Ureyleno Macrobicyclic Amines. 1. Cooperative Protonation of 4,6,12,14,19,21-Hexaaza-5,13,20-trioxobicyclo[7.7.7]tricosane

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Since their discovery few decades ago, cryptands have become a major subject of study in organic and bioorganic chemistry.[1] Of particular interest are the basic principles that govern the binding behavior of cryptands. Previous investigations clearly demonstrated that the size, the shape, the rigidity, and the noncovalent interactions of the cavity are extremely crucial for binding. At an early stage of cryptand studies, chemists recognized that highly flexible large cryptands often make the binding entropically unfavorable.[1] Accordingly, structurally rigid cryptands have become an important area of investigation.[2]

Our recent efforts have been focused on receptors bearing polar rigid linkages. We are intrigued with the *N,N′*-substituted ureyleno group because of its rigidity, polarity, and hydrogen-bonding characteristics. First, *N,N′*-substituted ureas are polar compounds that can act as hydrogen-bond donors as well as acceptors.[3] Moreover, the mesomeric π-character of the C(O)−N group restricts the C−N bond rotation. This makes the ureyleno unit a rigid-coplanar structure with the substituents in the sterically favored *Z,Z*-conformations. We report herein the synthesis and the unexpected protonation behavior of the rigid ureyleno cryptand (CT) **1**.

CT **1** was synthesized in a two-step sequence.[4] Treatment of **2** with 3 equiv of *n*-BuLi and 3 equiv of LiN-(SiMe₃)₂ at −78 °C followed by addition of (MeS)₂CO and subsequent warming to room temperature gave **3** in moderate yield. Coupling of **2** with **3** in methanol at 80 °C in high dilution conditions afforded CT **1** as colorless crystals (Scheme 1).

CT **1** is soluble in H_2O and MeOH, partially soluble in MeCN, and insoluble in most of the nonpolar solvents. The ^1H NMR spectrum of **1** in D_2O shows two multiplets centered at δ 2.36 and 2.92 ppm, respectively, in a ratio of 1:1. The multiplet at δ 2.36 ppm is assigned to the methylene protons adjacent to the bridgehead tertiary nitrogen. The other multiplet at δ 2.92 ppm is attributed to the methylene protons next to the ureyleno bridge. The ^{13}C NMR spectrum of **1** also agrees with the assigned structure. It shows three sets of resonance signals, including two signals at δ 37.4 and 51.1 ppm for the ethano

Scheme 1[a]

2   **3** R = (CO)SMe   **1**
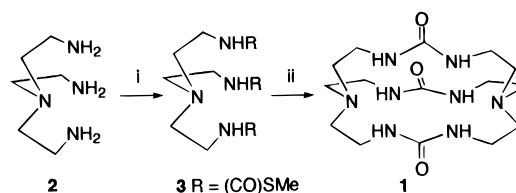
[a] Reagents and conditions: (i) 3 *n*-BuLi, 3 (Me₃Si)₂NH, −78 °C, then (MeS)₂CO, rt 6h; (ii) N(CH₂CH₂NH₂)₃, high dilution, reflux.

carbons and one signal at δ 161.1 ppm for the carbonyl carbons.

Protonation of **1** with 2 equiv of HCl leads to the diprotonated cryptand (DPCT) **4** as colorless crystals. The ^1H NMR spectrum of **4** in D_2O shows two sets of multiplets at δ 3.17 and 3.30 ppm. The downfield shift of the resonance signals is attributed to the electric-field effects arising from the positively charged quaternary ammonium groups. No in−out stereoisomerism of the tetrahedral bridgehead nitrogen atoms is evidenced on the basis of the NMR analysis. This observation is further confirmed by ^{13}C NMR analysis, which shows only three resonance signals at δ 34.6, 58.9, and 161.9 ppm.

The protonation behavior of **1** was first followed by titrimetric methods, using HCl (0.1N) as a titration standard. Surprisingly, the pH titration curve shows only a single sharp change at the second equivalence point; the change associated with the first equivalence point is indistinct. To further understand this unusual neutralization behavior, we monitored the reaction by using NMR experiments. CT **1** was treated with 1 equiv of aqueous HCl, followed by removal of H_2O under reduced pressure to afford colorless crystalline solid. The solid was then redissolved in D_2O and analyzed by NMR methods. The ^1H NMR spectrum shows four sets of distinctive methylene hydrogen signals, centered at δ 2.36, 2.91, 3.19, and 3.33 ppm in a ratio of 1:1:1:1, respectively. These findings indicate the coexistence of CT **1** and DPCT **4** in a ratio of 1:1; no monoprotonated cryptand (MPCT) **5** was identified according to the ^1H NMR analysis. In addition, proton exchange between **1** and **4** is relatively slow on the NMR time scale, and therefore, the average spectrum of **1**, and **4** would not be observed. This conclusion was further supported by the ^{13}C NMR analysis. The spectrum shows four distinctive methylene carbon signals and two carbonyl carbon signals. The signals appearing at δ 37.4, 51.1, and 161.1 ppm are well-matched with the spectrum of **1**, while other remaining signals at δ 34.6, 58.9, and 161.9 ppm are consistent with the spectrum of **4**. Except for the two minor signals at δ 53.4 and 55.0 ppm that were observed after careful examination of the spectrum, no further compelling evidence for the existence of MPCT **5** was found. Similar results were obtained when direct titration of **1** was performed in D_2O, using TsOH−H_2O as the standard.

(1) (a) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry, Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH: New York, 1993. (b) Vögtle, F.; Weber, E. *Host Guest Complex Chemistry, Macrocycles: Synthesis, Structures, Applications*; Springer-Verlag: Berlin, 1985. (c) Dietrich, B. In *Inclusion Compounds*; Atwood, J. C., Davies, T. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2, p 337. (d) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1995,** *95*, 2529.

(2) An, H.; Bradshaw, J. S.; Krakowiak, K. E.; Tarbet, B. J.; Dalley, N. K.; Kou, X.; Zhu, C.; Izatt, R. M. *J. Org. Chem.* **1993,** *58*, 7694 and references cited therein.

(3) For representative examples, see: (a) Ge, Y; Lilienthal, R. R.; Smith, D. K. *J. Am. Chem. Soc.* **1996,** *118*, 3976. (b) Schwiebert, K. E.; Chin, D. N.; MacDonald, J. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996,** *118*, 4018. (c) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhovers, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996,** *61*, 3476. (d) Hughes, M. P.; Shang, M.; Smith, B. D. *J. Org. Chem.* **1996,** *61*, 4510.
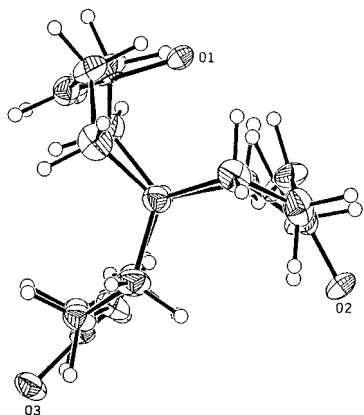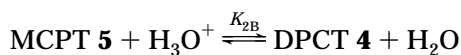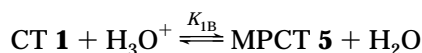

4   **5**
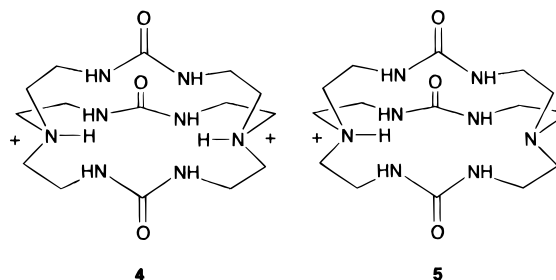
Figure 1. ORTEP drawing of cryptand **1**.

The results of the above experiments clearly illustrate that **1** and **4** are exclusively formed at the first equivalence point. This finding can be rationalized in terms of the higher basicity of MPCT **5** than that of CT **1**. The mathematical expressions for the equilibria can be written as where K_{1B} and K_{2B} are the basicity constants for

$$\text{CT } \mathbf{1} + \text{H}_3\text{O}^+ \xrightleftharpoons{K_{1B}} \text{MPCT } \mathbf{5} + \text{H}_2\text{O}$$

$$\text{MCPT } \mathbf{5} + \text{H}_3\text{O}^+ \xrightleftharpoons{K_{2B}} \text{DPCT } \mathbf{4} + \text{H}_2\text{O}$$

$$K_{1B} = \frac{[\text{MPCT } \mathbf{5}]}{[\text{CT } \mathbf{1}][\text{H}_3\text{O}^+]} \quad K_{2B} = \frac{[\text{DPCT } \mathbf{4}]}{[\text{MPCT } \mathbf{5}][\text{H}_3\text{O}^+]}$$

CT **1** and MPCT **5**, respectively. The disproportionation constant K_{disp} for MPCT **5** can therefore be expressed in terms of K_{1B} and K_{2B}. When K_{2B} is far larger than K_{1B}, MPCT **5** disproportionates into DPCT **4** and CT **1**.

$$2 \text{ MCPT } \mathbf{5} \xrightleftharpoons{K_{\text{disp}}} \text{CT } \mathbf{1} + \text{DPCT } \mathbf{4}$$
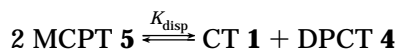
$$K_{\text{disp}} = \frac{[\text{DPCT } \mathbf{4}][\text{CT } \mathbf{1}]}{[\text{MPCT } \mathbf{5}][\text{MPCT } \mathbf{5}]} = \frac{K_{2B}}{K_{1B}}$$

These results also imply the cooperative protonation behavior of **1**. In other words, protonation of one of the bridgehead nitrogen atoms substantially enhances the basicity of the other bridgehead nitrogen atom.

To better understand the origin of the cooperativity, compounds **1** and **4** were subjected to single-crystal X-ray analysis.[5] Views of **1** and the perchlorate salt of **4** along the 3-fold axes are reported in Figures 1 and 2, showing the conformations of **1** and the perchlorate salt of **4** in the solid state. CT **1** adopts a distorted propeller-like conformation, with two of the ureyleno carbonyl groups being directed away from the central C_3 axis while the remaining one is tilted tangentially to the axis. This conformation could partially reduce the electrostatic repulsion between the lone-pair electrons on the bridgehead nitrogens and the partial negative charges on the carbonyl oxygens. On the other hand, DPCT **4** adopts a more compact and symmetrical conformation with all
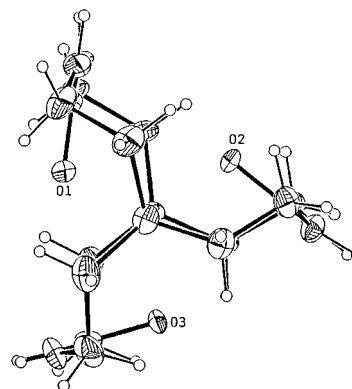
(4) Leung, M.-k.; Lai, J.-L.; Lau, K.-H.; Yu, H.-h.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175.

Figure 2. ORTEP drawing of the diprotonated cryptand **4**.

three carbonyl groups pointed inwards. The protons are unequivocally accommodated within the cage of the cryptand skeleton. These results indicate a strong electrostatic attraction between the positively charged quaternary ammonium groups and the partial negative charges on the carbonyl oxygens. Such an attractive interaction would be expected to be maximized when both of the bridgehead nitrogens are protonated. On the basis of these observations, it would be enticing to suggest that electrostatic attractions arising from the first protonation step may readily direct the ureyleno groups turning inwards. The first protonation thus establishes a cavity suitable for accommodating the second proton and therefore making the second protonation step entropically favorable. In addition, the conformation change would also make the second protonation enthalpically favorable since the positive charge that results from the second protonation would also be stabilized by the partial negative charges on the carbonyl groups.
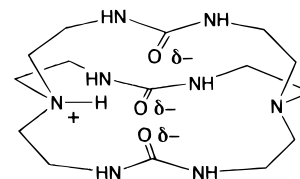
Our experiments have demonstrated that electrostatic interactions between the carbonyl groups and quaternary ammonium centers are essential for the stability of the molecular conformations. Efforts are underway to extend the idea of cooperative protonation to some other types of cryptands.

Supporting Information Available: Procedures for the synthesis of **1**, **3**, and **4**, characterization data and pH titration curve of **1**, and the ORTEP drawings of **1** and **4** from the side view (10 pages).

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(5) The author has deposited atomic coordinates for 4,6,12,14,19,-21-hexaaza-5,13,20-trioxobicyclo[7.7.7]tricosane bishydroperchlorate with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.