CHEMCOMM
Communication
www.rsc.org/chemcomm

Cystine-based cyclic oligoureas: a new class of hydrogen-bonding electroneutral anion receptors†

Darshan Ranganathan* and C. Lakshmi

Discovery Laboratory, Indian Institute of Chemical Technology, Hyderabad-500 007, India. E-mail: ranganathan@iict.ap.nic.in; Fax: 040-7173757/7173387

Received (in Cambridge, UK) 23rd March 2001, Accepted 21st May 2001
First published as an Advance Article on the web 20th June 2001

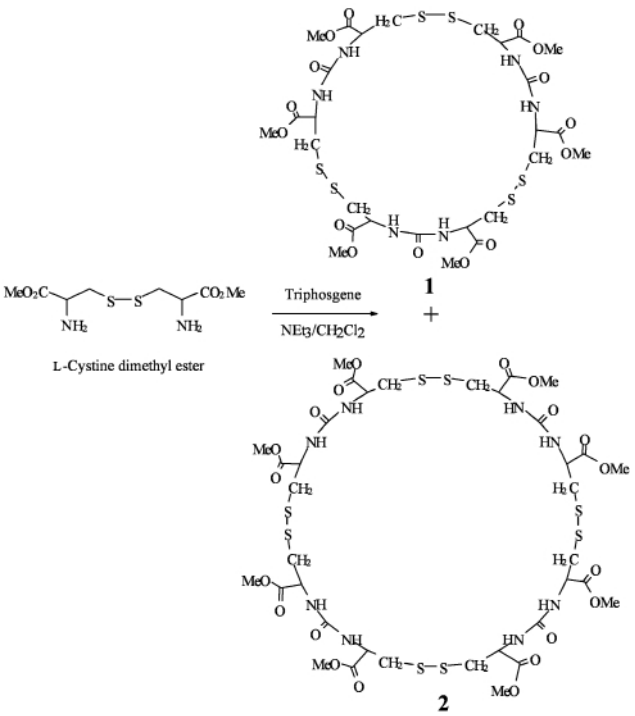
Cystine-based symmetrical cyclic oligoureas, synthesized in a one-pot reaction from L-cystine dimethyl ester and triphosgene, are demonstrated to act as versatile neutral receptors for both inorganic and organic anions operating exclusively through hydrogen bonds; ^{1}H NMR studies have shown that while the cyclic triurea prefers to complex with spherical (halides) and trigonal planar (nitrate) anions, the higher oligomer tetraurea can trap the tetragonal planar squarate dianion with modest efficiency.

Rational design of artificial receptors for anion complexation is an area of intense current interest[1] that has relevance to biology, industry and environment. Considering the intense activity and the vast literature that has accumulated over the past two decades in the field of supramolecular chemistry and the development of preorganization concepts in molecular recognition, it was surprising to find only a handful of designs for cyclic anion receptors and barring few exceptions of neutral cyclic anion hosts,[2] most of these interestingly, centred around the use of protonated macro mono or polycyclic amines.[3] Thus, whereas in Nature it is the neutral anion-binding proteins regulating the transport of anions largely through hydrogen bonds,[4] the synthetic designs of positively charged anion receptors operated mainly through coloumbic interactions. The idea of using amino acid-based macrocycles with multiple hydrogen-bonding pockets, uniformly distributed in the cyclic backbone, appeared an exciting possibility to create neutral receptors that would not only be close to natural systems but may also show high selectivity in multifunctional anion complexation.

In this communication, we provide the first illustration[5] of such a concept and report on the design, synthesis and anion recognition of L-cystine-based cyclic oligourea receptors wherein the multiple urea groups are held as part of the ring framework in a cyclic arrangement. Among the hydrogen bonding groups, the urea unit was particularly favoured because of its double hydrogen bond donor capacity. Choice of cystine unit was based on the consideration that apart from being a neutral amino acid, the presence of S–S linkage in its framework and its 1,ω-diamine nature would facilitate the ring closure to cyclicureas.

For the construction of homocyclic oligomers of cystine ureas, the synthetic strategy envisaged one-step condensation of L-cystine diOMe with triphosgene, a commercially available precursor of phosgene (Scheme 1). The reaction carried out under high dilution conditions afforded a mixture of two products with similar TLC behaviour, which were separated by chromatography on silica gel with dichloromethane–methanol (98 : 2) as eluent. The products **1** and **2** were isolated in yields of 37 and 15% respectively, and were fully characterized by spectroscopic and analytical data.[6] The ES-MS and FAB-MS results (ESI†) confirmed the cyclic trimeric and tetrameric nature of macrocycles **1** and **2** respectively. A noteworthy feature in the cyclization reaction of cystine dimethyl ester with triphosgene was the formation of 27-membered 3 + 3 macrocycle **1** as the major product (37%), followed by 15% of the 36-membered higher oligomer **2**, the 4 + 4 cyclization product. The near complete absence of 9- and 18-membered macrocycles that could arise from 1 + 1 and 2 + 2 cyclization reaction is in agreement with our earlier observations[7] with cystine-containing macrocycles where the most preferred ring size in cyclooligomerization was found to be 26-membered. Our recent finding[8] that 18-membered cyclic bisurea was the only product in the cyclooligomerization reaction of cystamine with triphosgene also supports the notion that the asymmetric cystine unit has more stringent steric demands with respect to the ring size.

The highly symmetrical structure of macrocycles **1** and **2** laced with multiple units of hydrogen-bonding urea functions, positioned equidistant from each other and all converging towards the centre of the cavity, appeared particularly suited for the molecular recognition of anionic substrates with spherical shapes. We also expected these receptors to bind polyoxyanions



Scheme 1 One step condensation of triphosgene and cystine dimethyl ester to give cyclic oligoureas **1** and **2**.

† Electronic supplementary information (ESI) available: ^{1}H NMR of **1** (Fig. S1), **2** (Fig. S2); ROESY NMR of **1** (Fig. S3), **2** (Fig. S4); ES-MS of **1** (Fig. S5), **2** (Fig. S6), FAB-MS of **1** (Fig. S7); NMR titration of **2** with squarate TBA salt (Fig. S8); ^{1}H NMR of **1** in $CDCl_3$ (host alone) (Fig. S9), **1** with Cl^- in 1 : 1 molar ratio (Fig. S10), **1** with Br^- in 1 : 1 molar ratio (Fig. S11), **1** with NO_3^- in 1 : 1 molar ratio (Fig. S12), **2** in $CDCl_3$ (host alone) (Fig. S13), **2** with squarate dianion in 1 : 1 molar ratio (Fig. S14). See http://www.rsc.org/suppdata/cc/b1/b102720b/

 DOI: 10.1039/b102720b

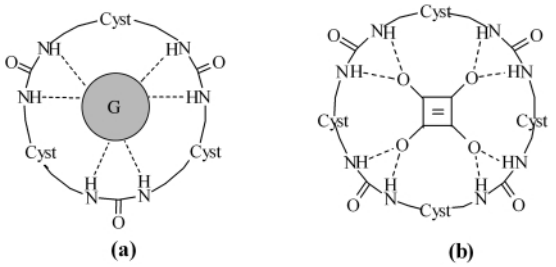


Fig. 1 (a) Proposed hexahydrogen-bonded complex of **1** with Cl^-/Br^- or nitrate anion; G = $Cl^-/Br^-/NO_3^-$; Cyst = L-cystine unit. (b) Proposed octahydrogen-bonded complex of **2** with squarate dianion.

provided their electronic and geometric features are compatible with each other.

Binding studies with halide anions (as tetrabutylammonium (TBA) salts) using ^{1}H NMR, showed that while cyclic triurea **1** showed modest affinity for chloride and bromide ions and no affinity for iodide ion, the macrocyclic tetraurea **2** was unable to bind any of the halide anions. Interestingly, the host **1**, only sparingly soluble in $CDCl_3$, was found to rapidly go into solution upon the addition of chloride or bromide TBA salt, indicating effective host–guest recognition. There was considerable downfield shift ($\sim$0.5–0.8 ppm) of NH protons in **1** suggesting their involvement in hydrogen bonding with the anion. Using NMR titration method,[9] the association constants (K_a) for **1** with chloride and bromide TBA salts were measured as 2.05×10^3 and 2.01×10^2 M^{-1} respectively. The triurea **1** with three-fold symmetry in its structure also suggested a possible complexation with trigonal anionic guests. Thus, while trimesic acid anion was found to be too big for the cavity of **1** to show any detectable NH shift, the trigonal planar geometry of nitrate anion seemed to have a complementary fit with **1** showing appreciable binding in $CDCl_3$ ($K_a = 5.2 \times 10^2$ M^{-1}). In conformity with the above notion, the cyclic tetraurea **2** was demonstrated to act as an excellent host for the squarate dianion $[SQ]^{2-}$, a truly delocalized planar tetraoxyanion[10] with four-fold symmetry. Using NMR titration, the association constant for **2** with squarate TBA salt in $CDCl_3$ was measured as 3.21×10^3 M^{-1}. The significant downfield shift ($\Delta\delta \sim 1.5$) observed for the urea NH protons of **2** is indicative of highly effective hydrogen bonding. The almost 100-fold selectivity of macrocyclic triurea **1** for planar, 3-fold symmetric nitrate anion and of cyclic tetraurea **2** for planar four-fold symmetric squarate tetraoxyanion guest was shown by complete absence of any anion induced shifts in the ^{1}H NMR of **1** and **2** in $CDCl_3$ even with excess molar proportions of the guest substrates. The proposed tris-bidentate or hexahydrogen-bonded structure for complex of **1** with Cl^-/Br^- or NO_3^- [Fig. 1(a)] and octahydrogen-bonded structure for the complex of **2** with $[SQ]^{2-}$ [Fig. 1(b)] is supported by the maximum NH shift at a mole ratio of 1:1 (ESI†).

The cystine-based macrocyclic oligoureas described here represent a new class of electroneutral anion receptors that operate exclusively through hydrogen bonds. The multiple hydrogen-bonding sites distributed symmetrically all over the ring make these macrocycles especially suited for molecular recognition of spherical and polyfunctional anions. Their remarkable affinity for planar polyoxyanions and selectivity according to size complementarity combined with extremely simple synthesis from commercially available materials should open up new challenges in this area. Additionally, the receptor modification through the COOH handles on the cystine unit should provide attractive hosts for membrane anion transport. Studies in this direction are in progress.

We thank Professor S. Ranganathan for valuable discussions. Financial support from DST, New Delhi is gratefully acknowledged. D. R. is also an honorary faculty member of Jawaharlal Nehru Centre for Advanced Scientific Research.

Notes and references

1 J. Scheerder, J. F. J. Engbersen and D. N. Reinhoudt, *Recl. Trav. Chim. Pays Bas.*, 1996, **115**, 307; F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609; J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, Germany, 1995; J. L. Atwood, K. T. Holman and J. W. Steed, *Chem. Commun.*, 1996, 1401; P. D. Beer, *Chem. Commun.*, 1996, 689; B. Dietrich, *Pure Appl. Chem.*, 1993, **65**, 1457; M. M. G. Antonisse and D. N. Reinhoudt, *Chem. Commun.*, 1998, 443.

2 A. M. Kelly-Rowley, V. M. Lynch and E. V. Anslyn, *J. Am. Chem. Soc.*, 1995, **117**, 3438; P. A. Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140.

3 E. Kimura, A. Sakonaka, T. Yatsunami and M. Kodama, *J. Am. Chem. Soc.*, 1981, **103**, 3041; M. W. Hosseini and J.-M. Lehn, *J. Am. Chem. Soc.*, 1982, **104**, 3525; M. W. Hosseini and J.-M. Lehn, *Helv. Chim. Acta*, 1998, **71**, 749.

4 J. J. He and F. A. Quiocho, *Science*, 1991, **251**, 1479; Z. F. Kanyo and D. W. Christianson, *J. Biol. Chem.*, 1991, **266**, 4246; H. Luecke and F. A. Quiocho, *Nature*, 1990, **347**, 402.

5 Although open chain urea-based hosts have been used for complexation of oxyanions (T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072; E. Fan, S. A. Van Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 369; C. Raposo, M. Almaraz, M. Martin, V. Weinrich, M. L. Mussons, V. Alcasar, M. C. Caballero and J. R. Moran, *Chem. Lett.*, 1995, 759; K. S. Jeong, J. W. Park and Y. L. Cho, *Tetrahedron Lett.*, 1996, **37**, 2795; P. Buhlmann, S. Nishizawa, K. P. Xiao and Y. Umezawa, *Tetrahedron*, 1997, **53**, 1647. To the best of our knowledge with the sole exception of one recent reference. B. H. M. Snellink-Ruël, M. M. G. Antonisse, J. F. J. Engbersen, P. Timmerman and D. N. Reinhoudt, *Eur. J. Org. Chem.*, 2000, 165 wherein phenylene-bridged macrocyclic tetraureas have been shown to bind $H_2PO_4^-$ with complete selectivity over Cl^- in DMSO solvent, there are no reports in literature on the use of cyclic oligoureas wherein the urea units form part of the ring backbone as anion receptors. However, urea-appended cyclic hosts for spherical halide anions R. C. Jagessar, M. Shang, W. R. Scheidt and D. H. Burns, *J. Am. Chem. Soc.*, 1998, **120**, 11684; J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815 have been reported.

6 Selected data: **1**: Yield 37%; mp 202–203 °C; IR (KBr) 3376, 2956, 1736, 1634, 1565 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.11 (m, 12H), 3.63 (s,18H), 4.42 (m, 6H), 6.81 (d, J = 7.5 Hz, 6H); FAB-MS *m/z*: (%) 905 (10) $[M + Na^+]$, 883 (45) $[M + H]^+$; ES-MS *m/z*: (%) 905 (100) $[M + Na^+]$, 883 (80) $[M + H]^+$. **2**: Yield 15%; mp 204–206 °C; IR (KBr) 3360, 2960, 1741, 1636, 1563 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.07 (m, 16H), 3.66 (s, 24H), 4.44 (m, 8H), 6.77 (d, J = 8.0 Hz, 8H); ES-MS *m/z*: (%) 1199 (100) $[M + Na^+]$.

7 D. Ranganathan, V. Haridas and I. L. Karle, *J. Am. Chem. Soc.*, 1998 **120**, 2695; D. Ranganathan, V. Haridas, K. P. Madhusudanan, R. Roy, R. Nagaraj, G. B. John and M. B. Sukhaswami, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1105; D. Ranganathan, V. Haridas, R. Nagaraj and I. L. Karle, *J. Org. Chem.*, 2000, **65**, 4415.

8 D. Ranganathan and C. Lakshmi, unpublished results.

9 The association constant (K_a) was obtained by using the following equation: $K_{assoc} = \alpha/[(1 - \alpha)([G] - \alpha[H])$, where $\alpha = (\delta - \delta_0)/(\delta_{max} - \delta_0)$, δ_0 is the initial chemical shift (host alone), δ is the chemical shift at each titration point, and δ_{max} is the chemical shift when the receptor is entirely bound. [*G*] and [*H*] are the concentrations of guest and host, respectively, at each titration point. (T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072 and references therein).

10 I. L. Karle, D. Ranganathan and V. Haridas, *J. Am. Chem. Soc.*, 1996, **118**, 7128.