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Macrocyclic Hexaureas: Synthesis, Conformation, and Anion Binding

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Abstract: Five macrocylic compounds XXXXXX, XXDXXD, XDXDXD, XDDXDD, and DDDDDD with 48-membered rings, in which six xanthene and/or diphenyl ether fragments are linked through six urea (-NH-C(O)-NH-) groups, have been synthesized. In the cyclization step, a linear diamine was allowed to react with the appropriate diisocyanate by using a [5+1] (i.e., "XDXDX+D" for XDXDXD), [4+2] (DDDDDD), or [3+3] (XDDXDD) procedure. Compounds XXXXXX and XXDXXD were prepared from two molecules of the dimeric amine XX and two molecules of the respective monomeric diisocyanate (X or D) in a [2+1+2+1] (or $2\times[2+1]$) reaction. The (nonoptimized) yields in the cyclization step ranged from 45 to 80%. The linear precursor diamines or diisocyanates were obtained by analogous condensation reactions by using partial protection with a *tert*-butoxycarbonyl group. All the macrocyclic compounds and synthetic intermediates were characterized by ^{1}H NMR and mass spectra. Three different crystal structures were obtained for XDDXDD, which show the molecule in a more or less strongly folded conformation determined by intramolecular hydrogen bonding. The interaction of the hexaureas with selected anions was studied by ^{1}H NMR spectroscopy and UV absorption spectrophotometry.

Keywords: anion binding · host–guest systems · macrocycles · template synthesis · urea

Introduction

Anion-receptor chemistry has continued to attract great interest over recent years.[1] Numerous synthetic hosts containing amide,[2] pyrrole,[3] or urea[4] groups incorporated in increasingly complicated supramolecular skeletons target the efficiency of natural receptors.[5]

Initially guided by the idea that the cyclic arrangement of three urea groups as hydrogen-bond donors separated by a suitably sized spacer should lead to a selective ligand for the nitrate anion,[6] we started with the synthesis of macrocyclic triurea compounds. According to molecular modeling studies, the 4,5-substituted xanthene skeleton[7] should be an appropriate rigid spacer ("X"). Furthermore, the spacer could be combined with the respective diphenyl ether fragment[8] ("D") to adjust the appropriate balance between rigidity (i.e., preorganization of the hydrogen-bond donors) and flexibility of the ligand. We thus synthesized and studied all possible cyclic tri- and tetraurea[9,10] derivatives of building blocks X and D. During these syntheses, we did not only observe the formation of a "monomeric"[11] and a dimeric cyclic urea,[12] but we also isolated cyclic hexamers. In the case of XXDXXD, the formation of the hexamer was obviously favored by a template effect exerted by two chloride ions.[13] To obtain a deeper understanding of the factors responsible for the easy formation of such large cyclic hexamers, we decided to prepare and study further examples. In addition to macrocycles XXXXXX and DDDDDD, eleven cyclic combinations of the X and D units are possible. We selected the most symmetric combinations, namely XDDXDD, XDXDXD, and XXDXXD, for synthesis.

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Results and Discussion

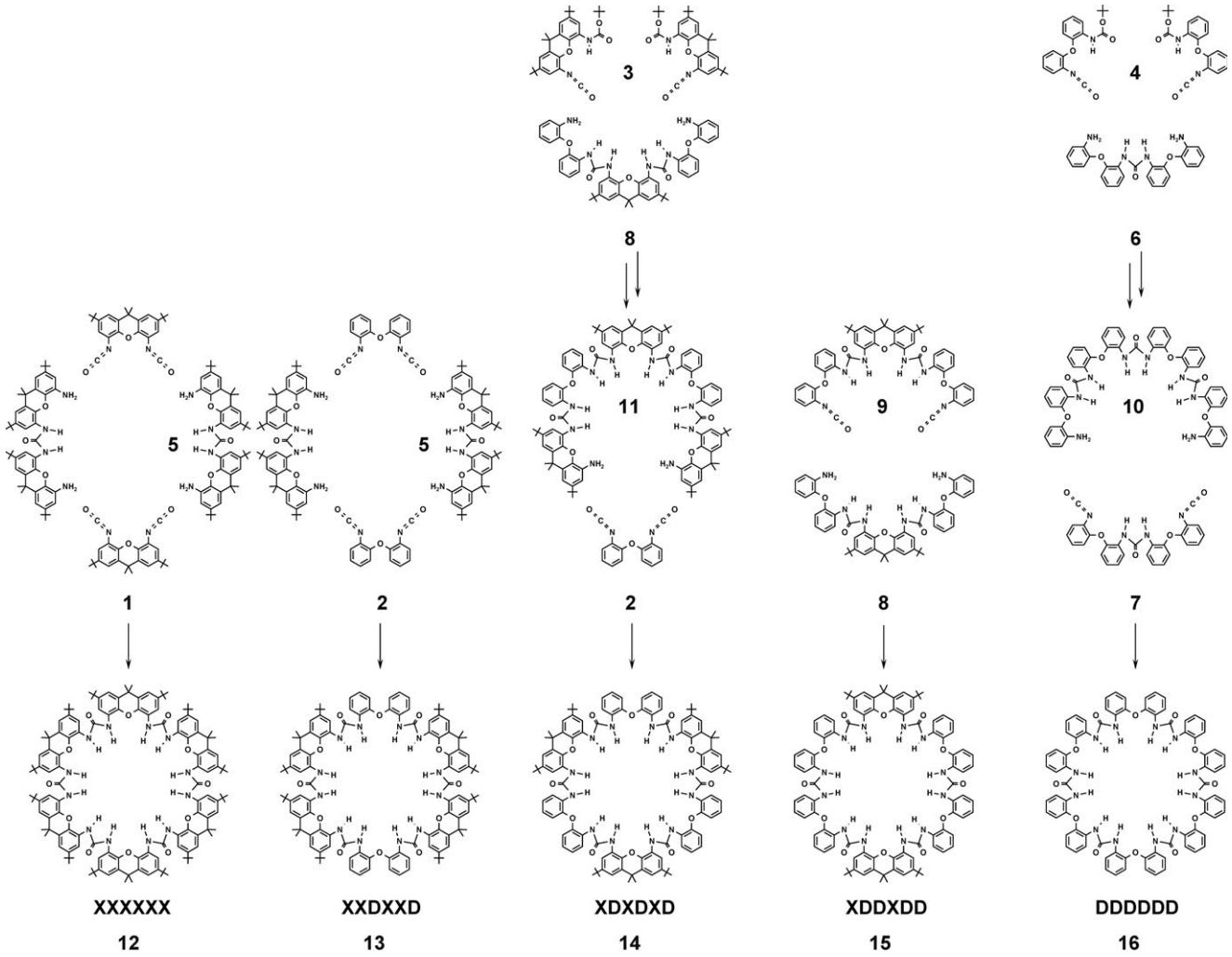
Syntheses: There are numerous ways to prepare a cyclic hexamer, which neither can be exhaustively discussed nor experimentally checked or compared. Scheme 1 summarizes the last, ring-closing condensation step for all the five examples that were realized (i.e., **12**–**16**) and the synthesis of essential intermediates.

Considering the number and size of the molecules in the final reaction step, we found [3+3], [4+2], and [5+1] reactions for **15**, **16**, and **14**, respectively. These strategies could also be used for **12** and **13**, but a 2×[2+1] reaction (e.g., XX+D+XX+D) appeared to be more convenient for both. However, a systematic study was neither done nor intended, and the synthetic pathway realized for a certain compound was (partly) also determined by economic reasons (e.g., the use of the same fragment for the preparation of different products).

Traces of six-membered macrocycles are usually detected by mass spectrometry of the reaction mixture when a "monomeric" diamine is allowed to react with an equimolar quantity of triphosgene in the presence of trialkylamines. However, this reaction, which is only suitable for hexamers that consist of the same unit, was not effective even in this case.

On the other hand, the [2+1] reaction between the dimeric diamine **5** (XX) connected through a urea group and diisocyanates **1** or **2**, initially planned for the synthesis of cyclic trimers, produced hexamers in surprisingly good yield. The conditions were finally found under which even the cyclic hexamer was obtained as the main product of the reaction.

Hexamer **12** (XXXXXX) was the first example of such an unexpected product obtained by the reaction of diamine **5** (XX) and diisocyanate **1** (X). With the intention of preparing the cyclic trimer XXX, we added a solution of the diamine in dichloromethane dropwise to a solution of the diisocyanate in dichloromethane. The crude product was triturated with hexane and a white solid was collected by filtration. The isolated product was practically insoluble in deuterated dimethyl sulfoxide ([D_6]DMSO) and the obtained ^{1}H NMR spectra in $CDCl_3$ were broad and unclear. ESI mass spec-



Scheme 1. Syntheses of cyclic hexaureas and their precursors.

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trometry revealed the nature of the compound: the solid was the cyclic product with six xanthene units. The pure compound **12** was isolated in a yield of as much as 49% under these conditions, while a significant amount remained in solution. The formation of the cyclic trimer, however, was not observed at all.

When diamine **5** (XX) was treated with diisocyanate **2** (D) under the same conditions, the corresponding hexamer **13** (XXDXXD) was formed along with the trimer XXD, but the highest isolated yield of the hexaurea was 20%. In this case, the cyclic trimer was the main product of the reaction. When the reaction was carried with the more-polar acetonitrile as the solvent instead of dichloromethane, the hexamer was not formed at all. This outcome indicates the importance of molecular association through hydrogen bonds for the formation of cyclic hexamers from four independent molecules, that is, "2×[2+1]"

The formation of hexamers **15** (XDDXDD) and **16** (DDDDDD) was also observed in two other examples of intended [2+1] reactions, that is, DD+X and DD+D, in which the cyclic hexamers could be obtained in up to 29 and 20% yield, respectively. However, the isolation and purification of these compounds was difficult because of the close similarity of their physical properties (i.e., solubility and R_F values) to other reaction products, such as the corresponding cyclic trimers.

Hexamer **15** (XDDXDD) was finally prepared by using the "[3+3]" method, which produces a smaller number of intermediates and consequently of by-products on its way to the target compound. The trimeric diamine **8** (DXD) was allowed to react with diisocyanate **9** (DXD, obtained from the same diamine). After trituration of the crude product with acetonitrile, the hexamer was isolated in 45% yield.

For the preparation of hexamer **14** (XDXDXD), the [3+3] and [5+1] strategies were checked, in which the latter gave better results in the cyclization step. A yield of 89% for the macrocycle was obtained by reaction of the linear diamino pentamer **11** (XDXDX) with D-diisocyanate **2**. The necessary pentameric diamine was prepared by a stepwise synthesis, in which trimeric diamine **8** (DXD) was allowed to react with two molecules of the isocyanate **3** (X-based) followed by subsequent deprotection of the resulting linear tetraurea XDXDX.

The isolation of the hexamer **16** (DDDDDD) was especially difficult. Preorganization seemed to play a less significant role in the assembly of the hexamers because of the flexibility of the diphenyl ether skeleton. Although the hexamer was formed in the reaction of diamine **6** (DD) with D-diisocyanate **2**, the chromatographic separation of the hexamer and trimer was nearly impossible. The hexaurea was finally isolated as the product of the [4+2] reaction of diamine **10** (DDDD) with diisocyanate **7** (DD).

Anions as templates: The oligoureas interact in solution through hydrogen bonds with other ureas and anions. In previous studies, we have demonstrated the complexation of anions by cyclic tri- and tetraurea compounds.[9,10] In addition, the influence of tetrabutylammonium (TBA) chloride on the reaction between diamine **5** (XX) and D-isocyanate **2** revealed a remarkable example in which two (!) chloride ions as a template control the formation of the hexamer **13** (XXDXXD). It was found that the molar ratio of trimer/hexamer changes drastically from 5:1 to 1:5 in the presence of TBA chloride. A significant but less pronounced increase in the ratio of trimer/hexamer to 1:3 was observed in the presence of the bromide ion.[13]

It has been already mentioned that the "[XX+X]" reaction does not yield the expected trimer but hexamer **12** (XXXXXX) as the only cyclic product. Further studies revealed that anions have a strong influence on the product of the reaction as well. Particularly, the presence of TBA acetate in the reaction mixture changes the outcome completely, because the trimer XXX is the only product formed in a significant quantity.[9]

These two striking examples of the templated formation of cyclic oligourea compounds gives rise to questions about the roles that anion-induced and structure-dependent preorganization factors play in the outcome of the reaction. With this idea in mind, a series of analogous [2+1] cyclizations (i.e., XX+X, XX+D, DD+X, and DD+D) were performed with and without the addition of acetate or chloride ions to the reaction mixture. The general conditions were: dichloromethane as a solvent with stirring for 18 h at room temperature. The cyclic products were isolated by column chromatography after the reaction, and the composition of the product mixtures were analyzed by NMR spectroscopy. The compositions of the trimer and hexamer are compared in Table 1.

Table 1. Influence of selected salts on the [2+1] reaction.

Salt	Compound	Yield [%]			
		5+1 (XX+X)	**5+2** (XX+D)	**6+1** (DD+X)	**6+2** (DD+D)
no anion	trimer	–	75	46	60
	hexamer	69	15	29	20
TBA chloride	trimer	–	8	86	63
	hexamer	55	82	–[a]	37
TBA acetate	trimer	≈100	40	71	51
	hexamer	–	–[b]	–	4

[a] The pentameric diamine DDXDD was detected. [b] The formation of up to 27% of the pentameric oligourea XXDXX was observed.

In each case, the anions have a rather strong influence on the result, but the effect was most pronounced for the reactions of "XX+X+acetate" and "XX+D+chloride". Not only the total yield of the cyclic products varied, but also the ratio of both oligomers changed drastically. A practically quantitative conversion of the starting compounds into cyclic products was observed in some cases, whereas a macrocycle was obtained only in 60–70% yield in others and the rest remained uncyclized. This outcome may be explained by different individual reaction rates in the different mixtures. The isocyanates are relatively stable as solids, but in solution they are destroyed within a few hours by moisture

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introduced most likely by the extremely hygroscopic TBA salts. To achieve higher yields of the cyclic compounds, the corresponding [2+1] and/or 2×[2+1] reactions must be able to compete with the rate of isocyanate hydrolysis.

In general, the formation of more rigid skeletons was more strongly influenced by the presence of the anions.

Crystal-structure analysis: Three different single-crystal X-ray structures were obtained for the hexamer XDDXDD. All the samples were prepared by the slow evaporation of a solution of the hexamer in a multicomponent mixture of solvents (see the Experimental Section). The conformations of the single molecules are shown and compared in Figure 1

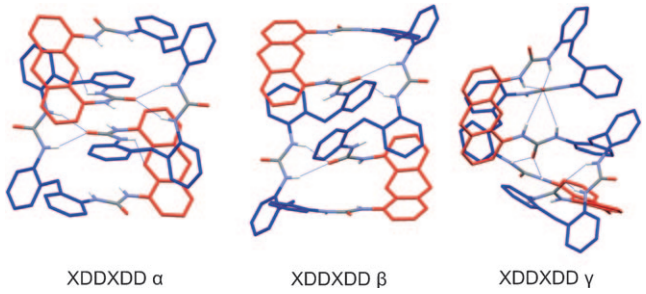

Figure 1. The conformation of **15** found in three different single crystals (α, β, γ). Solvent molecules, non-urea hydrogen atoms, and alkyl groups have been omitted for clarity. Xanthene: red; diphenyl ether: blue.

In the first case (α), the crystal contains eight molecules of acetone per hexamer (Figure 1). Two of these acetone molecules are strongly bound by two urea groups that connect X and D units (a typical six-membered cyclic binding motif[14]), whereas two others are weakly coordinated through a single hydrogen bond by a xanthene NH group. The remaining four acetone molecules fill gaps in the crystal lattice. The folded conformation of the hexamer molecule with an inversion centre is determined by a bifurcated hydrogen bond between the urea group that connects two D units and the carbonyl oxygen atom of the neighboring urea group (i.e., connecting X and D units). The system of hydrogen bonds is illustrated in Figure 2.

The second structure (β) contains two molecules of ethyl acetate and two molecules of ethanol per hexamer. The molecular conformation of β is very similar to that of α, again determined by the bifurcated hydrogen bonds between urea groups that connect the D units as hydrogen donors and the carbonyl oxygen atom of the neighboring urea groups that connect X and D units as acceptors. The ethanol molecules replace the acetone of the α structure as a hydrogen-bond acceptor, while simultaneously donating a hydrogen bond to a carbonyl oxygen atom of a xanthene-attached urea. The ethyl acetate molecules are not involved in hydrogen bonding.

In the third case (γ), the molecular conformation is more complicated as it no longer possesses an inversion center or any other symmetry element. Intramolecular bifurcated hydrogen bonds exist between one urea group that connects D–X units (acceptor) and the adjacent urea group that connects D–D units (donor) and also between two opposite urea compounds that connect D–X units. One ethanol molecule is bound through bifurcated hydrogen bonds by a urea group that connects X and D units, while an ethyl acetate molecule is bound to two adjacent urea groups that connect X–D units and additionally forms hydrogen bonds with a urea group that connects D–D units as an acceptor. Two cyclic hexaurea molecules form centrosymmetric dimers through a hydrogen-bonding system that also involves two acetonitrile, two water, and two ethanol molecules. The complicated system is illustrated in Figure 2, and the hydrogen-bonded dimer is shown in Figure 3.

Further information about the conformation of the three structures **15α, 15β,** and **15γ** is collected in Table 2, in which the interplanar angles for the aromatic rings are listed. At first glance (Figure 1) the two centrosymmetric structures/molecules **15α** and **15β** seem to have a similar conformation and although they even have the same hydrogen-bonding pattern (Figure 2), there are rather strong differences between these interplanar angles, mainly for the angles around the urea groups.

As in cyclic tri- and tetraurea molecules, no (direct) intermolecular hydrogen bonds between the hexaurea molecules were observed for **15α** and **15β**, although the flexibility of

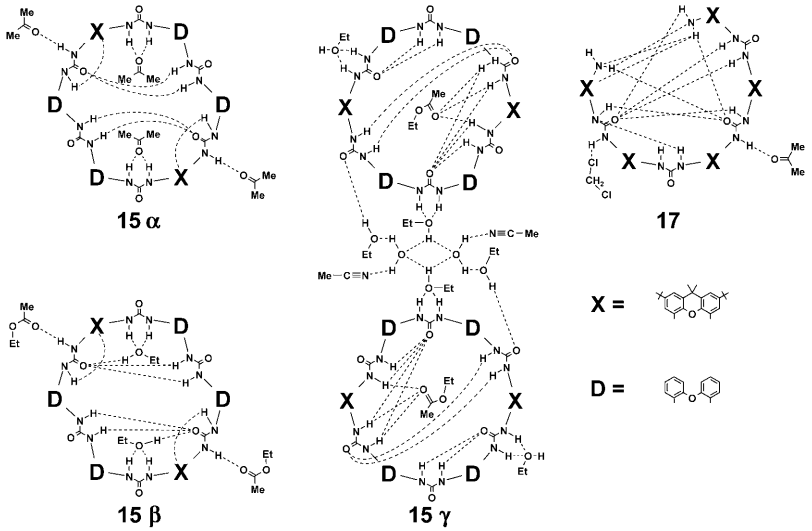

Figure 2. Illustration of the system of hydrogen bonds present in the crystals of cyclic hexaurea **15** and diamine **17**.

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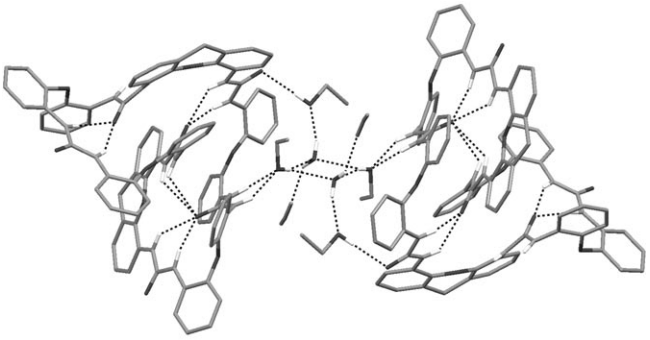

Figure 3. The network of hydrogen bonds formed with the participation of solvent molecules (ethanol, water, and acetonitrile) that connect two molecules of hexamer **15** in γ. Non-urea hydrogen atoms and xanthene alkyl groups have been removed for clarity.

Table 2. Interplanar angles [°] found in the X-ray structures of **15** (XDDXDD) for aromatic rings within xanthene and diphenyl ether units (first part of the table) and the angles [°] between the averaged planes of the urea groups (U) and the adjacent phenyl rings of units X and D (second part).[a]

Angle	**15α**	**15β**	**15γ**	**17**
Ph1/Ph2	−3.3 (X)	−27.3 (X)	−11.1 (X)	−19.2
Ph3–Ph4	+71.6 (D)	+70.0 (D)	+59.1 (D)	+7.9
Ph5–Ph6	+80.3 (D)	+83.6 (D)	−58.8 (D)	−6.1
Ph7–Ph8	+3.3 (X)	+27.3 (X)	+22.4 (X)	+6.7
Ph9–Ph10	−71.6 (D)	−70.0 (D)	−83.7 (D)	+5.7
Ph11–Ph12	+80.3 (D)	−83.6 (D)	+72.8 (D)	–
Ph2-U-Ph3	+30.7/+9.1 (X-U-D)	+26.2/−14.1 (X-U-D)	−12.8/−14.7 (X-U-D)	+16.9/+29.5
Ph4-U-Ph5	+38.1/+28.1 (D-U-D)	+30.0/−27.8 (D-U-D)	−141.3/−47.2 (D-U-D)	−133.3/+162.8
Ph6-U-Ph7	−6.3/−51.0 (D-U-X)	+25.6/+83.6 (D-U-X)	+43.2/−29.0 (D-U-X)	−29.6/+40.9
Ph8-U-Ph9	−30.7/−9.1 (X-U-D)	−26.2/+14.1 (X-U-D)	+41.7/−65.1 (X-U-D)	−79.9/−139.8
Ph10-U-Ph11	−38.1/−28.1 (D-U-D)	−30.0/+27.8 (D-U-D)	−9.4/−7.2 (D-U-D)	–
Ph12-U-Ph1	+6.3/+51.0 (D-U-X)	−25.6/−83.6 (D-U-X)	−35.9/−15.3 (D-U-X)	–

[a] The corresponding values for the linear diamine **17** (XXXXX) are also included.

the macrocyclic skeleton would surely allow this. And even the hydrogen-bonded, solvent-bridged dimeric structural element found for **15γ** (compare with Figure 3) shows no further interaction through hydrogen bonds in the crystal lattice. Intramolecular hydrogen bonding is obviously more favorable for these macrocyclic oligourea compounds; as an example, the packing of **15α** is shown in Figure 4.

Unfortunately, single crystals suitable for X-ray diffraction studies were not obtained for the "rigid" hexamer **12** (XXXXXX). However, we succeeded in growing single crystals for its immediate precursor, that is, the linear diamine that consists of five xanthene units. This compound was isolated as the product of an incomplete cyclization during the "2×[2+1]" synthesis of cyclic hexamer **12**.

The molecule assumes a densely folded conformation with strongly distorted urea groups determined again by strong intramolecular hydrogen bonds (Figure 5a). The linear chain is contorted and forms a compact "ball" in which most of the urea and amine hydrogen atoms are inwardly oriented, thus participating in the network of hydrogen bonds, whereas the alkyl groups (i.e., *tert*-butyl, methyl) of the xanthene units form the outer surface (Figure 6). This finding is especially surprising because single crystals were grown from a rather polar solvent mixture (acetone, dichloromethane, water). Some of the NH groups form hydrogen bonds with acetone, dichloromethane, and eventually water molecules, but no direct intermolecular interaction was found between separate molecules of the diamine. Two molecules of **17** form a hydrogen-bonded "cluster" that includes eight water molecules. Double layers of **17**, which also contain acetone molecules that extend in the *ab* plane, are separated by layers of dichloromethane (Figure 5b).

NMR spectroscopic studies: Similar to the cyclic tetraurea compounds, there were intrinsic restrictions in the NMR spectroscopic studies of the cyclic hexamers. The most rigid hexamers XXXXXX and XXDXXD are insoluble in DMSO, which is most frequently used as a polar solvent in NMR spectroscopy. In other cases, it was impossible to obtain a sharp spectrum of a hexamer alone or in the presence of salt, and other solvents had to be tried. Thus, a general comparison of **12**–**16** by using a single solvent was impossible.

Compound **12** (XXXXXX) shows a very well-resolved ^{1}H NMR spectrum in [D$_8$]THF and [D$_5$]pyridine, which is in full agreement with the proposed structure. However, the clear signal pattern was entirely unexpected: 12 *m*-coupled doublets for the aromatic protons (2 protons each), six urea NH peaks (2 protons each), six *tert*-butyl singlets (18 protons each), and six CH$_3$ singlets (6 protons each) could be clearly distinguished (Figure 7). All the peaks are very sharp and the signals of the same intensity have almost the same height, thus indicating a very stable conformation with a twofold symmetry of the molecule.

Whereas the signals for all the aromatic protons and five signals for the NH group appear in the range $\delta = 6.6$–8.9 ppm, one NH signal is strongly shifted downfield ($\delta =$ 11.7 ppm). Tentatively, this signal may be interpreted as a strong, bifurcated hydrogen bond between two opposite urea functions, thus "fixing" the molecule in an "eight" or propeller-shaped conformation. The spectrum remained practically unchanged when the sample was heated to 55 °C. A similar NMR spectrum with [D$_5$]pyridine as the solvent showed no essential changes up to 105 °C.

The addition of TBA chloride, acetate, or dihydrogen phosphate to a solution of **12** in THF led to very fast and complete precipitation of the hexamer (the same was true for pyridine as the solvent). The addition of other salts (bromide, iodide, nitrate, hydrogen sulfate) had no effect on the spectrum. Thus, there must be a system of intramolecular

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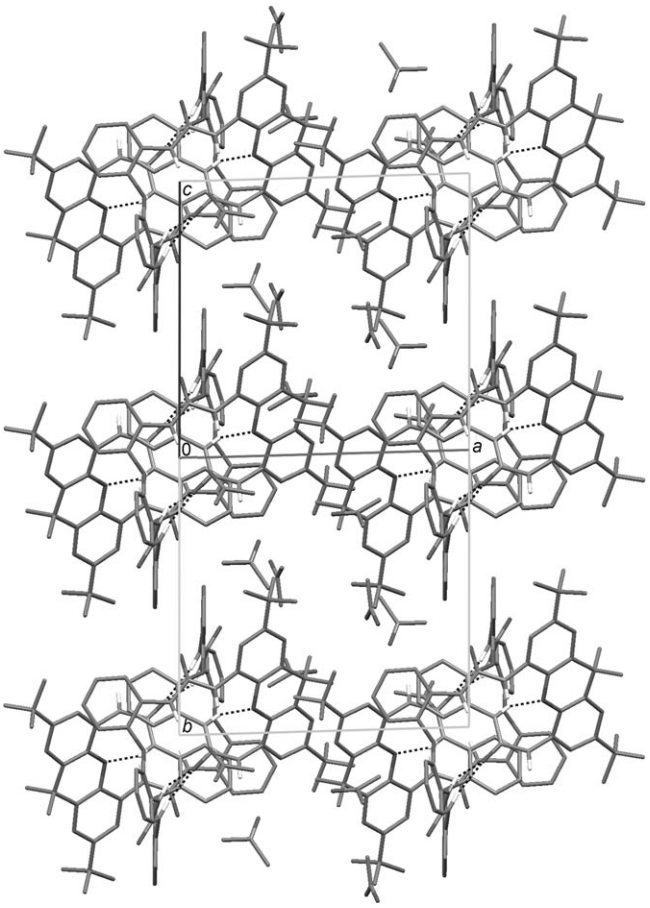

Figure 4. Packing of hexamer **15** in α seen along the bisection of the angle between the *c* and *b* axes.

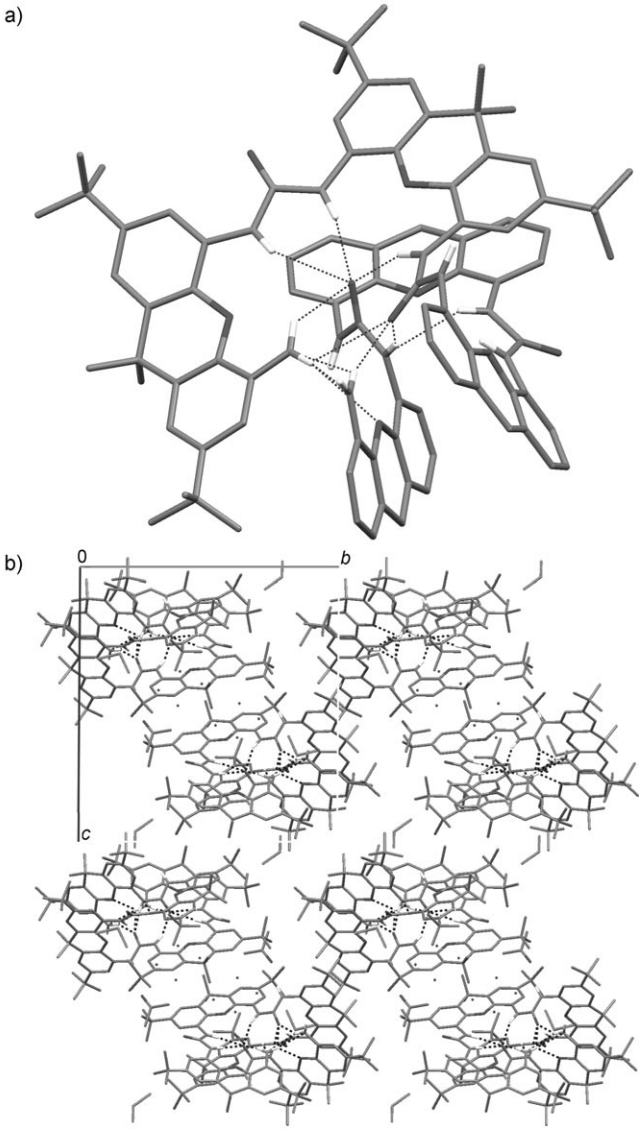

Figure 5. a) Molecular conformation of **17** (XXXXX diamine); the *tert*-butyl and methyl groups from three xanthene units have been omitted for clarity. b) Packing of **17** seen along the *a* axis.

hydrogen bonds that is stable in THF but destroyed upon the addition of salts or in the more polar DMSO.

The conformationally more flexible **13** (XXDXXD) showed a different behavior. The pure compound is either insoluble ([D_6]DMSO) or has a broad and unclear spectrum ([D_8]THF, [D_5]pyridine, $CDCl_3$). However, upon the addition of chloride ions a very characteristic spectrum was found (Figure 8). The strong complexation of chloride and bromide ions with **13** has already been reported.[13] Stable species were also formed with dihydrogen phosphate and hydrogen sulfate ions.

In contrast with chloride ions, a sharp spectrum was obtained with $H_2PO_4^{2-}$ ions in a 1:1 ratio, thus suggesting the formation of a 1:1 complex. The ^{1}H NMR spectrum has five signals for urea protons at $\delta = 11.05$, 10.55, 9.95, 9.15 (two protons), and 8.20 ppm. Four *meta*-coupled doublets at $\delta =$ 8.35, 8.20. 7.00, and 6.85 for the xanthene units are clearly seen, whereas the remaining signals appear close to one solvent peak (near $\delta = 7.2$ ppm). From four doublets and four triplets with *ortho* coupling for the diphenyl ether groups, three doublets at $\delta = 8.40$. 8.00, and 5.80 ppm and a triplet at $\delta = 6.5$ ppm are separated, while the remaining signals overlap at around $\delta = 6.8$ and 6.9 ppm (Figure 8). Four singlets for the methyl and four singlets for the *tert*-butyl groups

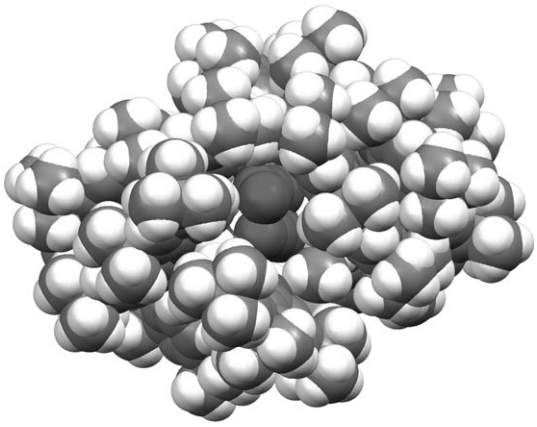

Figure 6. Pair of molecules of **17** (XXXXX diamine) in the crystal. Eight water molecules fill the cavity formed by two pentamer molecules, and the lypophilic alkyl groups form the outer surface.

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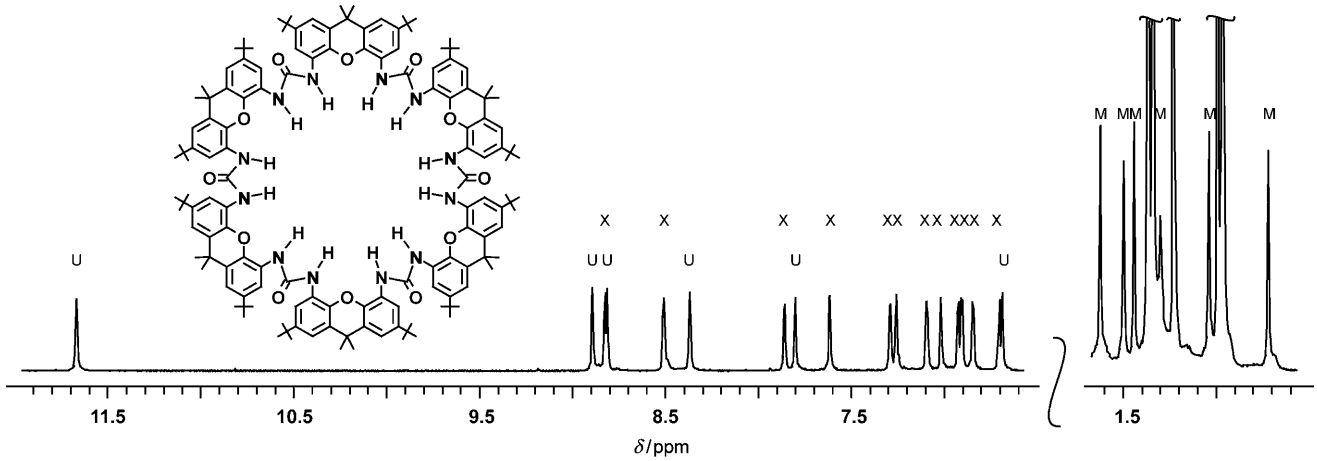

Figure 7. ^{1}H NMR spectrum of the xanthene-based cyclic hexamer **12** ([D_8]THF, 25 °C). Signals for the aromatic protons are marked with X, the urea protons with U, and the methyl groups with M. The signals for the six *t*Bu groups (highfield) are not marked.

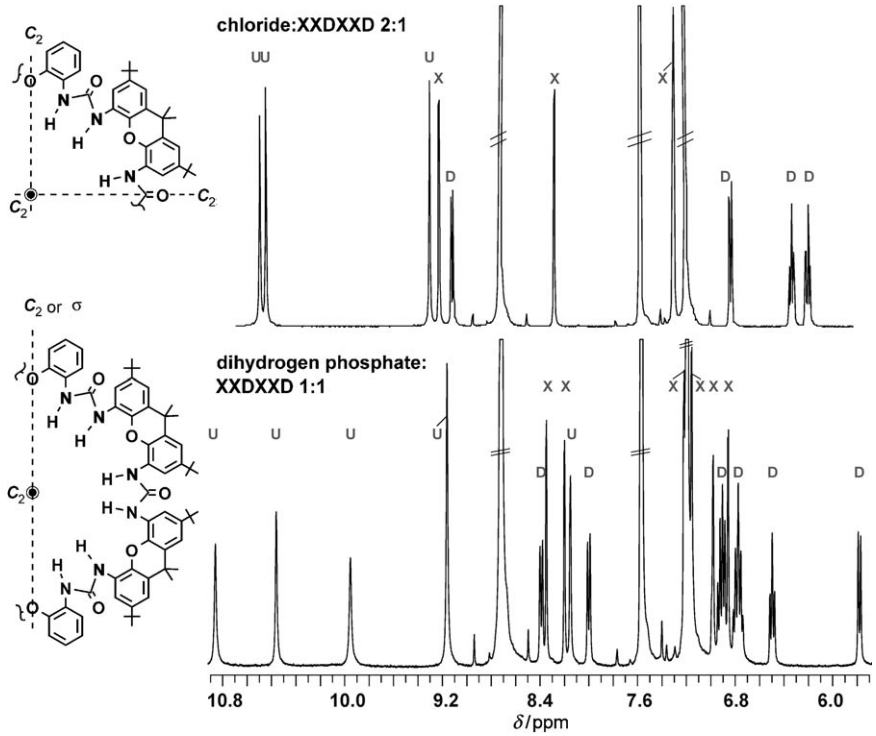

Figure 8. Top: a section of the ^{1}H NMR spectrum of the complex formed by hexamer **13** (XXDXXD) with two molecules of TBA chloride in [D_5]pyridine; the signals correspond to dynamic D_2 symmetry in solution. Bottom: a section of the ^{1}H NMR spectrum of the 1:1 complex of TBA dihydrogen phosphate/hexamer **13** in [D_5]pyridine; the spectrum corresponds to dynamic C_2 (or C_S) symmetry in solution (one possibility of a C_2 axis or σ-plane has been indicated).

appear in the aliphatic region. This pattern agrees with a conformation with a single C_2 axis or a plane of symmetry that crosses the urea groups between X units (or the oxygen atoms of the D units).

When the addition of the $H_2PO_4^{2-}$ ions is continued, another set of signals starts to arise. This new set contains fewer signals and obviously is similar to that with two chlorides, although the signals are not so sharp. Saturation is still not achieved at a 1:5 ratio (hexamers/salt), in which both sets are observed in a much higher intensity for the second set.

Two sets of signals are observed in pyridine for HSO_4^- ions. In contrast to the $H_2PO_4^{2-}$ ions, the more simple "fourfold" spectrum strongly prevails over the more complicated "twofold" spectrum, even if only 0.5 equivalents of the salt are added. The "fourfold" spectrum seems to correspond to a 1:1 complex, but it is difficult to judge the composition of another complex that corresponds to the "twofold" species because of the weakness of the signals. Upon further addition of HSO_4^- ions, the "twofold" set of signals weakens further, but does not completely disappear even when ten equivalents of the salt are added. Because the "twofold" set weakens upon the addition of the salt, it could be either a 2:1 or 1:1 (ligand/ion) complex with HSO_4^- ions.

The D_{3d} symmetrical hexamer **14** (XDXDXD) shows a far less-expressed response to the addition of various salts, although it is soluble in DMSO without limitations. The hexamer itself has a broad and unclear NMR spectrum. The interaction with anions could be usually detected in the spectrum only by general changes in the baseline shape. Acetate and dihydrogen phosphate ions seem to have the strongest influence on the spectra. In both cases, weak signals of a species with twofold symmetry

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appear, but their quantitative evaluation was not possible. TBA chloride and hydrogen sulfate cause minor spectral changes and nitrate and bromide have no influence at all.

The NMR spectroscopic studies brought only limited results in the case of **15** (XDDXDD) as well. The conformations of the molecule are neither flexible nor stable enough in solution to result in a sharp NMR spectrum, which was also found in the presence of salts. Thus, only cautious conclusions can be made. In contrast to XDXDXD, hexamer **15** seemed to be most responsive to the addition of $H_2PO_4^{2-}$ ions (small peaks appeared beside the broad "hills"), followed by chloride and acetate ions (general changes in the baseline shape).

The most flexible hexamer **16** (DDDDDD) has a clear spectrum in [D_6]DMSO, with four signals for aromatic protons and a singlet for the urea protons in accordance with the expected D_{6h} symmetry of this compound. The addition of TBA chloride, TBA acetate, and TBA dihydrogen phosphate affected the spectrum, whereas other salts had either marginal or no influence. In the case of the chloride or $H_2PO_4^{2-}$ ions, the spectrum is absolutely broad. Only the interaction of acetate ions led to an interpretable spectrum, in which the urea singlet, in addition to its broadening, was shifted downfield by approximately $\Delta\delta = 0.8$ ppm, whereas the signals for the aromatic protons were shifted slightly upfield ($\Delta\delta = 0.1$ ppm).

UV spectrophotometric studies: UV absorption spectrophotometric analysis was also used to study the interactions between the four hexamers **12** and **14**–**16** and chloride, bromide, acetate, and dihydrogen phosphate anions. The experiments were carried out under the same conditions as for **13**, that is, in a mixture of THF/acetonitrile[13] (1:3, v/v; Table 3).

In general, the spectral variations induced by the addition of the anions to solutions of the ligand were much weaker than those observed with the tetrameric and trimeric analogues,[9,10] especially in the presence of the spherical Cl^- and Br^- ions. With these anions, the changes were indeed not significant enough to allow any interpretation, with the exception of ligand **14** (XDXDXD), for which the 2:1 complex could be found. The complexation is stronger with the Cl^- than with Br^- ion ($\Delta\log\beta = 1.8$). In contrast, different stoichiometries, that is, 1:1 and 1:2, were found for the more rigid ligand **13**.

Remarkably, no spectral variation was observed at all with the most flexible hexamer **16** and all the anions studied, even with the oxoanions AcO^- and $H_2PO_4^-$, which led to important spectral changes with the other ligands. In these cases, complexes of different stoichiometries could be found, such as bisanion (1:2) complexes of similar stability with the more rigid ligand **12**. More stable complexes of the same stoichiometry were found with ligand **15** and an additional 1:1 acetate complex. The formation of bis-ligand complexes was shown with ligand **14** and the anions studied. Again, the acetate ion formed the most stable complex.

Table 3. Overall stability constants ($\log\beta \pm \sigma_{n-1}$)[a] of the complexes formed between the hexaurea ligands and anions in THF/acetonitrile (1:3, v/v).

Anion	Ratio ligand/anion	**12**	**13**[13]	**14**	**15**	**16**
Cl^-	1:2	–[b]	11.4		–[b]	–[b]
	1:1		6.16			
	2:1			11.2 ± 0.2		
Br^-	1:2	–[b]	7.7		–[b]	–[b]
	2:1			9.4 ± 0.3		
AcO^-	1:2	8.8 ± 0.3	–[c]		10.4 ± 0.9	–[b]
	1:1				6.0 ± 0.7	
	2:1			11.5 ± 0.1		
$H_2PO_4^-$	1:2	8.7 ± 0.4	–[c]		9.9 ± 0.2	–[b]
	2:1			10.2 ± 0.3		

[a] Mean values of at least three independent experiments; the precision corresponds to the standard deviation on these mean values. [b] Spectral changes were too small. [c] Not determined.

Conclusions and Outlook

Inspired by the results obtained with the first example XXDXXD, we extended our studies of cyclic oligoureas composed of xanthene and diphenyl ether units from trimers and tetramers to a series of five hexamers. Among 13 possible combinations of X and D units, we chose the most symmetrical structures with a C_n axis "perpendicular" to an idealized, planar, macrocyclic ring. The reaction between a diamine and diisocyanide group according either to a [5+1], [4+2], [3+3], or 2×[2+1] strategy was used in the cyclization step. In all cases, an influence of the anions on the trimer/hexamer ratio of the products was found, but the acetate-templated formation of the trimer XXX and the chloride-templated fomation of the hexamer XXDXXD was especially effective.

The interaction with various anions through hydrogen bonds has been established for all the hexaurea compounds. In general, the most stable complexes were formed by the most rigid hexamers XXXXXX and XXDXXD. Results similar to the complexation of two chloride anions by XXDXXD were not found for the other hexamers. Three different crystal structures for XDDXDD suggest that at least this compound prefers folded conformations with intramolecular hydrogen bonding over hydrogen-bonded networks formed by intermolecular hydrogen bonds.

Studies are in progress to synthesize even larger cyclic oligomers based on xanthene and diphenyl ether units.

Experimental Section

All the solvents were of analytical quality (p.a.) and were used without additional purification. Deuterated solvents for the NMR spectroscopic analysis were purchased from Deutero GmbH. The ^{1}H NMR spectra

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were recorded on a Bruker Avance DRX 400 spectrometer at 400 MHz and 25 °C using the solvent signals as internal references. Mass spectra were recorded on the Finnigan MAT 8230 instrument. The melting points were not corrected.

Xanthene-based/derived isocyanate 3: Monoprotected diamine **18** (200 mg, 0.44 mmol) and *N*-diisopropylethylamine (57 mg, 0.22 mmol) dissolved in dichloromethane (20 mL) were added dropwise over 1 h to a stirred solution of triphosgene (66 mg, 0.44 mmol) in dichloromethane (20 mL) under nitrogen. The reaction mixture was filtered after 3 h through silica gel (50 g), which was subsequently washed with dichloromethane (2×30 mL). The solvent was removed under reduced pressure, and the oily crude product was heated on a rotatory evaporator for 1 h at 80 °C to remove excess triphosgene and cooled. Isocyanate **3** (190 mg, 89 %) was obtained as a beige solid. M.p. 172 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.90 (s, NH, 1H), 7.56 (s, ArH, 1H), 7.37 (d, ArH, 1H, ^4J(H,H) = 2.0 Hz), 7.25 (d, ArH, 1H, ^4J(H,H) = 2.0 Hz), 7.02 (d, ArH, 1H, ^4J(H,H) = 2.0 Hz), 1.61 (s, CH$_3$, 6H), 1.44 (s, *t*Bu, 9H), 1.28 (s, *t*Bu, 9H), 1.26 ppm (s, *t*Bu, 9H).

Diphenyl ether-based isocyanate 4: Monoprotected diamine **19** (1.11 g, 3.69 mmol) and *N*-diisopropylethylamine (477 mg, 3.69 mmol) dissolved in dichloromethane (50 mL) were added dropwise over 1 h to a stirred solution of triphosgene (548 mg, 1.85 mmol) in dichloromethane (30 mL) under nitrogen. The reaction mixture was filtered after 3 h through silica gel (50 g), which was subsequently washed with dichloromethane (3× 50 mL). The solvent was removed under reduced pressure and the oily crude product was heated on a rotatory evaporator for 1 h at 80 °C to remove excess triphosgene and cooled. Isocyanate **4** (1.07 mg, 89 %) was obtained as a light-brown oil. The product is liquid at room temperature, cannot be stored, and should be used immediately after preparation. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.20 (d, ArH, 1H, ^3J(H,H) = 7.8 Hz), 7.14 (m, ArH, NH, 4H), 6.98 (m, ArH, 2H), 6.88 (dd, ArH, 1H, ^3J(H,H) = 8 Hz, ^4J(H,H) = 2 Hz), 6.79 (dd, ArH, 1H, ^3J(H,H) = 8 Hz, ^4J(H,H) = 2 Hz), 1.53 ppm (s, *t*Bu, 9H).

Diisocyanate 9 (DXD): A solution of the diamine **8** (136 mg, 0.17 mmol) with diisopropylethylamine (44 mg, 0.34 mmol) in dichloromethane (25 mL) was added dropwise to a solution of triphosgene (50 mg, 0.17 mmol) in acetonitrile (25 mL) with stirring under nitrogen. The reaction mixture was filtered after 3 h through silica gel, which subsequently was washed with dichloromethane (3×25 mL). The solvent was removed under reduced pressure and the crude product was heated on a rotatory evaporator for 1 h at 80 °C to remove excess triphosgene and cooled. Diisocyanate **9** was isolated as a glass-like solid (95 %, 138 mg). The ^{1}H NMR spectrum in CDCl$_3$ was broadened and unclear. M.p. > 185 °C (decomp).

Diamine 11 (XDXDX): A solution of diamine **8** (196 mg, 0.243 mmol) in THF (20 mL) was added to a solution of isocyanate **3** (234 mg, 0.487 mmol) in THF (20 mL) with stirring under nitrogen. The solvent was removed after 18 h under reduced pressure and the residue was dissolved in acetonitrile. A white precipitate appeared after 30 min to yield the *tert*-butoxycarbonyl (Boc)-protected pentameric diamine as a white powder after filtration. The compound was dissolved in dichloromethane (10 mL), trifluoroacetic acid (10 mL) was added, and the mixture was stirred for 3 h. The reaction mixture was poured slowly to a solution of sodium carbonate (5 N, 200 mL) to quench the reaction. The pH level was adjusted to 9–10. The organic layer was separated, and the aqueous layer was washed with dichloromethane (2×25 mL). The combined dichloromethane extracts were dried over MgSO$_4$ and the solvent was removed under reduced pressure, thus yielding the dimeric diamine **11** (0.22 g, 58 %) as a brownish glass-like solid. M.p. > 190 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.11 (s, NH, 2H), 9.00 (s, NH, 2H), 8.80 (s, NH, 2H), 8.68 (s, NH, 2H), 8.33 (dd, ArH$_{diph}$, 2H, ^3J(H,H) = 8.2, ^4J(H,H) = 1.2 Hz), 8.15 (d, ArH$_{xan}$, 2H, ^4J(H,H) = 2.4 Hz), 8.02 (d, ArH$_{xan}$, 2H, ^4J(H,H) = 2.4 Hz), 7.88 (dd, ArH$_{diph}$, 2H, ^3J(H,H) = 7.0. ^4J(H,H) = 2.5 Hz), 7.07 (m, ArH, 12H), 6.74 (d, ArH$_{diph}$, ^3J(H,H) = 7.0 Hz), 6.61 (m, ArH, 6H), 6.46 (d, ArH$_{xan}$, 2H, ^4J(H,H) = 2 Hz), 4.80 (s, NH$_2$, 4H), 1.55 (s, CH$_{3xan}$, 6H), 1.51 (s, CH$_{3xan}$, 12H), 1.27 (s, *t*Bu$_{xan}$, 18H), 1.18 (s, *t*Bu$_{xan}$, 18H), 1.13 ppm (s, *t*Bu$_{xan}$, 18H); MS(ESI): *m/z* (%): 1584.4 (100 %) [*M*$^+$+Na].

Diamine 10 (DDDD): A solution of diamine **6** (158 mg, 0.37 mmol) in dichloromethane (10 mL) was added to a solution of isocyanate **4** (242 mg, 0.75 mmol) in dichloromethane (10 mL) with stirring under nitrogen. Acetonitrile (50 mL) was added and the solvent was removed under reduced pressure after 18 h of stirring. The crude product was dissolved in dichloromethane (10 mL), trifluoroacetic acid (10 mL) was added, and the mixture was stirred for 3 h. The reaction mixture was poured slowly to a solution of sodium carbonate (5 N, 200 mL) to quench the reaction. The pH level was adjusted to 9–10, the organic layer was separated, and the aqueous layer was washed with dichloromethane (2×25 mL). The combined dichloromethane extracts were dried over MgSO$_4$. The solvent was removed under reduced pressure and the crude product was dissolved in methanol (20 mL). After 12 h the unprotected tetrameric diamine **10** (0.239 g, 73 %) separated as slightly brownish thin crystals. M.p. 176–180 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.22 (s, NH, 2H), 9.18 (s, NH, 2H), 9.11 (s, NH, 2H), 8.26 (d, ArH$_{diph}$, 2H, J(H,H) = 8.6 Hz), 8.24 (d, ArH$_{diph}$, 2H, J(H,H) = 8.6 Hz), 8.11 (d, ArH$_{diph}$, 2H, J-(H,H) = 7.8 Hz), 7.06 (br s, ArH$_{diph}$, 4H), 6.94–6.83 (m, ArH$_{diph}$, 10H), 6.77–6.71 (m, ArH$_{diph}$, 8H), 6.52–6.48 (m, ArH$_{diph}$, 4H), 4.89 ppm (s, NH$_2$, 4H); MS(ESI): *m/z* (%): 901.9 (100 %) [*M*$^+$+Na].

Cyclic hexaurea 12 (XXXXXX): Diamine **5** (234 mg, 0.25 mmol) was dissolved in dichloromethane (25 mL) and diisocyanate **1** (100 mg, 0.25 mmol) dissolved in dichloromethane (25 mL) was added dropwise with stirring over 20 min under nitrogen to this solution. The solvent was removed under reduced pressure after 18 h of stirring. The crude product was triturated with hexane (25 mL). A white solid was filtered off to yield hexamer **12** (129 mg, 49 %). M.p. > 370 °C (decomp); ^{1}H NMR (400 MHz, [D$_8$]THF): δ = 11.66 (s, NH, 2H), 8.89 (s, NH, 2H), 8.82 (d, ArH, 2H, ^4J(H,H) = 2.3 Hz), 8.81 (s, NH, 2H), 8.51 (d, ArH, 2H, ^4J-(H,H) = 2.0 Hz), 8.36 (s, NH, 2H), 7.85 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 7.80 (s, NH, 2H), 7.61 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 7.29 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 7.26 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 7.09 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 7.02 (d, ArH, 2H, ^4J(H,H) = 2.0 Hz), 6.92 (d, ArH, 2H, ^4J(H,H) = 1.6 Hz), 6.90 (d, ArH, 2H, ^4J(H,H) = 1.6 Hz), 6.84 (d, ArH, 2H, ^4J(H,H) = 2.3 Hz), 6.70 (d, ArH, 2H, ^4J(H,H) = 1.6 Hz), 6.68 (s, NH, 2H), 1.62 (s, CH$_3$, 6H), 1.49 (s, CH$_3$, 6H), 1.44 (s, CH$_3$, 6H), 1.36 (s, *t*Bu, 18H), 1.33 (s, *t*Bu, 18H), 1.29 (s, CH$_3$, 6H), 1.22 (s, *t*Bu, 18H), 1.03 (s, CH$_3$, 6H), 0.99 (s, *t*Bu, 18H), 0.96 (s, *t*Bu, 18H), 0.95 (s, *t*Bu, 18H), 0.71 ppm (s, CH$_3$, 6H); MS(ESI): *m/z* (%): 2293.3 (100 %) [*M*$^+$+Na].

Cyclic hexaurea 14 (XDXDXD): Diamine **11** (XDXDX, 18 mg, 0.015 mmol) and diisocyanate **2** (2.9 mg, 0.015 mmol) were dissolved in dichloromethane (3 mL) and stirred for 18 h. The solvent was removed under reduced pressure and the residue was triturated with acetonitrile. The white solid was filtered off to yield hexamer **14** (16 mg, 80 %). M.p. > 290 °C (decomp); MS(ESI): *m/z* (%): 1837.2 (100 %) [*M*$^+$+Na].

Cyclic hexaurea 15 (XDDXDD): Diamine **8** (DXD, 130 mg, 0.16 mmol) dissolved in dichloromethane (25 mL) was added to diisocyanate **9** (DXD, 138 mg, 0.16 mmol) dissolved in acetonitrile (75 mL) with stirring and under nitrogen. The solvent was removed after 18 h under reduced pressure, and the oily residue was triturated with acetonitrile. Hexamer **15** was isolated as a white powder (45 %, 120 mg). M.p. 243 °C; MS(ESI): *m/z* (%): 1684.8 (100 %) [*M*$^+$+Na].

Cyclic hexaurea 16 (DDDDDD): Diamine **10** (DDDD, 111 mg, 0.13 mmol) dissolved in ethyl acetate/acetonitrile (1:1 (v/v), 25 mL) was added to diisocyanate **7** (DD, 60 mg, 0.13 mmol) dissolved in the same solvent (30 mL) with stirring and under nitrogen. The solvent was removed under reduced pressure after 18 h, and the residue was separated by column chromatography on silica gel (chloroform/acetone, 50:1 (v/v), 200 mL). The isolated hexamer was slightly contaminated with other cyclic by-products. Therefore, the solid was triturated with methanol to remove the insoluble by-products. The filtrate was evaporated under reduced pressure and hexamer **16** was isolated as a white powder (53 %, 91 mg). M.p. 254–257 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.07 (br s, NH, 12H), 8.17 (d, ArH, 12H, ^3J(H,H) = 7.6 Hz), 7.06 (t, ArH, 12H, J-(H,H) = 7.6 Hz), 6.90 (t, ArH, 12H, J(H,H) = 7.6 Hz), 6.68 ppm (d, ArH, 12H, J(H,H) = 7.6 Hz); MS(ESI): *m/z* (%): 1380.1 (100 %) [*M*$^+$+Na].

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Stability-constant determination: UV absorption spectrophotometric titrations were carried out to obtain the stability constants ($\log\beta$) of the complexes formed between the hexameric ligands and the chloride, bromide, acetate, and dihydrogen phosphate anions provided as their tetrabutylammonium salts. All the experiments were carried out in a mixture of THF/acetonitrile (1:3, v/v). The procedure has been previously reported in detail.[9,10] The concentration of the ligand was in the range 2×10^{-6}–1.2×10^{-5} M, and the final anion/ligand ratios reached at the end of the titrations varied from 2:1 to 44:1, according to the strength of the complexes. The measurements were treated with the numerical program SPECFIT[15] to give the stoichiometries and the stability constants of the complexes.

Single-crystal X-ray diffraction studies

Preparation of crystals: In general, mixtures containing acetone, acetonitrile, chloroform, dichloromethane, ethanol, ethyl acetate, methanol, and THF were checked for crystallization to increase the probability of finding a suitable combination of solvents. The compound was dissolved in a solvent in which it was highly soluble, and the solution was mixed with another solvent in which the compound was poorly soluble. The resulting solution was allowed to evaporate slowly through a very small hole made by a needle in the plastic cap of the bottle. When a precipitate was formed in the bottle but no crystallization occurred, the compound was dissolved again in another pair of solvents, and so on until single crystals were obtained. Thus, in each single case every solvent listed above may be present in the mixture, but two of them were always the main components. The main pair of solvents were dichloromethane/acetone, ethyl acetate/ethanol, and ethyl acetate/acetonitrile for α, β, and γ, respectively.

Analysis: Data were collected on a STOE-IPDS-II two-circle diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation (0.71073 Å). Data reduction was performed with the X-AREA software.[16] Structures were solved by direct methods with SHELXS-90 and refined by using the full-matrix least-squares techniques with SHELXL-97.[17]

All non-hydrogen atoms, excluding the disordered *t*-butyl groups in **15α** and **15γ**, the water molecules, and disordered dichloromethane molecules in **17**, were refined with anisotropic displacement parameters. Hydrogen atoms bonded to carbon atoms were included at calculated positions and allowed to ride on their parent atoms. The hydrogen atoms bonded to nitrogen atoms in **15α** were freely refined, the hydrogen atoms bonded to oxygen atoms in **15γ** were refined with the O–H lengths restrained to 0.84 Å and with the H···H distances restrained to 1.4 Å. The hydrogen atoms of the water molecules in **17** could not be found in a difference map and were omitted from refinement. The two *t*-butyl groups in **15α** are disordered over two positions with a ratio of the site-occupation factors of 0.532(6)/0.468(6) and 0.588(6)/0.412(6), respectively. One of the *t*-butyl groups in **56** is disordered over two positions with a ratio of the site occupation factors of 0.767(8)/0.233(8). Bond lengths and angles of the disordered atoms were restrained to have the same geometric parameters as those of the non-disordered *tert*-butyl group. One of the *tert*-butyl groups in **17** is disordered over two positions with a ratio of the site-occupation factors of 0.50(2)/0.50(2) and the dichloromethane with site-occupation factors of 0.575(5)/0.425(5). The C–Cl bond lengths in this dichloromethane molecule were restrained to 1.7 Å and the Cl···Cl distances to 2.8 Å. The contribution of the ethyl acetate molecules in **15β** was suppressed using the SQUEEZE[18] option in PLATON.[19] The crystallographic data are summarized in Table 4.

Table 4. Crystallographic data.

	17	**15α**	**15β**	**15γ**
chemical formula	$C_{119}H_{152}N_{10}O_9\cdot C_3H_6O\cdot 2\,CH_2Cl_2\cdot 4\,H_2O$	$C_{100}H_{100}N_{12}O_{12}\cdot 8\,C_3H_6O$	$C_{100}H_{100}N_{12}O_{12}\cdot 2\,C_4H_8O_2\cdot 2\,C_2H_6O$	$C_{100}H_{100}N_{12}O_{12}\cdot 3\,C_2H_6O\cdot C_4H_8O_2\cdot C_2H_3N\cdot H_2O$
CCDC ref. numbers	706372	705736	705737	705738
M_r	2166.50	2126.54	1930.26	1947.30
crystal system	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a [Å]	14.9057(8)	15.2902(12)	12.3418(11)	15.5508(6)
b [Å]	20.4172(9)	15.3882(13)	15.1520(13)	18.1537(7)
c [Å]	21.4080(11)	15.7353(12)	15.2483(11)	21.1074(8)
α [°]	88.307(4)	117.903(6)	99.182(6)	78.610(3)
β [°]	80.779(4)	101.301(6)	109.839(7)	81.262(3)
γ [°]	76.888(4)	103.215(6)	97.578(7)	78.204(3)
V [Å^3]	6263.1(5)	2981.3(4)	2594.2(4)	5679.2(4)
Z	2	1	1	2
T [K]	173	173	173	173
reflections	83963	31249	24886	144878
unique reflections	24000	11153	9647	21582
R_{int}	0.0522	0.0567	0.0892	0.1483
$wR(F^2)$ all data	0.3233	0.1989	0.2050	0.3163

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