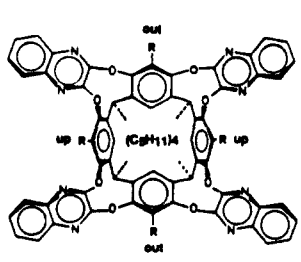
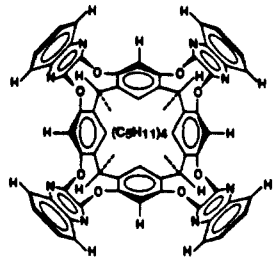
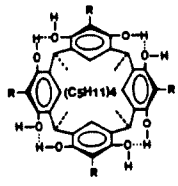
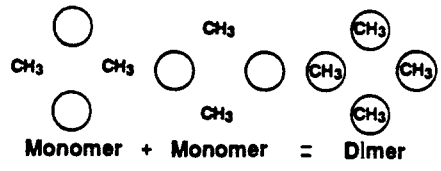




Kite: 1, R = H
2, R = CH_3
3, R = C_2H_5

Vase, 4



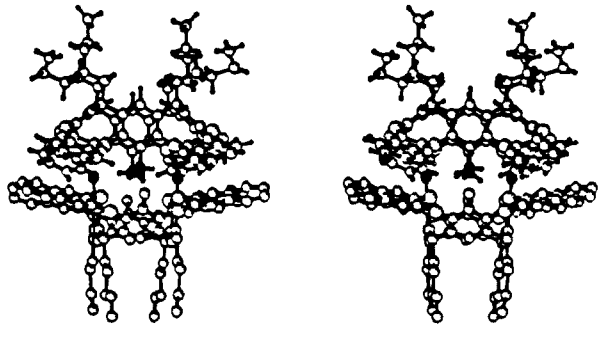


5, R = H
6, R = CH_3
7, R = C_2H_5

8 9 10

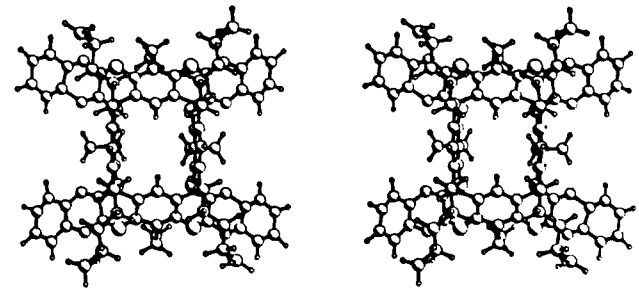
containing two protruding up-methyl groups and two methyl-sized indentations lined by a sloping aryl face, an out-methyl, and two oxygens. Rotation of **8** by 90° gives **9**. Superposition of **8** on **9** produces face-to-face dimer **10**, in which four methyl groups as guests occupy four host cavities. In models of **2·2**, two sets of quinoxalines contact one another. Two models of **3** are inhibited from dimerizing by the inability of ethyls to enter methyl-sized cavities.

Experimentally, **2** exists only as dimer in $CDCl_3$ (^1H NMR 360-MHz spectra, at available temperatures and vapor-phase osmometry, 27 °C, 10.9–40 mM, observed MW 2783 ± 280, calcd for **2·2** 2656). A crystal structure of **2·2** is shown in **11**.[6] It conforms in detail to expectations based on models. Intermolecular atom-to-atom van der Waals contacts in **11** number 70; 44 more are within contact distance plus 0.1–0.2 Å.



11, side stereoview of 2·2 crystal structure

In contrast, **3** exists detectably only as monomer in $CDCl_3$ (^1H NMR).[7] The crystal structure of **3** (**12**)[6] shows pentyl to quinoxaline layering.



12, bottom stereoview of 3 crystal structure

Binding in **2·2** is a unique expression of each monomer containing two hostlike and two guestlike parts that are preorganized[8] to dimerize. Changing four aryl methyls of **2** to four aryl hydrogens of **1** or to four aryl ethyls of **3** destroys the complementarity required for observable complexation.[9] The high structural recognition of **2** by **2** rivals that observed in the evolutionary systems of nature, but without hydrophobic, hydrogen-bonding, pole–pole, or pole–dipole binding forces.

(6) Crystallization of **2·2** from acetone gave **2·2·6**$(CH_3)_2CO$: monoclinic, $C2/c$, a = 23.780 (2) Å, b = 31.251 (3) Å, c = 23.391 (2) Å, β = 93.900 (4)°, V = 16.308 Å^3, Z = 8 (four dimers of $C2$ symmetry; the asymmetric unit contains two half-molecules), acetone disordered, R = 0.166. Crystallization of **3** from EtOAc–$C_6H_5NO_2$–CH_2Cl_2–$CHCl_3$ gave **3**·EtOAc: monoclinic, $C2/c$, a = 38.71 (1) Å, b = 8.907 (3) Å, c = 30.260 (8) Å, β = 114.53 (1)°, V = 9493 Å^3, Z = 4 (half-molecules related by 2-fold axis), ester disordered, R = 0.169. Details will be published elsewhere.

(7) The ^1H NMR spectrum of **3** in $CDCl_3$ is concentration independent. If the ^1H NMR spectrum of **2** vs **2·2** models that of **3** vs **3·3**, as little as 5% of **3·3** could have been detected.

(8) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1039–1057.

(9) The low-temperature ^1H NMR spectrum of **1** in $CDCl_3$, in which essentially only the kite form exists, shows no ^1H NMR concentration dependence and no detectable signals at positions characteristic of **2·2** and other similar dimers.

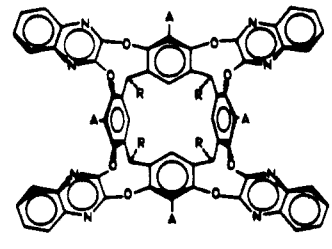
High Preorganization of Large Lipophilic Surfaces Common to Two Complexing Partners Provides High Binding Free Energies That Vary Dramatically with Changes in Organic Solvent Composition[1]

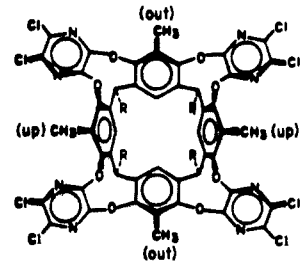
Judi A. Bryant, John L. Ericson, and Donald J. Cram*

Department of Chemistry and Biochemistry of the University of California at Los Angeles Los Angeles, California 90024

Received October 16, 1989

Previous work established that **1** (unlike **2** and **3**) when dissolved in $CDCl_3$ existed mainly as **1·1**, in which two molecules share a large preorganized surface composed of four methyls inserted into four complementary cavities, and four sets of quinoxalene faces contact one another.[2a] This paper reports quantitative studies of **1** + **1** ⇄ **1·1**, **5** + **5** ⇄ **5·5**, and **1** + **5** ⇄ **1·5**. Compounds





1, R = n-C_5H_{11}, A = CH_3
2, R = n-C_5H_{11}, A = C_2H_5
3, R = n-C_5H_{11}, A = H

4, R = CH_3
5, R = n-C_5H_{11}

4[3] and **5**[3] were prepared by condensing the appropriate octols[4]

(1) We warmly thank the U.S. Public Health Service for supporting Grant GM 12640.

(2) (a) Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) A crystal structure of **5·5** confirms this conjecture (C. B. Knobler, unpublished work).

0002-7863/90/1512-1255$02.50/0

with 4 mol of tetrachloropyrazine[5] (50% and 32%, respectively). The low solubility of **4** led us to **5**, whose dimerization was most conveniently studied. Vapor pressure osmometry showed that **5** at 27 °C in $CHCl_3$ (7.8–31 mM concentrations) gave molecular weights of 2665 ± 270, closer to that of dimer (2808) than of monomer (1404). In $CDCl_3$ at −18 °C, the 360-MHz ^1H NMR spectrum of monomer **5** gave δ 2.19 for the two up-methyls and δ 2.43 for the two out-methyls, whereas these respective signals moved to δ 1.69 and 2.63 in dimer. Irradiation of the δ 2.63 peak (500 MHz at −18 °C) produced −3% enhancements of the δ 1.69 peak. Irradiation of the δ 1.69 peak was unfruitful because it was partially obscured by water peaks. Control irradiations of aryl protons gave −3 to −10% enhancements.[6] Negative enhancements are frequently encountered in large molecules.[7] Intermolecular distances between up-methyls and out-methyls in CPK models of **5·5** are <5 Å. We concluded that **5·5**[2a] is structured much like **1·1**, whose crystal structure is known.[2b] Similar differences in ^1H NMR chemical shifts for **1** and **1·1** were observed.

Association constants (K_a, M^{-1}) and $-\Delta G°$ values for **5** + **5** ⇄ **5·5** were measured by employing 360-MHz ^1H NMR spectral differences between monomer and dimer. At −46 °C, $-\Delta G°$ (kcal mol^{-1}) values varied with solvent as follows: $CD_3C_6D_5$, 3.5; $CDCl_3$, 4.1; CD_2Cl_2, 4.3. At −18 °C, they varied as follows (solvent %, v/v): 100% $CDCl_3$, 4.1; 75% $CDCl_3$ −25% $(CD_3)_2CO$, 5.1; 75% $CDCl_3$ −25% CD_3NO_2, 5.3; 75% $CDCl_3$ −25% CD_3OD, >5.6 kcal mol^{-1}. Values of k_a (M^{-1}) for **5** dimerization in $CDCl_3$ changed with temperature (K) as follows: 2300 (263); 3070 (253); 4520 (241); 5270 (237); 7090 (227). The least-squares line ($r > 0.99$) of a van't Hoff plot provided $\Delta H° = -3.8 \pm 0.5$ kcal mol^{-1} and $\Delta S° = 1.1 \pm 3$ eu. Similar plots from data obtained in 90% $CDCl_3$ −10% $(CD_3)_2CO$ (v/v) and 90% $CDCl_3$ −10% CD_3OD (v/v) gave, respectively: $\Delta H°$, −4.0 ± 0.5 and −3.7 ± 0.5 kcal mol^{-1}; $\Delta S°$ = 2 ± 3 eu and 3 ± 3 eu. Typical entropy changes for host–guest complexation in organic solvents usually range from −11 to −15 eu.[8] Molecular model examination of **5** and **1** suggests that each face can be solvated by up to 9 mol of $CDCl_3$, which is released to solvent upon dimerization. Decollection of many solvent molecules probably pays the entropic cost of collecting and rigidifying two monomers during dimer formation. Thus the full $-\Delta H°$ values are felt in the $-\Delta G°$ binding values.

The $ArCH_3$ signals at 2.62 ppm (**5·5**) and 2.48 ppm (**5**) coalesced at 12 ± 5 °C, providing a $\Delta G^‡$ for dimer dissociation of 14.0 ± 0.3 kcal mol^{-1} and $k_{-1} = 106$ s^{-1}, which coupled with K_a gives $k_1 = 1.4 \times 10^5$ M^{-1} s^{-1}. We attribute the remarkably slow dissociation to the absence of incremental solvation–desolvation of faces involved in dimerization. The locking of four CH_3 groups into four cavities in the dimer[2b] inhibits monomer-to-monomer slippage. Insertion of one solvent molecule between the rigid dimer faces (clamlike opening) largely dissipates attractive forces.

Similar measurements applied to **1** + **1** ⇄ **1·1** at 500 MHz in $CDCl_3$ provided these values at 12 °C: $K_a = 87\,000 \pm 30\%$ M^{-1}; $-\Delta G°$, 6.6 ± 0.2 kcal mol^{-1}. Similar experiments applied to mixtures of **1** and **5** at −18 °C (500 MHz) in $CDCl_3$ provided the following: for **1** + **1** ⇄ **1·1**, $K_a = 650\,000 \pm 30\%$ M^{-1} and $-\Delta G° = 6.9 \pm 0.2$ kcal mol^{-1}; for **1** + **5** ⇄ **1·5**, $K_a = 263\,000 \pm 30\%$ M^{-1} and $-\Delta G° = 6.3 \pm 0.2$ kcal mol^{-1}; for **5** + **5** ⇄ **5·5**, $K_a = 3100 \pm 30\%$ M^{-1} and $-\Delta G° = 4.1 \pm 0.2$ kcal mol^{-1}. In mixtures of **2** with either **1** or **5**, no **2·1** or **2·5** formation was observed.[9] Extrapolations of our $-\Delta G°$ values using Diederich's[10] correlations ($-\Delta G°$ changes for a cyclophane host binding pyrene with solvent changes) suggest that, in pure CH_3OH, $-\Delta G°$ values for **1·1** formation could be ≈11 kcal mol^{-1} and, in H_2O ≈14 kcal mol^{-1}.

Our study, coupled with others (e.g., Diederich's,[8d] Still's,[11] and Whitlock's[12]), indicates that, given appropriate preorganization, complementarity, and binding surface sizes of host–guest systems, high and variable binding free energies are observed in organic solvents, with solvaphobic driving forces playing highly significant roles.

(3) New compounds' elemental analyses were within 0.3% of theory; ^1H NMR spectra were as expected; mass spectra contained substantial M^+ or M + H^+ peaks.

(4) Tunstad, L. A.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.

(5) Allison, C. G.; Chambers, R. D.; MacBride, A. A. H.; Musgrave, W. K. R. *J. Chem. Soc. C* **1970**, 1023–1024.

(6) We thank Michael Geckle for help with NOE experiments.

(7) Derome, A. E. *Modern NMR Techniques for Chemical Research*; Pergamon Press: Oxford, 1987.

(8) (a) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575. (b) Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *Ibid.* **1989**, *111*, 3688–3699. (c) Conceill, J.; Lacombe, L.; Collet, A. *Ibid.* **1986**, *108*, 4230–4232. (d) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386.

(9) We estimate that $-\Delta G°$ for dimerizations involving **1** as low as ~2.2 kcal mol^{-1} could have been detected, which provides our best model for $-\Delta G°$ values that *might have been* detected for **2·2** or **3·3**, should they exist at all.

(10) Smithrud, D.; Diederich, F. *J. Am. Chem. Soc.*, in press.

(11) Chapman, K. T.; Still, C. W. *J. Am. Chem. Soc.* **1989**, *111*, 3075–3079.

(12) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120–7121.

Spontaneous Assembly of a Double-Helical Binuclear Complex of 2,2′:6′,2″:6″,2‴:6‴,2⁗:6⁗,2⁗′:6⁗′,2⁗″-Sexipyridine

Edwin C. Constable* and Michael D. Ward

University Chemical Laboratory
Lensfield Road, Cambridge CB2 1EW, United Kingdom

Derek A. Tocher

Department of Chemistry, University College London
20 Gordon Street, London WC1H OAJ, United Kingdom

Received July 26, 1989

Double-helical molecules have attracted interest since DNA was demonstrated to adopt this molecular topology.[1] Until recently, this geometry was rare in inorganic coordination compounds,[2] although we[3] and others[4] have demonstrated the spontaneous assembly of double-helical complexes containing polypyridine ligands. We have probed the structural requirements for the formation of double-helical complexes and have demonstrated that it arises when a conjugated polydentate ligand interacts with a metal ion that is too small for the bonding cavity occurring in a *planar* ligand configuration. We have also shown that π-stacking interactions play a crucial role in dictating the stability of the double-helical geometry.

(1) Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737. Pauling, L.; Corey, R. B.; Branson, H. R. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 205. Florey, P. J.; Miller, W. G. *J. Mol. Biol.* **1966**, *15*, 284. Brewster, J. H. *Top. Curr. Chem.* **1974**, *47*, 29. Mislow, K.; Gust, D.; Finnocchiaro, P.; Böttcher, R. J. *Top. Curr. Chem.* **1974**, *47*, 1. Meurer, K. P.; Vögtle, F. *Top. Curr. Chem.* **1985**, *127*, 1.

(2) Stoddart, F. *Nature (London)* **1988**, *334*, 10. Libman, J.; Tor, Y.; Stanzer, A. *J. Am. Chem. Soc.* **1987**, *109*, 5880. Stuckmeier, G.; Thewalt, U.; Furhop, J.-H. *J. Am. Chem. Soc.* **1976**, *98*, 278.

(3) Constable, E. C.; Drew, M. G. B.; Ward, M. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1600. Constable, E. C.; Holmes, J. M. *Inorg. Chim. Acta* **1987**, *126*, 187. Barley, M.; Constable, E. C.; Corr, S. A.; Drew, M. G. B.; McQueen, R. C. S.; Nutkins, J. C.; Ward, M. D. *J. Chem. Soc., Dalton Trans.* **1988**, 2655. Constable, E. C.; Drew, M. G. B.; Forsyth, G.; Ward, M. D. *J. Chem. Soc., Chem. Sommun.* **1988**, 1450. Constable, E. C.; Drew, M. G. B.; Forsyth, G.; Ward, M. D. *Polyhedron*, in press. Constable, E. C.; Holmes, J. M.; Raithby, P. R. *J. Chem. Soc., Dalton Trans.*, submitted.

(4) Lehn, J.-M.; Rigault, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1095. Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. Lehn, J.-M.; Rigault, A.; Siegel, J.; Harrowfield, J.; Chevrier, B.; Moras, D. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2565. Lehn, J.-M.; Sauvage, J.-P.; Simon, J.; Ziessel, R.; Piccinni-Leopardi, C.; Germain, G.; Declercq, J.-P.; VanMeerssche, M. *Nouv. J. Chim.* **1983**, *7*, 413. Gisselbrecht, J.-P.; Gross, M.; Lehn, J.-M.; Sauvage, J.-P.; Ziessel, R.; Piccinni-Leopardi, C.; Arrieta, J. M.; Germain, G.; Van Meerssche, M. *Nouv. J. Chim.* **1984**, *8*, 661.

0002-7863/90/1512-1256$02.50/0