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PII: S0040-4020(16)30263-0

DOI: 10.1016/j.tet.2016.04.009

Reference: TET 27652

To appear in: Tetrahedron

Received Date: 3 February 2016

Revised Date: 24 March 2016

Accepted Date: 5 April 2016

Please cite this article as: Yawer MA, Necas M, Sindelar V, Rational construction of macrocycles consisting of methylene bridged ureas, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.04.009.

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## Rational construction of macrocycles consisting of methylene bridged ureas

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#### ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online Synthesis of two macrocycles formed by urea functions connected solely by methylene bridges is described. This is the first example of isolated and fully characterized macrocyclic compounds in which NH-containing urea units are separated by methylene bridges. X-ray diffractometry revealed formation of multiple intramolecular hydrogen bonds between acidic NH and oxygen atoms of urea within the macrocycles.

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Keywords: macrocycles, ureas, triazinanones, hydrogen bonding, condensation

#### **1. Introduction**

Urea represents one of the most popular building blocks used in supramolecular chemistry. Two nitrogen atoms of urea act as donor of hydrogen atoms allowing the urea to interact with hydrogen acceptors through intermolecular hydrogen bonding interactions.<sup>1,2</sup> Thus, urea containing compounds can act as neutral anion receptors. Affinity of these receptors can be enhanced by number of ways including attachment of electron withdrawing substituents, incorporation of two or more urea units into one receptor molecule, and arrangement of urea units into linear, branched or cyclic structures.<sup>3,4</sup> Urea and its derivatives can self-associate through the hydrogen bonding between acidic NH protons and oxygen atom of neighboring molecule. This enable design and formation of three-dimensional structures in the solid state usually represented by hollow tubes closely connected within a crystal.<sup>5,6</sup> The channels formed by urea framework are able to include organic molecules. Therefore, these nano-porous materials are used as the host matrixes for the hydrocarbon separation, nanoreactors for organic reactions, and X-ray dichroic filters.<sup>7–9</sup>

We decided to investigate synthetic approaches leading to macrocyclic compounds in which urea units are in close proximity connected only by methylene bridges. Several macrocycles containing this structural motives have been synthesized in past including cucurbiturils, hemicucurbiturils, bambusurils, and biotinurils.<sup>10–17</sup> However, all these macrocycles are composed of disubstituted urea units which do not contain NH protons enabling the formation of hydrogen bonds with guests. To the best of our knowledge, there has not been a single example of macrocycle based on alternating NH-containing urea and methylene units only. The required structural sequence can be found in urea based resins which are prepared by the direct reaction of urea and formaldehyde.<sup>18–20</sup> However, the reaction

based on the same starting materials is difficult to drive towards the formation of desired macrocycle as the polymerization, open chain reactions and degradation predominate. Here we present synthesis of two new macrocycles consisting of deprotected urea units connected by methylene bridges.

#### 2. Results and discussion

#### 2.1. Macrocycle 2

Our approach is based on the acid catalyzed reaction of protected urea, 5-*tert*-butylperhydro-1,3,5-triazin-2-one with paraformaldehyde. Starting material 5-*tert*-butylperhydro-1,3,5-triazin-2-one **1** was synthesized affording a slightly modified reported procedure.<sup>21</sup> The condensation of urea and *tert*-butylamine in boiling methanol was performed using paraformaldehyde instead formalin to achieve better yield.

Initially we tested reaction of **1** with paraformaldehyde in toluene in the presence of p-toluenesulfonic acid at reflux for 24 h (Scheme 1). This reaction leads to the formation of several oligomers that are difficult to isolate. We have demonstrated previously, that the formation of urea-based macrocycles such as bambusurils can be enhanced by the presence of tetrabutylammonium (TBA) salt of chloride, bromide and iodide<sup>14–16</sup>. Therefore, we repeated the macrocyclization reaction in the presence of TBAI. Slightly pink precipitate was obtained after 24 h of reflux and was collected by filtration. Pure macrocycle (2) was obtained after washing of the precipitate with methanol and recrystallizing from diluted HCl. We also succeeded to obtain single crystals of 2 suitable for X-ray diffraction analysis,<sup>22</sup> which revealed true composition of the macrocycle (Figure 1). The macrocycle 2 is composed of four urea units connected by four methylene bridges. Two of these urea units remained protected as triazinanones. Surprisingly, a urea ring within the macrocycle is overbridged via urea dimer

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using triazone cycles as a bridging point. The mechanism of the macrocycle formation is not yet clear. We propose that initially six units of 5-*tert*-butylperhydro-1,3,5-triazin-2-one (1) surround iodide in similar arrangement which can be found for building blocks in hemicucurbit[6]urils.<sup>13</sup> Four of these units undergo deprotection while two of them remain in the form of triazinanones. Subsequent rearrangement of urea units during condensation with paraformaldehyde result in the macrocycle **2**. Bridge of the macrocycle through two triazinanones further stabilizes the structure. The generation of a small three-dimensional cavity is most likely caused by formation of multiple N–H…O hydrogen bonds within macrocycle. It is also possible that four membered ring is thermodynamically more stable compared to six-membered one as it is described for some bambusuril macrocycles.<sup>22</sup>



Scheme 1. Synthesis of macrocycle 2.

The macrocycle **2** shows a two-fold rotational symmetry which is consistent with its positioning in a monoclinic cell; the asymmetric unit of the cell thus contains only a half of the molecule (Figure 1). Two intramolecular N–H···O hydrogen bonds are observed between the two symmetry related parts of the macrocycle. It is interesting to note an unusual *anti* N4(H)···N5(H) conformation in substituted urea moiety, which may be explained by a tendency to keep the O1 and O2 atoms apart.



**Figure 1.** The structure of **2** showing intramolecular hydrogen bonds. Note a rotational symmetry about a  $C_2$  axis passing through C8.

The molecules of **2** are tightly packed in the crystal without the presence of any solvent molecules or ions. Four pairs of N–H···O hydrogen bonds around each macrocycle are responsible for the formation of 1D supramolecular chains which propagate parallel to the *c* axis. In the *bc* plane, the hydrogen bonded chains are locked together *via* pairs of three-center C–H···O bonds with H···O distances of 2.61 and 2.63 Å (Figure S3 in Supplementary

data). Another set of C–H···O bonds (H···O distance 2.56 Å) is responsible for stacking in the third dimension.

#### 2.2. Deprotection

All tested approaches for the deprotection of remaining two urea units in triazone rings of macrocycle **2** failed. For example, heating in an acidic aqueous/methanol (1:1 v/v) solution of diethanol amine leads to the decomposition of the macrocycle,<sup>6</sup> even the macrocycle is not stable in boiling conc. HCl. Macrocycle **2** is comparatively stable in weaker acids and in dilute hydrochloric acid. This environment is not sufficient to achieve the deprotection of triazone moiety.

#### 2.3. Macrocycle 3

After successful development of strategy for the synthesis of macrocycle 2 in nonpolar solvent toluene, we worked more to advance the macrocyclization using polar protic solvents. Therefore the compound 1 was treated with paraformaldehyde in methanol in the presence of catalytic amount of HCl, which did not give the desired result. Succeeding macrocyclization trials in pure methanol and mixtures of methanol and water at different ratios, in the presence of various concentrations of aq. HCl also leads to the formation of acyclic oligomers instead of fruitful macrocyclization. After a number of unsuccessful attempts eventually the condensation of 1 with paraformaldehyde in 4N aq. hydrochloric acid solution in pure water was performed. Turbid suspension initially formed which dissolved upon heating at 80 °C for 2 h (Scheme 2). The reaction mixture was evaporated to dryness. Resulting white solid was obtained by slow crystallization from 2N aq. HCl. Particularly, the reaction was performed at 0.1M concentrations of protected urea and paraformaldehyde as further dilution leads to the failure of macrocyclization. he Higher concentrations of the reactants were avoided toreduce undesirable polymerization. X-ray diffraction analysis unveils the exact arrangement of eight urea units and ten methylenes bridges in macrocycle **3** (Figure 2).<sup>22</sup> Macrocycle **3** is constituted by two identical macrocycles, each macrocycle contains 4 urea and 4



Scheme 2. Synthesis of macrocycle 3.

methylene units attached alternately. Both macrocycles are further connected by two methylene bridges. In this way a symmetric macrocycle dimer is formed which, in contrast to macrocycle **2**, does not contain any triazinone units but only solely deprotected ureas. Because of the presence of numerous N–H and C=O groups and a spherical nature of the macrocycle, several moderate N–H···O contacts are allowed, showing an average donor-acceptor distance of 2.86 Å (Table S2 in Supplementary data). In contrast to the crystal structure of **2**, the structure of **3** contains four molecules of water per formula unit, M which form several intermolecular hydrogen bonds with the macrocycle. Overall, two double-hydrogen acceptors N- $H \cdots O \cdots H - N$ , one C= $O \cdots H - O - H \cdots O = C$ , and three C= $O \cdots H - O$  hydrogen bonding patterns are found (Figure 2). Such a solid-state "hydration shell" mediates a 3D crystal packing of which an arbitrary 2D section is shown in Figure S4 in Supplementary data.



**Figure 2.** Hydrogen bonding between the macrocycle **3** and the molecules of water in  $3.4H_2O$ . Symmetry codes: (i) -x+1, -y+1, -z+1; (ii) x+1/2, -y+3/2, z+1/2.

#### 2.4. Ion binding

A thorough study of physical properties and complexations of both macrocycles are not straightforward due to the lack of solubility in common organic solvents and in pure water. X-ray structure analysis shows strong intramolecular and intermolecular hydrogen bonding between C-H···O and N-H···O within the macrocycle and among the neighboring molecules in crystal packing. The studies on the solubility of macrocycles 2 and 3 show that both macrocycles require strong acidic condition of pH below 1 in order to be dissolved. We used <sup>1</sup>H NMR spectrometry to investigate binding of ions such as halides, nitrate, alkyl metal cations, with the macrocycles. Trifluoroacetic acid and 2N HCl were used as a solvent enabling dissolution of the macrocycle. However, no supramolecular interaction between the macrocycles and both anions and cations was detected. This is probably caused by net of hydrogen bonding interactions which successfully compete with possible anion binding site.

#### 3. Conclusions

In conclusion we have explicated simple and inexpensive one pot synthetic methodologies for the synthesis of two novel macrocycles based on condensation of 5-*tert*-butylperhydro-1,3,5-triazin-2-one with paraformadehyde in polar and in nonpolar solvents. We demonstrated that this approach can be used for the synthesis macrocyclic compounds 2 and 3 in which urea units are connected by methylene bridges. Moreover, prepared compounds are first examples of macrocycles in which urea units bearing acidic NH protons are in close distance separated just by one methylene bridge.

#### 4. Experimental

#### 4.1. General information

All solvents were dried and purified by standard methods for all reactions. For <sup>1</sup>H and <sup>13</sup>C NMR, the deuterated solvents

indicated were used. Calibration of spectra was carried out on the solvent signals (CF<sub>3</sub>COOD and CD<sub>3</sub>OD). NMR spectra were recorded on a Bruker Avance III 300 spectrometer with working frequency 300.15 MHz for <sup>1</sup>H and 75.47 MHz for <sup>13</sup>C, or a Bruker Avance III 500 spectrometer with working frequency 500.11 MHz for <sup>1</sup>H and 125.75 for <sup>13</sup>C. Both spectrometers were equipped with a BBFO probe. X-ray Diffraction data were collected at 120 K on a Kuma KM-4 CCD diffractometer for **2** and on a Rigaku MicroMax-007 HF rotating anode CCD diffractometer for **3**. HRMS data were obtained on a APCI+/MS-TOF apparatus equipped with an ESI interface.

#### 4.2. General procedures

4.2.1. 5-tert-Butylperhydro-1,3,5-triazin-2-one (1). Urea (12.0 g, 0.2 mol), tert-butylamine (14.6 g, 21 mL, 0.2 mol), and paraformaldehyde (12.0 g, 0.4 mol) were boiled in methanol (40 ml) for 5 h, reaction mixture was cooled down to room temperature and precipitate was separated by filtration. The filtrate was concentrated on rotavap to about 1/3 of the initial volume and left at room temperature for 3 h to yield a white precipitate. Pure compound was obtained by recrystallization of the precipitate from ethanol. Yield 12.0 g (38%); mp 197-199 °C. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  = 4.3 (4H, s, 2CH<sub>2</sub>), 1.2 (9H, s, C(CH3)<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  = 158.5, 57.0, 55.1, 27.7).

4.2.2. Macrocycle (2). 5-tert-Butylperhydro-1,3,5-triazin-2-one (6.45 mmol 1.00 g), p-toluenesulfonic acid (3.25 mmol, 0.613 g), paraformaldehyde (9.67 mmol, 0.290 mg) and TBAI (0.16 mmol, 0.228 g) were suspended in toluene (40 mL) and refluxed for 24 h. After that reaction mixture was cooled down to room temperature, precipitate was collected by filtration and washed with excess of methanol to give white powder. Recrystallized from 2N aq. HCl gave pure macrocycle 2. Yield (0.250 g, 50 %). <sup>1</sup>H NMR (500 MHz, CF<sub>3</sub>COOD)  $\delta = 2.82-2.89$  (2H, m, CH<sub>2</sub>), 3.02-3.50 (14H, mbr, 7CH<sub>2</sub>), 3.84-3.86 (2H, m, CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, CF<sub>3</sub>COOD)  $\delta$  = 160.7, 157.8, 157.4, 80.5, 75.1, 74.9, 64.6, 64.5, 53.8, 53.6, 53.5, 53.2. IR (KBr): 3283 (w), 2966 (w), 2874 (w), 1707 (s), 1628 (s), 1497 (m), 1365 (w), 1291 (s), 1177 (s), 1120 (s), 1008 (w), 980 (w), 936 (w), 848 (w), 680 (m). HRMS (APCI+): m/z calcd for  $[C_{15}H_{25}N_{12}O_6]^+$ : 469.2014, found: 469.2015.

4.2.3. *Macrocycle* (**3**). Paraformaldehyde (6.45 mmol, 193 mg) was added to a stirred suspension of 5-*tert*-butylperhydro-1,3,5-triazin-2-one (6.45 mmol, 1.00 g) in 4N *aq*. HCl 65 mL and mixture was heated at 80°C for 2 h. Reaction mixture was evaporated under vacuo to give white powder. Pure macrocycle **3** was obtained by slow recrystallization from 2N HCl. after 6 weeks. Yield (90 mg, 18 %). <sup>1</sup>H NMR (500 MHz, CF<sub>3</sub>COOD)  $\delta$  = 2.66-3.38 (18H, mbr, CH<sub>2</sub>), 3.63-3.66 (2H, m, CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, CF<sub>3</sub>COOD)  $\delta$  = 160.5, 155.9, 80.5, 52.1, 51.6. IR (KBr): 3302 (w), 3277 (w), 1673 (s), 1634 (s), 1546 (s), 1508 (m), 1468 (w), 1373 (s), 1233 (s), 1212 (s), 1105 (w), 984 (w), 831 (w), 790 (w), 670 (m). HRMS (APCI+): *m/z* calcd for [C<sub>18</sub>H<sub>33</sub>N<sub>16</sub>O<sub>8</sub>]<sup>+</sup>: 601.2661, found: 601.2662.

#### Acknowledgement

This work was supported by the Czech Science Foundation (13-15576S) and the Czech Ministry of Education (projects LM2011028 and LO1214). The X-ray part of the work was carried out with the support of X-ray diffraction and Bio-SAXS Core Facility of CEITEC.

#### **Supplementary Material**

<sup>1</sup>H, <sup>13</sup>C NMR, IR, and MS spectra of compounds **2** and **3** and Xray crystal data and refinement parameters of **2** and **3**. Supplementary data associated with this article can be found, in the online version...

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- Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1451138 and 1451139. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK).