

A Molecular Box, based on Bibracchial Lariat Ethers having Adenine and Thymine Sidearms, that Self-assembles in Water

MinSook Kim and George W. Gokel*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124, U.S.A.

Two 4,13-diaza-18-crown-6 derivatives in which the sidearms terminate in adenine or thymine residues have been prepared; molecular weight determinations indicate that they are associated in water and form a ternary complex with a dodecane-1,12-diammonium salt in the same solvent, presumably involving DNA-type interactions and a total of ten hydrogen bonds.

Recent studies of cyclophanes, macropolycyclic cryptands, cyclodextrins, and molecular clefts as hosts for inclusion complexation attest to the enormous interest in this field.¹ All the studies reported to date utilize covalent linkages to construct the essential complexing portion of the host, *i.e.* the molecular box. This approach offers the advantages of precise and stable spatial relationships. Nature also utilizes this technique but often relies upon much weaker individual interactions which, in concert, offer considerable conformational stability if not rigidity. We report here the formation of a macrobicyclic cryptand formed by hydrogen bonding between bibracchial lariat ether² precursors having adenine-terminated and thymine-terminated sidearms.

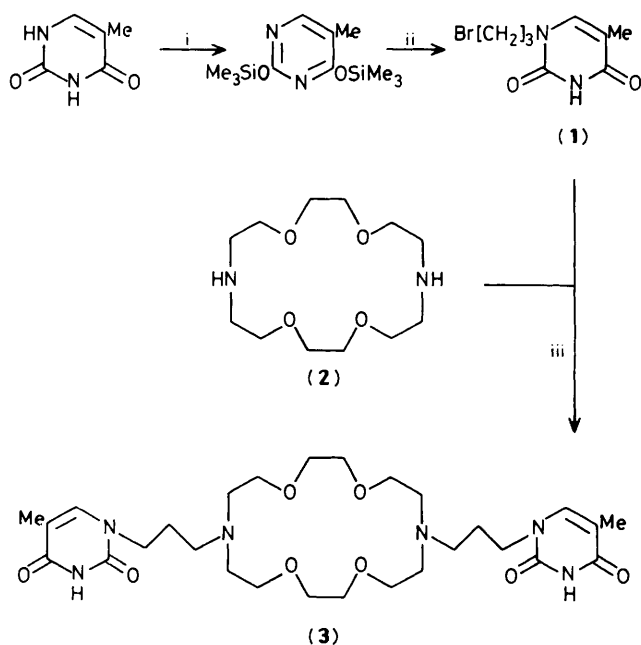
Purines and pyrimidines are well known to form hydrogen-bonded, unsymmetrical dimers in DNA and these structures have considerable cumulative energy. We envisioned the formation of a molecular box having 4,13-diaza-18-crown-6 units at each end and connector units that self-assemble from thymine and adenine. The conceptually simplest approach would be to attach thymine to one nitrogen of the macro-ring and adenine to the other. The single molecule would thus dimerize using two A/T interactions and a single monomer would afford the macrobicyclic cryptand. We chose instead to prepare two more accessible precursor units, one having

thymine-terminated and the other adenine-terminated sidearms.

Thymine was bis-*O*-trimethylsilylated with Me₃SiCl and hexamethyldisilazane. The product was stirred with 1,3-dibromopropane at ambient temperature for 10 days. 1-(3-Bromopropyl)thymine (**1**) was obtained (m.p. 135–136 °C; lit.³ 136–138 °C) in 60% yield after recrystallization from CHCl₃/hexane. 4,13-Diaza-18-crown-6 (**2**) (1 mmol) and (**1**) (2 mmol) were stirred for 5 days at ambient temperature in MeCN. The product, *N,N'*-bis-[3-(thymine-1-yl)propyl]-4,13-diaza-18-crown-6 bis(hydrobromide)[†] [(**3**)·2HBr, yield 86%, m.p. 230–235 °C (decomp.)], was treated with tetramethylammonium hydroxide pentahydrate to liberate (**3**) (67%) as a colourless oil.

Adenine was deprotonated with NaH in dimethylformamide and chloropropylated with 1-bromo-3-chloropropane. The product (**4**) was obtained (49%) after crystallization from ethanol as a white solid, m.p. >300 °C (resolidification at 190 °C); lit.⁴ 189–190 °C. The apparent discrepancy in m.p. required structural confirmation by combustion analysis, ¹H

[†] For (**3**)·2HBr: Found: C, 42.3; H, 6.5. C₂₈H₄₈O₈N₆Br₂·2H₂O requires C, 42.4; H, 6.6%; δ_H (CDCl₃) 7.15 (s, 2H), 3.55 (m, 20H), 2.65 (m, 12H), 1.85 (s, 6H), and 1.75 (m, 4H)].



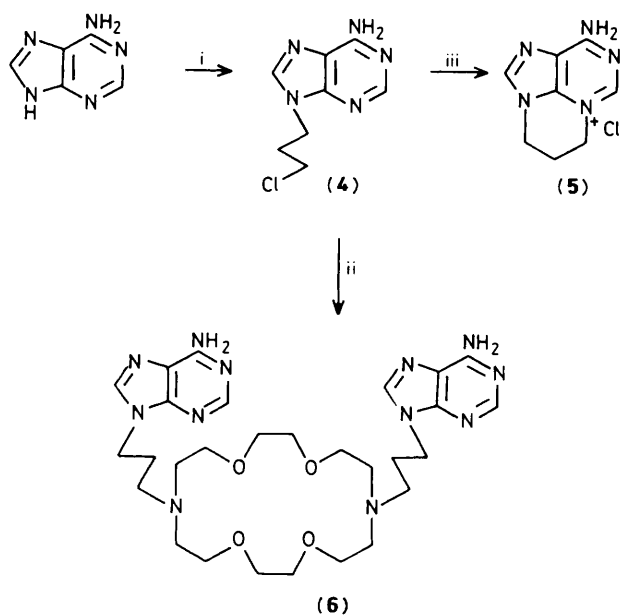
Scheme 1. Reagents: i, Me_3SiCl , $(\text{Me}_3\text{Si})_2\text{NH}$; ii, $\text{Br}[\text{CH}_2]_3\text{Br}$, room temp., 10 d; iii, MeCN , 5 d.

n.m.r. spectroscopy and solubility properties.[‡] Treatment of (4) with diaza-18-crown-6 (2) in refluxing MeCN afforded only the tricyclic hydrochloride derivative (5). After a number of other, unsuccessful attempts, compounds (4) (2 mmol) and (2) (2 mmol) were intimately mixed in a flask containing a stirring bar. The flask was sealed under vacuum and then gradually heated to 115–125 °C and kept at this temperature for 12 h. The mixture was cooled and dissolved in EtOH ; the solution was concentrated, and the residue dissolved in hot MeCN and kept at room temperature for 24 h during which time a precipitate was obtained. This mixture yielded four products: the two-armed crown (6) (24%), the tricyclic derivative (5) (35%), residual (2), and its bis(hydrochloride). The solid was dissolved in CHCl_3 ; the solution was filtered and concentrated, and the residue dissolved in MeCN . Crystallization from MeCN afforded *N,N'*-bis-[3-(adenin-1-yl)propyl]-4,13-diaza-18-crown-6 (6) as a white solid (24%, m.p. 154–157 °C).[§]

The association of (3) and (6) would be expected in non-polar solvents, but water is highly polar and well able to compete for hydrogen bonds. The expected complex is shown in Figure 1. Associative behaviour was demonstrated by assessing molecular weight in solution (Wescor 5100C vapour phase osmometer, all experimental errors $\leq \pm 5\%$). The osmometer was calibrated by determining the molecular weight of distilled 18-crown-6 (four trials each, in H_2O) in 50, 100, 150, 200, and 250 mM concentrations. Next, the molecular weight of *N,N'*-bis(2-hydroxyethyl)-4,13-diaza-18-crown-6⁵ was determined in H_2O . In this case, hydrogen bonding

[‡] For (4): Found: C, 45.2; H, 4.8; N, 33.0. $\text{C}_8\text{H}_{10}\text{N}_5\text{Cl}$ requires C, 45.4; H, 4.8; N, 33.1%; $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.1 (s, 2H), 7.15 (brs, 2H), 4.28 (t, 2H), 3.61 (t, 2H), and 2.3 (m, 2H). Compound (4) is soluble in Me_2SO and insoluble in H_2O , and resolidifies at 190 °C. Compound (5) is soluble in H_2O but not in Me_2SO and has m.p. >300 °C; $\delta_{\text{H}}(\text{D}_2\text{O})$ 8.5 (s, 1H); 8.3 (s, 1H); 4.5 (m, 4H); and 2.55 (m, 2H).

[§] For (6): Found: C, 52.9; H, 7.48. $\text{C}_{28}\text{H}_{44}\text{N}_{12}\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 53.3; H, 7.4%.



Scheme 2. Reagents: i, NaH , Me_2NCHO , then $\text{Cl}[\text{CH}_2]_3\text{Br}$; ii, 4, 1,3-diaza-18-crown-6 (2), heat; iii, heat.

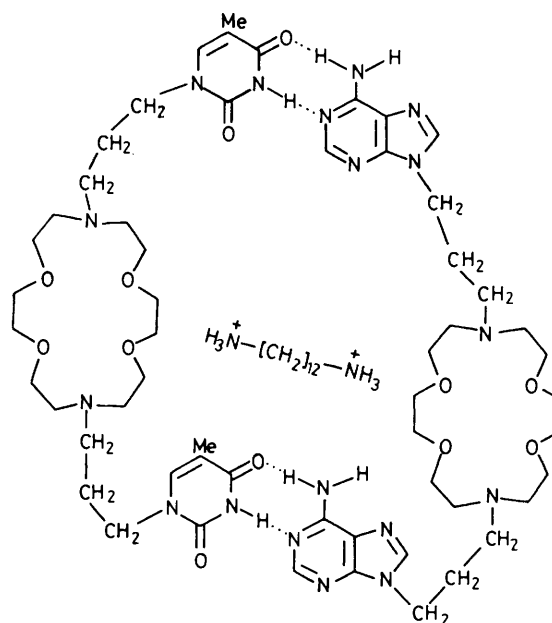


Figure 1. Proposed structure for complex between (3) and (6) with dodecane-1,12-diammonium ion.

sidearms and a macro-ring identical with that in (3) or (6) are present. The observed mol. wt. was 346 (theory 350; five trials). When dodecane-1,12-diammonium dihydrochloride was added (ratio host:guest 2 : 1) the apparent mol. wt. (three trials) was 335. The simple average mol. wt. is 324. A non-associated mixture of (3) (mol. wt. 630) and (6) (594) would be expected to show a mol. wt. of $(630 + 594)/2 = 612$. A completely associated system would show a value of 1224. In pure H_2O , at 25 °C, the apparent mol. wt. was 771. This indicates about 25% association [K_{eq} ca. 2 for complex of (3) + (6)]. The association of (3) and (6) in the presence of

dodecane-1,12-diammonium ion is far more complicated. Ammonium ion can complex individually with either (3) or (6). Oligomers of (3) or (6) or both with the diammonium salt can also form, and would complicate the molecular weight determination. All these possibilities should reduce the apparent molecular weight. When dodecane-1,12-diammonium bis(hydrochloride) was added to the aqueous solution, an apparent molecular weight of 1123 was observed. The ternary complex (see Figure 1) has a theoretical mol. wt. of 1498. We are currently refining these measurements but the implication of this result is that the bis(ammonium) ion enhances formation of the self-assembled box nearly three-fold. Although attempts to crystallize the complex from (3) and (6) have thus far failed, additional efforts to do so are under way, along with a detailed spectroscopic study.

We thank the National Institutes of Health for a grant (GM 36262) in support of this work.

Received, 11th June 1987; Com. 809

References

- 1 D. J. Cram, *Science*, 1983, **219**, 1177; K. Nagai, K. Hayakawa, and K. Kanematsu, *J. Org. Chem.*, 1984, **49**, 1022; S. P. Miller and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, 1984, **106**, 1492; J. M. Lehn, *Science*, 1985, **227**, 849; D. O. Krongly, S. R. Denmeade, M. Y. Chiang, and R. Breslow, *J. Am. Chem. Soc.*, 1985, **107**, 5544; M. Cesario, C. O. Dietrich-Buchecker, J. Guilhem, C. Pascard, and J. P. Sauvage, *J. Chem. Soc., Chem. Commun.*, 1985, 247; W. Kissener and F. Vögtle, *Angew. Chem.*, 1985, **97**, 782; J. Rebek, Jr., L. Marshall, R. Wolak, K. Parris, M. Killoran, B. Askew, D. Nemeth, and N. Islam, *J. Am. Chem. Soc.*, 1985, **107**, 7476; S. Misumi and Y. Sakata, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, 1985, **42**, 53; M. Momenteau, J. Mispelter, B. Looock, and J.-M. Lhoste, *J. Chem. Soc., Perkin Trans. 1*, 1985, 61; H. J. Bouas-Laurent, A. Castellan, M. Daney, J.-P. Desvergne, G. Guinand, P. Marsau, and M.-H. Riffaud, *J. Am. Chem. Soc.*, 1986, **108**, 315; T. Merz, H. Witz, and F. Vögtle, *Angew. Chem.*, 1986, **98**, 549; D. Heyer, and J.-M. Lehn, *Tetrahedron Lett.*, 1986, **27**, 5869; F. Diederich, K. Dick, and D. Griebel, *J. Am. Chem. Soc.*, 1986, **108**, 2273; I. O. Sutherland, *Chem. Soc. Rev.*, 1986, **15**, 63; J. A. Cowan, J. K. M. Sanders, G. S. Beddard, and R. J. Harrison, *J. Chem. Soc., Chem. Commun.*, 1987, 55; J. Rebek, *Science*, 1987, **235**, 1478.
- 2 G. W. Gokel, D. M. Dishong, and C. J. Diamond, *J. Chem. Soc. Chem. Commun.*, 1980, 1053; D. M. Dishong, C. J. Diamond, M. I. Cinoman, and G. W. Gokel, *J. Am. Chem. Soc.*, 1983, **105**, 586; R. A. Schultz, B. D. White, D. M. Dishong, K. A. Arnold, and G. W. Gokel, *J. Am. Chem. Soc.*, 1985, **107**, 6659.
- 3 D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Am. Chem. Soc.*, 1968, **90**, 7302.
- 4 N. J. Leonard, T. G. Scott, and P. C. Huang, *J. Am. Chem. Soc.*, 1967, **89**, 7137.
- 5 V. J. Gatto and G. W. Gokel, *J. Am. Chem. Soc.*, 1984, **106**, 8240.