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One-Pot Formation of Aromatic Tetraurea Macrocycles

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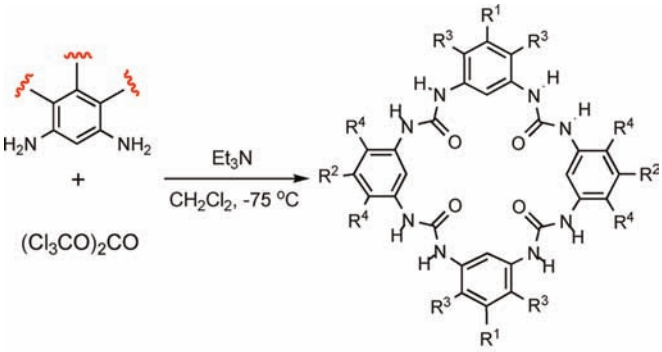
ABSTRACT



Treating derivatives of *m*-phenylenediamine having different electron-richness and reactivities with triphosgene in the presence of triethylamine led to aromatic tetraurea macrocycles in high yields. Factors important for efficiently forming these macrocycles include the molar ratio (2:1) between the diamine and triphosgene, reaction temperature (−75 °C), and solvent (CH_2Cl_2). By controlling the order and rate for adding diamines, tetraurea macrocycles consisting of two different types of monomeric residues have also been obtained in high yields.

The creation of unnatural oligomers that fold into well-defined conformations has attracted wide interest.[1] Among known strategies, enforcing folded conformations by introducing localized intramolecular hydrogen-bonding has proven to be effective for creating foldamers with persistent shapes.[2] We developed aromatic oligoamides that fold into well-defined conformations containing cavities of different sizes.[3] An attempted preparation of helical aromatic polyamides based on the same folding principle led to the discovery of a series of rigid aromatic oligoamide macrocycles.[4] This discovery marked the beginning of the synthesis of several classes of shape-persistent macrocycles with different backbones by us.[5] Along with other shape-persistent macrocycles,[6] these newly discovered macrocycles have started to exhibit interesting properties.[7]

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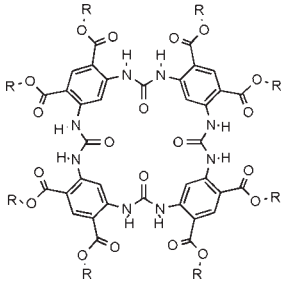
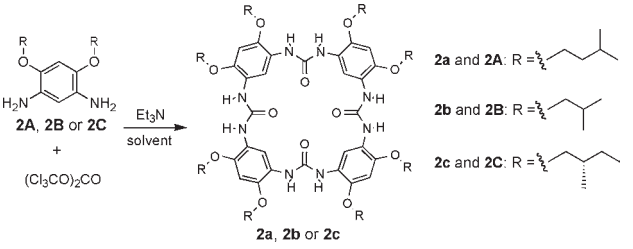
Among the shape-persistent macrocycles we reported are macrocycles **1** that consist of four benzene residues connected via urea linkages.[5a] The design of **1** was based on the assumption that the presence of intramolecular H-bonds would enforce crescent conformations on the corresponding uncyclized precursors and thus faciliatate similar macrocyclization observed for aromatic oligoamide macrocycles.[4b] Macrocycles **1** are featured by a rigid, planar backbone and a small (~5 Å across) internal cavity defined by four inward-pointing urea oxygen atoms.[5a] With their planar shape and noncollapsible cavities, these macrocyclic molecules are reminiscent of porphyrins[8] or expanded porphyrins.[9] Unfortunately, the efficient preparation of macrocycles **1** was hampered by the highly deactivated nature of the corresponding monomeric diamines that bear two electron-withdrawing ester groups. In fact, macrocycles **1** could only be obtained in multiple steps under harsh conditions from the condensation of the corrsponding dimeric precurosors, with low overall yields.[5a]



1

We report herein the highly efficient, one-pot formation of aromatic tetraurea macrocycles that share the same backbone with **1**. In this work, we have elucidated the optimal conditions for efficiently forming aromatic tetraurea macrocycles, with or without backbone-rigidifying intramolecular H-bonds, from the one-pot condensation of readily available monomeric diamines under mild conditions. The one-pot synthetic method described in this paper allows the introduction of a variety of side chains to the aromatic tetraurea backbones, leading to macrocycles of tunable properties.

Scheme 1. One-Pot Formation of Macrocycles **2**



The preparation of macrocycles **2** was first attempted by treating the corresponding diamine with triphosgene (Scheme 1). With their electron-donating alkoxy groups, the diamines were expected to have enhanced reactivity and may lead to improved yields of **2**. However, initial atttempts to convert the diamines into their corresponding isocyanates by heating with excess triphosgene led to complex mixtures of products.

The conditions for forming macrocycle **2a** were then systematically probed by adding diamine **2A** (0.96 mmol) and triethylamine in CH_2Cl_2 to triphosgene in CH_2Cl_2 under N_2 by varying temperature, concentration, and solvents (Scheme 1). As shown in Table 1, in CH_2Cl_2, no **2a** was formed when **2A** was treated with triphosgene by refluxing the reaction mixture, which may be due to the instability of either diamine **2A** or the intermediate formed in the reaction at elevated temperature.

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Table 1. Reaction Conditions for Forming Macrocycle **2a**

entry	solvent (mL)	triphosgene (mg)	temp (°C)	reaction time (h)	**2a** (%)
1	CH_2Cl_2(71)	140	reflux	2[c] + 5[d]	0
2	CH_2Cl_2(71)	140	20[a]	2[c] + 5[d]	0
3	CH_2Cl_2(71)	140	−10[b]	2[c] + 5[d]	0
4	CH_2Cl_2(71)	140	−25[b]	2[c] + 5[d]	0
5	CH_2Cl_2(71)	140	−40[b]	2[c] + 5[d]	53.8
6	CH_2Cl_2(71)	140	−50[b]	2[c] + 5[d]	61.4
7	CH_2Cl_2(71)	140	−60[b]	2[c] + 5[d]	76.3
8	CH_2Cl_2(71)	140	−75[b]	2[c] + 5[d]	80.3
9	CH_2Cl_2(91)	140	−75[b]	2[c] + 5[d]	80.5
10	CH_2Cl_2(71)	100	−75[b]	2[c] + 5[d]	70.6
11	CH_2Cl_2(71)	280	−75[b]	2[c] + 5[d]	21.5
12	CH_2Cl_2(71)	560	−75[b]	2[c] + 5[d]	6.2
13	THF(71)	140	−75[b]	2[c] + 5[d]	59.7
14	DMF(71)	140	−75[b]	2[c] + 5[d]	0

[a] Temperature was controlled with a water bath. [b] Temperature was controlled by using a low-temperature reactor. [c] Time for the dropwise addition of a solution of diamine **2A** (0.96 mmol, as HCl salt) and Et_3N (1.3 mL, 9.4 mmol) in CH_2Cl_2 to triphosgene in CH_2Cl_2. Shortening (< 1 h) or lengthening (> 2 h) the addition time led to reduced yields. Adding the solution of triphosgene to that of diamine did not lead to the formation of **2a**. [d] Time for stirring the reaction mixture at room temperature after the addition of diamine was finished. Stirring at room temperature for longer than 5 h did not lead to further change in yields.

Previous studies showed that in the presence of a base such as a tertiary amine or aqueous sodium bicarbonate, primary amines could be converted into the corresponding isocyanates in good yields by treatment with phosgene, diphosgene, or triphosgene at low temperature.[10] Efforts were thus made to probe the reaction of **2A** and triphosgene at reduced temperatures. It was found that reactions performed at 20 °C down to −25 °C did not lead to the formation of **2a** (entries 1−4). However, macrocycle **2a** started to appear as the temperature was further decreased. For example, macrocycle **2a** was obtained in 54% yield at −40 °C (entry 5). The yields of **2a** continued to improve as the reaction temperature was lowered and reached over 80% at −75 °C (entries 6−8). No additional improvement of yields was observed at temperatures below −75 °C. Further decrease of reaction temperature led to the precipitation of diamine and triethylamine, presumably as their hydochloride salts. At −75 °C, lowering the concentrations of **2A** and triphosgene by increasing the volume of CH_2Cl_2, which did not change the molar ratio of the two reactants, resulted in a slight improvement of the yield of **2a** (entry 9). In contrast, changing the ratio of triphosgene and **2A** decreased the yield of the macrocycle (entries 10−12). At −75 °C, macrocycle **2a** formed in significantly lower yield in THF (entry 13) and failed to form in DMF (entry 14).

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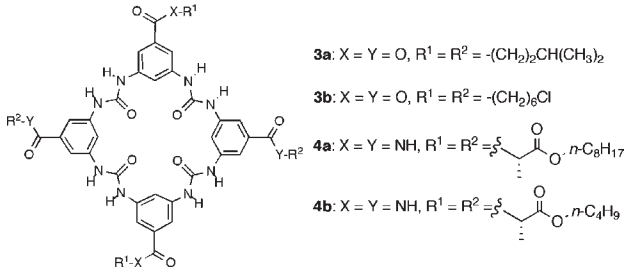
The above experiments revealed the major factors responsible for the highly efficient, one-pot formation of macrocycle **2a**. These include the molar ratio (2:1) between **2A** and triphosgene, the reaction temperature (around −75 °C), and solvent (CH_2Cl_2). It was found that applying the same procedure to the reaction of diamines **2B** and **2C** with triphosgene led to macrocycles **2b** and **2c** in high (81% for both) yields,[11] which demonstrates the reliability of this one-pot procedure.

The efficient formation of **2a**−**c** was originally attributed to the enhanced activity of the corresponding electron-rich diamines and the folded conformations of the uncyclized oligomeric precursors enforced by intramolecular H-bonds between the alkoxy oxygens and the urea hydrogens. The mild conditions revealed by the formation of macrocycles **2** prompted us to probe the macrocyclization of other diamines of reduced activity, which would show the generality of this system. The preparation of macrocycles **3a**, **3b**, **4a**, and **4b**, which lack intramolecular H-bonds, was attempted on the basis of the same procedures described above. The corresponding diamines were treated with triphosgene in the presence triethylamine in CH_2Cl_2 at −75 °C. Similar to the efficient formation of **2a**−**c**, macrocycles **3a**, **3b**, **4a**, and **4b** were obtained in high (76%, 78%, 80%, and 79%) yields after being purified with column chromatography.[11]



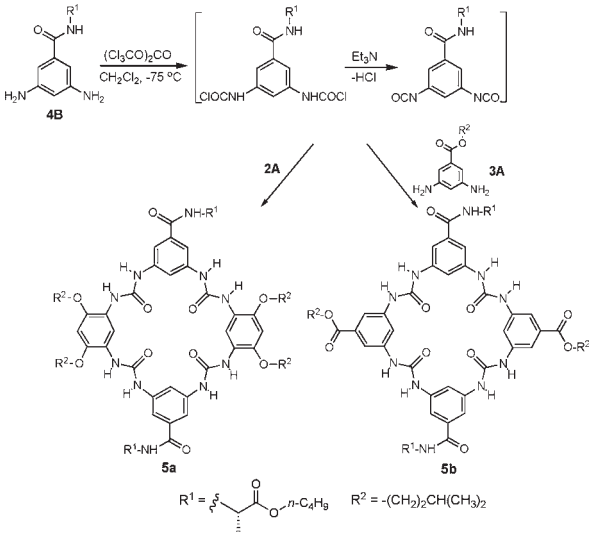
The successful one-pot preparation of macrocycles **3** and **4** indicates that rigidifying the oligourea precursors by introducing intramolecular H-bonds, which presumably preorganize the uncyclized precursor toward cyclization, is not necessary for the efficient formation of these aromatic tetraurea macrocycles. The partial rigidification and curvature introduced by *meta*-linked benzene resiudes, along with the *trans*−*trans* conformational preference[5a] of the urea linkage, seem to provide sufficient preorganization that promotes the macrocyclization process. In addition, backbone C−H···O interaction, which should be enhanced by the electron-withdrawing amide or ester side chains, is very likely an additional driving force that promotes the folding of the uncyclized precursors of these tetraurea macrocycles. It thus expected that the above one-pot procedure is generally applicable to the preparation of a variety of aromatic tetraurea macrocycles from various derivatives of 1,3-phenylenediamine.

The significantly reduced yields of **2a** with increasing percentages of triphosgene (entries 11 and 12, Table 1) imply that diamine **2A** did not undergo simultaneous cyclization. With excess triphosgene, diamine **2A** should

(11) See the Supporting Information for details.

be converted into the corresponding dicarbamoyl chloride that gives diisocyanate by eliminating HCl in the presence of triethylamine.[10] The formed dicarbamoyl chloride and diisocyanate could not undergo further reaction since, with excess triphosgene, most of the diamine molecules should have been consumed before further reaction, which resulted in the observed low yields.

Scheme 2. Preparation of Macrocycles **5a** and **5b**



The above reasoning suggests that the reaction of a diamine with triphosgene may stop at the stage of forming the corresponding dicarbamoyl chloride or diisocyanate, both of which can react with the same or different aromatic diamines to form tetraurea macrocycles. By adding a different diamine to the formed dicarbamoyl chloride or diisocyanate, tetraurea macrocycles consisting of two different monomeric residues were formed. Such a possibility was investigated by treating diamine **4B** with trisphosgene, followed by the rapid addition of a second diamine **2A** or **3A** (Scheme 2). Thus, a solution of **4B** (0.48 mmol) and triethylamine (4.7 mmol) in CH_2Cl_2 (11 mL) was slowly injected into a well-stirred solution of triphosgene (0.48 mmol) CH_2Cl_2 (60 mL) over a period of 1 h under N_2 at −75 °C, followed by rapid injection of diamine **2A** or **3A** (0.48 mmol) and Et_3N (4.7 mmol) in CH_2Cl_2 (10 mL). Macrocycles **5a** and **5b** were obtained in 77% and 79% yields, respectively, after being purified with column chromatography.[11] It was observed that slowly injecting diamine **4B** followed by rapidly adding the second diamine **3A** or **2A** was critical for forming the desired macrocyclic product. If the injection of the second diamine took too long, the yield of **5a** or **5b** was found to be compromised, which may be due to the instability of the formed dicarbamoyl chloride or diisocyanate.

In summary, aromatic tetraurea macrocycles are obtained in high yields from aromatic diamines of different reactivities. By including various diamines derived from *m*-phenylenediamine and its analogues, many of which are commercially available or can be prepared on the basis of simple procedures, this efficient one-pot macrocyclization allows the preparation of different shape-persistent aromatic tetraurea macrocycles. Sharing the same flat backbone and noncollapsible internal cavity but bearing different side chains that lead to different backbone electronic properties, these macrocycles are expected to have interesting recognition properties or self-assembling behavior. For example, macrocycles **1** had been shown to be selective toward K^+ over Na^+.[5a] Macrocycles **2**–**5** all give broad ^1H NMR signals in both polar and nonpolar solvents, suggesting their particularly strong tendency for self-association. In contrast to the limited accessibility of macrocycles **1**, the ready availability of **2**–**5** and analogous macrocycles should greatly facilitate the systematic study and applications of these compounds.

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Supporting Information Available. Synthetic procedures, NMR and mass spectra, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.