Chirality induction in a dibenzo-30-crown-10 congener promoted by an ion-pair coordinated self-assembly

Letter

Tomokazu Tozawa, Tatsuya Tachikawa, Sumio Tokita and Yuji Kubo*

Department of Applied Chemistry, Faculty of Engineering, Saitama University,
255 Shimo-ohkubo, Saitama 338-8570, Japan. E-mail: yuji@apc.saitama-u.ac.jp

Received (in Montpellier, France) 16th September 2002, Accepted 5th November 2002
First published as an Advance Article on the web 12th December 2002

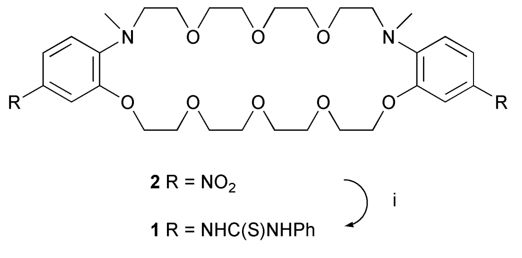
We report the first example of chirality induction in a large-sized crown ether congener with bis(arylthiourea) units, which serve as an anion binding site. The phenomenon arises *via* an achiral ion-pair coordinated self-assembly in which intermolecular head-to-tail hydrogen bonding interactions occur between the thiourea units in the solid state.

The concepts of preorganization and complementarity have triggered a search for artificial receptors possessing the "dynamic" function of molecular recognition in supramolecular chemistry. This allows us to design artificial allosteric molecules[1] and function-switchable systems[2] so as to explore molecular machines[3] and also to prepare self-assembled building blocks.[4] Crown ethers are very useful entities for constructing such systems because of their structural topology and easy synthetic modification. In particular, dibenzo-24-crown-8 has received much attention in the production of novel psudorotaxanes possessing dynamic functions.[5]Dibenzo-30-crown-10s, with their larger ring size and greater flexibility, tend to entangle cations of small size, resulting in a change of conformation.[6] Based on this phenomenon we have proposed a new preorganized allosteric system, a regioselectively bis(methylthiourea)-substituted dibenzo-diaza-30-crown-10, for cation-binding promoted anion recognition[7] and also as an activity-controllable enzyme model for cleavage of a phosphodiester bond.[8]

In the course of this project, during an X-ray crystallographic study for obtaining structural insights into cation-anion coordination using bis(arylthiourea)-derived dibenzo-diaza-30-crown-10, **1** (Scheme 1), we unexpectedly observed a novel achiral-to-chiral transformation of the diaza-crown ether unit. This new finding, obtained through K^+ and I^- coordinated self-assembly in the solid state, is reported here.

The employed system **1** was newly synthesized by reduction of the dinitro derivative **2**,[7,9] followed by a condensing reaction with PhNCS in CH_2Cl_2 for 37 h (43% yield of **1** from **2**). Two arylthiourea units at which efficient anion binding can take place are incorporated regioselectively on the benzene rings of the dibenzo-diaza-30-crown-10 skeleton. A single crystal suitable for X-ray study was obtained from an acetone solution of **1** with KI, the complex structure being determined. The unit cell is illustrated in Fig. 1 and shows a unique and independent self-assembly of (K^+-**1**) I^-. This self-assembly has the space group $P\bar{1}$ and forms a crystallographic centrosymmetric structure in which the U-shaped diaza-crown segments are located in opposite sites to each other. In Fig. 2, it is clear that K^+ is wrapped round to give eight K–O distances in the range 2.7870(9)–3.0363(12) Å, as well as two K–N distances of 3.0475(10) and 3.5094(10) Å, although the motif is different from the case of dibenzo-30-crown-10; the KI complex of dibenzo-30-crown-10 shows two-fold crystallographic symmetry.[10] In our case, the arylthiourea units of **1** were found to have a different orientation to each other in the self-assembled compound(*vide infra*), which could explain the differing K–N distances. The iodide ion, as expected, interacts with the one thiourea anion binding segment [I(1)–N(53) 3.5364(9) , I(1)–N(56) 3.6109(9) Å]. However, the further thiourea unit does not bind to I^-, but participates in an intermolecular hydrogen bonding interaction with a thiourea of a second **1** to assist in the self-assembly of the (K^+-**1**) I^- complex. This systematic hydrogen bonding network constitutes a head-to-tail binding mode between the thiourea units, in which the intermolecular N–S distances are 3.4610(12) Å for S′(55)–N(43) and 3.5658(10) Å for S′(55)–N(46).

The ORTEP drawing in Fig. 2 shows a further remarkable feature: the self-complementarity of (K^+-**1**) I^- implies that the ligand concerned becomes enantiomers **1a** and **1b**, as



Scheme 1 *Reactions and conditions*: (i) 10% Pd/C, H_2 atmosphere (2.3 atm), EtOH and then PhNCS, CH_2Cl_2 (43%).

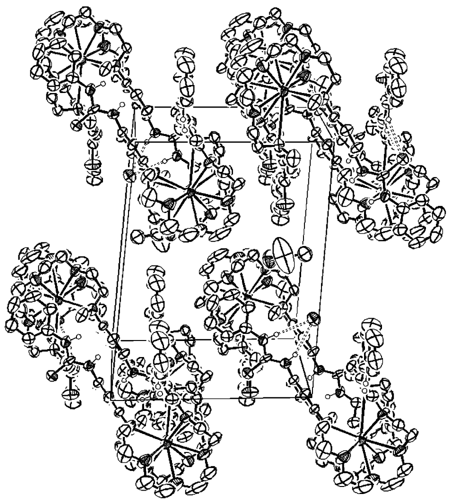


Fig. 1 Unit cell of self-assembled (K^+-**1**) I^-.

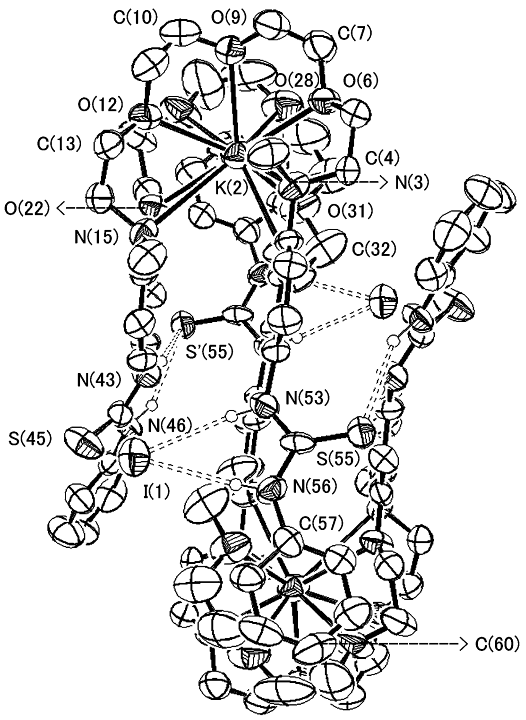


Fig. 2 Crystal structure (ORTEP) of self-assembled $(K^+\text{-}\mathbf{1})\ I^-$ showing the numbering scheme. The intermolecular hydrogen bonds are marked as dashed lines. Hydrogen atoms that are not involved in hydrogen bonding interactions have been omitted for clarity; selected bond lengths (Å): K(2)–O(6) 2.7879(9), K(2)–O(9) 2.7870(9), K(2)–O(12) 2.9144(9), K(2)–O(22) 2.8420(8), K(2)–O(25) 2.8398(10), K(2)–O(28) 3.0363(12), K(2)–O(31) 2.9585(9), K(2)–O(34) 2.8106(8), K(2)–O(15) 3.5094(10), K(2)–N(3) 3.0475(10), K(2)–N(15) 3.5094(10), I(1)–N(53) 3.5364(9), I(1)–N(56) 3.6109(9), S(55)–N(43) 3.4610(12), S(55)–N(46) 3.5658(10).

depicted in Fig. 3, which can refer to the chirality at the nitrogen [N(3) and N(15)] being considered to coordinate to the K^+. Although self-assembly using a bis(thiourea) receptor has been reported,[11] we believe that this is the first example of an achiral-to-chiral transformation caused by ion-pair-coordinated self-assembly.[12] Furthermore, it is noteworthy that one of the terminal benzene rings [C(57)–C(62)] has capped the lateral of the U-shaped K^+-diaza-crown segment in the self-assembly. This is a plausible candidate for an intermolecular cation-π interaction;[13] the K^+–C(57) distance of 6.45 Å is long compared to that for typical cation-π interactions in biological systems.[14] This could be due to interference involving the van der Waals surfaces of the poly(ether) chains of the diaza-crown segment. We therefore suppose that the self-assembled dimer, which forces **1** to become enantiomeric, is also stabilized by the benzene ring close to K^+.

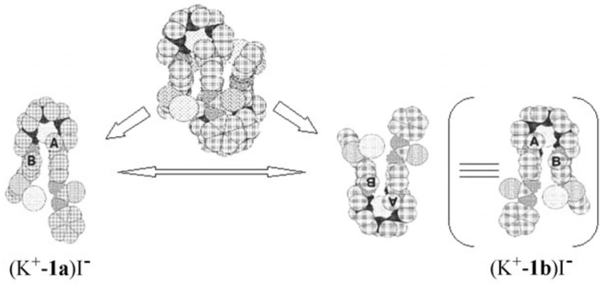


Fig. 3 Chirality induction of the diaza-crown segment through the self-assembled $(K^+\text{-}\mathbf{1})\ I^-$. The symbols "A" and "B" denote the methyl carbons attached to N(3) and N(15), respectively.

In summary, our new findings regarding chiality induction in a highly flexible macrocycle have been described through ion-pair-coordinated self-assembly. We believe that the present results provide a new approach for generating molecular systems with whatever chirality is desired. Further work to implement this program is now underway in our laboratory.

Experimental

Synthesis

To a suspended ethanolic solution of **2** (250 mg, 0.38 mmol) was added 10% Pd/C (204 mg). The suspended solution was stirred in an autoclave under H_2 atmosphere (2.3 atm) for 6 h at room temperature. The Pd/C was removed by filtration and the resulting solution was evaporated at room temperature under reduced pressure to give the corresponding reduced compound. Phenylisothiocyanate (174 mg, 1.29 mmol) was then added to a CH_2Cl_2 (20 mL) solution of the compound. The mixture was stirred at room temperature for *ca.* 18 h under Ar, during which time a further 425 mg of phenylisothiocyanate (3.14 mmol) was added to the solution. The reaction mixture was then stirred at 50 °C for *ca.* 19 h to drive the reaction further. After the solvent was removed, the crude compound was chromatographed using silica gel (Wakogel C-300) with MeOH–$CHCl_3$ (1:9 v/v), and was re-precipitated with acetone–Et_2O to provide 142 mg of **1** (43% yield from **2**).

^{1}H NMR (400 MHz, CD_3CN, TMS) δ 8.20 (bs, 2H), 8.16 (bs, 2H), 7.40–7.31 (m, 8H), 7.21–7.17 (m, 2H), 6.91 (d, 2H, $J = 1.9$ Hz), 6.86 (d, 2H, $J = 8.5$ Hz), 6.82 (dd, 2H, $J = 2.0$ and 8.4 Hz), 4.06–4.04 (m, 4H), 3.80–3.78 (m, 4H), 3.66 (t, 4H, $J = 6.1$ Hz), 3.63–3.60 (m, 4H), 3.59–3.56 (m, 4H), 3.53–3.48 (m, 8H), 3.21 (t, 4H, $J = 6.2$ Hz), 2.78 (s, 6H); ^{13}C NMR (100.7 MHz, CD_3CN) δ 181.69, 173.71, 169.06, 152.16, 141.86, 139.93, 129.62, 126.74, 126.47, 118.96, 118.83, 111.72, 71.32, 71.21, 71.11, 70.43, 70.30; 68.73, 55.27, 40.72; Anal. calcd for $C_{44}H_{58}N_6O_8S_2$: C, 61.23; H, 6.77; N, 9.74; found: C, 61.17; H, 6.79; N, 9.62; FAB MS: m/z 862 $[M]^+$.

X-Ray structural analysis

A mixture of **1** (7.5 mg, 8.7 μmol) and KI (1.7 mg, 10.2 μmol) was dissolved in a small amount of acetone and was heated at 45 °C using a thermostat. The solution was allowed to stand for 2 days in the thermostat (45 °C → 20 °C) to form a crystalline KI complex of **1** suitable for X-ray crystallographic analysis.

Crystallographic parameters of $[K^+\text{-}\mathbf{1}]\ I^-$ were measured at ambient temperature on a MAC Science MXC18K four-cycle diffractometer using graphite-monochromated Mo Kα radiation and an 18 kW rotating anode generator, using ϖ scans. The structure was deduced by direct methods using SIR92 in the maXus ver. 2.0 program system. Values of the atomic coordinates and anisotropic thermal parameters of the non-H atoms were refined by full-matrix least-squares. Three standard reflections (−5 −5 −10, 3 1 11, −4 0 −11) showed no significant variations throughout data collection; 12 063 reflections were measured, and 4839 independent reflections $[F_0 > 2\sigma(F_0)]$ were used for analysis. An absorption correction was not applied. Final refinement was made with anisotropic thermal factors for all non-hydrogen atoms; there were 683 parameters, $R = 0.076$ and $wR = 0.052$, GOF = 2.311. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were partly added in the calculated positions.

Crystal data for $(K^+\text{-}\mathbf{1})I^-$: $C_{47}H_{64}N_6O_9S_2KI$, $M = 1087.2$, triclinic, space group $P\bar{1}$, $a = 13.117(2)$, $b = 16.848(3)$, $c = 13.008(6)$ Å, $\alpha = 112.21(2)°$, $\beta = 95.65(2)°$, $\gamma = 83.44(1)°$, $V = 2639.2(1)$ Å^3, $Z = 2$.

CCDC reference number 198784. See http://www.rsc.org/suppdata/nj/b2/b209033c/ for crystallographic data files in CIF or other electronic format.

Acknowledgements

The authors thank Dr. L. J. Farrugia for use of the ORTEP-3 program.[15]

References

1 T. Mabeshima, *Coord. Chem. Rev.*, 1996, **148**, 151; S. Shinkai, M. Ikeda, A. Sugasaki and M. Takeuchi, *Acc. Chem. Res.*, 2001, **34**, 494.
2 V. Amedola, L. Fabbrizzi, M. Licchelli, C. Mangano, P. Pallavicini, L. Parodi and A. Poggi, *Coord. Chem. Rev.*, 1999, **190–192**, 649; *Molecular Switches*, ed. B. L. Feringa, Wiley-VCH, Weinheim, 2001.
3 V. Balzani, A. Credi, F. M. Raymo and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2000, **39**, 3348; for a special issue on molecular machines, see: *Acc. Chem. Res.*, 2001, **34**, issue 6; regarding the current topic, see: H. Yan, X. Zhang, Z. Shen and N. C. Seeman, *Nature*, 2002, **415**, 62.
4 Y. Miyatake, A. Hosoda, M. Takagishi, E. Nomura and H. Taniguchi, *Chem. Commun.*, 2002, 132.
5 M. C. T. Fyfe and J. F. Stoddart, in *Advances in Supramolcular Chemistry*, ed. G. W. Gokel, JAI Press, Inc., London, 1999, vol. 5, pp. 1–53.
6 F. Vögtle, *Supramolecular Chemistry, an Introduction*, John Wiley & Sons, New York, 1993.
7 T. Tozawa, Y. Misawa, S. Tokita and Y. Kubo, *Tetrahedron Lett.*, 2000, **41**, 5219.
8 T. Tozawa, S. Tokita and Y. Kubo, *Tetrahedron Lett.*, 2002, **43**, 3455.
9 S. Houbrechts, Y. Kubo, T. Tozawa, S. Tokita, T. Wada and H. Sasabe, *Angew. Chem., Int. Ed.*, 2000, **39**, 3859.
10 M. A. Bush and M. A. Truter, *J. Chem. Soc., Perkin Trans. 2*, 1972, 345.
11 Y. Tobe, S. Sasaki, K. Hirose and K. Naemura, *Tetrahedron Lett.*, 1997, **38**, 4791.
12 For a current review highlighting the co-ordination of inorganic ion pairs by ditopic receptors, see: G. J. Kirkovits, J. A. Shriver, P. A. Gale and J. L. Sessler, *J. Inclusion Phenom. Macrocycl. Chem.*, 2001, **41**, 69.
13 E. S. Meadows, S. L. De Wall, L. J. Barbour and G. W. Gokel, *J. Am. Chem. Soc.*, 2001, **123**, 3092.
14 J. P. Gallivan and D. A. Dougherty, *Proc Natl. Acad. Sci. USA*, 1999, **96**, 9459.
15 ORTEP-3 for Windows: L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.