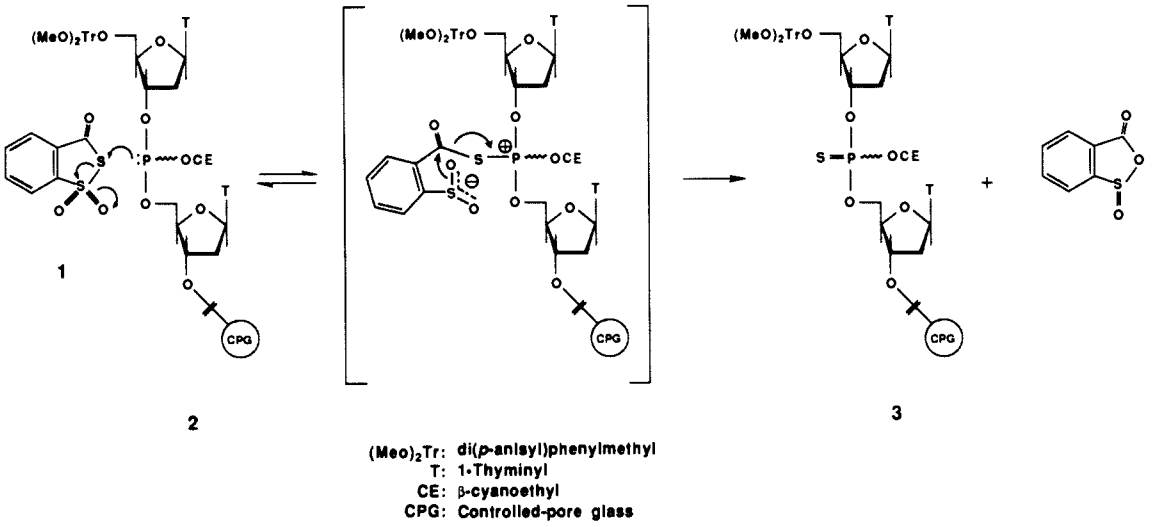

Figure 1. Sulfurization of a dinucleoside phosphite triester by 3*H*-1,2-benzodithiole-3-one 1,1-dioxide (**1**) as a model experiment for the preparation of oligodeoxyribonucleoside phosphorothioates.

acetonitrile and unreacted **2** was oxidized with aqueous iodine.[22] After standard deprotection, HPLC analysis showed that the phosphorothioate dimer S-d(TpT) was generated in greater than 99% yield as a mixture of R_p and S_p diastereoisomers.[7] Less than 1% of the natural phosphodiester d(TpT) was detected. Under similar conditions, an oligodeoxyribonucleoside phosphorothioate (28-mer) complementary to the messenger RNA of the HIV-1 *rev* gene[6,23] was synthesized with a 99% stepwise yield according to "trityl color" determination. ^{31}P NMR analysis of the fully deprotected and HPLC-purified oligonucleotide indicated that more than 96% of the resonances observed accounted for P(S) (δ 52 ppm) linkages whereas less than 4% of the resonances corresponded to P(O) (δ -4 ppm) linkages.[7,24] To demonstrate the versatility of the synthetic approach, a similar oligomer bearing only two P(S) links at predetermined positions was also prepared.[25] The purified oligonucleotide displayed the proper P(S) resonances in correct integrated ratio relative to the P(O) resonances according to ^{31}P NMR.

Finally, a random DNA sequence (28-mer)[26] bearing exclusively P(O) linkages and an equal number of the four nucleosidic bases was synthesized to investigate potential nucleosidic modification during the sulfurization step. The fully protected oligomer covalently attached to the solid support was incubated with a 0.2 M solution of **1** in acetonitrile for 24 h at ambient temperature. After deprotection and purification, the oligonucleotide was subjected to enzymatic degradation with snake venom phosphodiesterase and alkaline phosphatase. No evidence of nucleosidic base modification was detected from HPLC analysis of the hydrolysates as only peaks corresponding to the four nucleosides were observed.

We have demonstrated that, because of its solubility in common organic solvents, its rapid sulfurization kinetics, and its facile automation, the thiosulfonate **1** is a superior reagent relative to S_8 for the preparation of oligodeoxyribonucleoside phosphorothioates via the "phosphoramidite" approach. The high efficiency of the stepwise sulfurization has allowed the preparation of oligomers carrying either exclusively or a predetermined combination of P(S) linkages, with no observable modification of the nucleosidic bases. One can then speculate that the use of the thiosulfonate **1** in conjunction with the "deoxynucleoside phosphoramidite" approach may become the method of choice for the large-scale preparation of oligodeoxyribonucleoside phosphorothioates required for therapeutic applications.

Acknowledgment. Research funding earmarked for AIDS Targeted Antiviral Research to W.E. and R.P.I. from the Office of the Director, NIH, is gratefully acknowledged.

Supplementary Material Available: Detailed preparation of **1** and ^{31}P NMR spectra of oligodeoxyribonucleoside phosphorothioates[23,25] (3 pages). Ordering information is given on any current masthead page.

(22) Letsinger, R. L.; Lunsford, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 3655-3661.
(23) S-d(TCGTCGCTGTCTCCGCTTCTTCCTGCCA).
(24) The presence of endogenous P(O) linkages was also observed when S_8 was used as sulfurizing reagent during the synthesis of oligodeoxyribonucleoside phosphorothioates.[8]
(25) d(T_{PS}CGTCGCTGTCTCCGCTTCTTCCTGCC$_{PS}$A).
(26) d(TACCGTAGCTAAGGTCATGCAAGTTCCG).

Organic Molecules Dimerize with High Structural Recognition When Each Possesses a Large Lipophilic Surface Containing Two Preorganized and Complementary Host and Guest Regions[1]

Judi A. Bryant, Carolyn B. Knobler, and Donald J. Cram*

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

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We report here the unprecedented phenomenon of two identical molecules with large preorganized and complementary surfaces strongly binding each other in $CHCl_3$ in the absence of pole–pole, pole–dipole, metal ligation, hydrogen-bonding, or hydrophobic forces. As in an analogous synthesis,[2] **5**[3] was treated with 2,3-dichloroquinoxaline to give the mobile system **1** $\rightleftarrows$ **4** (37%).[4] Above -38 °C, only the *vase* form is detected (^{1}H NMR). Below -38 °C, only the *kite* conformation of **1** is detected (^{1}H NMR).[2a] No **1-1** was observed at any temperature (^{1}H NMR). Similarly, **6**[3] was converted to **2**[4] (30%). Octol **7**[4] was prepared[3] (87%) from 2-ethylresorcinol[5] and hexanal and similarly converted[2] to **3**[4] (16%).

Molecular models (CPK) of **2** and **3** indicate that the extra alkyl groups sterically inhibit *vase* formation. The *kite* conformation of **2** possesses a roughly planar (15 × 20 Å) rectangular face

(1) We warmly thank the U.S. Public Health Service for supporting Grant GE-12640.
(2) (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826-5828. (b) Dalcanale, E.; Soncini, P.; Bacchilega, G.; Ugzzoli, F. *J. Chem. Soc., Chem. Commun.* **1989**, 500-501.
(3) Tunstad, L. A.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B. *J. Org. Chem.* **1989**, *54*, 1305-1312.
(4) Carbon and hydrogen analyses were within 0.3% of theory; ^{1}H NMR spectra were as expected (refs 2 and 3); MS contained substantial M^+ or M + H^+ peaks.
(5) Limaye, D. B.; Ghate, I. *Rasayanam* **1936**, *1*, 39-42.

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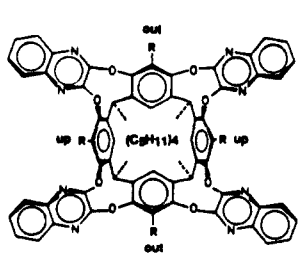
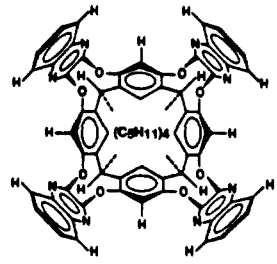
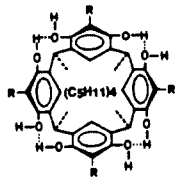
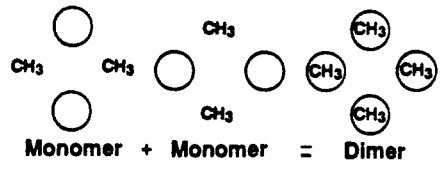




Kite: 1, R = H
2, R = CH_3
3, R = C_2H_5

Vase, 4





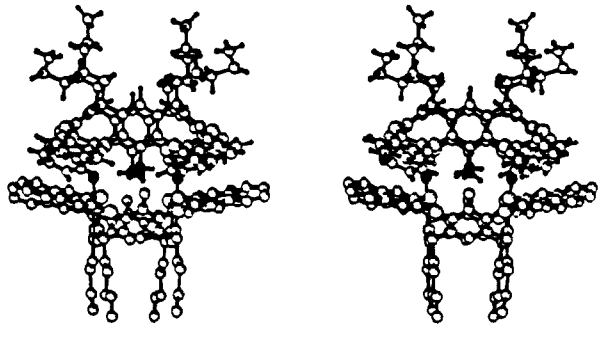
Monomer + Monomer = Dimer

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

8 9 10

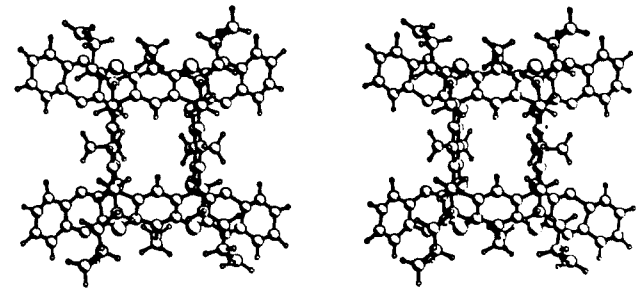
containing two protruding up-methyl groups and two methyl-sized indentations lined by a sloping aryl face, an out-methyl, and two oxygens. Rotation of **8** by 90° gives **9**. Superposition of **8** on **9** produces face-to-face dimer **10**, in which four methyl groups as guests occupy four host cavities. 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

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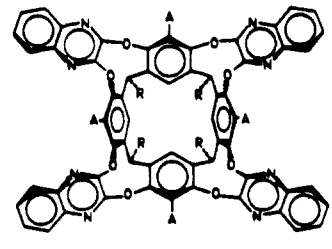
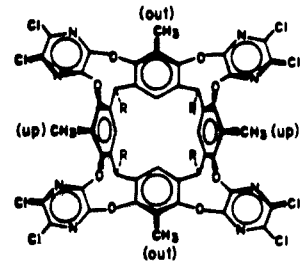
Previous work established that **1** (unlike **2** and **3**) when dissolved in $CDCl_3$ existed mainly as **1·1**, in which two molecules share a large preorganized surface composed of four methyls inserted into four complementary cavities, and four sets of quinoxalene faces contact one another.[2a]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

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