Macrocyclic oligoureas with xanthene and diphenyl ether units†

Denys Meshcheryakov,[a] Michael Bolte[b] and Volker Böhmer*[a]

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Two cyclic oligoureas with 64- and 80-membered rings in which two sets of three or four rigid xanthene (X) units are connected *via* flexible diphenyl ether (D) units were synthesized by a stepwise fragment condensation. The compounds were characterized by ^{1}H NMR and ESI mass spectrometry. The structure of the cyclic octamer (XXXDXXXD) was additionally confirmed by single crystal X-ray analysis. The molecule assumes a strongly folded conformation with distorted C_2-symmetry, stabilized by intramolecular hydrogen bonds. Surprisingly, intermolecular hydrogen bonds between the macrocycles were not observed. ^{1}H NMR spectra suggest a C_2 symmetrical conformation of the octamer in solution also, while its kinetically stable complex with three chloride ions has no symmetry element at all.

Introduction

Rapid developments have been observed for anion receptors during recent years.[1] The importance of anions in biology and other life science areas continuously stimulates the research, leading also to the construction of various supramolecular receptors.[2] Neutral molecules possessing NH binding groups—amide,[3] urea[4] and pyrrole-based[5]—are effective ligands able to bind anions by several directed hydrogen bonds, analogously to receptors in nature.[6]

Starting from the idea (based on MD-simulations) that a cycle in which three urea groups are linked *via* xanthene spacers should be a good ligand for nitrate anions,[7] we synthesized all possible tri- and tetraureas consisting of xanthene (X)[8] and diphenyl ether (D)[9] units.[10,11] While the expected selectivity for nitrate was not observed, we found during these studies, that the cyclic hexaurea XXDXXD showed a strong affinity for the simultaneous complexation of ***two*** chloride anions,[12] a tendency which is also found for XDXDXD, although less pronounced.[13] One of the questions arising from these results was whether larger cyclic ureas with a suitable combination of X and D units would be able to complex simultaneously more than two chloride (or other) anions. We describe below the synthesis and some properties of the cyclic octaurea XXXDXXXD—including its crystal structure—and of the cyclic decamer XXXXDXXXD.

Results and discussion

Syntheses

The general strategy for the preparation of the two macrocycles is based on the diamino-pentamer **6** which is cyclized in the final step with the trimeric diisocyanate **5** in a 3+5 reaction or the pentameric diisocyanate **7** in a 5+5 reaction. This allowed the economical use of the same intermediates/fragments during the synthesis, as shown in Scheme 1.

The synthesis starts with the reaction of diisocyanate **2** with the monoprotected amine **1** in chloroform.[13] The resulting trimer is deprotected with trifluoroacetic acid in dichloromethane to give diamine **3** (XDX, yield 91%). Reaction of **3** with excess triphosgene in dichloromethane/acetonitrile leads to the diisocyanate **5**, which can be obtained quantitatively.

For the preparation of the diamino-pentamer **6** (XXDXX) the diamine **3** was reacted with two equivalents of isocyanate **4**, which can be easily obtained from amine **1**. After deprotection the diamine **6** was isolated as a white solid in 62% yield by treatment of the crude product with methanol.

The reaction of **6** with the trimeric diisocyanate **5** (XDX) was carried out in a mixture of dichloromethane, THF and acetonitrile (1:3:3). After recrystallization from methanol the cyclic octamer **8** was isolated in yields up to 36%.

For the synthesis of the cyclic decamer **9** a portion of diamine **6** was converted to the respective diisocyanate **7** by reaction with an excess of triphosgene in THF. The resulting crude brown solid was then reacted with the stoichiometric amount of diamine **6** in chloroform. The crude reaction product was dissolved in ethanol and cooled. After 24 h a white solid was isolated by filtration and identified as cyclic decaurea **9**. The highest yields thus obtained were about 18%.

Crystal structure

Single crystals of the cyclic octaurea **8** were obtained by slow evaporation of a solution in DMSO and dichloromethane. The compound crystallizes with 8 molecules of CH_2Cl_2 and 9 molecules of DMSO.

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[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] *Fachbereich Chemie und Pharmazeutische Wissenschaften, Institut für Anorganische Chemie, Johann Wolfgang Goethe-Universität Frankfurt, Max-von-Laue-Str. 7, D-60438 Frankfurt/Main, Germany. E-mail: bolte@chemie.uni-frankfurt.de; Fax: +49 (0) 69 79829239; Tel: +49 (0) 69 79829136*

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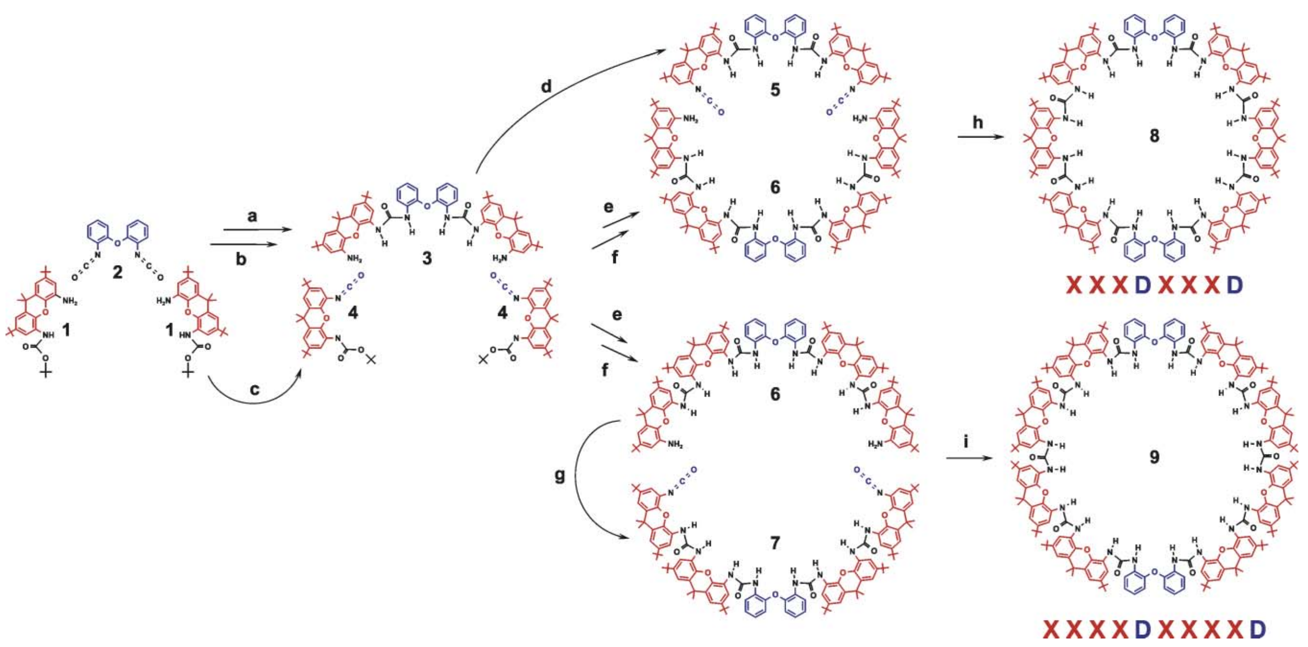

Scheme 1 Syntheses of cyclic polyureas and their precursors: a) reaction of diisocyanate **2** with monoprotected amine **1** followed by b) deprotection to give **3**; c) formation of isocyanate **4** from monoprotected diamine **1**; d) formation of diisocyanate **5** from diamine **3**; e) reaction of diamine **3** with isocyanate **4** followed by f) deprotection to give **6**; g) formation of diisocyanate **7** from diamine **6**; h) cyclization of diisocyanate **5** with diamine **6**; i) cyclization of diisocyanate **7** with diamine **6**.

To describe and discuss the conformation assumed by the molecule, the numbering scheme explained in Fig. 1 is used. The eight urea groups are characterized by capital letters *A* to *H* and the two aminophenyl fragments of each urea are distinguished by ′ and ″, *e.g.* N(*B*′) and N(*B*″) for the nitrogen atoms of urea *B*. The ether oxygens in the xanthene and diphenyl ether fragments are characterized by two capital letters *e.g.* O(*AB*) or O(*DE*).

As shown in Fig. 2 the molecule assumes a folded, compact conformation which is stabilized by several intramolecular hydrogen bonds. Intermolecular hydrogen bonds between molecules of **8** are not observed.

Although the 64-membered macrocycle should be flexible enough not to exert any remarkable steric strain, the interplanar angles found for the aromatic rings of the xanthene units vary from

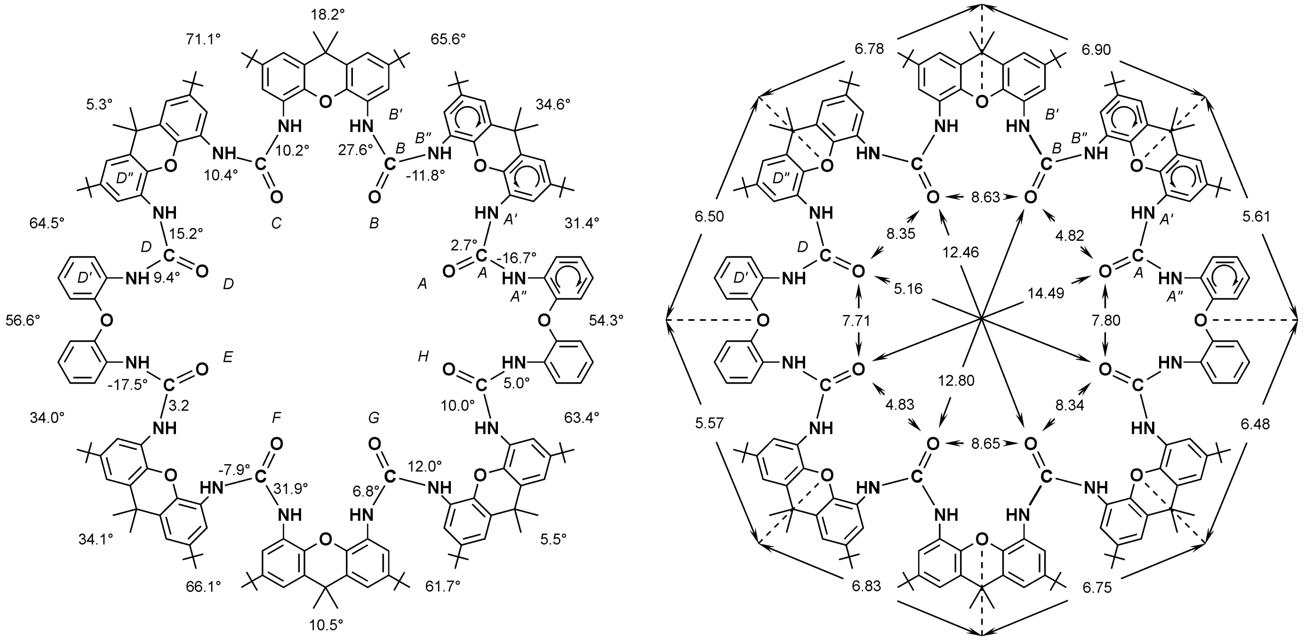

Fig. 1 Left: numbering scheme of cyclic octaurea **8** and interplanar angles of the aromatic rings (outside of the cycle) and the torsion angles around C–N bonds (mainly inside); right: intramolecular distances between carbonyl oxygens (inside of the cycle) and ether oxygens (outside of the cycle).

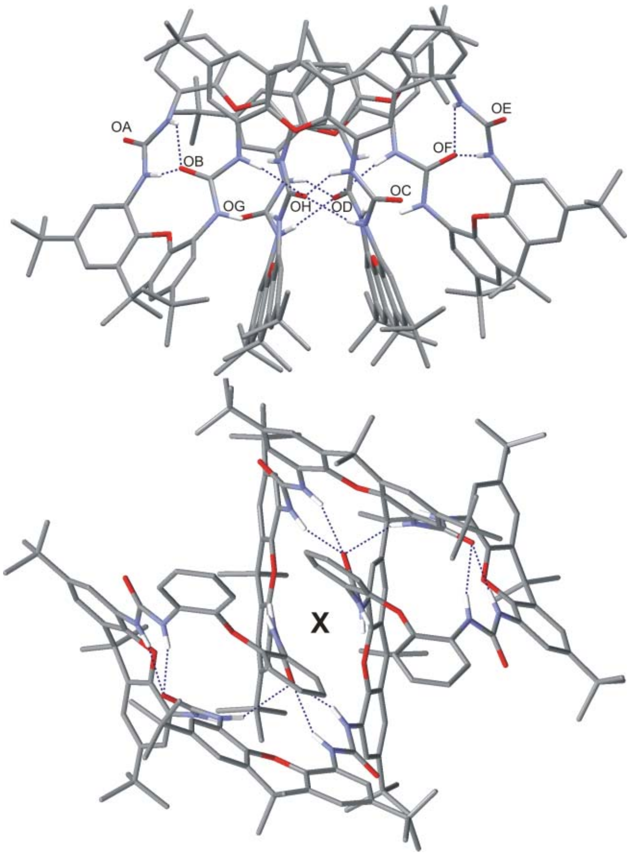

Fig. 2 Molecular conformation of the cyclic octaurea **8** seen from two directions turned by about 90° with respect to each other. The pseudo two-fold axis is indicated by a cross.

5.3/5.5° for the two opposite units *C*/*D* and *G*/*H* to 34.1/34.6 for the opposite pair *E*/*F* and *A*/*B*. This is more than half of the angles (54.3/56.6) found in the two flexible diphenyl ether units.

Also, for the torsion angles around the urea bonds (C–N) there is a striking similarity for the opposite pairs *A* (2.7°/–16.7°) and *E* (3.2°/–17.5°), *B* (–11.8°/27.6°) and *F* (–7.9°/31.9°), *C* (10.2°/10.4°) and *G* (6.8°/12.0°) and *D* (15.2°/9.4°) and *H* (10.0°/5.0°). This might be described by a virtual pseudo-C_2-axis perpendicular to the drawing plane of Fig. 2.

And finally this is also expressed by the O–O-distances of adjacent carbonyl groups which are strikingly similar for opposite pairs, ranging from 4.82 Å/4.83 Å for O(*A*)–O(*B*)/O(*E*)–O(*F*), over 7.71 Å/7.80 Å and 8.35 Å/8.34 Å to 8.63 Å/8.65 Å for O(*B*)–O(*C*)/O(*F*)–O(*G*).

Urea functions are able to form bifurcated hydrogen bonds with the carbonyl oxygen as an acceptor and the NH groups as hydrogen bond donors. Chains of such bifurcated H-bonds are found in the crystal lattice of various diarylureas[14] and in the hydrogen bonded belt of capsules formed by tetra-urea calix[4]arenes.[15]

In the structure of **8** two sequences of two bifurcated H-bonds are found: one between N(*C*) as the donor and O(*H*) as the acceptor and N(*H*) as the donor and O(1S), the oxygen of one of the included DMSO molecules, as the acceptor and the second between N(*G*) as the donor and O(*D*) as the acceptor and N(*D*) as the donor and O(3S) as the acceptor.

In addition N(*B*) forms a bifurcated hydrogen bond to O(4S) and single hydrogen bonds are found between N(*A*′) and O(*B*), N(*E*′) and O(*F*) and N(*F*″) and O(2S).

Fig. 3 shows the packing of the molecules, seen along the *a*-axis. While the DMSO molecules, even those which are not involved in hydrogen bonding, are situated in the close neighborhood of the octaurea the methylenchloride molecules form layers between sheets of molecules perpendicular to the *bc*-plane. The molecule is folded to form a compact conformation, where a "polar" layer of urea groups is located between two layers consisting of substituted benzene rings along with their alkyl groups. The whole conformation is fixed and held by a system of intramolecular hydrogen bonds connecting the "internal" urea groups, which are hindered in this way from forming hydrogen bonds with other octamer molecules.

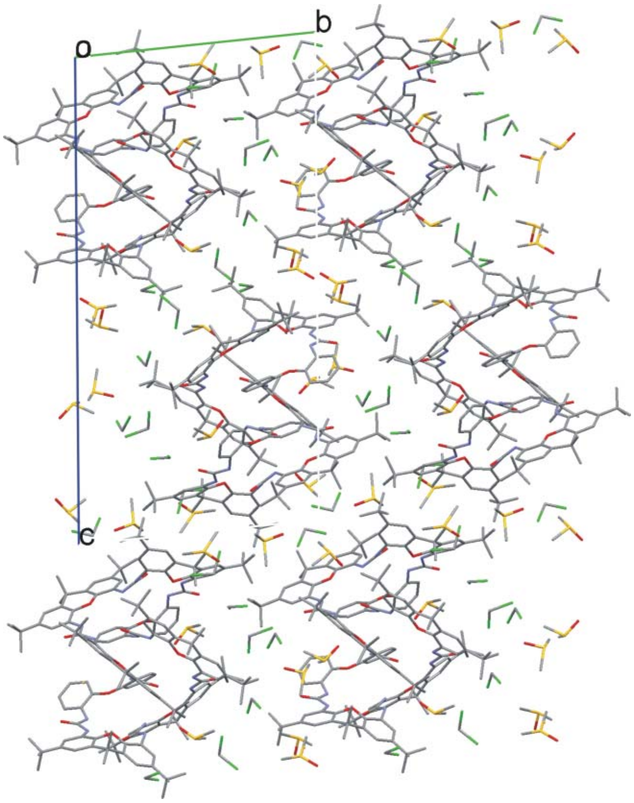

Fig. 3 Packing diagram, seen along the *a*-axis.

NMR studies

The pure octamer **8** is insoluble in DMSO-d_6 and can be solubilized only in the presence of tetrabutylammonium (= TBA) chloride. However, the resulting spectrum is broad and insignificant. On the other side, the compound is soluble in THF-d_8 where it produces a sharp spectrum, suggesting a stable conformation (Fig. 4).

In the "most ideal" case (*i.e.* fast conformational exchange on the NMR timescale, no intra- or intermolecular hydrogen bonding) a spectrum in accordance with time-averaged D_{2h} symmetry could be expected with three C_2 axes, one of them perpendicular to the drawing plane of the cycle (Fig. 2), along with three symmetry planes perpendicular to each other. Such a

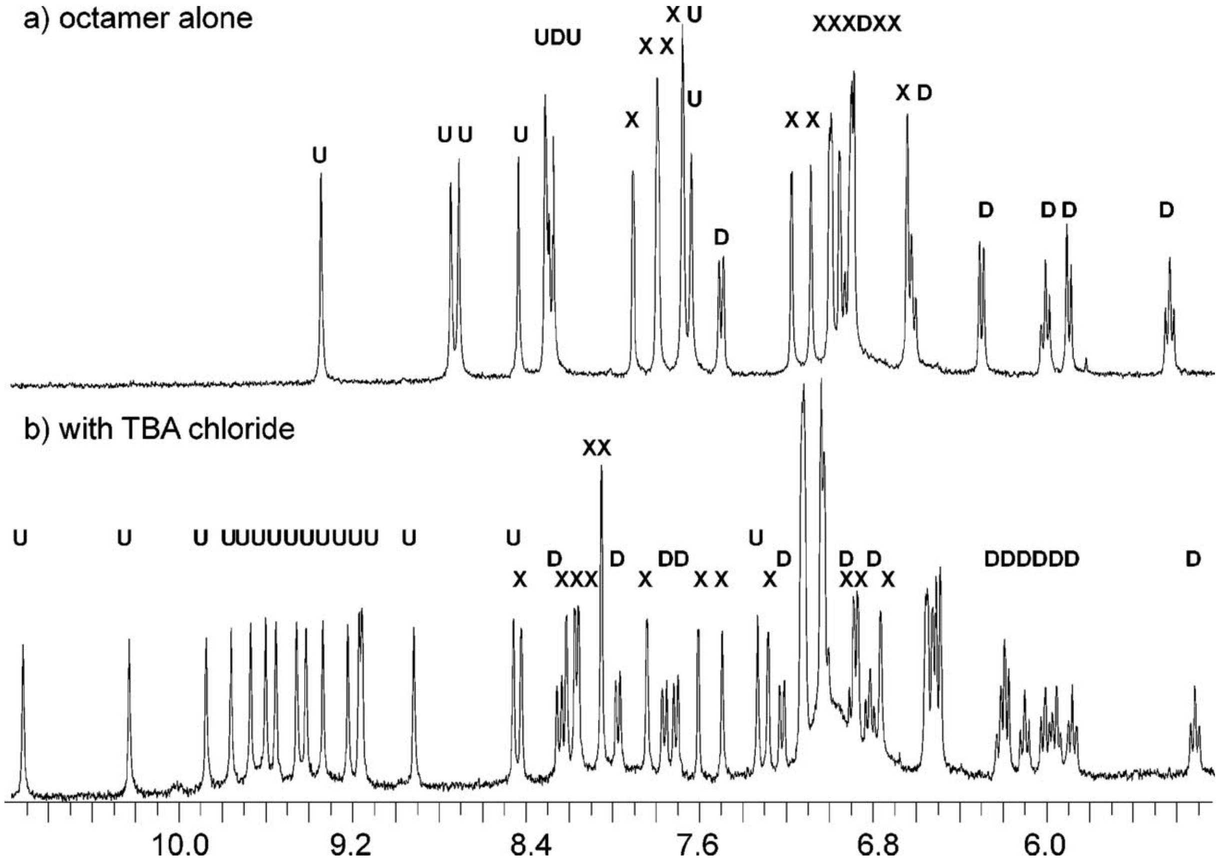

Fig. 4 Interaction of the octamer **8** with TBA chloride in THF-d_8; ^{1}H NMR spectrum of a) the pure octaurea **8**, and b) in the presence of 3 moles TBA chloride. The signals for urea (U), xanthene (X) and diphenyl ether (D) are marked as far as they are unambiguously assignable.

spectrum should contain signals for one fourth of the molecule, namely 4 singlets for urea protons, 4 signals for the aromatic protons of the D units (*ortho*- and *meta*-coupled), 6 signals for the aromatic protons of the xanthene units (*m*-coupled, all with the intensity of 4 H), 2 singlets for methyl groups (with intensities of 12 H and 24 H, respectively) and 3 singlets for tert-butyls (36 H each). However, the number of signals in the real spectrum is distinctly higher.

Six singlets with the same intensity (6 H each) are observed for the methyl groups (at 1.20–1.80 ppm) and the number of the other signals is doubled compared to the "ideal" case (see Fig. 4). Eight singlets for the NH-protons appear between 7.6 ppm and 9.4 ppm (indicating different hydrogen bonding and/or shielding). The xanthene protons (12 *m*-coupled doublets) are found between 6.6 ppm and 7.9 ppm. Three doublets (5.9, 6.3 and 7.5 ppm) and two triplets (5.45 and 6.0 ppm) of the diphenyl ether units are well resolved, while the remaining doublet (8.3 ppm) and triplets (6.65 and 6.9 ppm) overlap with other signals. This is in agreement with a conformation possessing either a mirror plane (C_S), or a twofold axis (C_2) or an inversion center (S_2). Considering the conformation found in the crystal, a time-averaged C_2-symmetry seems most likely. This means that the compact conformation, stabilized by intramolecular hydrogen bonds in solution, is incorporated with slight distortions into the crystal lattice.

When TBA chloride is added stepwise to a solution of the octamer **8** in THF-d_8, new peaks for the complex (with chloride) appear in the spectrum (in addition to the signals of the uncomplexed compound) as soon as 0.2–0.3 equivalents of chloride are added. Upon further addition of TBAC the peaks of the complex rise, while the last traces of free ligand disappear finally when (at least) 3 equivalents of salt have been added. Further portions of chloride do not influence the signal intensity of the complex. Thus, we can cautiously conclude, that one octamer molecule binds three chloride anions in a kinetically stable (NMR timescale) complex. This result is especially intriguing in connection with the complexation of two chloride anions by the smaller XXDXXD cycle, reported before.[13]

The spectrum of the chloride complex of **8** (Fig. 4) is well resolved. In comparison to **8** alone the number of signals is doubled again, indicating the absence of any symmetry element. The complex of octaurea **8** with three chloride anions is asymmetric!

Most of the NH signals are more or less strongly downfield shifted; 14 singlets are found between 8.9 ppm and 10.8 ppm, while the remaining two are found at 7.35 and 8.5 ppm. Five of eight doublets (at 7.2, 7.7, 7.75, 7.95 and 8.25 ppm) and seven triplets (5.3, 5.9, 5.95, 6.0, 6.1, 6.2 (overlapped with a doublet) and 6.8 ppm) of the diphenyl ether units are easily identified, as well as 14 doublets (of a total of 24) of the xanthene units. Only the remaining signals are overlapped between 6.9–7.15 ppm.

Interestingly, the protons of the tetrabutylammonium cation appear as unusually broad signals during addition. The only clearly visible peak, corresponding to the protons of the N–CH_2- group, shifts continuously up to 0.5 ppm upfield until approximately three equivalents of the salt are added. The signal migrates back downfield upon further addition of chloride (the starting position at 3.3 ppm is reached again when circa 10 equivalents of TBAC have been supplied). At higher chloride concentrations the signal continues to move and finally overlaps with the signal of THF at ratios of over 20. Thus, tetrabutylammonium also participates in complexation, though it does not bind that stably on the NMR timescale. The complexed and the free TBA are obviously exchanging faster, than the complexed and uncomplexed forms of the octamer. Perhaps, we deal here with the exchange of "loosely" bound TBA molecules surrounding the chloride complex of the octamer from the outside.

In contrast to chloride, TBA acetate and dihydrogen phosphate do not form kinetically stable complexes with interpretable NMR spectra, although the spectrum changes drastically upon addition of these salts.

The decameric cycle **9** does not produce clear spectra, neither in DMSO-d_6 nor in THF-d_8, although it dissolves well in both solvents. Upon addition of TBA chloride the spectrum becomes significantly clearer, although single signals remain broad at 25 °C. This allows only cautious conclusions about the conformation. At 120 °C, however, the signals sharpen and the spectrum is in agreement with time-averaged D_2 symmetry. 17 signals are found in the low field region (5 signals for NH protons, 8 for the protons of xanthene and 4 for the protons of diphenyl ether units).

Conclusions

In our previous studies with cyclic hexaureas the most promising results were obtained with the XXDXXD molecule, where two chains of rigid xanthene-based units are connected in the cycle by two more flexible D-units. This structure allowed the formation of a very stable complex where two chloride anions are wrapped by the macrocyclic hexamer and all urea hydrogens effectively participate in bonding. The present study describes the further development of this idea. The next two larger cycles consisting of 8 and 10 urea units were prepared and studied.

The crystal structure of the octamer revealed that, in analogy to the previously studied cyclic oligoureas, no intermolecular hydrogen bonds between octamer molecules are observed in the solid state. Each molecule tends to wrap itself compactly, even if this results in significant distortions of the xanthene skeletons and urea groups. Obviously, the hydrogen bonds are additionally stabilized, being "covered/protected" from external influence by the bulky xanthene-units.

In solution the cyclic octamer showed binding of chloride, which is stable on the NMR timescale similar to the hexamer. Moreover, the corresponding spectra indicate that one molecule of the ligand binds most likely three chloride anions, forming a rather stable complex. On the contrary, the decamer does not show any stable complexation of either chloride or acetate and dihydrogen phosphate. This may indicate that such a large cycle has more conformational freedom than is suitable for stable binding. It is tempting, however, to continue studies in the direction of larger polyurea molecules, which could again have more fixed and preorganized three-dimensional structures.

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