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Aromatic Oligoureas: Enforced Folding and Assisted Cyclization

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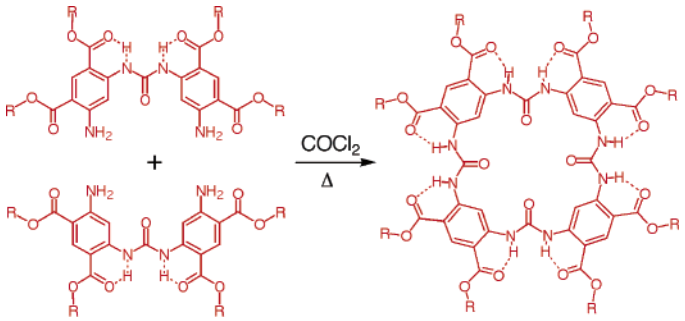
ABSTRACT



Aromatic oligoureas are forced into well-defined conformation by incorporated intramolecular hydrogen bonds. Shape-persistent tetraureas macrocycles were obtained in a one-step [2 + 2] reaction in good yields.

In recent years the design of folded unnatural oligomers has attracted intense interest.[1−4] We[5] and others[4−9] have described aromatic oligoamides that are forced into folded conformations by rigidifying the oligoamide backbones using localized intramolecular hydrogen bonds. Similar to the amide group, the urea group is also distinguished by its rigidity, planarity, and hydrogen bonding capability. Indeed, the urea functionality has already been adopted in the design of various folded structures. For example, peptidomimetic oligoureas were reported to fold into helical conformations,[10] and aromatic oligoureas were designed to adopt switchable conformations[11] or to cyclize into rigid macrocycles.[12] Backbone-rigidified aromatic polyureas were found to fold into a helical conformation according to circular dichroism spectroscopy.[13] Herein, we describe the design, enforced folding, and cyclization of backbone-rigidified aromatic oligoureas consisting of *meta*-linked benzene rings.[14]

Our design is based on diarylurea moiety **1**, which is rigidified by two very strong, intramolecularly H-bonded six-membered rings involving the urea hydrogens and the

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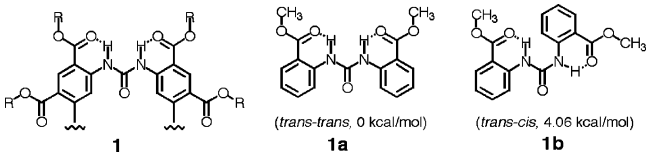
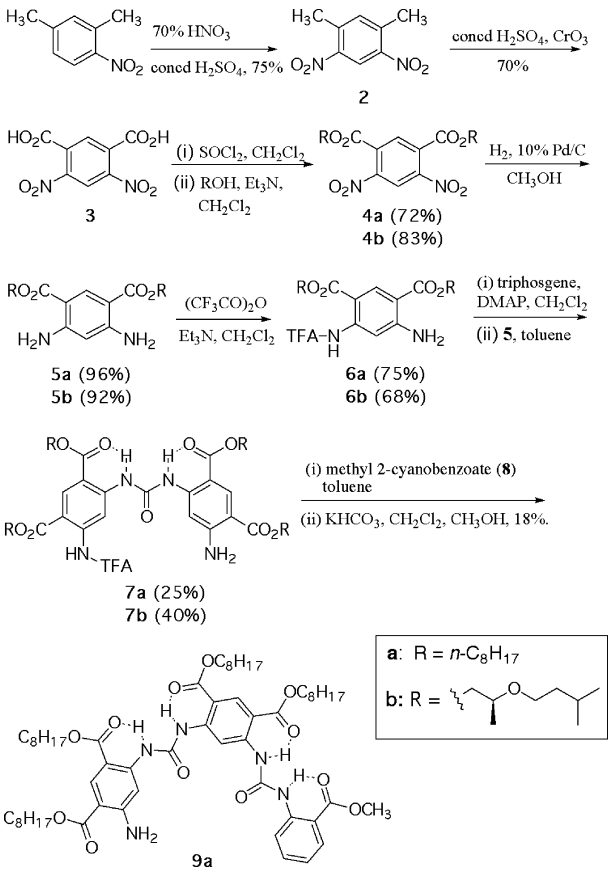
carbonyl oxygens of the flanking ester groups. Results from ab initio calculations[15] indicate that the *trans-trans* conformation, as represented by **1a**, is energetically favored over the alternative conformation **1b**. Depending on their lengths, oligomers consisting of **1** with urea linkages being placed at *meta* positions should fold into crescent or helical conformations. In such a design, the ester side groups can be easily adjusted, leading to folding oligomers with tunable solubilities and other properties. To probe the folding of such aromatic oligoureas, we prepared and characterized trimer **9a**.



The synthesis of **9a** is shown in Scheme 1. Compound **3** was prepared by nitrating the commercially available 4-nitro-

Scheme 1



m-xylene using 70% nitric acid and concentrated sulfuric acid, followed by oxidation of **2** into **3** using CrO_3 in concentrated H_2SO_4. Esterification of diacid **3** via its acid chloride led to esters **4a** and **4b**, which were then reduced

(15) See Supporting Information for details.

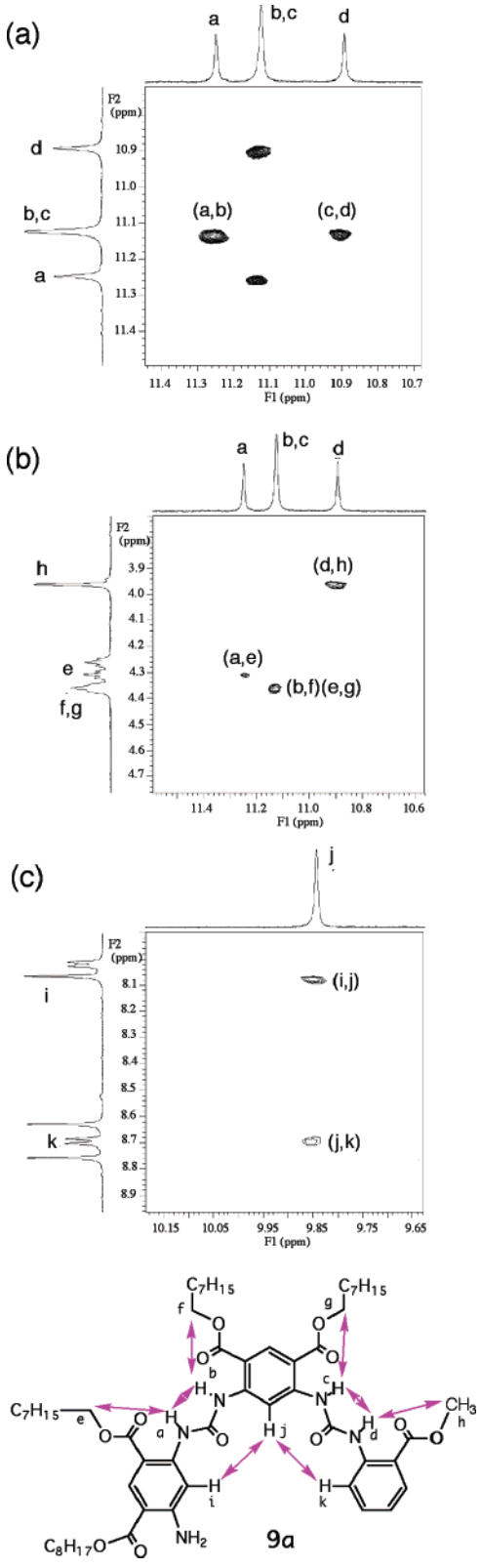
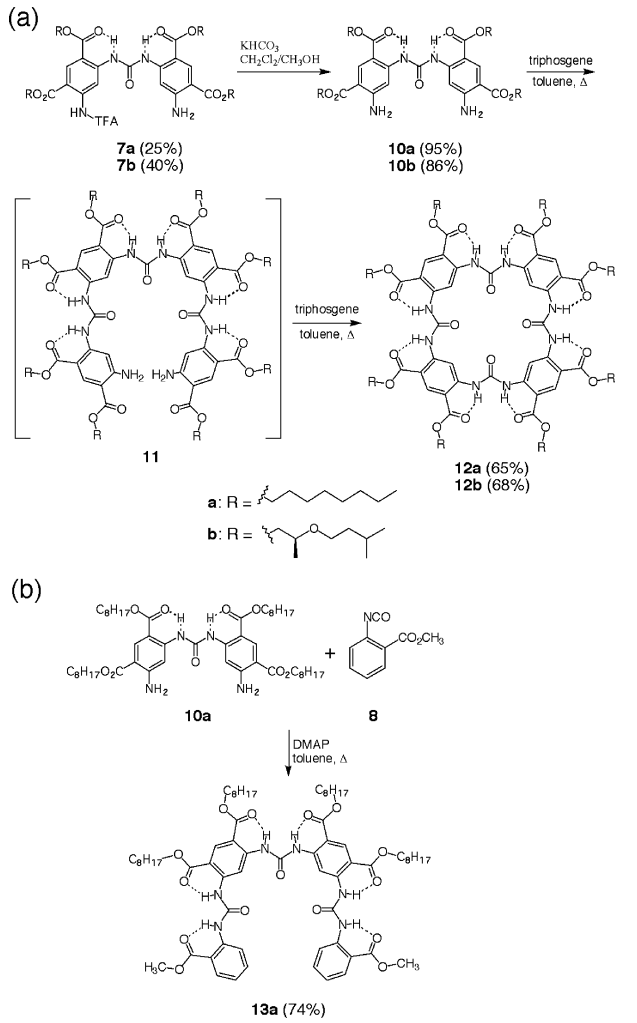


Figure 1. 2D ROESY spectrum of trimer **9a** in $CDCl_3$ (500 MHz, 10 mM, 298 K, mixing time 0.3 s).

into diamino esters **5a** and **5b**, respectively, by hydrogenation. Treating **5a** or **5b** with trifluoroacetic anhydride led to **6a** or **6b** with one protected amino group. Compound **6a** or

Scheme 2



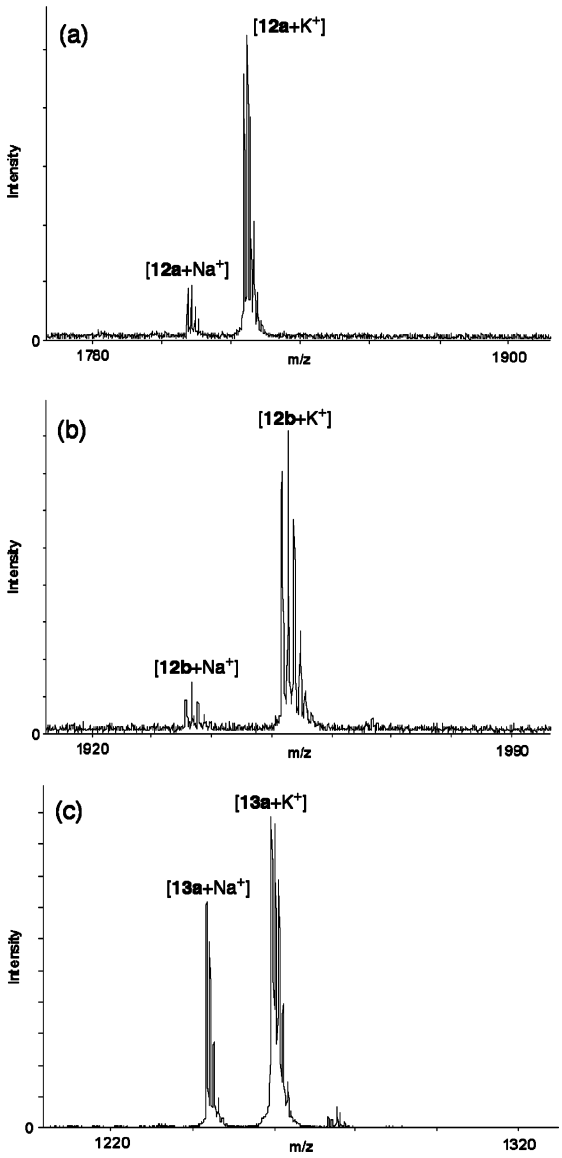


Figure 2. MALDI-TOF spectra of the mixtures of (a) **12a**, (b) **12b**, and (c) **13a** with $LiBPh_4$ (1 equiv), $NaBPh_4$ (1 equiv), and $KBPh_4$ (1 equiv).

6b was converted into the corresponding isocyanate, which upon reacting with **5a** or **5b** resulted in dimer **7a** or **7b**. Treating **7a** with the commercially available methyl 2-cyanobenzoate (**8**), followed by removing the TFA group, led to the unsymmetrical trimer **9a**. The relatively low yields of **7a,b** and **9a** were probably due to the highly deactivated nature of the corresponding precursor amines or the presence of the oxygen atom of the trifluoroacetyl group, which introduced repulsive interaction during the urea forming process.

The conformation of trimer **9a** was investigated using 2D NMR (ROESY). The partial ROESY spectra are shown in Figure 1. Strong ROEs were detected between protons *a* and *b*, and *c* and *d*, of the urea groups (Figure 1a) ROEs between the urea protons and protons *e*, *f*, *g*, and *h* of the side chains were also detected (Figure 1b). The existence of these ROEs is consistent with the persistence of the intramolecularly H-bonded six-membered rings and the *trans-trans* conformation adopted by the urea groups, which implies a crescent conformation for **9a**. Such a crescent conformation of **9a** is convincingly supported by the remote ROEs between protons *i* and *j*, and *j* and *k* (Figure 1c). These results clearly demonstrated a crescent conformation of **9a**, which is expected from backbone rigidification.

Such a curved conformation suggests that, with a sufficient length, an oligomer should curve into a full turn, leading to either a "broken ring" or a helix.[5] Indeed, molecular mechanics calculation (MM2)[16] indicates that, for this series of aromatic oligoureas, it takes four residues to complete a full turn, in which the two ends of the tetramer are placed into close proximity. It is expected that such a curved conformation of a tetramer should facilitate its cyclization into the corresponding macrocycle. To verify this expectation, dimers **10a** and **10b,** which were obtained by hydrolyzing **7a** and **7b**, respectively, were directly heated with

(16) Molecular mechanics (MM2) calculation was performed using the CAChe (version 3.2) software.

triphosgene in toluene in the presence of DMAP (Scheme 2a), which should first lead to the formation of the corresponding uncyclized tetramer diamine intermediate **11a** or **11b**. The preorganized conformation of these intermediates should facilitate their cyclization, leading to the corresponding macrocyclic oligomers. Indeed, MALDI-TOF indicated that cyclic tetraureas **12a** and **12b** were formed as the major products from the one-pot, four-component synthesis and were isolated in good yields (65% and 68%, respectively). The efficient macrocyclization is very likely due to backbone preorganization of the noncyclic oligomer precursors, which result from the combination of the rigid benzene rings and the urea groups, and the intramolecular hydrogen bonds that limit the overall conformational freedom of the uncyclized precursors.

Molecular modeling shows that both macrocycles **12a** and **12b** contain a small cavity ~5 Å across as measured by the distance between nonadjacent urea oxygens. Such a cavity, with its four inward-pointing urea oxygen atoms, may act as the site for binding metal ions. To probe whether these cyclic oligoureas can bind metal ions, **12a** (or **12b)** was mixed with 1 equiv each of lithium, sodium, and potassium tetraphenylborate in methanol for 1 h. The mixture was then examined using MALDI-TOF. As shown in Figure 2a and b, both **12a** and **12b** selectively bind the potassium ion in the presence of the other two metal ions. In each spectrum, the 1:1 complex of **12a** or **12b** with the potassium ion appears as the predominant species. Only a very small peak corresponding to the complex with the sodium ion was observed in either case. No complex with the lithium ion was observed.

For comparison, the noncyclic tetramer **13a** was prepared by treating **10a** with the commercially available **8** (Scheme 2b). MALDI-TOF showed that the noncyclic tetramer **13a** only had a slight preference toward the potassium ion. As shown in Figure 2c, examining the mixture containing **13a** and one equivalent of each of $LiBPh_4$, $NaBPh_4$, and $KBPh_4$ (mixed in methanol for 1 h) using MALDI-TOF revealed the existence of the 1:1 complexes of both sodium and potassium ions with **13a** in similar abundance. Similar to **12a** and **12b**, no complex between **13a** and the lithium ion was detected. The reason for the poor selectivity of **13a** toward sodium and potassium ions may be due to its insufficient number (three vs four of **12a** or **12b**) of oxygen atoms or its noncyclic backbone that is conformationally more flexible than those of macrocycles **12a** and **12b**. Nevertheless, these results clearly demonstrated the high selectivity of macrocycles **12a** and **12b** toward the potassium ion.

In summary, we have demonstrated the feasibility of limiting the conformational freedom of aromatic oligoureas by introducing intramolecular H-bonds. The folding of aromatic oligoureas has been enforced by backbone rigidification. The intramolecularly hydrogen-bonded groups, combined with *meta*-linked benzene rings, lead to crescent-shaped oligomers. The design principle was confirmed by characterizing a trimer using ROESY studies, which revealed ROEs that are fully consistent with the expected conformation. The preorganization of backbones facilitated the efficient preparation of macrocyclic tetraureas. These shape-persistent macrocyclic tetramers contain a well-defined, hydrophilic cavity. Preliminary MALDI studies demonstrated the highly selective complexation of potassium ion by these macrocyclic tetraureas. These macrocyclic oligoureas, with their large, flat aromatic surfaces, well-defined cavities, and easily adjustable ester side chains, should find applications in designing intercalators, hosts for metal ions, and building blocks for constructing large structures.

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Supporting Information Available: Experimental procedures, analytical data, computational method, and molecular models. This material is available free of charge via the Internet at http://pubs.acs.org.

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