The first supramolecular ion triplet complex†‡

Jens Eckelmann, Vittorio Saggiomo, Frank D. Sönnichsen and Ulrich Lüning*

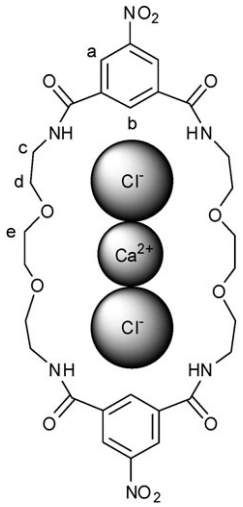
Received (in Montpellier, France) 1st March 2010, Accepted 5th May 2010
First published as an Advance Article on the web 27th May 2010
DOI: 10.1039/c0nj00160k

A neutral tritopic macrocycle 1 was obtained by condensation of a diacid dichloride 2 with a diamine 3. 1 contains three binding sites: two for anions by hydrogen bonding and one for cations by ether oxygen atoms. The selective binding of LiCl and $CaCl_2$ has been studied by NMR and MS techniques. 1 is the first host to form a supramolecular complex with an ion triplet: 1·$CaCl_2$.

In supramolecular chemistry, macrocycles have always been widely used to complex different organic and inorganic guests.[1] For a long time, chemists focused their attention on the complexation of cations and anions, with the latter task being more challenging due to the large size, different shapes and the high polarisability of anions.[2] Nowadays, the importance of targeting ion-pairs of salts as guests is growing.[3] In this field, ditopic hosts are usually synthesized as neutral compounds, in which the ditopic nature of the receptor allows to bind both cation and anion in adjacent binding units in close contact.[4] With the matching cation for the contact pair formation in the host–guest complex, it is possible to enhance the binding of a particular anion or *vice versa*.[5]

Although this field is growing and many different ditopic molecules have been synthesized in the last five years, there is still a lack of hosts for complexing alkaline earth metal halides. In order to reach this goal, chemists must move from ditopic hosts to tritopic hosts. In these, two binding units for anions and one for a cation comprise the sites needed for the complexation of an alkaline earth metal halide as ion triplet.[6,7] In this work, we present the neutral tritopic host **1** that is capable to bind an alkaline earth metal salt, and binds calcium dichloride as an ion triplet with high selectivity. To the best of our knowledge, the formation of complex **1**·$CaCl_2$ is the first description of a supramolecular ion triplet complex for alkaline earth metal salts (Fig. 1).[8]

The synthesis of macrocycle **1** is straightforward and starts from two building blocks: diacid dichloride **2** and diamine **3** (see Scheme 1). In order to obtain and study macrocycles of different sizes, we used a combinatorial approach which gave the [2 + 2]-macrocycle **1** (Fig. 1), together with [1 + 1]-, [3 + 3]-, and [4 + 4]-macrocycles and linear products which are not described here. After a simple one-step condensation of diacid

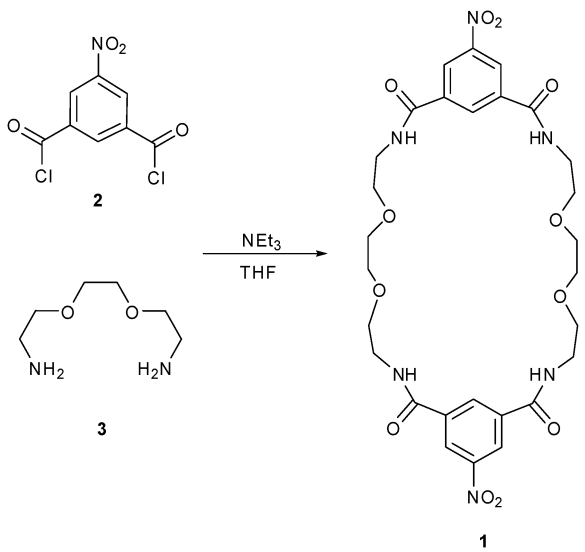


1

Fig. 1 Calcium dichloride complex with macrocycle **1** and hydrogen labeling scheme. For structural studies, see ESI.‡

dichloride **2** and diamine **3** in the presence of triethylamine, the [2 + 2]-macrocycle **1** could be isolated from the resulting mixture by chromatography (Scheme 1).

Macrocycle **1** displays three binding sites (tritopic macrocycle): four NH amides in two different isophthalamide residues, well known to complex anions,[9] and four oxygen atoms in the diethylene glycol part able to complex cations.



Scheme 1 Synthetic scheme for the formation of macrocycle **1**.

Otto-Diels-Institut für Organische Chemie, Christian-Albrechts-Universität zu Kiel, Olshausenstr. 40, D-24098 Kiel, Germany. E-mail: luening@oc.uni-kiel.de; Fax: +49 431 880 1558; Tel: +49 431 880 2450

† Dedicated to Prof. Dr Bernd Giese on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental and spectroscopic details of **1**. NMR and MS complexation studies, and calculations. See DOI: 10.1039/c0nj00160k

Additionally it has two nitro groups that can be further modified, *e.g.* by reduction. The neutral macrocycle **1** possesses D_{2h} symmetry giving rise to a simple ^{1}H-NMR spectrum: two triplets for the NH and H_d protons, a doublet for H_a, a broad singlet for the H_b and a singlet for the H_e protons.

The easily interpretable and clean ^{1}H-NMR spectra were used to investigate the capability of this tritopic macrocycle **1** to bind salts as contact ions, and to detect their extraction from solid into an organic solvent. A stock solution (2.5 mM) of **1** in $CDCl_3$ with 5% of DMSO-d_6 was allowed to stand over an excess of powdered alkaline and alkaline earth metal chlorides in different NMR tubes. After 12 h, ^{1}H-NMR spectra were recorded and analyzed for differences in chemically induced shifts (CIS) between the free macrocycle **1** and the complexes (Fig. 2).

When comparing the solutions containing the alkaline chlorides LiCl, NaCl and KCl, the NMR spectra clearly show that macrocycle **1** is capable of binding lithium chloride selectively over other alkaline metal chlorides, as the ^{1}H-NMR spectra do not show any change when sodium chloride or potassium chloride is used. In the case of lithium chloride, a significant CIS of NH (−0.88 ppm) and H_b (−0.65 ppm) was detected (Fig. 2, LiCl). The large downfield shift of almost 1 ppm of the amide proton is indicative of the formation of hydrogen bonds to the chloride anion (NH···Cl) in the presence of DMSO.[10] A small difference in the chemical shifts of H_a (−0.08 ppm), not involved in the binding, was also detected. In the diethylene glycol chains, upfield CIS for H_e (+0.04 ppm) and downfield CIS for H_d (−0.05 ppm) were observed. Due to the key importance of lithium salts as drug in different diseases,[11] it is an interesting goal to develop lithium receptors and sensors.[12] The challenge is to bind it selectively over competing ions such as sodium. Macrocycle **1** achieves this task in an organic solvent complexing selectively LiCl as contact ion pair over NaCl.

Additionally, alkaline earth metal dichlorides ($MgCl_2$, $CaCl_2$, $BaCl_2$) were screened applying the same methodology. Indeed, macrocycle **1** is able to form an ion triplet complex **1**·$CaCl_2$, but remarkably only with the calcium salt. The distinct differences in CIS for $MgCl_2$, $CaCl_2$ and $BaCl_2$ show a strong selectivity of macrocycle **1** for calcium dichloride over magnesium and barium dichloride. Although in the presence of magnesium and barium dichloride the NH signal shows a modest CIS (−0.14 and −0.24 ppm, respectively), a prominent NH downfield shift (−0.90 ppm) is observed only when calcium dichloride is used (Fig. 2, $CaCl_2$). The calcium dichloride complex (**1**·$CaCl_2$) shows proton shifts similar to the lithium chloride complex (**1**·LiCl). Only H_e is shifted more upfield (+0.06 ppm) with respect to **1**·LiCl which reflects a different side chain orientation. Due to different sizes of magnesium, calcium and barium, macrocycle **1** is able to complex selectively calcium dichloride as a *contact ion-triplet*. To the best of our knowledge, this is the first neutral macrocycle that binds an alkaline earth metal dihalide as contact ion-triplet.[13]

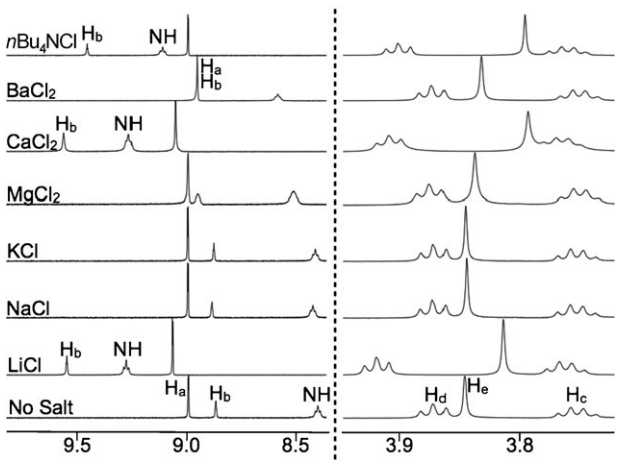


Fig. 2 Expanded sections of ^{1}H-NMR spectra (500 MHz, 298 K, $CDCl_3$/DMSO-d_6 95 : 5) of **1** in the presence of different salts. For proton assignments see Fig. 1.

Mass analyses confirm the strong complexing ability of macrocycle **1** for LiCl and $CaCl_2$ (see ESI‡). When ESI-MS spectra (negative ion mode) were recorded directly from the NMR solutions with either lithium chloride or calcium dichloride, it was possible to detect a single peak as **1** + Cl^- (m/z = 681.20). The ESI-MS scan of **1**·$CaCl_2$ in the positive mode showed two peaks attributable to complex **1**·$CaCl_2$: (**1** + Ca^{2+})/2 (m/z = 343.10) and **1** + $CaCl^+$ (m/z = 721.14). On the other hand, the ESI spectra of the lithium chloride complex **1**·LiCl showed only the protonated peak **1** + H^+, but for this complex the MALDI-TOF spectrum revealed **1** + Li^+ (m/z = 653.31).

To obtain further insight into the complexation of the salts by macrocycle **1**, detailed NOESY experiments were carried out.[14] A stock solution of **1** in $CDCl_3$ (*ca.* 2.5 mM) with 7% of DMSO-d_6[15] was used to record 2D-NOESY spectra in three different NMR tubes: in the absence of salt, in the presence of excess of powdered lithium chloride, and in the presence of excess of powdered calcium dichloride.

Table 1 compiles the proton–proton distances as calculated from the NOESY measurements. When the obtained distances for the free macrocycle **1** are compared to those in the complexes, significant differences are apparent. In pure macrocycle **1**, the average proton–proton distances of H_a–NH and H_b–NH were found to be quite similar. The NH proton is at the same average distance from H_a and H_b, indicating that the benzene ring is capable of rotating around the Ar–CO bond. Thus in about half of the population, NH is close to H_a, and in the other half, NH is close to H_b, resulting in almost identical average distances of 2.6 Å (H_b–NH) and 2.7 Å (H_a–NH) in the free macrocycle.

Table 1 Average proton–proton distances[16] (Å) in macrocycle **1** based on NOESY experiments. For proton labels see Fig. 1

	1	**1**·LiCl	**1**·$CaCl_2$
H_b–NH	2.6	2.85	2.5
H_a–NH	2.7	4.5	4.1
NH–H_c	3.1	3.3	2.95
NH–H_d	3.5	3.85	3.4
H_b–H_c	4.3	4.8	4.3
H_b–H_d	4.0	5.0	4.7
H_a–H_c	4.1	4.6	4.1
H_a–H_d	3.9	—	—

The distances H_a–NH and H_b–NH respond differently to the addition of salts, *i.e.* the binding of chloride anions by hydrogen bonding, as they become different in both the **1**·LiCl and **1**·$CaCl_2$ complexes. The average proton–proton distance between NH and H_a increased considerably, thus on average H_a moved away from NH, while at the same time the apparent NH–H_b distance is shortened. Both facts can be explained by the binding of the NH protons to the chloride anions. In fact, the complex must have been rigidified upon complexation and the two protons (NH and H_a) are now further away from one another, while at the same time H_b spends more time in close proximity to the NH proton. It is interesting to note that also the distances between H_b and H_d increase upon complexation from 4 Å to 5 Å (**1**·LiCl) and 4.7 Å (**1**·$CaCl_2$), respectively.

Finally, we carried out first orientational experiments to quantify the formation of the supramolecular complexes of **1**. The salts are insoluble in the solvents used for the NMR investigations, especially $CaCl_2$.[17] But with a mixture of anhydrous calcium perchlorate and tetrabutylammonium chloride in $CHCl_3$/DMSO (93 : 7), we were able to carry out isothermal titration calorimetry (ITC) experiments with receptor **1**. The results must not be overinterpreted due to the insolubility problems and also to the fact that the mixture changes the ionic strength. Nevertheless, binding constants for 1 : 1 complexes in the range of 10^3 to 10^4 in $CHCl_3$/DMSO could be determined for $CaCl_2$ (by use of a $Ca(ClO_4)_2$/$n$$Bu_4NCl$ mixture), and for LiCl (by use of a $Li(ClO_4)$/$n$$Bu_4NCl$ mixture) and $n$$Bu_4NCl$.

In conclusion, a facile and accessible synthesis of macrocycle **1** has been described. The ability of **1** to complex LiCl and $CaCl_2$ was proven by means of ^{1}H-NMR and mass analyses. In solution, its conformational change in the presence of guests was analyzed and described using NOESY experiments. All these experiments concentrate on the fact that the neutral macrocycle **1** complexes calcium dichloride in its ion-triplet form. This ion-triplet receptor should be useful in different applications such as selective extraction from solid mixtures (industrial application), membrane transport (calcium is an essential element for biological life, and chloride concentration controls several processes in the cell), chemosensing, homogeneous catalysis and phase transfer catalysis. In our laboratory the screening of some of these applications is work in progress.

Experimental

16,33-Dinitro-6,9,23,26-tetraoxa-3,12,20,29-tetraazatricyclo-[29.3.1.1^{14,18}]hexatriaconta-1(35),14,(36),15,17,31,33-hexaen-2,13,19,30-tetraone (**1**): a solution of 5-nitroisophthaloyl dichloride (1.00 g, 4.03 mmol) in tetrahydrofuran (20 mL) was added dropwise over 20 min to a stirred solution of 1,8-diamino-3,6-dioxaoctane (5.06 g, 5.00 mL, 34.1 mmol) and triethylamine (2.50 mL, 1.83 g, 18.0 mmol) in tetrahydrofuran (20 mL). The solution was stirred for 24 h. The solvent and excess of triethylamine was evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and washed with water (4 × 50 mL). The combined extracts were dried with magnesium sulfate and evaporated under reduced pressure to yield a yellow solid, which was purified by column chromatography on silica using dichloromethane/methanol/triethylamine (20 : 1 : 1, R_f = 0.47) as eluent to give macrocycle **1** (110 mg, 8%) as a white solid. δ_H (500 MHz; $CDCl_3$/DMSO-d_6 95 : 5 v/v; TMS): 3.59 (8H, m, O–CH_2–CH_2–NH), 3.68 (8H, s, O–CH_2–CH_2–O), 3.71 (8H, t, J = 5.2, O–CH_2–CH_2–NH), 8.39 (4H, t, J = 5.5, NH), 8.77 (2H, s, Ar), 8.84 (4H, d, J = 1.3, Ar); δ_C (125 MHz, $CDCl_3$/DMSO-d_6 95 : 5 v/v, TMS): 39.54, 39.71, 39.88, 40.05, 40.21, 40.38, 40.55 (DMSO-d_6 and CH_2–NH), 69.21, 70.14 (CH_2–O–CH_2), 125.04 (Ar-C-4, Ar-C-6), 131.05 (Ar-C-2), 136.22 (Ar-C-1, Ar-C-3), 148.27 (Ar-C-5), 164.66 (C=O); IR (ATR): $\tilde{\nu}_{max}$/cm^{-1} 3275 (NH), 3091 (Aryl-H), 2866 (CH_2), 1649 (CO), 1580, 1557 and 1528 (C=C), 1123 (C–O–C); m/z (ESI): 669.2284 (M + Na^+, $C_{28}H_{34}N_6O_{12}Na^+$ requires 669.2127).

Acknowledgements

We thank the EU for its support through the Marie Curie Research Training Network MRTN-CT-2006-035614 Dynamic Combinatorial Chemistry (DCC). Eva Mucke's help with the calculations is gratefully acknowledged.

Notes and references

1 J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, Wiley, New York, 2nd edn, 2009.
2 F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609–1646; A. Bianchi, K. Bowman-James and E. García-España, *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, 1997; A. J. Evans and P. D. Beer, *Dalton Trans.*, 2003, 4451–4456; M. T. Reetz, C. M. Niemeyer and K. Harms, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1472–1474.
3 B. D. Smith, *Ion-Pair Recognition By Ditopic Receptors*, in *Macrocyclic Chemistry: Current Trends and Future*, ed. K. Gloe and B. Antonioli, Kluwer, London, 2005, pp. 137–152.
4 Some recent examples of ditopic receptors: K. Salorinne, T.-R. Tero, K. Riikonen and M. Nissinen, *Org. Biomol. Chem.*, 2009, **7**, 4211–4217; N. Bernier, S. Carvalho, F. Li, R. Delgado and V. Félix, *J. Org. Chem.*, 2009, **74**, 4819–4827; M. D. Lankshear, I. M. Dudley, K.-M. Chan, A. R. Cowley, S. M. Santos, V. Félix and P. D. Beer, *Chem.–Eur. J.*, 2008, **14**, 2248–2263; M. D. Lankshear, A. R. Cowley and P. D. Beer, *Chem. Commun.*, 2006, 612–614; J. M. Mahoney, K. A. Stucker, H. Jiang, I. Carmichael, N. R. Brinkmann, A. M. Beatty, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.*, 2005, **127**, 2922–2928; J. M. Mahoney, A. M. Beatty and B. D. Smith, *Inorg. Chem.*, 2004, **43**, 7617–7621.
5 J. M. Mahoney, A. M. Beatty and B. D. Smith, *J. Am. Chem. Soc.*, 2001, **123**, 5847–5848; S. Kubik, *J. Am. Chem. Soc.*, 1999, **121**, 5846–5855.
6 There is a discussion on how to name an ionic aggregate such as $CaCl_2$: triple ion or ion triplet. We have chosen ion triplet to highlight the fact that three ions are bound as a unit, and we have not chosen triple ion to avoid the impression that there is a remaining charge (see ref. 7). **1**·$CaCl_2$ is the first neutral supramolecular ion triplet complex.
7 G. V. Oshovsky, D. N. Reinhoudt and W. Verboom, *J. Am. Chem. Soc.*, 2006, **128**, 5270–5278.
8 With a dichloride of a more electrophilic transition metal (palladium), a structurally related complex has been described: B. A. Blight, J. A. Wisner and M. C. Jennings, *Chem. Commun.*, 2006, 4593–4595.
9 P. V. Santacroce, J. T. Davis, M. E. Light, P. A. Gale, J. C. Iglesias-Sánchez, P. Prados and R. Quesada, *J. Am. Chem. Soc.*, 2007, **129**, 1886–1887; K. Kavallieratos and B. A. Moyer, *Chem. Commun.*, 2001, 1620–1621; A. Szumna and J. Jurczak, *Eur.*

J. Org. Chem., 2001, 4031–4039; K. Kavallieratos, C. M. Bertao and R. H. Crabtree, *J. Org. Chem.*, 1999, **64**, 1675–1683.
10 M. J. Deetz, M. Shang and B. D. Smith, *J. Am. Chem. Soc.*, 2000, **122**, 6201–6207.
11 N. J. Birch, *Chem. Rev.*, 1999, **99**, 2659–2682; C. J. Phiel, C. A. Wilson, V. M.-Y. Lee and P. S. Klein, *Nature*, 2003, **423**, 435–439; H. R. Pilcher, *Nature*, 2003, **425**, 118–120.
12 S. Rochat, Z. Grote and K. Severin, *Org. Biomol. Chem.*, 2009, **7**, 1147–1153.
13 To provethe chloride complexing abilities of macrocycle **1**, tetrabutylammonium chloride (nBu$_4$NCl) was used as salt. And even in this case, the shifts of the protons are comparable with **1**·LiCl and **1**·$CaCl_2$ complexes. Nevertheless, the NH protons are shifted more when $CaCl_2$ or LiCl was used instead of nBu$_4$NCl (naked chloride). The CIS of the ethylene glycol protons are more similar to the CIS of **1**·$CaCl_2$ than to that of **1**·LiCl.
14 Unfortunately, up to now it was not possible to obtain a single crystal of **1**·$CaCl_2$. Besides, if the complexation shall be exploited in applications such as for instance transport it must be studied in solution anyway.
15 In comparison to the first binding experiments, a slightly higher concentration of DMSO was used in order to ensure a homogeneous organic phase, needed to record reliable NOESY spectra.
16 2D-NOESY experiments with varying mixing times were used to analyze the conformation and mobility of the free macrocycle and the complexes. Using a two-spin approximation and two known distances as a reference, average interproton distances were calculated from all observed NOE intensities after peak integration as described in ESI.‡ In a mobile structure, the distances are physically meaningless *i.e.* they do not describe a single conformation, their differences upon ion binding however indicate changes in the combination of short distances and population of the conformations present.
17 $CaCl_2$ and LiCl are insoluble in the solvent mixture used and are extracted into these solvents only by **1**. Therefore, a titration with portions of the solid salt into a solution of host **1** cannot be interpreted when excess salt is added. For this reason, the preliminary binding studies were done with salts which are soluble in the solvent mixture: $Ca(ClO_4)_2$, $Li(ClO_4)$ and nBu$_4$NCl.

