Cyclic triureas—synthesis, crystal structures and properties†

Denys Meshcheryakov,[a] Françoise Arnaud-Neu,[b] Volker Böhmer,*[a] Michael Bolte,[c] Véronique Hubscher-Bruder,[b] Emilie Jobin,[b] Iris Thondorf[d] and Sabine Werner[d]

Received 22nd November 2007, Accepted 18th January 2008
First published as an Advance Article on the web 14th February 2008
DOI: 10.1039/b718114k

The synthesis of 24-membered macrocycles is described, in which rigid xanthene units (X) and/or diphenyl ether units (D) as flexible analogues are linked *via* urea groups. All four possible combinations (XXX, XXD, XDD, DDD) have been obtained with yields of 40–72% for the cyclisation step. In two cases, the respective cyclic hexamers (XXDXXD, XXXXXX) were also isolated. Two compounds have been characterised by a single crystal X-ray analysis of the free triurea (XXD, XDD) and one example (DDD) by its complex with tetrabutylammonium chloride. It shows the chloride anion in the centre of the macrocycle, held by six NH $\cdots$ Cl^- hydrogen bonds. The interaction with various other anions has been studied by ^{1}H NMR. Complexation constants for chloride, bromide and acetate have been measured for all trimers by UV spectrophotometry. Molecular dynamics simulations have been carried out to determine the conformation of the free receptors in chloroform and acetonitrile. They show that in chloroform, intramolecular hydrogen bonding occasionally facilitated by *trans*→*cis* isomerisation of an amide bond dominates the conformation of the macrocycles while in acetonitrile (the solvent used for complexation measurements), the ligating urea NH protons are properly arranged for the complexation of anions, however, their strong solvation is counteractive to the complexation.

Introduction

Amide groups are often used as hydrogen bond donors in synthetic anion receptors.[1] They have been combined as podands on a suitable platform, *e.g.* a calix[4]arene,[2] or included into macrocyclic[3] or macrobicyclic molecules.[4] Urea or thiourea functions are able to form "three centered" hydrogen bonds to an appropriate acceptor atom.[5] Consequently, various anion receptors based on oligoureas have been described, in which the urea groups are either arranged as podands or incorporated into a macrocycle,[6] while macrobicyclic oligourea molecules are not known.

In spite of these numerous examples, anion binding by neutral cyclic oligoureas has not yet shown remarkable results. This may be due to an insufficient complementarity or to intramolecular hydrogen bonding in the macrocycle. On the other hand, it is tempting to envisage anion receptors for the planar nitrate anion based on a suitable cyclic arrangement of three urea groups.[7] We therefore started with the question, what would be an appropriate spacer holding three urea groups in the optimum position, and we tried to find some guidelines by molecular modelling.

Based on molecular modelling studies,[8] the 4,5-substituted xanthene skeleton was evaluated as an appropriate spacer between the urea functions (Fig. 1). Along with its rigidity, it has an additional advantage. The repulsion between the xanthene oxygens and the urea oxygens should favour conformations in which the urea hydrogens are oriented towards the centre of the macrocycle. This "preorganization" should also minimise intermolecular hydrogen bonding.

The known 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-diamino-xanthene **1** (X-unit) was chosen as a building block for the synthesis of macrocycles, since it is easily prepared from the commercially available dicarboxylic acid.[9] This xanthene-derived spacer was already used in some simple open chain urea-based anion receptors, which demonstrated promising results.[10]

In general, the receptor properties of a host molecule are determined by a delicate balance between the prearrangement of ligating functions due to a certain "rigidity" and the ability to adapt to the target guest by a sufficient "flexibility". Thus we decided to introduce, besides the rigid xanthene units, the more flexible diphenyl ether derivative **2** (D-unit), which could also be prepared following relatively simple procedures.[11]

Results and discussion

Syntheses

The family of cyclic trimers based on these two units X and D consists of four possible compounds **10** (XXX), **11** (XXD),

[a]*Fachbereich Chemie, Pharmazie und Geowissenschaften, Abteilung Lehramt Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, D-55099 Mainz, Germany. E-mail: vboehmer@mail.uni-mainz.de; Fax: +49 (0) 6131 3925419; Tel: +49 (0) 6131 3922319*

[b]*IPHC-DSA, ULP, CNRS, 25 rue Becquerel, F-67087 Strasbourg, France. E-mail: farnaud@chimie.u-strasbg.fr; Fax: +333 90242747; Tel: +333 90242749*

[c]*Fachbereich Chemie und Pharmazeutische Wissenschaften, Institut für Anorganische Chemie, Johann Wolfgang Goethe-Universität Frankfurt, Marie-Curie-Straße 11, D-60439 Frankfurt/Main, Germany. E-mail: bolte@chemie.uni-frankfurt.de; Fax: +49 (0) 69 7982 9239; Tel: +49 (0) 69 79829136*

[d]*Fakultät für Naturwissenschaften I—Biowissenschaften, Institut für Biochemie und Biotechnologie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Straße 3, D-06099 Halle/Saale, Germany. E-mail: iris.thondorf@biochemtech.uni-halle.de; Fax: +49 (0) 345 5527011; Tel: +49 (0) 345 5524862*

† Electronic supplementary information (ESI) available: Table S1: Compounds used for the calculation of RESP charges and the corresponding RESP derived charges for the constituting fragments of the macrocycles **10–13**. Also given are the corresponding atom types used for the AMBER calculations. See DOI: 10.1039/b718114k

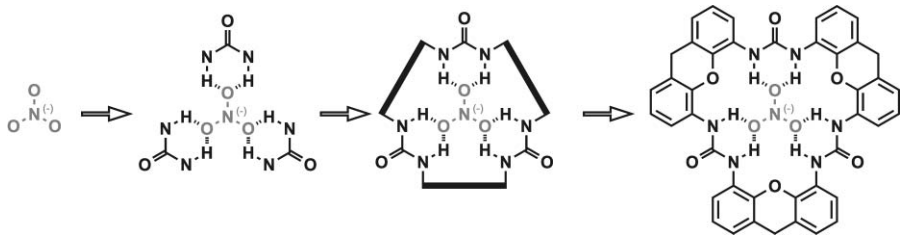
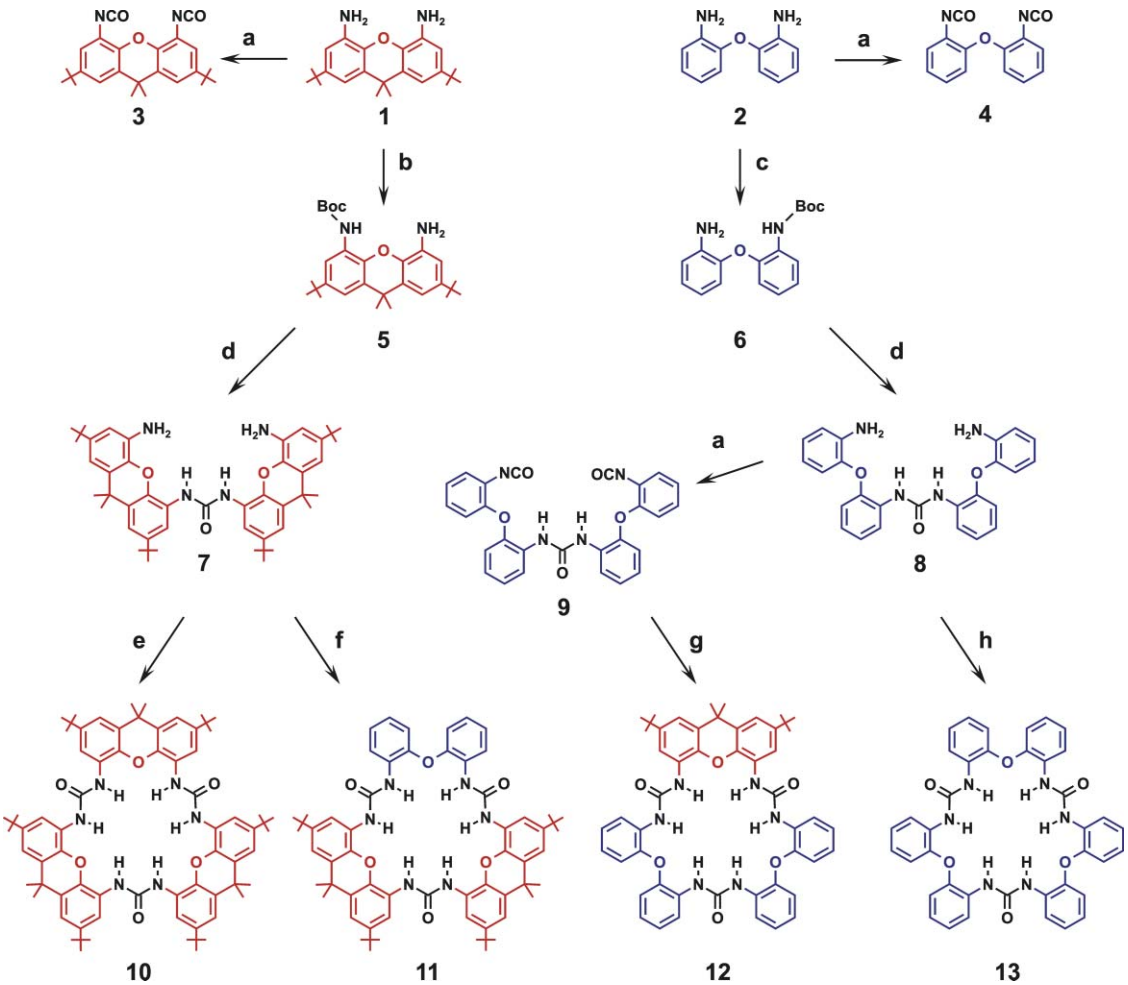


Fig. 1 Cyclic triureas with rigid spacers as potential receptors for the nitrate anion.

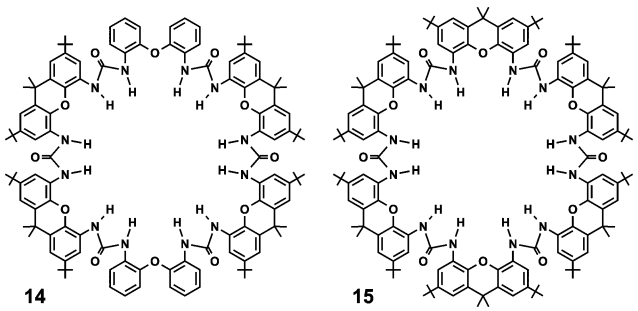


Scheme 1 *Reagents and conditions:* (a) triphosgene, diisopropylethylamine, CH_2Cl_2, r. t., 3 h; (b) Boc-anhydride, THF, 25 °C, 18 h; (c) Boc-anhydride, THF, 60 °C, 48 h; (d) *N*-acylation: *p*-nitrophenyl chloroformate, diisopropylethylamine, THF, 60 °C, 18 h; deprotection: trifluoroacetic acid, CH_2Cl_2, r. t., 3 h; (e) **7** as bis-trifluoroacetate, diisocyanate **3**, triethylamine, CH_2Cl_2, r. t., 12 h; (f) diisocyanate **4**, acetonitrile, r. t., 12 h; (g) diamine **1**, CH_2Cl_2, r. t., 18 h; (h) diisocyanate **4**, CH_2Cl_2, r. t, 18 h.

12 (XDD) and **13** (DDD). Their synthesis is summarised in the general Scheme 1.

Both diamines **1** and **2** were prepared according to the slightly improved literature procedures. Reaction with triphosgene in the presence of diisopropylethylamine led to the corresponding diisocyanates **3** and **4** in 76 and 88% yield, respectively. The preparation of mono-protected diamines **5** and **6** was possible by reaction with di-*tert*-butyl dicarbonate in THF (molar ratio 1 : 1), followed by chromatographic separation. The compounds were isolated with yields of 55 and 42%, respectively. **5** and **6** form the corresponding ureas almost quantitatively when they are reacted in a 2 : 1 ratio with *p*-nitrophenyl chloroformate in the presence of base (Scheme 1). The subsequent deprotection with trifluoroacetic acid yields the dimeric diamines **7** or **8**. Isocyanates were preferred over the active urethanes for the formation of urea groups in the further reaction steps since the absence of bulky residues resulted in better yields and higher purity of the products.

For the synthesis of cyclic trimers, we envisaged the reaction of the diisocyanates **3** or **4** with the dimeric diamines **7** or **8**. The concentration of the reactants was kept between 2.9 mM and 6.0 mM, but no general procedure can be given, due to their different solubility and the different solvents used.



Thus, the trimer XXD (**11**) was obtained in 62% yield when the diisocyanate **4** was reacted with the diamine **7** in acetonitrile. Interestingly, the cyclic hexamer XXDXXD (**14**) was formed (up to 20% yield) in addition to **11**, when the reaction was carried out in the less polar methylene chloride.[12]

When the more rigid xanthene-based diisocyanate **3** was reacted with the diamine **7** in dichloromethane under analogous conditions, the corresponding hexamer XXXXXX (**15**), consisting of xanthene units, appeared to be the main product with yields up to 49%, while the triurea XXX (**10**) was not isolated at all. In contrast to the synthesis of the trimer **11**, the change of the solvent to the more polar acetonitrile did not lead to the preferred formation of the trimer. A mixture of oligoureas with different chain lengths was formed instead of the desired product. However, the trimer **10** is formed preferably and can be isolated by crystallization with yields up to 40% when the trifluoroacetate of the diamine **7** was used in the reaction instead of the non-protonated diamine.

The formation of side products hinders also the isolation of the trimers XDD (**12**) and DDD (**13**), but the formation of hexamers was not detected during attempts to synthesise these more flexible compounds. Trimer **12** was prepared by the "reversed 2 + 1" strategy reacting the diisocyanate **9** with the diamine **1**. The reaction of the xanthene-based diisocyanate **3** with the flexible diamine **8** produced so many byproducts, that the isolation of the pure macrocycle **12** was nearly impossible, while the reaction of **9** with **1** allowed us to isolate the trimer with 40% yield. Probably, the conversion of both amino groups to isocyanate groups in **9** decreases the possibility of undesired hydrogen bonding and association in solution. The trimer **13** was prepared by the reaction of the diamine **8** with diisocyanate **4** in THF and was isolated with a yield of 72%.

X-Ray structures

Three of the four cyclic trimers were confirmed by single crystal X-ray diffraction. Crystallographic details are collected in Table 1.

Suitable crystals of **11** where obtained by slow evaporation of a solution in a mixture of chloroform–dichloromethane–ethanol. The unit cell contains two molecules of **11** related by an inversion center and four molecules of chloroform (two of which are disordered over two positions). The urea groups linking the diphenylether unit with the two xanthene units adopt a *trans* conformation.

Their NH-protons form intramolecular hydrogen bonds to the oxygen of the third urea group connecting the two xanthene units (N–H · · · O=C distances 2.48–2.60 Å). This urea is found in the *cis* conformation with the H- and O-atoms pointing roughly in the same direction. Fig. 2 shows the molecular conformation of **11** seen from two directions. The packing is best illustrated by Fig. 3. Intermolecular hydrogen bonds are not formed.

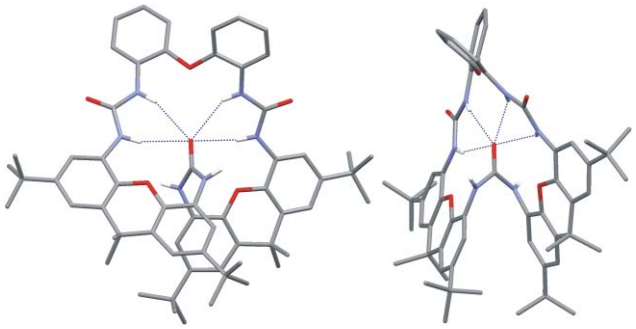


Fig. 2 Molecular conformation of **11**, seen from two different directions. Intramolecular hydrogen bonds are indicated by dashed lines.

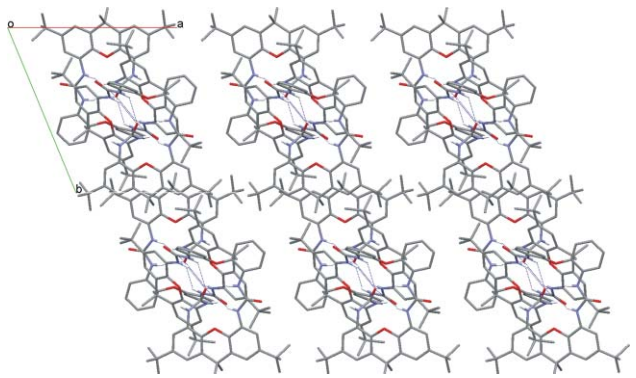


Fig. 3 Packing diagram of **11**, seen along the *c*-axis.

Single crystals of **12** were formed by slow evaporation of a solution in DMSO–methanol. The unit cell contains four molecules of **12** related by three two-fold screw axes. Two molecules of DMSO and one molecule of methanol are incorporated per molecule of **12**. Fig. 4 shows the asymmetric unit of the crystal and illustrates the molecular conformation of **12**.

Table 1 Characterisation of the conformation in the crystal by interplanar angles between phenyl rings (first three columns) and between urea groups (N–C(O)–N) and the adjacent phenyl units (last three columns)

Compound	Ph_1/Ph_2	Ph_3/Ph_4	Ph_5/Ph_6	Ph_2–Ur–Ph_3	Ph_4–Ur–Ph_5	Ph_6–Ur–Ph_1
11 (XXD)	3.0	11.4	62.2	69.9/74.9	27.2/17.3	8.9/7.3
	X	X	D	X–X	X-D	D-X
12 (XDD)	4.8	72.6	62.0	20.2/37.4	4.8/26.0	44.6/35.0
	X	D	D	X-D	D-D	D-X
13 (DDD)	70.3	61.8	51.9	24.1/54.0	36.2/28.7	38.0/46.4

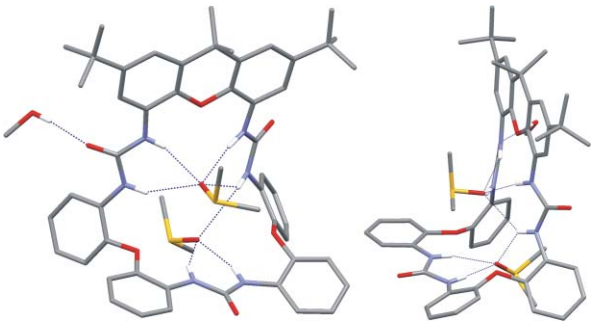


Fig. 4 Molecular conformation of **12** seen from two directions. Hydrogen bonds to solvent molecules are indicated by dashed lines.

All urea groups assume the *trans* conformation and the NH-protons point to the center of the macrocycle forming hydrogen bonds to the DMSO molecules. One of them is held by two three-center hydrogen bonds from the urea groups adjacent to the xanthene unit, while the second molecule of DMSO is bound analogously by the third urea group and connected to another urea also by a bifurcated hydrogen bond. The methanol molecule is hydrogen bonded to one urea carbonyl group. Thus, again no intermolecular hydrogen bonds exist between the molecules of **12** (Fig. 5).

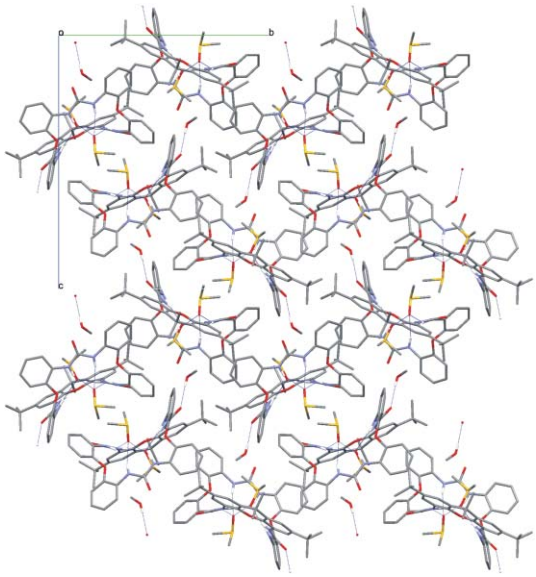


Fig. 5 Packing diagram of **12**, seen along the *a*-axis.

Slow evaporation of a solution of DDD (**13**) and tetrabutylammonium chloride in a mixture of acetone–acetonitrile–chloroform–dichloromethane–ethanol–ethyl acetate[13] gave single crystals containing both components in a 1 : 1 ratio. No solvent is incorporated in the crystal lattice.

Each macrocycle includes one (spherical!) chloride anion (Fig. 6) in the way envisaged for the planar (!) nitrate anion. (Unfortunately all attempts to get crystals also with tetraethyl or tetrabutyl nitrate have failed so far.) The *trans* urea groups form six N–H · · · Cl hydrogen bonds with N–Cl distances between 2.47 to 2.75 Å. Their arrangement resembles a three-bladed propeller formed by the three urea planes (–NH–C(O)–NH–), which are

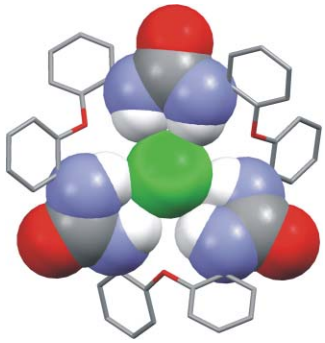


Fig. 6 Molecular conformation of (**13**@Cl^-); the chloride anion and the urea groups of the macrocycle are shown in a space filling representation.

inclined by angles of 20°–28° with respect to the planes through the carbonyl C- or O-atoms.

The complexed chloride anions and the tetrabutylammonium cations are ordered alternately to columns extending along the *c*-axis (Fig. 7, left). Subsequent molecules of **13** in a column are found in enantiomeric conformation symmetry related by a glide plane. Cl–N distances are 4.464 Å and 4.546 Å, and the distances between subsequent Cl (or N) atoms are 8.351 Å. These columns are packed in a "pseudo" hexagonal arrangement, as illustrated by Fig. 7 (right).

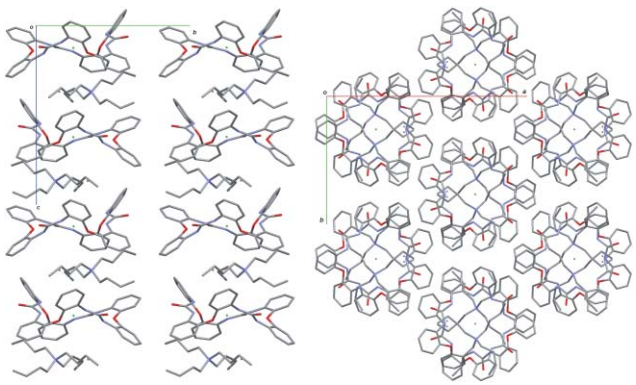


Fig. 7 Packing of (**13**@Cl^-)$C_4H_9^+$ seen from different directions.

^{1}H NMR studies

Since the ^{1}H NMR spectra in $CDCl_3$ are broad for all compounds, due to various intra- and intermolecular hydrogen bonds, DMSO-d_6 was chosen for a comparative study. Fig. 8 shows the low field section (aromatic and urea protons). Still, the spectrum of **10** remains broad and does not show any significant sharpening upon heating nor upon addition of anions, although a strong interaction with such anions as chloride, fluoride or dihydrogen phosphate is evident.

The spectrum of **11** is sharp and well resolved at room temperature (see also Fig. 9). Three singlets for NH, four *m*-coupled doublets (8.16 and 7.15 ppm) for the xanthene units, two *o*-coupled doublets (8.13 and 6.92 ppm) and two *o*-coupled triplets (7.12 and 7.02 ppm) for the diphenylether unit correspond to the expected C_{2v} symmetry.

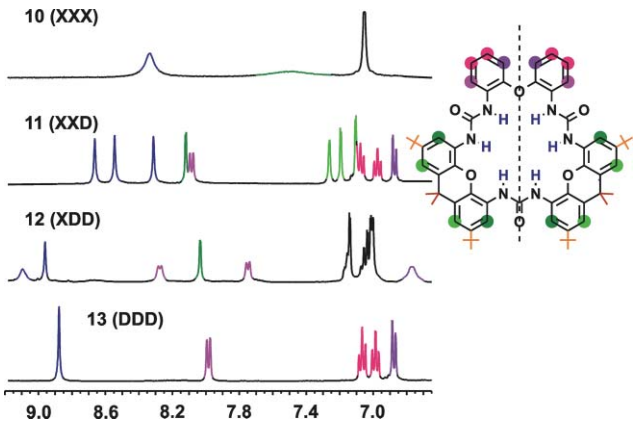


Fig. 8 Sections of the ^{1}H NMR spectra of the cyclic tri-urea compounds **10–13** in DMSO-d_6. The trimer **11** is used to show the signal assignment.

Addition of tetrabutylammonium salts caused no changes for I^-, NO_3^-, HSO_3^-, BF_4^- and SCN^-, while broadened spectra were obtained for $H_2PO_4^-$ and F^-. Sharp spectra, indicating a new, kinetically stable species were obtained for Cl^-, Br^- and CH_3COO^-, as shown for Cl^- in Fig. 9. The similarity of the spectral changes observed suggests the formation of a 1 : 1 complex for the three anions, although for acetate a fivefold excess is required to obtain again a sharp spectrum.

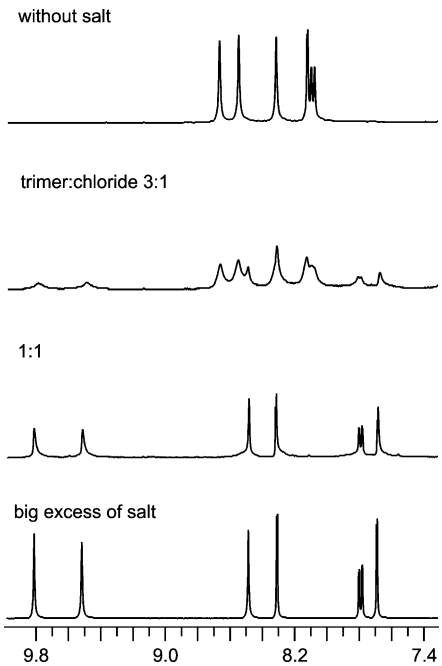


Fig. 9 Aromatic section of the ^{1}H NMR spectra obtained upon stepwise addition of tetrabutylammonium chloride to a 0.1 mM solution of **11** in DMSO-d_6.

For XDD (**12**) the same symmetry is expected as for XXD (**11**). However, the spectrum is generally broadened and several signals are overlapping around 7 ppm (Fig. 8). Four NH protons appear as two peaks (at 9.14 and 8.93 ppm) and are downfield shifted in comparison to **11** and **10**, while the singlet for the remaining two urea protons, which usually appears around 8 ppm, is not visible in Fig. 8. The signals for aromatic protons appear generally slightly shifted upfield. The addition of various anions causes similar spectral changes as observed for **11**, but smaller shifts.

The sharp, well resolved spectrum for **13** is in complete agreement with the expected, time-averaged D_{3h} symmetry, showing a singlet for NH at low field (8.86 ppm), and two doublets (7.97 and 6.87 ppm) and two triplets (7.06 and 6.98 ppm) with *o*-coupling, all with the same intensity. Based on the chemical shifts, all protons experience practically the same environments as the diphenylether unit in **11**. Only small downfield shifts are observed for the signals of **13** upon addition of various anions. This suggests that the high flexibility of the macrocycle weakens any cooperative interaction of the three urea functions with an anion.

UV spectrophotometry

The interaction of all cyclic trimers with various anions was quantitatively studied by UV spectrophotometry. This requires sufficient spectral changes upon complexation (for an example see Fig. 10), which were not obtained in all cases. The spectral variations observed for nitrate, for instance, were not sufficiently significant to allow any interpretation. Stability constants, which could be determined in this way, are collected in Table 2.

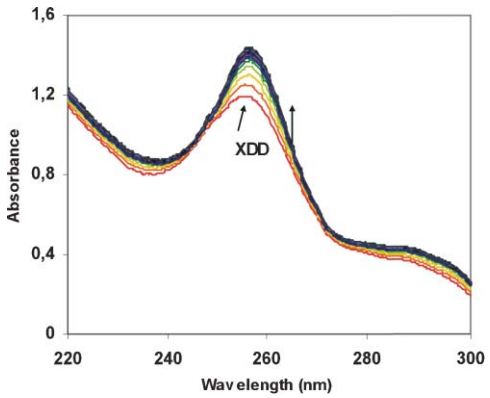


Fig. 10 Experimental spectra obtained upon addition of increasing amounts of chloride to the solution of XDD (**12**) ($c_L = 10^{-5}$ M; $0 \leq R = c_A/c_L \leq 4$).

The evaluation of the spectroscopic data reveals that, in addition to 1 : 1 complexes, 1 : 2 complexes (anion to ligand) may also be formed. It must be kept in mind, however, that a missing constant in Table 2 could be either due to a small value for this constant or to a small spectral change connected with its formation.

The following trends can be extracted from Table 2:

(a) XXD (**11**) and DDD (**13**) form 1 : 1 and 1 : 2 complexes with Cl^- while XDD (**12**) forms only a 1 : 2 complex and XXX (**10**) only a 1 : 1 complex.

(b) As shown for chloride, the values of the stability constants obtained may depend on the counter cation.

(c) Complexes with chloride and acetate show similar stability,[15] while bromide is more weakly bound.[16]

(d) **11** (and chloride) forms the strongest complexes (*e.g.* log $\beta = 6.1$ (1 : 1 complex) and 12.9 (1 : 2 complex) with Bu_4N^+ as counterion).

(e) **12** (1 : 2 complex) and **10** (1 : 1 complex) show the weakest binding.

Table 2 Overall stability constants (log $\beta \pm \sigma$) of the complexes formed by the trimers with chloride, bromide and acetate (counterion : $[Na + 222]^+$ or Bu_4N^+)[14] in acetonitrile ($T = 25\ ^\circ C$)

Anion	Composition (A^- : L)	**10** (XXX)	**11** (XXD)	**12** (XDD)	**13** (DDD)
$\mathbf{Cl}^-$ ($[Na + 222]^+$)	1 : 1	4.5 ± 0.1	5.5 ± 0.2	—	5.1 ± 0.2
	1 : 2	—	11.7 ± 0.1	10.5 ± 0.2	11.3 ± 0.4
$\mathbf{Cl}^-$ (Bu_4N^+)	1 : 1	4.6 ± 0.2	6.1 ± 0.2	—	6.0 ± 0.1
	1 : 2	—	12.9 ± 0.1	10.6 ± 0.5	11.5 ± 0.2
$\mathbf{Br}^-$ (Bu_4N^+)	1 : 1	np[a]	3.9 ± 0.4	—	4.3 ± 0.1
	1 : 2	np[a]	—	8.7 ± 0.2	—
$\mathbf{CH_3COO}^-$ (Bu_4N^+)	1 : 1	np[a]	5.7 ± 0.3	4.7 ± 0.2	5.9 ± 0.4
	1 : 2	np[a]	—	10.0 ± 0.5	—

[a] Determination was not possible.

(f) A small cooperative effect is observed for the formation of the 1 : 2 complexes (Δ = log β (1 : 2 complex)–2 log β (1 : 1 complex) = 0.6–1.1) except with DDD (**13**) and chloride with Bu_4N^+ as counterion where this effect is slightly negative. This means that the formation of biligand complexes is usually favoured as compared to the 1 : 1 complexes.

Microcalorimetric studies are currently being undertaken to obtain a deeper insight by a complete set of thermodynamic data (ΔG, ΔH, and ΔS).

Molecular dynamics calculations

While our design of anion hosts mostly relied on geometrical considerations, fragment search and molecular mechanics calculations, we used molecular dynamics simulations to elucidate the flexibility and the preorganisation of the receptors for anion recognition. In order to investigate the effect of solvent polarity on the conformation, the four triurea hosts were simulated in a box of chloroform and acetonitrile molecules, respectively. MD calculations are currently being carried out for complexes with chloride, bromide, nitrate and mesylate as models for spherical, trigonal planar and trigonal pyramidal anions, and will be published in due course.

The conformations[17] averaged over the whole course of the simulations are shown in Fig. 11. Differences of the structures in chloroform and acetonitrile result from different solvation of the macrocyclic hosts and differences in hydrogen bonding.

In the less polar chloroform, intramolecular hydrogen bonding plays the dominant role due to the poor solvation of the hydrogen bond donor and acceptor groups (Fig. 12). In the case of **10** and **11**, a *trans* → *cis* isomerisation of one of the urea amide bonds occurs during the first ps of the dynamics since the macrocyclic building blocks are too rigid to enable intramolecular hydrogen bonding without significant conformational transitions.

When the MD simulation was started from the crystal structure of **11** (with two *cis* configured amide bonds), the input geometry was stable over the time course of the calculation. Due to the presence of more than a single diphenyl ether unit, the hosts **12** and **13** are flexible enough to enable intramolecular hydrogen bonding without the necessity of a *cis* configured amide bond. Both compounds exhibit on average a C_2 symmetrical conformation, which is characterised by an inward directed carbonyl oxygen hydrogen bonded by four urea protons. Thus, in chloroform, the four anion receptors do not show the expected geometry with the urea hydrogens pointing toward the center of the macrocyclic cavity. Prior to the complexation of anions, the hosts have to rearrange to the proper geometry, which is accompanied by considerable energetic demand (Table 3) and hence by weakening the binding affinity.

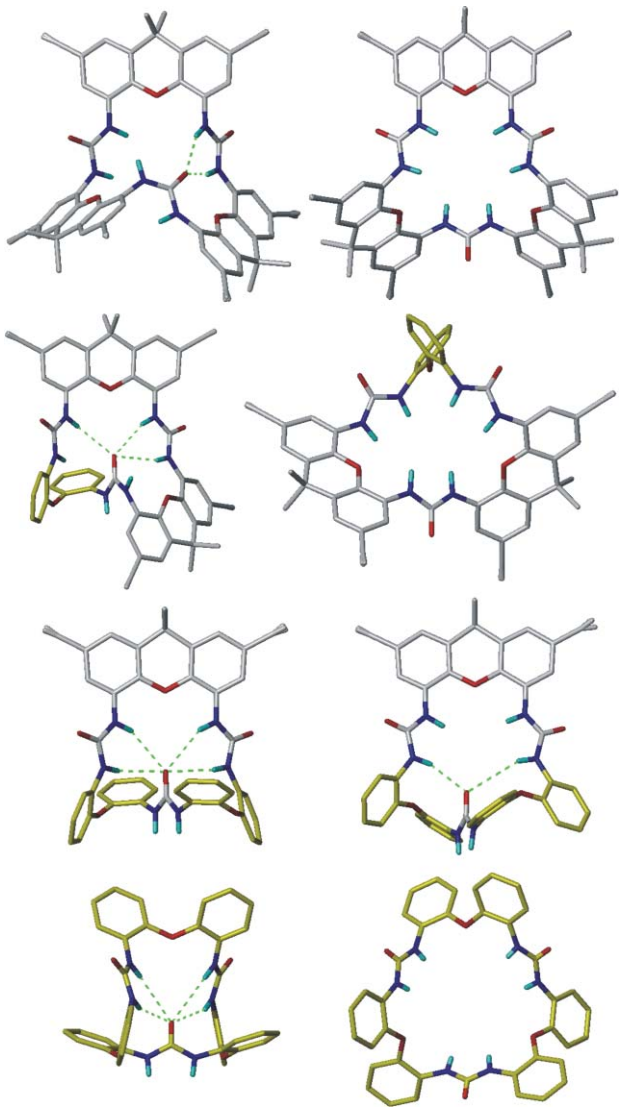


Fig. 11 Average structures obtained from the MD simulations in chloroform (left column) and acetonitrile (right column) for the macrocycles **10–13** (from top to bottom). Nonpolar hydrogen atoms have been omitted, the carbon atoms of the diphenylether units are drawn in yellow.

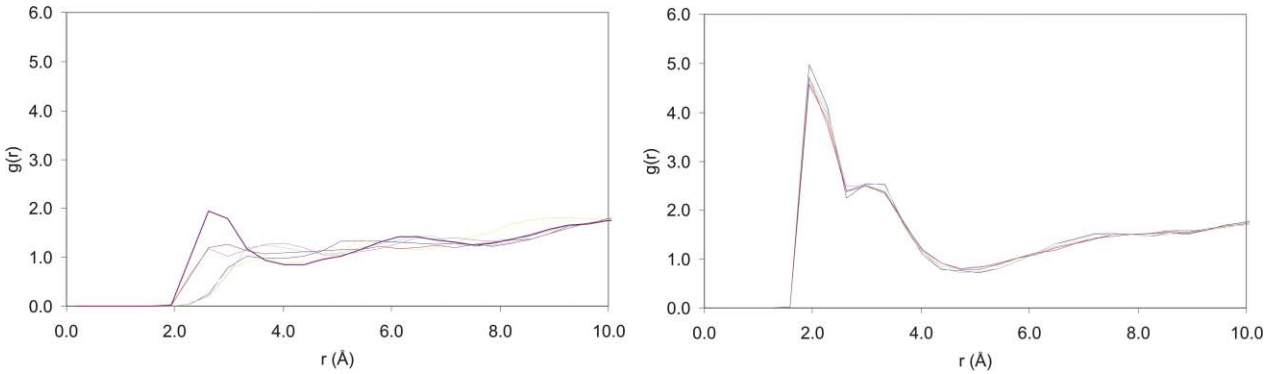


Fig. 12 Radial distribution functions N–H · · · C_{CHCl_3} (left) and N–H · · · N_{CH_3CN} (right) of the six NH protons.

Table 3 Average reorganization energies ($E_{host,complexed} - E_{host,free}$, in kcal mol^{-1}) necessary for the binding of different anions

	Cl^-	Br^-	NO_3^-	Mes^-
10–$CHCl_3$	38.4	32.2	31.9	34.5
11–$CHCl_3$	36.8	34.8	33.3	35.4
12–$CHCl_3$	41.1	37.5	32.2	34.2
13–$CHCl_3$	39.1	31.5	28.3	27.7
10–CH_3CN	11.2	5.7	4.7	5.3
11–CH_3CN	10.9	10.9	7.2	9.1
12–CH_3CN	21.5	15.7	11.8	11.5
13–CH_3CN	17.8	9.5	5.7	5.4

In acetonitrile (the solvent used for the determination of stability constants), the behaviour of the receptor molecules is completely different. The radial distribution functions illustrated for **10** as an example in Fig. 12 reveal that the urea protons are strongly solvated by acetonitrile (forming intermolecular hydrogen bonds) while intramolecular hydrogen bonding was observed only in the case of **12**. The XDD receptor **12** rearranges after about 5 ns to a structure similar to that found in chloroform in which the carbonyl group of the urea flanked by the two diphenyl ether units points to the center of the macrocycle, hydrogen bonded by two urea protons. This conformation is more stable by about 10 kcal mol^{-1} than the initial geometry and does not undergo a further transition during the remaining simulation. The macrocycle **11** adopts a twisted structure in which the planes of the three urea units are stacked on top of each other. Only small conformational changes are necessary to get a suitable structure for the complexation of anions. Indeed, the reorganisation energies upon binding of chloride, bromide, nitrate or mesylate (Table 3) are by far less than for the same host in chloroform and for **12** in acetonitrile. The same is also valid for the hosts **10** and **13**, which adopt on average nonplanar C_s and C_3 structures, respectively, with all the NH protons pointing towards the center of the macrocycle. From the comparison of the two sets of MD simulations it can be concluded that the strong solvation in acetonitrile results in a better preorganisation of the host for anion binding, however, a higher energetical price must in turn be paid for the desolvation in the more polar solvent.

Conclusions

Regarding the initial plan, based on rational considerations backed by advanced molecular modelling, we have to state that the

Table 4 Summary of crystallographic data[aa] CCDC reference numbers 667517–667519. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718114k

	11 (XXD)	**12** (XDD)	**13**·Bu_4NCl (DDD)
Chemical formula	$C_{61}H_{70}N_6O_6 \cdot 2CHCl_3$	$C_{50}H_{50}N_6O_6 \cdot 2DMSO \cdot CH_3OH$	$C_{39}H_{30}N_6O_6 \cdot C_{16}H_{36}NCl$
CCDC ref. numbers	667517	667519	667518
M	1221.97	1019.26	956.60
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	$P\bar{1}$	$P2_12_12_1$	$P2_1/c$
a, Å	14.2014(19)	13.8190(8)	21.9730(16)
b, Å	15.4184(19)	17.9176(10)	14.2644(6)
c, Å	15.7438(17)	21.6376(10)	16.7013(12)
α, °	73.389(9)	90	90
β, °	81.409(10)	90	96.085(6)
γ, °	66.041(9)	90	90
V, $Å^3$	3016.6(6)	5357.5(5)	5205.2(6)
Z	2	4	4
T, K	173	173	173
Reflections	24329	19313	66076
Unique reflections	10411	9414	9795
R_{int}	0.0882	0.0298	0.0866
$wR(F^2)$, all data	0.3167	0.0859	0.1056
Flack-parameter	—	0.02(5)	—

experimental results were different from our expectations. Among the four cyclic triureas **10–13**, the envisaged XXX (**10**) shows the lowest affinity to a simple spherical anion such as chloride, while the binding of the target anion nitrate is considerably weaker. Rigidification of the linkers between the three urea groups does not prevent their intramolecular hydrogen bonding as shown by the crystal structure of XXD (**11**). A similar conformation seems to be possible also for XXX (**10**) for which we have not yet obtained single crystals. Surely the progress in supramolecular chemistry will depend in the future, to a certain degree, on lucky chances, as shown in the present case by the unexpected complexation of two chloride anions[12] by a cyclic hexaurea XXDXXD (**14**).

Experimental

Syntheses

All solvents were of analytical quality (p. a.) and were used without additional purification. All solvents for NMR were purchased from Deutero GmbH. All ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400 MHz using the solvent signals as internal reference. Mass spectra were recorded with the Finnigan MAT 8230 instrument. The melting points were not corrected.

Diisocyanate 3. A solution of the diamine **1** (818 mg, 2.5 mmol) and diisopropylethylamine (746 mg, 2.5 mmol) in dichloromethane (20 cm^3) was added dropwise under a nitrogen flow over 1 h to a vigorously stirred solution of triphosgene (650 mg, 5 mmol) in dichloromethane (20 cm^3). After 3 h the mixture was filtered through silica gel (100 g), which was subsequently washed with dichloromethane (2 × 50 cm^3). The solvent was removed under reduced pressure and the crude product was kept on the rotavap for 1 h at 80 °C to remove excess triphosgene. The diisocyanate **3** (781 mg, 76%) was obtained after cooling as a light-brown solid; mp 168 °C; δ_H (400 MHz, $CDCl_3$): 7.22 (2 H, d, *J* 2.4, Ar*H*), 7.01 (2 H, d, *J* 2.4, Ar*H*), 1.62 (6 H, s, CH_3), 1.30 (18 H, s, *tBu*).

Diisocyanate 4. A solution of diamine **2** (1.48 g, 7.37 mmol) and diisopropylethylamine (1.91 g, 14.7 mmol) in dichloromethane (50 cm^3) was added dropwise under a nitrogen flow over 1 h to a vigorously stirred solution of triphosgene (84 mg, 0.28 mmol) in dichloromethane (50 cm^3). After 3 h the reaction mixture was filtered through silica gel (100 g), which was subsequently washed with dichloromethane (2 × 50 cm^3). The solvent was removed under reduced pressure and the crude oily product was kept on the rotavap for 1 h at 80 °C to remove excess triphosgene. After cooling, the isocyanate **4** (1.64 g, 88%) was obtained as a light-brown oil. The compound could be crystallised to a light-brown solid after initiation with a small crystalline particle; mp > 95 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 7.25 (6 H, m, Ar*H*), 7.01 (2 H, d, *J* 8.2, Ar*H*).

Mono Boc-protected amine 5. A solution of di-*tert*-butyl dicarbonate (5.26 g, 24 mmol) in THF (200 cm^3) was added dropwise over 1 h to a stirred solution of the diamine **1** (8.50 g, 24 mmol) in THF (500 cm^3). After 18 h the solvent was removed under reduced pressure. The residual yellow oil was dissolved in a mixture of ethyl acetate (2 cm^3) and hexane (18 cm^3) and separated by column chromatography (silica gel 1000 cm^3, ethyl acetate–hexane 1 : 8 (v/v)). The monoprotected diamine **5** (6.10 g, 56%) was isolated as a white powder; mp 173 °C; δ_H (400 MHz, DMSO-d_6): 8.86 (1 H, s, N*H*), 7.63 (1 H, d, *J* 2, Ar*H*), 7.13 (1 H, d, *J* 2, Ar*H*), 6.64 (1 H, d, *J* 2.4, Ar*H*), 6.59 (1 H, d, *J* 2.4, Ar*H*), 5.21 (2 H, s, NH_2), 1.53 (6 H, s, CH_3), 1.49 (9 H, s, *tBu*), 1.27 (9 H, s, *tBu*), 1.23 (9 H, s, *tBu*).

Mono Boc-protected amine 6. A solution of di-*tert*-butyl dicarbonate (6.86 g, 31.4 mmol) in THF (150 cm^3) was added dropwise over 1 h with stirring to a solution of the diamine **2** (6.30 g, 31.4 mmol) in THF (200 cm^3). After 48 h at 60 °C the solvent was removed under reduced pressure. The residual brown oil was dissolved in a mixture of toluene (2 cm^3), ethyl acetate (2 cm^3) and hexane (16 cm^3) and was separated by column chromatography (silica gel 1000 cm^3, ethyl acetate–hexane 1 : 5 (v/v)). The monoprotected diamine **6** (4.00 g, 42%) was isolated as a white powder; mp 112 °C; δ_H (400 MHz, DMSO-d_6,): 8.54 (1 H, s, N*H*), 7.64–7.57 (1 H, m, Ar*H*), 7.00–6.87 (3 H, m, Ar*H*), 6.78 (2 H, dd, ^3J 8.0, ^4J 1.6, Ar*H*), 6.58–6.50 (2 H, m, Ar*H*), 1.46 (9 H, s, *tBu*).

Diamine 7. A solution of 4-nitrophenyl chloroformate (1.04 g, 5.1 mmol) in THF (100 cm^3) was added dropwise over 1 h to a stirred solution of the monoprotected diamine **5** (4.65 g, 10.2 mmol) and diisopropylethylamine (1.33 g, 10.2 mmol) in THF (100 cm^3). After stirring at 60 °C for 18 h the solvent was removed under reduced pressure. The residual yellow oil was dissolved in ethyl acetate (100 cm^3) and the solution was washed with 5 N sodium carbonate solution until the yellow colour of nitrophenol disappeared. Then, the solution was washed with distilled water (2 × 100 cm^3) and dried over $MgSO_4$. Evaporation of the solvent gave the protected dimeric diamine **7** as a foam-like solid. The product was dissolved in dichloromethane (50 cm^3), the solution was cooled in an ice bath and trifluoroacetic acid (30 cm^3) was added. The mixture was allowed to reach room temperature during the next 4 h of stirring. Then the reaction mixture was slowly poured into a 5 M solution of sodium carbonate (300 cm^3). The pH was adjusted to 9–10; the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 cm^3). The organic solutions were combined and dried over $MgSO_4$. Evaporation under reduced pressure yielded the dimeric diamine **7** (3.85 g, 98%) as a light-brown powder; mp >200 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 8.90 (2 H, s, N*H*), 8.13 (2 H, d, *J* 2, Ar*H*), 7.11 (2 H, d, *J* 2, Ar*H*), 6.68 (2 H, d, *J* 2, Ar*H*), 6.62 (2 H, d, *J* 2, Ar*H*), 5.26 (4 H, s, NH_2), 1.57 (12 H, s, CH_3), 1.31 (18 H, s, *tBu*), 1.26 (18 H, s, *tBu*); *m/z* (FD) 731.6 (M^+, 100%).

Diamine 8. A solution of 4-nitrophenyl chloroformate (1.34 g, 6.66 mmol) in THF (100 cm^3) was added dropwise over 1 h to a stirred solution of the monoprotected diamine **6** (4.0 g, 13.3 mmol) and diisopropylethylamine (1.72 g, 13.3 mmol) in THF (100 cm^3). After stirring at 60 °C for 18 h the solvent was removed under reduced pressure. Trituration of the oily residue with methanol (100 cm^3) produced a crystalline solid which was filtered off and washed with methanol (3 × 50 cm^3) to remove the residual nitrophenol. The Boc-protected dimeric diamine **8** was isolated as a microcrystalline powder. The product was dissolved in dichloromethane (60 cm^3), the solution was cooled in an ice bath and trifluoroacetic acid (30 cm^3) was added. The mixture was allowed to reach room temperature during the next 4 h of stirring.

The reaction was stopped by slowly pouring the mixture into a 5 M solution of sodium carbonate (300 cm^3). The pH was adjusted to 9–10. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 cm^3). The combined organic solutions were dried over $MgSO_4$. Evaporation under reduced pressure yielded the dimeric diamine **8** (1.83 g, 87%) as a light-brown powder; mp 200 °C; δ_H (400 MHz, DMSO-d_6): 9.16 (2 H, s, N*H*), 8.17 (2 H, dd, ^3J 8.2, *J* 1.5, Ar*H*), 7.01–6.83 (6 H, m, Ar*H*), 6.80 (4 H, d, *J* 8.2, Ar*H*), 6.59–6.50 (4 H, m, Ar*H*), 4.97 (4 H, s, NH_2); *m/z* (FD) 427.0 (M^+, 100%).

Diisocyanate 9. A solution of diamine **8** (1,0 g, 2.34 mmol) and diisopropylethylamine (0.61 g, 2.34 mmol) in a mixture of THF (10 cm^3) and dichloromethane (20 cm^3) was added dropwise under nitrogen during 1 h to a vigorously stirred solution of triphosgene (696 mg, 4.7 mmol) in dichloromethane (20 cm^3). After 3 h the mixture was filtered through silica gel (100 g), which was subsequently washed with dichloromethane (2 × 50 cm^3). The solvent was removed under reduced pressure and the crude product was kept on the rotavap for 1 h at 80 °C to remove excess triphosgene. The diisocyanate **9** (890 mg, 79%) was obtained, after cooling, as a brownish solid; mp 205 °C; δ_H (400 MHz, $CDCl_3$): 8.12 (2 H, dd, ^3J 8.2, ^4J 1.2, Ar*H*), 7.18–6.98 (12 H, m, N*H*, Ar*H*), 6.87–6.80 (4 H, m, Ar*H*).

Cyclic trimer 10. Trifluoroacetic acid (0.3 cm^3) was added to a solution of the diamine **7** (120 mg, 0.12 mmol) in dichloromethane (10 cm^3). After 15 min of stirring, the solvent was evaporated under reduced pressure and the residual light-brown oil was dissolved in dichloromethane (10 cm^3). A solution of the diisocyanate **3** (51 mg, 0.12 mmol) in dichloromethane (10 cm^3) and triethylamine (0.2 cm^3) was added with stirring. After 12 h, the solvent was evaporated, the oily residue was dissolved in ethyl acetate (10 cm^3) and filtered through silica gel (20 g), which was subsequently washed with ethyl acetate (2 × 20 cm^3). The yellow oil obtained after evaporation was dissolved in hexane (10 cm^3). After 2 h the cyclic trimer **10** started to precipitate. It was filtered off, yielding 50 mg (37%) as thin white flakes; mp >340 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 8.34 (6 H, s, N*H*), 7.50 (6 H, br.s, Ar*H*), 7.06 (6 H, s, Ar*H*), 1.44 (18 H, s, CH_3), 1.23 (54 H, s, *tBu*); *m/z* (FD) 1134.8 (M^+, 100%).

Cyclic trimer 11. The diamine **7** (120 mg, 0.164 mmol) was dissolved in acetonitrile (25 cm^3). A solution of the diisocyanate **4** (42 mg, 0.164 mmol) in acetonitrile (15 cm^3) was added dropwise over 30 min with vigorous stirring under nitrogen. After 12 h a white precipitate of the trimer **11** (100 mg, 62%) was filtered off; mp >280 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 8.71 (2 H, s, N*H*), 8.59 (2 H, s, N*H*), 8.36 (2 H, s, N*H*), 8.16 (d, 2 H, *J* 2.0, ArH_{xan}), 8.13 (2 H, d, *J* 7.8, ArH_{diph}), 7.30 (2 H, d, *J* 2.0, ArH_{xan}), 7.24 (2 H, d, *J* 2.0, ArH_{xan}), 7.15 (2 H, d, *J* 2, ArH_{xan}), 7.12 (2 H, t, *J* 7.6, ArH_{diph}), 7.02 (2 H, t, *J* 7.0, ArH_{diph}), 6.92 (2 H, d, *J* 7.8, ArH_{diph}), 1.61 (12 H, s, CH_{3xan}), 1.29 (18 H, s, *tBu*), 1.21 (18 H, s, *tBu*); *m/z* (ESI) 1005.6 (M^+ + Na, 100%).

Cyclic trimer 12. Solutions of the diisocyanate **9** (100 mg, 0.201 mmol) in dichloromethane (25 cm^3) and the diamine **1** (73 mg, 0.201 mmol) in dichloromethane (25 cm^3) were added simultaneously with stirring under nitrogen over 2 h to a flask containing dichloromethane (20 cm^3). After 18 h the solvent was evaporated under reduced pressure, and the trimer **12** (70 mg, 40%) was isolated by column chromatography (ethyl acetate–hexane, 1 : 5) as a white powder; mp >340 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 9.14 (2 H, s, N*H*), 8.93 (2 H, s, N*H*), 8.30 (2 H, d, *J* 7.3, ArH_{diph}), 8.07 (2 H, d, *J* 1.5 Hz, ArH_{xan}), 8.01 (2 H, s, N*H*), 7.75 (2 H, d, *J* 7.3, ArH_{diph}), 7.25–7.13 (2 H, m, ArH_{diph}, overlapped with d at 7.17, 2 H, *J* 1.8, ArH_{xan}), 7.10–6.99 (8 H, m, ArH_{diph}), 6.74 (2 H, d, *J* 7.7, ArH_{diph}), 1.74 (3 H, s, CH_{3xan}), 1.49 (3 H, s, CH_{3xan}), 1.30 (18 H, s, *tBu*); *m/z* (ESI) 853.4 (M^+ + Na, 100%).

Cyclic trimer 13. Solutions of the diisocyanate **4** (80 mg, 0.32 mmol) in dichloromethane (25 cm^3) and the diamine **8** (135 mg, 0.32 mmol) in THF (25 cm^3) were added simultaneously with stirring under nitrogen over 2 h to a flask containing dichloromethane (50 cm^3). After 18 h the solvent was evaporated under reduced pressure and the crude product was triturated with hexane (50 cm^3). The solid was filtered off and washed with hexane (2 × 25 cm^3) to yield the trimer **13** (156 mg, 72%) as a beige powder; mp >184 °C (decomp.); δ_H (400 MHz, DMSO-d_6): 8.86 (6 H, s, N*H*), 7.97 (6 H, dd, ^3J 7.8, ^4J 1.2, Ar*H*), 7.06 (6 H, ddd, ^3J 7.4, ^3J 7.8, ^4J 1.2, Ar*H*), 6.98 (6 H, ddd, ^3J 8.2, ^3J 7.4, ^4J 1.6, Ar*H*), 6.87 (6 H, dd, ^3J 8.2, ^4J 1.2, Ar*H*); *m/z* (ESI) 701.2 (M^+ + Na, 100%).

Absorption spectrophotometric titrations

Stability constants were determined by absorption spectrophotometry using a VARIAN (Cary 3) spectrophotometer equipped with a thermoregulated cell compartment (25.0 ± 0.1 °C). Small volumes (0.02 cm^3) of a solution containing the anion were added to 2 cm^3 of the ligand solution, directly in the spectrophotometric cell of 1 cm path length.

Spectra were recorded in the wavelength range 220–300 nm after each addition. The ratio anion : ligand (A : L), reached at the end of the titration, was between 2 and 100 according to the ligands and the anions studied. Preliminary kinetic studies were performed to make sure that the equilibrium of the systems was reached. For each system, at least two independent measurements were performed. The software SPECFIT Global Analysis System V3.0 32 bit for Windows was used to calculate the stability constants (log β) of the complexes formed.[18]

The various anions studied were provided as tetraalkylammonium salts: Bu_4NCl (Fluka, ≥97%), Bu_4NBr (Fluka, ≥99%), Bu_4NAcO (Aldrich, ≥97%), Et_4NNO_3 (Fluka, ≥99%). In the case of chloride, a mixture of NaCl (SDS, ≥95.5%) + 222 (Merck, Kryptofix) was also used to provide a bulky cation. These salts were dried under vacuum at room temperature during 24 h.

All the solutions were prepared in acetonitrile (Riedel de Haën, ≥99.5%). No supporting electrolyte was added to the solution because of (i) the insolubility of most inert salts in this solvent and (ii) the very small ligand and anion concentrations used (2 × 10^{-5} M).

Molecular modelling

All molecular dynamics simulations were performed using the AMBER 7 and AMBER 9 software packages and the *gaff* parameter set.[19] The initial geometry of the macrocycles was obtained by manual construction with an *all-trans* arrangement of the urea amide groups. Charges (see ESI†) were derived following the standard RESP procedure[20] from a 6-31G*

electrostatic potential calculated with the Gaussian98 program[21] and the molecule structures were transferred into the LEaP format. Subsequently, a rectangular box of chloroform or acetonitrile molecules, respectively (approximately 14 Å solvent layer thickness on each side), was added. For the chloroform solvent model, the corresponding parameters[22] of AMBER 7 and for the acetonitrile model the parameters by Kollman *et al.*[23] were used. Missing parameters for the ca–oh bond length, the ca–ca–oh and ca–oh–ho bond angles, as well as the X–ca–oh–X and ca–ca–c–oh dihedral angles were adopted from the AMBER 7 *parm98* parameter set. The missing parameter for ca–c3–ca was taken from Kirchhoff *et al.*[24] The solvated structures were subjected to 5000 steps of minimisation followed by a 30 ps belly dynamics (300 K, 1 bar, 1 fs timestep) for solvent relaxation and a 100 ps equilibration period. Subsequently, MD simulations were performed in a NTP (300 K, 1 bar) ensemble for at least 9 ns using a 1 fs time step. Constant temperature and pressure conditions were achieved by the weak coupling algorithm and isotropic position scaling. Temperature and pressure coupling times of 0.5 ps and 1.0 ps, respectively, and the experimental compressibility values of 100×10^{-6} bar^{-1} for chloroform and of 87.1×10^{-6} bar^{-1} for acetonitrile were used. The particle mesh Ewald (PME) method[25] was applied to treat long-range electrostatic interactions, and the van der Waals interactions were truncated by using a cut-off value of 9 Å. Bonds containing hydrogen atoms were constrained to their equilibrium length using the SHAKE algorithm. Snapshots were recorded every 2 ps.

Geometrical and energetical analyses of the trajectories were carried out with the carnal and anal modules of AMBER 7. Graphical analysis of the results was performed with the SYBYL program.[26]

Single-crystal X-ray diffraction

Data were collected on a STOE-IPDS-II two-circle diffractometer employing graphite-monochromated MoKα radiation (0.71073 Å). Data reduction was performed with the X-Area software.[27] An empirical absorption correction was performed using the MULABS[28] option in PLATON.[29] Structures were solved by direct methods with SHELXS-90[30] and refined by full-matrix least-squares techniques with SHELXL-97.[31]

All non-H atoms were refined with anisotropic displacement parameters. Hydrogens were included at calculated positions and allowed to ride on their parent atoms. The H atoms at the urea nitrogens of **13@Bu$_4$NCl** and **12** were freely refined. One chloroform molecule of **11** is disordered over two positions with a ratio of the site occupation factors of 0.528(9) : 0.472(9). In **13@Bu$_4$NCl** the terminal ethyl group of a butyl side chain is disordered over two positions with a ratio of the site occupation factors of 0.551(8) : 0.449(8). The C–C bond lengths of this butyl chain were restrained to 1.50(1) Å and the 1–3 C–C distances were restrained to 2.4(1) Å.

Crystallographic data are summarised in Table 4.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (Bö523/17-1,2 and TH 520/6-1) and CNRS is gratefully acknowledged. We thank Dr Werner Mögelin for preliminary calculations and Dr Uta Schädel for preliminary screening experiments.

Notes and references

1 S. O. Kang, R. A. Begum and K. Bowman-James, *Angew. Chem.*, 2006, **118**, 8048–8061, (*Angew. Chem., Int. Ed.*, 2006, **45**, 7882–7894).
2 Y. Morzherin, D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1993, **58**, 7602–7605; A. Casnati, L. Pirondini, N. Pelizzi and R. Ungaro, *Supramol. Chem.*, 2000, **12**, 53–65; M. D. Lankshear, A. R. Cowley and P. D. Beer, *Chem. Commun.*, 2006, 612–614; B. Schazmann, N. Alhashimy and D. Diamond, *J. Am. Chem. Soc.*, 2006, **128**, 8607–8614.
3 K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 10241–10249; S. Kubik, R. Goddard, R. Kirchner, D. Nolting and J. Seidel, *Angew. Chem.*, 2001, **113**, 2722–2725, (*Angew. Chem., Int. Ed.*, 2001, **40**, 2648–2651); M. A. Hossain, S. O. Kang, D. Powell and K. Bowman-James, *Inorg. Chem.*, 2003, **42**, 1397–1399.
4 A. A. P. Bisson, V. M. Lynch, M. C. Monahan and E. V. Anslyn, *Angew. Chem.*, 1997, **109**, 2435–2437, (*Angew. Chem., Int. Ed.*, 1997, **36**, 2340–2342); S. O. Kang, M. A. Hossain, D. Powell and K. Bowman-James, *Chem. Commun.*, 2005, 328–330.
5 K. D. Shimizu and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, 1995, **92**, 12403–12407; A. Shivanyuk, M. Saadioui, F. Broda, I. Thondorf, M. O. Vysotsky, K. Rissanen, E. Kolehmainen and V. Böhmer, *Chem.–Eur. J.*, 2004, **10**, 2138–2148; Y. Rudzevich, V. Rudzevich, D. Schollmeyer, I. Thondorf and V. Böhmer, *Org. Lett.*, 2005, **7**, 613–616.
6 For a general review on anion receptor chemistry see: J. L. Sessler, P. A. Gale, and W. Cho, in *Anion Receptor Chemistry, Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, UK, 2006 (for the urea-based receptors see pp. 193–205); P. D. Beer and P. A. Gale, *Angew. Chem.*, 2001, **113**, 502–532, (*Angew. Chem., Int. Ed.*, 2001, **40**, 486–516); for relevant examples on macrocyclic urea-based receptors see also: S. J. Brooks, S. E. García-Garrido, M. E. Light, P. A. Cole and P. A. Gale, *Chem.–Eur. J.*, 2007, **13**, 3320–3329; B. H. M. Snellink-Ruël, M. M. G. Antonisse, J. F. J. Engbersen, P. Timmermann and D. N. Reinhoudt, *Eur. J. Org. Chem.*, 2000, 165–170; R. Herges, A. Dikmans, U. Jana, F. Köhler, P. G. Jones, I. Dix, T. Fricke and B. König, *Eur. J. Org. Chem.*, 2002, 3004–3014; D. Ranganathan and C. Lakshmi, *Chem. Commun.*, 2001, 1250–1251.
7 For the complexation of nitrate by a macrocycle containing two urea units see: P. Blondeau, J. Benet-Buchholz and J. de Mendoza, *New J. Chem.*, 2007, **31**, 736–740.
8 Manuscript in preparation.
9 B. B. C. Hamann, N. R. Branda and J. Rebek, Jr., *Tetrahedron Lett.*, 1993, **34**, 6837–6840.
10 P. Bühlmann, S. Nishizawa, K. P. Xiao and Y. Umezawa, *Tetrahedron*, 1997, **53**, 1647–1654; V. Alcázar, M. Segura, P. Prados and J. de Mendoza, *Tetrahedron Lett.*, 1997, **39**, 1033–1036.
11 P. R. Ashton, B. Hörner, O. Kocian, S. Menzer, A. J. P. White, J. F. Stoddart and D. J. Williams, *Synthesis*, 1996, **8**, 930–940.
12 D. Meshcheryakov, V. Böhmer, M. Bolte, V. Hubscher-Bruder, F. Arnaud-Neu, H. Herschbach, A. Van Dorsselaer, I. Thondorf and W. Mögelin, *Angew. Chem.*, 2006, **118**, 1679–1682, (*Angew. Chem., Int. Ed.*, 2006, **45**, 1648–1652).
13 The complicated solvent mixture developed since, upon evaporation, an "unsuccessful" solvent was replaced by a different one and so on, until finally, suitable single crystals were obtained.
14 The 222 cryptand is known to be a good complexant for Na^+ cation. See for instance: M. K. Chantooni and I. M. Kolthoff, *J. Solution Chem.*, 1985, **14**, 1–12.
15 The urea moiety should be well adapted to acetate because of its ability to form two N–H···O bonds with two oxygen atoms of the anion, see: M. Boiocchi, L. Del Boca, D. Esteban-Gomez, L. Fabbrizzi, M. Licchelli and E. Monzani, *J. Am. Chem. Soc.*, 2004, **126**, 16507–16514.
16 The interaction *via* hydrogen bonds decreases for the spherical halides with increasing radius since it leads to a decrease of their charge density in the order $Cl^- > Br^- > I^-$, see: V. Amendola, M. Boiocchi, B. Colasson and L. Fabbrizzi, *Inorg. Chem.*, 2006, **45**, 6138–6147.
17 The macrocyclic receptors were constructed manually with an *all-trans* arrangement of the urea amide groups.
18 H. Gampp, M. Maeder, C. J. Meyer and A. D. Zuberbühler, *Talanta*, 1985, **32**, 257–264.
19 D. A. Case, D. A. Pearlman, J. W. Caldwell, T. E. Cheatham III, J. Wang, W. S. Ross, C. L. Simmerling, T. A. Darden, K. M. Merz,

R. V. Stanton, A. L. Cheng, J. J. Vincent, M. Crowley, V. Tsui, H. Gohlke, R. J. Radmer, Y. Duan, J. Pitera, I. Massova, G. L. Seibel, U. C. Singh, P. K. Weiner and P. A. Kollman, *AMBER 7*, University of California, San Francisco, USA, 2002; D. A. Pearlman, D. A. Case, J. W. Caldwell, W. S. Ross, T. E. Cheatham III, S. DeBolt, D. Ferguson, G. Seibel and P. A. Kollman, *Comput. Phys. Commun.*, 1995, **91**, 1–41.
20 C. I. Bayly, P. Cieplak, W. D. Cornell and P. A. Kollman, *J. Phys. Chem.*, 1993, **97**, 10269–10280.
21 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98*, Revision A.11, Gaussian, Inc., Pittsburgh PA, USA, 2001.
22 T. Fox and P. Kollman, *J. Phys. Chem. B*, 1998, **102**, 8070–8079; P. Cieplak, J. Caldwell and P. Kollman, *J. Comput. Chem.*, 2001, **22**, 1048–1057.
23 X. Grabuleda, C. Jaime and P. A. Kollman, *J. Comput. Chem.*, 2000, **21**, 901–908.
24 P. D. Kirchhoff, M. B. Bass, B. A. Hanks, J. M. Briggs, A. Collet and J. A. McCammon, *J. Am. Chem. Soc.*, 1996, **118**, 3237–3246.
25 T. Darden, D. York and L. Pedersen, *J. Chem. Phys.*, 1993, **98**, 10089–10092; U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee and L. G. Pederson, *J. Chem. Phys.*, 1995, **103**, 8577–8593.
26 *Sybyl 7.2*, Tripos Ass., Inc., South Hanley Rd., St. Louis, Missouri, 63144, USA, 1699.
27 *X-Area. Area-Detector Control and Integration Software*, Stoe & Cie, Darmstadt, Germany, 2001.
28 R. H. Blessing, *Acta Crystallogr., Sect. A*, 1995, **51**, 33–38.
29 A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7–13.
30 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467–473.
31 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.

