Rational design of selective anion receptors

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Denys Meshcheryakov
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Contents

1 Anion recognition: a survey

1.1 Introduction

The recognition of anionic species has emerged from the late 1960s with positively charged ammonium cryptand receptors for halide binding.[1] At the same time synthesis and coordination properties of crown ethers were reported, which pushed the development of the host-guest chemistry ahead. In the 1970s the coordination chemistry of group 1 and 2 metal and ammonium cations was growing rapidly. This led to the result that the cation recognition is now a well developed branch of supramolecular chemistry. At the same time the coordination chemistry of anions received comparatively minor attention. But during the last two decades the interest for anion coordination increased and extensive studies done by many researchers led to the remarkable progress.[2]

There are numerous reasons for the sudden growth of this formerly "quiet" area of the coordination chemistry. Anions act in biological systems - they carry genetic information since the DNA is a polyanion; most of enzyme substrates and cofactors are anionic.[3] Anions are involved in medicine and catalysis. Several pollutant anions are a matter of environmental concern, for example phosphate[4] and nitrate[5] as a part of numerous fertilizers as well as pertechnetate produced during the reprocessing of nuclear fuel.

Modern anion receptors include a lot of different systems. Charged and neutral, cyclic and acyclic, inorganic and organic supramolecular constructions were built for the complexation, recognition, sensing and separation of different anionic species. The recent developments include remarkable advances in anion-templated synthesis, directed self-assembly, ion-pair recognition and the use of anions in supramolecular catalysis.

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[1] C. H. Park, H. E. Simmons, *J. Am. Chem. Soc.* **1968**, *90*, 2431 - 2432.

[2] *Supramolecular Chemistry of Anions* (Eds.: A. Bianchi, K. Bowmann-James, E. Garcia-España), WILEY-VCH, New-York, **1997**.); P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502 - 532; *Angew. Chem. Int. Ed.* **2001**, *40*, 486 - 516.

[3] D. W. Christianson, W. N. Lipscomb, *Acc. Chem. Res.* **1989**, *22*, 62.

[4] B. Moss, *Chem. Ind.* **1996**, *28*, 14.

[5] C. Glidewell, *Chem. Br.* **1990**, *26*, 137.

In this introductory chapter the current state of anion recognition will be shortly are reviwed and our way through will be outlined.

1.2 General considerations

The design of the anion receptors is particularly nontrivial. There are certain reasons for this. Anions are significantly larger than analogous cations carrying the same charge and therefore have lower charge to radius ratio (see Table 1). The electrostatic binding forces are correspondingly weaker than they would be for the smaller cation.

Table 1. A comparison of the radii of isoelectronic cations and anions in octahedral environments.[6]

Cation	Radius, Å	Anion	Radius, Å
Na^+	1.16	F^-	1.19
K^+	1.52	Cl^-	1.67
Rb^+	1.66	Br^-	1.82
Cs^+	1.81	I^-	2.06

Anions are often sensitive to pH values of the environment, as they become protonated at low pH and therefore lose their negative charge. The receptor must be able to function within the pH window of the target anion.

Another important feature of anions is the diversity of their geometries (Figure 1). Therefore each structural variation of the anionic guest requires suitable spatial properties from the host system. Excellent examples of the geometric complementarity can be found in nature. Natural periplasmatic protein PBP (Phosphate Binding Protein) acts in the cell transport systems. It has the cavity for anion binding which perfectly fits phosphate and the completely desolvated anion is bound with twelwe hydrogen bonds with exceptional selectivity.[7]

[6] R. D. Shannon, *Acta Crysallogr. Sect. A* **1976**, 32, 751.

[7] H. Luecke, F. A. Quiocho, *Nature* **1990**, *347*, 402 - 406; B. L. Jacobson, F. A. Quiocho, *J. Mol. Biol.* **1988**, *204*, 783.

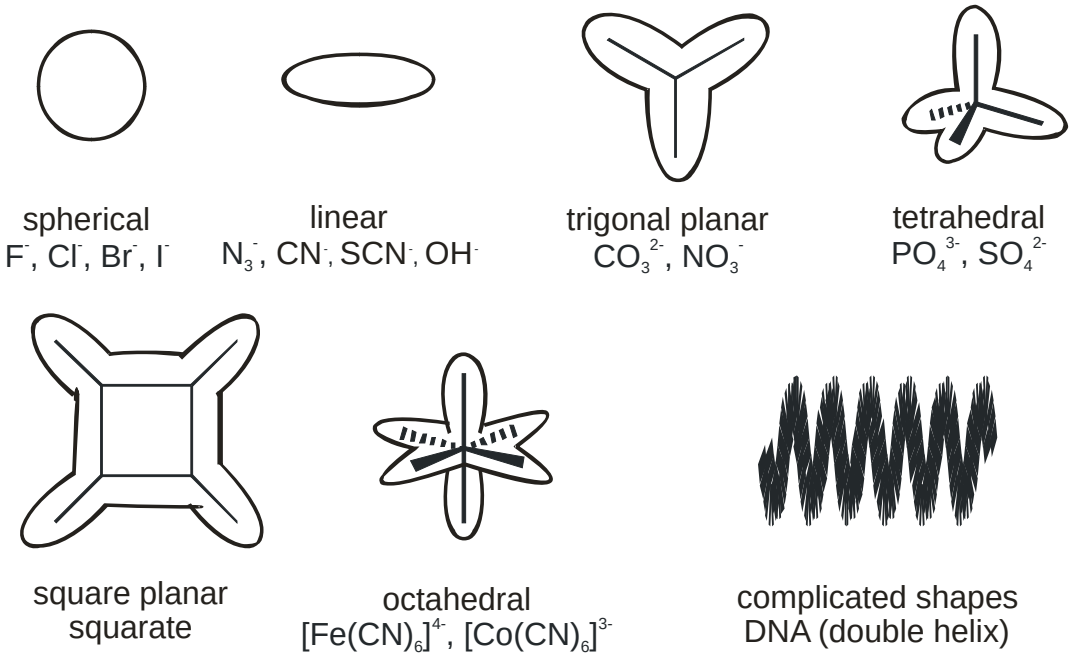

Figure 1. Examples of anionic species geometries.

The influence of a solvent should be also taken into account. Solvation plays crucial role in controlling anion binding strength and selectivity. Electrostatic interactions are generally predominant in anion solvation. Hydroxylic solvents in particular can form strong hydrogen bonds with anions. Anions hydrate more strongly than cations for the same ionic radius as water hydrogen atoms can approach (about 0.8 Å) more closely to the anion than the water oxygen atoms to the cation. Obviously the potential anion receptor must be able to compete with the solvent environment in which the anion recognition takes place. For example, a neutral receptor that binds anions solely through ion-dipole interactions may only complex anions in aprotic organic solvents, whereas a charged anion receptor has the capacity to bind highly solvated (hydrated) anions in protic solvent media. Biological anion receptor systems are optimized to operate in a very specific range of environments where the source of selectivity for the biological anion is the difference in free energy lost on dehydrating the anion and that gained by the interaction of the anion with the binding site.[8]

Anions are also far more polarizable than cations (compare polarizabilities: Na^+ 0.12; K^+ 0.78; Cl^- 4.00 $Å^3$)[9] due to their more diffuse extra electron(s) and breaking hydrogen bonds

[8] S. Mangani, M. Ferraroni, P. Orioli, *Inorg. Chem.* **1994**, *33*, 3421 - 3423

[9] A. Grossfield, P. Ren and J. W. Ponder, *J. Am. Chem. Soc.* **2003**, *125*, 15671 - 15682.

around anions is relatively slow due to the difficulty in finding a new hydrogen-bonding partner.[10]

Another property which affects the anion binding and therefore determines the design is hydrophobicity. Anions are ordered by their hydrophobicity in accordance with so called Hofmeister series[11], (Fig. 2) which originates from the ranking of various ions toward their ability to precipitate a mixture of hen egg white proteins from water. Simplistically, this protein precipitation can be explained in terms of the strength of the ions affinity to water. Hydrophobic anions are generally bound more strongly in hydrophobic binding sites.

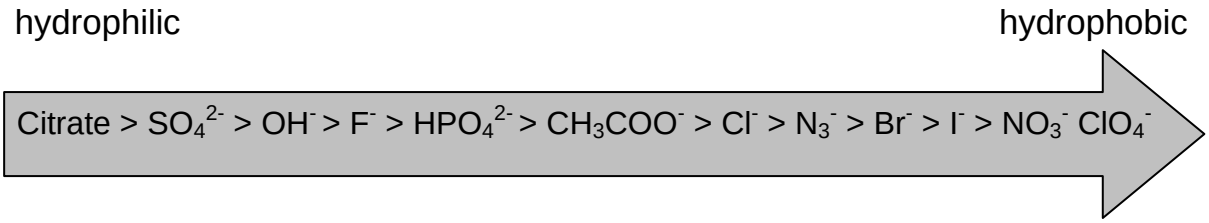

Figure 2. Anions arranged in order of their hydrophobicity (Hofmeister series).

Therefore, the design of selective anion receptors requires that the geometry and basicity of the anion and the properties of the solvent medium should be taken into account. Also the complementarity between the host and the anionic guest is crucial in determining selectivities.

1.3 Interactions between host and the anion

It may be useful to mention shortly the types of noncovalent interactions used to complex an anionic guest. These include:

- electostatic interactions;[12]
- hydrogen bonding;[13]

[10] M. F. Kropman and H. J. Bakker, *Science* **2001**, *291*, 2118 - 2120.

[11] F. Hofmeister, *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247 - 260; translated in W. Kunz, J. Henle and B. W. Ninham, *Curr. Opin. Coll. Interface Sci*. **2004**, *9*, 19 - 37.

[12] F. P. Schmidtchen, G. Muller, *J. Chem. Soc. Chem. Commun.* **1984**, 1115.

- hydrophobicity;[14]
- coordination to a metal ion;[15]
- … and combinations of these interactions acting together.

Sometimes other types of interaction play a role in anion binding. For example, the influence of anion-π interactions on the incapsulation of chloride between pyridine rings of a dendritic octadentate ligand was recently shown.[16]

Systems based on hydrogen bonds have especially promising potential. Directionality of hydrogen bonds allows to design receptors with specific shapes which are capable of differentiating between anionic guests with various geometries. It was already mentioned before, that natural anion receptors which are based on hydrogen bonding have exceptional selectivity and binding strength in such a competitive environment as water.[7] Such high selectivity can be achieved in neutral receptor molecules, because the merely distance-dependent coulombic interactions are much stronger than spatially more specific hydrogen bonding.

At the same time additional factors must be taken into account when anion receptors based on hydrogen bonds are designed. The anion is not necessary the only target for the hydrogen bond. Solvent molecules can hinder the formation of the bonding network enormously; molecules of the receptor may be involved in various intra- or intermolecular interactions, which compete with anion binding. Thus, the design of such receptor requires a proper arrangement of ligating groups and it is not always possible to get an effective host system within a few simple synthetic steps. Although the main factors determining the effectivity of an anion binding system are known and described before, sometimes only serendipity helps chemists to find the successful design. For example, the whole class of pyrrolic and polypyrrolic receptors is the result of such serendipity.[17]

There are three main classes of hydrogen bond donors for a neutral anion receptors:

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[13] For one of the first examples see S. Valiyaveettil, J. F. J.Engbersen, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1993**, *105*, 942 - 944; *Angew. Chem. Int. Ed.* **1993**, *32*, 900 - 901; for the recent review see K. Choi, A. D. Hamilton, *Coord. Chem. Rev.* **2003**, *240*, 101 - 110.

[14] For example, receptor based on cyclodextrine macrocycle, see Y. Inoue, T. Hakushi, Y. Liu, L.-H. Tong, D.-S: Jin, *J. Am. Chem. Soc*. **1993**, *115*, 475 - 481.

[15] For the recent review see P. D. Beer,.; S. R. Bayly, *Top. Curr. Chem.* **2005**, *255*, 125 - 162.

[16] P. de Hoog, P. Gamez, I. Mutikainen, U. Turpeinen, J. Reedijk, *Angew. Chem. Int. Ed.* **2004**, *43*, 5815-5817; *Angew. Chem.* **2004**, *116*, 5939 - 5941.

[17] J.L. Sessler, M.J. Cyr, V. Lynch, E. McGhee, J.A. Ibers, *J. Am.Chem. Soc.* **1990**, *112*, 2810 - 2813.

- amide-based[18]
- pyrrole-based[19]
- urea and thiourea-based

These functional types are used within one molecule either alone or in combination.

Among these hydrogen bond donating groups urea groups have especially promising potential. The NH groups of dialkyl or diarylurea are strong hydrogen donors, which are able to build two hydrogen bonds to an acceptor, while amide or pyrrole group are able to form only one bond. This property of the urea is widely used not only in anion receptors, but in general for the development of self-assembled structures.[20] The proper placement of several urea functions within a single molecule and their intramolecular interaction leads to the remarkable properties.

But in fact there are not many solely urea-based receptors exist. And what is especially surprising, there was no systematic effort applied to the problems of the rational arrangement of the urea groups. Such an arrangement is particularly important for the urea-based receptors, because the urea tends to form strong hydrogen bonds between hydrogens of one group and oxygen of another group.

1.4 A new family of urea-based anion receptors

Among other anions nitrate attract special interest. Nitrates are part of numerous fertilizers in agriculture. Some technologies of the nuclear waste reprocessing are based on the separation of nitrates of the radioactive elements. The development of selective anion receptor for nitrate is therefore a task of a great practical importance. However, the low basicity of the nitrate anion weakens the binding with a receptor. This problem could be overcome by the development of a structure wich has multiple binding sites ensuring strong binding arranged with a high grade of complementarity towards nitrate.

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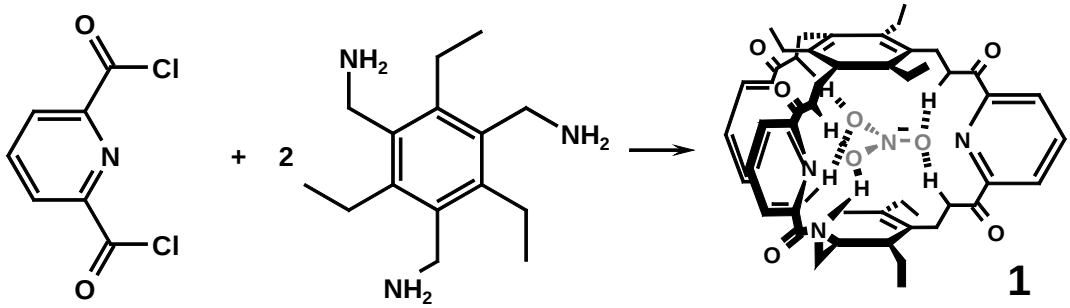
[18] For the recent review see C. R. Bondy, S. J. Loeb, *Coord. Chem. Rev.* **2003**, *240*, 77 - 99.

[19] For the recent review see J. L. Sessler, S. Camiolo, P. A. Gale, *Coord. Chem. Rev.* **2003**, *240*, 17 - 55.

[20] K. D. Shimizu, J. Rebek, Jr., *Proc. Nat. Acad. Sci*. **1995**, *92* (26), 12403 - 12407; O. Mogck, V. Böhmer, V. Vogt, *Tetrahedron* **1996**, *52* (25), 8489 - 8496; R. K. Castellano, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998,** *120,* 3657 - 3663; Y. Rudzevich, V. Rudzevich, C. Moon, I. Schnell, K. Fischer, V. Böhmer, *J. Am. Chem. Soc.* **2005**, *127*, 14168 – 14169.

It is self-evident that the trigonal arrangement of ligating groups is optimal when dealing with nitrate. This concept was successfully employed by Anslyn and Snowden in 1997. They have synthesized bicyclic cyclophane **1** containing six amide functions. The cyclophane showed exceptionally high affinity towards nitrate (and in general for trigonal anions), while the more basic chloride is bound much weaker.[21] As shown on the scheme, each oxygen of the nitrate is bound by the two hydrogen bonds.



Scheme 1. Synthesis of the bicyclic cyclophane anion receptor.

The molecule is a brilliant example for the preorientation of ligating functions combined with geometrical complementarity in the threedimensional cage, which in the same time can be obtained by a relatively simple synthesis.

Various other C_3 symmetrical macrocycles have been developed as receptors.

Hamilton and Choi have synthesized the macrocycle **2** using the step-by-step assembly of simple building blocks.[22] The macrocycle has a trigonal structure in which three hydrogen-bonding amide groups are pointing into the central cavity to bind anions with trigonal geometry. According with these expectations the macrocycle (R = COOEt) forms a 1:1 complex with tetrabutylammonium *p*-tosylate (K_a = 2.6•10^5 M^{-1} in $CDCl_3$ with 2% DMSO-d_6) as well as with nitrate (K_a = 4.6•10^5 M^{-1} in $CDCl_3$ with 2% DMSO-d_6). Interestingly, that upon addition of an increasing amount of the TBA salt (iodide, chloride, nitrate) two molecules of the macrocycle initially form a 2:1 complex with one anion and upon further addition of the salt a 1:1 complex is formed. Molecular modeling suggests a sandwich-like binding in case of 2:1 (ligand:anion) complex.

Another C_3-symmetrical "sandwich" with anions was prepared by Kubik et. al. They have obtained the cyclic hexapeptide **3** which showed affinity predominantly to halide

[21] A. P. Bisson, V. M. Lynch, M. C. Monahan, E. V. Anslyn, *Angew. Chem. Int. Ed.* **1997**, *36*, 2340 - 2342.

[22] K. Choi, A. D. Hamilton, *J. Am. Chem. Soc.* **2003**, *125*, 10241-10249.

anions.[23] ESI - mass spectroscopy confirmed the presence of both 2:1 (ligand:anion) and 1:1 complexes with halides in highly polar water/methanol (8:2 *v/v*) solution. Especially interesting, that upon simultaneous addition of Cl^-, Br^- and I^- salts to the solution of the hexapeptide, MS peaks corresponding to all 2:1 (ligand:anion) complexes emerged with increasing intensity in the row $Cl^- < Br^- < I^-$. At the same time peaks corresponding to the 1:1 complexes appeared with significantly lower intensity. The X-ray structure of the iodide complex showed that iodide is located between two receptor molecules and is bound by six convergent hydrogen bonds (three from each molecule).

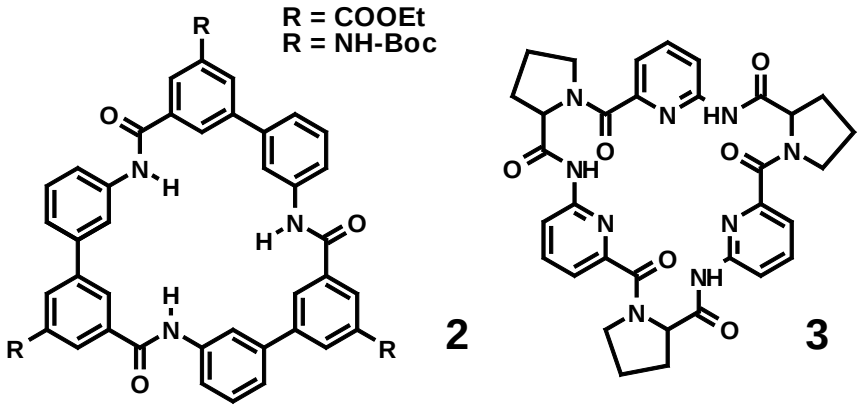


Figure 3. Examples of C_3 symmetrical macrocyclic receptors.

Unfortunately the compound **3** showed only weak binding of nitrate. The whole structure is flexible and has a conformation where amide bonds are not directed in the center of the internal cavity.

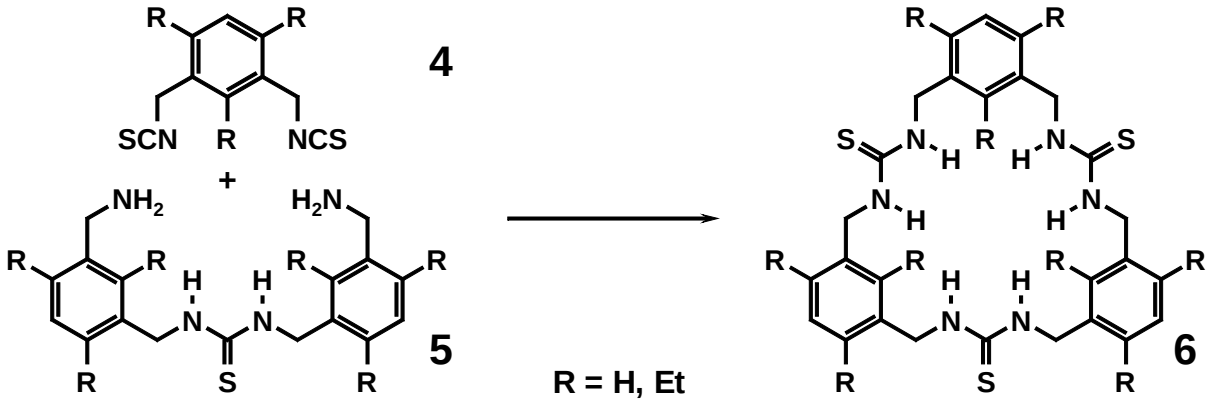
Single examples of tripodal urea-based receptors are also known.

Hong and Lee prepared the trimeric macrocycles **6** by the reaction of diisothiocyanate **4** with dimeric thiourea **5** (obtained by the reaction of two mono-BOC protected diamines).[24]

According to molecular modeling performed by authors the replacement of hydrogens in R positions by ethyl groups must lead to the preorganization of urea groups in a way that they all are directed into the cavity of the trimer.

[23] S. Kubik, R. Goddard, R. Kirchner, D. Nolting, J. Seidel, *Angew. Chem. Int. Ed* **2001**, *40*, 2648 - 2651.

[24] K. H. Lee, J. Hong, *Tetrahedron Lett.* **2000**, *41*, 6083 - 6087.



Scheme 2. Synthesis of the macrocyclic triurea.

The ^{1}H NMR titrations in DMSO-d_6 showed the formation of the 1:1 complex with halides, azide, phosphate and acetate. The triurea **6** (R = ethyl) showed association constants from 5300 M^{-1} for acetate to as low as 11 M^{-1} for bromide; but in every case values for the trimer with R = Et were higher (K_a rose from 320 to 5300 M^{-1} for acetate, from 800 to 1600 M^{-1} for dihydrophosphate). Unfortunately no studies with nitrate were performed, but moderate values of the association constant for such basic anions like phosphate and acetate allow the assumption that the binding of nitrate is very weak.

Highly flexible and large macrocycles (Fig. 4) were prepared by Ranganathan and Lakshmi.[25] They reacted L-cystine dimethyl ether with triphosgene in the presence of triethylamine in dichloromethane under high dilution conditions.

The 27-membered trimer **7** and 36-membered tetramer **8** were isolated after column chromatography with yields of 37 and 15% respectively. No other cycles or linear oligomers were isolated. The authors explain the nearly complete absence of the product of intramolecular cyclization and the dimer by the sterical factors.

The trimer **7** shows moderate affinity to the chloride and bromide (K_a = 2500 and 201 M^{-1} respectively), but not for iodide. Tripodal nitrate anion was bound with K_a = 520 M^{-1} (all measurements were made in $CDCl_3$). The tetramer was checked (^{1}H NMR titration) with D_{4h} symmetrical squarate anion and showed 1:1 complex with K_a = 3210 M^{-1}, while binding of halides was not observed for this macrocycle.

The binding of nitrate is again relatively weak. Urea groups in these cycles are connected by flexible spacers and the whole molecule has many hydrogen bond acceptors, so

[25] D. Ranganathan, C. Lakshmi, *Chem. Commun.* **2001**, 1250 - 1251.

the formation of intramolecular hydrogen bonds can be the alternative to the binding of anions.

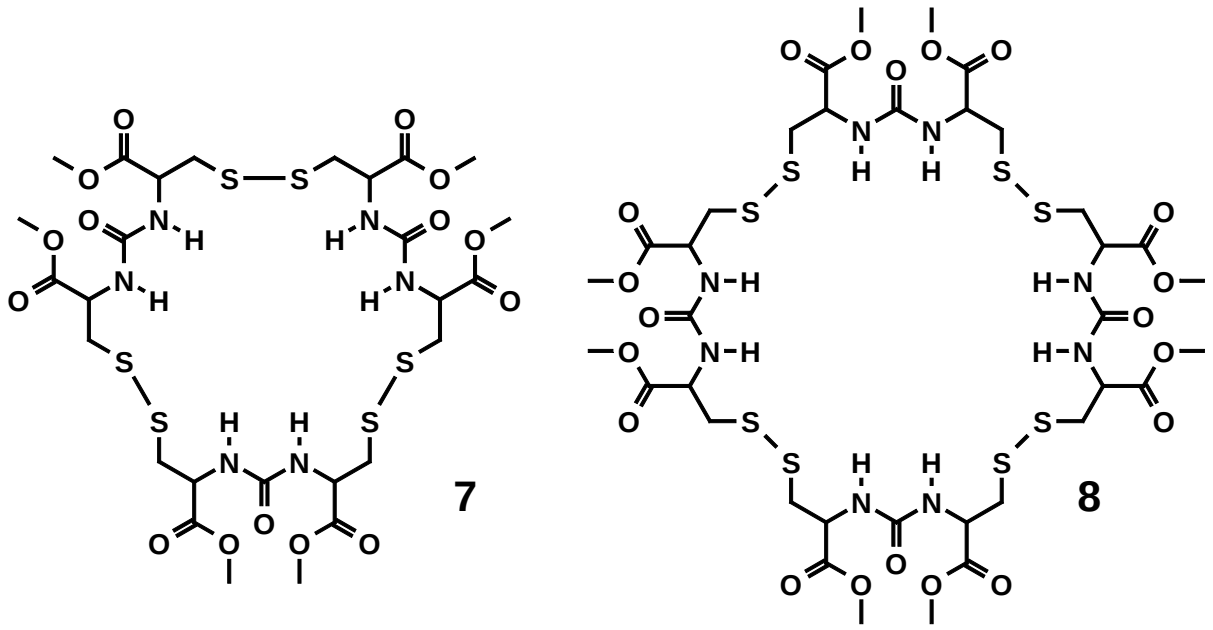


Figure 4. Marocycles synthesized by Ranganathan and Lakshmi.

König, Herges et. al. presented the work exploiting the idea of the nitrate binding tripodal triurea or trithiourea. They have sythesized two cyclic thiourea receptors **9** and **10** with the trimeric structure starting from the same considerations about the geometry of the complex with nitrate anion, which we also had at that time (Fig. 5).

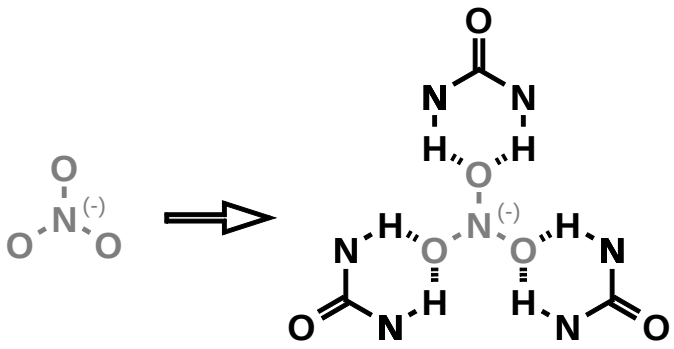
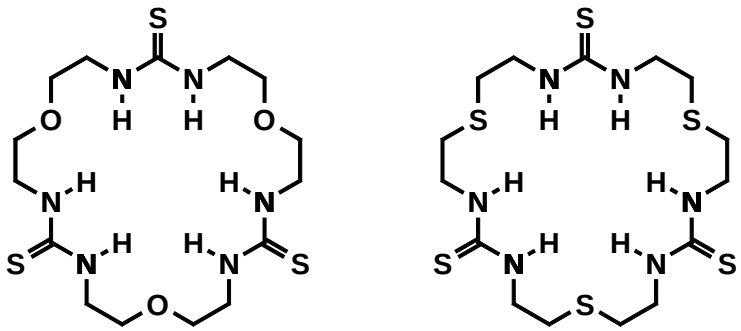


Figure 5. Tripodal arrangement of the urea groups for nitrate binding.

They used the highly flexible 2,2'-oxybisethylamine or 2,2'-thiobisethylamine units, to obtain macrocycles with three units interconnected by thiourea moieties. In case of the oxybisethylamine-based **9** receptor they have observed complexation with tetrabutylammonium nitrate in DMSO with 1:1 stoichiometry with the association constant of

17.1 M^{-1}, while the thiobisethylamine-based macrocycle **10** showed no affinity to nitrate at all.[26]



9 **10**

Figure 6. Macrocyclic receptors synthesized by König et. al.

Binding of two chlorides by **9** with K_a = 200 M^{-2} was also observed. Bromide demostrated 1:1 binding with K_a = 400 M^{-1}, acetate with K_a = 1260 M^{-1} and dihydrogenphosphate formed a 1:2 complex with K_a = 53 000 M^{-2}. Participation of the tetrabutylammonium cation in the binding was also detected.

Unfortunately the binding with nitrate is disappointing again. But why? The C_3-symmetric cycle with three urea groups should be especially advantageous for trigonal planar anions such as nitrate or carbonate. The efficiency of the geometry chosen for the complexation of the nitrate was recently confirmed in two subsequent publications of Moyer et. al., in which the rational design of the receptor for nitrate and other anions based on the electronic structure calculations was reported.[27]

We supposed that the effectivity of tripodal urea-based receptor can be significantly increased by the introduction of the rigid spacers into the molecule instead of flexible chains.

The rigid xanthene unit as a spacer for the cyclic triurea was first suggested. Therefore the whole structure is highly rigid and (almost) flat.

[26] R. Herges, A. Dikmans, U. Jana, F. Köhler, P. G. Jones, I. Dix, T. Fricke, B. König, *Eur. J. Org. Chem.* **2002**, 3004-3014.

[27] B. P. Hay, M. Gutowski, D. A. Dixon, J. Garza, R. Vagras, B. A. Moyer, *J. Am. Chem. Soc.* **2004**, *126*, 7925-7934; B. P. Hay, T. K. Firman, B. A. Moyer, *J. Am. Chem. Soc.* **2005**, *127*, 1810-1819.

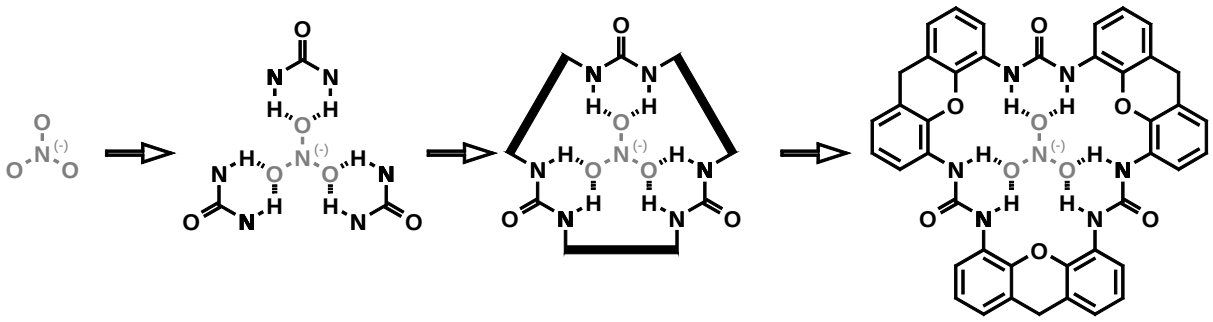


Figure 7. Cyclic triurea with rigid spacers.

Along with rigidity xanthene has also additional favorable feature for our receptors. The repulsion of the xanthene oxygen and the oxygen of the urea groups should favour the orientation of the urea hydrogens inside the cavity. With such highly preorganised structure we expected to achieve much higher affinities and selectivity together with minimized possibilities for the unwanted hydrogen bonding.

Following this general idea a C_3-symmetrical macrocycle consisting of three xanthene units linked via urea functions was designed by computer simulation. The molecule was proved to possess the proper arrangement of the ligating functions. MD simulations with cycle **11** reveal strong binding of nitrate via six NH---O hydrogen bonds. The inclusion occurs not only in the anticipated form **11**, but also in the orientation **12**. Calculated complexation energies differ strongly for halides (Br^- and Cl^-) and nitrate. Furthermore the potential receptor X showed even stronger affinity to "tripodal" anions such as R-SO_3^- and R-PO_3^{2-}. MD simulations of X+NO_3^- in water showed that complexes are stable over the whole simulation time (2 ns) suggesting remarkable stability even in aqueous solution. Analogous MD simulations involving for example the cycles **6** and **2** showed that complexes with them dissociate already after a few picoseconds.[28]

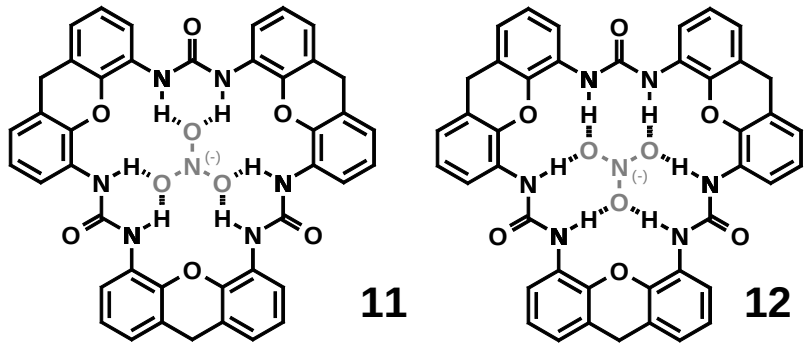


Figure 8. Inclusion of nitrate.

[28] I. Thondorf, unpublished results.

Table 2. Complexation energeis calculated from MD simulations (kcal/mol)

Complex	**6** + HPO_4^{2-}	**2** + Cl^-	**2** + Br^-	**11** + Cl^-	**11** + Br^-	**11** + NO_3^-
$-\Delta E_{comp}$	36.7	23.1	24.0	39.4	36.6	54.1

Modifications of this basic structure offers many additional possibilities. The receptor properties can be changed by tuning a delicate balance between the prearrangement of ligating functions ("rigidity") and the ability to adapt to the target guest ("flexibility"). This may be done by exchanging one or more spacers in the cycle by units with the same basic skeleton, but with more flexibility, for example diphenyl ether derivatives, where the phenyl rings are connected only via oxygen. The family of these tunable receptors can include cycles with different number of units, e.g. tetramers, hexamers and so on.

Linear molecules which consist of xanthene (and eventually diphenyl ether) units offer yet another interesting aspect. The urea tends to be coplanar with the adjacent aromatic system, so for the whole molecule the arrangement close to planar is preferred. The position of the urea group when its oxygene is situated in close proximity to xanthene oxygens must be strongly unfavorable. Therefore in general xanthenes linked via urea groups should preferably arrange with certain deviations in a way similar to those in cycle. Thus, when long oligoureas (with four, six and more units) form such a pseudo-cycle, they may asssume helical conformations. This tendency may also be additionally induced by the binding of spherical anions, such as halides.

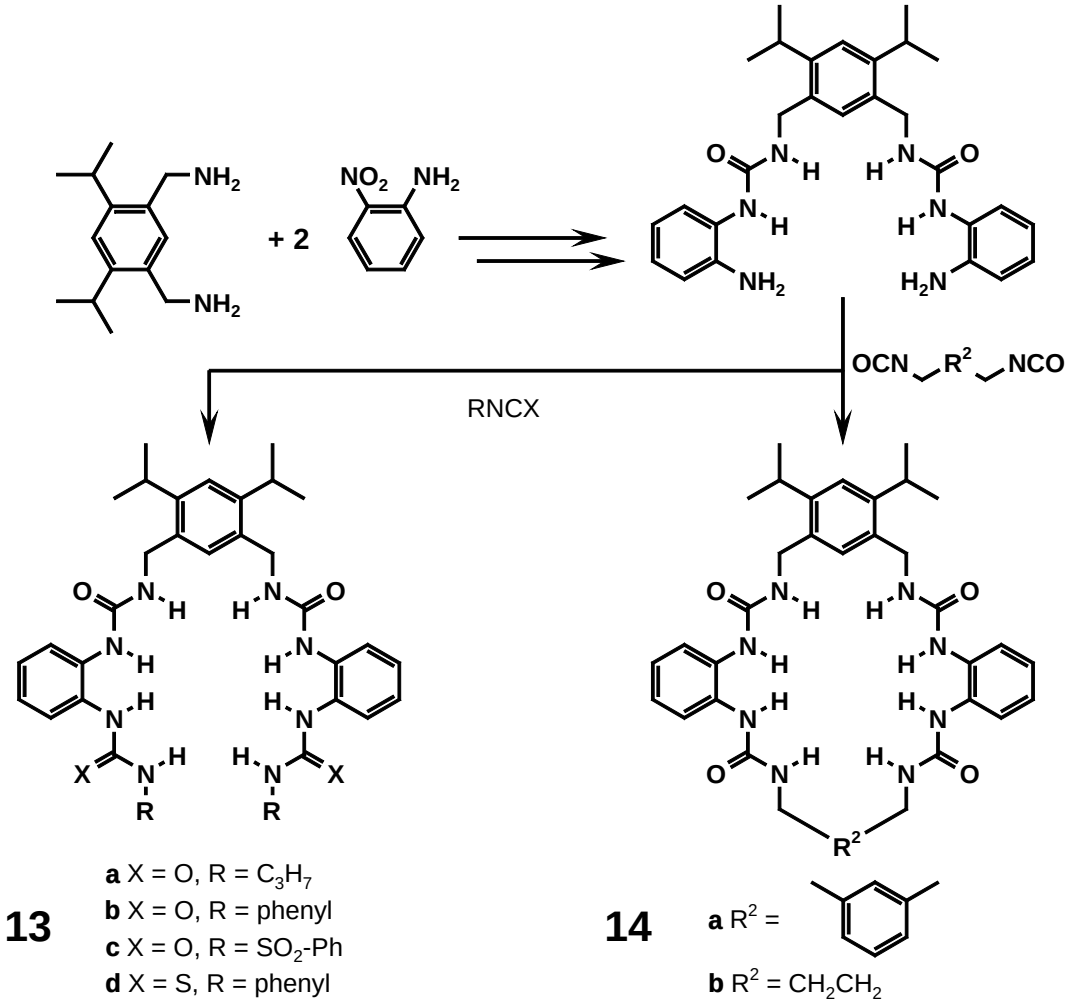
In certain cases linear receptors could demonstrate higher affinity to anions than cyclic ones. At this point it is reasonable to mention the work of Reinhoudt et. al., who developed a family of cleft-like **13** and cyclic receptors **14** based on xylylenediamine.[29] These receptors and their synthesis are presented briefly in Scheme 3.

Cyclic receptors **14** have a comparatively fixed conformation and eight urea hydrogen atoms are directed into the cavity, while clefts **13** are much more flexible.

The activity of the molecules towards Cl^-, Br^-, NO_3^-, HSO_4^- and $H_2PO_4^-$ was checked by ^1H NMR titration in DMSO-d_6. For the cleft-like receptor **13a** all anions induce shifts of the signals of NH protons, as well as the aromatic hydrogen atoms. Unfortunately the authors could not determine accurate association constants due to either unclear stoichiometry of the complexes or weakness of the induced NMR shifts. **13b** appeared to be more selective. The

[29] B. H. M. Snellink-Ruël, M. M. G. Antonisse, J. F. J. Engbersen, P. Timmermann, D. N. Reinhoudt, *Eur. J. Org. Chem.* **2000**, 165 - 170.

2:1 (host:guest) complex with dihydrophosphate was formed with remarkably high constant of $5 \cdot 10^7$ M^{-2}, while all other anions did not induce changes in the spectrum.



Scheme 3. Anion receptors prepared by Reinhoudt et. al.

Thiourea moieties in **13d** do not increase the binding of the dihydrogenphosphate. The stoichiometry was not changed and the constant changed insignificantly. But the molecule **13d** appeared to be able to bind chloride with $K_a = 250$ M^{-1}.

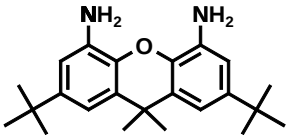
Cyclic compounds showed affinity to $H_2PO_4^-$ and Cl^-. Dihydrophosphate is bound in both cases strictly 1:1 with constants of 2500 and 4000 M^{-1} for **14a** and **14b** respectively. Chloride is bound remarkably weaker with constants of 500 and 50 M^{-1} respectively. Other anions have only small influence on the NMR signals.

Such a moderate binding with cyclic receptors in comparison with conformationally free "clefts" can be explained by the ability of open-chain receptors to adjust to the geometry of their binding sites to anion. At the same time cycles may be unable to use urea groups

effectively due to the conformational strain. These observations underline once more the fact that rigid receptor must fit anion, otherwise their binding is weak.

In the next chapter we discuss considerations on practical implementation of our ideas.

1.5 General considerations on the synthesis of perspective receptors



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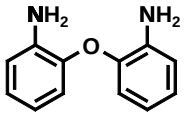
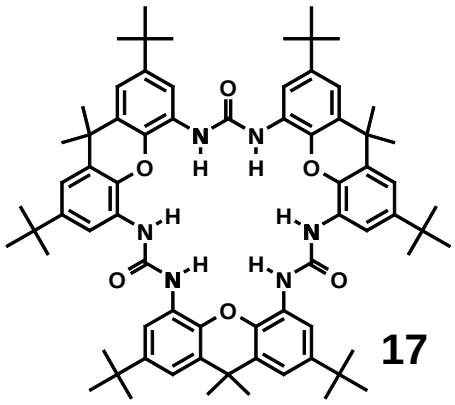


16

Figure 9. Rigid and flexible units for anion receptors.

Both rigid and flexible units were chosen in accordance with our considerations mentioned before. Two molecules were picked up which could be easily prepared from commercially available precursors.

As a rigid building block for our oligoureas we have selected 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenediamine **15**. The synthesis of this compound from commercially available 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid was previously described.[30] This xanthene-based spacer was used in some urea-based anion receptors and demonstrated promising results.[31] As flexible unit we have chosen 2,2'-oxydianiline **16**, which could be also prepared following relatively simple procedures.



17

Figure 10. Xanthene-based rigid cyclic triurea (XXX cyclic trimer).

These diamino-units have to be combined in the cycles like trimer **17** shown in Fig. 10 and interconnected via urea groups. For simplicity we will use "X" for "rigid" xanthene-based unit and "D" for "flexible" diphenyl ether-based unit.

There are two well-elaborated reactions to prepare the urea group which we have used. Urea is formed when an amino group reacts with an isocyanate or with a so called active urethane (see Fig. 11). Isocyanates (active urethanes) are formed when

[30] B. C. Hamann, N. R. Branda, J. Rebek, Jr., *Tetrahedron Lett.* **1993**, *34*, 6837 - 6840.

[31] P. Bühlmann, S. Nishizawa, K. P. Xiao, Y. Umezawa, *Tetrahedron* **1997**, *53*, 1647 - 1654; V. Alcázar, M. Segura, P. Prados, J. de Mendoza, *Tetrahedron Lett.* **1997**, *39*, 1033 - 1036.

phosgene or triphosgene (*p*-nitrochloroformate) is added to the solution of amine in the presence of base (usually trialkylamines) in order to avoid protonation of the amine with hydrochloric acid produced in the reaction.

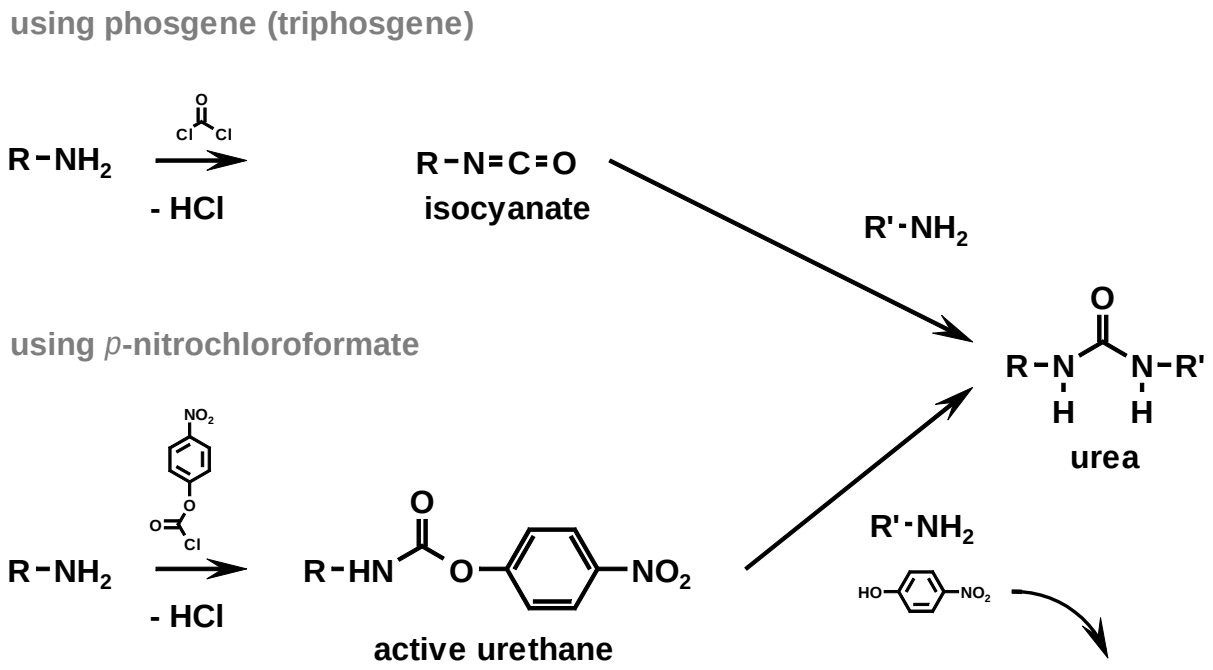


Figure 11. Two synthetic pathways to prepare urea.

Each of these pathways has its own benefits and disadvantages. Phosgene (triphosgene) is much more toxic than *p*-nitrochloroformate. Isocyanates in general are more sensitive to moisture than active urethanes, which are often easily crystallizable. However, in the latter case we have a reagent with a bulky residue (active ureathane) which could hinder the urea formation when it is spatially difficult. In addition, we have the free nitrophenole (i.e. nitrophenolate anion) in the reaction mixture which could also interact with readily formed urea groups. This nitrophenole must be washed away to get the pure product, while reaction of isocyanate with an amine proceeds without additional products.

The synthesis of a macrocycle implies the subsequent formation of several urea groups and the cycle is closed when the last urea is formed from linear precursor. There are two general strategies for this.

One approach in macrocycle synthesis is cyclization of a linear precursor that is assembled from monomers (diamino units) in a stepwise manner. This stepwise synthesis usually consists of a repeated cycle of reactions leading to an appropriate oligomer that is then cyclized in the final step. It is obvious that such approach allows to combine different units in the cycle following a planned sequence. Several successful stepwise syntheses of macrocycles

containing an interior cavity with multiple groups are shown among the examples in the subchapter 1.4.[22, 23, 24, 26]

Obviously, each elongation step assumes partial protection or partial functionalization of a diamino unit.

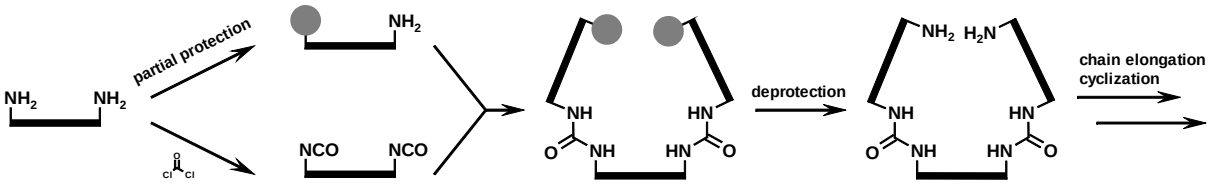


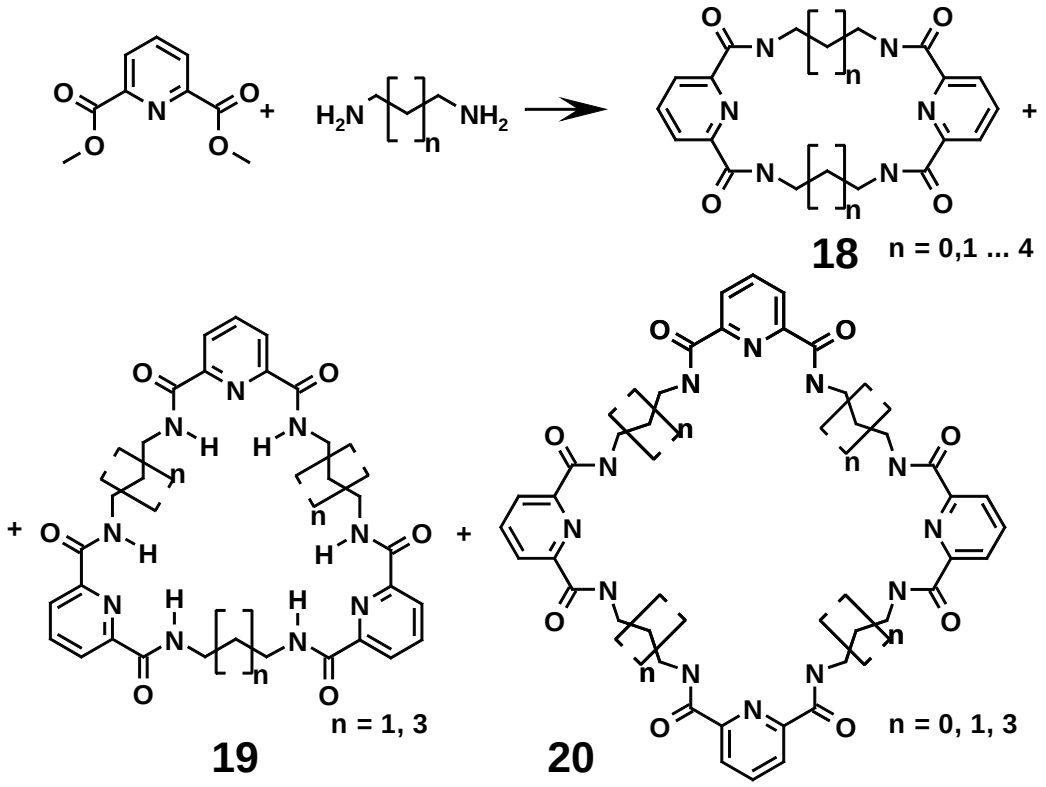
Figure 12. Preparation of linear oligoureas (partial protection – reaction - deprotection) using isocyanate as active compound.

For the protection of aminogroups the reaction of a diamine with di-*tert*-butyl dicarbonate (BOC) followed by chromatographic separation was envisaged.

Symmetrical macrocycles are usually synthesized by condensation of repeating units followed by cyclization often in a single step. Efficient one-pot synthesis of large macrocycles with multiple functional groups, like calixarenes or porphyrins, has led to the widespread use of these derivatives in molecular recognition studies. Several one-step syntheses of cyclic anion receptors are also known. Beside the synthesis of Ranganathan and Lakshmi described in the subchapter 1.4,[25] it is reasonable to mention extensive studies performed by Jurczak *et. al.* as a good example.

A series of amide-based anion receptors derived from 2,6-pyridinedicarboxylic acid were synthesized.[32] The separation of the macrocycles was especially easy - to get the cyclic products it was enough to dissolve the precursors in methanol and wait for a week (Scheme 4). The macrocycles precipitate from the reaction mixture. Although yields varied from only 2 to 8% for different cycles, it was possible to separate them by column chromatography. Linear compounds were not isolated. The compounds were investigated to establish the effect of the ring size on the stability constants of anion complexes. Interestingly, the 20-membered macrocyclic tetraamide **18** (n = 1) is a better anion receptor than both its 18- and 24-membered analogues. This effect is explained by a compromise between their ability to adapt to the anionic guest and the preorganization of amide function. Complexation with various anions was confirmed by ^{1}H NMR titrations in DMSO-d_6 and numerous X-ray structures.

[32] M. J. Chmielewski, J. Jurczak, *Chem. Eur. J.* **2005**, *11*, 6080 - 6094.



Scheme 4. The family of hosts prepared by Jurczak et.

The structure **20** (n = 0) shown of Fig. 13 is especially intriguing.[33] Two chlorides are bound in the cavity of the 36-membered macrocycle by a network of hydrogen bonds, involving 2 water molecules. The network is so stable, that electrostatic repulsion of two chlorides is overcompensated, despite the short distance between them (5.52 Å).

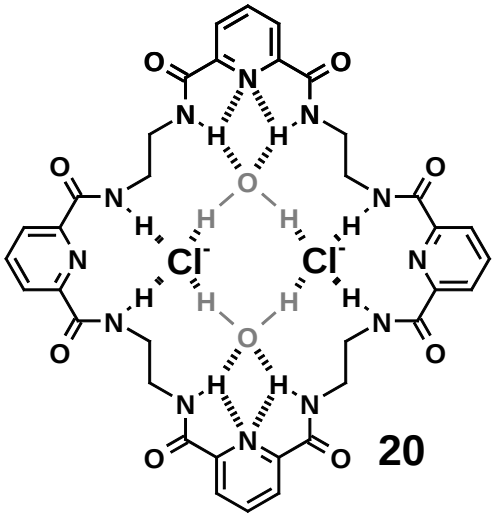


Figure 13. Complexation of two chloride ions by the tetraamide macrocycle **20** (n = 0)

The macrocycle is almost flat. The planarity of the structure is only slightly distorted by the ethylene spacers when looked along the axis containing two chloride ions.

We decided to use both, a one-step approach beside of stepwise one.

Beside of that, the interaction with anions during the reaction of direct cyclization from units offers another possibility to affect the composition of

[33] A. Szumna, J. Jurczak, *Helv. Chim. Acta.* **2001**, *84*, 3760 - 3765.

the product. Although there were not many cases of anion templation reported, such interaction should be envisaged in the synthesis of receptors as a noticeable factor. For example, recently Beer et. al. prepared catenanes using anion templation.[34] Anion was bound between two rings by 4 amido-groups, but also binding of cation (pyridinium chloride) as well as π-stacking contribute to the complex formation. Earlier bypirrole-based [2]catenane was employed as anion receptor by Sessler and Vögtle, showing remarkable binding towards dihydrophosphate (up to 10^7 M^{-1}).[35] Such a high stability is attributed to the formation of a tetrahedral cavity between the rings which provides an ideal coordination geometry for tetrahedral anion coordination. Thus, it could be expected, that an anion is able also to direct the arrangement of oligoureas in the cyclization towards a certain preferred macrocycle or linear receptor.

1.6 Conclusion

Summarizing the ideas discussed above the following directions of the present work can be distinguished:

- Preparation of two types of diamino-units: one based on the xanthene skeleton and another based on the more flexible diphenyl ether.
- The practical elaboration of the synthetic methods for preparation of cyclic and linear oligoureas, where type and number of units is varied; evaluation of their complexation properties towards different anions.
- Development of the synthesis of linear oligoureas with 4 and more units, also with regualar distribution of flexible and rigid units in chain.
- Synthesis of big macrocycles consisting of six and more units. Such macrocycles with different combinations of rigid and flexible units will be also studied.
- Influence of anions in the formation of macrocycles will be checked (template effect).

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[34] M. R. Sambrook, P. D. Beer, J. A. Wisner, R. L. Paul, A. R. Cowley, *J. Am. Chem. Soc*. **2004**, 126, 15364 - 15365.

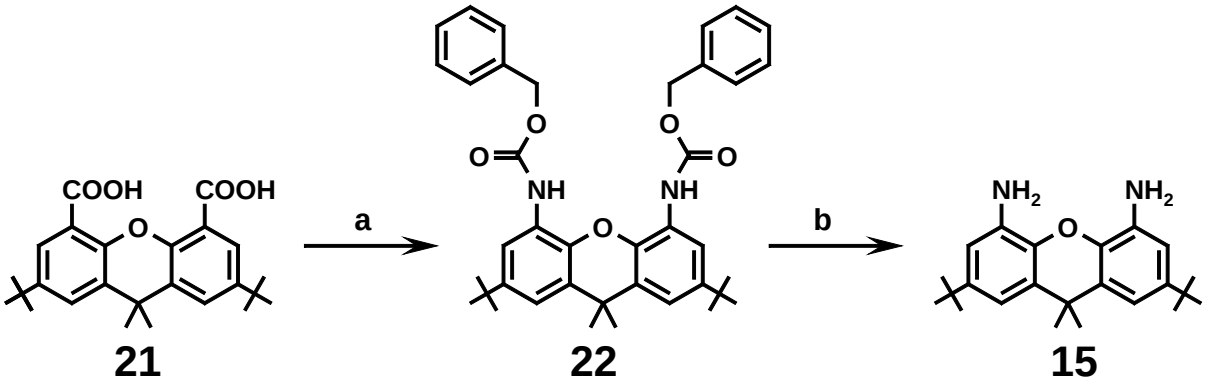
[35] A. Andrievsky, F. Ahuis, J. L. Sessler, F. Vögtle, D. Gudat, M. Moini, *J. Am. Chem. Soc*. **1998**, *120*, 9712 - 9713.

Based on these tasks, the research project was founded. The work was initially distributed into three parts among research groups in Mainz (leader Dr. V. Böhmer), Halle (Dr. I. Thondorf), and Strasbourg (Dr. F. Arnaud-Neu). According to this distribution, the molecular modeling should be performed in Halle, the synthesis guided by these calcualtions should be performed in Mainz along with general NMR measurements. A thorough evaluation of the complexation properties should be performed in Strasbourg using spectrophotometry and microcalorimetry. Unfortunately, due to bureaucratic and organizational problems not all our plans were accomplished. While the synthesis was successfully elaborated after initial difficulties, the measurements in Strasbourg were possible only partly. Therefore, evaluation of the complexation properties of our compounds was performed mostly by NMR and is not comprehensive.

2 Development of the general synthetic approach

2.1 Synthesis of diamino units

Diamine **15** was obtained from commercially available 2,7-di-*tert*-butyl-9,9-dimethylxanthene-4,5-dicarboxylic acid **21** in two steps. In the first step the diacid was converted to the carbamate **22** using a modified Curtius rearrangement reaction[36] generally following the procedure reported by Rebek *et al*[30] with slight changes. The diacid **21** was reacted with diphenylphosphoryl azide (DPPA) and benzyl alcohol in the presence of triethylamine in toluene at 80°C for 18 hours. Crystallization from methanol yielded up to 74% of the bis-carbamate **22**. This product was subjected to hydrogenolysis in the presence of catalysts. However, several attempts employing procedures in the presence of palladium on activated carbon (Pd/C) or Raney nickel at room temperature failed. The reaction led only to not identified side products. When the reaction mixture was heated up to 60°C, the diamine **15** can be formed in the presence of 10% Pd/C in THF. The product was obtained nearly quantitatively as a yellowish powder, which in most cases was used without additional purification.



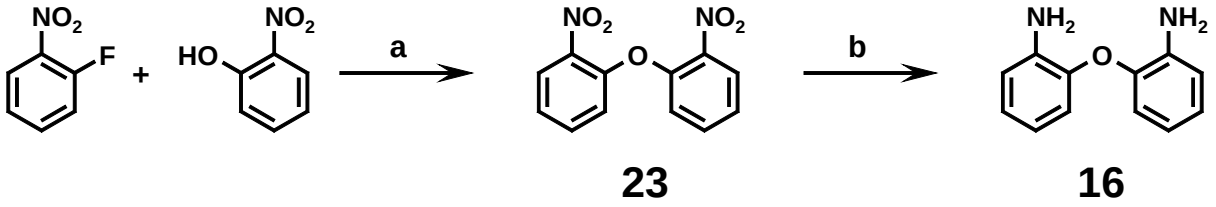
Scheme 5. Synthesis of the xanthene-based diamine **15**; a) DPPA, TEA, BnOH, toluene, 80°C, 12 h; b) Pd/C, THF, 60°C, 3 h.

The color and quality of the product may vary depending on the quality of the commercially available dicarboxylic acid **21** and the DPPA used. In rare cases crystallization

[36] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.,* **1972,** *94*, 6203-6205; K. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron* **1974**, *30*, 2151-2157.

from hexane must be done to purify the diamine **15**. The overall yield of the diamine was significantly improved in comparison with that reported in the literature (22% for the first step, 65% for the second step).[31]

Another unit – the diamine **16** - was obtained in two steps. On the first step *o*-nitrofluorobenzene and *o*-nitrophenole were reacted in the presence of potassium carbonate in DMSO at 105°C[37] yielding **23** quantitatively as a yellow precipitate. This compound was subjected to the catalytical hydrogenation in THF using 10% Pd/C as a catalyst. The reaction proceeds at room temperature yielding quantitatively the diamine **16** as a brown oil (initially clear and colorless, the liquid diamine becomes deep brown on the air in minutes). The oil can be easily crystallized upon initiation with a small crystalline particle.



23 **16**

Scheme 6. Synthesis of 2,2'-oxydianiline **16**; a) K_2CO_3, DMSO, 105°C, 16 h; b) Pd/C, THF, r.t., 3 h.

2.2 Preparation of basic ureas

In the introductory Chapter 1 we mentioned two strategies to obtain a cyclic molecule: step-by-step approach - where precursors for the cycle are synthesized and then cyclized; and direct one-step cyclization. We decided to attempt both for the synthesis of the XXX trimer **17** and other symmetric cycles. However, for trimers with varied number of flexible units we needed to develop step-by-step synthesis in any case, so this approach was investigated from the beginning.

The following general strategy was envisaged: the initial diamine is converted to the monoprotected amine and to the "activated" compound (bifunctional active urethane or isocyanate). The monoprotected diamine was dimerized, the protective groups removed. The dimeric diamine thus formed is reacted with the bifunctional activated compound, producing cyclic triurea.

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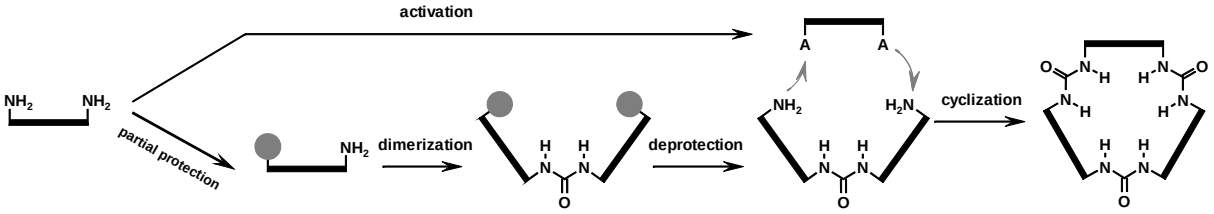
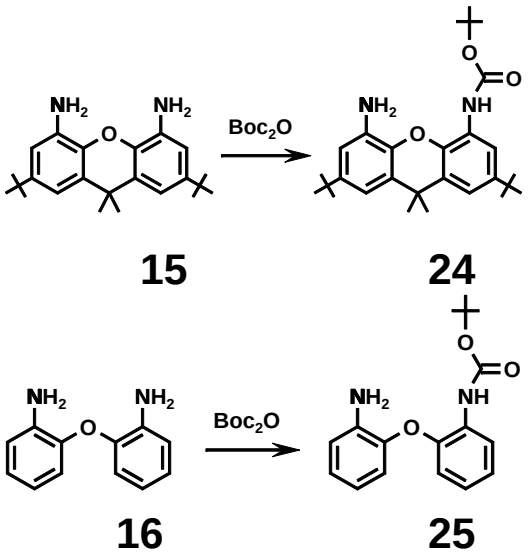
[37] P. R. Ashton, B. Hörner, O. Kocian, S. Menzer, A. J. P. White, J. F. Stoddart, D. J. Williams, *Synthesis,* **1996**, *8*, 930-940.

In most cases similar methods were applied to both diamino-units and their derivatives, taking into account differences in their reactivity and solubility properties.



Scheme 7. General approach for the preparation of trimers.

For the partial protection one amino group of the diamino-unit was converted to N-*tert*-butoxycarbonyl group by the reaction with di-*tert*-butyl dicarbonate (molar ratio 1:1), followed by chromatographic separation. For the conversion of the "rigid" diamine **15** solution of the BOC-anhydride in THF was added dropwise over 1 h to the vigorously stirred solution of the diamine in THF. The reaction was controlled by TLC where three spots were observed (fully protected product, the mono protected BOC-derivative **24** and the starting compound). After approximately 18 h no further changes were observed in the reaction mixture in case of **15**, while for the diphenyl ether unit **16** the reaction required 48 h at 60°C to be complete. After the column separation using ethylacetate:hexane mixture as eluent (1:7 *v/v* for **24**, 1:5 for **25**) the monoprotected diamines were isolated as white solids with yields of 50-56% and 40-45% for **24** and **25** respectively. The difference may be explained by spatial difficulties for the introduction of the second protecting group in the **24** as well as by the lower reactivity of the diamine **16**.



Scheme 8. Partial protection of the diamines.

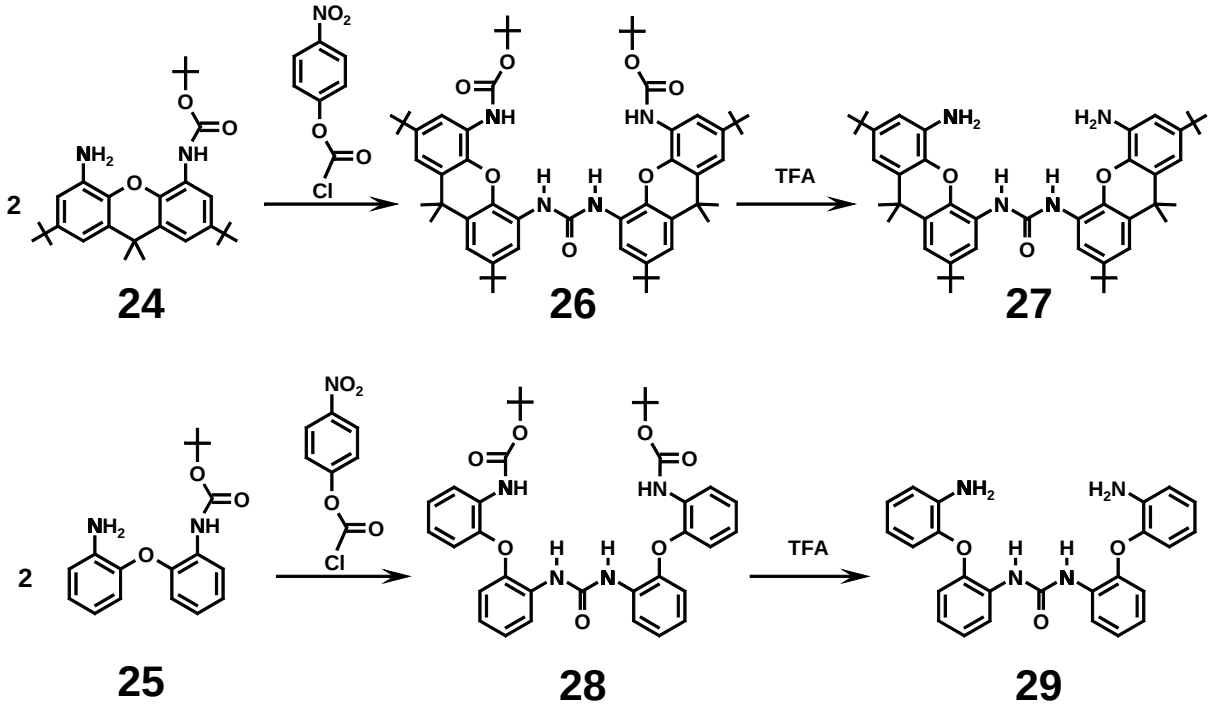
The monoprotected amine can be converted to the active derivative or isocyanate and then this compound can react with monoprotected amine, forming the dimeric urea with two protected amino groups. However when we need a symmetric dimer we can avoid separation of the activated intermediate. The triphosgene or *p*-nitrochloroformate was dissolved in dichloromethane and then added dropwise to the stirred solution of the monoprotected amine together with base in the ratio, where only ½ of all amino groups could convert to the active groups (e.g. 1 mole of *p*-nitrochloroformate per 2 moles of the monoprotected diamine).

When active compound is formed it reacts with free amino group of the next molecule, forming dimeric urea with two protected amino groups.

Both triphosgene and *p*-nitrochloroformate were checked for this reaction, varying solvent and temperature. Finally the procedure involving *p*-nitrochloroformate was elaborated to produce practically quantitative yield of the dimer. THF was used as a solvent. The solution of *p*-nitrochloroformate was added dropwise to the solution of monoprotected amine and diisopropylethylamine with stirring. Then the reaction mixture was stirred at 60°C for 12 h. After that the solvent was removed under reduced pressure.

Further handling is different for xanthene and diphenyl ether derivatives. In case of XX dimer **26** the oily yellow residue was dissolved in ethylacetate. The organic layer was washed with sodium carbonate solution and water until the yellow color of the nitrophenole disappeared (in fact it is impossible to remove the nitrophenole completely only by washing and the very light yellow color is acceptable; however the nitrophenole must not be detectable in the NMR spectrum). The organic layer was dried and the solvent was removed under reduced pressure yielding dimeric diprotected diamine **26** as a glass-like foam which usually required no further purification. The yield was not less that 95%.

In case of the diphenyl ether based dimeric compound **28** the crude product was dissolved in warm methanol. Upon cooling a crystalline solid precipitated from the solution. The compound was filtered off and washed with methanol, giving the dimeric diprotected diamine **28** with the yield 80-90%.



Scheme 9. Synthesis of the dimeric diamines.

Deprotection of the dimers was performed in the similar way. The fully protected compound was dissolved in dichloromethane, the mixture was cooled down with ice bath and the trifluoroacetic acid was added. After 3-4 h the mixture was diluted with dichloromethane and slowly added to the water solution of sodium carbonate. pH was controlled to be basic. The organic layer was then separated, washed with water, dried and the solvent was removed under reduced pressure yielding 95-98% of the amine **27** or **29** as a white solid.

Diisocyanates were formed when the solution of a diamine together with alkylamine was added to the solution of the triphosgene (the reagent was taken in excess) with stirring. TLC and NMR analysis showed the conversion of an amine to isocyanate, but at that point no easy method of purification and separation from the reaction mixture was found. Although formation of isocyanate proceeds significantly faster than side reaction between isocyanate and amine, some amount of oligomeric byproducts was formed in the reaction. To minimize these contaminations, an excess of triphosgene must be added and this compound must be then also removed. Simplest diisocyanates **31** and **33** appeared to be oily amorphous compounds which cannot be crystallized and destroyed very fast in solution. Attempts to use crude product for further syntheses leaded to the amount of byproducts which hindered further separation and identification.

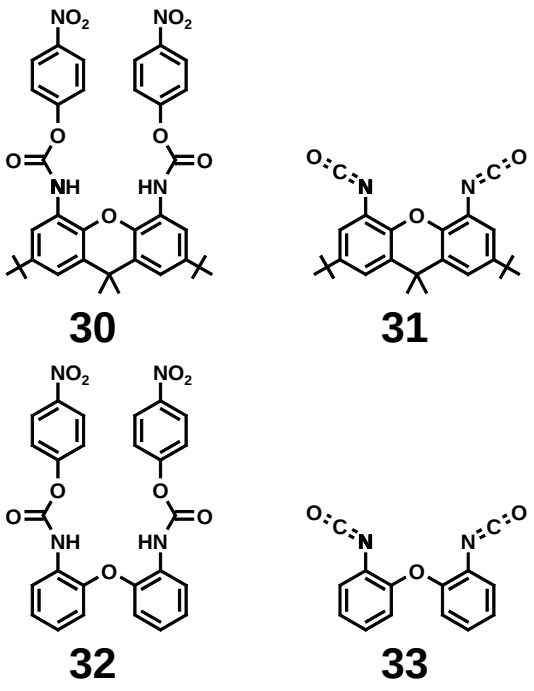


Figure 14. Diactive urethanes and diisocyanates.

On the contrary active urethanes can be easily crystallized and therefore were used in the initial stage of the synthetic pathway. When the method of purification of isocyanates was discovered (see below), the synthesis was almost completely switched to isocyanates, because formation of urea using them proceeds more smoothly than in case of active urethanes. But in simple cases both are equally able to act as urea precursors.

Reactions with isocyanates have also additional advantage. Since there are only the reagents present in the reaction mixture, it is possible to detect and observe the influence of inorganic salts on the composition of the product precisely (e.g. for detection of the template effects).

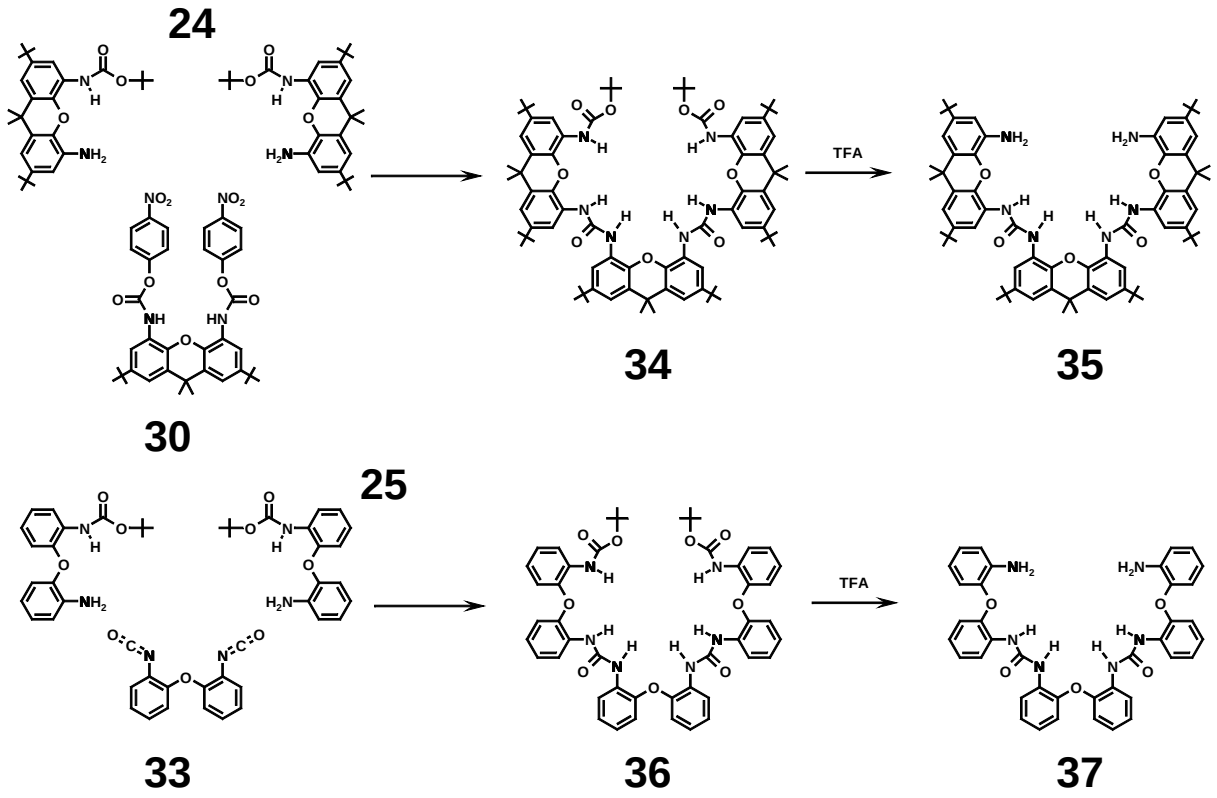
Finally the proper procedure for the preparation of pure isocyanates without crystallization was elaborated. Isocyanates are much less polar compounds in terms of chromatography than all oligomeric byproducts, amines and also alkylammonium chloride. This feature was used to isolate isocyanate (and excessive triphosgene) by filtration of the reaction mixture through the small amount of silica gel.

The solution of the diamine and *N*-diisopropylethylamine in dichloromethane (molar ratio 1:2) was added dropwise to the vigorously stirred solution of triphosgene (molar ratio diamine:triphosgene was 1:1, i.e. 1,5-fold excess of triphosgene) in the same solvent under nitrogen flow. After 3 h of further stirring the reaction mixture was filtered on the glass filter filled with silica gel, which was beforehand moistened with dichloromethane. After filtration the silica gel was washed with small portions of the solvent. In this way side products and the alkylamine salt were almost completely removed. The mother liquor was concentrated and the excess of triphosgene and eventually some traces of the *N*-diisopropylethylamine were removed by heating of the crude product up to 80°C in vacuo for one hour. In this way pure isocyanate in the form of sticky oily mass was isolated. In case of "rigid" diisocyanate **31** product hardens upon cooling to a brown solid; diisocyanate with diphenyl ether skeleton **33** is viscous clear liquid which can be crystallized only upon initiation. The yield was 78% for **31** and 88% for **33**. Solid products can be stored in sealed bottle for several months without noticeable loss of reactivity, while liquids or solutions are very unstable and should be prepared directly before their use and stored under inert atmosphere.

An active urethane can be prepared from the diamine by the reaction with 2 molecules of 4-nitrophenyl chloroformate in the presence of *N*-diisopropylethylamine. When the diamine solution in ethylacetate is added dropwise over 10 min to the solution of the chloroformate in ethylacetate a white solid is precipitated. Then the solution of the base in the same solvent was added over 30 min. White precipitate should dissolve. After 1 h of stirring the reaction mixture was filtered through silica gel in the same way as for isocyanate, but using ethylacetate. The solvent was removed and the crude product was triturated with ether (1:1 mixture of ether/hexane (*v/v*) in case of "rigid" diurethane **30**).The active urethane **30** was obtained after filtration and drying with the yield 77% as a white powder; the diphenyl ether based product **32** was obtained with the yield of 78% as a light-brown powder.

The presence of all necessary precursors allowed also to synthesize trimeric diamine, where three units are interconnected by two urea moieties.

The trimeric diamines were obtained similar to dimeric diamines.



Scheme 10. Synthesis of linear trimers.

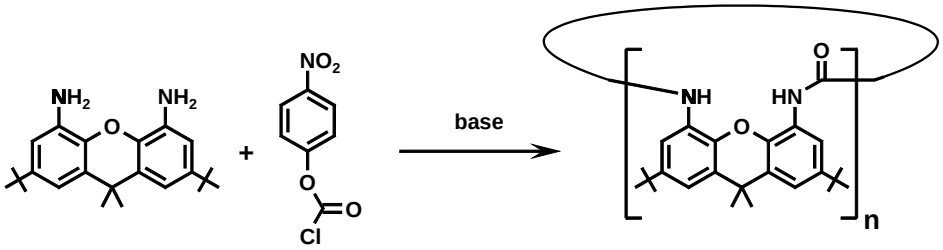
For the preparation of the xanthene-based linear oligourea with three units reaction of diactive urethane **30** with 2 molar equivalents of the monoprotected amine **24** in the presence of base was used initially. The fully protected trimeric diamine **34** was obtained with yield of 52%. More effective procedure (with 72% yield) involving reaction of a diamine with isocyanate prepared from the monoprotected amine was elaborated later and will be discussed in the chapter dedicated to the long linear oligoureas.

The trimer of flexible units **36** was prepared by the reaction of diisocyanate **33** and two monoprotected amines **25**. The reagents were mixed in dichloromethane and stirred for 18 h. Then the solvent was removed under reduced pressure producing diprotected trimeric diamine **36** quantitatively as a brown solid.

The deprotection of both products was carried out in a similar way with trifluoroacetic acid. After the reaction mixture was neutralized and the organic layer was washed with water, dryed and concentrated, crude diamines **35** and **37** were isolated as brown solids. The diphenyl ether derivative **37** has acceptable quality and ready for use without further purification (yield 98%), while other trimer **35** required trituration with acetonitrile, The trimeric diamine **35** was obtained after filtration as a white solid with the yield of 83%.

2.3 One-step formation of cyclic oligoureas from diamino units

As has been discussed in the subchapter 1.5 we expected that one-step cyclization may produce some preferred cylic products, especially employing anions as a template. Our expectations were not completely justified, but by this synthetic method the first macrocycles were prepared and important general experience on handling mixtures and identification of single components was gained.



Scheme 11. Direct formation of macrocycles from diamines.

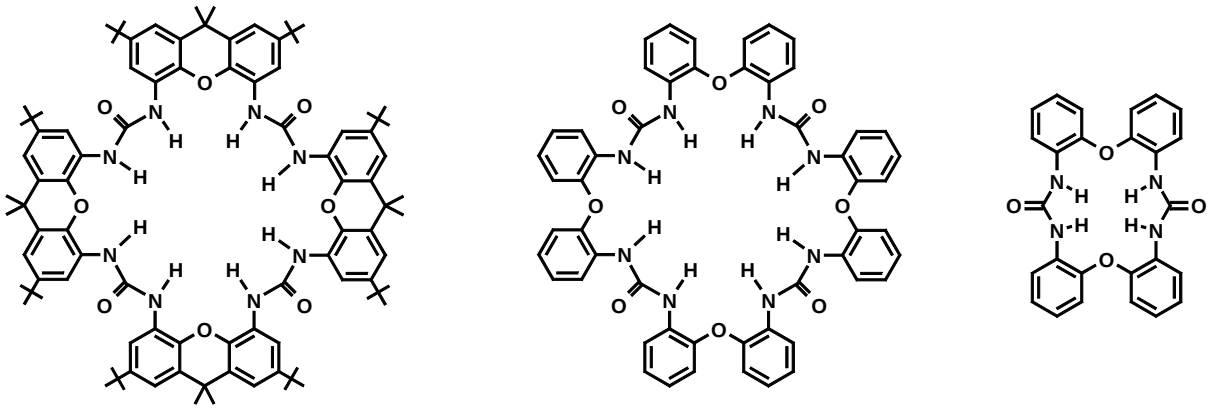
The reaction of the rigid diamine **15** with of *p*-nitrochloroformate in the presence of triethylamine (molar ratio 1:1:1) was attempted initially. In fact in such a case chloride anion is always present in the mixture. Already first attempts showed that this reaction led to a mixture of several compounds (around ten can be defined on TLC), and only some of them could be separated. Unfortunately intermolecular interactions have some influence not only on the formation but also hinders the separation of oligoureas. The mixture of oligoureas has solubility and crystallization properties different from single compounds. The chaotic hydrogen bonding hinders also identification enormously. NMR signals of single compounds change their shape and position when ^{1}H NMR spectrum of the mixture is recorded, even in such polar solvents as DMSO-d_6.

Mass spectroscopic analysis of the crude product showed the presence of cyclic compounds with up to six units and also a lot of particles of lower molecular weight, including species corresponding to cycles with 2, 3 and 4 xanthene units. In general, the peak corresponding to the cyclic tetraurea is the most significant in the crude product after the direct cyclization in apolar solvents (dichloromethane, chloroform). The peak corresponding to the tetramer observed along with the “cyclic dimer” peak, while the peaks of trimer and other cycles are weaker. Of course, this cannot be considered as an unambiguous proof, but later it was found that all “X”-cycles are reasonably stable in the conditions of mass-spectroscopy. Therefore this is highly possible that in general case the cyclic product of direct

cyclization is mainly formed by the tetrameric cycle and eventually also by the dimeric XX-cycle along with number of linear oligoureas.

Obviously, these peaks could also indicate fragments of larger cycles. Anyway the number of species formed is significant and it is difficult to detect certain selectivity in such distribution.

Nevertheless, in these experiments the cyclic oligourea **38** consisting of four xanthene units connected *via* urea functions was separated. The compound can be crystallized with the yield up to 25% from the reaction mixture due to its low solubility. The white powder was identified by its MS (FD) spectrum. ^{1}H NMR shows one singlet for NH-protons, 4 meta-coupled doublets for the aromatic protons, one singlet for CH_3 groups and one singlet for *tert*-butyls, what corresponds to (time-averaged) D_{4v} symmetry. Unfortunately this tetramer has very limited use as an anion receptor because of its extremely low solubility in common NMR solvents. The compound can only be dissolved in DMSO-d_6 in the temperature range 100-120°C producing ^{1}H NMR spectrum mentioned above. The interaction with some anions was checked in these conditions showing remarkable downfield shift of the signal of the urea protons and will be discussed in the corresponding chapter.



38 **39** **40**

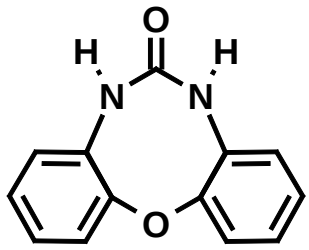
Figure 15. Products of the one-step cyclizations.

The same "one step assembly" approach was also attempted with other diamino-unit **16**. Reactions of this diamine with *p*-nitrochloroformiate were performed and three new oligoureas were isolated.

The reaction was attempted under different conditions, varying solvent, concentration, sequence and time of addition of reagents. Finally as standard following conditions were chosen: ethylacetate as a solvent, addition of both diamine and *p*-nitrochloroformate simultaneously for 10 h and after that addition of diisopropylethylamine.

The first separated compound in these reactions with flexible diamine was the cyclic dimer **40**. It has very low solubility and precipitates from the reaction mixture as a white powder with the yield up to 20%. The crude product was analyzed by TLC. A picture analogous to the case of xanthene unit was found. Multiple spots are present on the plate, partly overlapped, partly with long smeared trails (such trails are produced usually by oligoureas with free amino groups, as established later), what made the chromatographic separation senseless.

Several attempts to crystallise single compounds from various solvents were made. The next isolated compound was the tetrameric oligourea **39**, analogous to **38** – formed single crystals upon the slow evaporation of the crude product from THF with the yield up to 15%. ^{1}H NMR of the residue usually shows though that some amount of both dimer **40** and tetramer **39** are still left in the mixture after these crystallisations.



41

Figure 16. "Cyclic monomer"

The conformational freedom of the diphenyl ether unit **16** allows also intramolecular cyclization. The "cyclic monomer" **41** was isolated as single crystals upon slow evaporation of the solution of the crude product in THF and methanol with the yield less than 10%. Later this compound was synthesized with better yield and selectivity (the synthesis and X-ray structure are discussed in subchapter 2.4).

Mass-spectroscopy showed that the dimer **40** and the tetramer **39** both are main products formed in this synthesis. Peaks of the cyclic trimer (not isolated on this stage) and the "monomeric" urea **41** were present in smaller intensity as well as several other peaks with molecular weight in the range between dimer and tetramer. Species with the number of units higher than 5 were not detected with MS (FD). However, the conditions of MS (FD) is quite harsh and obviously larger molecules may be destroyed.

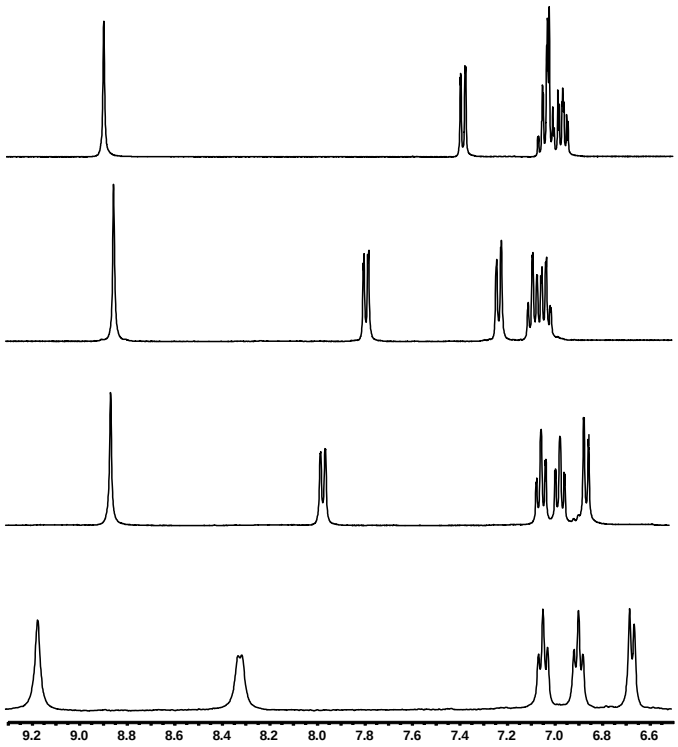


Figure 17. Section of NMR spectra in DMSO-d_6: derivatives of flexible unit **16** (from top to bottom): "monomer" **41**, dimer **40**, the trimer (compounds **44**, synthesis and properties are described in the Chapter 3) and tetramer **39**. Signals of urea protons are found in the low field, the doublet in the middle belongs to the aromatic hydrogen of the phenyl ring which is found in immediate proximity to the urea group.

According to ^{1}H NMR data in DMSO-d_6 the conformation of both dimer **40** and tetramer **39** in solution corresponds to thetime-averaged D_{2h} and D_{4h} symmetry respectively; the "cyclic monomer" **41** shows also analogous spectrum.. The interaction of these cyclic ureas with anions will be discussed in details in corresponding chapters.

It became clear at this point that the expected selectivity in the direct synthesis of oligoureas was not achieved (or correct conditions are not easy to find). The reactions produced more or less multicomponent mixtures without any remarkable selectivity, so they cannot be used for methodical retrieval of single oligoureas, especially containing ordered combinations of different units. Therefore we switched completely to the stepwise synthesis of oligoureas. This approach allowed us to synthesize a number of cylcic and linear oligoureas, which are discussed in the next chapters.

2.4 Properties of the simplest cycles

In this subchapter the cyclic dimer **40** and "monomer" **41** of the diphenyl ether will be discussed. These simplest compounds have no major importance, but some of their remarkable properties should be mentioned.

2.4.1 The eight-membered cyclic "monomer" 41

As described before, the single crystals of **41** (product of the ring closure in the single molecule) were obtained when the crude product after the direct cyclization was dissolved in THF/methanol mixture and left to evaporate slowly. ^{1}H NMR confirmed that the crystals consist of the new cyclic compound, since its spectrum was similar to the spectra of dimer **40** and tetramer **39** known at that time (Fig. 17).

X-ray analysis and mass-spectroscopy revealed that in this case we deal with the product of the cyclization of the single diphenyl ether unit molecule. The urea function is incorporated into the eight-membered ring in such a way that the hydrogens and oxygen of the urea function are pointing in the same direction. [38]

Table 3. Selected crystal data and structure refinement for "monomer" **41**.

Empirical formula	$C_{13}H_{10}N_2O_2$	Volume	2151.72(19) Å^3
Formula weight	226.23	Z	8
Temperature	100(2) K	Density (calculated)	1.397 Mg/m^3
Crystal system	monoclinic	Absorption coefficient	0.097 mm^{-1}
Space group	P21/n	Crystal size, mm	0.42x0.32x0.28
Unit cell dimensions	a = 17.5679(10) Å	Reflections collected	35184
	b = 7.1586(3) Å	Independent reflections	5093
	c = 17.7300(10) Å	Final R indices	R_1 = 0.0346
	α = 90°		wR_2 = 0.0906
	β = 105.203(4)°	R indices (all data)	R_1 = 0.0421
	γ = 90°		wR_2 = 0.0932

The compound is the first example of a crystal structure containing this type of eight-membered macrocycle. The asymmetric unit contains two almost identical molecules (Fig. 18). The conformation of the eight-membered macrocycle may be described as an envelope consisting of two nearly planar moieties; one contains the C11-C16 aromatic ring and the attached atoms N1 and O2, while the other contains the C21 – C26 aromatic ring and atoms

[38] V. Böhmer, D. Meshcheryakov, I. Thondorf, M. Bolte, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2004**, *60*, o136-o139.

N2, C1 and O2. The dihedral angles between these two planes are 72.19 and 68.97°, respectively.

The C-N-C bond angle at one of the two N atoms is considerably widened (135.41 and 135.27° respectively), the other angle only slightly so (128.85 and 128.26° respectively). The two N—C_{ar} bonds are of equal length but the N—$C_{carbonyl}$ bonds differ markedly.

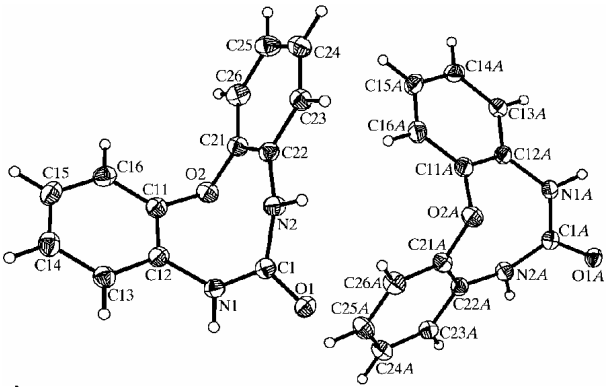


Figure 18. Perspective views of the two independent molecules of **41**, with the atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms are shown as small spheres of arbitrary radii.

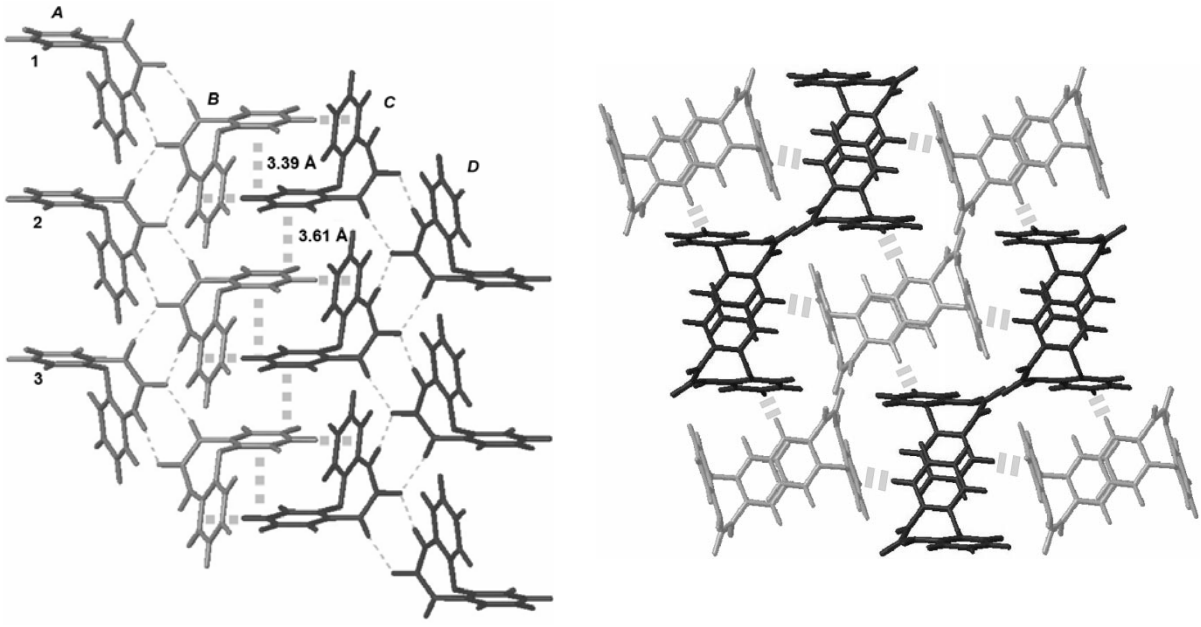


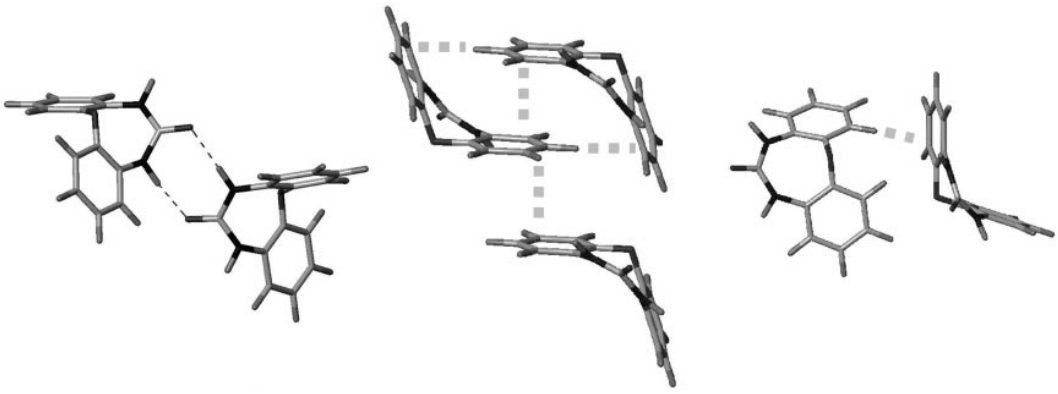
Figure 19. On the left: infinite tapes of hydrogen-bonded molecules of **41** (hydrogen bonds are shown by dashed thin lines) and the connections of these tapes via π-π stacking (vertical dashed thick lines) and π-facial hydrogen bonds (horisontal dashed thick lines); the view is along *a* axis. **On the right:** the molecular arrangement of **41** seen along *c* axis, perpendicular to π-π stacks. The two molecules in the asymmetric unit are represented as light and dark grey, respectively. Edge-to-face contacts are represented by wide dashed lines.

The molecules are interconnected via hydrogen bonds to form infinite tapes, which include one benzene ring of each molecule. Due to the asymmetric conformation of the cyclic urea, these tapes are not planar and the D···A distances differ. The second benzene ring is oriented perpendicular to the tape, pointing alternately to either side. The distance between parallel rings (1···2···3) on one side if 7.00 Å. Their zip-like intercalation leads to the arrangement shown in Fig. 19 (left), where we can distinguish (along the tape) π-π stacked dimers with centroid separations of 3.91 Å, while the distance between these dimers is 4.07 Å. In addition the π-π stacked dimers are held together by two close edge-to-face contacts (centroid separations of 4.80 Å).

The two-dimensional arrangement described so far ocurs between symmetry-related molecules of **41**. The second molecule in the asymmetric unit displays the same arrangement and both are combined in the third direction, as shown on Fig. 19 (right). Here, short contacts of the edge-to-face type (5.15 Å between centroids of the aromatic rings) are found.

Interaction energies for molecules in the crystal lattice were calculated (Fig. 20).[39]

In summary, the cyclic urea **41** forms a unique three-dimensional network in the crystal structure, which is built up by hydrogen bonding (calculated interaction energy E = -56.1 kJ/mol per molecule) in one direction, by π-π stacking and edge-to-face interactions (E = -23.0 kJ/mol) in the second dimension and by the edge-to-face contacts (E = -9.2 kJ/mol) in the third dimension.



E = -56.1 kJ/mol	E = -23.0 kJ/mol	E = -9.2 kJ/mol
(hydrogen bonding)	(π-π, CH-π)	(CH-π)

Figure 20. The optimized structures for the central units of the hexameric fragments of the crystal lattice. E is the interaction energy per molecule.

[39] Performed by Dr. I. Thondorf, Martin-Luther-Universität Halle-Wittenberg.

Despite the good crystallization, the amount of the "monomer" **41** in the crude product after ordinary direct cyclization is low and its signals are barely visible on ^{1}H NMR. It was clear that "usual" procedure is unsuitable as a reproducible synthesis for this compound. But after several attempts it became clear that the amount of the "monomer" in the crude product can be changed by varying the reaction conditions. The best results were achieved when 4-nitrophenylchloroformate and Hünig base were added to the reaction mixture not simultaneously, but subsequently. The hypothesis was set up that the hydrochloride of the diamine **16** which is formed in the latter case reacts with active urethane in a different way or forms some different intermediate than in case of non-protonated amine.

In order to prove this idea the reaction conditions were changed. The diamine **16** was converted to the bis-trifluoroacetate by treatment with trifluoroacetic acid solution. The excess of the acid was removed in vacuo and the salt was dissolved in dichloromethane together with 4-nitrophenylchloroformate. *N*-ethyldiisopropylamine was added dropwise to the mixture over 2 h with stirring. After 4h of stirring the solvent was removed under reduced pressure and the crude product was triturated with ethyl acetate. A white solid (cyclic dimer **40**, 15%) was filtered off. ^{1}H NMR of the rest of the crude product showed that the "monomer" **41** is the main component in the mixture, so the conjecture about the reactivity of the salt was likely.

Unfortunately it turned out that is is not easy to isolate the "monomer", and the pure compound was separated in only 23% yield by precipitation from ethylacetate with hexane, after the nitrophenole and the chloride of *N*-ethyldiisopropylamine were removed from the solution by washing with water.

2.4.2 The cyclic dimer DD 40

Another simple compound - the dimer **40** - is usually separated from the reaction mixture of the direct cyclization as a white solid, as mentioned earlier. This product is poorly soluble or not soluble in common organic solvents; but the compound can be solubilized in DMSO-d_6 with heating, what made limited NMR-experiments possible.

Fluoride was suggested as an anion which would be able to fit into the small internal cavity of the cyclic urea to be bound by the four convergent hydrogen bonds. The series of NMR spectra in DMSO-d_6 were recorded in order to establish the nature of interaction of the dimer and the tetrabutylammonium fluoride (Fig. 21).

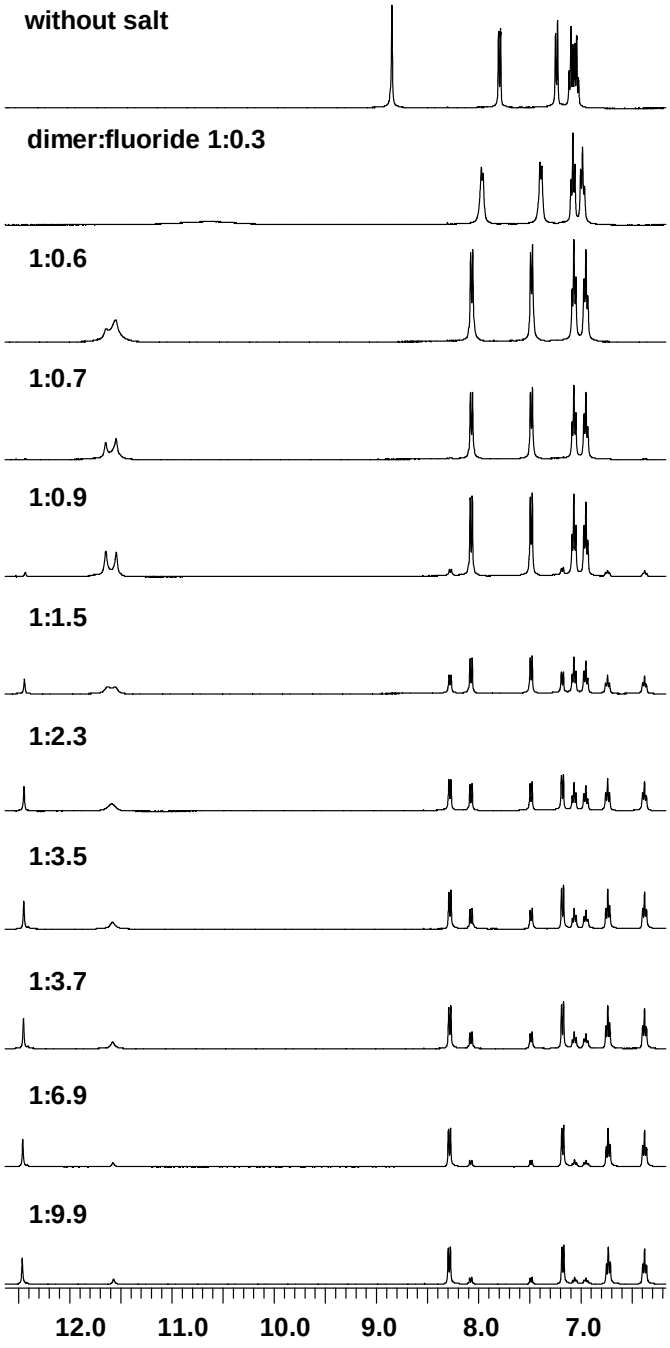


Figure 21. Stepwise addition of the tetrabutylammonium fluoride to the solution of the dimeric cylic urea **40** in DMSO-d_6.

The peak of NH urea protons broadens immediately after the addition of the first small amounts of the salt to the solution of the dimer is started, and no regular hydrogen bonding is observed until the molar ratio of approximately 1:1 is reached. Signals of aromatic protons shift slightly upfields. When the addition is continued to ratios over 1:1, the new set of signals emerge, including heavily downfield shifted signal for urea protons. Upon further addition of the salt the initial set of signals starts to disappear. The new set does not shift anymore with further salt addition.

We conclude, that the dimer **40** forms subsequently complexes with one and then with two fluoride anions, and these complexes are stable in the NMR time scale.

During these experiments it was observed that crystals are formed in the NMR tube after 24 - 48 h. Single crystals good for structure determination were isolated from the multicomponent mixture of organic solvents[40] which contained DMSO.

[40] In general case such mixture contained acetone, acetonitrile, chloroform, dichloromethane, ethanol, ethylacetate, methanol, THF. It was used to increase the probability to find the right combination of the solvent(s) and the molecule for packing into crystal.

Table 4. Selected crystal data and structure refinement for the X-ray structure of the cylic dimer **40**.

Empirical formula	$C_{32}H_{38}N_4O_7S_3$	Volume	3383.4(5) $Å^3$
Formula weight	686.84	Z	4
Temperature	173(2) K	Density (calculated)	1.348 Mg/m^3
Crystal system	monoclinic	Absorption coefficient	0.271 mm^{-1}
Space group	P21/n	Crystal size, mm	0.24x0.12x0.12
Unit cell dimensions	a = 7.9794(6) Å	Reflections collected	44396
	b = 23.942(2) Å	Independent reflections	5960
	c = 17.9586(14) Å	Final R indices	R_1 = 0.1059
	α = 90°		wR_2 = 0.2250
	β = 99.545(6)°	R indices (all data)	R_1 = 0.1740
	γ = 90°		wR_2 = 0.2522

X-ray structure showed that against all expectations the crystals contained only the dimer **40** without included fluoride. Three molecules of DMSO per one molecule of the dimer **40** form the crystal lattice. Each urea group binds one molecule of DMSO by two hydrogen bonds and both molecules are found on different sides of the average plane of the macrocycle. The third solvent molecule is not bound to the molecules of the dimer (Fig. 22).

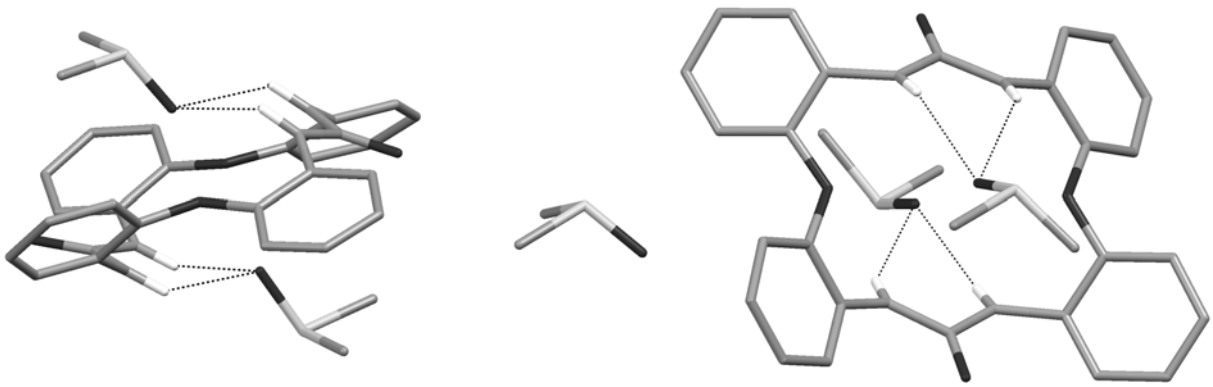


Figure 22. Binding of DMSO molecules by the molecule of dimer **40** in the crystal structure.

The planarity of the cycle is remarkably distorted, but obviously the distance between hydrogen atoms of opposite urea groups is too short to include a hydrogen bond acceptor in the central cavity. Therefore molecule binds one acceptor molecule with each urea group. The geometry of the cycle is characterized by selected angles which are summarized in the Table 5.

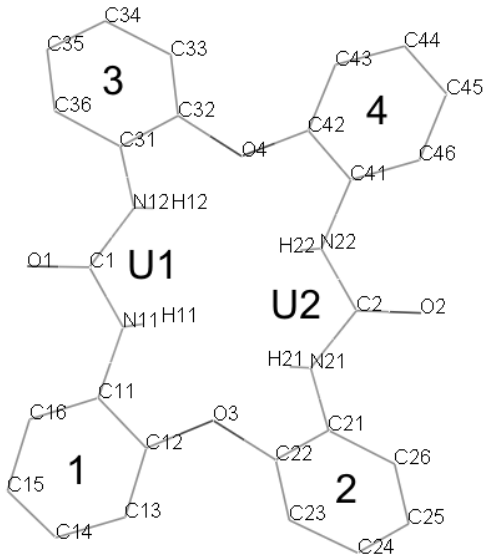


Figure 23. The numbering scheme of the cyclic dimer.

Table 5. Selected angles between averaged planes in the crystal structure of the dimer **40**.

Averaged planes	Angle, °
1 and 2 benzene rings	50.76
3 and 4 benzene rings	56.56
benzene ring 1 and the urea group U1	50.20
benzene ring 3 and the urea group U1	41.71
benzene ring 2 and the urea group U2	41.03
benzene ring 4 and the urea group U2	51.64
urea groups U1 and U2	7.58

One crystall cell contains four dimers and 12 DMSO molecules. Molecules form endless columns in the crystal. In the same time we see no pronounced rows or slices. The colums are arranged into some wavy rows and molecules aro not found on the same level in two neighbouring columns. Columnar cavities formed due to such “waves are filled in with DMSO molecules.

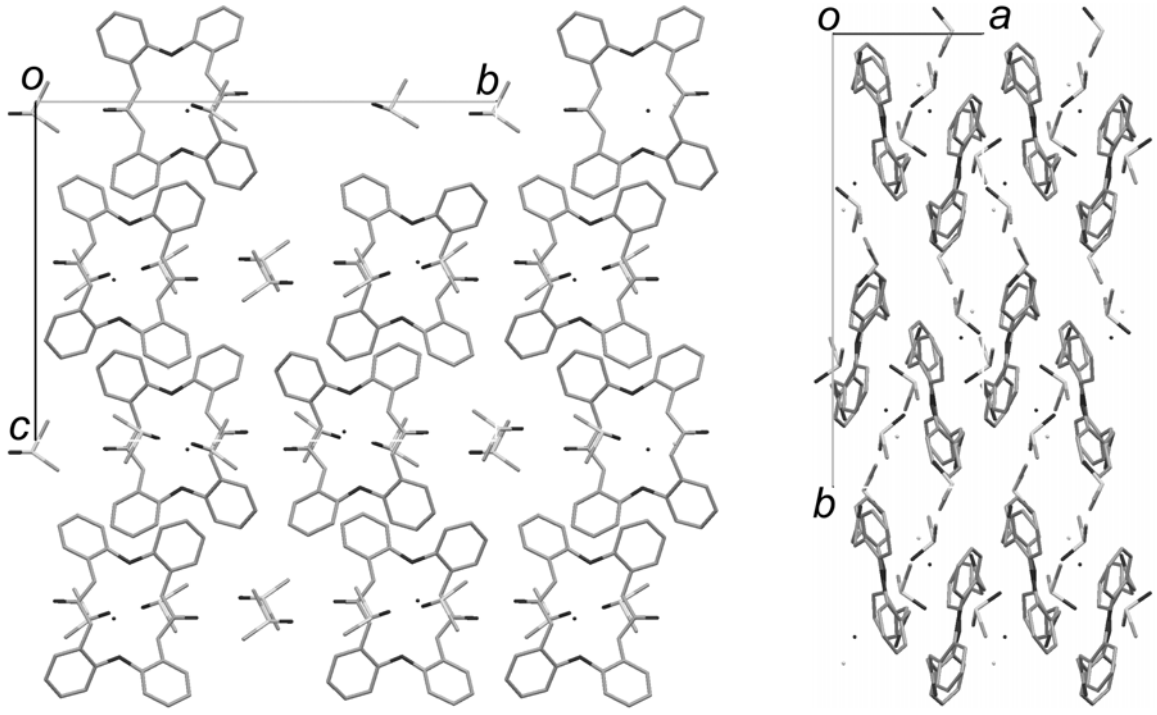


Figure 24. Arrangement of dimer molecules in the crystal lattice.

2.5 Conclusion

The syntheses decribed in the present chapter are of great importance for the development towards the synthesis of more complicated structures. The following tasks were accomplished:

- The synthesis of “rigid” **15** and “flexible” **16** diamino units for the preparation of oligoureas was elaborated.
- Direct cyclization and stepwise approaches of oligourea formation were studied. Although the direct cyclization has readily produced macrocycles, the desired control and selectivity were not achieved. The stepwise approach was subsequently preferred.
- The synthesis of linear di- and trimeric oligoureas using isocyanates or active urethanes was developed. An effective procedure for the synthesis of pure isocyanates was elaborated.
- The simple cycles – “monomer” **41** and cyclic dimer **40** – consisting of the diphenyl ether based units were prepared and studied.

3 Trimeric cyclic oligoureas: synthesis and evaluation of properties

3.1 Synthesis of trimers

The XXX trimer **17** consisting of three "rigid" diamino-units **15** (**X**) was defined as starting point of our considerations about anion receptors. However, since also the "flexible" (**D**) unit **16** was included in our work, the family of trimers increased and included four possible compounds: XXX, XXD, XDD and DDD.

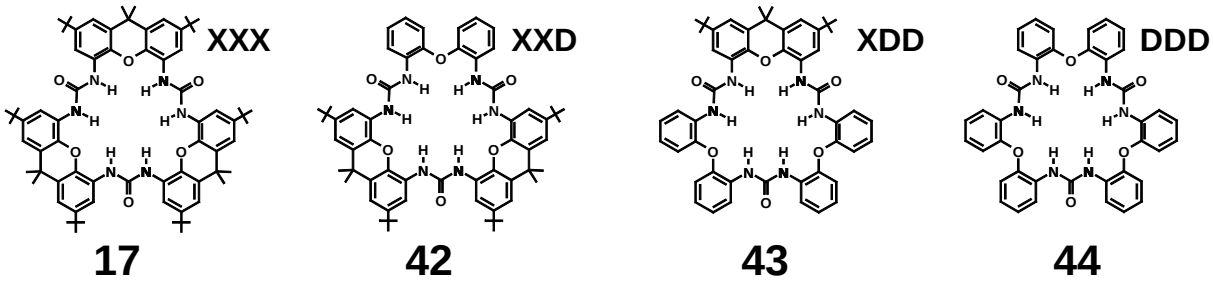


Figure 25. Trimers formed by combination of the two diamino-units **X** and **D**.

A cyclic trimer may be obtained in three ways. One of them, the direct cyclization, produces mixtures which did not allow to isolate eventually formed trimers.

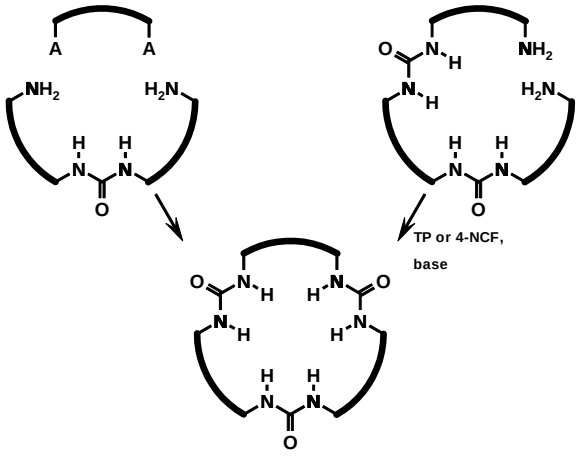


Figure 26. Rational ways for the cyclization to the trimer: condensation/addition 2+1 and a simple ring closure.

The other two possibilities are condensation/addition of a dimeric diamine (**27** or **29**) with a diisocyanate (**31** or **33**) or active diurethane (**30** or **32**) and a ring closure reaction of a linear trimer (Fig. 26). The reversed 2+1 reaction (for example a dimeric diisocyanate with a monomeric diamine, "1+2") is of course also possible. Formation of larger cycles (for example 1+2+1+2 ond so on) is possible as well, but it is more probable that reaction will happen with two molecules than with four.

These approaches allow numerous variations to play with reactivity and different spatial properties of these compounds in order to achieve the optimal results.

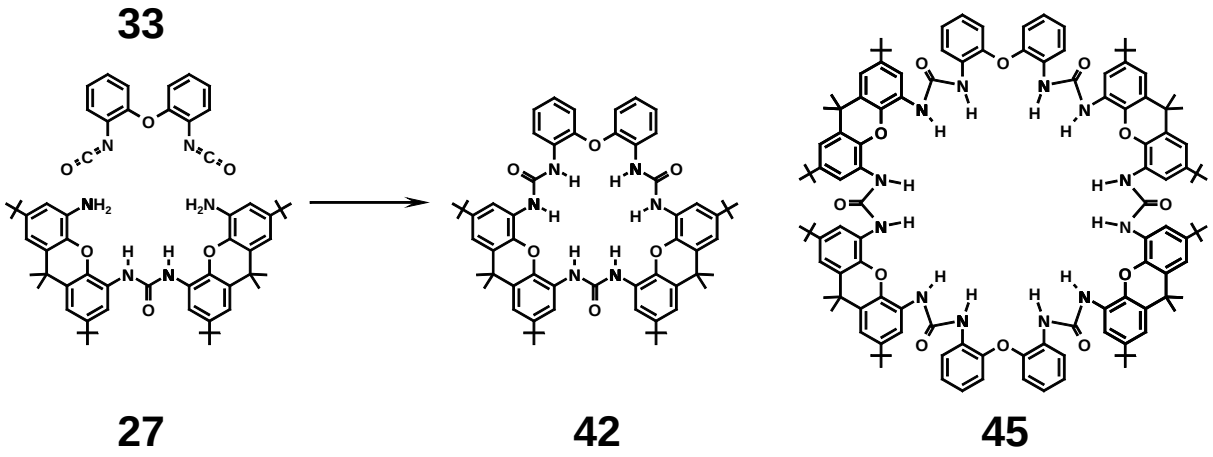
3.1.1 Preparation of the XXD trimer 42

An early procedure for the preparation of trimers, based on the "2+1" principle, where a dimeric diamine reacted with an active diurethane was rather complicated. The active diurethane was prepared immediately before the synthesis (by the reaction of 4-nitrophenyl chloroformate with diamine in the presence of base). The urethane was not isolated after the synthesis and the product solution was directly added dropwise to the solution of the diamine. This way was chosen to avoid handling of eventually moisture sensitive active urethane and was attempted in various solvents employing the diamine XX and the X-diamine. Unfortunately the synthesis did not lead to interpretable result and produced mixtures of several compounds.

However the reaction of the same XX diamine with D diurethane **32** succeeded. The solution of the diurethane was added dropwise to a solution of the diamine in THF. This procedure produced 20-25 % yield on a 200 mg scale, but the purity of the product was not always satisfactory. The yield was improved significantly when the pure diurethane was used instead of its crude solution. The same procedure but using the pure D diurethane **32** compound now allowed yields of the trimer **42** in the range of 60-70%, although the problem of its unsatisfactory purity was still actual.

The elaboration of the procedure for the preparation of pure isocyanates (See subchapter 2.2) had given the possibility to use diisocyanate **33** instead of diurethane in the cyclization. The solution of the diisocyanate was added dropwise to a solution of the diamine similarly to the reaction with diurethane. A white solid was separated after the reaction and showed the typical ^{1}H NMR spectrum of the trimer **42**. Single crystals were obtained and confirmed the cyclic XXD structure.

When the synthesis is performed in such an apolar solvent as dichloromethane the final product is in fact always contaminated by the cyclic hexamer XXDXXD (10-20% mol.) which is formed in the reaction beside the main product. The hexamer contamination was not detected by NMR because it is completely insoluble in DMSO-d_6, but it forms a fine-dispersed suspension. Since the solubility of the trimer **42** in DMSO-d_6 is also limited, the small amount of the hexamer powder was confused with undissolved trimer and overlooked in early experiments.



Scheme 12. The trimer XXD and the hexamer XXDXXD as cyclization products in "2+1" synthesis.

It was found that the composition of the reaction product depends strongly on the polarity of the solvent media. The hexamer is not formed when the reaction of the diisocyanate and the diamine is carried out in acetonitrile. Then the trimer XXD was obtained in excellent purity with the yield of 62%.

The properties of the hexamer **45** as well as other hexamers are discussed in the corresponding chapter.

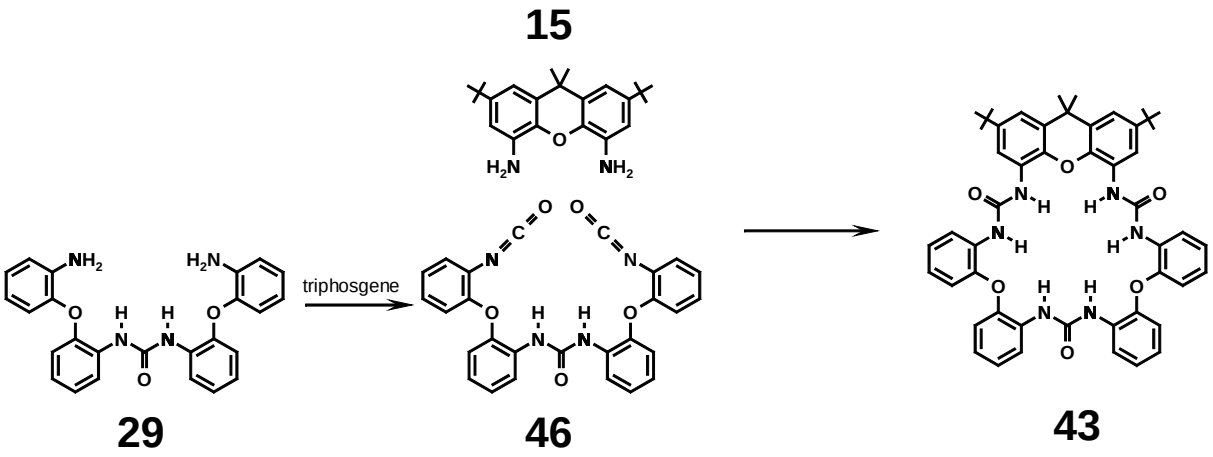
3.1.2 Preparation of the trimer XXD 43

The synthesis of the XDD trimer **43** was attempted in two ways. Initially the same approach was used as for the preparation of the trimer **42**: the X diisocyanate **31** was reacted with DD-diamine **29**. The reaction produced the expected trimer, but beside of it a significant amount of byproducts, which hindered the separation of the main compound. The active X diurethane **30** did not produce reliable result as well. After several attempts to prepare the trimer failed we decided to "swap" reagents: the DD diisocyanate **46** would react with X-diamine **15**.

The diisocyanate DD was obtained using the previously elaborated procedure for isocyanates. The solution of the DD diamine and *N*-diisopropylethylamine in THF was added dropwise to the solution of the triphosgene in dichloromethane under nitrogen with vigorous stirring. The diisocyanate DD was isolated as a brownish liquid, hardening upon cooling, with the yield of 79%.

The preparation of the trimer XDD was slightly modified to minimize the amount of side products by using lower concentrations. The solution of the diisocyanate DD and the

diamine **15** in dichloromethane was added dropwise over 2 h to the flask containing dichloromethane with stirring under nitrogen. The procedure yielded up to 80% of the trimer XDD as a white powder.



Scheme 13. Preparation of the trimer XDD.

3.1.3 Preparation of the trimer DDD 44

Separation difficulties are a common feature of our oligoureas where diphenyl ether units are in minority. All these compounds tend to have similar solubility and chromatograpahic properties with side products based on diphenyl ether units. The side products overlap with the target product when the chromatography is performed, and they precipitate together with the product when crystallization is attempted. Among the trimers the trimer DDD appeared to be the most "unisolable" compound.

The trimer was detected as the main compound in the reaction mixture already in the early syntheses based on the interaction of the active diurethane D and diamine DD, but initially it was impossible to isolate the pure compound. The purity of the trimer DDD increased significantly when the D-diisocyanate was employed. The similar procedure was used for this cyclization as for trimer XDD (THF was used as a solvent). This procedure followed by trituration with hexane yielded 72% the trimer DDD.

3.1.4 Towards the trimer XXX 17

The trimer XXX produced enormous synthetic difficulties and was prepared much later than all three related trimers. Numerous cyclization ways were attempted in order to prepare this compound (Scheme 14).

The reaction of direct cyclization was attempted using 4-nitrophenyl chloroformate as well as triphosgene in several ways, also involving tetrabutylammonium nitrate as template; different solvents were used. However the cyclic XXXX tetramer **38** was the only compound isolated

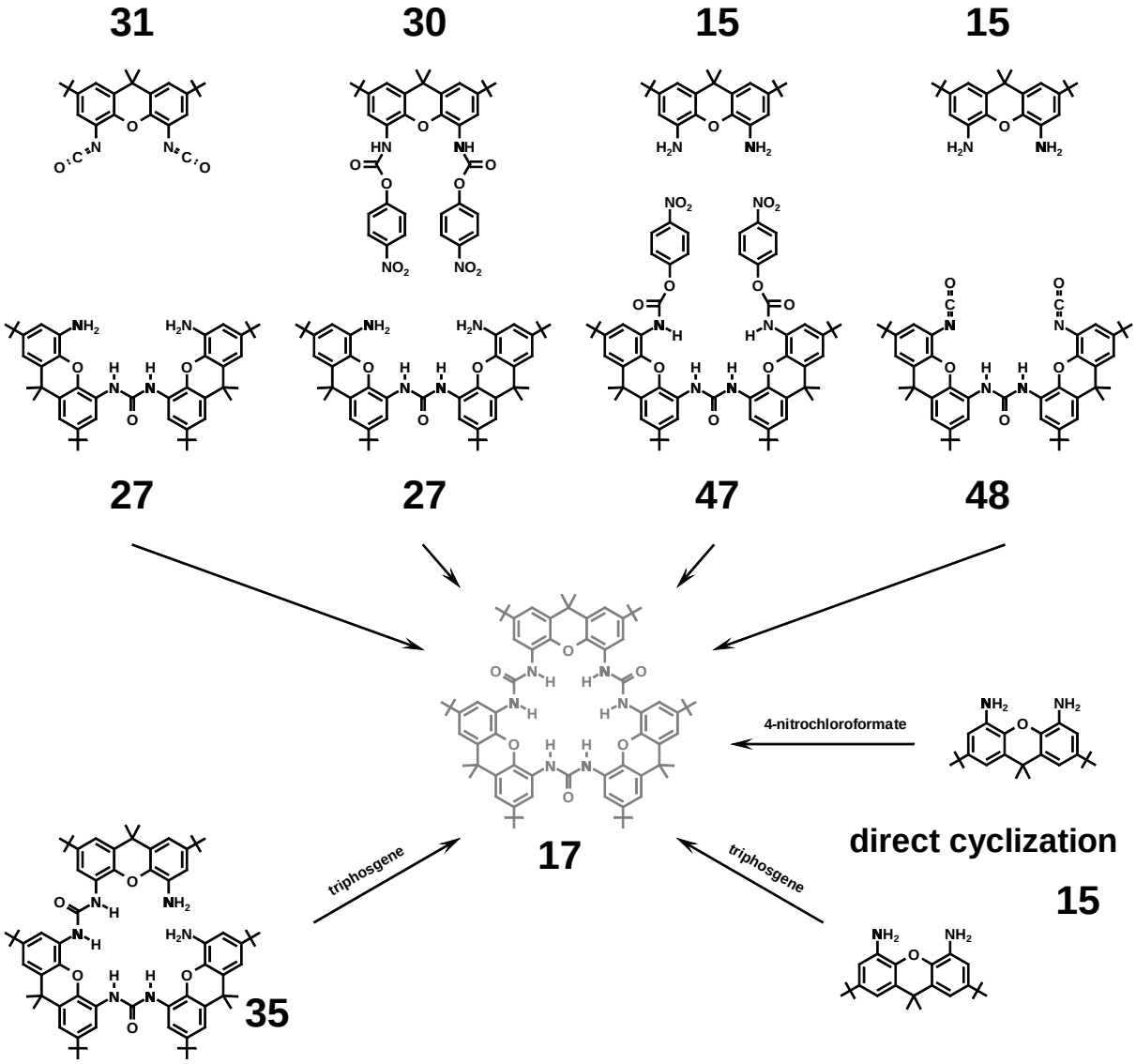
While other trimers were successfully prepared by using this approach, the trimer XXX was unexpectedly neither produced nor detected after these reactions.

Two new active compounds – active diurethane XX **47** and diisocyanate XX **48** - were prepared in order to perform "1+2" cyclizations with X-diamine **15**. Some interesting observations were made during that work.

The active diurethane XX 47 was prepared by the reaction of the XX-diamine **27** with 4-nitrophenyl chloroformate. Both compounds were mixed in ethylacetate and then *N*-diisopropylethylamine was added to the solution. After 12 h of stirring the solvent was removed under reduced pressure and the crude product was triturated with ether. In contrast to the simpler urethanes the crude product dissolved in ether completely. After 12 h white precipitate appeared from the solution. Surprisingly instead of the expected diurethane the mixture of it with *N*-diisopropylethylammonium chloride (approximately 1 molecule of diurethane per 3 molecules of the salt) was obtained, which was impossible to separate only by crystallization. Obviously the dimeric urethane is able to interact with ions due to its hydrogen bond donating groups and cleft-like structure. The solution of the crude product in ethylacetate was then filtered through silicagel in order to remove salt, and the residue after the evaporation of the filtrate was triturated with ether, yielding 48% of the active diurethane **47** as a white solid.

The diisocyanate XX 48 also produced difficulties in the synthesis. The solution of the XX-diamine **27** and *N*-diisopropylethylamine was added to the solution of triphosgene (solvent: dichloromethane). In contrast to the synthesis of simpler isocyanates TLC showed the presence of significant amount of side products in the reaction mixture. The solution was filtered through silicagel, which was then subsequently washed with small portions of dichloromethane. The pure diisocyanate was isolated with the yield 60 – 80%.

Interestingly, that in ^{1}H NMR spectra strange signals were detected among signals of other side products of the reaction, which cannot be attributed to any known cyclic compound built from xanthene units and most probably belong to the cyclic XX dimer, which can be also formed in this reaction. cyclic tetramer XXXX **38** was also detected.



Scheme 14. All synthetic attempts for the preparation of the trimer XXX **17**: unfortunately, they did not lead to the isolation of the target compound.

Unfortunately, several cyclizations attempted with these dimeric diactivated compounds and X-diamine were unsuccessful and did not produce interpretable product. The same is true for the 2+1 cyclization of diamine XX **27** and X diurethane **30**.

However, the reaction of the XX diamine and the X diisocyanate in dichloromethane brought an unexpected and remarkable result. The product of "2+1+2+1" cyclization of four molecules – the cyclic hexamer XXXXXX **49** was obtained with the surprisingly high yield

of 49%, instead of trimeric "2+1" product –trimer XXX **17**. This hexameric product is described more in detail in the corresponding chapter.

At this point it seemed as if the trimer synthesis is totally impossible due to sterical factors, which hinder the "2+1" cyclization reaction, in the same time promoting the formation of long oligoureas (the linear pentameric diamine XXXXX was also detected in the reaction mixture) and the hexameric macrocycle.

3.1.5 Preparation of the trimer XXX.

One example for the synthesis of sterically hindered compound is already described in this work. This is the synthesis of the "cyclic monomer" **41** of a diphenyl ether unit, which is practically not formed under "normal" conditions when diamine is reacted, but appeared to be the main product when the amine reacted in form of its ammonium salt. This approach was also checked for the synthesis of the XXX-trimer **17**.

Instead of XX-diamine **27** its trifluoroacetic salt was used in the reaction. Two hours after protonated diamine and X-diisocyanate were mixed the stoichiometric amount (2 moles per one mole of diamine salt) of the *N*-diisopropylethylamine was added. After 12 h of stirring TLC showed the presence of one main product. A white flaky precipitate was isolated from hexane solution. ^{1}H NMR showed the presence of the new xanthene-based macrocycle (one singlet for urea NH-protons, two signals for the aromatic protons, singlet for the methyl groups and the singlet for *tert*-butyl) and ESI mass spectroscopy confirmed the formation the trimeric macrocycle **17**. The isolated yield of the pure compound was as high as 40% (some amount of the trimer still left in the mother liquor).

Therefore the family of the trimers was completed. Let's have a look now on the x-ray structures and NMR spectra of these macrocycles, in order to study their conformations and eventual interaction with anions.

3.2 X-ray structures

Crystallization of the newly synthesized trimers was attempted intensively, with ot without addition of inorganic salts. Single crystals good for x-ray structure determination were obtained for the two cylclic trimers: XXD and DDD. In the latter case inclusion of the chloride anion into the internal cavity of the cycle was observed.

3.2.1 Crystal structure of the trimer XXD 42

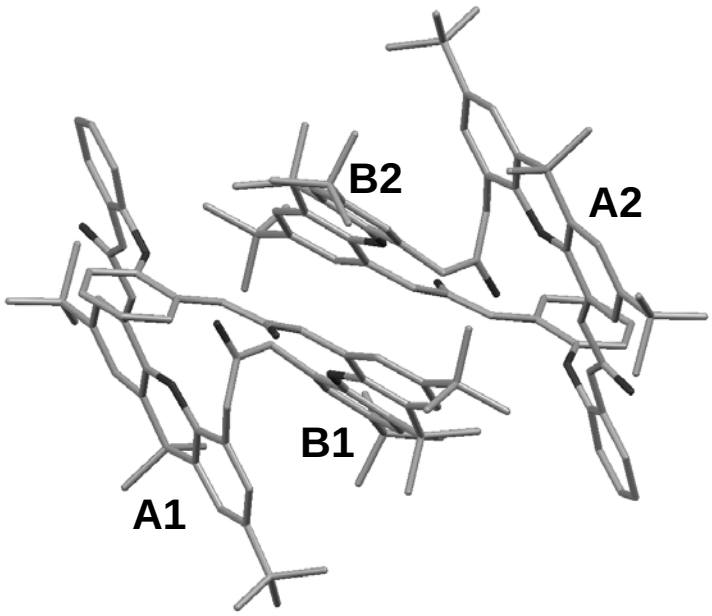


Figure 27. View on the two separate molecules of the trimer i XXD n the crystal cell. Hydrogens and solvent molecules are omitted for clarity.

The single crystals of the trimer XXD were isolated from the chloroform - dichloromethane - ethanol solution upon the slow evaporation. The crystal cell contains two trimer molecules and four molecules of chloroform. Xanthene units have a slightly distorted planarity but (averaged) planes of the opposite units (A1 and A2, B1 and B2 on the Fig. 27) of molecules in the cell are parallel. Distances between averaged planes A1-A2 and B1-B2 are 7.860 Å and 3.491 Å respectively.

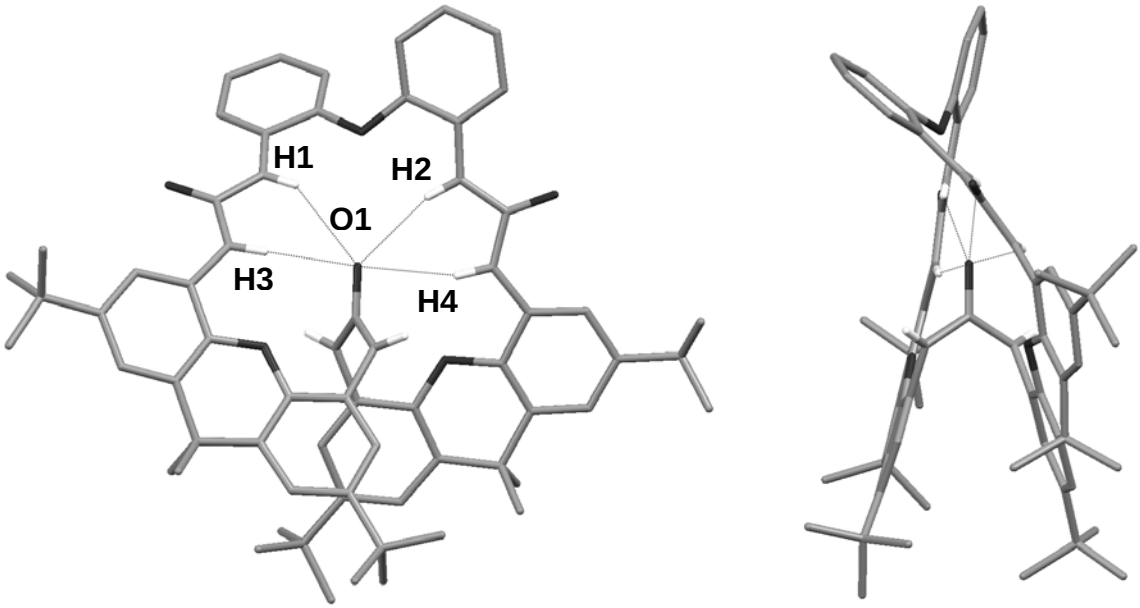


Figure 28. Views of a single molecule of the trimer XXD in the crystalline state. Non-urea hydrogen and solvent molecules are omitted.

Table 6. Hydrogen bond length in the X-ray structure of the trimer 42. For the numbering see Fig. 28 (left).

Hydrogen bond	Bond length, Å
H1-O1	2.478
H2-O1	2.451
H3-O1	2.604
H4-O1	2.504

Each single molecule of the trimer XXD is strongly folded. The oxygen of the urea group between two xanthene units (X-X) is drawn into the internal cavity and bound by four hydrogen bonds with two "X-D" urea groups. The "X-X" urea group is distorted in a way, that its hydrogens and oxygen point in the same direction (analogously to the urea group in the crystal structure of the D-"monomer" **41**). Two adjacent xanthene units are shifted towards each other and partially overlapped.

The angle between the averaged planes of benzene rings of the diphenyl ether units is 62.24°. The angle between the averaged planes of xanthene units is 31.25°.

Table 7. Selected crystal data and structure refinement for X-ray crystal structure of trimer **42**.

Empirical formula	$C_{63}H_{72}Cl_6N_6O_6$	Volume	3016.6(6) $Å^3$
Formula weight	1221.97	Z	2
Temperature	173(2) K	Density (calculated)	1.345 Mg/m^3
Crystal system	triclinic	Absorption coefficient	0.341 mm^{-1}
Space group	P - 1	Crystal size, mm	0.33x0.27x0.25
Unit cell dimensions	a = 14.2014(19) Å	Reflections collected	24329
	b = 15.4184(19) Å	Independent reflections	10411
	c = 15.7438(17) Å	Final R indices	R_1 = 0.1050
	α = 73.389(9)°		wR_2 = 0.2809
	β = 81.409(10)°	R indices (all data)	R_1 = 0.1506
	γ = 60.041(9)°		wR_2 = 0.3167

3.2.2 Crystal structure of the trimer DDD 44 with tetrabutylammonium chloride

The single crystals of the trimer **44** with included tetrabutylammonium chloride were formed by the slow evaporation of the multicomponent solvent mixture (aceton, acetonitrile, chloroform, dichloromethane, ethanol, ethylacetate). The crystal lattice does not contain any solvent molecules. Trimer molecules alternating with tetrabutylammonium cations form endless staples.

There are two distances between chloride anions and nearest tetrabutylammonium cations: 4.464 Å and 4.546 Å. The distances between two chloride in a staple 8.351 Å, the closest distance between two chlorides in neighbouring staples is 13.451 Å.

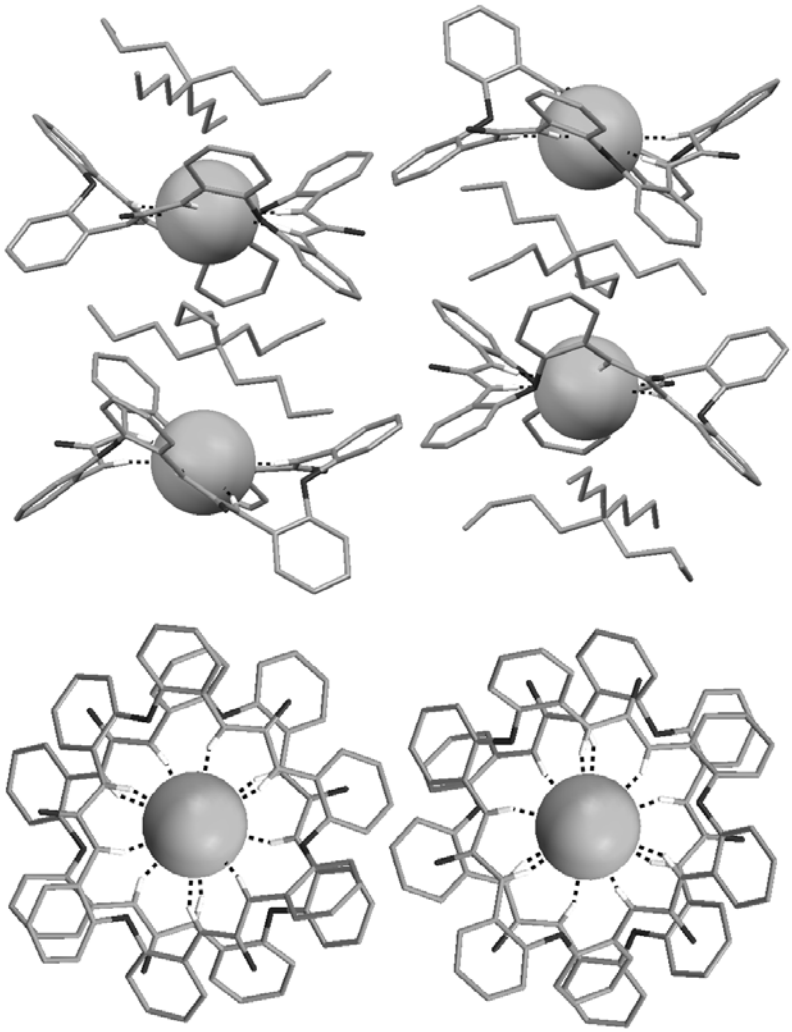


Figure 29. Packing of the trimer XXD **44** and tetrabutylammonium salt in the crystal lattice (one cell is shown). Non-urea hydrogens are omitted on both views, cations are omitted on the lower view for clarity.

Table 8. Selected crystal data and structure refinement for X-ray crystal structure of trimer **44**.

Empirical formula	$C_{55}H_{66}ClN_7O_6$	Volume	5205.2(6) $Å^3$
Formula weight	956.60	Z	4
Temperature	173(2) K	Density (calculated)	1.221 Mg/m^3
Crystal system	monoclinic	Absorption coefficient	0.129 mm^{-1}
Space group	P -21/c	Crystal size, mm	0.32x0.19x0.10
Unit cell dimensions	a = 21.9730(16) Å	Reflections collected	66076
	b = 14.2644(6) Å	Independent reflections	9795
	c = 16.7013(12) Å	Final R indices	R_1 = 0.0464
	α =90°		wR_2 = 0.0944
	β = 96.085(6)°	R indices (all data)	R_1 = 0.0833
	γ = 90°		wR_2 = 0.1056

Each chloride is bound within the cycle with six hydrogen bonds which are between 2.472 and 2.748 Å long. The trimeric cycle is folded in order to fit the chloride. The angles between averaged planes of the phenyl rings and betweeen averaged planes of the phenyl rings and urea groups are collected in the Table 5.

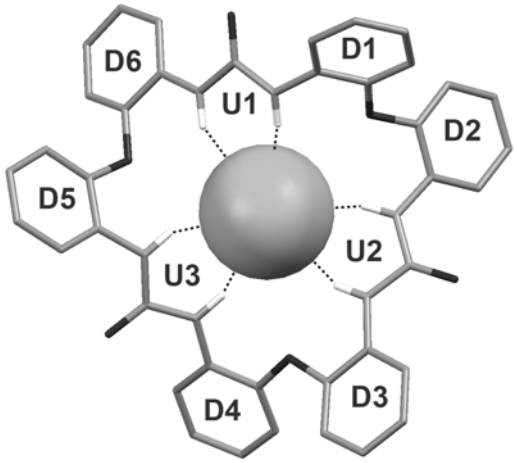


Figure 30. Single molecule of the trimer **44** with chloride anion included in the cental cavity. Non-urea hydrogens and cations are omitted.

Table 9. Selected angles between averaged planes in the crystal structure of the trimer DDD (For numbering see Fig. 30)

Units	Angle, °	Phenyl rings and adjacent urea groups[a]	Angles, °	
D1-D2	61.78	D6-U1-D1	24.13	54.00
D3-D4	51.91	D2-U2-D3	36.15	28.67
D5-D6	70.26	D4-U3-D5	38.00	46.39

[a] averaged planes of the urea groups contain oxygen, nitrogens and carbon of the urea groups.

Therefore, "rigidified" trimer XXD preferred intramolecular hydrogen bonding instead of binding of anions, while the more flexible trimer DDD can "adapt" to the anion which is obviously smaller than internal cavity of the flat trimer molecule.

3.3 Complexation properties of trimers

3.3.1 Trimer XXD 42

The compound shows good solubility and produces more or less interpretable spectra (DMSO-d_6, pyridine-d_5 and chloroform-d_1). In accordance with the trimer XXD structure three peaks for urea hydrogens, four meta-coupled doublets for the xanthene units, two pseudo doublets and two pseudo triplets for the diphenyl ether, one singlet for methyl groups and two singlets for *tert*-butyls units are observed in NMR spectra (DMSO-d_6). The spectra correspond to dynamic C_{2v} symmetry. Obviously, molecule can have also C_2 or C_s symmetry (dynamic), but since signal of methyl groups appear as the singlet, we speak here about C_{2v}. Would we see changes in apolar solvent or at the lower temperature?

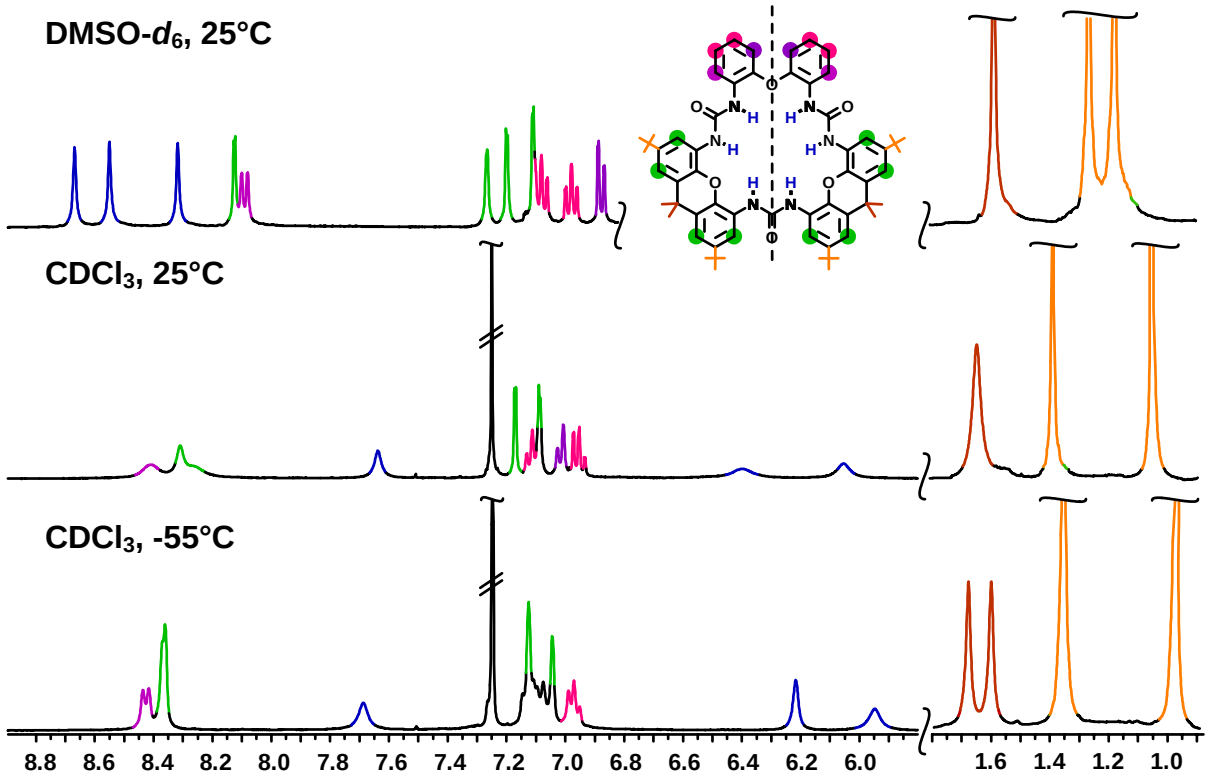


Figure 31. 400 MHz ^{1}H NMR spectra of the trimer XXD (c = 0.1 mM).

Spectra in chloroform-d_1 contain strongly broaden und upfield shifted signals of urea hydrogens. The two signals for the aromatic protons of xanthene units and one of the four diphenyl ether protons (most probably protons, whose signals appear in the low field are adjacent to the urea groups) are strongly broadened as well. The relative positions of signals did not change even when the sample was cooled to -55°. Broadened signals sharpen, especially those for aromatic protons. However, the singlet for methyl groups splits into two signals, what indicates changes in symmetry. If we compare this behaviour with the X-ray structure, we may conclude that at the low temperature the molecule may be present in the conformation similar to that in the crystalline state. This conformation is relatively stable at -55°, but it is less stable at 25°C, what leads to the fusion of the methyl groups signals.

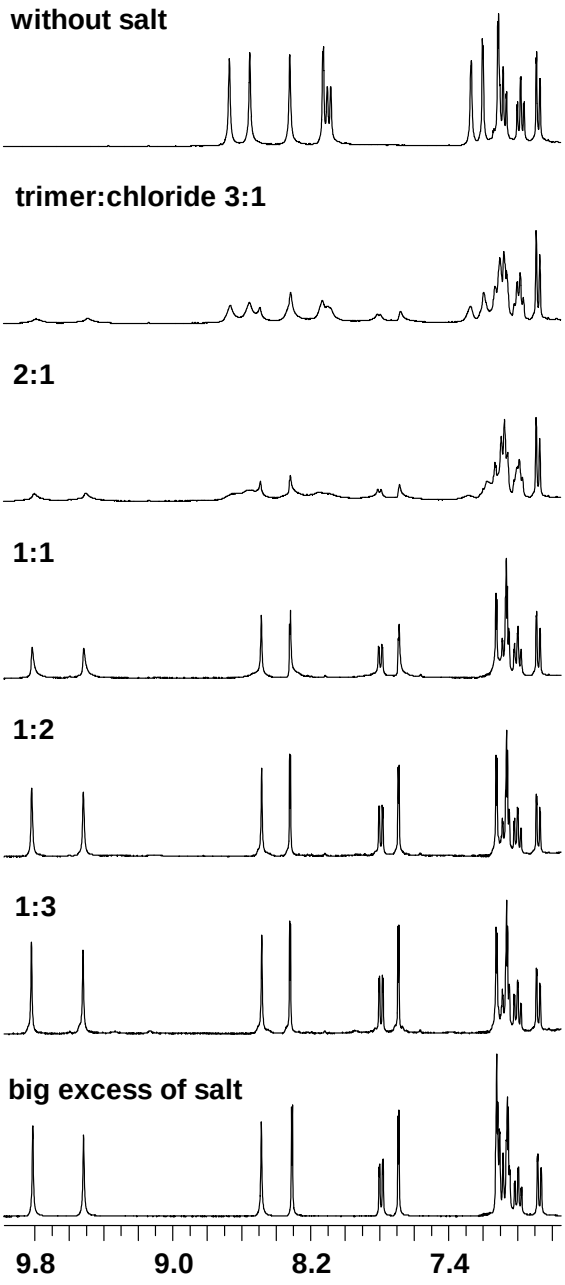


Figure 33. Stepwise addition of tetrabutylammonium chloride to a 0.1 mM solution of the trimer **42** in DMSO-d_6.

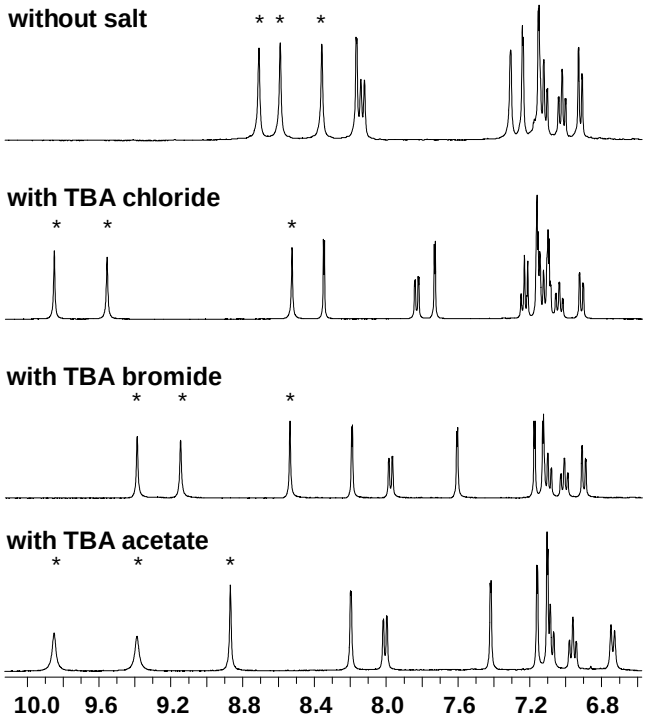


Figure 32. Interaction of the trimer **42** with selected anions (400 MHz, DMSO-d_6, 25°C, c = 0.1 mM). Urea protons are marked with *.

Surprisingly, the spectra in pyridine were far less readable than in chloroform. The signals which were broadened in chloroform, appeared to be hardly visible in pyridine or not visible at all; the signal for the methyl groups is strongly broadened. Probably, molecules of pyridine are too bulky to solvate the urea hydrogens effectively and prevent the formation of intra- and intermolecular connections.

DMSO-d_6 was chosen as a solvent for further experiments due to good solubility of the trimer and easy readable spectrum. A series of the spectra with different anions were recorded.

An interaction of the triurea **42** with added salts was observed in the ^{1}H NMR spectra only in some cases. Upon addition of tetrabutylammonium salts of I^-, NO_3^-, HSO_3^-, BF_4^-, SCN^- to the trimer solution in DMSO-d_6 the signals remain unchanged.

On the other side, the spectrum of the trimer **42** changes significantly in the presence of Cl^-, Br^-, $H_2PO_4^-$, F^- and CH_3COO^- TBA salts.[41] Among these anions Cl^-, Br^-, CH_3COO^- produce a similar effect on the lowfield region (around 6 and more ppm) and the new spectrum was observed (see Fig 32).[42]

Addition of fluoride and dihydrophosphate leads to less defined interactions, resulting in insignificant NMR spectra.

The complex with chloride was studied

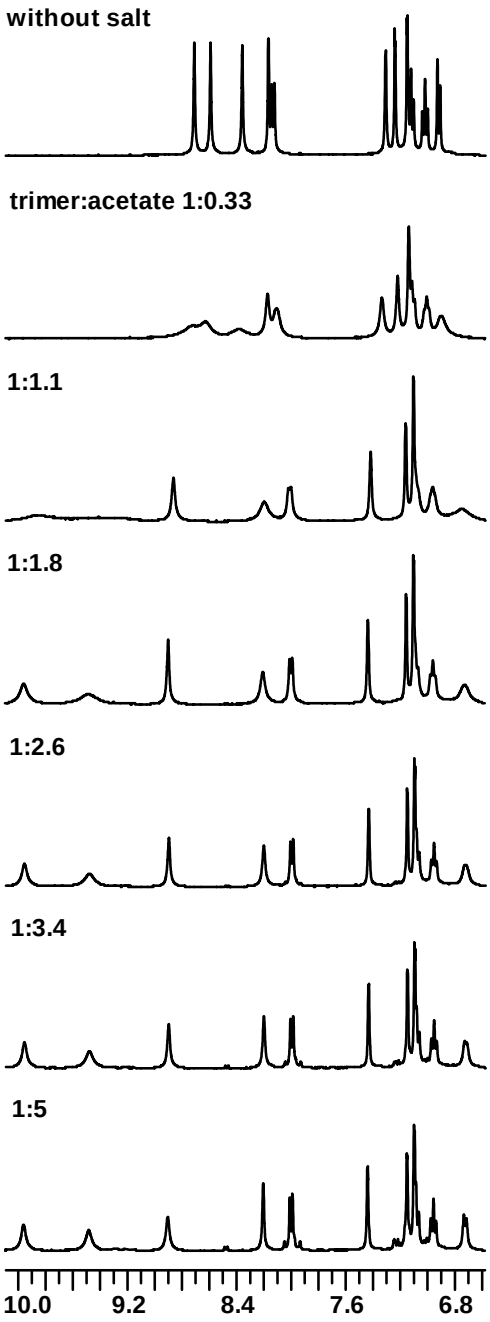


Figure 34. Stepwise addition of tetrabutylammonium acetate to a 0.1 mM solution of the trimer **42** in DMSO-d_6.

[41] At the same time trifluoroacetate has no influence on the spectra.

[42] Interestingly, a splitting of the methyl group peak is observed in case of acetate addition (non-spherical anion), what indicates different geometry of the complexed trimer in that case.

more in detail as an example with the most pronounced difference between spectra with and without anion. Therefore a highly concentrated solution of the TBA chloride was added stepwise to the solution of the trimer XXD (Fig. 32).

After addition of the first portion of the salt the trimer spectrum loses clarity. Upon further addition of chloride the signals of the uncomplexed trimer broaden and disappear, while signals of the chloride complex rise and sharpen. After a 1:1 ratio is reached, further significant changes were not observed. Peaks of the complexed trimer became only slightly sharper with further addition of chloride. Therefore 1:1 complexation stoichiometry is observed although the complex is not entirely stable in the NMR timescale.

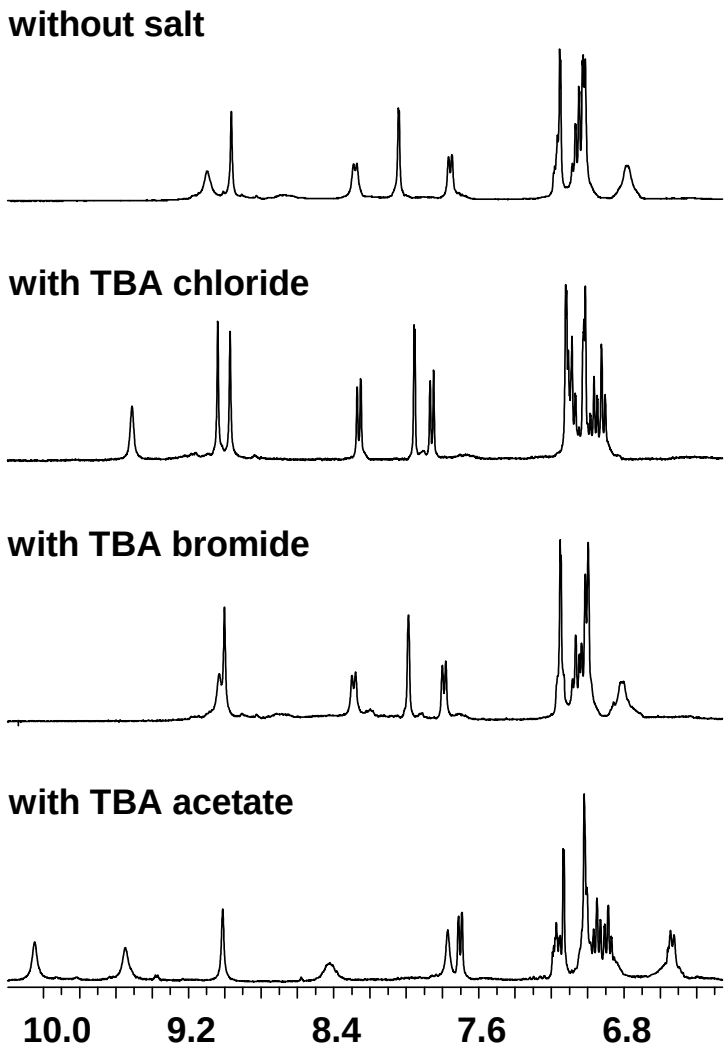


Figure 35. Interaction of the trimer **43** with tetrabutylammonium salts (400 MHz, DMSO-d_6, 25°C).

The complexation with acetate was studied in analogous way by stepwise addition of the salt (Fig. 33).[43] We see again the conversion of the pure trimer spectrum to the complexed trimer spectrum. Signals of the newly formed complex are not sharp at ratio 1:1.1 yet, although all aromatic signals are already present and upon further addition of salt no additional shift of signals happens, but only sharpening of them.

3.3.2 Trimer XDD 43

The compound shows NMR properties similar to the XXD trimer. The spectrum of the pure compound in DMSO-d_6 corresponds to C_{2v} symmetry. It

[43] Not entirely distinct ratios between ligand and anion due to the high hygroscopicity of the tetrabutylammonium acetate.

contains three singlets for urea protons, however only one of them is sharp; another one is remarkably broad and the third one is practically not visible above the baseline. Signals for 12 aromatic protons, singlet for methyl groups (broaded) and the singlet for *tert*-butyl are present.

Also analogously to the trimer **42** changes in ^{1}H NMR spectra were observed in the presence Cl^-, Br^-, $H_2PO_4^-$, F^- and CH_3COO^- TBA salts, while addition of I^-, NO_3^-, HSO_3^-, BF_4^-, SCN^-salts does not change the shape and the position of the peaks. Spectra for chloride, bromide and acetate complexation are shown on Fig. 34. Obviously, bromide makes smaller changes to the spectrum than in case of XXD trimer **42**.

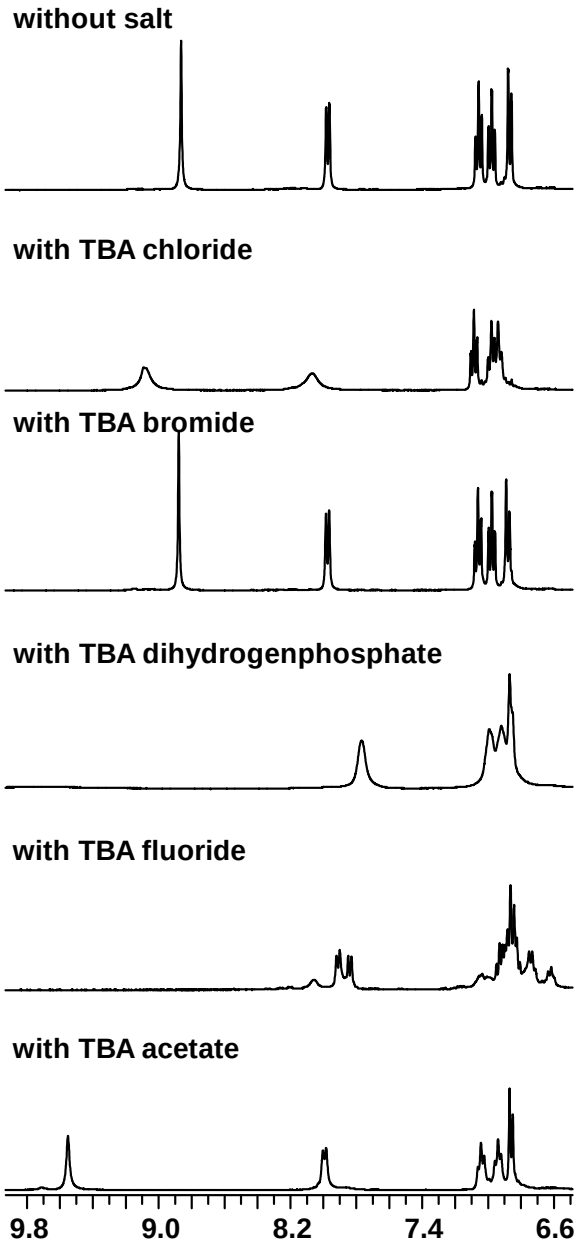


Figure 36. Interaction of the trimer **44** with tetrabutylammonium salts (400 MHz, DMSO-d_6, 25°C).

Interaction with F^- and especially with $H_2PO_4^-$ is chaotic and no regular structure for the complex could be defined from the spectra. In the presence of fluoride some aromatic peaks shift to low field, but at the same time signals for urea hydrogens are not visible anymore and an irregular hydrogen bonding pattern is present instead.

3.3.3 Trimer DDD 44

The completely "flexible" cyclic triurea **44** produces a clear spectrum in DMSO-d_6, which contains a singlet for NH-protons, two pseudo doublets and two pseudo triplets for the diphenyl ether. All signals are sharp.

The activity of the DDD trimer towards anions evaluated by NMR has decreased in comparison with rigidified mixed trimers. For example, addition of TBA bromide brings only very minor changes to the spectrum (downfield shift of peaks by 0.01 - 0.02 ppm), addition of chloride only broadens peaks of the urea and the adjacent aryl proton, but downfield shift is

not as pronounced as in case of XXD and XDD. Addition of the TBA acetate produces downfield shift of the urea proton signal, other signals are shifted not significantly.

Analogously to the other trimers addition of TBA salts of I^-, NO_3^-, HSO_3^-, BF_4^-, SCN^- does not change the ^1H NMR spectra of the trimer **44**.

In the spectra of the trimer DDD with TBA fluoride and dihydrogenphosphate strong change of the signal of aromatic protons is observed (signals of the urea protons are totally broadened and not visible); these spectra for trimer **44** slightly more clear than corresponding spectra of mixed trimers, however it is still too ambiguous to interpret them.

3.3.4 Trimer XXX 17

The ^1H NMR spectrum of the trimer **17** is significantly broaded both in DMSO-d_6 and chloroform-d_1 (see Fig. 36). The signal of the urea protons is broad and the signal of the adjacent aromatic protons are practically not visible even in the polar solvent, while other signals (the second signal for aromatic protons, singlets for methyl groups and *tert*-butyls) are clearly sharp. The signals of the urea protons and the neighbouring aromatic protons in chloroform are razed to the baseline and *tert*-butyl peak is visibly broadened.

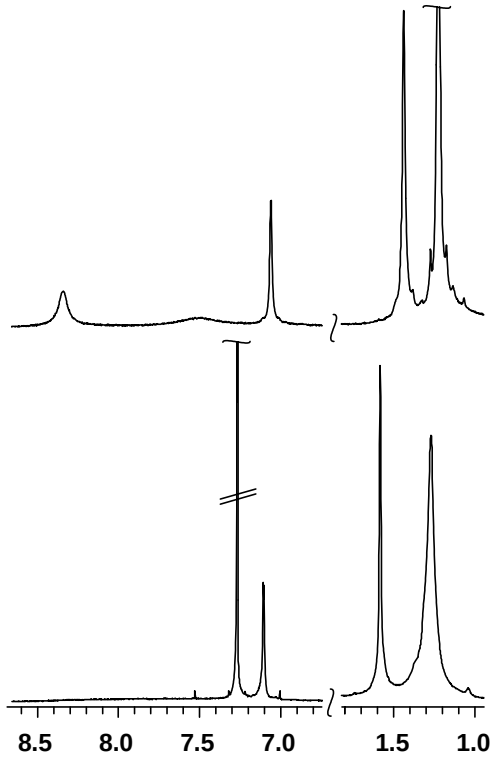


Figure 37. Spectra of the trimer XXX in DMSO-d_6 (upper view) and in chloroform-d_1.

Such spectra show unambiguosly that against expectations the trimer does not have time-averaged "flat" conformation in solution. Its urea protons are involved in some undefined interactions in such a way, that magnetic environment of the neighbouring aromatic protons is continuosly affected even in such rigid system as the xantene-based cyclic trimer. Therefore we can conclude that most probably in the case of the trimer XXX we observe dynamic switching between a number of distorted conformations in solution, caused by hydrogen bonding between the urea protons.

Similar undefined hydrogen bonding patterns are usually cleared dramatically upon addition of a TBA salt to the solution of a compound and there are many examples of that in this work. Surprisingly the salts have minor influence on the trimer's spectrum. Even addition of the TBA chloride causes comparatively slight sharpening and lowfield shift of the aromatic and the urea proton signals. The sharp spectrum can be achieved only when solution was heated to 100°C.[44]

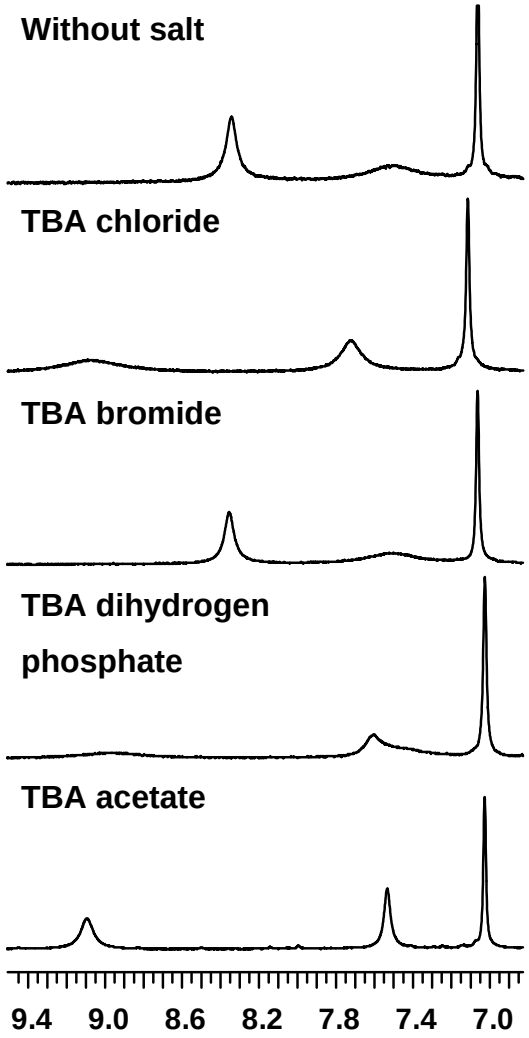


Figure 38. Interaction of the trimer **17** with tetrabutylammonium salts (400 MHz, DMSO-d_6, 25°C).

The TBA bromide was checked as well and had practically no influence on the NMR spectrum at all, despite of larger radii of the anion which should fit the trimer internal cavity better. The acetate has the same influence on the spectrum as the chloride anion, but corresponding effects (sharpening, lowfield shift) are weaker than those in case of chloride. Spectra of the trimer with small amout (less than 1:1 molar ratio) of the TBA acetate showed that there is no indication of the complexation, which would be stable in NMR timescale. Only gradual lowfield shift was observed.

Unfortunately, the TBA nitrate also has no influence on the trimer's spectrum in DMSO-d_6 (along with other "weak" anions such as I^-, HSO_3^-, BF_4^- and SCN^-). From other side "strong" dihydrophosphate and fluoride anions interact strongly with the trimer in the solution, but it is not possible to describe possible conformation(s), since these spectra are also strongly broaded.

[44] Interestingly, when the heated trimer sample with TBA chloride was cooled back to 25°C, the signal of urea proton appeared at 9.30 ppm and slightly sharper than before heating (initially br s, 9.05 at 25°C). The „active" aromatic protons signal shifted less significantly by 0.02 ppm, but was sharpened as well.

3.4 Conclusion

A set of new cyclic triureas with a stepwise varied rigidity skeleton were prepared. Methods of their synthesis and purification were elaborated well enough to enable the synthesis of further similar compounds. The compounds were studied by ^{1}H NMR and partly by X-ray analysis. Triureas showed acceptable solubility in common organic solvents and high affinity to anions, what makes them attractive for further studies, as well as for synthesis of trimers with modified skeleton and for the inclusion into ion pair receptors.

The strong binding with nitrate anion, expected on the basis of computer modeling and geometrical complementarity, was not detected in all four cases. Our studies showed a number of reasons for this.

The anion have to compete with solvent molecules and other urea functions of the receptor molecule(s) when binding to the urea group. We expected to minimize the intramolecular interaction between urea groups by using "rigid" xanthenes as spacers, but the rigidity of the molecule was obviously overestimated. As can be concluded from the x-ray structure of the trimer XXD, the attractive forces by intramolecular hydrogen bonds are strong enough to distort even the xanthene-based skeleton strongly. Most probably the same effect is observed in case of XXX trimer, additionally increased by the shielding of the intramolecular hydrogend bonds for the solvation by the bulky alkyl groups of the xanthene units. Therefore the hydrogen bonding between the urea groups of the trimer XXX is appeared to be strong enough to "overcome" the geometric complementarity between the trimer molecule and the nitrate anion. The unclear ^{1}H NMR spectrum of the trimer XXD in highly polar pyridine-d_5 may be taken as confirmation for the importance of the sterical factor in case of triurea solvation.

The trimer XXD with one "flexible" diphenyl ether unit appeared to be the strongest anion receptor in the set. The molecule has the optimal proportions for the preorientation of the ligating urea groups, accessibility of the hydrogen bonds and ability to adapt to the guest anion. At the same time no certain selectivity can be noted; more detailed studies (microcalorimetry, NMR) would be useful to evaluate the binding quantitatively.

In the next chapter a set of cyclic tetramers also with varied flexibility will be discussed.

4 Tetramers: synthesis and evaluation of complexation properties

4.1 Synthesis of tetramers

Due to the expansion of the cycle size the family of tetramers increased in comparison to the trimers. Now we deal with six cyclic tetraurea compounds: XXXX, XXXD, XXDD, XDXD, XDDD and DDDD.

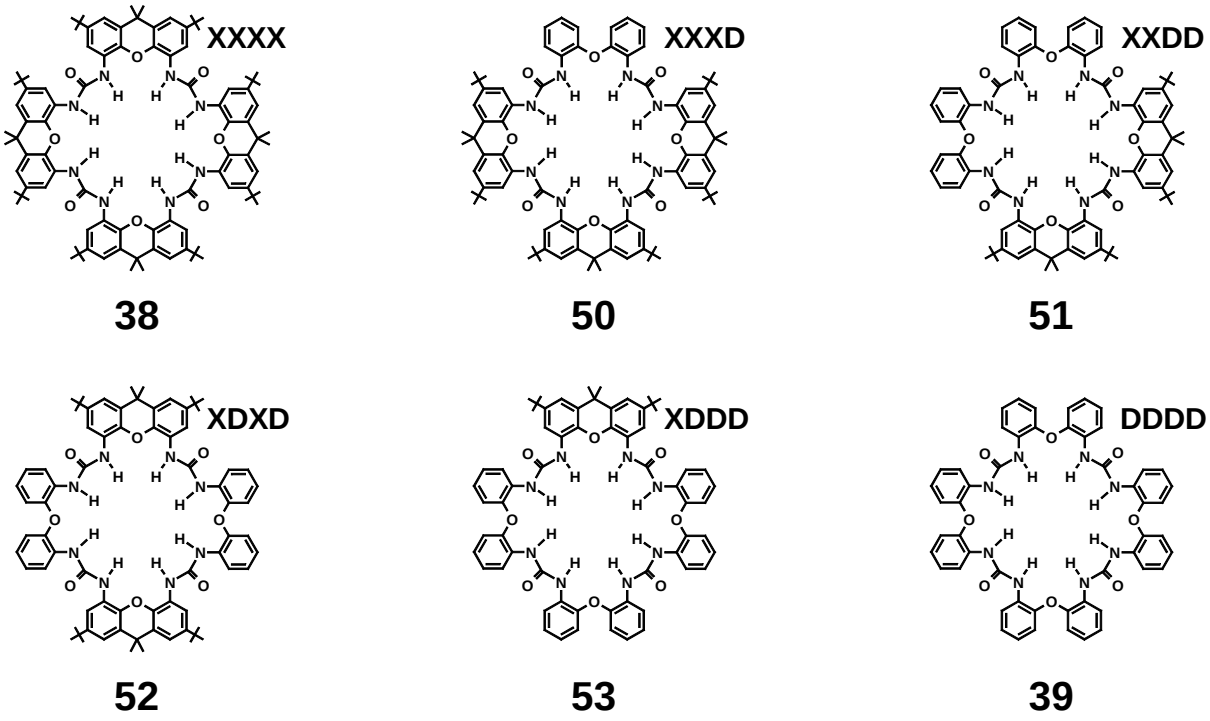


Figure 39. Possible tetramers formed by combination of the two diamino-units **X** and **D**.

The number of possible synthetic pathways was increased correspondingly. Beside of the direct condensation from diamine units (which has already produced the tetramers XXXX and DDDD, as shown in Chapter 2) we have also "3+1", "2+2" options and a ring closure reaction. It is obvious that the "3+1" approach is the most rational for tetramers XXXD and XDDD. The "2+2" pathway would require the preparation of an unsymmetric dimeric units with additional synthetic steps. XXXD and XDDD are such tetramers. And the selective preperation of the tetramer XDXD from dimers is impossible at all.

The "2+2" approach is useful for the tetramer XXDD and eventually also for XXXX and DDDD, but the last two were already prepared by the direct condensation from diamine units.

For the preparation of the tetramers and their precursors the same general approach was used as in the case of the trimers, although the isolation of each compound was different depending on the number and the arrangement of the two different units in the molecule.

4.1.1 "3+1" synthesis: tetramers XXXD, XDXD and XDDD

Tetramer XXXD. The diamine XXX **35** and the D-diisocyanate were reacted in dichloromethane over 18 h in order to obtain the desired tetramer XXXD. After the reaction mixture was evaporated in vacuo, the residue was triturated with acetonitrile. The pure tetramer XXXD was isolated as a white powder with 68% yield. The compound was identified by ESI-MS and ^{1}H NMR at 120°C in DMSO-d_6. It is insoluble in DMSO-d_6 at room temperature and produces only an unclear, broad spectrum in other solvents (THF-d_8, $CDCl_3$).

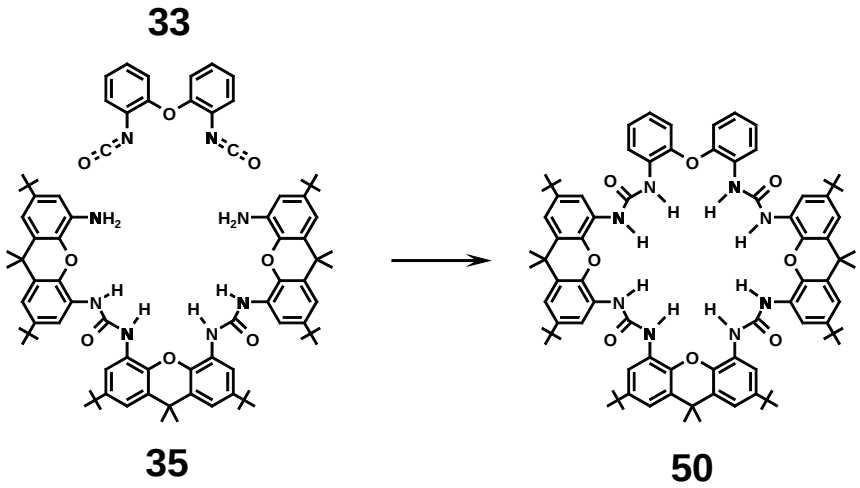


Figure 40. Preparation of the tetramer XXXD.

XDXD tetramer. The diamine DXD was synthesized initially using the "reversed" way compared to previously synthesized trimeric diamines. Instead of X-diisocyanate **31** and monoprotected D diamine **25**, X-diamine **15** and newly prepared monoproteced D-isocyanate were used as starting compounds. The significantly higher price for the xanthene-based diamine was the reason for this change since by this approach we save one conversion step for this compound.

The new isocyanate was prepared by reaction of the monoprotected D-diamine **25** with triphosgene, and after filtering through the silicagel and removal of the solvent the target compound was isolated as a clear oil. The monoprotected D-isocyanate was the only one which could not be obtained as solid. The liquid compound was very sensitive to humidity. In contrast to other isocyanates it is decomposed significantly while being handled.

This sensitivity caused impurities in the target diprotected trimeric diamine and it appeared very difficult to isolate this from the reaction mixture. The reaction was then attempted using the X-diisocyanate **33** and the monoprotected D-diamine **24**. Both compounds (molar ratio 1:2) were reacted in dichloromethane. After 12 h the solvent was removed in vacuo and the diprotected diamine DXD was obtained as a brownish powder. The deprotection with trifluoroacetic acid was performed immediately in the same flask. The diamine **34** was isolated as a brownish powder in 94% yield over two steps.

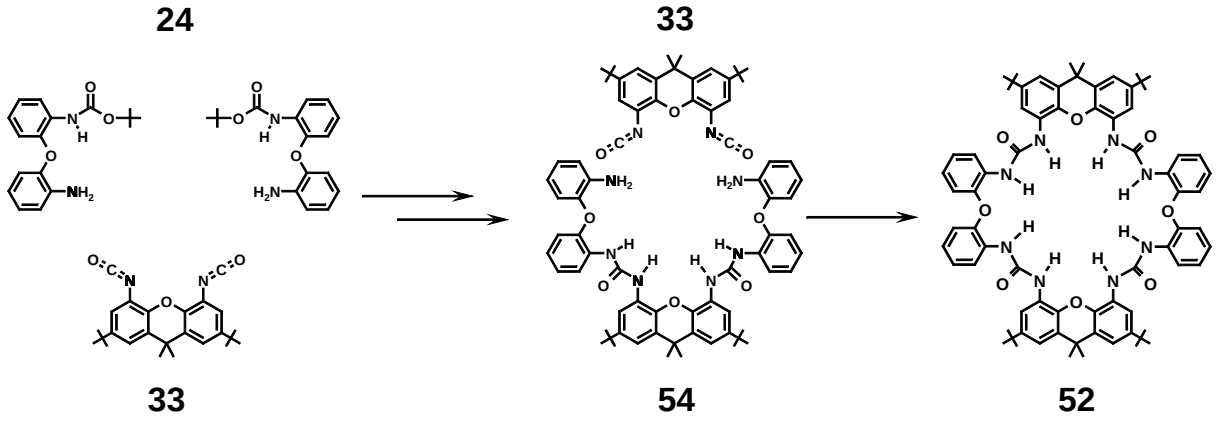


Figure 41. Preparation of the tetramer XDXD.

To prepare the tetramer XDXD the trimeric diamine **54** was reacted with X-diisocyanate **33**. Two solutions were added dropwise over 30 min to a flask, which contained vigorously stirred dichloromethane under nitrogen.[45] After 8 h the the solvent was removed under reduced pressure and the crude product was dissolved in boiling acetonitile. After approximately 1 h a beige precipitate appeared in the flask. The solid was filtered off and dried, yielding 55% of the tetramer **52**.

Tetramer XDDD 53. This compound has caused the biggest difficulties in the series of tetramers due to its moderate, but at the same time unspecific solubility. "Not specific" means that the compound practically cannot be separated from the contaminations of

[45] In this case such slow and accurate addition is absolutely necessary. When reagents were mixed fast, experiments ended with a product significantly contaminated with impurities.

oligourea byproducts by crystallization. In the same time unsufficient solubility of the compound(s) does not allow an effective column chromatography. This problem is common for all oligoureas containing several D-units, and we have met it already when we attempted to isolate DDD-trimer **44**.

The traditional "3+1" approach initially failed in different combinations: DDD diamine **37** with X-diisocyanate **31** or active X-diurethane **30** and DDD-diisocyanate with X-diamine **15** were attempted, unfortunately producing more or less contaminated products.

Since all purification methods had only a limited effect, it was especially important to achieve the highest possible purity already on the stage of the crude reaction product.

To avoid the unwanted formation of associates by hydrogen bonding, the reaction was performed in acetonitrile. Moreover, tetrabutylammonium chloride was added to the DDD-diamine solution (one mole per one mole of diamine) as an additional acceptor of hydrogen bonds. The X-diisocyanate **31** solution was added dropwise over 1 h to the solution of the diamine and the TBA salt. After 12 h TLC showed the full conversion of the reagents. The solvent was removed under reduced pressure and the crude product was dissolved in small portion of ethylacetate. Then the compound was precipitated by addition of hexane (approximately 5 volumes per 1 volume of ethylacetate). The beige solid was filtered off, yielding 25% of tetramer XDDD **53**.

4.1.2 "2+2" synthesis: XXDD tetramer

The DD-diisocyanate **46** and XX-diamine **48** were used for the preparation of the tetramer XXDD **51**. Both reagents were added simultaneously with vigorous stirring under a nitrogen stream to a flask containing dichloromethane.

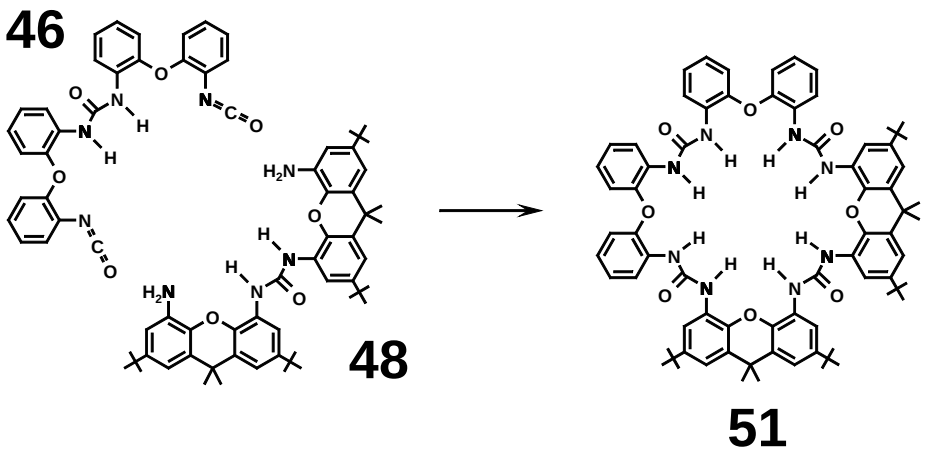


Figure 42. "2+2" synthesis of the XXDD tetramer.

After removal of the solvent the residue was washed with acetonitrile. In contrast to other compounds the product could be dissolved and the impurities remained insoluble. The solid was filtered off and the filtrate was evaporated. The resulting brown residue was washed with hexane. The XXDD tetramer **51** was isolated as a brownish powder with a yield of 42%.

With the XXDD tetramer the synthesis of the series of tetramers was complete.

4.2 X-ray structures

Attempts to crystallize the tetramers were performed intensively combining various solvents and inorganic salts. Beside of the tetramer DDDD, which was separated in form of single crystals, two different single crystals (from different solvents) were obtained for the tetramer XXXD.

4.2.1 Crystal structure of the tetramer DDDD 39

Single crystals of the cyclic DDDD appropriate for X-ray diffraction were formed during the slow evaporation of its THF solution.

Table 10. Selected crystal data and structure refinement for cyclic DDDD **39**.

Empirical formula	$C_{72}H_{80}N_8O_{13}$	Volume	13071(2) $Å^3$
Formula weight	1265.44	Z	8
Temperature	100(2) K	Density (calculated)	1.286 Mg/m^3
Crystal system	monoclinic	Absorption coefficient	0.089 mm^{-1}
Space group	P21/c	Crystal size, mm	0.32x0.31x0.13
Unit cell dimensions	a = 25.808(2) Å	Reflections collected	112990
	b = 19.667(2) Å	Independent reflections	24137
	c = 25.792(2) Å	Final R indices	R_1 = 0.0476
	α = 90°		wR_2 = 0.0663
	β = 93.206(7)°	R indices (all data)	R_1 = 0.2012
	γ = 90°		wR_2 = 0.0915

The crystal lattice contains five THF molecules per molecule of the tetramer. Four of them are bound by urea groups of the tetramer, so all hydrogen bonds in the lattice occur

between urea hydrogens and THF molecules; no intra- or intermolecular hydrogen bonds "tetramer-to-tetramer" are present. The fifth THF molecule is located between tetramer molecules.

Each tetramer molecule is folded into a nearly-cubic compact box with THF molecules laying between the phenyl rings of the opposite sides of this "box".

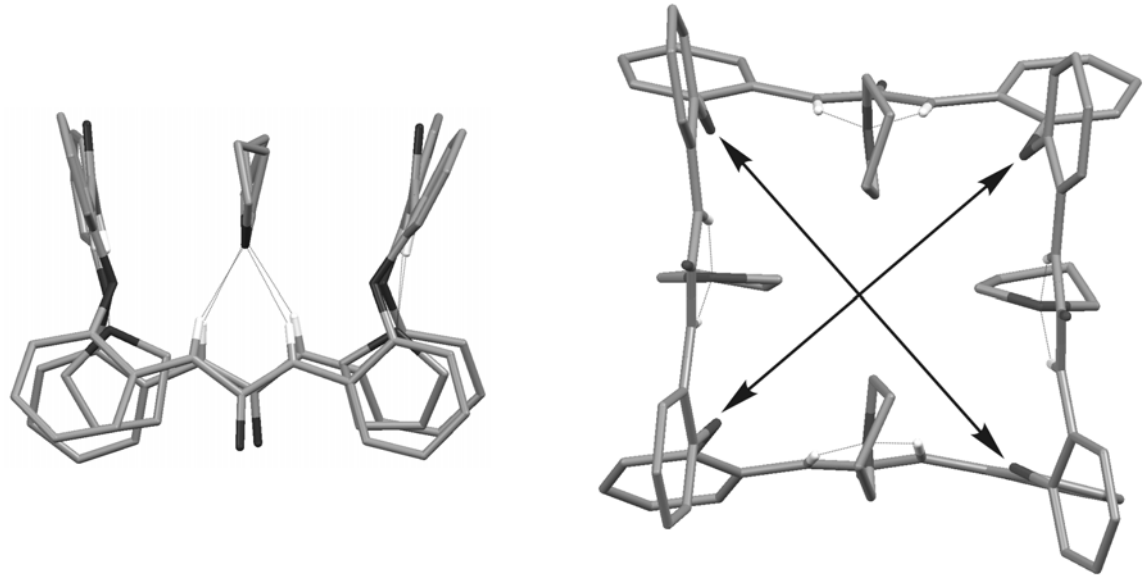


Figure 43. Side views of the tetramer molecule.

The urea groups are nearly coplanar with the neighbouring phenyl rings, while the angles between the planes of the phenyl rings in each diphenyl ether unit are in the range of 74 – 82°. The box-like conformation is possible due to the flexibility of these units.

The crystal cell contains two molecules with slightly different geometry. Therefore, there are two pairs of distances between two opposite urea carbons (N-**C**(O)-N): 7.443 – 7.458 and 7.802 – 7.428 Å. The corresponding diagonal distances between opposite diphenyl ether oxygens (9.095 – 8.152 and 8.539 – 8.848 Å), are presented by arrows and show that each single cycle is not exactly square.

The crystal cell contains 8 tetramer molecules arranged in two sheets and the corresponding number of THFs. Both sheets are shifted and molecules are not located directly in line and not exactly stapled. There is no linear arrangement within a sheet and no columnar arrangement is observed.

We could say that we observe a "complex" of the tetramer DDDD with 4 THF molecules in crystalline state, which is possible due to the high flexibility of the DDDD cycle and the compact packing of the molecules.

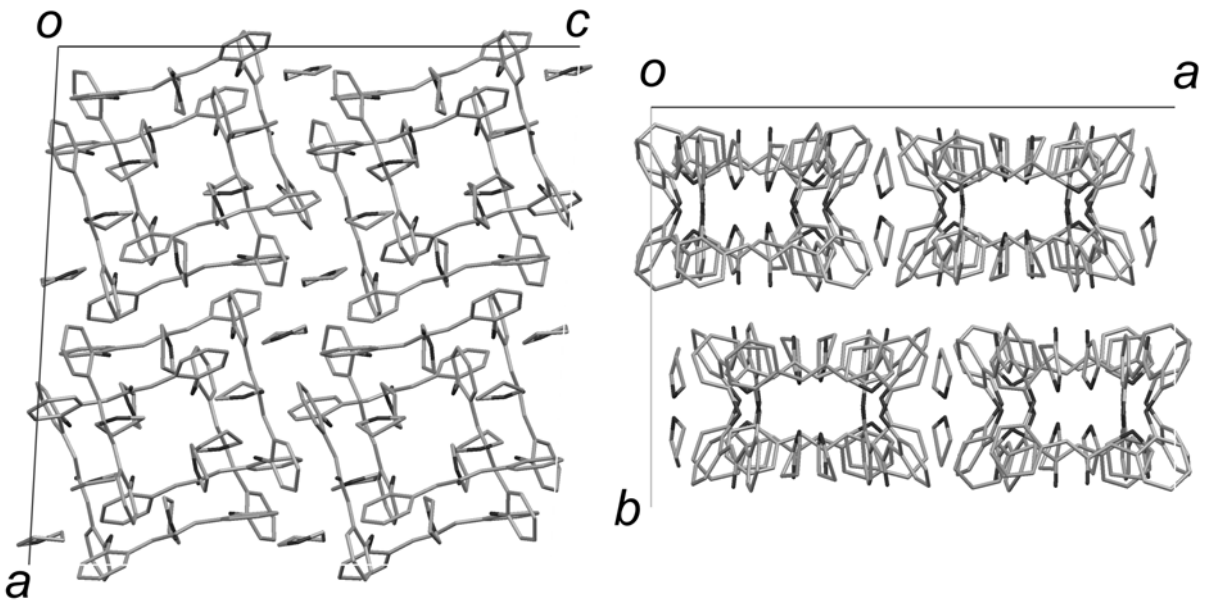


Figure 44. Arrangement of molecules in the crystal cell of the tetramer DDDD. Hydrogen atoms are omitted for clarity.

4.2.2 Crystal structures of the tetramer XXXD 50

Two different samples of single crystals of the tetramer XXXD were obtained. One sample was prepared by the slow evaporation of a solution in dichloromethane / acetonitrile and another one was obtained analogously from dichloromethane / ethanol. Both X-ray structures were solved.

In one case the unit cell contains two tetramer molecules and four molecules of acetonitrile. In the other case the cell contains four tetramers along with 20 molecules of ethanol. Crystal system and space group in both cases are different as well as other parameters (see table below).

Table 11. Selected crystal data and structures refinement for cyclic XXXD **50**.

	acetonitrile included	ethanol included
Empirical formula	$C_{89}H_{106}N_{10}O_8$	$C_{95}H_{130}N_8O_{13}$
Formula weight	1443.84	1592.07
Temperature	173(2) K	173(2) K
Crystal system	triclinic	monoclinic
Space group	P-1	P 21/c
Unit cell dimensions	a = 14.9282(13) Å	a = 29.7280(13) Å
	b = 18.9297(17) Å	b = 16.1350(5) Å
	c = 19.2836(16)Å	c = 20.0431(9)Å
	α = 61.351(6)°	α = 90°
	β = 86.758(7)°	β = 107.696(3)°
	γ = 71.553(7)°	γ = 90°
Volume	4506.7(7) $Å^3$	9159.0(6) $Å^3$
Z	2	4
Density (calculated)	1.064 Mg/m^3	1.155 Mg/m^3
Absorption coefficient	0.069 mm^{-1}	0.077 mm^{-1}
Crystal size, mm	0.49x0.43x0.36	0.48x0.26x0.24
Reflections collected	47861	73886
Independent reflections	16476	16079
Final R indices	R_1 = 0.0992	R_1 = 0.0873
	wR_2 = 0.2860	wR_2 = 0.2404
R indices (all data)	R_1 = 0.1361	R_1 = 0.1171
	wR_2 = 0.3104	wR_2 = 0.2593

Despite the different arrangement of molecules in the cells, the skeletons of a single molecule in both cases adopt a highly similar conformation (see figure below). We see a strongly folded cyclic molecule with a conformation obviously determined by intramolecular hydrogen bonding. The root mean square deviation (rms or rmsd value) is 0.47 Å for the skeleton (all heavy atoms excluding the *tert*-butyl groups and the methyl groups attached to the xanthene).

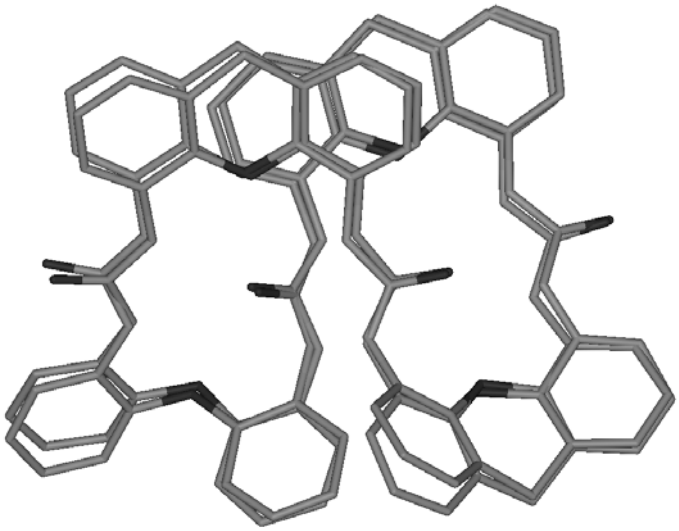


Figure 45. Superimposition of the molecule skeletons from the two different X-ray structures of the tetramer XXXD. Hydrogen atoms, methyl and *tert*-butyl groups as well as solvent molecules are omitted for clarity.

However, when we have a look on the structures in which the solvent molecules and hydrogen bonding patterns are shown, we observe distinct differences.

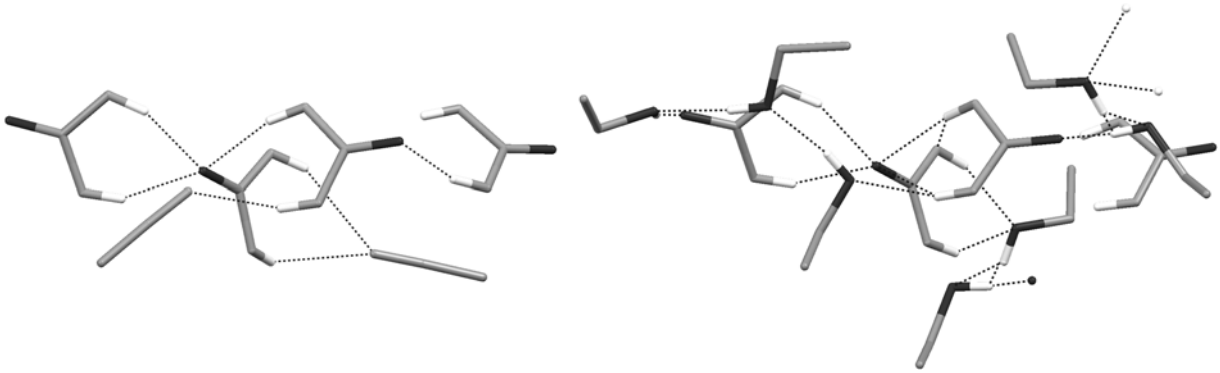


Figure 46. The urea groups of the trimer molecules surrounded by solvent molecules with all hydrogen bonds. Left view: acetonitrile as the solvent, right view: ethanol as the solvent.

While acetonitrile is able to accept hydrogen bonds with its nitrogen atom, ethanol is able both to donate and to accept them. Therefore ethanol forms a network of hydrogen bonds, which interconnects the tetramer molecules in the lattice and strengthens it. Due to close proximity and direction of hydrogen bond donors and acceptors it also is highly possible, that some weaker interactions exist beside the defined hydrogen bonds (bonds shown by dashed lines were defined by the *Mercury v. 1.41*[46]).

Remarkably, despite the different bonding properties of both solvents, the conformation of the tetramer molecule and the arrangement of intramolecular H-bonds

[46] Mercury: visualization and analysis of crystal structures. C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453-457.

remains stable and is only slightly changed. On the other hand in case of the entirely "flexible" tetramer DDDD no intramolecular bonds were built and all urea hydrogens are bound to molecules of THF.

Therefore we can confirm again, that the presence of the rigid xanthene units with their bulky substituents preserve intramolecular hydrogen bonds by hindering them from solvation. (see also 3.4).

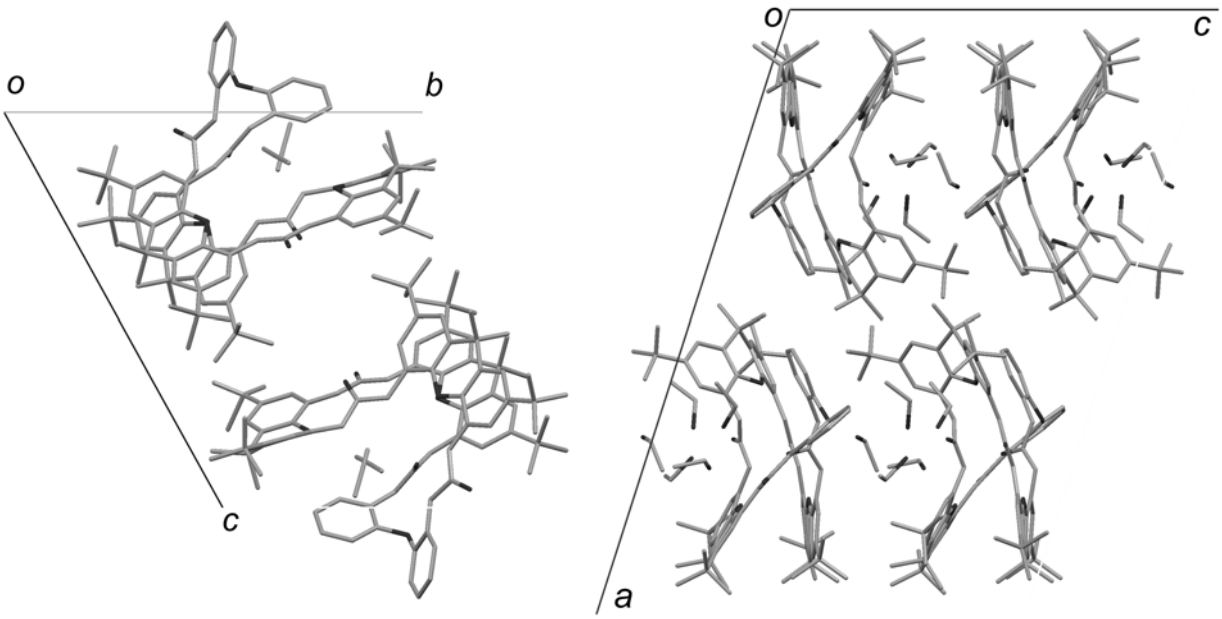


Figure 47. Crystal cells of two different single crystals of the XXXD tetramer (left view: with acetonitrile, seen along *a* axis; right view: with ethanol, seen along *b* axis). Hydrogen atoms are omitted for clarity.

4.3 Complexation properties of tetramers

The difference in physical properties between the tetramers is much more significant than for trimers. Limited or extremely low solubility of the compounds in NMR solvents made measurements difficult. Moreover, several tetramers do not produce a clear spectrum at room temperature even in DMSO-d_6. This all together made a direct and accurate comparison of anion binding abilities of tetramers difficult.

In this subchapter we survey the general complexation properties of the compounds by NMR and at the end of the subchapter we attempt to compare their affinity towards chloride under the same conditions. This becomes possible at 120°C in DMSO-d_6 where all tetramers are soluble and produce a sharp spectrum with and without the TBA chloride.

4.3.1 Tetramer XXXX 38

As described in subchapter 2.3, the tetramer consisting of xanthene units is separated with yields up to 25% after the one-step reaction of the diamine and *p*-nitrochloroformate (or triphosgene) in the presence of base. Unfortunately, the tetramer XXXX is either low soluble or completely insoluble in the majority of organic solvents, what makes NMR studies difficult.

Measurements in DMSO-d_6 were performed at the beginning of the studies. The tetramer is insoluble in this solvent at 25°C, but the solubility increases with the temperature and is virtually unlimited at 120°, what allows evaluation of its properties towards anions.

In all cases the tetramer shows a simple spectrum with one singlet for urea protons, two meta-coupled doublets for the protons of the xanthene unit, a singlet for methyl groups and a singlet for *tert*-butyls, all in the expected ratio.

In the presence of anions mainly a downfield shift of the urea signal is observed. The shifts of other signals are far less significant, reaching maximum 0.03 ppm. Addition of a salt stabilizes the solution of the tetramer upon cooling and the compound precipitates[47] several minutes or hours after being cooled, while the pure compound precipitates immediately. Signals on the ^{1}H NMR of such an "undercooled" solution are similar to those at high temperature (the relative position and amount of signals remains unchanged, while the absolute shift values lower upon cooling).

Downfield shifts of the signal for urea protons interacting with TBA salts in DMSO-d_6 solution are summarized in table below. As can be concluded from the data, the position of the urea singlet is most strongly affected by the addition of TBA chloride, where we observe an upfield shift of 1.02 ppm. Bromide produces a comparatively small shift of only 0.19 ppm, while the effect of iodide is marginal. Next effective acceptors of hydrogen bonds are dihydrogen phosphate and acetate with shifts of 0.39 and 0.27 ppm, respectively. Salt of squaric acid also produces a remarkable shift of 0.33 ppm, but in this case we deal with another cation (triethylammonium). Other anions have only limited influence on the signal of urea protons, producing shifts of 0.08 – 0.16 ppm.

[47] The precipitate consists of pure tetramer; TBA salt remains in solution.

Table 12. Influence of different salts on the signal of the urea proton in the NMR spectrum of XXXX (DMSO-d_6, 120°C).

Anion	Urea signal, ppm	Shift of the signal, ppm
without anion	8.66	-
chloride	9.69	1.02
bromide	8.85	0.19
iodide	8.74	0.08
hydrogen sulphate	8.76	0.10
trifluoroborate	8.74	0.08
dihydrogen phosphate	9.05	0.39
acetate	8.93[a]	0.27
trifluoroacetate	8.82	0.16
squarate[b]	8.99	0.33

[a]broad singlet; [b]triethylammonium salt.

4.3.2 Tetramer XXXD 50

The XXXD cyclic tetraurea has a better solubility in common solvents, but unfortunately not in DMSO-d_6. It is possible to get an interpretable spectrum only at temperatures higher than 80°C. The compound is soluble in THF-d_8 at 25°C, but the spectrum shows only several broad peaks which are impossible to interprete. The similar picture is observed at temperatures up to 55°C as well. The spectrum of the tetramer in the $CDCl_3$ is even more unclear and broad. However, it was found that the spectra both in THF-d_8 and $CDCl_3$ at room temperature become clear upon addition of tetrabutylammonium salts, what allows the evaluation of the tetramer's properties towards anions.

The sharp spectrum of the XXXD tetramer (in THF-d_8 in the presence of TBA salt) contains signals which are in agreement with dynamic C_{2v} symmetry. Four singlets for urea protons appear at low field; then four signals for the aromatic protons appear at 7.8 – 8.2 ppm (see figure below; aromatic protons neighbouring the urea groups; one doublet for the protons of D-unit and three singlets for the protons of X-units). The rest of the signals of the aromatic protons appears between 6.5 and 7 ppm.

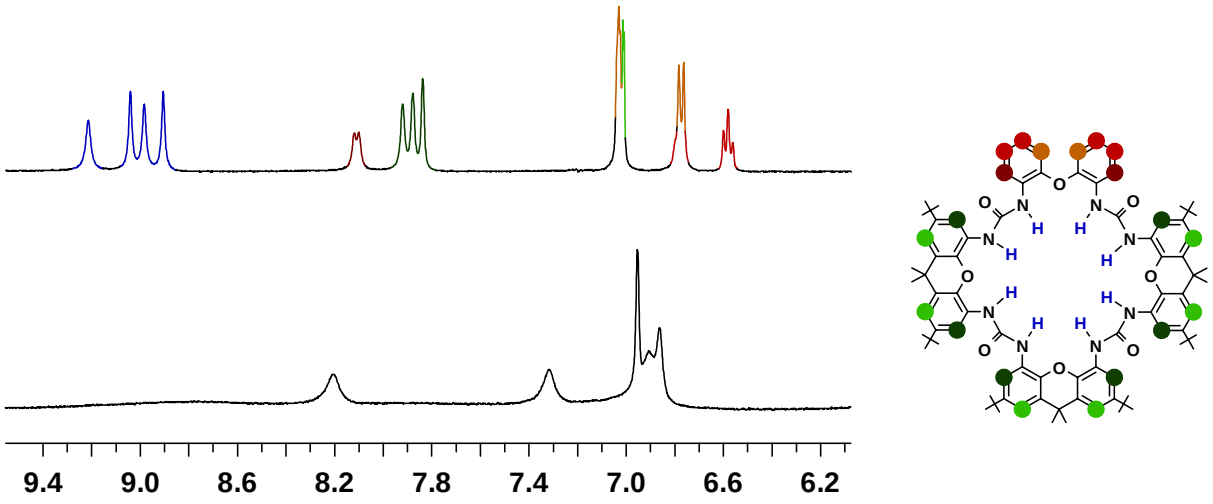


Figure 48. Upper view: the lowfield part of the XXXD spectrum in THF-d_8 with excess of TBA chloride; lower view: the same without salt.

The region where signals of alkyl residues typically appear (1 – 2 ppm) is hardly readable due to the overlap of the signals with peaks of butyl chains of the TBA salt. However, comparing different spectra we could conclude, that signals of xanthene methyl groups appear as two broad singlets (with 6 and 12 protons respectively), and the *tert*-butyls are present as three realtively sharp singlets with 18 protons each.

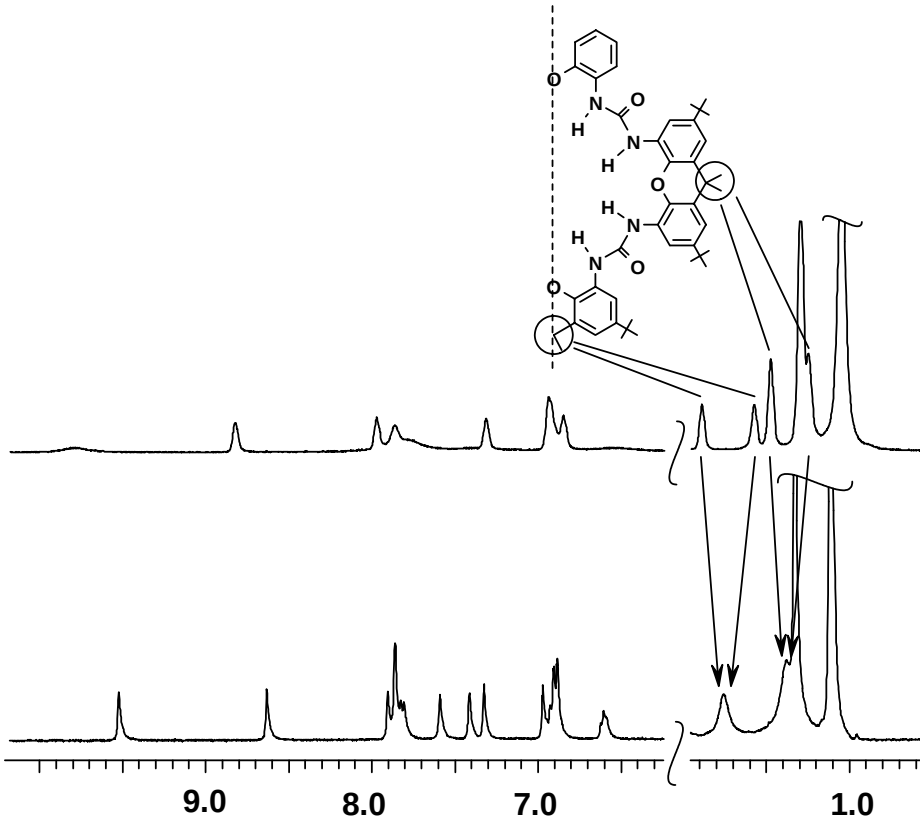


Figure 49. Spectra of XXXD in DMSO-d_6 at 40°C (upper view) and at 120°C (lower view).

Unusually, shape and number of these signals depend very much on the conditions (solvent, temperature, addition of salts). For example, there are two pairs of signals for xanthene methyls (one pair with three protons per signal and one with six per signal) in DMSO-d_6 at 40°C, while at 120°C two broad singlets appear instead (in the lowfield area the amount of aromatic and urea signals increases and these signals also sharpen significantly; the whole spectrum gets more detailed look; see figure below).

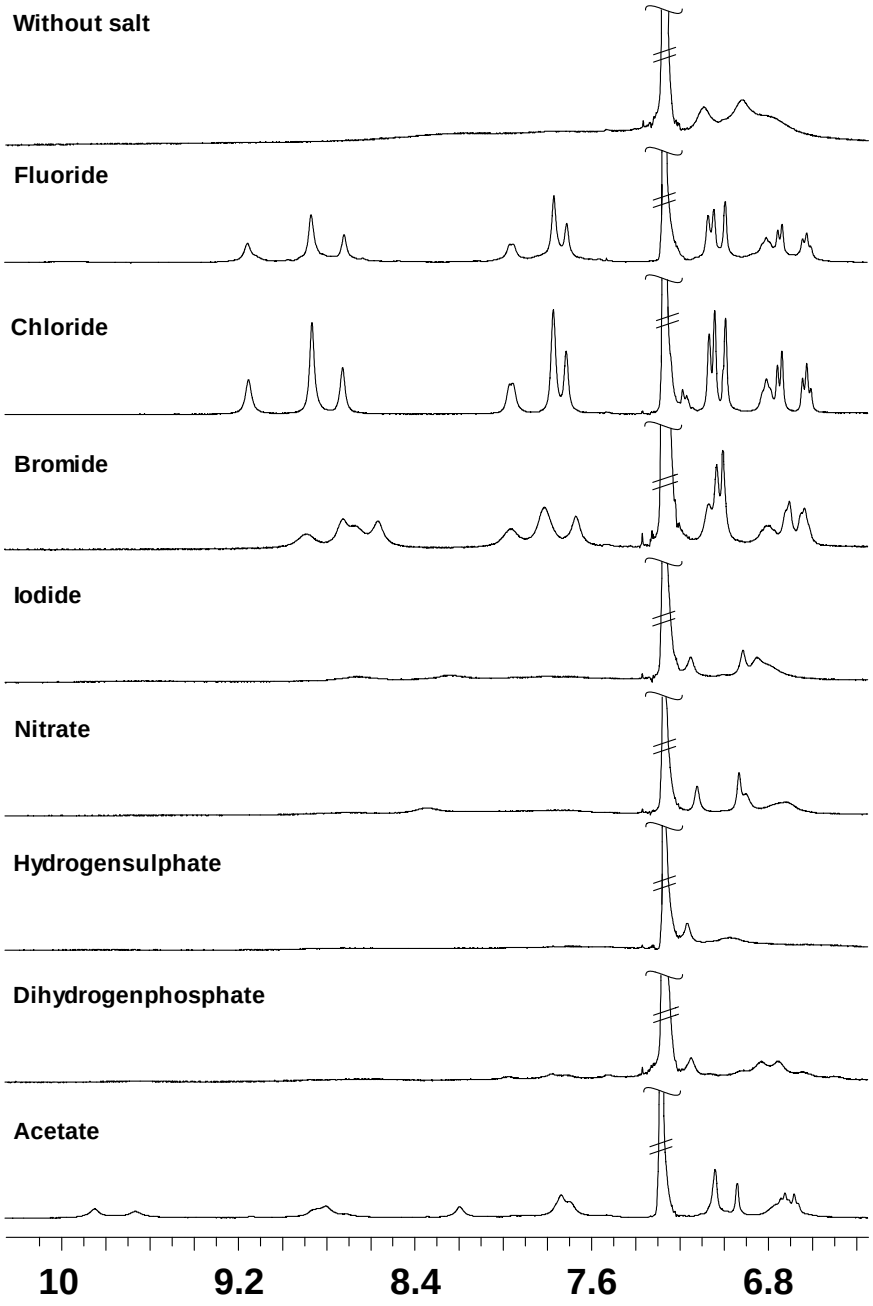


Figure 50. Interaction of the XXXD tetramer with selected anions (^{1}H NMR 400 MHz, $CDCl_3$, 25°C, *c* = 0.1 mM).

The evaluation of the interaction with different anions was performed in $CDCl_3$.

The interaction with halides was checked in the usual way. Chloride has the strongest influence on the spectrum, making the initially broad and insignificant spectrum clear. Bromide also has a "cleaning" effect on the spectrum, however peaks remain broad and far less defined than in case of TBAC. Iodide have only a weak influence on the spectrum, changing only the shape of the broad "hills". This is also true for the TBA nitrate and hydrogensulphate.

Dihydrogen phosphate also causes only a minor changes in the spectrum of the tetramer, similar to iodide. The strongest downfield shift was observed in the spectrum with TBA acetate, although all peaks are broad. The interaction with fluoride is similar to that with chloride (see picture below).

Obviously, only chloride and fluoride are able to destroy the intramolecular hydrogen bonds effectively and to form an associate, stable on the NMR timescale.

4.3.3 Tetramer XDXD 52

The compound is soluble in DMSO-d_6 and produces a clear spectrum which corresponds to the time-averaged D_{2h} symmetry and contains two signals for urea protons, two for aromatic protons of the xanthene skeleton, four for aromatic protons of diphenyl units, a singlet for methyl protons and a singlet for *tert*-butyl groups.

The spectrum remains sharp upon addition of halides and we observe several downfield shifted signals in the case of bromide and chloride (the shift is more significant for chloride). In case of fluoride we observe perceptible shifts and a rearrangement of other signals in the lowfield area, what indicates changes in the magnetical environment of these protons (i. e. conformational changes). Moreover, two signals of the urea protons are not only strongly shifted downfields, but also appear as four signals (see Fig.51).[48]

[48] In case of the fluoride complex more than one fluoride anion is bound. When we mixed ligand and anion in approximately 1:1 ratio, spectrum was completely different, looking similar to that with tetrabutylammonium chloride, but broadened.

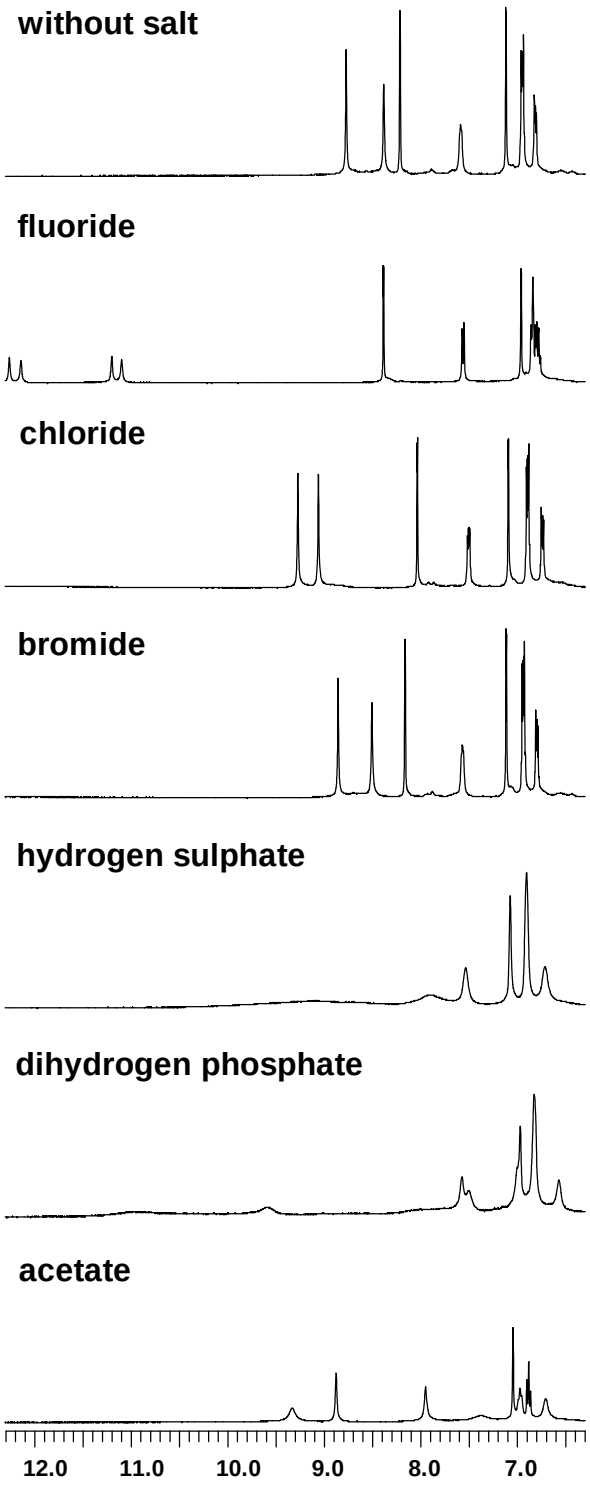


Figure 51. Interaction of the tetramer **52** with selected anions (400 MHz, DMSO-d_6, 25°C, c = 0.1 mM).

Addition of nitrate and iodide leaves the spectrum unchanged. Addition of acetate resulted in a broaded spectrum. Signals of urea protons as well as diphenyl ether protons are affected especially strongly. Addition of hydrogen sulphate and dihydrogen phosphate broadens the spectra so strong, that the lowfield area cannot be interpreted anymore. Signals of xanthene methyl and *tert*-butyl groups remain in all cases sharp and show no splitting or broadening. In case of strong visible interaction with an anion the *tert*-butyl peak also shifts 0.05 ppm upfields; the methyl peak overlaps with the signals of the tetrabutyl cation and is not always clearly visible.

4.3.4 Tetramer XXDD 51

In contrast to XDXD this tetramer produced an unclear spectrum in DMSO-d_6. However upon slow stepwise addition of chloride the initially broad spectrum converts to a sharp one and after the ratio 1:1 is reached no further changes are observed.

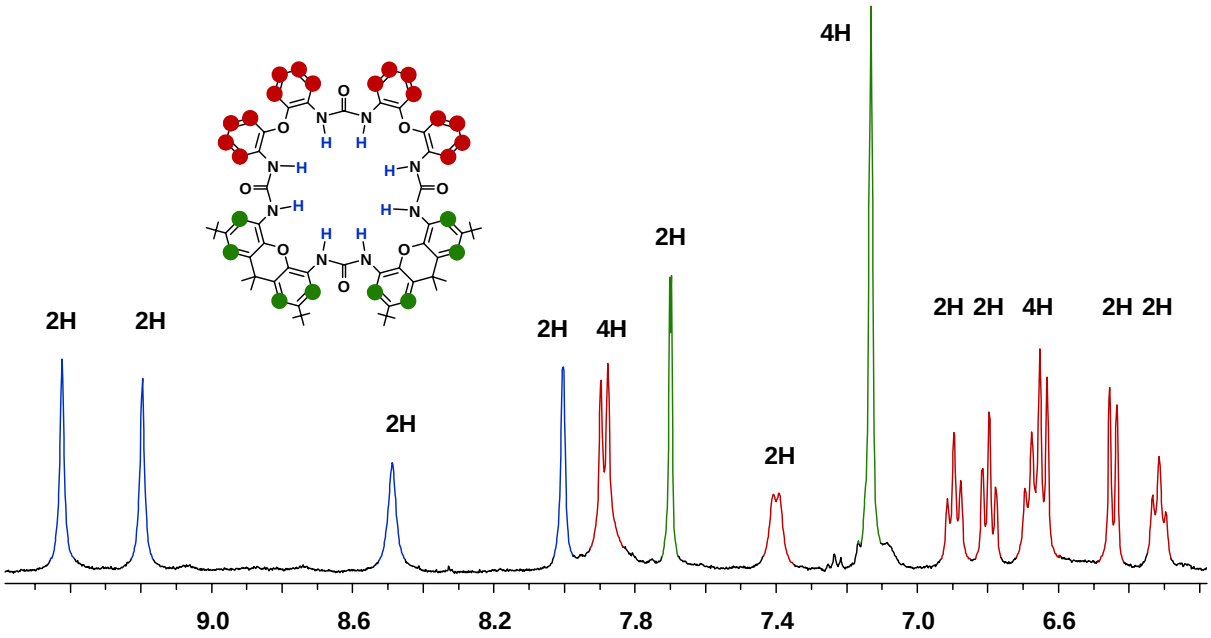


Figure 52. The ^{1}H NMR spectrum of the solution of tetramer **51** mixed with tetrabutylammonium chloride (DMSO-d_6, 25°C).

The spectrum contains 4 singlets for urea protons, 8 signals for diphenyl ether aromatic protons, 4 for aromatic protons of the xanthene skeleton. Unfortunately alkyl signals are not visible due to their overlapping with signals of tetrabutyl. They appear though on the spectrum of the pure compound as three broad singlets (i.e. one for methyl groups and two for *tert*-butyls). Overall such picture corresponds to time-averaged C_{2v} symmetry.

Unfortunately, chloride was the only anion producing a sharp, interpretable spectrum. Bromide gave completely unreadable ^{1}H NMR looking nearly identical to that without salt (see figure below). Hydrogen sulphate shows single broad peaks which are impossible to interprete. Dihydrogen phosphate and fluoride show already some sharp peaks, but at the same time other peaks are not visible at all. However in these two cases we can observe some broad signals at low field which can be attributed to the complexed urea protons. Acetate shows a picture similar to that with hydrogen sulphate. Therefore it is especially difficult to track the binding ability and conformational properties of the XXDD tetramer by NMR.

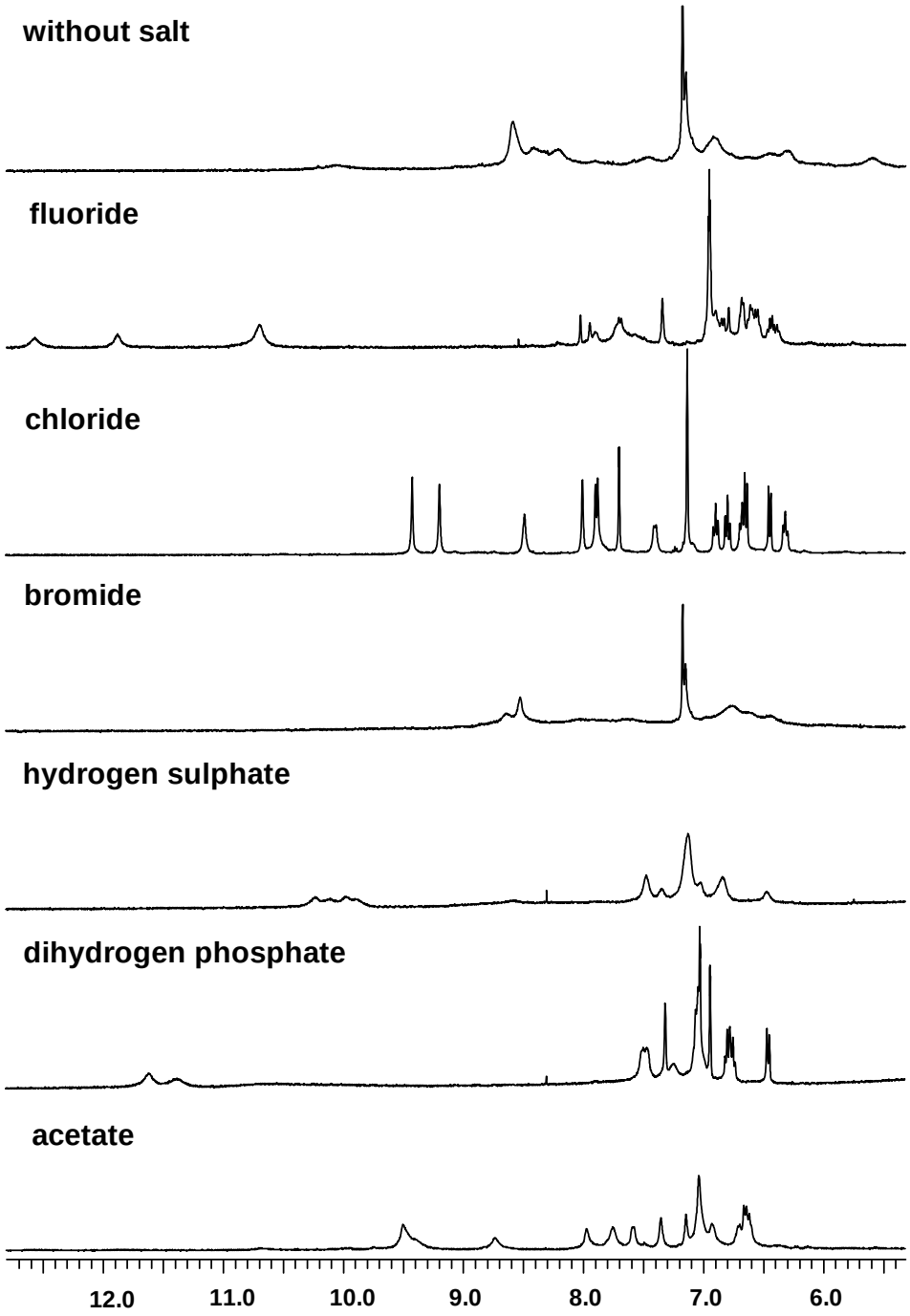


Figure 53. Interaction of the tetramer **51** with selected anions (400 MHz, DMSO-d_6, 25°C, c = 0.1 mM).

4.3.5 Tetramer XDDD 53

The compound **53** is easily soluble in DMSO-d_6 and produces a comparatively clear ^{1}H NMR spectrum, where only the signal for the urea protons and for the neighbouring protons of the aromatic rings are broad. The amount and arrangement of the signals are in

agreement with the dynamic C_{2v} symmetry (see figure below). At low field we observe four signals for the urea protons, two signals for the xanthene aromatic protons and 12 signals for the aromatic protons of diphenyl ether units. At high field we observe two sharp singlets for xanthene methyls and *tert*-butyls.

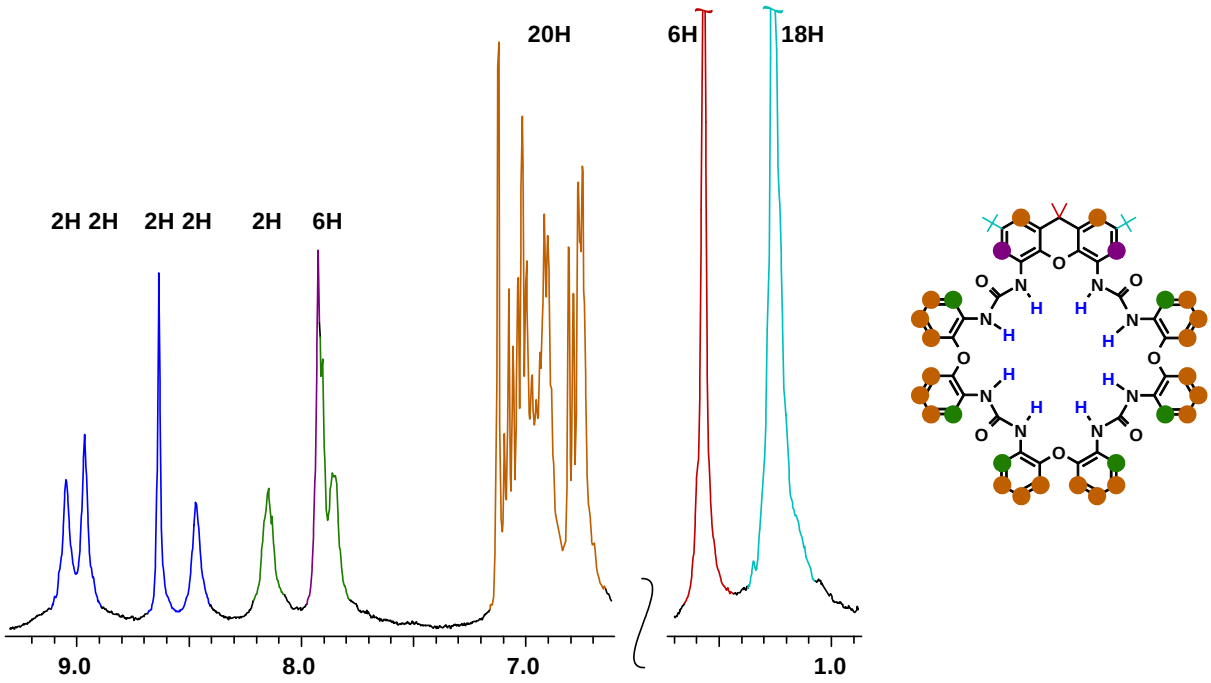


Figure 54. The ^{1}H NMR spectrum of the solution of tetramer **53** in DMSO-d_6 at 25°C).

The tetramer **53** also has quite clear spectra in mixtures with all checked tetrabutylammonium salts (see figure below). Additionally we observe comparatively reach diversity in NMR response to the addition of different anions to the tetramer solution.

Fluoride causes the most prominent changes. The whole spectum losts its broadening, we could easily observe ortho-coupling of the signals for the corresponding aromatic protons. Signals of the urea protons appear between 10.5 and 12.5 ppm. Moreover, these signals have complicated structure and appear as broad multiplets.

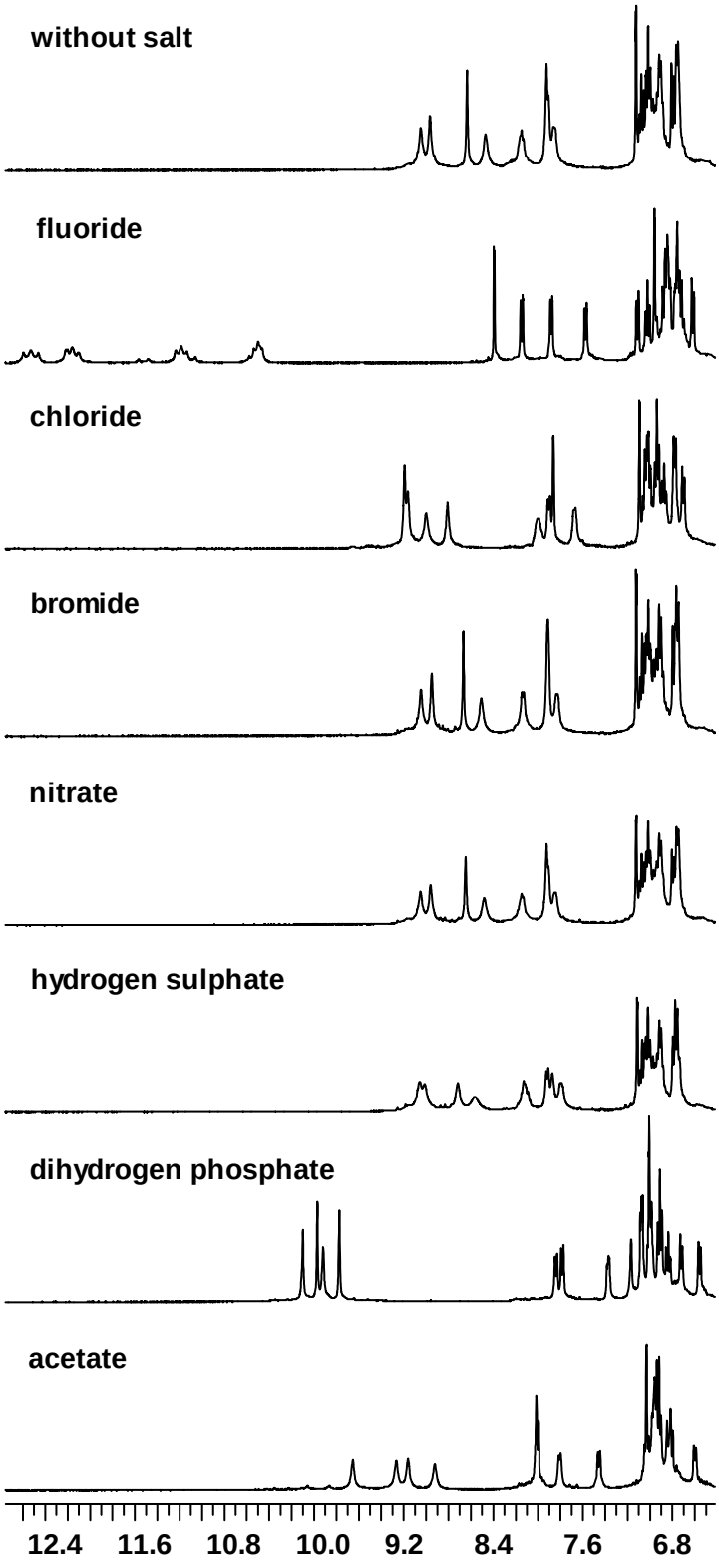


Figure 55. Interaction of the tetramer **53** with selected anions (400 MHz, DMSO-d_6, 25°C, c = 0.1 mM).

Chloride causes not very pronounced shift of the signals for the urea and the neighbouring aromatic protons. Some urea singlets also change their relative positions. Bromide causes no visible effect on the spectrum, as well as nitrate. Addition of hydrogen sulphate makes signals for the urea and the neighbouring aromatic protons slightly broader, but causes only unsignificant changes of their position.

Dihydrogen phosphate has strongly pronounced effect on the signals of the tetramer hydrogen atoms. All four urea singlets appear sharp and close to each other on the small section between 9.7 and 10.1 ppm. Significant rearrangement of the aromatic protons signals is observed as well. Such pronounced effect is especially interesting in connection with such an anion as dihydrogen phosphate, which could be present in the solution also as mono- and not hydrogenated form, and all these species are able to interact with our host molecule. However we got a sharp spectrum instead of

uninterpretable broad one in the case of other tetramers.

Addition of tetrabutylammonium acetate also changes the spectrum of the tetramer significantly. Although urea signals are still slightly broaded, they are shifted downfields and appear between 8.8 and 9.7 ppm. Signals of the aromatic protons are sharpened and a slight rearrangement of them is observed. Overall the spectral changes are less pronounced than in cases of fluoride and dihydrogen phosphate, but stronger than in the case of chloride.

4.3.6 Tetramer DDDD 39

In the spectra of tetramer DDDD only four signals are present: singlet for the urea protons, two pseudo-doublets and two pseudo-triplets for the aromatic protons of diphenyl ether units, what corresponds to a time-averaged D_{4h} symmetry. All signals are relatively sharp in comparison to other tetramers, but they are slightly broaden in comparison to the smaller cycles based on diphenyl ether unit (see also Fig. 17), especially the doublet for the aromatic protons neighbouring urea groups.

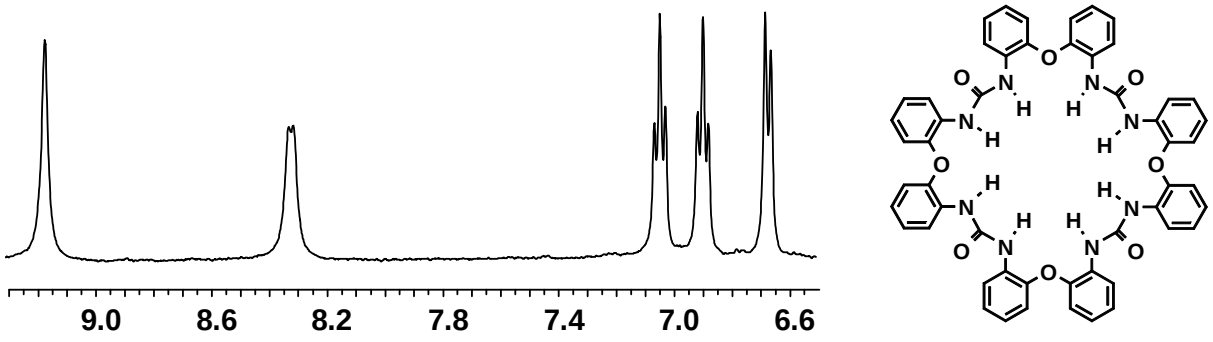


Figure 56. The ^{1}H NMR spectrum of the solution of tetramer **39** in DMSO-d_6 at 25°C.

All salts with the exception of fluoride do not change the number of and the general arrangement of signals. Addition of some anions causes a downfield shift of the urea protons signal and an upfield shift of the neighbouring aromatic protons doublet, while other signals for aromatic protons remain intact or undergo insignificant upfield shift.

Fluoride is the only anion causing strong changes of the NMR spectrum. The urea signal is observed as a broad singlet at 11 ppm. However the signal of the neighbouring aromatic proton appears now as three doublets with different integral intensity, being strongly upfield shifted in comparison with uncomplexed DDDD.

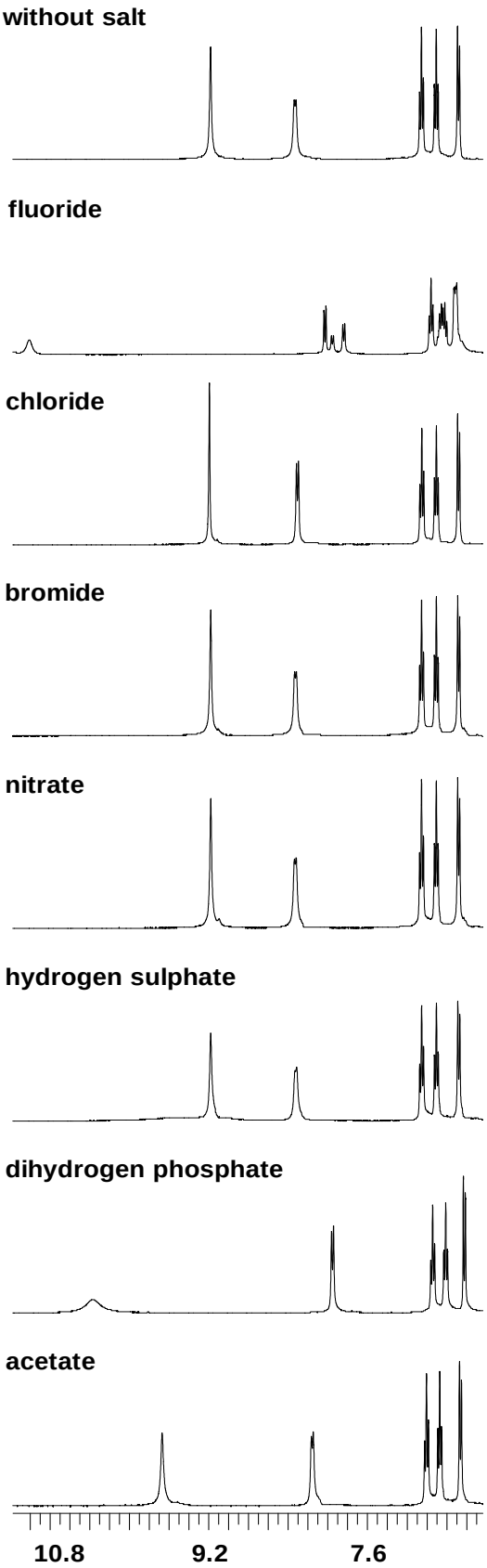


Figure 57. Interaction of the tetramer **53** with selected anions (400 MHz, DMSO-d_6, 25°C, c = 0.1 mM).

The ratio between these signals changes with the addition of fluoride, and these changes continue even in the presence of a twenty-fold and more excess of salt. The observation is true also for other aromatic signals, which change its number and intensity.

In contrast to all other tetramers chloride has only marginal influence on the tetramer's spectrum. The urea signal and the neighbouring aromatic protons signal change their positions only by as low as 0.02 ppm. Effect of the addition of bromide is absent at all. Nitrate and hydrogen sulphate cause no effect as well.

Dihydrogen phosphate is the second strongly influencing anion. Broad signals of the urea protons were shifted strongly to 10.4 ppm., while the next signal of the aromatic protons shifts upfields from 8.32 to 7.95 ppm. Three other aromatic signals shift in the same direction by 0.06 – 0.13 ppm.

The influence caused by the adddition of TBA acetate has similar character, but is weaker. The urea signal shifted from 9.17 to 9.66 ppm, the next aromatic signal from 8.32 to 8.15 ppm. Other aromatic signals change their position insignificantly (up to 0.05 ppm upfields).

4.3.7 Comparison of complexation properties of the tetramers

As has been shown, substitution of a single unit in the tetramer skeleton by another one leads to significant changes of the physical properties and the NMR spectrum of the compound. Some of the substances have sharp spectra at the room temperature in certain solvent in the presence of certain salt, while others show only broad peaks and there could be also a tetramer which is not soluble under these conditions at all.

In order to evaluate and compare binding abilities of our tetramers side-by-side, we needed common conditions to get a sharp spectrum of every single compound both alone and also in the presence of some salt. This was possible in the highly polar DMSO-d_6 at 120°C for all tetramers, where comparative measurements were performed. TBA chloride was chosen as the salt for these studies.

Effects caused by the chloride on the ^{1}H NMR spectrum of **tetramer XXXX 38** were already described in subchapter 4.3.1: the singlet corresponding to the urea protons strongly shifts downfields from 8.66 to 9.69 ppm, while two signals of the aromatic protons shift slightly upfields (7.86 – 7.69 and 7.19 – 7.11 ppm, respectively).

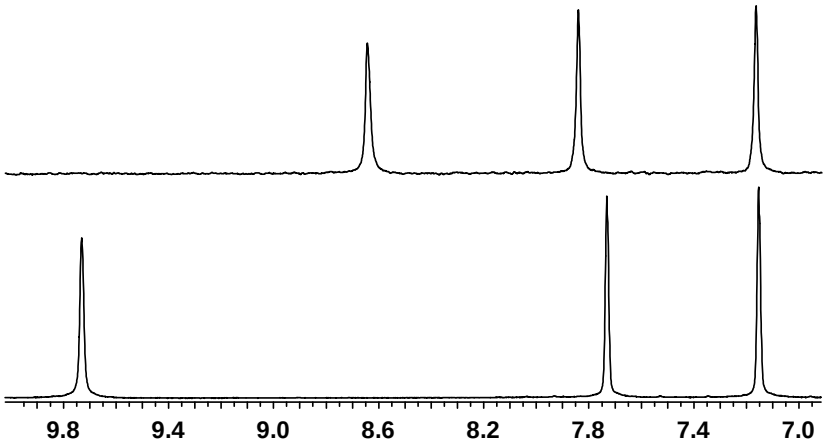


Figure 58. Effect of the interaction of the tetramer XXXX with TBA chloride at 120°C (upper view: without salt added), on the low field part of the ^{1}H NMR spectrum.

Alkyl signals were only very slightly affected (methyl and tert-butyl signals were shifted upfield by only 0.02 and 0.05 ppm respectively).

The response of the **tetramer XXXD 50** to the addition of TBA chloride has a different character. In the spectrum of the pure compound signals of the urea protons are distributed in a wide range between 7.8 and 9.51 ppm. Such a pronouncing difference of the signals for the urea proton may be due to strong intramolecular hydrogen bonding, what is actually the case for the XXXD (see its X-ray structures in subchapter 4.2.2).

Addition of the salt changes the pattern of the urea protons signals dramatically and all these singlets appear as the compact group of four peaks at 8.67-8.93 ppm. The same is true for signals of the adjacent aromatic protons, which appear at 7.63 – 7.81ppm. In general signals of the aromatic protons undergo significant shift (see figure below).

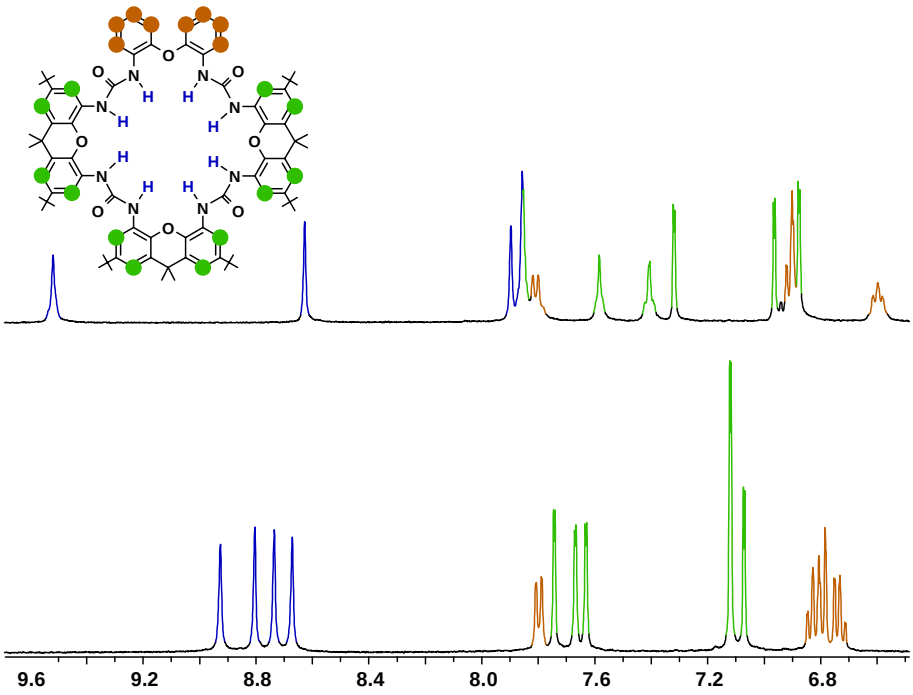


Figure 59. Effect of the interaction of the tetramer XXXD with TBA chloride at 120°C. Low field region (upper view: without salt added).

In contrast to the tetramer XXXX the alkyl signals of XXXD changed their pattern more significant. Two of three *tert*-butyl signals shifted downfields, the third remained almost on the same position at 3 ppm. The methyl signals remained broad and overlap with signals of tetrabutylammonium, the only visible is the upfield shift of on methyl signal ("6 protons").

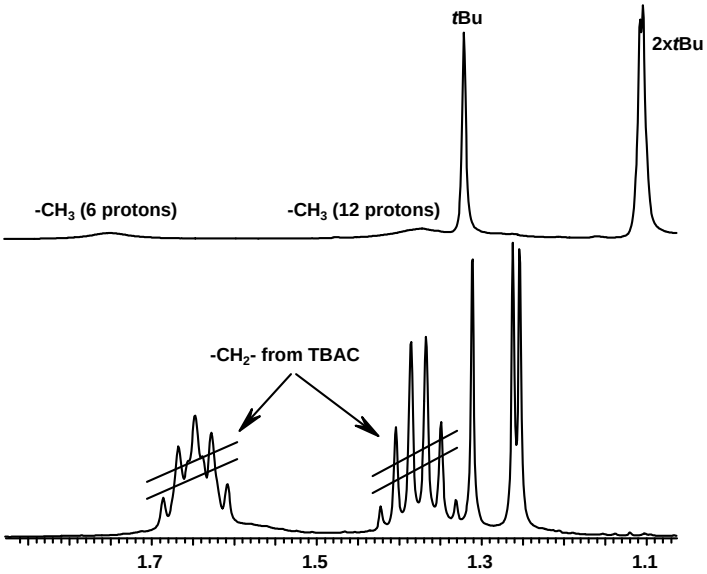


Figure 60. Effect of the interaction of the tetramer XXXD with TBA chloride at 120°C. High field region (upper view: without salt added).

Such a remarkable shift of almost all signals in the spectrum upon addition of the salt indicates significant changes in the conformation of the molecule.

The more flexible **tetramer XDXD 52** shows no significant shift of the signals, but they change their position in the same way as XXXX: urea signals shift downfields, other signals shift more or less strongly upfields. The signal for the methyl groups of xanthene units remains unaffected, the signal for the *tert*-butyls shifted by only 0.02 ppm downfields.

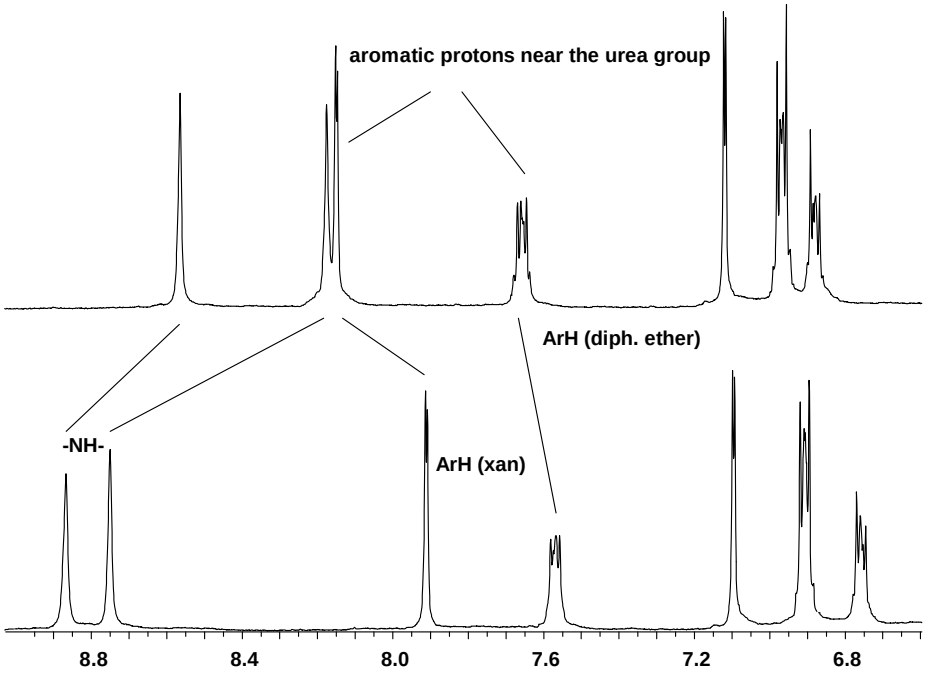


Figure 61. Effect of the interaction of the tetramer XDXD with TBA chloride at 120°C. High field region (upper view: without salt added).

Tetramer XXDD 51 has some broad peaks in its spectrum even at 120°C. The signals of the aromatic protons neighbouring to the urea group are affected. At the same time the signals of the urea protons are realtively sharp with exception of the singlet which appears strongly shifted downfields (9.25 ppm). After the addition of the TBA chloride spectrum was changed quite significantly. All signals were sharpened and the urea signals were shifted downfileds; the signals for the aromatic protons are shifted in different directions (see picture below.)

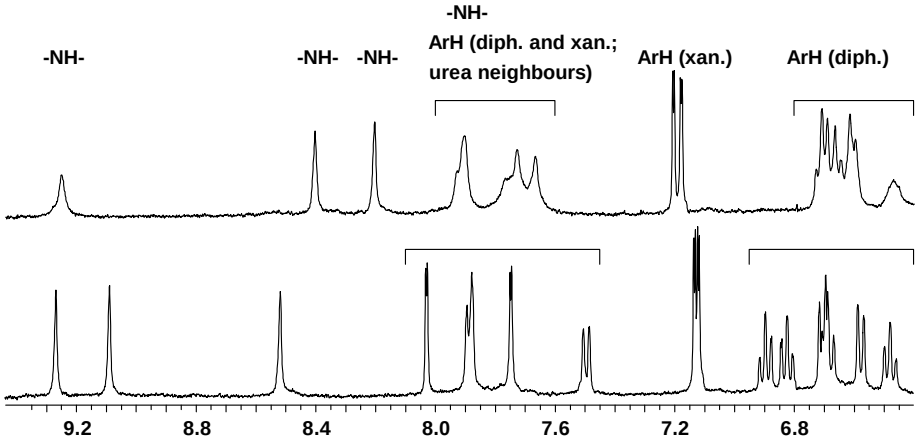


Figure 62. Effect of the interaction of the tetramer XXDD with TBA chloride at 120°C. High field region (upper view: without salt added).

Changes in the high field area are not so significant. The singlet for xanthene's methyl groups kept its position at 1.64 ppm. The two singlets for *tert*-butyls, which were observed at 1.29 and 1.31 ppm without salt, appear at 1.30 and 1.37 in the presence of TBA chloride.

Tetramer XDDD 53 shows a slightly different behaviour. All four signals for the urea protons were downfield shifted almost identically, so their relative position left almost unchanged. Simultaneously the signals of the aromatic protons adjacent to the urea functions undergo a noticeable shift. Other signals for the aromatic protons change their position and shape less significantly. No changes were observed in the lowfield area for the alkyl protons.

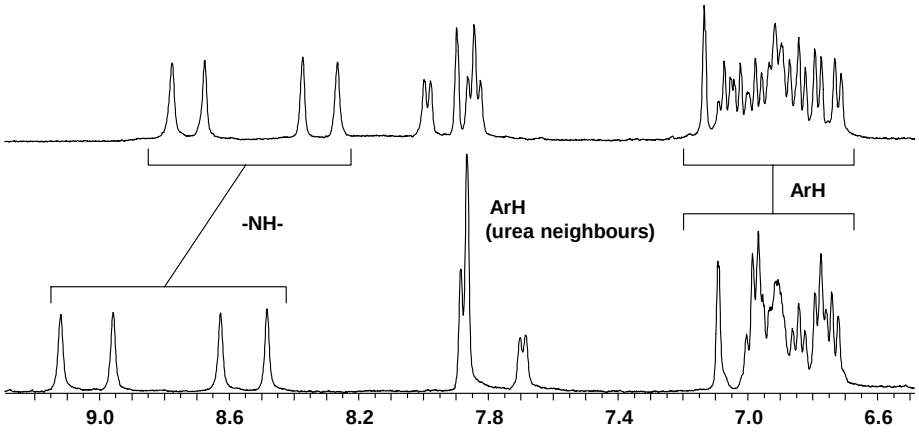


Figure 63. Effect of the interaction of the tetramer XDDD with TBA chloride at 120°C. High field region (upper view: without salt added).

Tetramer DDDD 39 shows the weakest changes in the spectrum among all six tetramers upon addition of the chloride. However this can be also explained by the unsufficient complementarity with the chloride anion, since the tetramer is known to show strong interaction with some other anions (see previous subchapter 4.3.6).

The urea protons signal shifts by 0.05 ppm downfield upon addition of TBA chloride. The neighbouring aromatic protons signal shifts upfields by 0.1 ppm; all other signals for the aromatic protons change their postion insignificantly by 0.01 – 0.02 ppm.

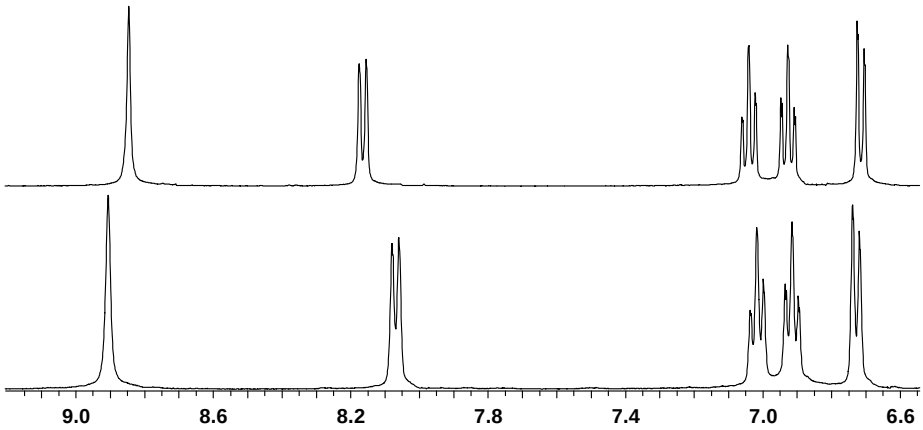


Figure 64. Effect of the interaction of the tetramer DDDD with TBA chloride at 120°C. High field region (upper view: without salt added).

Thus, we have surveyed all tetramers prepared by the combination of xanthene and diphenyl ether units. The compounds show quite different behaviour towards chloride addition, which is difficult to place in a row. In all cases more or less significant upfield shifts of the urea protons signals were observed, while the aromatic protons signals (especially those which neighbouring urea group) shift mostly upfields. This indicates a certain change in the time-averaged interaction or orientation of the urea group in the molecule.

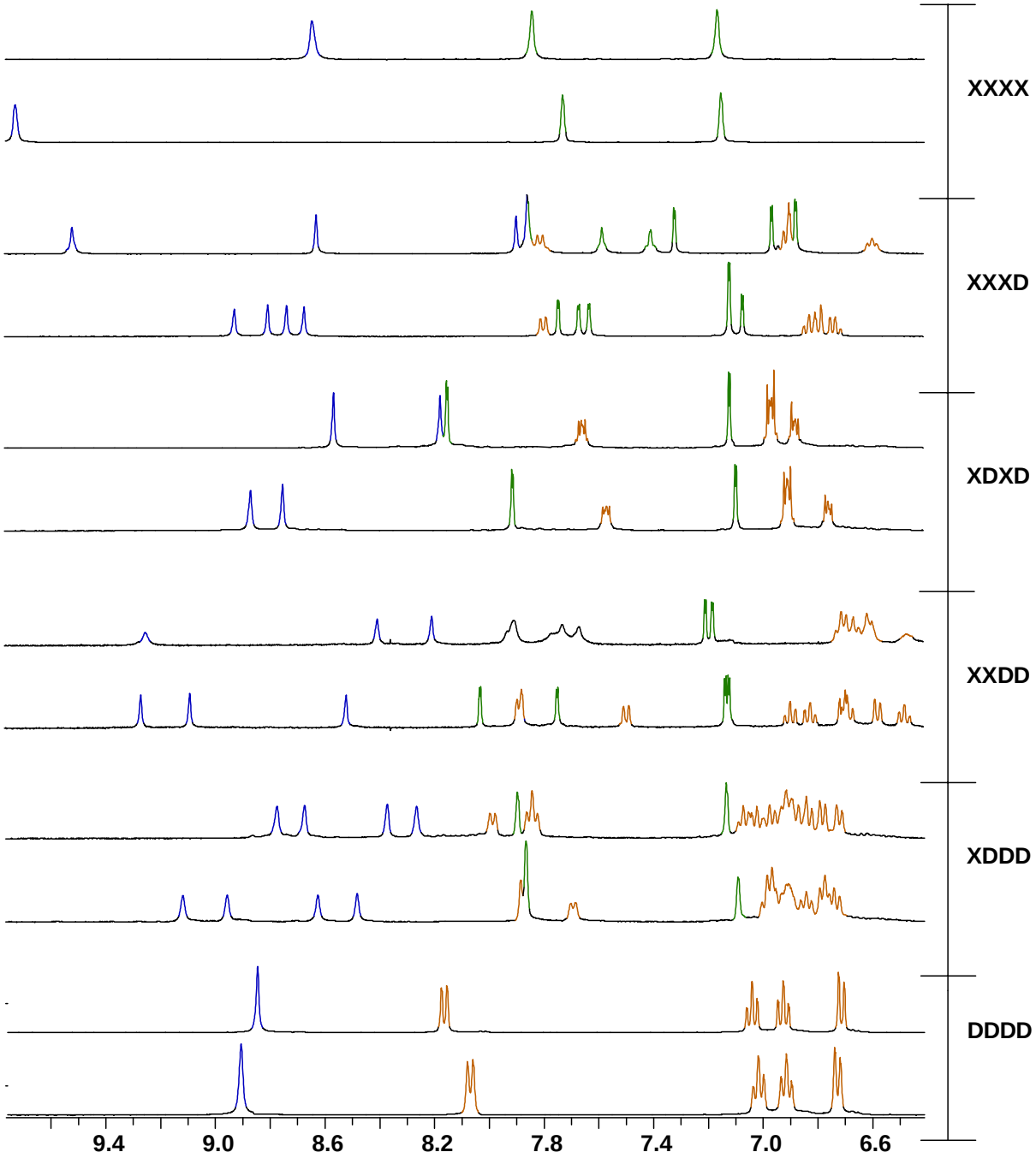


Figure 65. Summarized view of the spectra of all tetramers interacting with TBA chloride at 120°C in DMSO-d_6. Colored signals: blue for urea protons, green for xanthene aromatic protons, brown for diphenyl ether units protons.

Simultaneously, in some cases we observe only significant changes in the position of the urea proton signals, while the aromatic part of the spectrum remains more or less unchanged (for example XXXX, DDDD). In other cases we observe also pronounced rearrangement of the signals of the aromatic protons as well, what indicates changes in the conformation of the whole molecule.

The combined view of the NMR spectra of all tetramers in one picture is presented on the Fig. 65.

4.4 Conclusions

Six new cyclic tetraureas with all possible combinations of rigid xanthene and more flexible diphenyl ether units were synthesized and their conformational behaviour and complexation properties towards anions were evaluated by X-ray and ^{1}H NMR.

Although we did not succeed in obtaining single crystals of tetramer complexes with anions, NMR measurements showed the pronounced interactions with anions, which can be observed due to the significant shift of signals (especially for those of the urea protons), change of their shape or their broadening and also rearrangement of signals in the spectrum.

According to NMR and X-ray observations tetramers tend strongly to assume folded conformations stabilized by intramolecular hydrogen bonds. Even molecules of highly polar solvents hardly can compete with the system of these bonds, especially when dealing with the compound built with several rigid units with bulky alkyl substituents, such as XXXD or XXXX, which are soluble in DMSO-d_6 only at elevated temperature.

Anions also must compete with this intramolecular bonding in complexation. While the XXXX in the presence of chloride can stay dissolved at room temperature for less than an hour, the solution of XXXD with TBA chloride is stable after cooling. The more flexible tetramers are soluble in DMSO-d_6 without an addition of salts.

However with the increase of "flexibility" of our compounds we observe that intensity of their interaction with chloride decreases (as far as it is possible to follow by NMR). While XXXX tetramer demonstrates the strongest shift of the urea protons signal among all tetramers, the entirely "flexible" DDDD has a very weak response to the chloride addition. At the same time the tetramer DDDD has a quite pronouncing effect of addition of other anions at 25°C, for example acetate or dihydrogen phosphate. This may indicate the ability of the flexible DDDD to adjust its urea groups to the anions with a complicated non-spherical shape.

5 Cyclic hexamers

Synthesis of the oligourea cycles with the number of units more than four is of the great interest for possible application of them as anion receptors. The increased number of units implies not only additional urea groups and increased conformational freedom of the molecule, but also more wide possibilities for the tuning of the structure by introduction more or less “flexible” units.

We decided not to prepare cycles with five units at this moment and go directly for hexamers. The main reason for the decision was that we already had two different hexamers – XXXXXX and XXDXXD – prepared simultaneously with the corresponding trimers.

Combination of two of our units in a hexameric cycle produces 13 possible cyclic molecules. Although all these hexamers might be interesting as the potential anion receptors, this would take too much time and effort to prepare them all within the framework of this thesis. Therefore we decided to limit ourselves to the synthesis of selected molecules (see picture below).

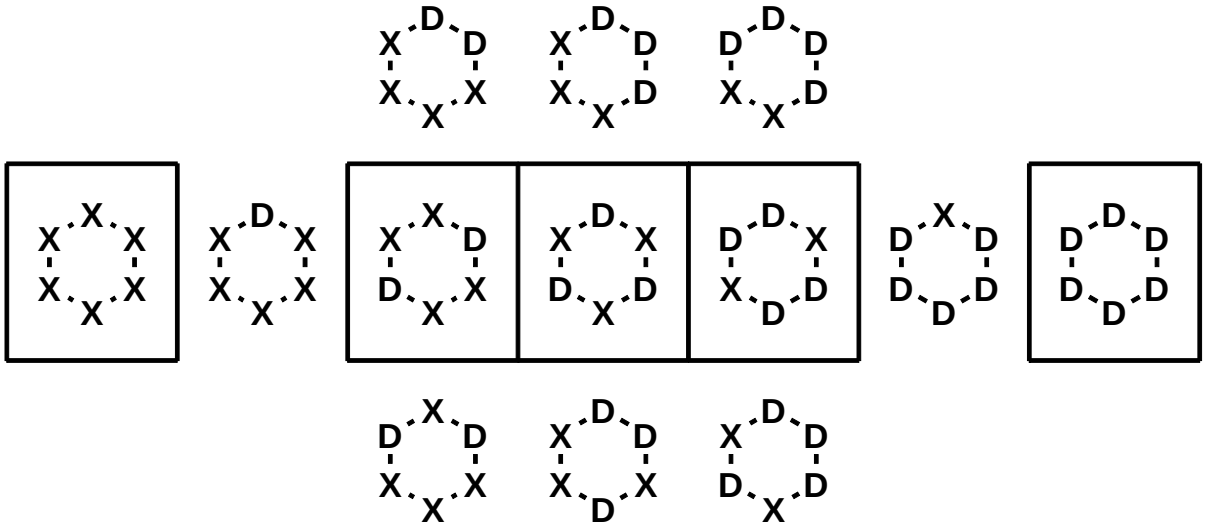


Figure 66. Hexamers that could be obtained by combination of the X and D units. Number of diphenyl ether units grows from left to right. Cycles selected for the synthesis are depicted in frames.

Beside of the hexamers consisting of exclusevely X or D units we decided to prepare compounds contained certain repeating sequences of units: “XXD”, “XD” and “XDD”.

Several approaches may be proposed for the synthesis of hexamers. The condensation from the single units can be applied only to the preparation of compounds consisting of only

one unit type (i.e. $[X]_6$ or $[D]_6$). However it is hardly possible to assemble all the six units in the necessary hexameric cycle due to the low probability of such reaction. Only traces of corresponding hexamers were sometimes detected by the mass-spectroscopy in the performed condensations of the basic units.

Ironically, the first hexamers were obtained by another method with an expected low probability. Hexamers XXXXXX and XXDXXD were obtained by the "2+1+2+1" cyclization with unexpectedly high yield together with the corresponding trimers or instead of them (see subchapters 3.1.1 and 3.1.5). In both cases combination of factors contributed to these unusual results, such as structural properties of the rigid cleft-like XX-unit, intramolecular hydrogen bonding, which helped to the necessary preorientation of the intermediates, the low polarity of the solvent medium and also anion templation.

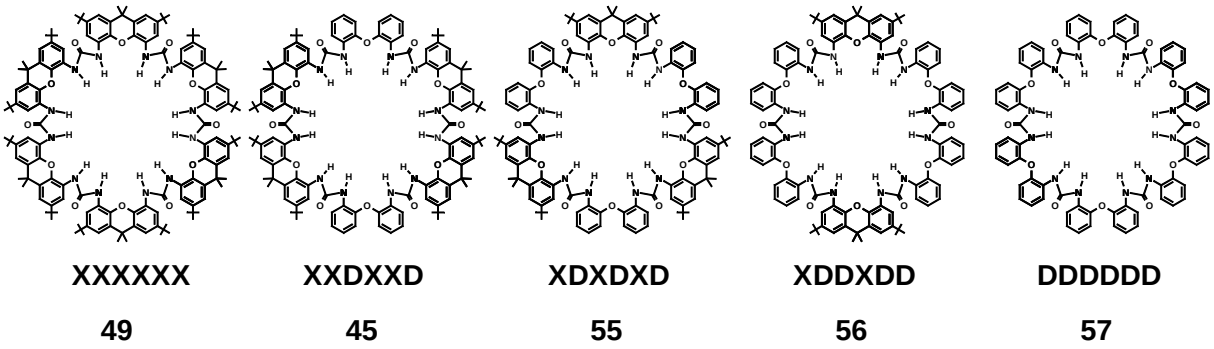


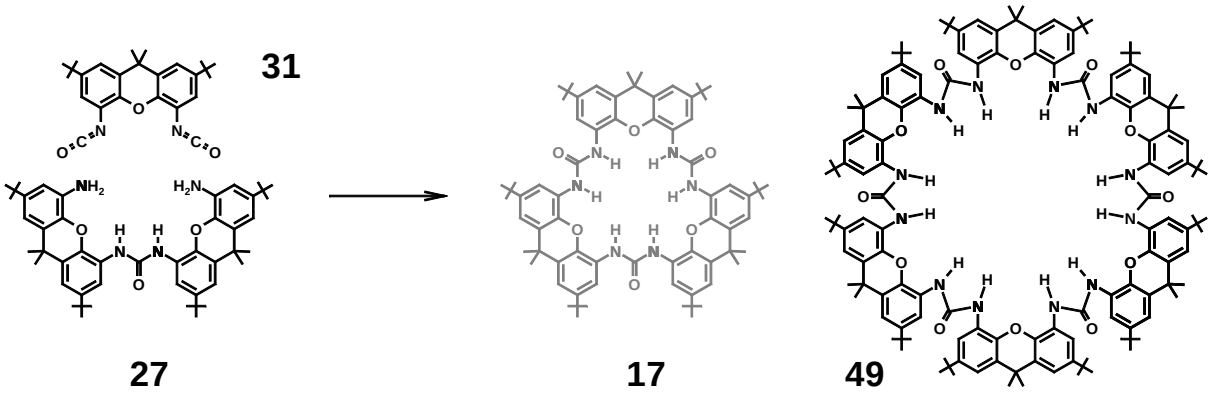
Figure 67. Hexamers planned for synthesis.

5.1 Hexamer XXXXXX 49 as a byproduct in the synthesis of the trimer XXX

It was mentioned in the subchapter 3.1.4, that the reaction of the XX-diamine **27** and the X-diisocyanate **31** in dichloromethane brought an unexpected and remarkable result – the cyclization of two isocyanates and two diamines into the hexameric product **49**.

With the intention to obtain the trimer XXX **17** we added the solution of the diamine XX in dichloromethane dropwise to the solution of the X diisocyanate. After 12 h the reaction mixture was filtered through silicagel in order to remove byproducts and impurities and then the solvent was removed under reduced pressure. The crude product was triturated with hexane and a significant amount of a white solid was filtered off. The product appeared to be absolutely insoluble in DMSO-d_6. The spectra in $CDCl_3$ are broad and unclear. ESI mass

spectroscopy revealed the nature of the compound – the solid appeared to be cyclic hexamer XXXXXX **49**. The overall isolated yield of this product was as high as 49%.



Scheme 15. Synthesis of the $[X]_6$ cyclic hexamer **49**.

The compound shows a very clear ^{1}H NMR spectrum in THF-d_8 suggesting its purity, but the signals themselves initially were hard to interprete. 12 doublets for the aromatic protons (2 protons each), 6 urea-NH peaks (2 protons each), 6 *t*Bu singlets (18 protons each) as well as 6 CH_3 singlets (6 protons each) could be clearly distinguished. All peaks are very sharp and the signals of the same intensity have almost the same height, what indicates a stable conformation of the molecule with two-fold symmetry. At the same time clearly resolved aromatic *m*-coupling allows to separate the signals of the urea protons and the signals of the aromatic protons of the xanthene skeleton.

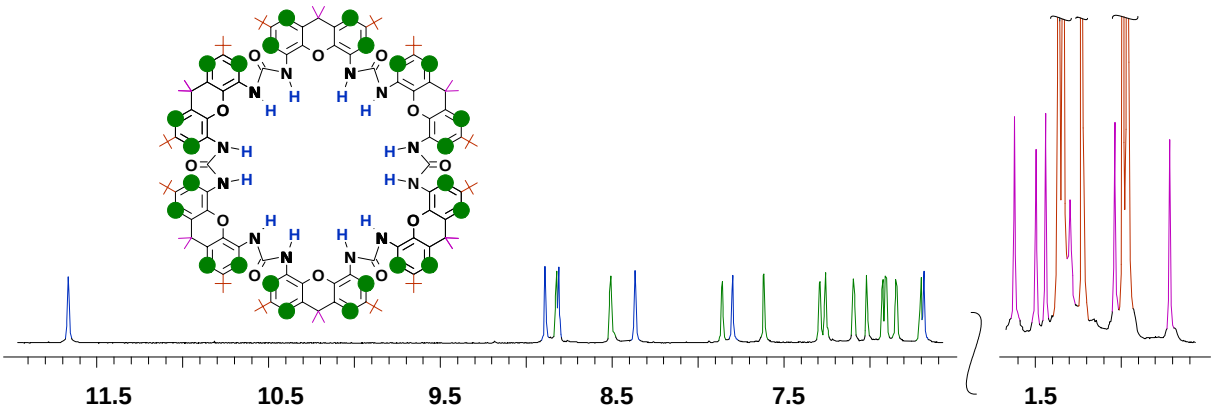


Figure 68. ^{1}H NMR spectrum of the xanthene-based cyclic hexamer **49** (THF-d_8, 25°C).

As can be seen on the spectrum above, one signal corresponding to two urea protons is strongly shifted downfields. This may be an indication that these protons are strongly involved in hydrogen bonding. Other 5 signals of the urea protons are mixed with 12 signals

of aromatic protons and appear distributed in the unusually wide range between 6,5 and 9 ppm.

From the amount and the arrangement of signals in the NMR spectrum we can conclude that in this case we deal with quite complicated and at the same time highly stable conformation. The spectrum is in agreement with an "eight"-shaped molecule, interconnected by the stable hydrogen bonds built by the urea groups from 1st and 4th units. Each of the two loops should contain three full xanthene skeletons.

Obviously, after "2+1" reaction the trimeric intermediate does not cyclize into the trimer, but its reactive groups interact with further molecules in the solution, resulting in the hexameric oligourea, which cyclizes finally into the hexamer. Such an unexpected result of the planned "2+1" synthesis showed clearly the importance of conformational and spatial factors in the synthesis of our macrocyclic oligoureas.

The synthesis of the cyclic hexamer XXDXXD **45**, mentioned in the subchapter 3.1.1, may also be explained in this way, as well as its lower yield due to the higher spatial freedom of the molecule and intermediates caused by the higher flexibility of the diphenyl ether unit.

5.2 Hexamer XXDXXD: "2+1+2+1 cyclization

As has been told in the subchapter 3.1.1, the XXDXXD hexamer **45** forms with the 10-20% yield along with XXD trimer **42** when XX diamine **27** and D isocyanate **33** were reacted in dichloromethane. At the same time the hexamer was not formed when reaction was carried out in more polar acetonitrile, what indicates the participation of hydrogen bonding in the assembly of four particles into the six-membered cycle.

5.2.1 X-ray structure of the complex of the hexamer XXDXXD with two chloride anions

The hexamer XXDXXD forms single crystals when crystallized from a dichloromethane/chloroform/ethanol mixture in the presence of tetrabutylammonium

chloride. X-ray structure determination revealed remarkable complex of the hexamer XXDXXD with two chloride anions (see figure below).[49]

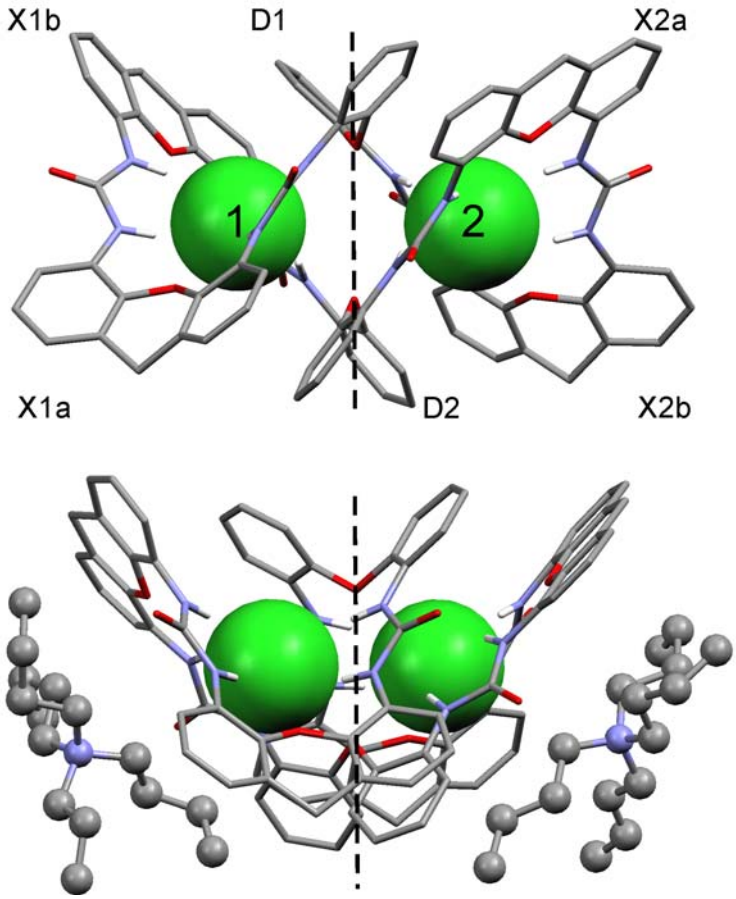


Figure 69. Crystal structure of the 1:2 complex of hexamer **45** with tetrabutylammonium chloride. For the lower view the structure is turned by 45° around the (non-crystallographic) pseudo-C_2 axis (dashed line) to show the tetrabutylammonium cations (ball and stick). Non-urea hydrogens, solvent molecules, *tert*-butyl and methyl groups of xanthene units and tetrabutylammonium cations (in the upper view) are omitted for clarity.

The macrocyclic hexaurea wraps around the two chloride anions (Cl···Cl distance 6.029 Å) in a way, which allows three adjacent urea functions to interact with one chloride anion (N···Cl distances between 3.18 and 3.34 Å). The shape of the macrocycle may be described as an "eight",[50] which is additionally slightly folded in the middle to leave only a

[49] D. Meshcheryakov, V. Böhmer, M. Bolte, V. Hubscher-Bruder, F. Arnaud-Neu, H. Herschbach, A. Van Dorsselear, I. Thondorf, W. Mögelin, *Angew. Chem.*, **2006**, *118*, 1679-1682; *Angew. Chem. Int. Ed.*, **2006**, *45*, 1648-1652.

[50] A regular "eight-shaped" macrocycle would have D_2-symmetry, which is in agreement with the NMR-data in solution.

(non crystallographic) C_2-axis perpendicular to the plane of the original "eight". Two tetra-butylammonium cations are arranged from one side close to the two chloride anions, sitting in the loops of the "eight".

Typical distances and angles for the structure are collected in the table below.

Table 13. X-ray structure of the complex of the hexamer **45** with two molecules of TBA chloride, typical distances [Å] and angles [°] in comparison with averaged values from MD-simulations (last two columns). For the numbering of units see Fig. 68.

Atoms	Distance	Atoms	Distance	Calculated for	
				Cl[a]	Br[a]
Cl1-N11[b]	3.341	Cl2-N41	3.246	3.06	3.32
Cl1-N12[b]	3.299	Cl2-N42	3.276	3.18	3.40
Cl1-N21	3.180	Cl2-N51	3.225	3.06	3.27
Cl1-N22	3.227	Cl2-N52	3.242	3.06	3.26
Cl1-N31	3.233	Cl2-N61	3.268	3.14	3.37
Cl1-N32	3.252	Cl2-N62	3.307	3.05	3.33
Cl1-N300[c]	5.070	Cl2-N200[c]	5.535	5.59	5.69
Cl1-Cl2	6.029			7.04	6.34
Interplanar angles for aromatic rings within xanthene (X) and diphenylether (D) units					
Unit	Angle	Unit	Angle	Angle	Angle
D1	88.38	D2	74.36	67	84
X1a	12.20	X2a	0.70	≈0[d]	≈0[d]
X1b	37.51	X2b	36.70	≈0[d]	≈0[d]
Angles between the averaged planes of the urea units (U) and the adjacent phenyl rings of units X and D					
Units	Angle	Units	Angle	Angle	Angle
D1-U1-X1a	13.9 / 22.0	D2-U4-X2a	6.2 / 36.0	38 / 44	26 / 43
X1a-U2-X1b	30.1 / 30.4	X2a-U5-X2b	39.1 / 22.7	44 / 33	43 / 39
X1b-U3-D2	33.9 / 3.5	X2b-U6-D1	29.6 / 17.5	33 / 38	39 / 26

[a] Calculation performed by Dr. I. Thondorf. Only one calculated value or pair of values as a result of the dynamic D_2 symmetry of the time-averaged structure.

[b] Nitrogen atoms of the urea U1 (between D1 and X1a) have numbers N11 and N1, etc.

[c] N200 and N300 are nitrogen atoms of Bu_4N^+ cation.

[d] All four xanthene units are equivalent and planar in the time-averaged structure.

The crystal packing is quite complicated. There are four molecules of the complex (the hexamer + 2 molecules of TBA chloride) in the lattice along with 8 molecules of chloroform and 8 molecules of dichloromethane.

Table 14. Selected crystal data and structure refinement for cyclic XXDXXD **45**.

Empirical formula	$C_{156.5}H_{215.75}Cl_{8.25}N_{14}O_{12}$	Volume	13071(2) $Å^3$
Formula weight	2777.64	Z	4
Temperature	173(2) K	Density (calculated)	1.159 Mg/m^3
Crystal system	orthorombic	Absorption coefficient	0.206 mm^{-1}
Space group	P212121	Crystal size, mm	0.36x0.28x0.24
Unit cell dimensions	a = 17.0189(11) Å	Reflections collected	104218
	b = 17.7753(11) Å	Independent reflections	28175
	c = 52.633(4) Å	Final R indices	R_1 = 0.1254
	α = 90°		wR_2 = 0.2541
	β = 90°	R indices (all data)	R_1 = 0.1734
	γ = 90°		wR_2 = 0.2766

Looking on a single cell, the arrangement of the molecules seems quite chaotic. The space between molecules of the complex is filled by the tetrabutylammonium cations and the solvent molecules.

No staples, columns or sheets could be found in the crystal lattice.

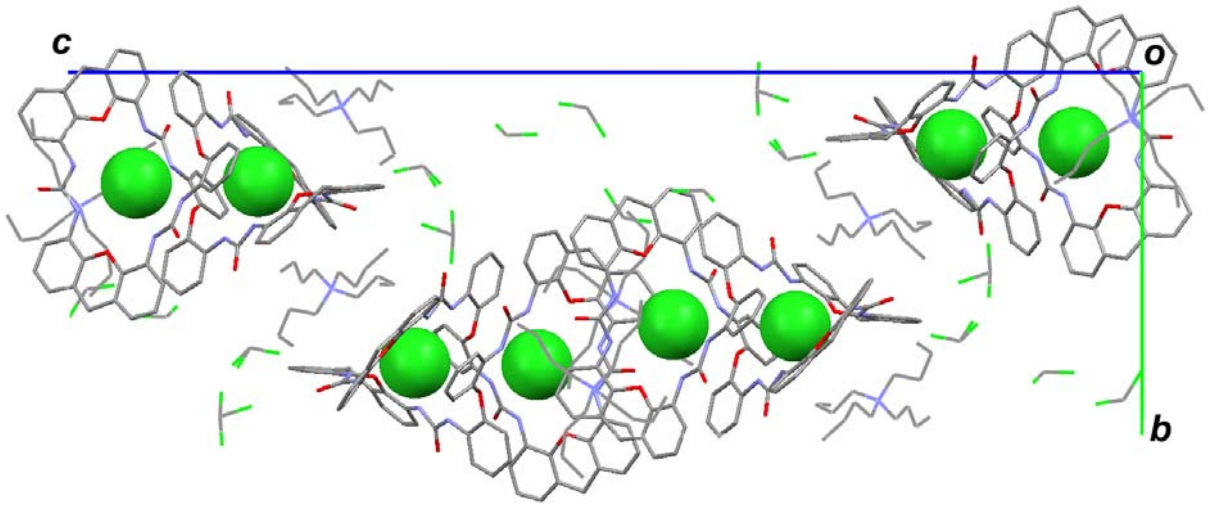


Figure 70. Arrangement of the molecules in the crystal cell. Hydrogen atoms and alkyl groups of xanthene units are omitted for clarity.

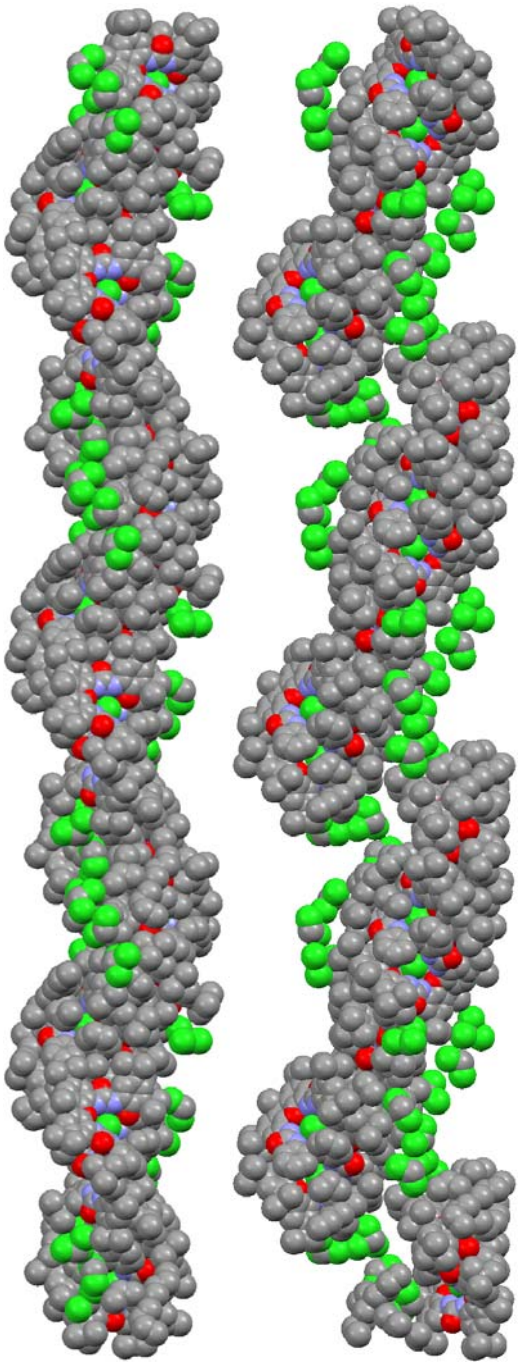


Figure 71. Views presenting arrangement of molecules of the complex in the crystal lattice down the crystallographic axis *c*.

If we present two or more neighbouring cells along the crystallographic *c*-axis as the space-filling model, we obtain a spectacular view: molecules of the complex are arranged in pseudo-helical order (Fig. 70).

We could see on the right view that molecules form "groups" of four tightly neighbouring molecules which form the fiber of the "helix".

5.2.2 1H NMR studies of the complexation properties of the hexamer XXDXXD

The X-ray structure poses many questions on the complexation and also the synthesis of the compound.

The new hexamer is not soluble in DMSO-d_6 as well as hexamer XXXXXX, but at the same time does not produce a clear spectrum in THF-d_8 as hexamer XXXXXX did. The same unclear broad spectra were obtained in other NMR solvents too.

The conformation of hexamer **45** in solution is determined obviously by various intra and/or intermolecular hydrogen bonds between urea functions resulting in a broad and insignificant ^{1}H NMR spectrum. Changing the measurement temperature in both directions in every solvent did not lead to a spectrum, which could be interpreted.

Addition of the TBA chloride resulted in a drastically different behaviour. The hexamer **45** dissolves in DMSO-d_6 under these conditions producing a sharp spectrum; but at the same time precipitation of the compound from THF was observed. In cases of $CDCl_3$ and pyridine-d_5 we observe the immediate conversion of the unclear spectrum into the entirely

sharp one, closely similar to that in DMSO-d_6. If increasing amounts of tetrabutylammonium chloride are added, a single set of sharp signals appears with increasing intensity until a ratio TBAC/hexamer = 2 is reached. Further addition of chloride does not change the spectrum anymore.[51]

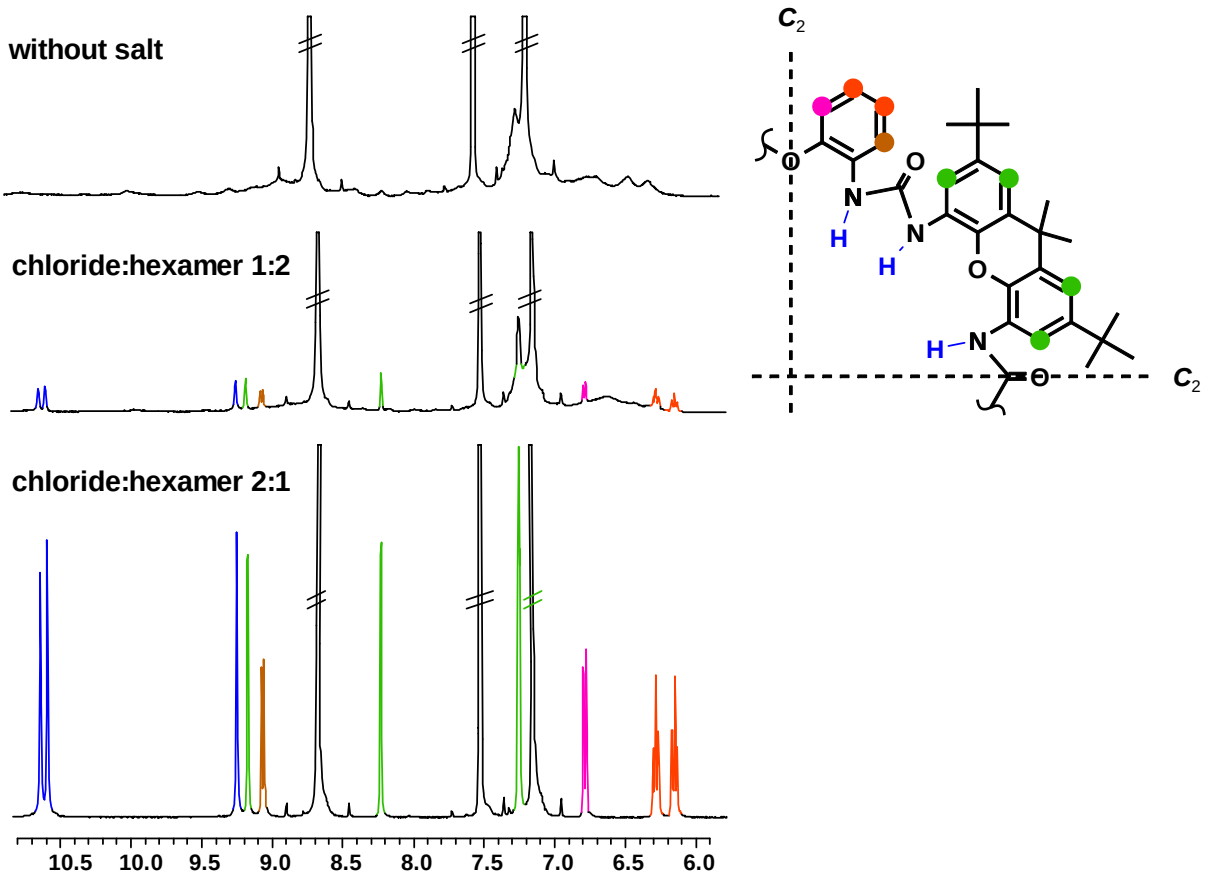


Figure 72. The addition of TBA chloride to the hexamer XXDXXD **45** in pyridine-d_5. Only one fourth of the molecule is present due to D_2 dynamic symmetry in solution.

2 singlets for *tert*-butyl and for methyl groups, 2 pseudo triplets and 2 pseudo doublets (*o*-coupling only) for the aromatic protons of the diphenylether units and 4 *m*-coupled doublets for the aromatic protons of the xanthene units, along with 3 singlets for the urea protons are observed, all in the expected ratio. The set of signals obviously corresponds to the assembly with a (dynamic) D_2-symmetry. It can be explained by the formation of a 2:1 complex of chloride and hexamer **45**, in which two chloride anions are bound in the same way

[51] An addition of inorganic chlorides, such as NH_4Cl or NaCl, to the hexamer in DMSO-d_6 produces the same spectrum with marginal differencies as in case of addition of TBA chloride. In the NaCl case both compounds separately are not soluble in DMSO-d_6, but after 1 h of sonication together in the NMR tube all the hexamer goes into solution and demostrates typical spectrum of the chloride complex.

as in the crystalline state. A similar spectrum with slightly different chemical shifts is found in the presence of bromide, although no saturation is reached at the ratio of 2 (see figure below). Moreover, the formation of the bromide complex takes place not immediately after the addition of the salt as in the case of chloride, but takes up to 15 minutes.

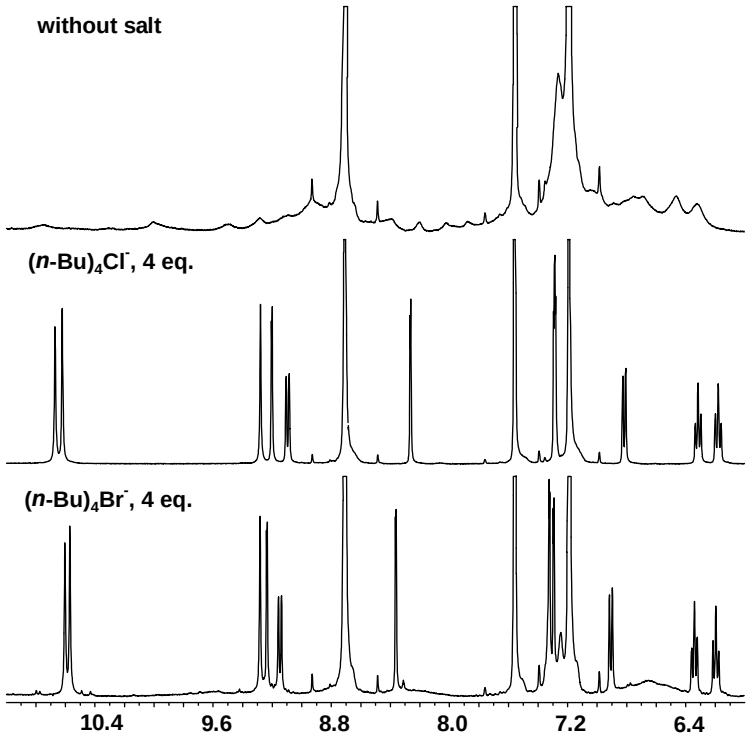


Figure 73. Section of the ^{1}H NMR spectra (400 MHz, pyridine-d_5) of the cyclic hexamer **45** (c = 0.1 mM) alone ; with 4 eq. of tetrabutylammonium chloride; with 4 eq. of tetrabutylammonium bromide.

The stability constants for the chloride complex were determined in the group of the Dr. F. Arnaud by the UV spectroscopy and microcalorimetry. The addition of chloride to a solution of **45** in acetonitrile:THF (3:1 *v/v*) leads to changes in the UV-spectrum between 240-310 nm, which allow the determination of stability constants. Values of log β_{11} = 5.6±0.5 and log β_{21} = 11.2±0.7 have been found with Bu_4NCl for [**45**·Cl^-] and [**45**·$2Cl^-$] respectively.

Microcalorimetric titrations with Bu_4NCl confirmed the spectroscopically determined stability constants (see Table 15). Overall the complexation is enthalpically driven. A positive $T\Delta S$ for the first step can be understood by the release of solvent molecules from the solvation shells, while the strong negative value for the second step reflects the high order assumed by the macrocycle in the final complex, where the most perfect interaction (negative ΔH) between urea functions and the chloride anions is reached.

Table 15. Thermodynamic parameters [kJ mol^{-1}] for the complexation of chloride by the hexamer **45** (L), (acetonitrile:THF 1:3 *v/v*, Bu_4NCl, 25°C).

Reaction	log β	$-\Delta G$	$-\Delta H$	$T\Delta S$
$L + Cl^- = LCl^-$	6.16	35.1	23.4	11.7
$LCl^- + Cl^- = (LCl_2)^{2-}$	5.25	29.9	43.6	-13.6
$L + 2\ Cl^- = (LCl_2)^{2-}$	11.4	65.1	67.0	-1.9

The ^1H NMR spectrum of the chloride complex remains stable in a wide range of temperatures in pyridine-d_5 and other NMR solvents. The only observed change appear at temperatures below zero – the ppm distance between singlets of methyl groups, very small at room temperature, increases and both signals broaden.

Interaction with other anions was investigated also. TBA fluoride does not produce the sharpening of the hexamer spectrum and it remains unreadable also with the big excess of the salt. TBA bromide shows the same type of interaction as a chloride does, but the complexation is weaker. Iodide seemed to have no interaction at all.

Nitrate and hydrosulphate belong to the anions which promote the spectrum of the hexamer molecule analogous to that in the presence of chloride, while dihydrophosphate shows different behaviour. When addition of the salt is continued over the molar ratio 2:1 (phosphate:hexamer) a new set of signals appears and its intensity grows with the further addition of the salt, while the initial set disappeared when the big excess of the dihydrophosphate is added.[52]

5.2.3 Chloride-templated formation of the hexamer XXDXXD

The strong complexation of chloride and other ions suggested that the yield of the hexamer **45** could be increased if the cyclization reaction between XX diamine **27** and X diisocyanate **33** is carried out in the presence of anions.

We have attempted a series of reactions in the presence of various tetrabutylammonium salts (using 1:1 molar ratio between diamine XX and the salt). The reactions were performed following the same procedure as it was used initially without an

[52] In cases of nitrate, hydrosulphate and dihydrophosphate bigger distance between signals of the xanthene methyl groups protons was observed (0.3 – 0.4 ppm instead of 0.02 ppm in case of chloride).

addition of salts. Then the crude product left after the evaporation of dichloromethane was analyzed by ^{1}H NMR of the DMSO-d_6 solution in the presence of an excess of TBA chloride (to sharpen the spectra of the hexamer XXDXXD).

The molar ratio between the trimer XXD **42** and the hexamer XXDXXD **45** determined by NMR in the crude product is 5:1 for reactions carried out in dichloromethane without a salt. The ratio changes drastically to 1:5 when 2 equivalents of tetrabutylammonium chloride are present in the reaction mixture and to 1:3 in the presence of bromide, while iodide has no influence. That even the presence of bromide anions (less tightly bound than chloride as shown above) leads to an increase of the amount of hexamer **45** is perhaps (partly) also due to the fact, that the formation of the trimer XXD **42** is disfavoured by bromide.

TBA phosphate increases the yield of the hexamer **45** as well, but not so strong as chloride, at the same time promoting the formation of increased amounts of byproducts (linear oligoureas).

The tight binding of two chloride anions (in a short distance of 6.03 Å)[53] by a macrocyclic hexaurea molecule is a striking example for an "induced fit" of the ligand, which becomes possible due to the combination of rigid and flexible units in one molecule. Advantage may be taken from the complexation of two halide anions also during the macrocyclisation reaction. Such a template effect by two anions,[14] or more general by two spherical particles, is unprecedented to the best of our knowledge for the synthesis of large and hence flexible macrocycles. It is especially remarkable since unlike to templation by transition metal cations no geometrical requirements exist for the complexation.

5.3 Hexamer XDDXDD 56

The "2+1+2+1" cyclization worked well enough in the cases of XXXXXX and XXDXXD hexamers due to the combination of spatial properties of the compounds involved and the environment. However for hexamers containing more flexible units (XDDXDD and DDDDDD) this method does not work; it is also unapplicable to another planned compound – XDXDXD hexamer.

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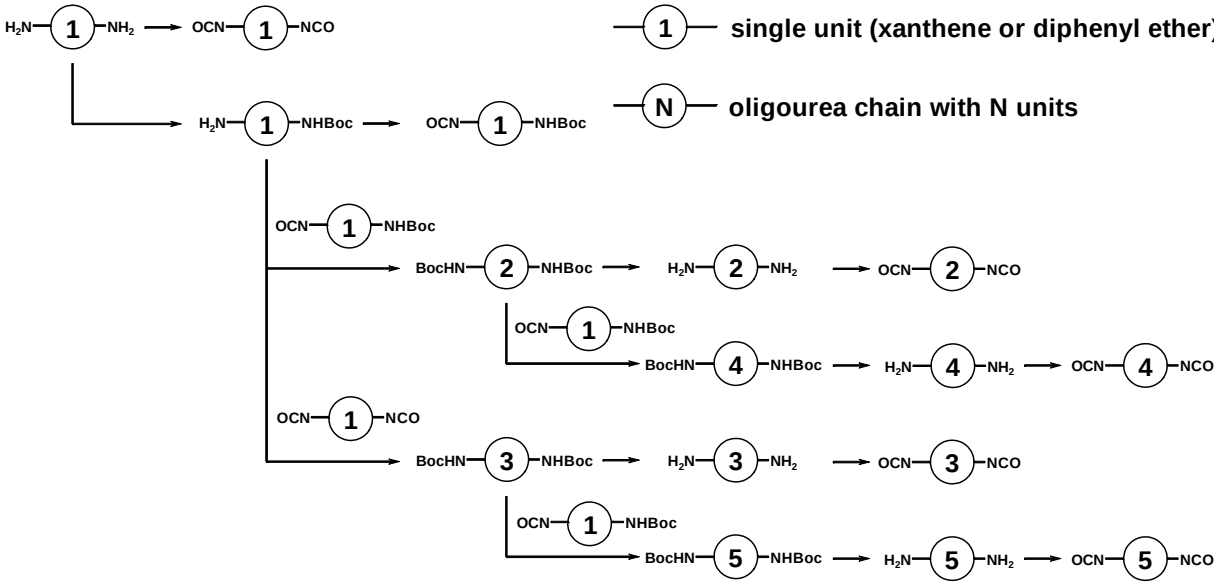
[53] A short distance of 5.52 Å between two chloride anions (additionally bridged by two water molecules) was also found in the nearly planar complex with a cyclic octalactam: A. Szumna, J. Jurczak, *Helv. Chim. Acta* **2001**, *84*, 3760-3765.

Beside of the "2+1+2+1" assembly there are also methods which involve the formation of the hexamer from the two molecules of precursors. This way was widely used in the preparation of the tetramers and trimers. In the case of hexamers these approaches are "5+1", "4+2" and "3+3".

Obviously, for the preparation of the XDDXDD and DDDDDD cycle all these strategies may be used, while for XDXDXD only "5+1" and "3+3" (XDXDX + D and XDX + DXD) could be used.

Let's evaluate which way is the most rational. All building blocks which might be used for the preparation of a cyclic hexamer are presented on the scheme below.



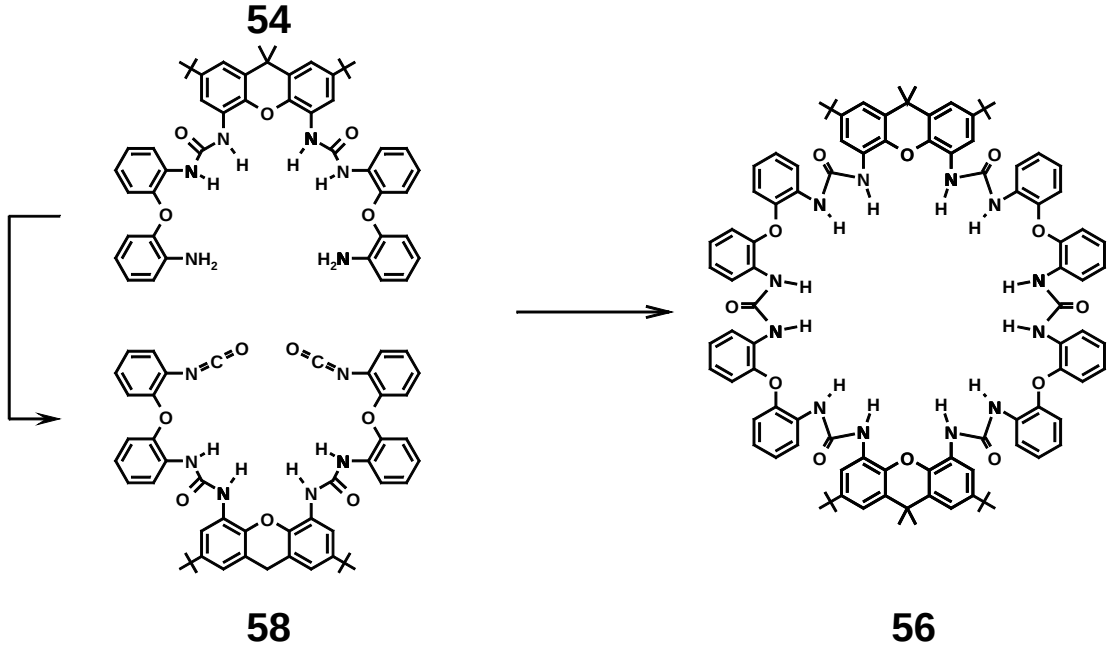
Scheme 16. Synthesis of building blocks for the preparation of the cyclic hexamer and the cyclization methods.

We could calculate, that the preparation of the XDDXDD hexamer from two identical trimeric units (DXD) would require 6 synthetic steps. If the linear trimeric blocks are not identical (XDXDXD = XDX+DXD), the number of necessary steps increases to 9. "4+2" will include 9 steps for XDDX+DD=XDDXDD. "5+1" will include 10 steps for the XDXDXD and 7 for XDDXDD.

Therefore we concluded that the most rational way is to use "3+3" where possible. However, additional factors may also have influence on the decision, for example yields of separate steps and availability of some building blocks from previously made syntheses.

5.3.1 Synthesis of the cyclic hexamer XDDXDD 56

For the preparation of the six-membered cycle XDDXDD the optimal "3+3" way was chosen. The necessary precursor – the linear trimeric diamine **54** (DXD diamine) – was already obtained for the synthesis of the tetramer **52**. For the "3+3" cyclization we needed to prepare the corresponding DXD diisocyanate **58** from the diamine.



Scheme 17. Synthesis of the hexamer XDDXDD **56**.

The known procedure involving triphosgene and Hünig base was used for the preparation of the diisocyanate **58**. However, the reaction was carried out in polar acetonitrile in order to exclude unwanted hydrogen bonding.

The solution of the diamine **54** with Hünig base in dichloromethane was added dropwise to the solution of triphosgene in the acetonitrile under nitrogen. The reaction was controlled by TLC. After the whole amount of diamine was converted (it takes not more than 2-3 h) the reaction mixture was filtered through silicagel. The solvent was removed under reduced pressure yielding 95% of the diisocyanate **58** as a glass-like solid.

The cyclization to the hexamer **56** was attempted also in a polar solvent. The diamine DXD **54** was dissolved in dichloromethane and added to the solution of the diisocyanate **58** in acetonitrile (final composition of the solvent – dichloromethane: acetonitrile 1:3 *v/v*) with stirring under nitrogen. After 18 h the solvent was removed under reduced pressure and the

oily residue was triturated with acetonitrile. The hexamer XDDXDD **56** was isolated as a white powder with 45% yield and some amount of compound was still present in the filtrate.

5.3.2 X-ray structures of the hexamer XDDXDD

The hexamer XDDXDD readily forms single crystals. Three different crystalline samples from the hexamer **56** were obtained. All samples were prepared by the slow evaporation of the hexamer solution in the multicomponent mixture of solvents.[54] In the first case (we assign the name *alpha* to this structure) one crystal cell contains two symmetry-related molecules of the hexamer and four acetone molecules. In the second structure (*beta*) beside of two symmetry-related molecules of the hexamer two molecules of ethylacetate and two molecules of ethanol were present. And in the third case (*gamma*) we had a crystal cell containing two symmetry-related molecules of the XDDXDD, six molecules of ethanol, two molecules of ethyacetate, two molecules of acetonitrile and two water molecules. Selected crystal parameters for all three samples are collected in Table 16.

In all three cases we observe a strongly folded molecule of the hexamer. The structures are determined by a network of intra- and intermolecular hydrogen bonds. In the *alpha* structure molecules are packed quite tightly, but all hydrogen bonds are either intramolecular or connected to acetone molecules, so no connection between hexamer molecules exist. In the *beta* structure we have ethanol instead of acetone, while the conformation of the hexamer structure changed not very much. Each single ethanol molecule accepts and donates hydrogen bonds for two different urea groups of the same hexamer molecule. No connection between separate hexamer molecules was found as well. In general *alpha* and *beta* have similar conformation and hydrogen bonding pattern.

[54] In each single case every solvent from mentioned earlier may be present in the mixture, but two of them are always the main components. The pair of solvents is formed by a solvent which dissolves the compound good and another one, which dissolves the compound bad. Resulting solution is allowed then to evaporate slowly through the very small hole made by a needle. When solid appears in the bottle and no crystallization occurs, the compound is dissolved again with other pair of solvents and so on until we get single crystal(s). Thus, in *alpha* case the pair of solvents was dichloromethane/acetone, for *beta* these were ethylacetate/methanol and for *gamma* ethylacetate-acetonitrile.

Table 16. Selected crystal data and structures refinement for the cyclic hexamer XDDXDD **56**.

	alpha	*beta*[55]	*gamma*
Empirical formula	$C_{124}H_{148}N_{12}O_{20}$	$C_{112}H_{128}N_{12}O_{18}$	$C_{95}H_{130}N_8O_{13}$
Formula weight	2126.54	1930.84	1947.30
Temperature	173(2) K	173(2) K	173(2) K
Crystal system	triclinic	triclinic	triclinic
Space group	P-1	P-1	P-1
Unit cell dimensions	a = 15.2902(12) Å	a = 12.3418(11) Å	a = 15.5508(6) Å
	b = 15.3882(13) Å	b = 15.1520(13) Å	b = 18.1537(7) Å
	c = 15.7353(12)Å	c = 15.2483(11)Å	c = 21.1074(8)Å
	α = 117.903(6)°	α = 99.182(6)°	α = 78.610(3)°
	β = 101.301(6)°	β = 109.839(7)°	β = 81.262(3)°
	γ = 103.215(6)°	γ = 97.578(7)°	γ = 78.204(3)°
Volume	2981.3(4) $Å^3$	2594.2(4) $Å^3$	5679.2(4)$Å^3$
Z	1	1	2
Density (calculated)	1.184 Mg/m^3	1.236 Mg/m^3	1.139 Mg/m^3
Absorption coefficient	0.081 mm^{-1}	0.084 mm^{-1}	0.078 mm^{-1}
Crystal size, mm	0.35x0.33x0.28	0.25x0.24x0.19	0.48x0.36x0.18
Reflections collected	31249	24886	144878
Independent reflections	11153	9647	21582
Final R indices	R_1 = 0.0992	R_1 = 0.0714	R_1 = 0.1021
	wR_2 = 0.1812	wR_2 = 0.1850	wR_2 = 0.2767
R indices (all data)	R_1 = 0.0987	R_1 = 0.1083	R_1 = 0.1662
	wR_2 = 0.1989	wR_2 = 0.2050	wR_2 = 0.3163

The *gamma* structure is more complicated. The conformation of a single molecule and its system of intramolecular hydrogen bonds are quite different from *alpha* and *beta*. The molecule lost its symmetrical look (see figure below).

[55] Since the ethylacetate in the crystal cell was heavily disordered, both molecules of it were excluded from the refinement.

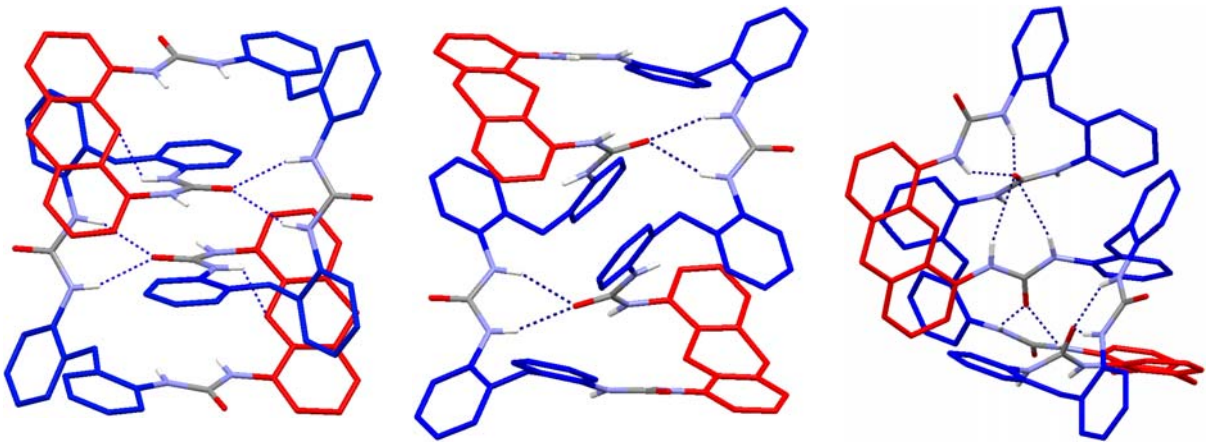


Figure 74. Conformations of a single molecule of the hexamer **56** in the crystal structures *alpha*, *beta* and *gamma* (from left to right). Solvent molecules, non-urea hydrogens and alkyl groups of the xanthene units are omitted for clarity. Xanthene units are colored in red, diphenyl ether units – in blue.

Beside the intramolecular hydrogen bonding, the hexamer molecules in the crystal lattice of the *gamma* are connected into pairs with the help of a network of hydrogen bonds formed between nearby situated urea groups of the molecules from the neighbouring crystalline cells with the help of different solvent molecules (ethanol, acetonitrile and water are involved, see figure below).

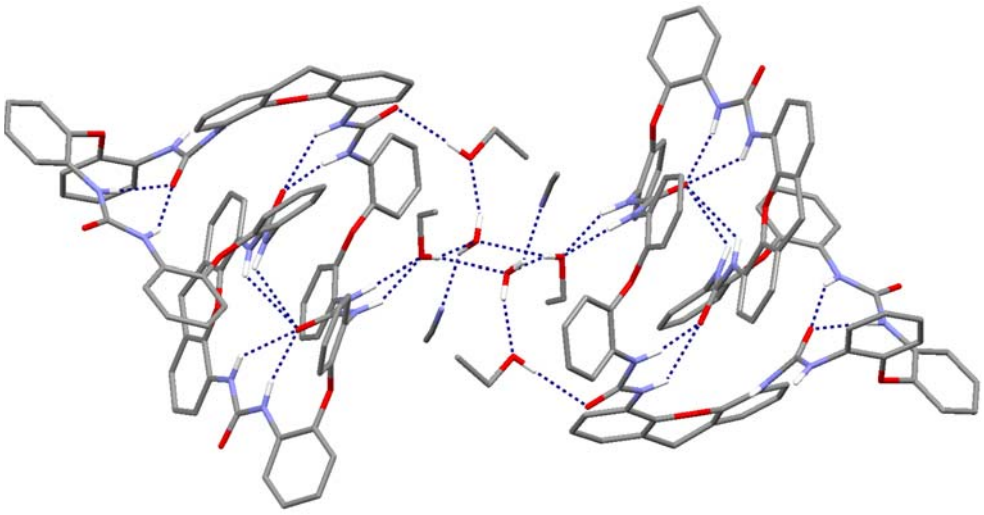


Figure 75. .The hydrogen bond network formed with participation of the solvent molecules connecting two molecules of the hexamer in "gamma" structure.

Alpha and a little less *beta* have distorted "eight"-like conformation similar to the XXDXXD hexamer **45**. At the same time, numerous attempts to co-crystallize the hexamer XDDXDD **56** with salts failed, while XXDXXD hexamer readily crystallizes with chloride.

Probably, due to the increased flexibility the structure of XDDXDD is strained less upon the formation of intramolecular hydrogen bonds, without inclusion of guest anion.

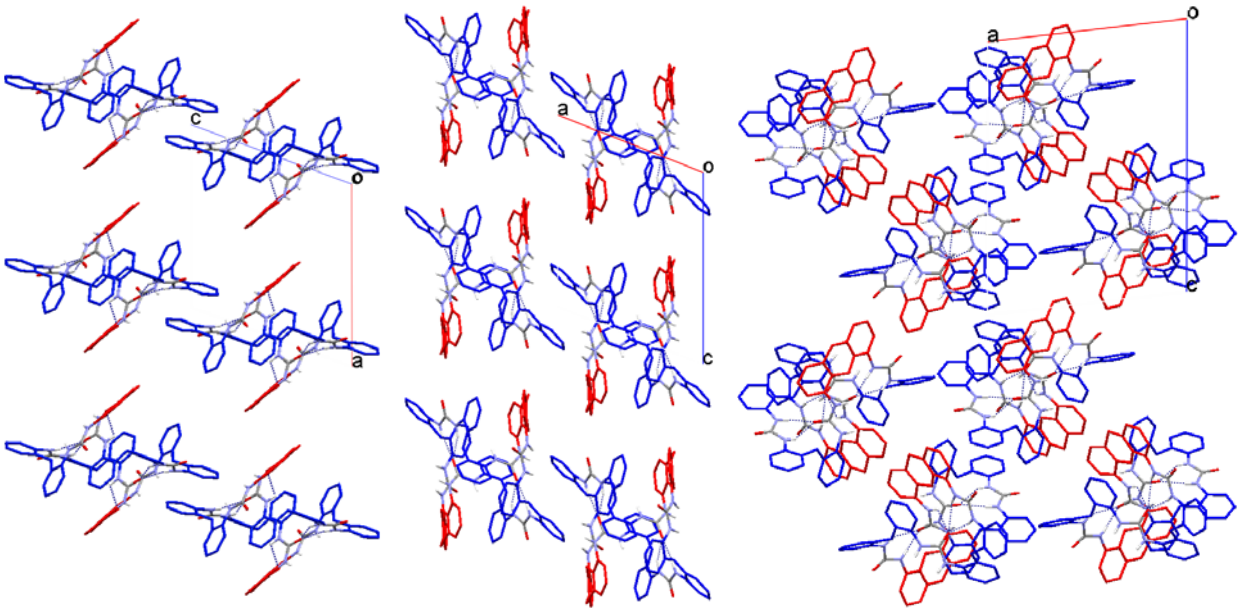


Figure 76. Packing of **45** in the crystal structures *alpha*, *beta* and *gamma* (from left to right). Solvent molecules, non-urea hydrogens and alkyl groups of the xanthene units are omitted for clarity. Xanthene units are colored in red, diphenyl ether units – in blue.

Thus, each separate molecule of the hexamer **56** in each structure is far from being flat, but assumes a three-dimensional folded conformation. In the crystal lattice no connection or interaction between single molecules for *alpha* and *beta* can be found. As has been told before, in *gamma* we observe couples which are connected via hydrogen bonded pattern supported by solvent molecules, but no further interaction was observed. The distance between urea groups of neighbouring molecules is relatively large (see picture above) in all three lattices, and the space is filled by xanthene alkyls and solvent molecules, what eliminates possible stacking.

5.3.3 ^{1}H NMR studies of the hexamer XDDXDD

The XDDXDD has good solubility in DMSO-d_6, but shows at the same time a broad and unclear ^{1}H NMR spectrum at 25°C. What is more surprising, the spectrum does not sharpen in the presence of salts. Even the shape of the observed signals changes unsignificantly (see picture below). The structure of the compound after its synthesis was

confirmed initially by ESI mass spectroscopy[56] and later also by X-ray analysis of single crystals.

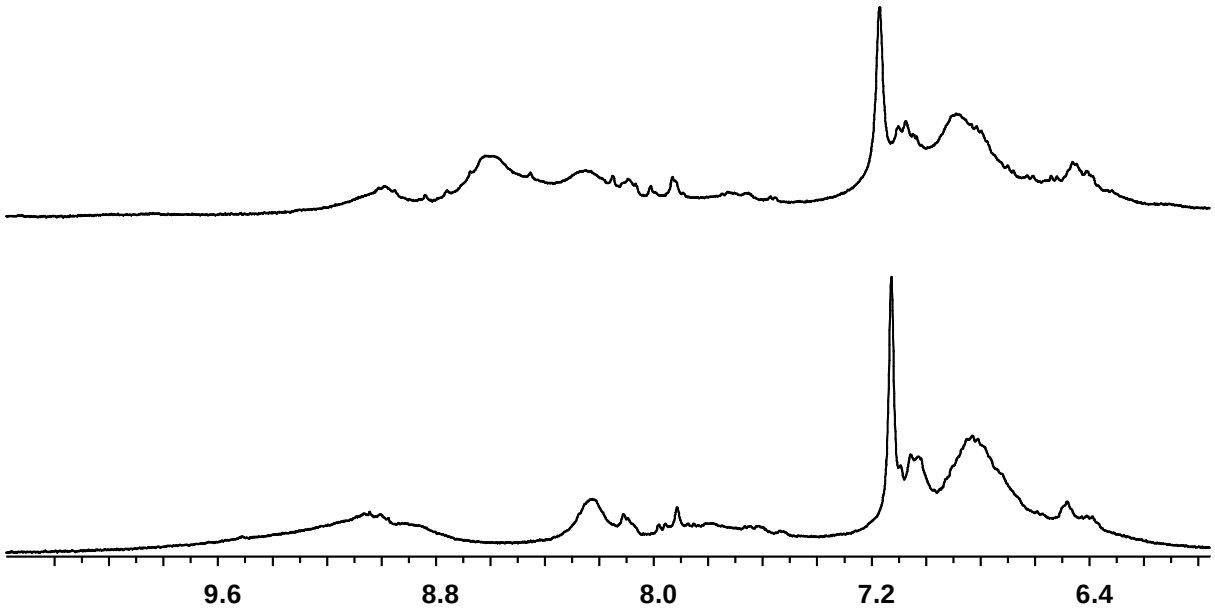


Figure 77. Upper view: the lowfield part of the XDDXDD spectrum in DMSO-d_6 without salt; lower view: the same in the presence of an excess of TBA chloride.

Thus, while hexamer XXDXXD shows distinct changes in the ^{1}H NMR spectrum upon addition of TBA chloride, the spectrum of the XDDXDD remains almost completely intact. The more flexible hexamer obviously prefers to keep the system of hydrogen bonds without inclusion of an anion.

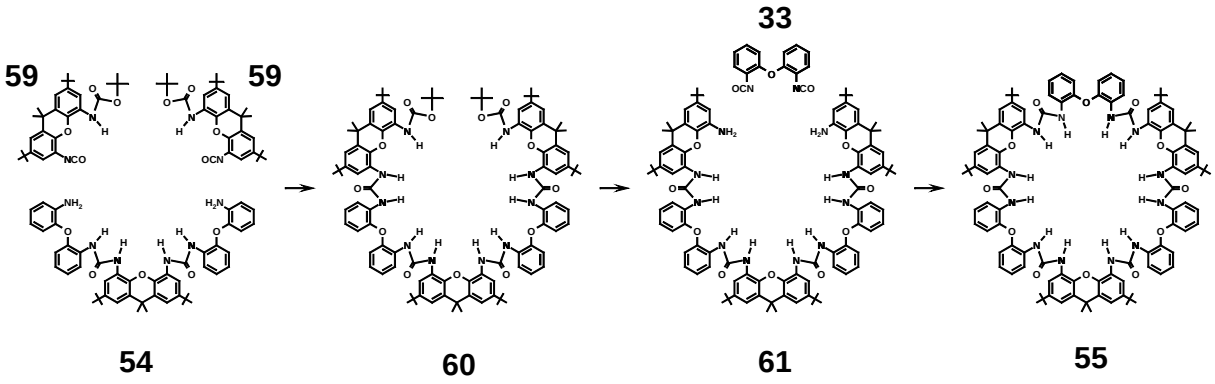
Thus, the introduction of two diphenyl ether units instead of the more rigid xanthenes changed the properties of the hexameric cycle towards anions quite drastically in the direction of more stable intramolecular hydrogen bonding, which neither solvents, nor anions could not overcome.

[56] ESI mass spectroscopy showed high reliability with our oligoureas. In most cases the peak corresponding to molecular weight plus sodium cation was totally predominant. Thus, we relied upon such spectra, even if it was not possible to confirm the structure with other method.

5.4 Hexamer XDXDXD 55

5.4.1 Synthesis of the cyclic hexamer XDXDXD 55

For the preparation of the hexamer **55** the "5+1" way was chosen. Since we had in hand the linear DXD diamine **54**, prepared for the synthesis of the hexamer XDDXDD, we were only some synthetic steps away from the XDXDXD precursor – the linear pentameric diamine XDXDX **60**.



Scheme 18. Synthetic route to the hexamer XDXDXD.

We needed to prepare the monoprotected X-isocyanate **59**, then to react it with the trimeric diamine **54** and to deprotect the product **60**. Resulting diamine will be reacted with D-diisocyanate **33**, which reaction yields the desired six-membered cycle **55**.

Isocyanate **59** was prepared similarly to other isocyanates known in this work. The solution of the monoprotected X-amine **24** together with Hünig base in dichloromethane was added with stirring to the solution of triphosgene in dichloromethane under nitrogen. After 3h reaction mixture was filtered through silicagel followed by washing with dichloromethane. Then the solvent was removed under reduced pressure yielding the isocyanate **59** as a glass-like solid with the yield up to 89%. To facilitate handling of the compound it was dissolved one more time in acetonitrile and then the solvent was removed on rotavap again. The product was thus converted to a bright white powder.

In order to prepare the diprotected linear pentamer **60** two molecules of isocyanate **59** were reacted with one molecule of trimeric diamine **54** in THF under nitrogen. After 12 h the solvent was removed under reduced pressure. The glass-like residue was triturated with

acetonitrile. The diprotected pentamer **60** was isolated as a white powder with the yield of 45%.

The deprotection was performed in usual way using trifluoroacetic acid in dichloromethane. After 3 h the reaction mixture was slowly poured into the water solution of sodium carbonate. The organic layer was separated, washed with water, dryed over magnesium sulphate. The pentameric diamine was isolated after removal of solvent as a brownish glass-like solid with nearly quantitative yield.

The diamine XDXDX was reacted with D-diisocyanate **33** in a small volume of dichloromethane. After 18 h the solvent was removed under reduced pressure and the residue was triturated with acetonitrile. White power was formed and consequently filtered off, yielding 80% of the hexamer **55**.

5.4.2 ^{1}H NMR studies of the hexamer XDXDXD

Similarly to the hexamer XDDXDD, the cycle **55** can be easiliy dissolved in DMSO-d_6 , but also produces unclear ^{1}H NMR spectrum. The similar unclear spectrum was observed when tetrabutylammonium chloride was added to the solution.

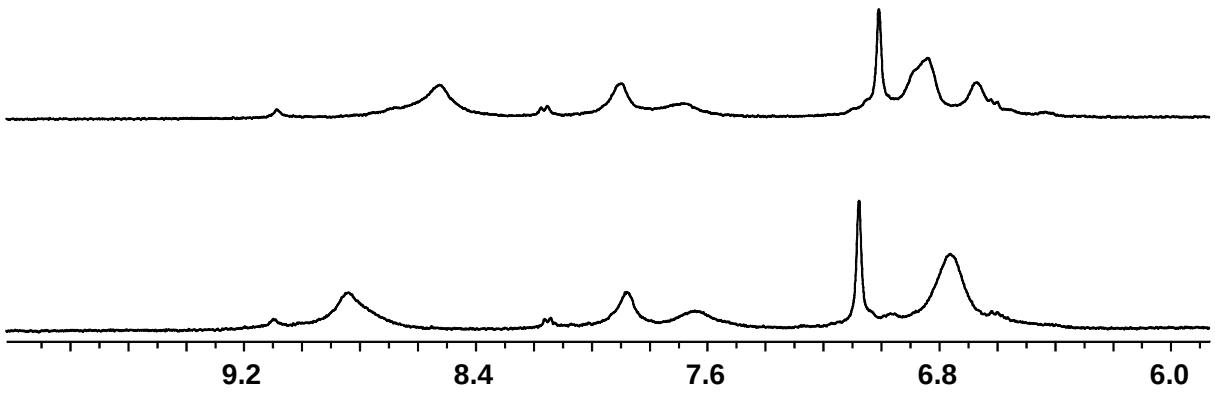


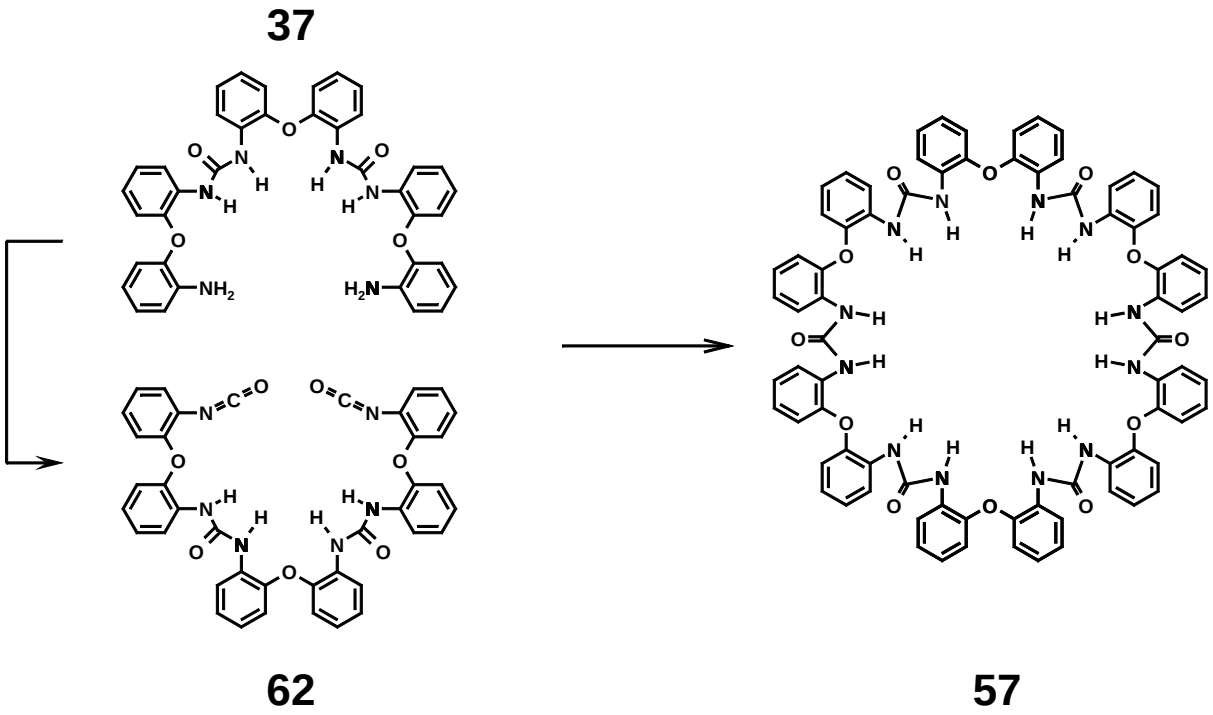
Figure 78. Upper view: the lowfield part of the spectrum of the XDXDXD in DMSO-d_6 without salt at 25°C; lower view: the same in the presence of an excess of TBA chloride.

The nature of the newly prepared hexamer was confirmed by ESI mass spectroscopy.

Thus, the hexamer XDXDXD also prefers to keep its dynamic system of hydrogen bonds instead forming of a stable complex with an anion.

5.5 Towards hexamer DDDDDD 57

The synthesis of the entirely "flexible" hexamer was planned following the "3+3" scheme, where diamine DDD **37** and diisocyanate DDD **62** are to be reacted.



Scheme 19. The formation of the hexamer DDDDDD using "3+3" scheme from diamine DDD **37** and diisocyanate DDD **62**.

The linear diamine DDD **37** was converted to diisocyanate with the help of triphosgene in the presence of the Hünig base in the mixture of acetonitrile, THF and dichloromethane (3:1:2 *v/v*) under nitrogen. After filtration through silicagel and removal of the solvent the trimeric diisocyanate **62** was isolated as a brown glass-like solid with a yield of 90-95%. To facilitate further handling the solid can be converted to powder by triturating with hexane.

The trimeric diamine **37** and diisocyanate **62** were reacted in a polar environment (THF:acetonitrile mixture 1:1 *v/v*) to avoid unwanted hydrogen bonding and therefore to decrease the byproduct formation. Unfortunately, all efforts did not succeed and the TLC showed the presence of several byproducts in the reaction mixture. ESI mass spectroscopy revealed the massive presence of the desired hexamer in the reaction mixture, but all attempts to isolate it as a pure compound from there failed. The main problem is that the long linear

oligoureas which may be formed in this reaction have practically the same solubility and chromatographic properties as our cyclic compound, especially when the chain contains more than 3 units.

5.6 Conclusions

Four new cyclic hexaureas with four different combinations of rigid xanthene and more flexible diphenyl ether units were synthesized and their conformational behaviour and complexation properties towards anions were evaluated by X-ray and ^{1}H NMR.

Our investigations showed that these properties are depending strongly on the number and distribution of the xanthene and diphenyl ether units. The entirely "rigid" hexamer XXXXXX form stable conformation with the help of intramolecular hydrogen bonds, which is hardly accessible for solvation, as well as for anion complexation. The XXDXXD with two more flexible diphenyl ether units has undefined conformation, determined by a chaotic hydrogen bonding. Upon addition of an anion the conformation is drastically stabilized. The stability of the complex formed with two chloride anions is so high that addition of a chloride strongly increases yield of the hexamer XXDXXD when 2 molecules of diamine XX and 2 molecules of D-diisocyanate are reacted in dichloromethane, demonstrating therefore the prominent and unprecedented example of the templation by the two anions.

After the addition of the next "flexible" diphenyl ether units the hexameric cycle gains additional abilities for intramolecular hydrogen bonding. We have found that hexamers XDDXDD and XDXDXD are heavily folded due to the intramolecular interaction of the urea groups, which are at the same time not active towards anions.

Therefore, the most important results were achieved when the cycle is built using "XXD" unit sequence. An analogous conclusion we have made also after analysis of the complexation properties of the trimers.

6 Towards oligoureas with more than six units.

The preparation of long oligourea chains is of great interest from different points of view. First of all, our macrocycles were prepared from the linear chain precursors. Therefore, effective methods for the synthesis of longer oligoureas should lead finally to the preparation of larger cycles as well.

Another important question is the anion complexation activity of the long chain oligoureas. What would be the properties of these compounds? Would they be active towards anions at all? Which conformations would they adopt in the presence of and without anions?

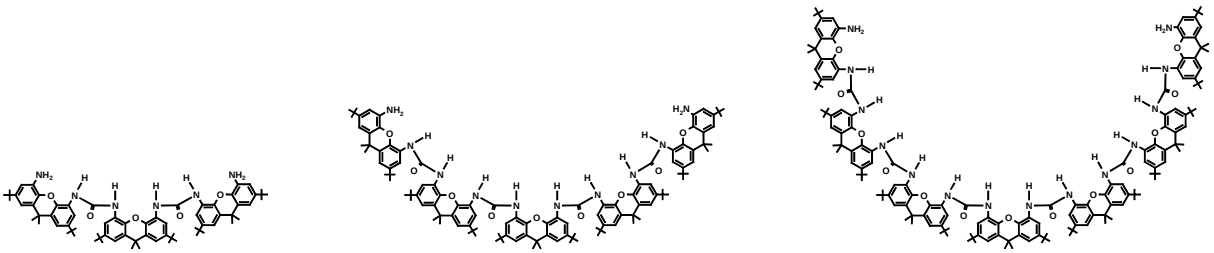
Initially, the preparation of long chains from xanthene units was planned with the idea to study conformational properties of such oligoureas (see subchapter 1.4). Later our attention was attracted by the properties shown by the cycles containing the XXD sequence.

In this chapter we shortly summarize our experience in connection with the preparation of the long oligourea chains and outline further perspectives for the synthesis of large cycles.

6.1 Oligourea chains built from xanthene units

6.1.1 Synthesis and ^{1}H NMR spectra of the xanthene-based linear oligomers

The previously synthesized dimeric and trimeric X diamines **27** and **35** (see subchapter 2.2) were successfully used for the preparation of cyclic trimers and tetramers. These shortest oligomers XX and XXX could be also elongated in a stepwise manner using the reaction with the monoprotected X isocyanate **59.** The following deprotection reaction yields the diamine XXXXX when we start from the diamine XXX. The elongation procedure is to be repeated to get the next oligourea and so on.



35 **64** **66**

Figure 79. Products of stepwise elongation of chain. Depicted conformation of the molecules is arbitrary.

In order to prepare the diprotected precursor of the linear pentamer **64** a solution of the diamine **35** in THF was added over 2 h to a vigorously stirred solution of monoprotected X isocyanate **59** in dichloromethane under nitrogen. After 18 h the solvent was removed under reduced pressure and the crude product was dissolved in acetonitrile. The diprotected diamine XXXXX **63** crystallized after 2 h in thin colorless needles. The solid was filtered off, yielding 76% of the pure compound. The product has an absolutely unclear broad ^{1}H NMR spectrum and the structure was initially based on by ESI-MS analysis. The spectrum showed practically a single peak corresponding to the molar mass of the pentamer plus sodium.

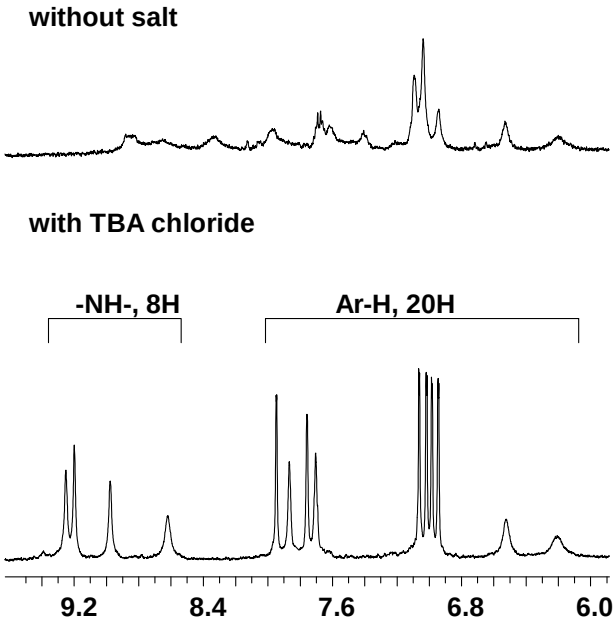


Figure 80. Part of the ^{1}H NMR spectrum of the diamine XXXXX **64** (DMSO-d_6, 25°C)

The deprotection was performed using trifluoroacetic acid in dichloromethane. The pentameric diamine **64** was isolated quantitatively as a white powder after workup. The ^{1}H NMR was broad for this compound as well. The structure was confirmed initially by mass spectroscopy (ESI). Later it was established that a clear spectrum can be obtained in the presence of TBA chloride (see Fig. 79).

Attempts to prepare the diprotected heptamer **65** were performed in the same manner as for the diprotected pentamer **63**. The product was precipitated as a white powder from acetonitrile after the synthesis with the calculated yield of 56%. Unfortunately, no method

was found to prove the structure and check the purity of the compound. ^{1}H NMR was expectedly unclear, also at elevated temperature and in the presence of salts (measurements were performed in THF-d_8, because the compound was absolutely insoluble in DMSO-d_6). ESI-MS analysis showed 2 peaks. The stronger peak corresponded to our desired product but another smaller one (with a relative intensity of approx. 20% compared to the peak of the heptamer+Na) - to the monoprotected hexameric derivative. The synthesis was repeated to ensure that no mistake occurred, but the product showed exactly the same mass spectrum. ESI mass spectroscopy generally was very reliable during our work, almost always producing spectra containing only the molecular peaks for our ureas. Thus, we concluded that in this case the reaction can be completed only with difficulties, probably due to some sterical reasons. The long molecule tends to fold and the broad ^{1}H NMR spectra at a wide range of conditions confirm that the folded molecules keep their conformation quite tight.

These conclusions found additional proof by an X-ray structure of the XXXXX diamine.

6.1.2 Crystal structure of the linear diamine XXXXX 64

Single crystals suitable for X-ray analysis were isolated from a dichloromethane/acetone mixture upon slow evaporation.

Table 17. Selected crystal data and structure refinement for linear XXXXX **64**.

Empirical formula	$C_{124}H_{170}Cl_4N_{10}O_{14}$	Volume	6263.1(5) Å^3
Formula weight	2166.50	Z	2
Temperature	173(2) K	Density (calculated)	1.149 Mg/m^3
Crystal system	triclinic	Absorption coefficient	0.156 mm^{-1}
Space group	P - 1	Crystal size, mm	0.45x0.38x0.14
Unit cell dimensions	a = 14.9057(8) Å	Reflections collected	83963
	b = 20.4172(9) Å	Independent reflections	24000
	c = 21.4080(11) Å	Final R indices	R_1 = 0.1092
	α = 88.307(4)°		wR_2 = 0.2967
	β = 80.779(4)°	R indices (all data)	R_1 = 0.1391
	γ = 76.888(4)°		wR_2 = 0.3233

The asymmetric unit contains one molecule of the linear prentamer along with 2 molecules of dichloromethane and 1 molecule of acetone. The pentamer molecule is rolled up in a way that 6 of 8 urea hydrogens as well as hydrogens of the aminogroups are directed into the internal cavity, where they are interconnected by a network of hydrogen bonds. Two urea protons form hydrogen bonds with solvent molecules and do not take part in the intramolecular network.

As a result of the folding of the molecule two urea groups are far from coplanarity and their hydrogens point in different directions, while the other two groups change their "normal" conformation less significantly. At the same time the xanthene units are deformed only slightly and remain almost flat.

It is especially interesting, that both aminogroups are directed "inside" the folded molecule and participate in the internal hydrogen bond network. This may be the reason for lowered reactivity of the pentameric diamine towards the isocyanate in the elongation reaction.

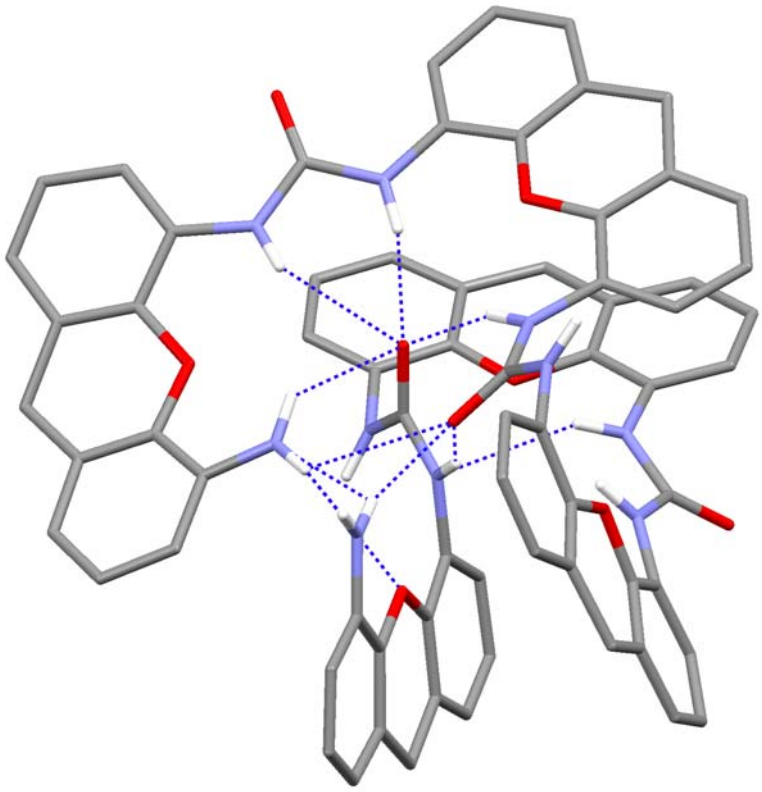


Figure 81. The conformation of a single molecule of the linear pentamer XXXXX in single crystal shown with the system of intramolecular hydrogen bonds. *tert*-Butyls and methyls of the xanthene units, as well as non-urea hydrogens are omitted for clarity.

The molecules of the linear pentamer do not interact via H-bonds in the crystal lattice. Similar to structures of other oligoureas the bulky alkyl groups of the xanthene units prevent the interaction between molecules in the lattice.

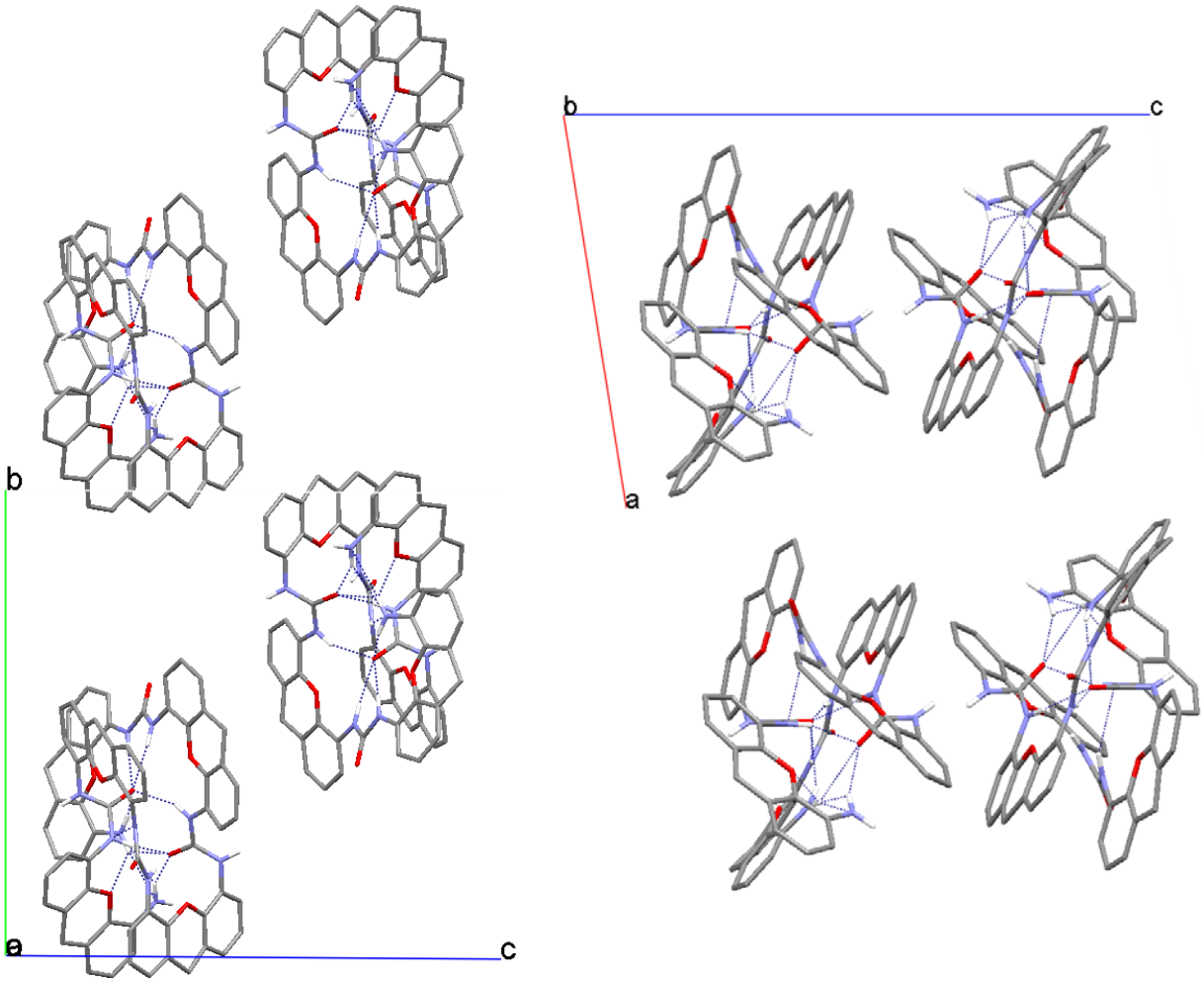


Figure 82. Arrangement of molecules of the linear pentamer XXXXX in the crystal lattice in the single crystal shown with the system of intramolecular hydrogen bonds. *tert*-Butyls and methyls of xanthene units, as well as non-urea hydrogens are omitted for clarity.

Obviously, even in the case of long oligourea based on rigid xanthene units we have met the well-known problem, that the molecules "prefer" to fold with the help of intramolecular hydrogen bonds. These bonds are built by the majority of the molecule's urea hydrogens, while only some H atoms interact with surrounding solvent molecules. Bulky residues of the unit hinder the solvation of the urea groups and additionally promote formation of the closed internal system of bonds.

There are other difficulties for the further studies and syntheses. The difference in physical properties (important for their chromatography and crystallization) between oligourea derivatives decreases with the increase of the chain length. Chromatographic separation and crystallization are less effective then. At the same time, if we would use the excess of the isocyanate in the elongation reaction it would result with additional

contaminations in the reaction mixture - either isocyanate itself, or, more probable, products of its hydrolisis and following reactions. In addition, the determination of the product purity is additionally complicated by the fact that ^{1}H NMR is useless for the evaluation of purity as well as for complexation studies of xanthene-based oligoureas with more than five units. No sharp spectra were obtained from the products of the reaction of elongation of pentameric diamine XXXXX.

In this situation the easiest and the most perspective way is to prepare more flexible oligoureas using diphenyl ether units instead of some of the xanthenes in the chain. At least in two cases – tetramers and hexamers - we have profited from the inroduction of D-unit(s) into the macromolecule. The most prominent example are hexamers, when we got effective and structurally unique anion host XXDXXD instead of cycle XXXXXX, fixed with stable system of hydrogen bonds, hardly soluble and passive towards anions.

6.2 The linear long oligourea chains on the basis of -[XXD]- blocks

It was already mentioned that compounds where two xanthene units are combined with one diphenyl ether based unit show a strong interaction with anions along with interesting conformational properties. These compounds are less subjected to folding to fixed conformations as mentioned before (i.e. we avoid the problem discussed in the prevoius subchapter) and their increased flexibility results in more accurate adjustment to anionic guests. Thus, the decision was taken to prepare a series of oligoureas, where two X-units would alternate with one D-unit in chain.

As the first target we took the hexameric oligourea XDXXDX **71** with amino-groups at both ends. Analogously to the synthesis of the xanthene-based chains (see 6.1.1) we planned to get the new compound by performing several elongation/deprotection reaction steps subsequently.

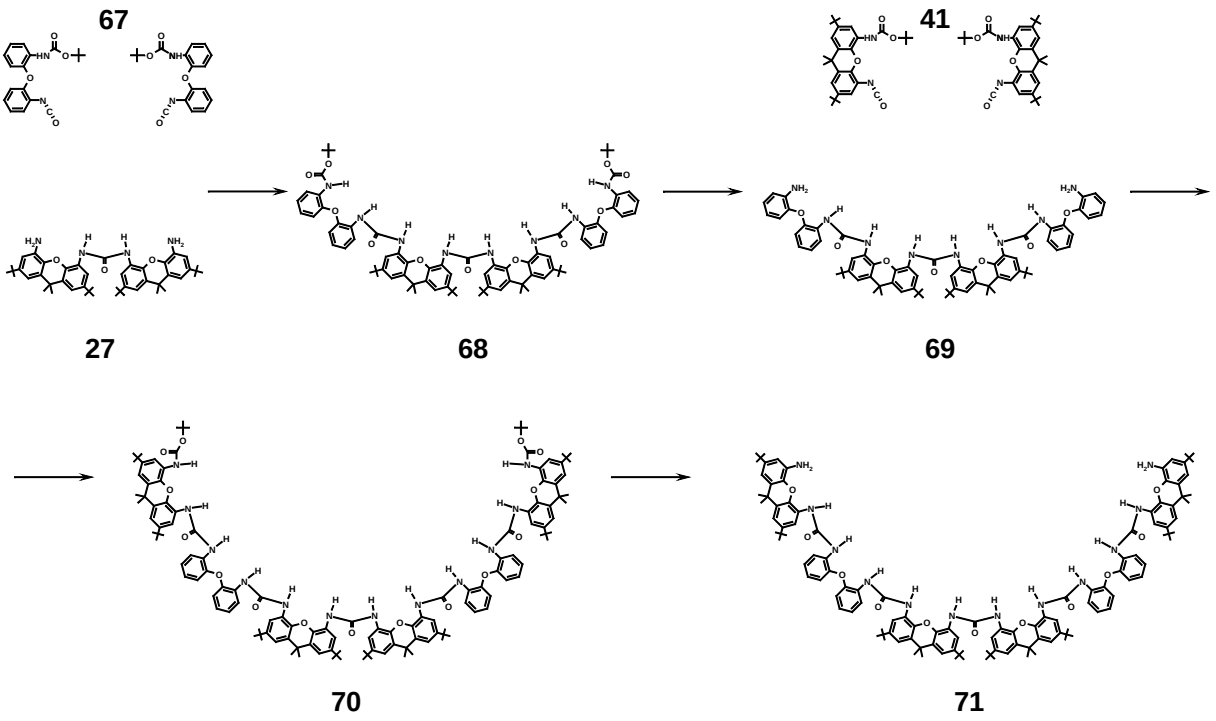


Figure 83. The subsequent chain elongation/deprotection reactions used for the preparation of the linear diamine XDXXDX **71.**

The synthesis of a long chain XXD starts from the XX-diamine **27**. In order to obtain the tetrameric molecule we need either to react the XX-diisocyanate **48** with monoprotected D-amine **25**, or the diamine **27** with the corresponding monoprotected D-isocyanate **67**. The second option was chosen, while the precursor for the isocanate **67** is much more cheaper and also prepared in 2 steps instead of 4 for the XX-diisocyanate.

Howewer, the synthesis of the monoprotected isocyanate **67** met some difficulties. The isocyanate was prepared in the known way using triphosgene and the Hünig base (diisopropylethylamine). After filtration through silicagel with subsequent evaporation a clear oil was isolated. According to the TLC and NMR spectrum the desired compound was successfully formed. However, in contrast to other isocyanates, the oil cannot be crystallized and remained liquid. After some unsuccessful synthetic attempts where the isocyanate it become clear that it cannot be stored due to the unusually high sensitivity to moisture. The isocyanate was partially destroyed already after 12-24 h and the precipitation of the crystalline diprotected DD-diamine **28** from the oil was observed, which is obviously formed in the reaction of the isocyanate with the monoprotected amine – product of the hydrolisis. Therefore the isocyanate should be prevented from contact with air and used immediately after the preparation or kept well isolated from moisture.

Later the corresponding corrections to the procedure of the preparation of the linear tetramer DXXD **68** were made. The compound was obtained by the reaction of the XX diamine and the monoprotected D-isocyanate in ethylacetate solution under nitrogen. The crude product was recrystallized from acetonitrile, yielding 84% of the pure oligourea **68**. The deprotection of the product with trifluoroacetic acid yielded the corresponding DXXD diamine **69** quantitatively.

The next elongation step was the reaction of the tetrameric diamine **69** with the monoprotected X isocyanate **59**. The reaction was performed analogously to the formation of the tetramer DXXD (only solvent was changed to the more polar THF). The desired diprotected linear hexamer XDXXDX **70** was isolated with a yield of 60-70%.

In contrast to the xanthene linear derivatives the newly prepared oligourea **70** is easily soluble in DMSO-d_6 and shows a pretty clear ^{1}H NMR spectrum without addition of any salt. The spectrum contains sharp signals in accordance with the expected (time-averaged) C_{2v} symmetry.

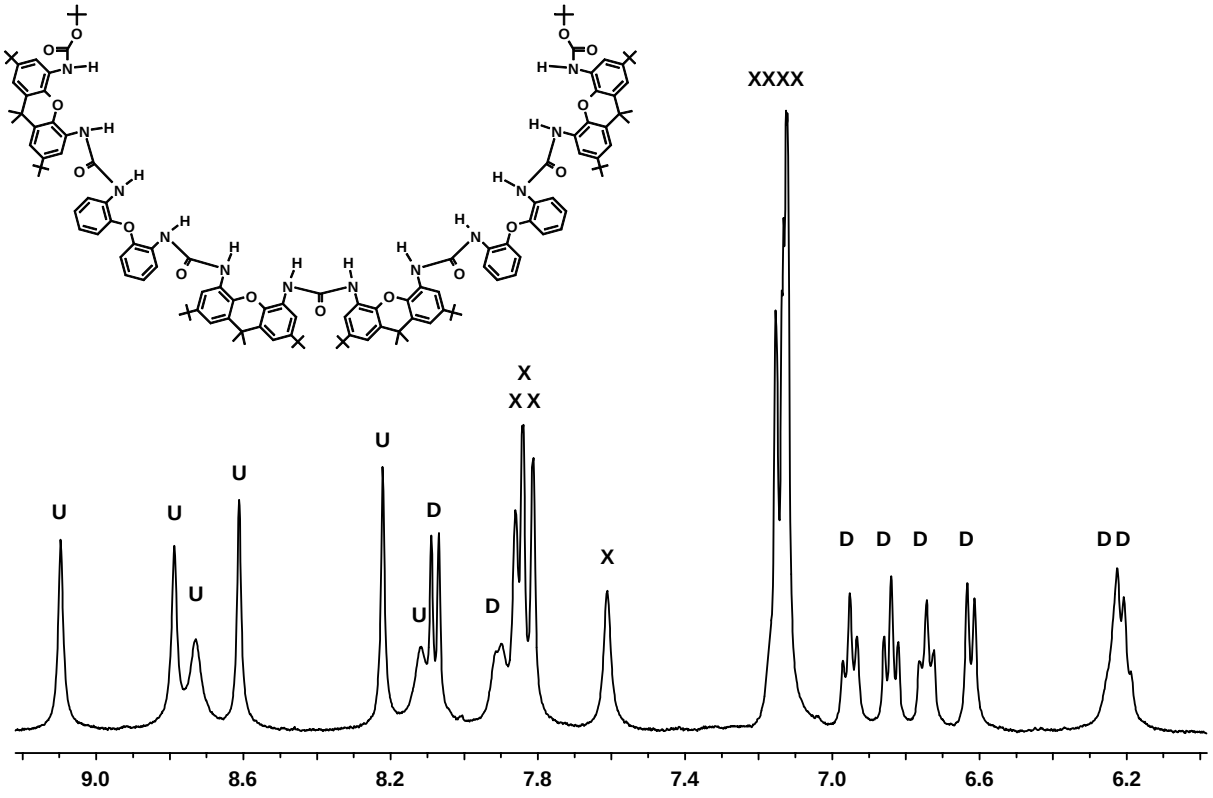


Figure 84. The low field region of the ^{1}H NMR spectrum of the diprotected hexamer **70**. Signals for the urea protons are marked with "**U**", aromatic protons of xanthene units with "**X**" and diphyenyl ether units with "**D**". Single signals (**U**, **D** or **X**) have 2H intensity each.

The high field region has five singlets for the five *tert*-butyls and two singlets for the methyl groups as expected.

Thus, our assumption that long oligourea molecules will have more conformational freedom with the introduction of diphenyl ether units was true.

This is the current stand of the work. After the next step – deprotection – the hexameric diamine may be used for either further elongation of the chain or other reactions. Such oligourea diamine unveils a bunch of possibilities beside of further elongation of the chain. The preparation of perspective cylcic macromolecules is also very promising. For example, the diamine could react with the trimeric diisocyanate with XDX structure. This "3+6" reaction could lead to the formation of the 72-membered nine-unit $[XXD]_3$ cycle ("nonamer"). An even more attractive possibility appears with the conversion of the hexameric diamine **71** to the corresponding diisocyanate. If such isocyanate would react with the XDXXDX diamine (i.e. "6+6" reaction), the 96-membered twelwe-unit cycle $[XXD]_4$ should be formed.

6.3 Conclusion.

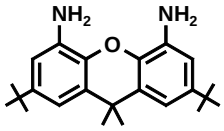
Synthesis of the long oligoureas brought almost the same difficulties as the synthesis of cycles. Compounds consisting exclusively of rigid xanthene units tend to assume folded conformations which are kept together with the network of the intramolecular hydrogen bonds. As a result of this folding we get molecules where urea groups are "hidden" from solvent molecules, as well as anions. The reactive amino groups can be involved in the network as well, what is confirmed by X-ray analysis of the pentamer XXXXX **64**, as well as by incomplete conversion in corresponding elongation reactions.

When we replaced each third unit with the more flexible diphenyl ether, we were able to prepare the hexameric oligourea XDXXDX **70** with clear spectrum. The compound may be used for the further elongation reactions, as well as for synthesis of large cycles.

7 Experimental part

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 or Bruker 200 spectrometers at 400 and 200 Hz respectively, and ^{13}C NMR on a Bruker Avance DRX 400 at 100 MHz using the solvent signals as internal reference. Mass spectra were recorded with the Finnigan MAT 8230 instrument. The melting points were not corrected.

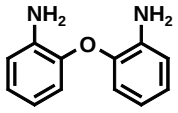
7.1 Diamine 15



The dicarbamate **22** (16,43 g, 26.5 mmol) was dissolved in THF (700 ml) and hydrogenated for 3 h at 60°C in the presence of catalyst (10% Pd/C, 1.3 g). Then the catalyst was filtered off and subsequently washed with THF (2x50 ml). The solvent was removed under reduced pressure and the yellow oily residue was dissolved in hexane (50 ml) with heating. The solution was kept at 0°C for 24 h, the yellowish precipitate was filtered off yielding X-diamine **15** (7.89 g, 85%). m.p. 200-205°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 6.59 (d, Ar*H*, 2 H, ^{4}J(H,H) = 2.4 Hz), 6.56 (d, Ar*H*, 2 H, ^{4}J(H,H) = 2 Hz), 1.50 (s, CH_3, 6 H), 1.23 (s, *tBu*, 18 H).

7.2 2,2'-oxydianiline 16



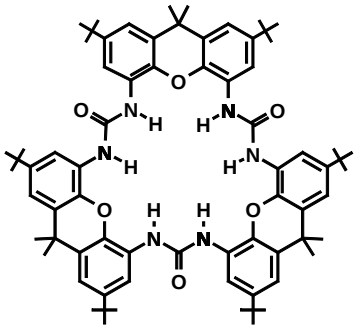
The 2,2'-oxydinitrobenzene **23** (10.2 g, 39 mmol) was dissolved in THF (600 ml) and hydrogenated for 3 h at room temperature in the presence of catalyst (10% palladium on activated carbon, 1.3 g). Then the catalyst was filtered off and subsequently washed with THF (2x50 ml). The solvent was removed under reduced pressure yielding diamine **16** as a dark-brown oil (7.84 g, 100%). The compound can be crystallized to a brown solid after initiation (for example by addition of a small particle of the crystalline diamine). m.p. 65°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 6.82 (t, Ar*H*, 2 H, ^{3}J(H,H) = 7.4 Hz), 6.76 (dd, Ar*H*, 2 H, ^{3}J(H,H) = 7.4 Hz, ^{4}J(H,H) = 1.6 Hz), 6.63 (d, Ar*H*, 2 H, ^{3}J(H,H) = 7.4 Hz), 6.48 (td, Ar*H*, 2 H, ^{3}J(H,H) = 7.4 Hz, ^{4}J(H,H) = 1.6 Hz), 4.89 (s, NH_2, 4 H).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.93 (td, Ar*H*, 2 H, ^{3}J(H,H) = 7.6 Hz, ^{4}J(H,H) = 0.7 Hz), 6.81 (dd, Ar*H*, 2 H, ^{3}J(H,H) = 7.8 Hz, ^{4}J(H,H) = 1.6 Hz), 6.77 (dd, Ar*H*, 2 H, ^{3}J(H,H) =

7.8 Hz, ^4J(H,H) = 1.6 Hz), 6.67 (ddd, Ar*H*, 2 H, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.4 Hz), 3.86 (br.s, NH_2, 4 H).

7.3 Trimer XXX 17

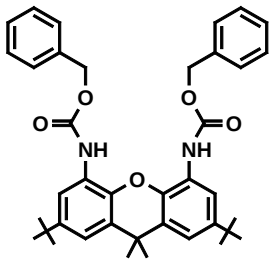


The dimeric diamine **27** (120 mg, 0.12 mmol) was dissolved in dichloromethane (10 ml) and then trifluoroacetic acid was added (0.3ml). The solvent was removed under reduced pressure after 15 min of stirring and the residual light-brown oil was dissolved in dichloromethane (10 ml). Then the solution of diisocyanate **31** (51 mg, 0.12 mmol) in dichloromethane (10 ml) along with triethylamine (0.2 ml) were added with stirring. The reaction mixture was stirred for the next 12 h. The solvent was removed under reduced pressure, the oily residue was dissolved in ethylacetate (10 ml) and filtered through silica gel (20 g) which was subsequently washed with ethylacetate (2x20 ml). The solvent was removed under reduced pressure and the residual yellow oil was dissolved in hexane (10 ml). After 2 h the precipitate appeared and was filtered off yielding the cyclic trimer **17** (50 mg, 37%) as thin white flakes. m.p. >340°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.34 (s, N*H*, 6 H), 7.50 (br.s, Ar*H*, 6 H), 7.06 (s, Ar*H*, 6 H), 1.44 (s, CH_3, 18 H), 1.23 (s, *tBu*, 54 H).

MS (FD): *m*/*z* 1134.8 [M^+].

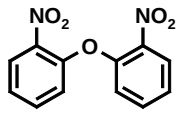
7.4 Bis-carbamate 22



The diacid **21** (16.04 g, 39 mmol) was dissolved in toluene (600 ml) and then benzyl alcohol (9.29 g, 86 mmol), triethylamine (8.68 g, 86 mmol) and DPPA (25.81 g, 94 mmol) were added to the solution. The solution was heated to 80°C and stirred for the next 18 h. The solvent was removed under reduced pressure, the oily residue was dissolved in 500 ml of methanol and left at 0°C for 48 h. The crystalline yellowish precipitate was filtered off, yielding bis-carbamate **22** (17.9 g, 74%). m.p. 195-198°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.56 (s, N*H*, 2 H), 7.70 (s, ArH_{xan}, 2 H), 7.38 (m, ArH_{Bz}, 8 H), 7.19 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 5.17 (s, OCH_2, 4 H), 1.58 (s, CH_{3xan}, 6 H), 1.26 (s, *tBu*, 18 H).

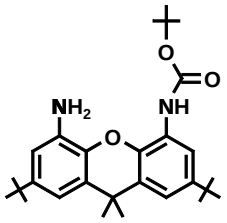
7.5 2,2'-dinitro diphenyl ether 23



2-nitrofluorobenzene (46.1 g, 327 mmol), *o*-nitrophenole (45.45 g, 327 mmol) and potassium carbonate (99.34 g, 719 mmol) were dissolved in DMSO (600 ml) and the bright red solution was stirred for the next 16 h at 105°C. The reaction was stopped by pouring the solution into 1800 ml of ice/water mixture. The yellow precipitate was filtered off and washed with water (3x200 ml) yielding 2,2'-dinitro diphenyl ether **23** (80.43 g, 94%) as a yellow solid. m.p. 119°C.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.04 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.5 Hz), 7.56 (ddd, Ar*H*, 2 H, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.8 Hz), 7.31 (ddd, Ar*H*, 2 H, ^3J(H,H) = 7.9 Hz, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.6 Hz), 7.05 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 1.1 Hz).

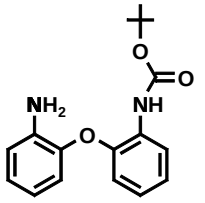
7.6 Mono BOC-protected X-amine 24



The solution of di-*tert*-butyl dicarbonate (5.26 g, 24 mmol) in THF (200 ml) was added dropwise over 1 h to the stirring solution of diamine **15** (8.50 g, 24 mmol) in THF (500 ml). After 18 h the solvent was removed under reduced pressure. The residual yellow oil was dissolved in the mixture of ethylacetate (2 ml) and hexane (18 ml) and was subjected to separation by column chromatography (silica gel 1 L, ethylacetate:hexane 1:8 (*v/v*)). The monoprotected diamine **24** (6.09 g, 55.8%) was isolated as a white powder. m.p. 173°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.86 (s, N*H*, 1 H), 7.63 (d, Ar*H*, 1 H, ^4J(H,H) = 2 Hz), 7.13 (d, Ar*H*, 1 H, ^4J(H,H) = 2 Hz), 6.64 (d, Ar*H*, 1 H, ^4J(H,H) = 2.4 Hz), 6.59 (d, Ar*H*, 1 H, ^4J(H,H) = 2.4 Hz), 5.21 (s, NH_2, 2 H), 1.53 (s, CH_3, 6 H), 1.49 (s, *tBu*, 9 H), 1.27 (s, *tBu*, 9 H), 1.23 (s, *tBu*, 9 H).

7.7 Mono BOC-protected D-amine 25

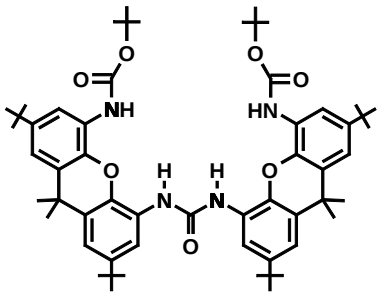


The solution of di-*tert*-butyl dicarbonate (6.86 g, 31.4 mmol) in THF (150 ml) was added dropwise over 1 h to the stirring solution of D-diamine **23** (6.30 g, 31.4 mmol) in THF (200 ml). The solution was stirred for the next 48 h at 60°C. Then the solvent was removed under reduced pressure. Residual brown oil was dissolved in the mixture of toluene (2 ml),

ethylacetate (2 ml) and hexane (16 ml) and was subjected to separation by a column chromatography (silica gel 1 L, ethylacetate:hexane 1:5 (v/v)). The monoprotected diamine **25** (4 g, 42%) was isolated as a white powder. m.p. 112°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.54 (s, N*H*, 1 H), 7.64-7.57 (m, Ar*H*, 1 H), 7.00-6.87 (m, Ar*H*, 3 H), 6.78 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.6 Hz), 6.58-6.50 (m, Ar*H*, 2 H), 1.46 (s, *tBu*, 9 H).

7.8 BOC-protected diamine XX 26

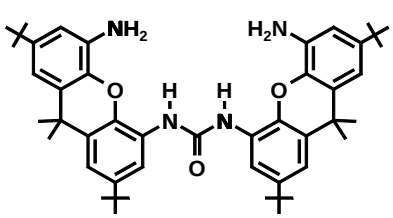


The solution of 4-nitrophenyl chloroformate (1.04 g, 5.1 mmol) in THF (100 ml) was added dropwise over 1 h to the stirring solution of monoprotected diamine **24** (4.65 g, 10.2 mmol) and diisopropylethylamine (1.33 g, 10.2 mmol) in THF (100 ml). The solution was stirred at 60°C for 18 h. Then the solvent was removed under reduced pressure. The residual yellow oil was dissolved in ethylacetate (100 ml) and the solution was washed with 5N sodium carbonate solution until the yellow color of nitrophenole disappeared. Then it was washed with distilled water (2x100 ml) and dried over $MgSO_4$. The solvent was removed in *vacuo* to give the protected dimeric diamine **26** (4.75 g, 99%) as a foam-like solid. m.p. >240°C (decomp.)

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.19 (s, N*H*, 2 H), 7.78 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 7.67 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 7.21 (d, Ar*H*, 2 H, ^4J(H,H) = 2.4 Hz), 7.19 (d, Ar*H*, 2 H, ^4J(H,H) = 2.4 Hz), 1.60 (s, CH_3, 12 H), 1.29 (s, *tBu*, 18 H), 1.27 (s, *tBu*, 18 H), 1.26 (s, *tBu*, 18 H).

MS(FD): *m/z* 931.8 [M^+].

7.9 XX-diamine 27



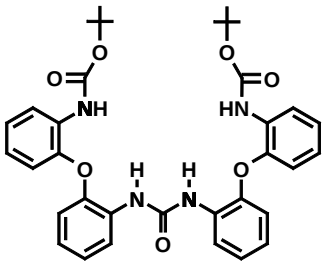
The BOC-protected dimeric diamine **26** (4.973 g, 5.33 mmol) was dissolved in dichloromethane (50 ml), the solution was cooled in ice bath and then trifluoroacetic acid (30 ml) was added to the flask. The reaction mixture was allowed to heat to the room temperature during the next 4 h of stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (300 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x50 ml).

Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding the dimeric diamine **27** (3.85 g, 98.6%) as a light-brown powder. m.p. >200°C (decomp.)

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.90 (s, N*H*, 2 H), 8.13 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 7.11 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 6.68 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 6.62 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 5.26 (s, NH_2, 4 H), 1.57 (s, CH_3, 12 H), 1.31 (s, *tBu*, 18 H), 1.26 (s, *tBu*, 18 H).

MS(FD): *m/z* 731.6 [M^+].

7.10 BOC-protected DD-diamine 28

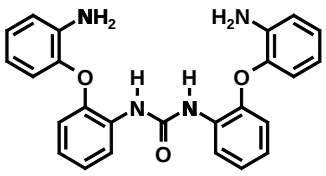


The solution of 4-nitrophenyl chloroformate (1.34 g, 6.66 mmol) in THF (100 ml) was added dropwise over 1 h to the stirring solution of the monoprotected diamine **25** (4 g, 13.3 mmol) and diisopropylethyl amine (1.72 g, 13.3 mmol) in THF (100 ml). The solution was stirred at 60°C for 18 h. Then the solvent was removed under reduced pressure. The oily residue was triturated with methanol (100 ml) resulting in a crystalline solid. The solid was filtered off and washed with methanol (3x50 ml) to remove residual nitrophenole. The BOC-protected dimeric diamine **28** (3.75 g, 90%) was obtained as a thin crystalline powder. m.p. 215°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.19 (s, N*H*, 2 H), 8.65 (s, N*H*, 2 H), 8.11 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.6 Hz), 7.84 (d, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz), 7.14-6.98 (m, Ar*H*, 6 H), 6.95 (td, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.6 Hz), 6.80 (dd, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 6.69 (dd, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 1.41 (s, *tBu*, 18 H).

MS(FD): *m/z* 627.3 [M^+].

7.11 DD-diamine 29



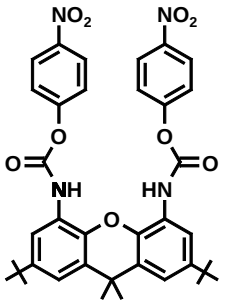
The BOC-protected dimeric diamine **28** (2.743 g, 4.37 mmol) was dissolved in dichloromethane (60 ml), then the solution was cooled in ice bath and the trifluoroacetic acid (30 ml) was added. The reaction mixture was allowed to heat to the room temperature during the next 4 h of stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (300 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with

dichloromethane (2x50 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding the dimeric diamine **29** (1.83 g, 97%) as a light-brown powder. m.p. 200°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.16 (s, N*H*, 2 H), 8.17 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.5 Hz), 7.01-6.83 (m, Ar*H*, 6 H), 6.80 (d, Ar*H*, 4 H, ^3J(H,H) = 8.2 Hz), 6.59-6.50 (m, Ar*H*, 4 H), 4.97 (s, NH_2, 4 H).

MS(FD): *m/z* 427.0 [M^+].

7.12 Active X-diurethane 30

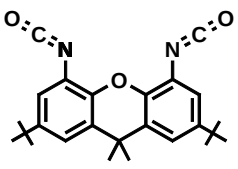


The solution of the diamine **15** (300 mg, 0.85 mmol) in ethylacetate (30 ml) was added dropwise over 10 min to the solution of 4-nitrophenyl chloroformate (342 mg, 1.7 mmol) in ethylacetate (30 ml). A white precipitate appeared in the reaction mixture. Then the solution of *N*-diisopropylethylamine (220 mg, 1.7 mmol) in ethylacetate (20 ml) was added dropwise over 30 min. White precipitate was dissolved completely. After 1 h of stirring the reaction mixture was filtered through silica gel (100 g) which was subsequently washed with ethylacetate (2x60 ml). The solvent was removed under reduced pressure and the residual white powder was washed with 1:1 (v/v) mixture of ether and hexane (2x25ml). The active uretane **30** (449 mg, 77%) was obtained as a white powder. m.p. 175°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 10.26 (s, N*H*, 2 H), 8.27 (d, Ar*H*, 4 H, ^3J(H,H) = 9.2 Hz), 7.77 (s, ArH_{xan}, 2 H), 7.57 (d, Ar*H*, 4 H, ^3J(H,H) = 9.2 Hz), 7.31 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.2 Hz), 1.64 (s, CH_{3xan}, 6 H), 1.29 (s, *tBu*, 18 H).

MS(FD): *m/z* 683.0 [M^+].

7.13 X-diisocyanate 31

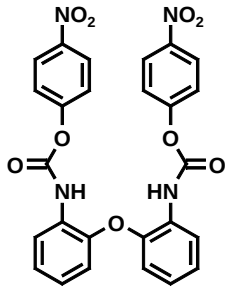


The diamine **15** (818 mg, 2.5 mmol) and the diisopropylethylamine (746 mg, 2.5 mmol) were dissolved in dichloromethane (20 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (650 mg, 5 mmol) in dichloromethane (20 ml) under the nitrogen flow. After 3 h the reaction mixture was filtered through silica gel (100 g) which was subsequently washed with dichloromethane (2x50 ml). The solvent was removed under reduced pressure and the crude product was heated on

rotavap for 1 h at 80°C to remove the excess of triphosgene. The diisocyanate **31** (781 mg, 76%) was obtained after cooling as a light-brown solid. m.p. 168°C.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.22 (d, Ar*H*, 2 H, ^4J(H,H) = 2.4 Hz), 7.01 (d, Ar*H*, 2 H, ^4J(H,H) = 2.4 Hz), 1.62 (s, C*H*$_3$, 12 H), 1.30 (s, *tBu*, 18 H).

7.14 Active X-diurethane 32

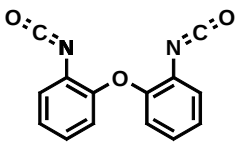


The solution of the diamine **16** (544 mg, 2.72 mmol) in ethylacetate (30 ml) was added dropwise over 10 min to the solution of 4-nitrophenyl chloroformate (1.37 mg, 6.79 mmol) in ethylacetate (30 ml). A white precipitate appeared in the reaction mixture. Then the solution of *N*-diisopropylethylamine (878 mg, 6.79 mmol) in ethylacetate (20 ml) was added dropwise over 30 min. The precipitate was dissolved completely. After 1 h of stirring the reaction mixture was filtered through silica gel (100 g) which was subsequently washed with ethylacetate (2x60 ml). The solvent was removed under reduced pressure and the residual solid was washed with ether (2x25ml). The active uretane **32** (1138 mg, 78%) was obtained as a light-brown powder. m.p. 171°C.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.26 (d, Ar*H*, 4 H, ^3J(H,H) = 9.2 Hz), 8.10 (br.d, Ar*H*, 2 H, ^3J(H,H) = 7.7 Hz), 7.68 (br.s, N*H*, 2 H), 7.36 (d, Ar*H*, 4 H, ^3J(H,H) = 9.2 Hz), 7.21 (dd, Ar*H*, 2 H, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.1 Hz), 7.12 (td, Ar*H*, 2 H, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.5 Hz), 6.90 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.1 Hz).

MS(FD): *m/z* 530.8 [M^+].

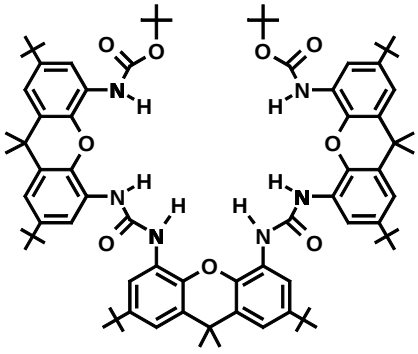
7.15 D-diisocyanate 33



The diamine **16** (1.477g, 7.37 mmol) and the *N*-diisopropylethylamine (1.91g, 14.7 mmol) were dissolved in dichloromethane (50 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (84 mg, 0.28 mmol) in dichloromethane (50 ml) under the nitrogen flow. After 3 h the reaction mixture was filtered through silica gel (100 g) which was subsequently washed with dichloromethane (2x50 ml). The solvent was removed under reduced pressure and the crude oily product was heated on rotavap for 1 h at 80°C to remove an excess of triphosgene. After cooling the isocyanate **33** (1.643 g, 88%) was obtained as a light-brown oil. The compound can be crystallized to a light-brown solid after initiation (for example by addition of small particle of the crystalline diisocyanate from previous syntheses). m.p. >95°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.35-7.18 (m, Ar*H*, 6 H), 7.02 (d, Ar*H*, 2 H, ^{3}J(H,H) = 8.3 Hz).

7.16 BOC-protected diamine XXX 34

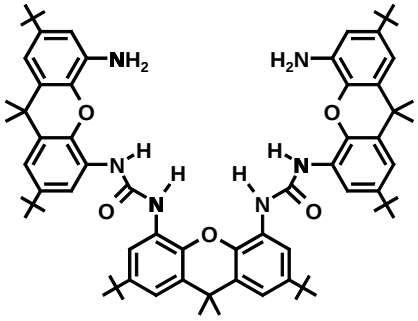


The solution of diamine **15** (0.88 g, 2.5 mmol) in dichloromethane (90 ml) was added dropwise over 30 min to the solution of BOC-protected isocyanate **34** (2.4 g, 5 mmol) in dichloromethane (90 ml) with stirring under the nitrogen. The solvent was removed under reduced pressure after 18 h of stirring. The residual sticky solid was triturated with acetonitrile (20 ml). The solid was filtered off and washed with acetonitrile (2x10ml) yielding BOC-protected trimeric diamine **11** (2.37g, 72%) as a light-yellow powder. m.p. >355°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.83 (s, N*H*, 2 H), 8.78 (s, N*H*, 2 H), 8.37 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.1 Hz), 7.77 (s, N*H*, 2 H), 7.73 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.8 Hz), 7.31 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.8 Hz), 7.18 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.1 Hz), 7.17 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.8 Hz), 7.13 (d, Ar*H*, 2 H, ^{4}J(H,H) = 1.8 Hz), 1.61 (s, CH_3, 6 H), 1.55 (s, CH_3, 6 H), 1.28 (s, *tBu*, 18 H), 1.27 (s, *tBu*, 36 H), 1.07 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1332.8 [M^{+}+Na].

7.17 Diamine XXX 35



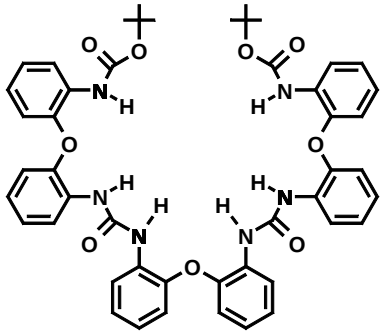
Trifluoroacetic acid (30 ml) was added to the solution of protected diamine **34** (2.375 g, 1.81 mmol) in dichloromethane (50 ml) cooled in ice bath with stirring. The reaction mixture was allowed to heat to the room temperature during the next 3 h of stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (400 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x50 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was triturated with 20 ml of acetonitrile. The solid was filtered off yielding dimeric diamine **35** (1678 mg, 83%) as a white powder. m.p. >360°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.79 (s, N*H*, 2 H), 8.74 (s, N*H*, 2 H), 8.08 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 7.97 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 7.20 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.13 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 6.62 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 6.26 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 4.83 (s, NH_2, 4 H), 1.66 (s, CH_3, 6 H), 1.50 (s, CH_3, 12 H), 1.32 (s, *tBu*, 18 H), 1.27 (s, *tBu*, 18 H), 1.15 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1132.4 [M$^+$+Na].

7.18 BOC-protected diamine DDD 36

The solution of diisocyanate **33** (329 mg, 1.3 mmol) in dichloromethane (10 ml) and was mixed with the solution of monoprotected diamine **25** (300 mg, 2.6 mmol) in dichloromethane (10 ml) with stirring under nitrogen. After 18 h the solvent was removed under reduced pressure yielding diprotected trimeric diamine **36** (1.1 mg, 99 %). m.p. >260°C (decomp.).

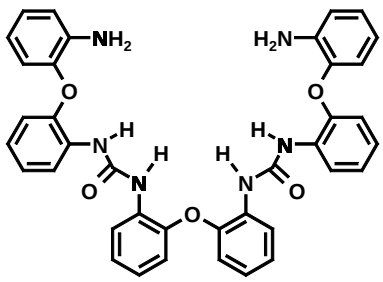


^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.08 (s, N*H*, 2 H), 8.95 (s, N*H*, 2 H), 8.62 (s, N*H*, 2 H), 8.29 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz), 8.05 (dd, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 7.81 (d, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz), 7.13-6.90 (m, Ar*H*, 12 H), 6.78 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz), 6.73 (d, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz), 6.69 (d, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz), 1.38 (s, *tBu*, 18 H).

MS(ESI): *m/z* 875.9 [M$^+$+Na].

7.19 Diamine DDD 37

Trifluoroacetic acid (10 ml) was added to the solution of protected diamine **36** (1.18 g, 1.3 mmol) in dichloromethane (20 ml) with stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (150 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x10 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding dimeric diamine **37** (510 mg, 60%) as a brownish powder. m.p. 185°C.

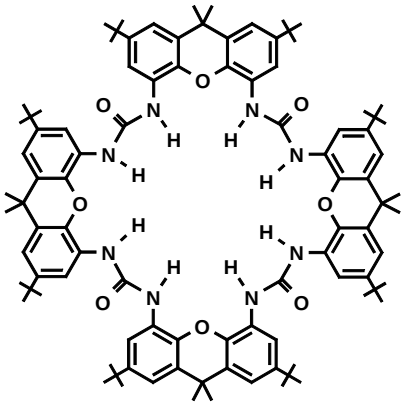


^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.23 (s, N*H*, 2 H), 9.17 (s, N*H*, 2 H), 8.29 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz), 8.15 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz,

^4J(H,H) = 1.6 Hz), 7.10 (td, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.6 Hz), 7.00-6.83 (m, Ar*H*, 8 H), 6.81-6.72 (m, Ar*H*, 6 H), 6.57-6.50 (m, Ar*H*, 4 H), 4.92 (s, N*H*, 4 H).

MS(ESI): *m/z* 675.7 [M^++Na].

7.20 Cyclic tetramer XXXX 38

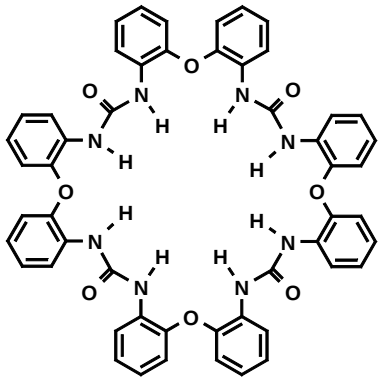


Solutions of the diamine **15** (124 mg, 0.35 mmol) and 4-nitrophenyl chloroformate (71 mg, 0.35 mmol) in $CHCl_3$ (50 ml each) were added simultaneously dropwise to a flask containing 100 ml of chloroform over 10 h with stirring. Then the solvent was removed in vacuo and a solution of *N*-ethyldiisopropylamine (46 mg, 0,35 mmol) in THF (xx ml) was added. Stirring was continued for the next 4 h. A white solid appears in the reaction mixture. The solid was filtered off and identified as the cyclic tetramer **38** (33 mg, 15%). m.p. >320°C (decomp.)

^{1}H NMR (400 MHz, DMSO-d_6, 120°C, δ): 8.67 (s, N*H*, 8 H), 7.87 (s, Ar*H*, 8 H), 7.19 (s, Ar*H*, 8 H), 1.65 (s, CH_3, 24 H), 1.38 (s, *tBu*, 72 H).

MS(FD): *m/z* 1514.9 [M^+].

7.21 Cyclic tetramer DDDD 39

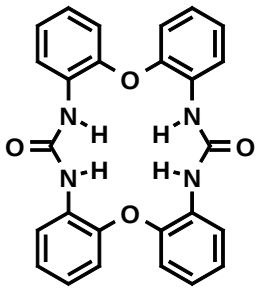


Solutions of the diamine **23** (500 mg, 2.5 mmol) in ethylacetate (50 ml) and the 4-nitrophenyl chloroformate (503 mg, 2.5 mmol) in ethylacetate (50 ml) were added simultaneously dropwise over 10 h to the flask containing ethylacetate (100 ml) with stirring under nitrogen. A white precipitate appeared in the reaction mixture. Then the solution of *N*-diisopropylethylamine (323 mg, 2.5 mmol) in ethylacetate (25 ml) was added dropwise over 2 h. The reaction mixture was left stirring for next 12 h. The white precipitate (112 mg, 20%) was filtered off, identified as cyclic DD-dimer **40**. The mother liquor was filtered through silica gel (100 g) which was washed with ethylacetate (3x60 ml). The solvent was evaporated so the volume decreased to 10 ml and left for 12 h in an opened 250 ml flask. The tetramer **39** (330 mg, 58%) was obtained as a colorless crystals. m.p. >215°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.19 (s, N*H*, 8 H), 8.34 (d, Ar*H*, 8 H, ^3J(H,H) = 6.6 Hz), 7.06 (t, Ar*H*, 8 H, ^3J(H,H) = 7.6 Hz), 6.91 (t, Ar*H*, 8 H, ^3J(H,H) = 7.4 Hz), 6.69 (d, Ar*H*, 8 H, ^3J(H,H) = 7.8 Hz).

MS(ESI): *m/z* 927.1 [M^++Na].

7.22 Cyclic DD-dimer 40

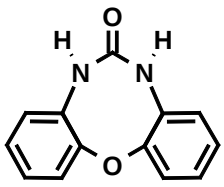


See 1.21 for the preparation procedure. m.p. >325°C (decomp.).

^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.86 (s, N*H*, 4 H), 7.80 (dd, Ar*H*, 4 H, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.8 Hz), 7.25 (dd, Ar*H*, 4 H, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz), 7.15-7.00 (m, Ar*H*, 8 H).

MS(FD): *m/z* 452.5 [M^+].

7.23 Cyclic urea 41



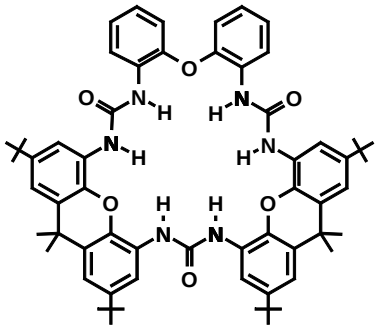
Solutions of the bis-trifluoroacetate of bis(2-aminophenyl) ether **16** (150 mg, 0.75 mmol) and of 4-nitrophenyl chloroformate (152 mg, 0.75 mmol) in CH_2Cl_2 (50 ml each) were mixed. A solution of *N*-ethyldiisopropylamine (388 mg, 3 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 2 h. Stirring was continued for the next 4 h. The solvent was removed under reduced pressure and the crude product was triturated with ethyl acetate (30 ml). A white solid was filtered off and identified as the cyclic dimer (25 mg, 15%). The filtrate was washed with 5% sodium carbonate solution and water until the yellow colour of *p*-nitrophenol disappeared. The organic layer was then filtered through silica gel (30 g), which was subsequently washed three times with ethyl acetate (3 × 25 ml). The final product **41** was precipitated from ethyl acetate (5 ml) with hexane (25 ml) as a brown powder (39 mg, 23%). m.p. >216°C (decomp.).Colourless crystals of **41**, suitable for X-ray analysis, separated from a solution of the product in a mixture of tetrahydrofuran and methanol (1:1) upon slow evaporation.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.89 (s, N*H*, 2H), 7.396 (dd, Ar*H*, 2H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.0 Hz) coupled with ^3J(H,H) to 7.065 (td, Ar*H*, 2H, ^3J(H,H) = 7.2 Hz, ^4J(H,H) = 1.4 Hz), 7.028 (dd, Ar*H*, 2H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 2.4 Hz) coupled with ^3J(H,H) to 6.98 (*ddd*, Ar*H*, 2H, $^3J(H,H)_1$ = 6.8 Hz, $^3J(H,H)_2$ = 7.8 Hz, ^4J(H,H) = 2.4 Hz);

^{13}C NMR (100 MHz, DMSO-d_6, δ): 154.86, 150.45, 132.89, 126.32, 124.83, 123.30, 123.06;

MS (FD) *m*/*z* 226.5.

7.24 Cyclic trimer XXD 42

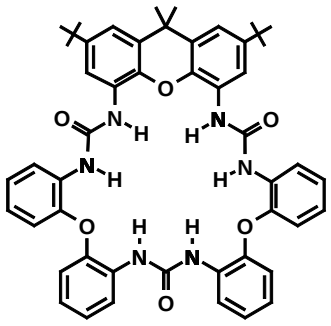


The diamine **27** (120 mg, 0.164 mmol) was dissolved in acetonitrile (25 ml). A solution of the diisocyanate **33** (42 mg, 0.164 mmol) in acetonitrile (15 ml) was added dropwise over 30 min with vigorous stirring under nitrogen. A white precipitate was filtered off after 12 h, yielding the trimer **42** (100 mg, 62%); m.p. >280°C (decomp.)

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.71 (s, N*H*, 2 H), 8.59 (s, N*H*, 2 H), 8.36 (s, N*H*, 2 H), 8.16 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 8.13 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 7.30 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.24 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.15 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 7.12 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.6 Hz), 7.02 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.0 Hz), 6.92 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 1.61 (s, CH_{3xan}, 12 H), 1.29 (s, *tBu*, 18 H), 1.21 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1005.6 [M$^+$+Na].

7.25 Cyclic trimer XDD 43

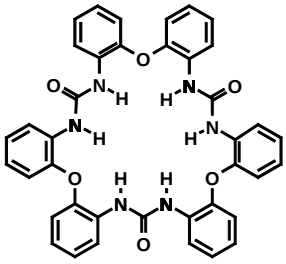


Solutions of the DD-diisocyanate **46** (100 mg, 0.201 mmol) in dichloromethane (25 ml) and the X-diamine **15** (73 mg, 0.201 mmol) in dichloromethane (25 ml) were added simultaneously dropwise over 2 h to the flask containing dichloromethane (20 ml) with stirring under nitrogen. The solvent was removed under reduced pressure after 18 h of stirring. The trimer **43** (70 mg, 40%) was separated from the residue by column chromatography (ethylacetate:hexane, 1:5) as a white powder. m.p. >340 °C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.14 (s, N*H*, 2 H), 8.93 (s, N*H*, 2 H), 8.30 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.3 Hz), 8.07 (d, ArH_{xan}, 2 H, ^4J(H,H) = 1.5 Hz), 8.01 (s, N*H*, 2 H), 7.75 (d, ArH_{diph}, 2 H, ^4J(H,H) = 7.3 Hz), 7.25-7.13 (m, ArH_{diph}, 2 H, overlapped with d at 7.17, ArH_{xan}, 2 H, ^4J(H,H) = 1.8 Hz), 7.10-6.99 (m, ArH_{diph}, 8 H), 6.74 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.7 Hz), 1.74 (s, CH_{3xan}, 3 H), 1.49 (s, CH_{3xan}, 3 H), 1.30 (s, *tBu*, 18 H).

MS(ESI): *m/z* 853.4 [M$^+$+Na].

7.26 Cyclic trimer DDD 44

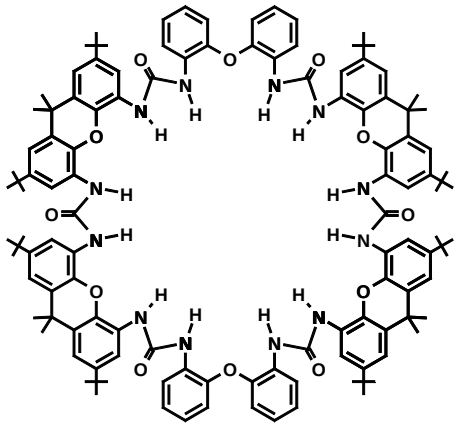


Solutions of the D-diisocyanate **33** (80 mg, 0.32 mmol) in dichloromethane (25 ml) and the DD-diamine **29** (135 mg, 0.32 mmol) in THF (25 ml) were added simultaneously dropwise over 2 h to the flask containing dichloromethane (50 ml) with stirring under nitrogen. The solvent was removed under reduced pressure after 18 h of stirring. The crude product was triturated with hexane (50 ml). The solid was filtered off and washed on the filter with hexane (2x25 ml). The trimer DDD (156 mg, 72%) was obtained as a beige powder. m.p. >184°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.86 (s, N*H*, 6 H), 7.97 (dd, Ar*H*, 6 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 7.06 (ddd, Ar*H*, 6 H, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 6.98 (ddd, Ar*H*, 6 H, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.6 Hz), 6.87 (dd, Ar*H*, 6 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz).

MS (ESI): *m*/*z* 701.22 [M^++Na].

7.27 Cyclic hexamer XXDXXD 45



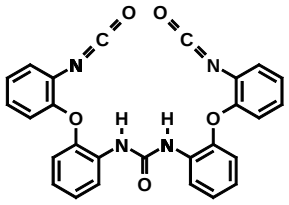
The diamine **27** (120 mg, 0.164 mmol) and tetrabutylammonium chloride (92 mg, 0.33 mmol) were dissolved in dichloromethane (20 ml). A solution of diisocyanate **33** (42 mg, 0.164 mmol) in dichloromethane (15 ml) was added dropwise over 30 min with vigorous stirring under nitrogen. After 12 h the solvent was removed under reduced pressure. The residue was triturated with ethyl acetate (10 ml) and the white solid was filtered off yielding 88 mg of the 1:2 complex of hexamer **45** with tetrabutylammonium chloride. The white powder was completely dissolved with dichloromethane (50 ml) and water (50 ml) and the organic layer was washed with water (2x50 ml), dried over $MgSO_4$ and evaporated, yielding hexamer **45** (66 mg, 41%) as a white solid; m.p. 254-256°C. The ^{1}H NMR data belong to a solution of **45** with TBA chloride (1:2) since the spectrum of hexamer **45** alone could not be interpreted.

^{1}H NMR (400 MHz, pyridine-d_5, δ): 10.69 (s, N*H*, 4 H), 10.64 (s, N*H*, 4 H), 9.29 (s, N*H*, 4 H), 9.22 (d, ArH_{xan}, 4 H, ^4J(H,H) = 2.0 Hz), 9.11 (dd, ArH_{diph}, 4 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz), 8.27 (d, ArH_{xan}, 4 H, ^4J(H,H) = 2.0 Hz), 7.29 (d, ArH_{xan}, 4 H, ^4J(H,H) =2.7

Hz), 7.28 (d, ArH_{xan}, 4 H, ^4J(H,H) = 2.4 Hz), 6.83 (dd, ArH_{diph}, 4 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 6.32 (td, ArH_{diph}, 4 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 6.18 (td, ArH_{diph}, 4 H, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.4 Hz), 3.28 (m, NCH_2, 16 H), 1.86 (s, CH_{3xan}, 12 H), 1.83 (s, CH_{3xan}, 12 H), 1.78 (s, *tBu*, 36 H), 1.65 (m, NCH_2CH_2, 16 H), 1.31 (s, *tBu*, 36 H), 1.29 (m, CH_2CH_3, 16 H), 0.83 (t, CH_2CH_3, 24 H, ^3J(H,H) = 7.4 Hz).

MS(ESI) *m/z* (%) 1989.2 [M^++Na].

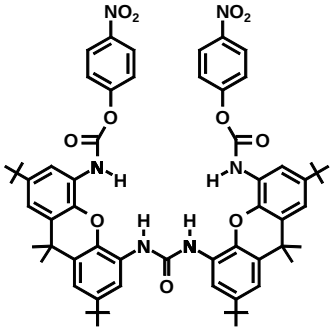
7.28 DD-diisocyanate 46



The dimeric diamine **29** (1 g, 2.345 mmol) and *N*-diisopropylethylamine (606 mg, 4.69 mmol) were dissolved in ethylacetate (20 ml) and THF (10 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (696 mg, 2.345 mmol) in dichloromethane (20 ml) under the nitrogen. After 3 h the reaction mixture was filtered through silica gel (50 g) which was subsequently washed with dichloromethane (2x50 ml). The solvent was removed under reduced pressure and the crude oily product was heated on rotavap for 1 h at 80°C to remove an excess of triphosgene. After cooling the isocyanate **46** (890 mg, 79%) was obtained as a brownish solid. m.p. 205°C.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.12 (dd, Ar*H*, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz), 7.18-6.98 (m, N*H*, Ar*H*, 12 H), 6.87-6.80 (m, Ar*H*, 4 H).

7.29 Active diurethane XX 47



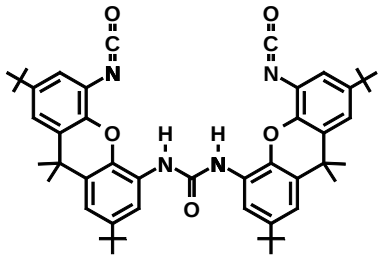
The solution of the diamine **27** (134 mg, 0.18 mmol) in ethylacetate (10 ml) was added dropwise over 10 min to the solution of 4-nitrophenyl chloroformate (111 mg, 0.55 mmol) in ethylacetate (10 ml). A white precipitate appeared in the reaction mixture. Then the solution of *N*-diisopropylethylamine (47 mg, 0.36 mmol) in ethylacetate (10 ml) was added dropwise over 30 min. White precipitate was dissolved completely. After 1 h of stirring the reaction mixture was filtered through silica gel (100 g) which was subsequently washed with ethylacetate (2x20 ml). The solvent was removed under reduced pressure and the residual white powder was washed with ether (2x25ml). The active uretane **47** (150 mg, 77%) was obtained as a light-brown powder. m.p. >170°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 11.03 (s, N*H*, 2 H), 8.12 (d, Ar*H*, 2 H, ^3J(H,H) = 9.4 Hz), 7.95 (s, N*H*, 2 H), 7.67 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.40 (d, Ar*H*, 2 H, ^4J(H,H) =

2.0 Hz), 7.26 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.08 (d, Ar*H*, 2 H, ^4J(H,H) = 2.3 Hz), 6.93 (d, Ar*H*, 2 H, ^3J(H,H) = 9.0 Hz), 1.65 (s, CH_3, 12 H), 1.30 (s, *tBu*, 18 H), 1.29 (s, *tBu*, 18 H).

MS(FD): *m/z* 1061.3 [M^+].

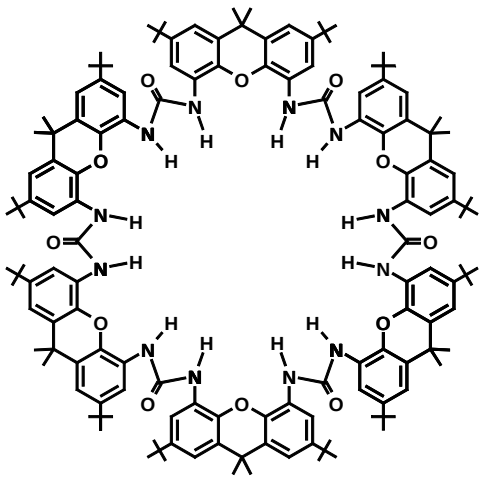
7.30 XX-diisocyanate 48



The dimeric diamine **27** (208 mg, 0.28 mmol) and the *N*-diisopropylethylamine (73 mg, 0.56 mmol) were dissolved in dichloromethane (15 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (84 mg, 0.28 mmol) in dichloromethane (10 ml) under the nitrogen. After 3 h the reaction mixture was filtered through silica gel (50 g) which was subsequently washed with dichloromethane (2x30 ml). The solvent was removed under reduced pressure and the crude oily product was heated on rotavap for 1 h at 80°C to remove the excess of triphosgene. After cooling the isocyanate **48** (190 mg, 85%) was obtained as a brownish solid. m.p. 158°C.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08 (d, Ar*H*, 2 H, ^4J(H,H) = 2.3 Hz), 7.30-7.17 (m (under solvent peak), Ar*H*, N*H*, 4 H), 7.10 (d, Ar*H*, 2 H, ^4J(H,H) = 2.3 Hz), 6.95 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 1.65 (s, CH_3, 12 H), 1.35 (s, *tBu*, 18 H), 1.30 (s, *tBu*, 18 H).

7.31 Cyclic hexamer XXXXXX 49



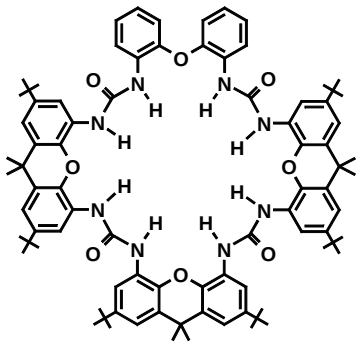
The diamine **27** (234 mg, 0,25 mmol) was dissolved in dichloromethane (25 ml). A solution of the diisocyanate **31** (100 mg, 0.25 mmol) in dichloromethane (25 ml) was added dropwise over 20 min with vigorous stirring under nitrogen. The solvent was removed in vacuo after 18 h of stirring. The crude product was triturated with hexane (25 ml). A white solid was filtered off, yielding hexamer **42** (129 mg, 49%); m.p. >370°C (decomp.).

^{1}H NMR (400 MHz, THF-d_8, δ): 11.66 (s, N*H*, 2 H), 8.89 (s, N*H*, 2 H), 8.82 (d, Ar*H*, 2 H, ^4J(H,H) = 2.3 Hz), 8.81 (s, N*H*, 2 H), 8.51 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 8.36 (s, N*H*, 2 H), 7.85 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.80 (s, N*H*, 2 H), 7.61 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.29 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.26 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.09 (d, Ar*H*, 2 H, ^4J(H,H) = 2.0 Hz), 7.02 (d, Ar*H*, 2 H,

^4J(H,H) = 2.0 Hz), 6.92 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 6.90 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 6.84 (d, Ar*H*, 2 H, ^4J(H,H) = 2.3 Hz), 6.70 (d, Ar*H*, 2 H, ^4J(H,H) = 1.6 Hz), 6.68 (s, N*H*, 2 H), 1.62 (s, CH_3, 6 H), 1.49 (s, CH_3, 6 H), 1.44 (s, CH_3, 6 H), 1.36 (s, *tBu*, 18 H), 1.33 (s, *tBu*, 18 H), 1.29 (s, CH_3, 6 H), 1.22 (s, *tBu*, 18 H), 1.03 (s, CH_3, 6 H), 0.99 (s, *tBu*, 18 H), 0.96 (s, *tBu*, 18 H), 0.95 (s, *tBu*, 18 H), 0.71 (s, CH_3, 6 H).

MS(ESI): *m/z* 2293.3 [M^++Na]

7.32 Cyclic tetramer XXXD 50

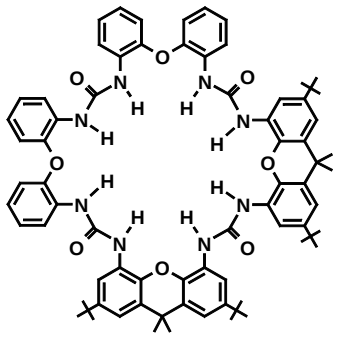


Solutions of the diisocyanate **33** (40 mg, 0.158 mmol) in dichloromethane (10 ml) and the XXX-diamine **35** (176 mg, 0.158 mmol) in dichloromethane (10 ml) were added simultaneously dropwise over 10 mi to the flask containing dichloromethane (20 ml) with stirring under nitrogen. The solvent was removed under reduced pressure after 18 h of stirring. The crude product was triturated with acetonitrile (15 ml). The solid was filtered off yielding the tetramer **50** (148 mg, 68.5%) as a white powder. m.p. >270°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, 120°C, δ): 9.53 (s, N*H*, 2 H), 8.64 (s, N*H*, 2 H), 7.90 (s, N*H*, 2 H), 7.86 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.82 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.4 Hz), 7.59 (s, N*H*, 2 H), 7.42 (ddd, ArH_{diph}, 2 H, ^3J(H,H) = 6.0 Hz, ^3J(H,H) = 5.0 Hz, ^4J(H,H) = 1.5 Hz), 7.33 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.3 Hz), 6.97 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.3 Hz), 6.93 (ddd, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.2 Hz), 6.91 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 6.88 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 6.60 (ddd, ArH_{diph}, 2 H, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.6 Hz), 1.76 (s, CH_3, 6 H), 1.38 (s, CH_3, 6 H), 1.33 (s, *tBu*, 18 H), 1.12 (s, *tBu*, 18 H), 1.11 (s, *tBu*, 18 H).

MS(FD): *m/z* 1362.6 [M^+].

7.33 Cyclic tetramerXXDD 51

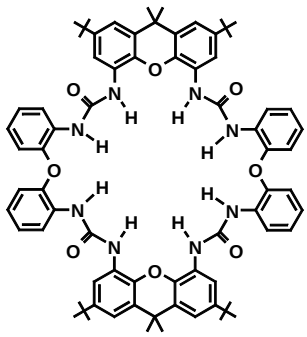


Solutions of the diisocyanate **46** (100 mg, 0.21 mmol) in dichloromethane (25 ml) and the dimeric diamine **27** (153 mg, 0.21 mmol) in dichloromethane (25 ml) were added simultaneously dropwise over 30 min to the flask containing dichloromethane (20 ml) with stirring under nitrogen. The solvent was removed under reduced pressure after 18 h of stirring. The crude product was triturated with acetonitrile (15 ml). The tetramer **51** (104 mg, 41%) was obtained as a white powder. m.p. >260°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, 120°C, δ): 9.25 (s, N*H*, 2 H), 8.40 (s, N*H*, 2 H), 8.21 (s, N*H*, 2 H), 7.97-7.59 (br.m, ArH_{diph}, ArH_{xan}, N*H*, 10 H), 7.21 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.18 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 6.75-6.42 (br.m, ArH_{diph}, 12 H), 1.65 (s, CH_3, 12 H), 1.31 (s, *tBu*, 18 H), 1.29 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1231.9 [M$^+$+Na].

7.34 Cyclic tetramer XDXD 52

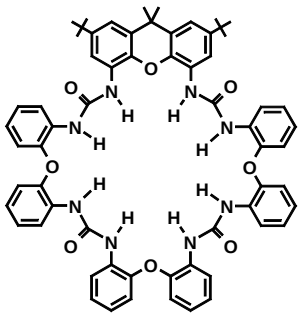


Solutions of the diisocyanate **31** (85 mg, 0.21 mmol) in dichloromethane (25 ml) and the trimeric DXD diamine **54** (170 mg, 0.21 mmol) in dichloromethane (25 ml) were added simultaneously dropwise over 30 min to the flask containing dichloromethane (25 ml) with stirring under nitrogen. The solvent was removed under reduced pressure after 8 h of stirring. The crude product was triturated with hot acetonitrile (15 ml, with boiling). After 1 h a beige solid appeared and was filtered off. The tetramer **52** (140 mg, 55%) was obtained as a light-beige powder. m.p. >235°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.78 (s, N*H*, 4 H), 8.39 (s, N*H*, 4 H), 8.22 (d, ArH_{xan}, 4 H, ^4J(H,H) = 2.0 Hz), 7.60 (m, ArH_{diph}, 4 H), 7.13 (d, ArH_{xan}, 4 H, ^4J(H,H) = 2.0 Hz), 7.00-6.92 (m, ArH_{diph}, 8 H), 6.86-6.79 (m, ArH_{diph}, 4 H), 1.59 (s, CH_3, 12 H), 1.28 (s, *tBu*, 36 H).

MS(ESI): *m/z* 1231.8 [M$^+$+Na].

7.35 Cyclic tetramer XDDD 53

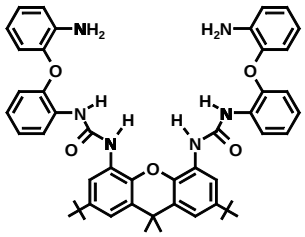


The DDD diamine **27** (100 mg, 0.15 mmol) and tetrabutyammonium chloride (43 mg, 0.15 mmol) were dissolved in acetonitrile (25 ml). The solution of the diisocyanate **31** (62 mg, 0.15 mmol) in acetonitrile (10 ml) was added dropwise over 1 h to the stirring diamine solution under the nitrogen. After 12 h the solvent was removed under reduced pressure and the crude product was dissolved in ethylacetate (10 ml). The solution was washed three times with 10 ml water each to remove the chloride. The organic layer was dried with magnesium sulphate. Then hexane (50 ml) was added to the solution. The beige precipitate was filtered off yielding the tetramer **53** (41 mg, 25%). m.p. >220°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, 120°C, δ): 8.78 (s, N*H*, 2 H), 8.68 (s, N*H*, 2 H), 8.38 (s, N*H*, 2 H), 8.27 (s, N*H*, 2 H), 8.00 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz), 7.90 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.85 (ddd, ArH_{diph}, 4 H, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.6 Hz), 7.14 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.12-6.82 (m, ArH_{diph}, 14 H), 6.79 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 6.74 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 1.61 (s, CH_3, 6 H), 1.30 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1079.5 [M^++Na].

7.36 Diamine DXD 54



The solution of monoprotected diamine **25** (215 mg, 0.716 mmol) in dichloromethane (10 ml) was added to the solution of diisocyanate **31** (145 mg, 0.358 mmol) in dichloromethane (10 ml) with stirring under the nitrogen. The solvent was removed under reduced pressure after 12 h of stirring yielding BOC-protected trimeric diamine (360mg, 100%) as a light-brown glass-like solid.

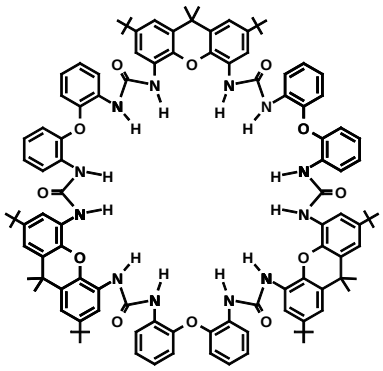
The BOC-protected dimeric diamine (360 mg, 0.358 mmol) was dissolved in dichloromethane (10 ml), the solution was cooled in ice bath and then the trifluoroacetic acid (10 ml) was added. The reaction mixture was allowed to heat to the room temperature during the next 4 h of stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (100 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x25 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was

removed under reduced pressure yielding dimeric diamine **34** (0.272 g, 94%) as a brown powder. m.p. >190°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.91 (s, N*H*, 2 H), 8.67 (s, N*H*, 2 H), 8.19 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.3 Hz), 7.86-7.80 (m, ArH_{diph}, 2 H), 7.14 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.3 Hz), 7.00-6.92 (m, ArH_{diph}, 4 H), 6.86 (ddd, ArH_{diph}, 2 H, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 1.6 Hz), 6.71 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.4 Hz), 6.63 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.2 Hz), 6.53-6.47 (m, ArH_{diph}, 2 H), 6.34 (ddd, ArH_{diph}, 2 H, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.4 Hz), 4.89 (s, NH_2, 4 H), 1.62 (s, CH_3, 6 H), 1.30 (s, *tBu*, 18 H).

MS(ESI): *m/z* 827.6 [M^++Na].

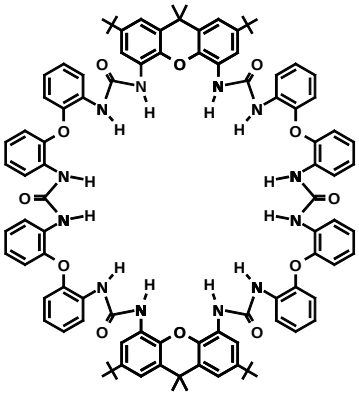
7.37 Cyclic hexamer XDXDXD 55



The diamine XDXDX **61** (18 mg, 0.015 mmol) and the diisocyanate 33 (2.9 mg, 0.015 mmol) were dissolved in dichloromethane (3 ml). The reaction mixture was stirred for 18 h. Then the solvent was removed under reduced pressure and the residue was triturated with acetonitrile. The white solid was filtered off yielding hexamer **55** (16 mg, 80%). m.p. >290°C (decomp.).

MS(ESI): *m/z* 1837.2 [M^++Na].

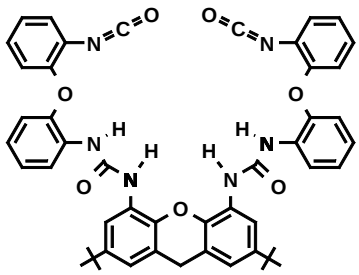
7.38 Cyclic hexamer XDDXDD 56



The diamine DXD **54** (130 mg 0,16 mmol) was dissolved in dichloromethane (25 ml) and added to the solution of the DXD diisocyanate **58** (138 mg 0,16mmol) in acetonitrile (75 ml) with stirring under nitrogen. After 18 h the solvent was removed under reduced pressure and the oily residue was triturated with acetonitrile. The XDDXDD hexamer **56** was isolated as a white powder (45%, 120 mg). m.p. 243°C.

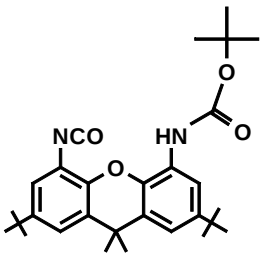
MS(ESI): *m/z* 1684.8 [M^++Na].

7.39 Diisocyanate DXD 58



The solution of the diamine **54** (136 mg, 0.17 mmol) with diisoprpylethylamine (44 mg, 0.34 mmol) in dichloromethane (25 ml) was added dropwise to the solution of triphosgene (50 mg, 0.17 mmol) in the acetonitrile (25 ml) with vigorous stirring under nitrogen. After 3 h the reaction mixture was filtered through silicagel followed by subsequent washing with dichloromethane (3x25 ml). The solvent was removed under reduced pressure yielding the diisocyanate **58** as a glass-like solid (95%, 138 mg). m.p. >185°C (decomp.).

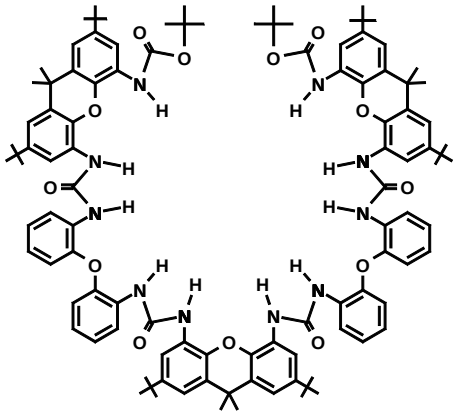
7.40 Monoprotected X-isocyanate 59



The monoprotected diamine **6** (200 mg, 0.44 mmol) and the *N*-diisopropylethylamine (57 mg, 0.22 mmol) were dissolved in dichloromethane (20 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (66 mg, 0.44 mmol) in dichloromethane (20 ml) under the nitrogen. After 3 h the reaction mixture was filtered through silica gel (50 g) which was subsequently washed with dichloromethane (2x30 ml). The solvent was removed under reduced pressure and the crude oily product was heated on rotavap for 1 h at 80°C to remove the excess of triphosgene. After cooling the isocyanate **59** (190 mg, 89%) was obtained as a beige solid. m.p. 172°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.90 (s, N*H*, 1 H), 7.56 (s, Ar*H*, 1 H), 7.37 (d, Ar*H*, 1 H, ^{4}J(H,H) = 2.0 Hz), 7.25 (d, Ar*H*, 1 H, ^{4}J(H,H) = 2.0 Hz), 7.02 (d, Ar*H*, 1 H, ^{4}J(H,H) = 2.0 Hz), 1.61 (s, CH_3, 6 H), 1.44 (s, *tBu*, 9 H), 1.28 (s, *tBu*, 9 H), 1.26 (s, *tBu*, 9 H).

7.41 Diprotected diamine XDXDX 60

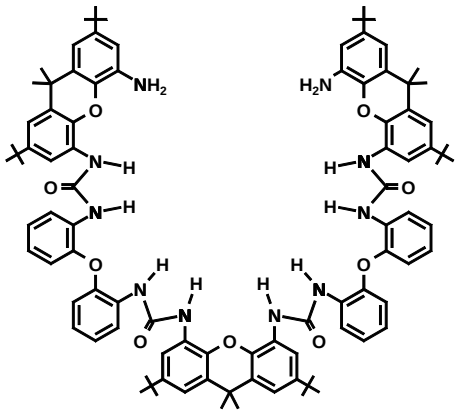


The solution of the diamine **60** (227 mg, 0.281 mmol) in THF (20 ml) was added to the solution of the isocyanate **34** (270 mg, 0.562 mmol) in THF (20 ml) with stirring under the nitrogen. The solvent was removed under reduced pressure after 18 h of stirring . The crude product was dissolved in acetonitrile. After 30 min a white precipitate appeared. The precipitate was filtered off yielding BOC-protected pentameric diamine **65** (290 mg, 58.3%) as a white powder. m.p. >210°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.10 (s, N*H*, 2 H), 8.73 (s, N*H*, 2 H), 8.69 (s, N*H*, 2 H), 8.67 (s, N*H*, 2 H), 8.22 (s, N*H*, 2 H), 8.17 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz), 7.90 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 7.86 (dd, ArH_{diph}, 2 H, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 2 Hz), 7.82 (d, ArH_{xan}, 2 H, ^4J(H,H) = 1.6 Hz), 7.77 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.4 Hz), 7.15 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.4 Hz), 7.14 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.4 Hz), 7.09 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 7.02 (m, ArH_{diph}, 4 H), 6.95 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.4 Hz), (dd, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 2 Hz), 6.76 (m, ArH_{diph}, 4 H), 1.56 (s, CH_{3xan}, 12 H), 1.54 (s, CH_{3xan}, 6 H), 1.26 (s, *tBu*, 18 H), 1.24 (s, *tBu*, 36 H), 1.18 (s, *tBu*$_{xan}$, 18 H).

MS(ESI): *m/z* 1784.7 [M^++Na].

7.42 Diamine XDXDX 61

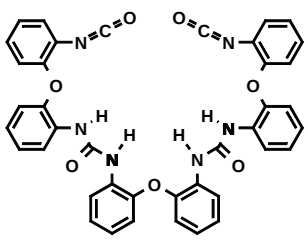


The BOC-protected dimeric diamine **60** (251 mg, 0.142 mmol) was dissolved in dichloromethane (10 ml) and then the trifluoroacetic acid (10 ml) was added. The reaction mixture was stirred for the next 3 h. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (200 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x25 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding dimeric diamine **61** (0.22 g, 99%) as a brownish glass-like solid. m.p. >190°C (decomp.)

^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.11 (s, N*H*, 2 H), 9.00 (s, N*H*, 2 H), 8.80 (s, N*H*, 2 H), 8.68 (s, N*H*, 2 H), 8.33 (dd, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz), 8.15 (d, ArH_{xan}, 2 H, ^{4}J(H,H) = 2.4 Hz), 8.02 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.4 Hz), 7.88 (dd, ArH_{diph}, 2 H, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 2.5 Hz), 7.07 (m, Ar*H*, 12 H), 6.74 (d, ArH_{diph}, ^3J(H,H) = 7.0 Hz), 6.61 (m, Ar*H*, 6 H), 6.46 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 4.80 (s, NH_2, 4 H), 1.55 (s, CH_{3xan}, 6 H), 1.51 (s, CH_{3xan}, 12 H), 1.27 (s, *tBu*$_{xan}$, 18 H), 1.18 (s, *tBu*$_{xan}$, ´18 H), 1.13 (s, *tBu*$_{xan}$, 18 H).

MS(ESI): *m/z* 1584.4 [M$^+$+Na].

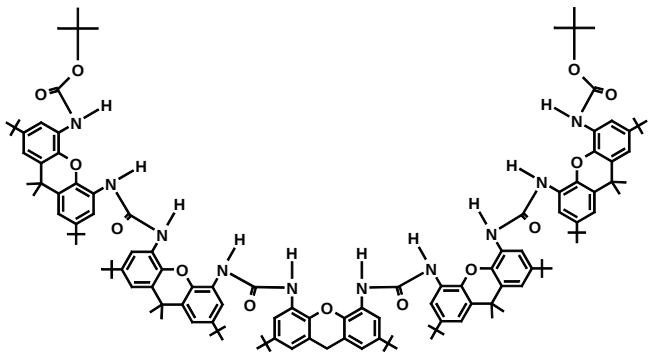
7.43 Diisocyanate DDD 62



The solution of the diamine **37** (0,8 g, 1.23 mmol) with diisoprpylethylamine (316 mg, 2.5 mmol) in the mixture of THF (50 ml) and dichloromethane (100 ml) was added dropwise over 30 min to the solution of triphosgene (364 mg, 1.23 mmol) in the acetonitrile (150 ml) with vigorous stirring under nitrogen. After 3 h the reaction mixture was filtered through silicagel followed by subsequent washing with dichloromethane (3 times 200 ml each). The solvent was removed under reduced pressure and the crude product was triturated with 50 ml of hexane. The trimeric diisocyanate **62** was isolated as a brownish powder (95%, 820 mg). m.p. >140°C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6, δ):9.14 (s, N*H*, 2 H), 9.10 (s, N*H*, 2 H), 8.24 (t, Ar*H*, 4 H, ^3J(H,H) = 6.9 Hz), 7.21 (m, Ar*H*, 4 H), 7.10 (m, Ar*H*, 6 H), 6.92 (m, Ar*H*, 6 H), 6.81 (d, Ar*H*, 2 H, ^3J(H,H) = 7.4 Hz), 6.72 (d, Ar*H*, 2 H, ^3J(H,H) = 7.8 Hz).

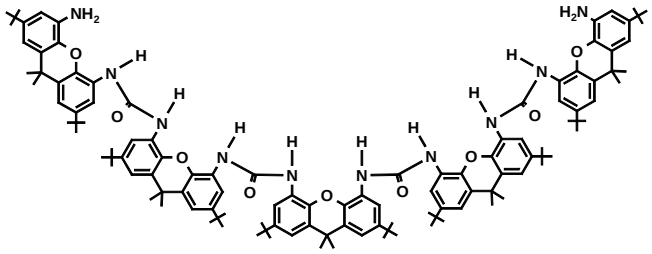
7.44 Diprotected diamine XXXXX 63



The solution of diamine **45** (873 mg, 0.78 mmol) in THF (50 ml) was added dropwise over 2 h to the stirring solution of isocyanate **34** (753 mg, 1.57 mmol) in dichloromethane (100 ml) under nitrogen. After 18 h the solvent was removed under reduced pressure and the crude product was dissolved in acetonitrile (80 ml) and left for 48 h at 0°C. Thin needle-like crystals were filtered off yielding protected pentameric diamine **40** (1420 mg, 76%). m.p. >210°C (decomp.).

MS(ESI): *m/z* 2089.2 [M^++Na].

7.45 Diamine XXXXX 64

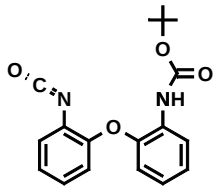


Trifluoroacetic acid (30 ml) was added to the solution of the protected diamine **40** (1 g, 0.48 mmol) in dichloromethane (30 ml) cooled in ice bath with stirring. The reaction mixture was allowed to heat to the room temperature during the next 4 h of stirring. The reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (400 ml). pH of the solution was controlled to be 9-10. The organic layer was separated, the water layer was washed with dichloromethane (2x50 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding pentameric diamine **64** (910 mg, 99%) as a brownish powder. m.p. >200°C (decomp.). The ^{1}H NMR data belong to a solution of **64** with TBA chloride (1:2) since the spectrum of hexamer **45** alone could not be interpreted.

^{1}H NMR (400 MHz, DMSO-d_6, δ):9.25 (s, N*H*, 2 H), 9.20 (s, N*H*, 2 H),8.98. (s, N*H*, 2 H), 8.62 (s, N*H*, 2 H), 7.94 (s, Ar*H*, 2 H), 7.87 (br s, Ar*H*, 2 H), 7.76 (s, Ar*H*, 2 H), 7.70 (br s, Ar*H*, 2 H), 7.06 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 7.02 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 6.98 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 6.94 (d, Ar*H*, 2 H, ^4J(H,H) = 2 Hz), 6.52 (br s, Ar*H*, 2 H), 6.20 (br s, Ar*H*, 2 H), 3.15 (m, NCH_2-, 16H,), 1.55 (m, NCH_2CH_2-, 16H), 1.42 (s, CH_{3xan}, 12 H), 1.28 (m, $NCH_2CH_2CH_2$-, *tBu*$_{xan}$, CH_{3xan}, 52H), 1.19 (s, *tBu*$_{xan}$, 18 H), 1.15 (s, *tBu*$_{xan}$, 36 H), 1.02 (s, *tBu*$_{xan}$, 18 H), 0.92 (t, $NCH_2CH_2CH_2CH_3$, 24H).

MS(ESI): *m/z* 1889.2 [M^++Na].

7.46 Monoprotected D-isocyanate 67

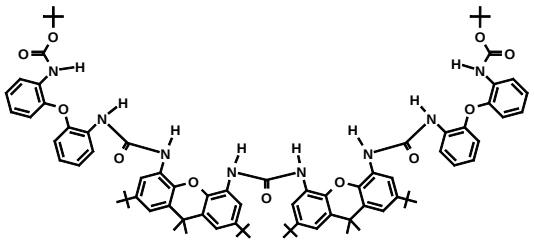


The monoprotected diamine **5** (1.11 g, 3.69 mmol) and the *N*-diisopropylethylamine (477 mg, 3.69 mmol) were dissolved in dichloromethane (50 ml) and this solution was added dropwise over 1 h to the vigorously stirred solution of triphosgene (548 mg, 1.85 mmol) in dichloromethane (30 ml) under nitrogen. After 3 h the reaction mixture was filtered through silica gel (50 g) which was subsequently washed with dichloromethane (3x50 ml). The solvent was removed under reduced pressure and the crude oily product was heated on

rotavap for 1 h at 80°C to remove an excess of triphosgene. After cooling the isocyanate **55** (1.07 mg, 89%) was obtained as a light-brown oil. The product is liquid at the room temperature which cannot be stored and should be used immediately after preparation.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (d, Ar*H*, 1 H, ^3J(H,H) = 7.8 Hz), 7.14 (m, Ar*H*, N*H*, 4 H), 6.98 (m, Ar*H*, 2 H), 6.88 (dd, Ar*H*, 1 H, ^3J(H,H) = 8 Hz, ^4J(H,H) = 2 Hz), 6.79 (dd, Ar*H*, 1 H, ^3J(H,H) = 8 Hz, ^4J(H,H) = 2 Hz), 1.53 (s, *tBu*, 9 H).

7.47 Diprotected diamine DXXD 68

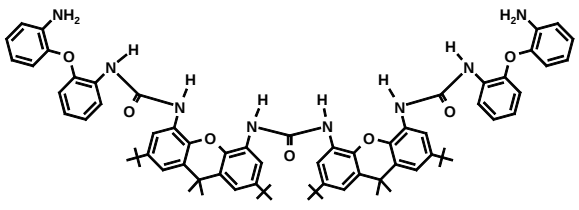


The solution of the XX diiamine **27** (570 mg, 0,78 mmol) in ethylacetate (20 ml) was added dropwise to the solution of the fresh prepared monoprotected isocyanate **67** (509 mg, 1.56 mmol) in ethylacetate (15 ml) and dichloromethane (15 ml) with stirring under nitrogen. After 12 h the solvent was removed under reduced pressure and the residue was dissolved in the boiling acetonitrile and then allowed to cool down to the room temperature. After 12 h the crystalline precipitate appeared and was filtered off. The diprotected DXXD compound **68** was isolated as a white crystalline powder (908 mg, 84%). m.p. 190°C

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.70 (s, N*H*, 2 H), 8.61 (s, N*H*, 2 H), 8.51 (s, N*H*, 2 H), 8.35 (s, N*H*, 2 H), 7.95 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 7.72 (s, ArH_{diph}, 2 H ArH_{xan} 2 H), 7.62 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 7.18 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 7.14 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2 Hz), 6.90 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 6.81 (m, ArH_{diph}, 4 H), 6.53 (t, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz), 6.40 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz), 6.33 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 1.59 (s, CH_{3xan}, 12 H), 1.32 (s, *tBu*, 18 H), 1.28 (s, *tBu*, 18 H), 1.22 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1405.8 [M^++Na].

7.48 Diamine DXXD 69



Trifluoroacetic acid (30 ml) was added to the stirring solution of protected diamine **68** (2 g, 3.2 mmol) in dichloromethane (30 ml). After 3 h the reaction was stopped by slow pouring of the reaction mixture to the 5N solution of sodium carbonate (400 ml). pH of the solution was controlled to be 9-10. The

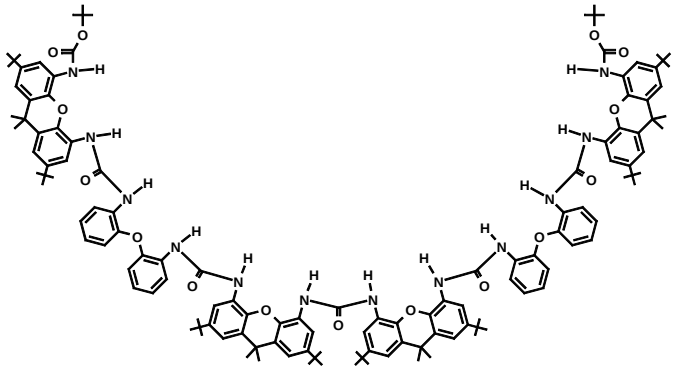
organic layer was separated, the water layer was washed with dichloromethane (2x100 ml). Dichloromethane solutions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure yielding tetrameric diamine **69** (1133 mg, 99%) as a white powder. m.p. 185°C.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.81 (s, N*H*, 2 H), 8.73 (s, N*H*, 2 H), 8.43 (s, N*H*, 2 H), 8,03 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.82 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.8 Hz), 7.75 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.19 (d, ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 7.14 *d*, (ArH_{xan}, 2 H, ^4J(H,H) = 2.0 Hz), 6.79 (m, ArH_{diph}, 6 H), 6.59 (d, ArH_{diph}, 2 H, ^3J(H,H) = 7.0 Hz), 6.31 (t, ArH_{diph}, 4 H, ^3J(H,H) = 8.4 Hz), 6.13 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.0 Hz), 4.68 (s, NH_2, 4 H), 1.60 (s, CH_{3xan}, 12 H), 1.28 (s, *tBu*, 18 H), 1.20 (s, *tBu*, 18 H).

MS(ESI): *m/z* 1206.0 [M$^+$+Na].

7.49 Diprotected diamine XDXXDX 70

The solution of the DXXD diiamine **69** (628 mg, 0.53 mmol) in THF (50ml) was added dropwise to the solution of the isocyanate **59** (508 mg, 1.06 mmol) in THF (50 ml) with stirring under nitrogen. After 12 h the solvent was removed under reduced pressure and the residue was dissolved in boiling acetonitrile and then allowed to cool down to the room temperature. After 48 h a white precipitate appeared which was then filtered off. The diprotected XDXXDX **70** was isolated as a white crystalline powder (771 mg, 68%). m.p. >190°C (decomp.).



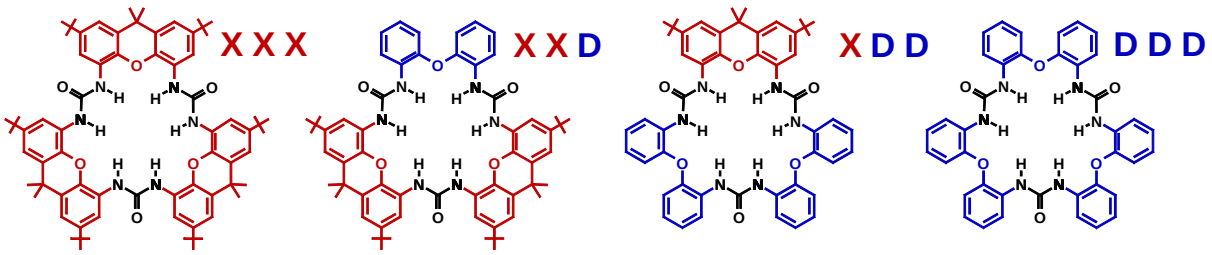
^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.10 (s, N*H*, 2 H), 8.79 (s, N*H*, 2 H), 8.73 (br s, N*H*, 2 H), 8.61(s, N*H*, 2 H), 8,22 (s, N*H*, 2 H), 8.12 (br s, N*H*, 2 H), 8.07 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.6 Hz), 7.91 (br s, ArH_{diph}, 2 H), 7.86 (s, ArH_{xan}, 2 H), 7.84 (s, ArH_{xan}, 2 H), 7.81 (s, ArH_{xan}, 2 H), 7.61 (br s, ArH_{xan}, 2 H), 7.24 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.4 Hz), 7.14 (m, Ar*H*, 6 H), 6.95 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.6 Hz), 6.84 (t, ArH_{diph}, 2 H, ^3J(H,H) = 7.6 Hz), 6.74 (t, ArH_{diph}, 2 H, ^3J(H,H) = 8. Hz), 6.62 (d, ArH_{diph}, 2 H, ^3J(H,H) = 8.2 Hz), 6.23 (br s, ArH_{diph}, 4 H), 1.56 (s, CH_{3xan}, 12 H), 1.55 (br s, CH_{3xan}, 12 H), 1.26 (s, *tBu*$_{xan}$, 18 H), 1.23 (s, *tBu*$_{xan}$, 18 H), 1.22 (s, *tBu*$_{xan}$, 36 H), 1.16 (s, *tBu*$_{xan}$, 18 H).

MS(ESI): *m/z* 2163.2 [M$^+$+Na].

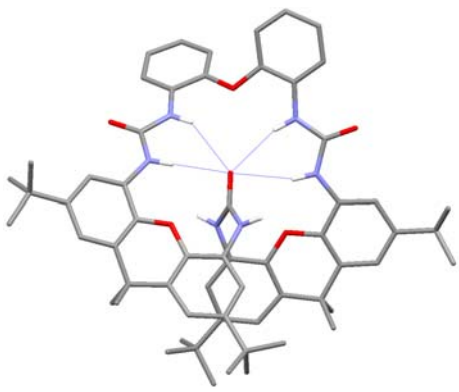
Summary

The NH-groups of dialkyl or diarylurea derivatives are strong hydrogen bond donors. This property has been frequently used for the development of self-assembled structures and for the construction of anion receptors. The special features of anions (such as low charge density, polarizability, variety of geometries) require from a receptor the cooperative interaction of preorganized ligating groups. Thus, it was decided to prepare new anion receptors using a combination of several urea functions within a (rigidified) supramolecular structure.

Based on computer simulations the cyclic arrangement of three urea groups interconnected by rigid structural elements of the xanthene type seemed promising for the binding of nitrate. Since receptor properties are in general determined by a delicate balance between the prearrangement of ligating functions ("rigidity") and the ability to adapt to the target guest ("flexibility") we decided to replace the xanthene units (**X**) partly by the more flexible diphenylether unit (**D**).



A series of cyclic triureas was synthesized, representing all possible combinations of the two units. The compounds were prepared by the reaction of the diamine consisting of two units connected via urea group and a diisocyanate (or activated diurethane) made from a single diamine ("2+1" cyclization).

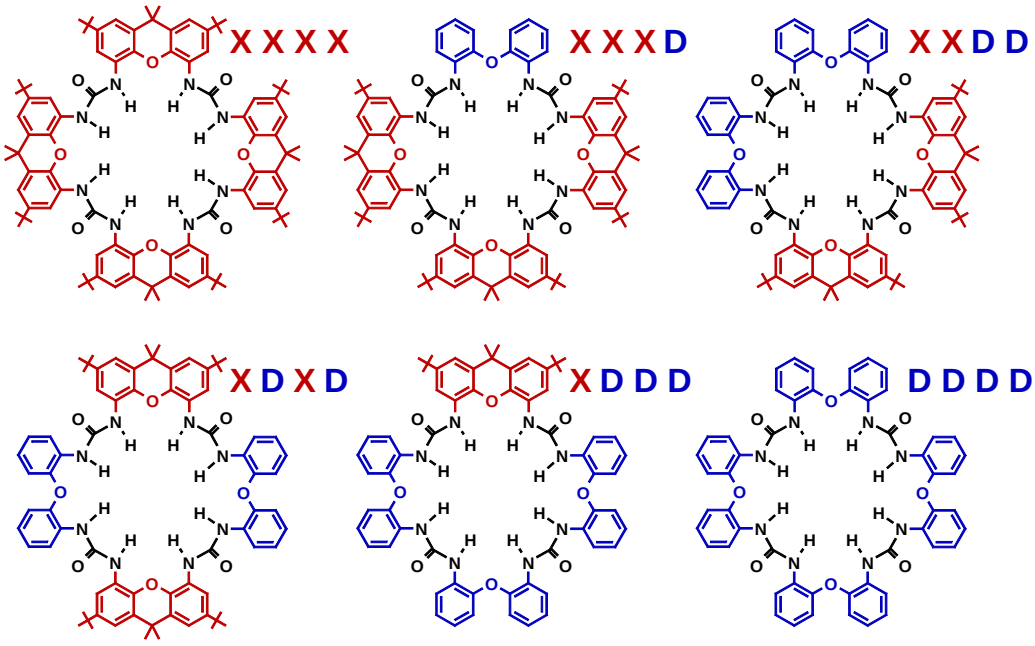


X-ray structure of the trimer XXD

The trimers showed strong binding with anions, especially with chloride and bromide, which was confirmed by significant changes in NMR spectra in solution. In contrast to halides nitrate anions are bound much weaker. Further studies as well as X-ray structure determinations revealed the formation of strong intramolecular hydrogen bonds as the main reason. Despite the strong skeleton distortion the

hydrogen bonding between urea groups of the cycle competes with anion complexation, even in case of the "rigid" trimer XXX. The strongest activity towards anions was shown by the more flexible trimer XXD, followed by XDD and DDD, while in case of XXX the urea hydrogens are obviously not accessible for anions due to the bulky and rigid skeleton.

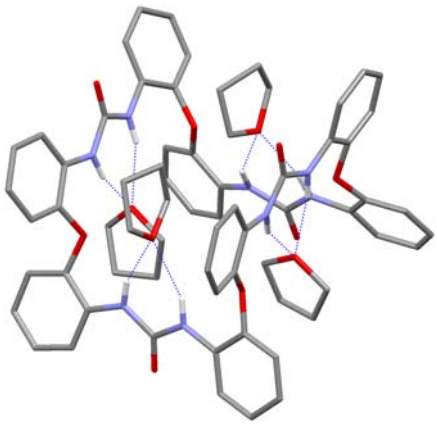
The full set of tetrameric cycles combined from the X and D units was prepared using different approaches. The XXXX and DDDD were prepared directly from diamines by the reaction with triphosgene (or *p*-nitrophenyl chloroformate). The preparation of mixed cycles required the synthesis of dimeric and trimeric linear diamino-oligoureas with their subsequent cyclization ("3+1" and "2+2") to the tetramer using the corresponding isocyanates or active urethanes.



Interactions of these compounds with anions were studied by ^{1}H NMR. A significant shift of the signals (especially for those of the urea protons), their sharpening or broadening and also a rearrangement of the signals in the spectrum were observed.

According to NMR and X-ray observations tetramers tend strongly to assume folded conformations stabilized by intramolecular hydrogen bonds. Even solvents of high polarity hardly can compete with the system of these bonds when dealing with a compound built with several rigid units with bulky alkyl substituents, such as XXXD or XXXX, which are soluble in DMSO-d_6 only at elevated temperature.

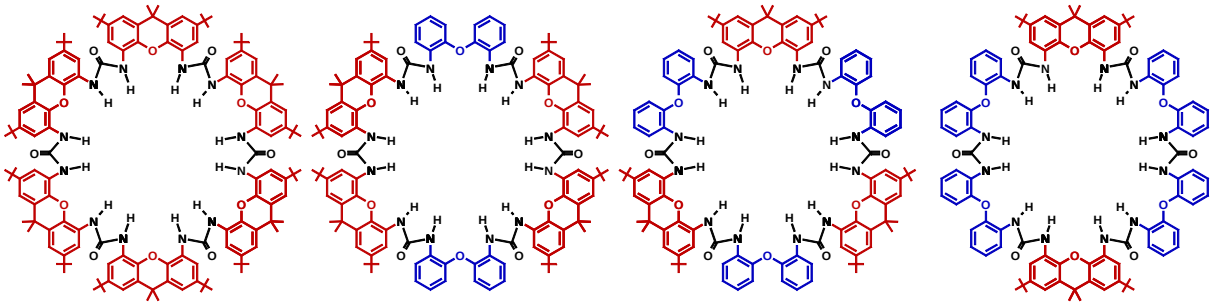
The same factors affect also the complexation of anions. For example, the rigid XXXX cycle can stay dissolved at room temperature for less than an hour in the presence of chloride, while the solution of XXXD with TBA chloride is stable after cooling. The more flexible tetramers are soluble in DMSO-d_6 without an addition of salts.



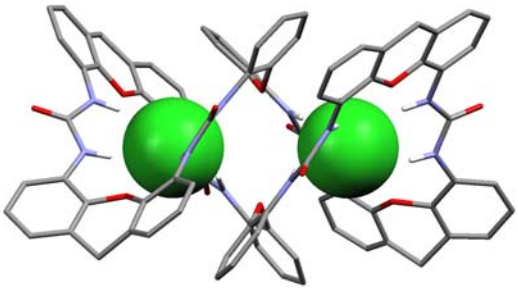
X-ray structure of the cyclic DDDD

However, with the increase of "flexibility" of our compounds we observe that intensity of their interaction with chloride decreases (as far as it can be followed by ^{1}H NMR). While the XXXX demonstrates among all tetramers the strongest shift of the urea protons signal, the entirely "flexible" DDDD shows a very weak response to the chloride addition. At the same time a quite pronounced effect upon addition of other anions can be observed in the ^{1}H NMR spectra of the DDDD cycle. This indicates the ability of the flexible DDDD to adjust its urea groups to the anions with a complicated non-spherical shape.

Four new cyclic hexaureas with different combinations of X and D units were synthesized and their conformational behaviour and complexation properties towards anions were evaluated by X-ray and ^{1}H NMR.



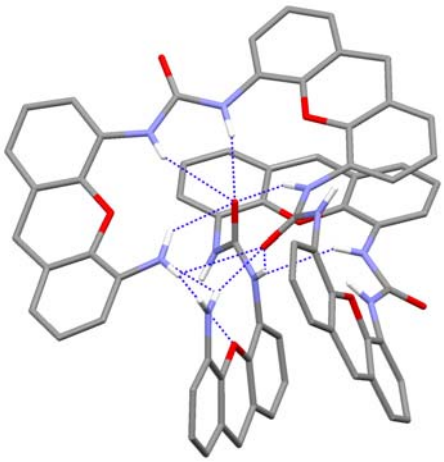
The studies showed that these properties depend strongly on the number and distribution of the xanthene and diphenyl ether units. The entirely "rigid" hexamer XXXXXX forms a stable conformation with the help of intramolecular hydrogen bonds, which is hardly accessible for solvation, as well as for anion complexation. The XXDXXD with two more flexible diphenyl ether units has an undefined conformation, determined by a "chaotic" system of hydrogen bonds. Upon addition of an anion the conformation is drastically changed and stabilized. The stability of the complex formed with two chloride anions is so high that addition of a chloride strongly increases the yield of the hexamer XXDXXD when two molecules of XX-diamine and two molecules D-diisocyanate are reacted in dichloromethane, demonstrating therefore the unprecedented example of the templation by the two anions.



X-ray structure of the complex of XXDXXD with two chloride anions

With the introduction of the next "flexible" diphenyl ether units the hexameric cycle gains additional freedom for intramolecular hydrogen bonding. We have found that hexamers XDDXDD and XDXDXD are heavily folded due to the intramolecular interaction of the urea groups, which are at the same time not active towards anions. Therefore, the strongest affinities to anions were found when the cycle is built using the "XXD" sequence. An analogous conclusion has been made also after analysis of the complexation properties of the trimers.

The synthesis of long oligoureas chains was also developed. Compounds consisting exclusively of rigid xanthene units tend to assume folded conformations which are kept together with the network of the intramolecular hydrogen bonds. As a result of this folding we obtained molecules where the urea groups are "hidden" from solvation, as well as from anions. The reactive amino groups can be involved in the network as well, what is confirmed by X-ray analysis of the linear compound XXXXX.



X-ray structure of the folded linear oligourea-based diamine XXXXX

When we replaced each third unit with the more flexible diphenyl ether, we were able easily to prepare the hexameric oligourea XDXXDX. The compound may be used for the further elongation reactions, as well as for the synthesis of large cycles featuring the promising XXD-sequence.

Author's list of publications

Publications.

3-Oxa-6,8-diaza-1,2:4,5-dibenzocycloocta-1,4-dien-7-one: a three-dimensional network assembled by hydrogen-bonding, - and edge-to-face interactions.

V. Böhmer, D. Meshcheryakov, I. Thondorf and M. Bolte, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, **2004**, (60), o136-o139.

Formation of a Cyclic Hexaurea Templated by Two Chloride Anions.

D. Meshcheryakov, V. Böhmer, M. Bolte, V. Hubscher-Bruder, F. Arnaud-Neu, H. Herschbach, A. Van Dorsselear, I. Thondorf, W. Mögelin, *Angew. Chem.,* **2006**, *118*, 1679-1682; *Angew. Chem. Int. Ed.*, **2006**, *45*, 1648-1652.

Presentation on conferences.

Formation of a Cyclic Hexaurea Templated by Two Halide Anions.

D. Meshcheryakov, V. Böhmer, M. Bolte, V. Hubscher-Bruder, F. Arnaud-Neu, H. Herschbach, E. Leize, I. Thondorf and W. Mögelin. Poster presentation on the XXX International Symposium on Macrocyclic Chemistry, **2005**.

New polyurea based macrocycles as anion receptors.

V. Hubscher-Bruder, U. Schädel, F. Arnaud-Neu, H. Herschbach, E. Leize, A. VanDorsselaer, V. Böhmer, D. Meshcheryakov and M. Bolte. Poster presentation on the XXX International Symposium on Macrocyclic Chemistry, **2005**.