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A macrocyclic diurea derived from diphenylether

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ABSTRACT

A new 16-membered cyclic diurea was synthesized and tested as potential receptor for fluoride. ^{1}H and ^{19}F NMR spectroscopy revealed an unexpected deprotonation of both urea groups after initial 1:1 binding. A single crystal X-ray structure shows bifurcated hydrogen bonds to two DMSO molecules.

1. Introduction

Various hydrogen bond donors (podands,[1] macrocyclic,[2] and macro-bicyclic[3] compounds) have been proposed, synthesized, and studied as anion receptors.[4] Oligourea (or thiourea)[5] derivatives, able to interact via bifurcated hydrogen bonds[6] with the targeted anion seem especially promising. In course of our studies on cyclic polyurea compounds composed of three,[7] four,[8] six,[9] and more[10] urea-bridged xanthene (X) and diphenylether (D) units, we also obtained smaller cycles, based on the more flexible D-unit. In addition to the product of the intramolecular cyclization ('cyclic monomer'),[11] the cyclic dimer **2**, in which two diphenylether units are connected by two urea groups via the 2,2′-positions, has been isolated. Here we report the crystal structure of this cyclic diurea **2** and its interaction with fluoride.

2. Results and discussion

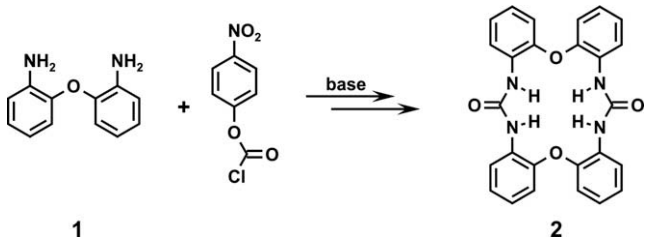
2.1. Synthesis

The cyclic dimer **2** is always formed when the diamine **1** is reacted with *p*-nitro chloroformate or triphosgene in the presence of a trialkylamine (Scheme 1). Depending on the solvent, the yield varies and reaches 20% when the reaction is carried out in ethylacetate, in the presence of diisopropyl-ethylamine and when the reagents are added slowly at room temperature (over 10 h) to the reaction flask. Since the pure dimer precipitates from the mixture and can be easily isolated in pure form simply by filtration we did not try to improve this simple procedure. Attempts to synthesize the analogous urea bridged dimer of xanthene, or to incorporate at least one xanthene unit into the dimer failed, however.

2.2. Interaction with fluoride anions

Since the cyclic diurea **2** might be a ligand sized for fluoride anions, we followed its interaction with tetrabutylammonium fluoride in DMSO-d_6 by ^{1}H NMR. The spectrum of the free dimer **2** (Fig. 1) shows a sharp singlet for the four NH protons at 8.85 ppm, two doublets (*ortho*-coupling, J = 7.8 Hz) for the four aryl protons adjacent to NH and O, and a multiplet (two overlapping triplets) for the remaining aryl protons.

Upon addition of small amounts of fluoride, the NH-signal strongly broadens and practically disappears. Small shifts occur for the aryl protons, 0.2 ppm downfield for the doublets and slightly upfield for the triplets, which now are clearly separated. Since still only one set of signals appears, the free macrocycle **2,** and its complex with fluoride must be rapidly exchanging on the NMR-time scale. The NH-signals become sharper again, and for a 1:1 ratio (**2**/F^-) we observe (mainly) one species, according to the aromatic signals (2 d, 2 tr), with two (!) rather broad NH signals. Assuming a 1:1 complex, where the F^- anion is not in the geometric center of **2**, but moves between two positions, this exchange must be 'rapid' for the aromatic signals, but 'slow' for the NH signals. This is not unreasonable, since the chemical shift difference should be larger for the NH-proton (close to the fluoride anion) than for the aromatic protons.



Scheme 1. Formation of the dimeric cycle **2**.

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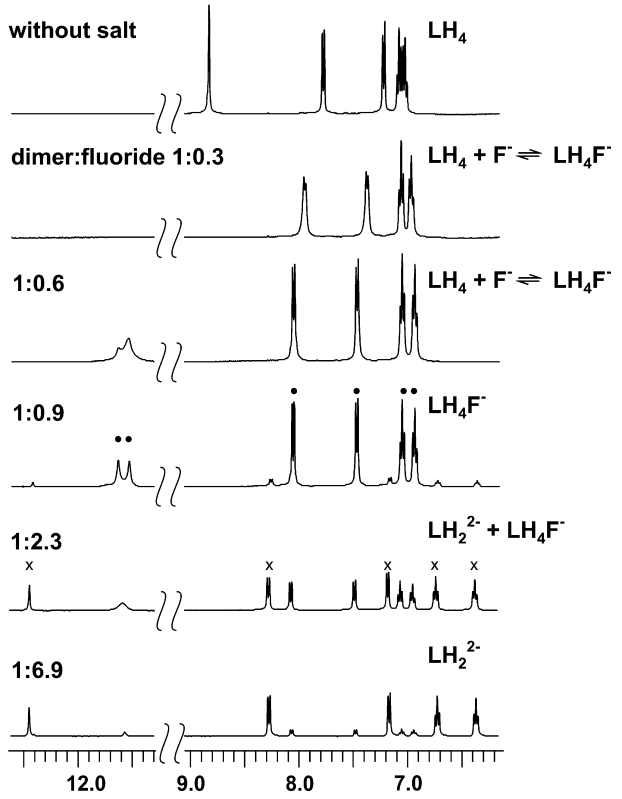

Figure 1. Stepwise addition of tetrabutylammonium fluoride solution to the solution of the dimeric cycle **2** (DMSO-d_6, 25 °C); peaks for LH_4F^- (•) and LH_2^{2-} (×) are marked. The main species are indicated at the right side of the spectra.

Already before, in the presence of ~0.9 mol of F^-, a sharp signal at 12.45 ppm appears, together with aromatic signals (two doublets, and two triplets) for another complex species, which obviously is *not* in fast exchange with the first one. These doublets (up- and downfield shifted) and triplets (both upfield shifted) are stronger separated, than the corresponding signals of the first species. At the ratio of about 1:2 (**2**/F^-), both species are obviously present in nearly equal amounts, but even with a large excess of F^- (about 10-fold), the first set of signals is still clearly visible.

This can be explained by the initial formation of a 1:1 complex, which is in rapid equilibrium with the free cyclic ligand LH_4

$$LH_4 + F^- \leftrightarrows LH_4F^-$$

Further addition of F^- leads to a twofold deprotonation of the diurea **2**:

$$LH_4F^- + 3F^- \leftrightarrows LH_2^{2-} + 2FHF^-$$

A similar behavior (elimination of several protons from NH-groups of a molecule by fluoride) was reported for a tripodal pyrrole-based receptor,[12] and even for a receptor with a single urea group.[13]

This interpretation is in agreement with a series of ^{19}F NMR spectra, where the quintuplet of the LH_4F^- appears and increases until one equivalent of fluoride is added. Upon further addition it decreases again, while an increasing doublet for FHF^- appears instead.

2.3. Crystal structure

Crystals of **2**·**3** DMSO were obtained from a solvent mixture containing dichloromethane, chloroform, and DMSO by slow evaporation.[14] The molecular conformation (including the numbering scheme) is shown in Figure 2. The molecule assumes a conformation with 'distorted' C_{2h}-symmetry, with the C_2-axis passing O3 and O4 and the σ-plane intersecting the carbonyl groups. Both urea groups are 'exactly' planar (the distance of the carbon atom from the plane defined by the oxygen and the two nitrogen atoms is 0.004 and 0.006 Å). The angle between these two planes (8.03°) characterizes the deviation from an ideal conformation with S_2-symmetry.

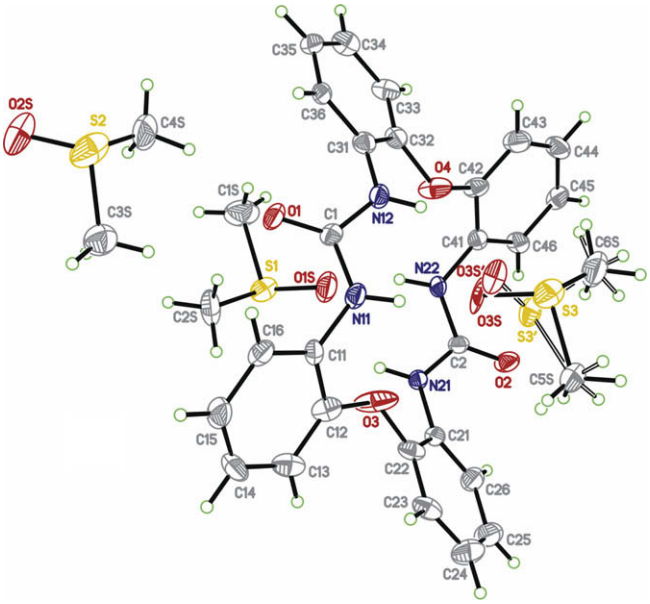

Figure 2. Structural view of the single molecule of **2** in the crystalline state (thermal ellipsoids at 50% probability level).

The two DMSO molecules[15] are hydrogen bonded by the two urea functions (bifurcated H-bonds) with N···O-distances of 2.911 Å and 2.943 Å for O3S (to N11 and N12) and 2.906 Å and 2.847 Å for O1S (to N21 and N22), thus 'closing' from both sides the hole in the 16-membered macrocycle. A third DMSO molecule being not involved in hydrogen bonds obviously fills gaps in the crystal lattice.

The packing is illustrated in Figure 3. The molecules of **2**, solvated by two hydrogen-bonded DMSO molecules form staples parallel to the *a*-axis including channels 'filled' by the non-hydrogen-bonded DMSO molecules (Fig. 3).

A molecular main plane through C11, C21, C31, and C41 may be defined to further characterize the conformation. The planes of aromatic rings I (24.1°), II (25.9°), and III (24.8°) have very similar angles with this plane, while it is somewhat larger (32.4°) for IV. The conformation of the two diphenyl urea sections is also similar. The plane defined by O1, N11, and N12 includes angles of 46.0° and 37.8° with the planes of I and III, respectively, while the corresponding angles with II and IV are 37.3° and 47.5° for the plane through O2, N21, and N22. For both pairs the difference (8–10°) is rather similar.

3. Conclusion

From three potential combinations of xanthene and diphenylether units only the cyclic diurea **2** with the flexible 2,2′-diphenyl ether connections is sterically possible for the 16-membered ring. It forms a 1:1 complex with a fluoride anion in solution, which is deprotonated to the dianion $[\mathbf{2}]^{2-}$ and FHF^- anion when tetrabutylammonium fluoride is added in excess.

Although these species are stable on the NMR-time scale, the cocrystallization with TBA fluoride was not successful. Single

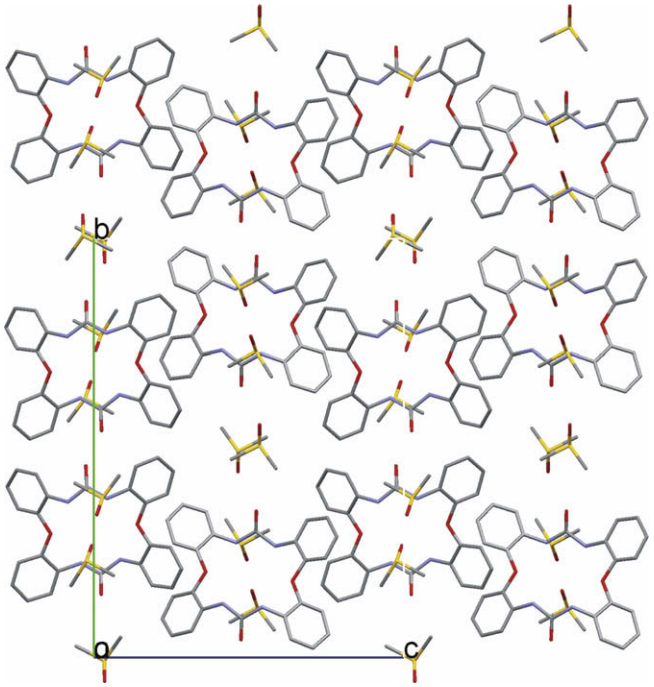

Figure 3. Packing diagram for the molecules of **2**, seen along the *a*-axis.

crystals [**2**·3 DMSO] were obtained, however. Like the larger oligoureas the dimer molecules are not connected in the crystal lattice, but use oxygen atoms from neighboring DMSO molecules as H-bond acceptor.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.087.

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15. One of them is disordered with two positions for the S- and O-atoms. Discussed is the main position.