarity. Na–O bond length range: 2.4–2.8 Å. b) Attempted self-assembly based on the *meso* diol *RS*-**1** (no cryptate formation observed by either NMR spectroscopy or ESI$^+$-MS). c) Self-assembly based on pseudo-racemate: 1:1 mixture of *SS*-**1** and deuterated enantiomer d$_4$-*RR*-**1**. Formation of a statistical mixture of all four cryptate stereoisomers, as indicated by ESI$^+$-HRMS (bottom). Reaction conditions: trimethyl orthoacetate (0.12 mmol, 2.0 equiv), diol (0.18 mmol, 3.0 equiv), NaBArF (0.06 mmol, 1.0 equiv), TFA (trifluoroacetic acid, 1.2 μmol, 2 mol%) in 6 mL CDCl$_3$ with 5 Å M.S. Yields: 15–53%.

In conclusion, we have demonstrated that dynamic orthoester cryptands can shrink or expand by subcomponent exchange in response to the addition of alkali-metal ions. We found that certain host-guest pairs represent pronounced thermodynamic minima, which allowed us to use spherical metal templates for the desymmetrization of symmetric cryptands and to carry out an unprecedented cryptate metathesis reaction. We now plan to extend this concept to the combination of transition metals with diols featuring heteroatoms other than oxygen, where added selectivity based on the HSAB principle and applications in sensing and delivery might become viable.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cryptands · dynamic combinatorial chemistry · host–guest chemistry · NMR spectroscopy · supramolecular chemistry

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[1] a) E. Moulin, G. Cormos, N. Giuseppone, *Chem. Soc. Rev.* **2012**, *41*, 1031 – 1049; b) Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634 – 6654; c) J. Li, P. Nowak, S. Otto, *J. Am. Chem. Soc.* **2013**, *135*, 9222 – 9239; d) Y. Jin, Q. Wang, P. Taynton, W. Zhang, *Acc. Chem. Res.* **2014**, *47*, 1575 – 1586; e) G. Zhang, M. Mastalerz, *Chem. Soc. Rev.* **2014**, *43*, 1934 – 1947; f) A. Herrmann, *Chem. Soc. Rev.* **2014**, *43*, 1899 – 1933; g) A. G. Slater, A. I. Cooper, *Science* **2015**, *348*, aaa8075.

[2] a) S. J. Rowan, P. A. Brady, J. K. M. Sanders, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2143 – 2145; *Angew. Chem.* **1996**, *108*, 2283 – 2285; b) S. J. Rowan, D. G. Hamilton, P. A. Brady, J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, *119*, 2578 – 2579; c) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *Science* **2002**, *297*, 590 – 593.

[3] a) B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956 – 10962; b) K. S. Chichak, S. J. Cantrill, A. R. Pease, S.-H. Chiu, G. W. V. Cave, J. L. Atwood, J. F. Stoddart, *Science* **2004**, *304*, 1308 – 1312; c) D. Schultz, J. R. Nitschke, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11191 – 11195; d) D. A. Leigh, R. G. Pritchard, A. J. Stephens, *Nat. Chem.* **2014**, *6*, 978 – 982.

[4] a) B. de Bruin, P. Hauwert, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2006**, *45*, 2660 – 2663; *Angew. Chem.* **2006**, *118*, 2726 – 2729; b) F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211 – 2221; c) J.-F. Ayme, J. E. Beves, C. J. Campbell, D. A. Leigh, *Chem. Soc. Rev.* **2013**, *42*, 1700 – 1712; d) M. Zhang, X. Yan, F. Huang, Z. Niu, H. W. Gibson, *Acc. Chem. Res.* **2014**, *47*, 1995 – 2005; e) S. Zarra, D. M. Wood, D. A. Roberts, J. R. Nitschke, *Chem. Soc. Rev.* **2015**, *44*, 419 – 432.

[5] a) I. A. Riddell, M. M. J. Smulders, J. K. Clegg, Y. R. Hristova, B. Breiner, J. D. Thoburn, J. R. Nitschke, *Nat. Chem.* **2012**, *4*, 751 – 756; b) J. K. Clegg, J. Cremers, A. J. Hogben, B. Breiner, M. M. J. Smulders, J. D. Thoburn, J. R. Nitschke, *Chem. Sci.* **2013**, *4*, 68 – 76; c) I. A. Riddell, Y. R. Hristova, J. K. Clegg, C. S. Wood, B. Breiner, J. R. Nitschke, *J. Am. Chem. Soc.* **2013**, *135*, 2723 – 2733; d) W. Meng, T. K. Ronson, J. K. Clegg, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2013**, *52*, 1017 – 1021; *Angew. Chem.* **2013**, *125*, 1051 – 1055; e) I. A. Riddell, T. K. Ronson, J. K. Clegg, C. S. Wood, R. A. Bilbeisi, J. R. Nitschke, *J. Am. Chem. Soc.* **2014**, *136*, 9491 – 9498; f) I. A. Riddell, T. K. Ronson, J. R. Nitschke, *Chem. Sci.* **2015**, *6*, 3533 – 3537.

[6] a) S. Freye, J. Hey, A. Torras-Galán, D. Stalke, R. Herbst-Irmer, M. John, G. H. Clever, *Angew. Chem. Int. Ed.* **2012**, *51*, 2191 – 2194; *Angew. Chem.* **2012**, *124*, 2233 – 2237; b) S. Freye, R. Michel, D. Stalke, M. Pawliczek, H. Frauendorf, G. H. Clever, *J. Am. Chem. Soc.* **2013**, *135*, 8476 – 8479; c) S. Löffler, J. Lübben, L. Krause, D. Stalke, B. Dittrich, G. H. Clever, *J. Am. Chem. Soc.* **2015**, *137*, 1060 – 1063; d) R. Zhu, J. Lübben, B. Dittrich, G. H. Clever, *Angew. Chem. Int. Ed.* **2015**, *54*, 2796 – 2800; *Angew. Chem.* **2015**, *127*, 2838 – 2842; e) M. Frank, M. D. Johnstone, G. H. Clever, *Chem. Eur. J.* **2016**, *22*, 14104 – 14125.

[7] R. Custelcean, *Chem. Soc. Rev.* **2014**, *43*, 1813 – 1824.

[8] a) G. R. L. Cousins, R. L. E. Furlan, Y.-F. Ng, J. E. Redman, J. K. M. Sanders, *Angew. Chem. Int. Ed.* **2001**, *40*, 423 – 428; *Angew. Chem.* **2001**, *113*, 437 – 442; b) B. Fuchs, A. Nelson, A. Star, J. F. Stoddart, S. Vidal, *Angew. Chem. Int. Ed.* **2003**, *42*, 4220 – 4224; *Angew. Chem.* **2003**, *115*, 4352 – 4356; c) A. González-Álvarez, I. Alfonso, F. López-Ortiz, Á. Aguirre, S. García-Granda, V. Gotor, *Eur. J. Org. Chem.* **2004**, 1117 – 1127; d) 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.

[9] a) S. Otto, S. Kubik, *J. Am. Chem. Soc.* **2003**, *125*, 7804 – 7805; b) H. Y. Au-Yeung, F. B. L. Cougnon, S. Otto, G. D. Pantos, J. K. M. Sanders, *Chem. Sci.* **2010**, *1*, 567 – 574; c) J. A. Berrocal, R. Cacciapaglia, S. D. Stefano, *Org. Biomol. Chem.* **2011**, *9*, 8190 – 8194; d) Y. Zhang, Y.-M. Legrand, A. van der Lee, M. Barboiu, *Eur. J. Org. Chem.* **2016**, 1825 – 1828.

[10] Lehn and Nelson reported imine-based, bimetallic cryptates, yet their dynamic behavior was not explored. a) J. Jazwinski, J.-M. Lehn, D. Lilienbaum, R. Ziessel, J. Guilhem, C. Pascard, *J. Chem. Soc. Chem. Commun.* **1987**, 1691 – 1694; b) D. MacDowell, J. Nelson, *Tetrahedron Lett.* **1988**, *29*, 385 – 386; c) Q. Lu, J.-M. Latour, C. J. Harding, N. Martin, D. J. Marrs, V. McKee, J. Nelson, *J. Chem. Soc. Dalton Trans.* **1994**, 1471 – 1478; d) O. W. Howarth, G. G. Morgan, V. McKee, J. Nelson, *J. Chem. Soc. Dalton Trans.* **1999**, 2097 – 2102.

[11] R.-C. Brachvogel, F. Hampel, M. von Delius, *Nat. Commun.* **2015**, *6*, 7129.

[12] a) R.-C. Brachvogel, M. von Delius, *Chem. Sci.* **2015**, *6*, 1399 – 1403; b) R.-C. Brachvogel, M. von Delius, *Eur. J. Org. Chem.* **2016**, 3662 – 3670.

[13] N.-D. H. Gamage, Y. Mei, J. Garcia, M. J. Allen, *Angew. Chem. Int. Ed.* **2010**, *49*, 8923 – 8925; *Angew. Chem.* **2010**, *122*, 9107 – 9109.

[14] a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40 – 49; b) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657 – 4673.

[15] R. D. Shannon, *Acta Crystallogr. Sect. A* **1976**, *32*, 751 – 767.

[16] We also explored the ammonium ion as a possible nonspherical template. Preliminary results indicate that ammonium cryptates such as $[\mathbf{NH_4^+}\subset\boldsymbol{o}\textbf{-Me}_\mathbf{2}\textbf{-2.1.1}]$ are intrinsically dynamic, which merits comprehensive experimental and computational studies that are beyond the scope of this manuscript.

[17] R.-C. Brachvogel, H. Maid, M. von Delius, *Int. J. Mol. Sci.* **2015**, *16*, 20641 – 20656.

[18] By "stoichiometrically unbiased" we refer to potential mass balance effects, which can override thermodynamic preferences in DCLs, but do not play a role in experiments such as $[\mathbf{K^+}\cdot\boldsymbol{o}\textbf{-Me}_\mathbf{2}\textbf{-1.1.1}] + \text{TEG} \leftrightarrow [\mathbf{K^+}\subset\boldsymbol{o}\textbf{-Me}_\mathbf{2}\textbf{-2.1.1}] + \text{DEG}$ (assuming perfect stoichiometry control and negligible oligomer formation). For seminal contributions on mass balance effects see: a) K. Severin, *Chem. Eur. J.* **2004**, *10*, 2565 – 2580; b) P. T. Corbett, J. K. M. Sanders, S. Otto, *Chem. Eur. J.* **2008**, *14*, 2153 – 2166.

[19] a) S. Begel, A. Scheurer, R. Puchta, *J. Coord. Chem.* **2015**, *68*, 3374 – 3387; b) S. Begel, A. Scheurer, R. Puchta, R. van Eldik, *Z.

Anorg. Allg. Chem. **2016**, *642*, 395 – 402; c) S. Begel, R. Puchta, R. van Eldik, *J. Mol. Model.* **2014**, *20*, 1 – 11; d) S. Begel, R. Puchta, R. van Eldik, *Beilstein J. Org. Chem.* **2013**, *9*, 1252 – 1268.

[20] a) M. Ziegler, A. V. Davis, D. W. Johnson, K. N. Raymond, *Angew. Chem. Int. Ed.* **2003**, *42*, 665 – 668; *Angew. Chem.* **2003**, *115*, 689 – 692; b) C. Gütz, R. Hovorka, G. Schnakenburg, A. Lützen, *Chem. Eur. J.* **2013**, *19*, 10890 – 10894; c) W. Meng, T. K. Ronson, J. R. Nitschke, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 10531 – 10535; d) C. Gütz, R. Hovorka, C. Klein, Q.-Q. Jiang, C. Bannwarth, M. Engeser, C. Schmuck, W. Assenmacher, W. Mader, F. Topić, K. Rissanen, S. Grimme, A. Lützen, *Angew. Chem. Int. Ed.* **2014**, *53*, 1693 – 1698; *Angew. Chem.* **2014**, *126*, 1719 – 1724; e) A. M. Castilla, W. J. Ramsay, J. R. Nitschke, *Acc. Chem. Res.* **2014**, *47*, 2063 – 2073; f) L.-L. Yan, C.-H. Tan, G.-L. Zhang, L.-P. Zhou, J.-C. Bünzli, Q.-F. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 8550 – 8555; g) A. Schaly, Y. Rousselin, J.-C. Chambron, E. Aubert, E. Espinosa, *Eur. J. Inorg. Chem.* **2016**, 832 – 843; h) X. Wang, Y. Wang, H. Yang, H. Fang, R. Chen, Y. Sun, N. Zheng, K. Tan, X. Lu, Z. Tian, X. Cao, *Nat. Commun.* **2016**, *7*, 12469.

[21] CCDC 1505902 (**[K$^{+}\subset$*o*-Me$_{2}$-2.1.1]**), 1505906 (**[Rb$^{+}\subset$*o*-Me$_{2}$-2.2.1]**), 1505905 (**[Cs$^{+}\subset$*o*-Me$_{2}$-2.2.1]**), 1505904 (**[Cs$^{+}\subset$*o*-Me$_{2}$-2.2.2]**), and 1505903 (**[Na$^{+}\subset$*o*-Me$_{2}$-*SS*,*SS*,*SS*]**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Communications

Supramolecular Chemistry

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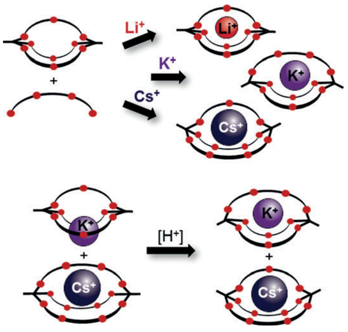
Adaptive Behavior of Dynamic Orthoester Cryptands



A lid for every pot: Cryptands based on orthoester bridgeheads offer an elegant entry to experiments in which a metal ion selects its preferred host from a dynamic mixture of competing subcomponents. In such dynamic mixtures the alkali metal ions Li^+, Na^+, K^+, Rb^+, and Cs^+ exhibit pronounced preferences for the formation of cryptands of certain sizes and donor numbers.