Convergent Functional Groups. 15. Synthetic and Structural Studies of Large and Rigid Molecular Clefts

Ken D. Shimizu, Torin M. Dewey, and J. Rebek, Jr.*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received December 13, 1993®

Abstract: A series of highly preorganized molecular clefts were prepared from the condensation of a 4-amino-2,7-bis(1,1-dimethylethyl)-9,9-dimethylxanthene-5-carboxylic acid with aromatic dianhydrides. The clefts are locked in a convergent C-shape by restricted rotation about two $C_{(aryl)}$–$N_{(imide)}$ bonds. The synthesis and derivatization are reported. In addition, structural information is presented including the X-ray structure of the S-isomer of naphthalene diacid **3**.

Introduction

Given the proliferation of cleftlike structures in the recent literature of molecular recognition,[1] another version could be hard to justify. Nonetheless, we introduce here a new family of molecular clefts. Like their predecessors, they present functional groups on their inner, concave surfaces that converge on and are complementary to smaller, convex guest molecules. Unlike the previous acridine systems **1**, the new **3** and **4** provide a deeper, roomier cavity and easier derivatization.[1a] They also feature restricted internal rotations that give rise to a preorganization lacking in earlier xanthene-derived clefts **2**.[2] A large aromatic shelf, well situated for stacking interactions with guest species, completes their attributes.

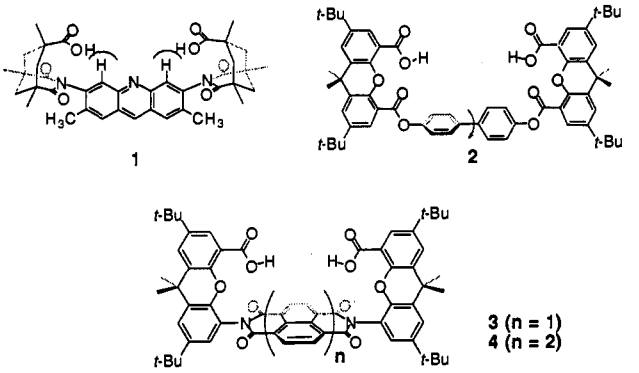
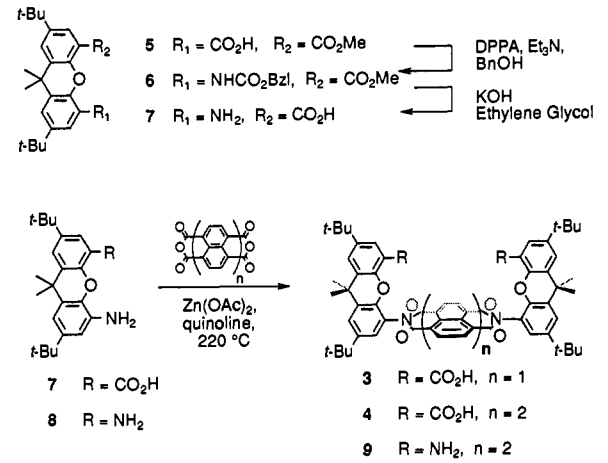


Figure 1.

Synthesis

The new concave molecules **3** and **4** were prepared by joining two U-shaped molecules through a rigid spacer unit (Scheme 1). By starting with xanthene acid ester **5**,[3] a Shioiri rearrangement[4] and subsequent hydrolysis gave amino acid **7**. For one spacer, the notoriously insoluble 3,4,9,10-perylenetetracarboxylic acid dianhydride was chosen. The condensation occurs cleanly in hot quinoline with zinc acetate as a catalyst,[5] and both the convergent C-shaped isomer **4** and the divergent S-shaped isomer (not shown) were obtained as brilliant red compounds. The smaller naphthalene version **3** was prepared from the condensation of amino acid **7** with the 1,4,5,8-naphthalenetetracarboxylic acid dianhydride. In each case, the two rotamers of the diacids were easily separated by chromatography.

Scheme 1. Syntheses of Clefts



Derivatization was equally straightforward. Either isomeric diacid, when treated with $SOCl_2$ and then an amine, gave the corresponding diamide. In this way, individual rotamers were functionalized with a variety of amines including ammonia **10** and amino alcohols **12** and **13**. Treatment of the diacid chloride with an alcohol yielded the dibenzyl diester **11**.

The rigid dianhydride spacers present new possibilities when condensed with other aryl amines. For example, 3,4,9,10-perylene dianhydride when treated with xanthene diamine **8**[6] yields the perylene diamine cleft **9**. Like the diacid clefts **3** and **4**, the structure exhibits restricted rotation and provides an alternatively functionalized C-shaped surface.

* Abstract published in *Advance ACS Abstracts,* May 1, 1994.

(1) (a) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255. (b) Pascal, R. A.; Ho, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 8507–8508. (c) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055–8057. (d) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549–6551. (e) Galán, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511–1512. (f) Tecilla, P.; Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586–9590. (g) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054–8055. (h) Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439–3430. (i) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493–4496. (j) Medina, J. C.; Gay, I.; Chen, Z.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 365–366. (k) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673–3674. (l) Guther, R.; Nieger, M.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 601–603.

(2) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902–8906. Park, T.-K.; Feng, Q.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 4529–4532.

(3) Park, T.-K.; Feng, Q.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 4529–4532.

(4) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.

(5) Rademacher, A.; Markle, S.; Langhals, H. *Chem. Ber.* **1982**, *115*, 2927–2934. Langhals, H. *Chem. Ber.* **1985**, *118*, 4641–4645.

(6) Hamann, B.; Branda, N.; Rebek, J., Jr. *Tetrahedron Lett.* **1993**, *34*, 6837–6840.

0002-7863/94/1516-5145$04.50/0

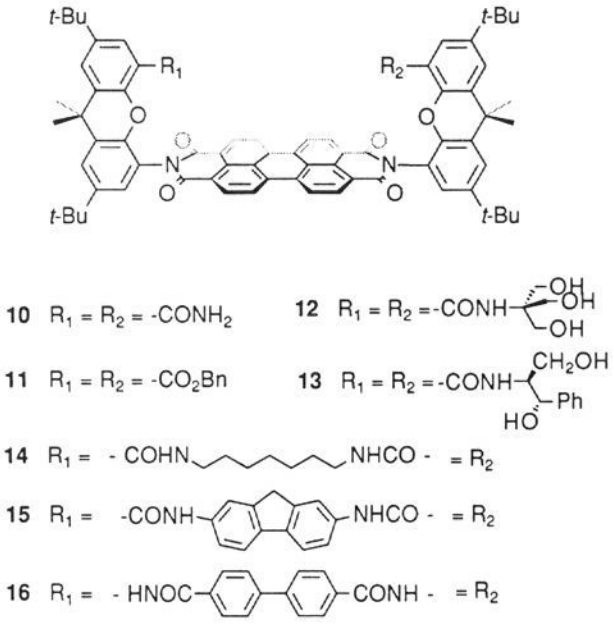


Figure 2. Perylene cleft derivatives.

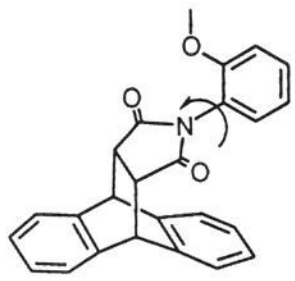


Figure 3.

Structural Studies

In each condensation reaction to form diacids **3** and **4**, two very similar compounds were isolated. Two-dimensional TLC experiments were performed in which the two compounds were separated in one direction, heated (300 °C for 10 min), and run in the other direction. The appearance of new spots off the diagonal, corresponding to the other compound demonstrated that interconversion was occurring. Clearly, the isolation of the two isomers of **3** and **4** at room temperature implies restricted rotation around the $N_{(imide)}$–$C_{(aryl)}$ bond. In handling and in the reactions mentioned above, isomerization was never observed. Heating experiments using dibenzyl diester **11** in toluene showed little isomerization at 70 °C overnight. Only when the temperature was raised to 110 °C did the mixture reach equilibrium in a few hours.[7] These observations extrapolate to a significantly higher barrier of rotation than the 20.6 kcal/mol measured for a similar imide–aryl bond (Figure 3).[8] The discrepancy may be due to (1) the more convergent carbonyls of a 6-membered vs 5-membered cyclic imide and (2) the rigidification of the aryl ether of the xanthene. Molecular modeling[9] supports the observed high barrier of rotation and predicts a value of ~28 kcal/mol.[10]

The isomers of the perylene clefts were tentatively identified by the higher polarity of the C-isomers as evidenced by a lower R_f on silica gel (a common method for identification of rotational isomers in porphyrins).[11] Confirmation of a proper assignment was provided by the formation of bridged derivatives of the C-isomer. Separate treatment of each rotamer of **4** with $SOCl_2$ and then a diamine yielded a complex mixture in one case. In the other, a single product resulted, corresponding to macrocycles

(7) A minimum barrier of rotation of >25 kcal/mol can be calculated from the Eyring equation and by assuming first order kinetics. After one month at room temperature no isomerization could be observed by ^1H NMR; the maximum extent of reaction is <5% ($[A]_n/[A]_0 = 0.95$). $[A]_n/[A]_0 = 1 + e^{(-2kt)}$. $k = (2.08 \times 10^{10})Te^{(-\Delta G/RT)}$.

(8) Verma, S. M.; Singh, N. B. *Aust. J. Chem.* **1976**, *29*, 295–300.

(9) The MM2* forcefield was used as implemented in Macromodel (Clark Still, Columbia University).

(10) The rotational barriers were found using MM2* with perylene diacid cleft **4**. The potential energy landscape of the C(aryl)–N(imide) bond was explored by fixing the dihedral in periodic increments and reminimizing each structure.

(11) Sanders, G. M.; van Dijk, M.; Machiels, B. M.; van Veldhuizen, A. *J. Org. Chem.* **1991**, *56*, 1301–1305.

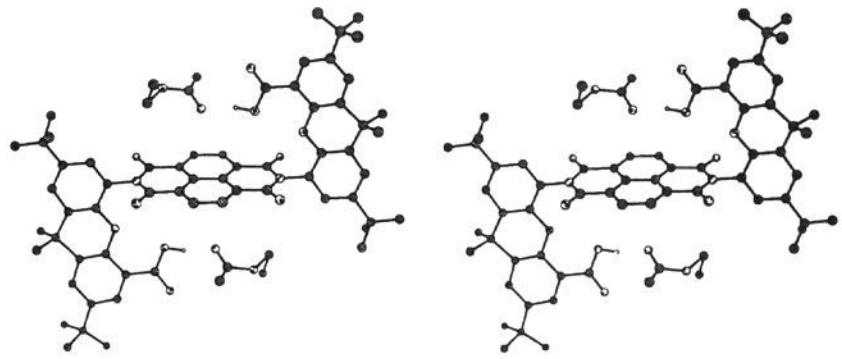


Figure 4. Stereoview of the X-ray structure of the S-isomer of **3** with two hydrogen-bonded ethyl acetates.

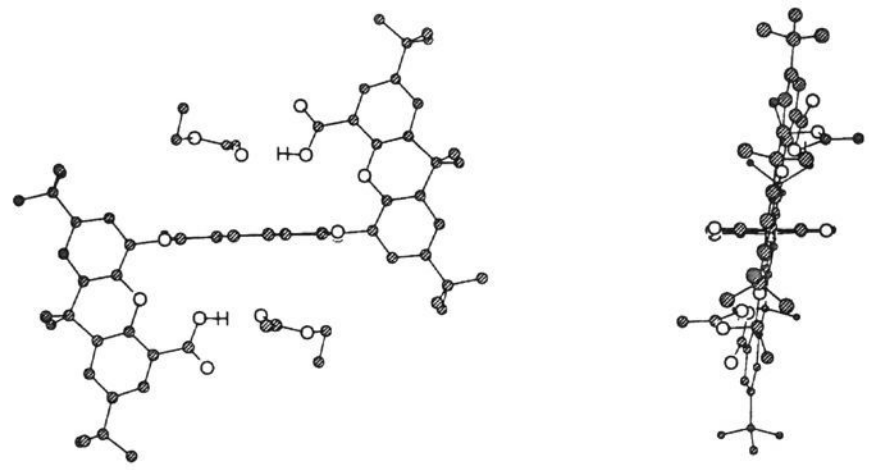


Figure 5. Chem 3D representation of the crystal coordinates (side and end views).

14 and **15**. Formation of a similar bridged compound **16** was used to identify the C-isomer of diamino cleft **9**. In this case a 4,4′-biphenyldicarboxylic acid dichloride was used to span the cleft.

For the smaller naphthalene clefts, the polarity argument proved misleading (see the Experimental Section) in assigning the C- and S-isomers. However, an X-ray structure of **3** provided direct evidence for their conformations. Crystals were obtained of the lower R_f isomer from the slow evaporation of a CH_2Cl_2/EtOAc solution. Evaluation of the unit cell revealed that the molecule was in the centric space group $P\bar{1}$ with one diacid molecule and two ethyl acetates per unit cell. The diacid therefore must sit on an inversion center, and only the S-shaped isomer can accommodate this symmetry. A stereoview of the structure is shown in Figure 4.

Each ethyl acetate appears to be hydrogen-bonded to a xanthene carboxylic acid with an O–O distance of 2.64 Å and floats above the naphthalene surface (Figure 5). A side view also shows that the xanthene carboxylic acids are bent inward toward the spacer. This tilt is the result of a slight pyrimidalization of the imide nitrogen and the longer C–C bonds (1.58 Å) at the "back" of the center xanthene ring versus the inner C–O bonds (1.39 Å). An end view shows that the planes of the xanthenes and naphthalene spacer are nearly perpendicular. The angle formed between the least-squares planes of these components is 81.2°.

Using the X-ray data, the approximate dimensions of the C-isomers of both the naphthalene and perylene clefts were calculated. In each case, two structures are possible depending upon which way the xanthenes tilted relative to each other: one with a mirror plane and the other with a C_2 axis. The extrapolated $O_{(carboxyl\ C=O)}$–$O_{(carboxyl\ C=O)}$ distances are shown in Table 1. In the case of the larger perylene cleft **4**, there is a sizable cavity for either derivatization or guest inclusion. The naphthalene cleft **3** has the acids just beyond hydrogen bonding distance and presents a cavity for suitably small guests such as divalent metal ions.

Properties

Shape imparts very different chemical properties upon the C- and the S-isomers which provides further evidence of their accurate

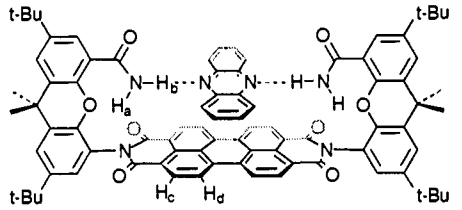


Figure 6. Proposed complex between diamide cleft **10** and phenazine.

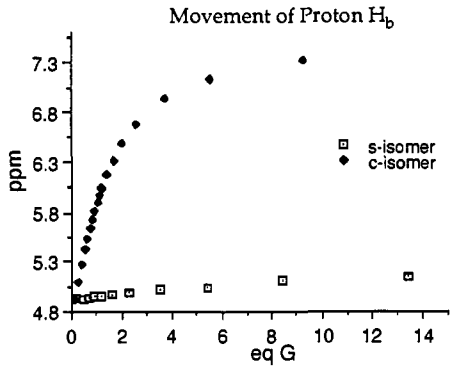


Figure 7. Titration of C- and S-isomers of naphthalene diamide cleft **10** with phenazine.

Table 1. Extrapolated Dimensions of C-Shaped Clefts ($O_{(carboxyl\ C=O)}$–$O_{(carboxyl\ C=O)}$ Distances)

Cleft		
Naphthalene	4.32 Å	5.61 Å
Perylene	8.65 Å	9.47 Å

assignment. The perylene diacid **4** was not exceedingly soluble in $CHCl_3$, and therefore, the possiblity of comparing binding constants available for acid–amine interactions with those of other diacid clefts was not feasible. The diamide cleft **10** provided a more soluble host.

For example, on titration with phenazine, the C-isomer of **10** showed regular changes in chemical shift consistent with a 1:1 complex.[12] The most likely structure is depicted in Figure 6, and a binding constant of $K_a = 149\ M^{-1}$ was measured in chloroform. By comparison, the S-isomer, when titrated with phenazine, showed small and irregular shifts by ^1H NMR. The convoluted titration curve for the S-isomer is attributed to a variety of association processes occurring simultaneously (see Figure 7) and could easily be differentiated from that of the C-isomer.

In addition, the titration of the C-isomer of diamide **10** yields subtle structural information. The syn- and anti-amide protons are in very different environments. The syn-proton (H_b) extends out over the perylene surface and shows a considerable upfield chemical shift (4.80 ppm). The anti-proton (H_a) appears to be tucked back and possibly hydrogen-bonded to the xanthene ether oxygen and is further downfield (6.77 ppm). During the course of the titration with phenazine, the syn-proton (H_b) moves 2.5 ppm downfield and past the almost stationary anti-proton (H_a). The syn-proton appears to be actively involved in complexation while the anti-proton is preoccupied and oriented in such a way that makes it unavailable for additional hydrogen-bonding to the guest (as shown in Figure 6). This suggests that the cleft is already highly preorganized, not only by restricted rotation about the $C_{(aryl)}$–$N_{(imide)}$ bond but also by fixing of the $C_{(acid)}$–$C_{(aryl)}$ bond by an internal hydrogen bond.

(12) Changes in chemical shift on addition of phenazine to C-shaped diamide cleft **10**: $\Delta H_a = 6.77 \rightarrow 6.95$, $\Delta H_b = 4.80 \rightarrow 7.30$, $\Delta H_c = 8.74 \rightarrow 8.55$, $\Delta H_d = 8.67 \rightarrow 8.01$.

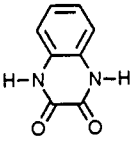


Figure 8. Quinoxalinedione.

Outlook

We have introduced new molecular clefts **3**, **4**, and **9** that combine the better characteristics of our previous synthetic structures: (1) functional groups locked in a convergent orientation, (2) a rigid framework preventing collapse, (3) a sizable cavity, and (4) easy synthesis and derivatization. These new structures offer the possibility for presenting an array of functionality, poised for complementary guests or transition states, yet prevented from collapse by the rigidity of the spacers. Preliminary binding studies have certified our premise for the synthesis of these structures. Solid–liquid extractions with the C-isomer of diamide **10** show strong 1:1 complexations with guests such as quinoxalinedione (Figure 8) that take advantage of the highly preorganized structure. We will report on these developments in due course.

Experimental Section

Crystallography. Data were collected with a Enraf-Nonius CAD-4 diffractometer with Mo Kα radiation ($\lambda = 0.711$ Å). The structure was solved by direct methods. The non-hydrogen atoms were refined either anisotropically or isotropically. The final cycle of full-matrix least-squares refinement was based on 1993 observed reflections ($I > 3.00\sigma(I)$) and 360 variable parameters and converged with unweighted and weighted agreement factors of $R = \sum||F_o| - |Fc||/\sum|F_o| = 0.098$ and $R_w = [(\sum(|F_o| - |F_c|^2/\sum wF_o^2)]^{1/2} = 0.103$.

The data were collected from colorless plates having approximate dimensions of 0.300 × 0.400 × 0.090 mm which were obtained from the slow evaporation of an ethyl acetate/CH_2Cl_2 solution. Crystal data for $C_{70}H_{78}N_2O_{14}$: M_r 1171.39, space group $P\bar{1}$, $a = 13.785(1)$ Å, $b = 19.940(1)$ Å, $c = 5.993(1)$ Å, $\alpha = 98.01(2)°$, $\beta = 87.29(2)°$, $\gamma = 100.48(2)°$, volume = 1603.6(6) Å^3, $Z = 1$, ρ(calcd) = 1.213 g/cm^3, $\mu_{(Mo\ K\alpha)} = 0.78$ cm^{-1}, $T = 21$ °C.

Additional ORTEP views and tables of positional parameters, bond angles, bond lengths, torsional angles and ansiotropic thermal factors are found in the supplementary material.

C- and S-Naphthalene Diacid Cleft (3). Xanthene amino acid **7** (352 mg, 0.922 mmol), 1,4,5,8-naphthalenetetracarboxylic acid dianhydride (110 mg, 0.410 mmol), and $Zn(OAc)_2{\cdot}2H_2O$ (45 mg, 0.205 mmol) were heated in quinoline (15 mL) for 4.5 h at 200 °C. The solution was cooled to room temperature, diluted with CH_2Cl_2 (125 mL), and washed with 1.0 HCl (3 × 200 mL) and brine (1 × 100 mL). The organic layer was concentrated by rotary evaporation to a dark brown solid. Column chromatography on silica gel (1–3% MeOH/CH_2Cl_2) separated the two isomers, but they eluted in reverse of their R_f values on TLC (Kieselgel 60) as yellow crystalline solids. The C-isomer (187 mg, 46%) had the higher R_f and the *S*-isomer (153 mg 38%) the lower R_f by TLC. C-isomer: mp >330 °C; IR (KBr) 3386, 2962, 2869, 1718, 1684, 1581, 1449, 1397, 1350, 1273, 1251, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 4 H, Naph), 7.72 (d, 2 H, $J = 0.6$ Hz, Xan), 7.62 (d, 2 H, $J = 1.5$ Hz, Xan), 7.58 (d, 2 H, $J = 2.1$ Hz, Xan), 7.40 (d, 2 H, $J = 1.2$ Hz, Xan), 1.71 (s, 12 H, Me), 1.43 (s, 18 H, *t*-Bu), 1.29 (s, 18 H, *t*-Bu); HRMS (EI) calcd for $C_{62}H_{62}N_2O_{10}$ 994.4404, found 994.4409. S-isomer: mp >330 °C; IR (KBr) 3388, 2962, 2868, 1718, 1682, 1582, 1449, 1348, 1249, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 4 H, Naph), 7.78 (d, 2 H, $J = 2.4$ Hz, Xan), 7.67 (d, 2 H, $J = 2.4$ Hz, Xan), 7.63 (d, 2 H, $J = 2.1$ Hz, Xan), 7.28 (d, 2 H, $J = 2.1$ Hz, Xan), 1.75 (s, 12 H, Me), 1.42 (s, 18 H, *t*-Bu), 1.33 (s, 18 H, *t*-Bu); HRMS (EI) calcd for $C_{62}H_{62}N_2O_{10}$ 994.4404, found 994.4413.

C- and S-Perylene Diacid Cleft (4). Zinc(II) acetate 2.5 hydrate (23.5 mg, 0.107 mmol), xanthene amino acid **7** (200 mg, 0.524 mmol), and 3,4,9,10-perylene dianhydride were suspended in 7 mL of quinoline. The reaction mixture was heated at 220 °C for 1 h without a reflux condenser

to allow evaporation of excess water and then heated an additional 15 h with a reflux condenser. The clear dark purple reaction mixture was taken up in 75 mL of CH_2Cl_2 and washed with 1 N HCl (4 × 150 mL). The organic layer was concentrated to a dark red solid *in vacuo*. Column chromatography on silica gel (3–6% MeOH/CH_2Cl_2) yielded two isomers, S (higher R_f, 63.3 mg, 24%) and C (lower R_f, 60 mg, 23%), as dark red solids which fluoresce strongly. C-isomer: mp >300 °C; IR (KBr) 3386, 2962, 1707, 1671, 1595, 1450, 1402, 1360, 1258 cm^{-1}; ^1H NMR (300 MHz, pyr-d_5) δ 8.82 (d, 4 H, J = 7.8 Hz, Per), 8.39 (d, 4 H, J = 8.1 Hz, Per), 8.22 (s, 2 H, Xan), 7.96 (s, 2 H, Xan), 7.78 (s, 2 H, Xan), 7.71 (s, 2 H, Xan), 1.72 (s, 12 H, Me), 1.44 (s, 18 H, *t*-Bu), 1.24 (s, 18 H, *t*-Bu); MS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{72}H_{67}N_2O_{10}$ (M^+H) 1119.0, found 1119.5. S-isomer: mp >300 °C; IR (KBr) 3385, 2965, 1707, 1673, 1594, 1451, 1360, 1359, 1263, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 4 H, J = 7.8 Hz, *o*-Per), 8.51 (d, 4 H, J = 8.2 Hz, *m*-Per), 7.55–7.65 (m, 6 H, Xan), 7.34 (d, 2 H, J = 2.2 Hz, Xan), 1.72 (s, 12 H, Me), 1.45 (s, 18 H, *t*-Bu), 1.24 (s, 18 H, *t*-Bu); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{72}H_{67}N_2O_{10}$ (M^+H) 1119.4796, found 1119.4807.

Xanthene Benzyl Carbamate Methyl Ester (6). Xanthene acid methyl ester **5** (8.39 g, 19.76 mmol), diphenylphosphoryl azide (5.1 mL, 23.71 mmol), and $(Et)_3N$ (3.30 mL, 23.71 mmol) were dissolved in toluene (50 mL) under an Ar atmosphere. The solution was stirred for 10 min and then BnOH (2.87 mL, 27.66 mmol) was added. The reaction was stirred for 1 h, during which N_2 evolution was observed, and then heated at 80–85 °C for an additional 2 h. The reaction mixture was concentrated to a thick oil by rotary evaporation. Column chromatography on silica gel (10–15% EtOAc/Hex) yielded a white solid, 9.73 g (93%): mp 217–219 °C; IR (KBr) 3430, 3386, 2964, 1730, 1707, 1445, 1276, 1240, 1102, 1008, 785 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.24 (s, 1 H, Xan), 8.15 (br s, 1 H, –NH), 7.89 (d, 1 H, J = 2.3 Hz, Xan), 7.62 (d, 1 H, J = 2.2 Hz, Xan), 7.30–7.50 (m, 5 H, Ph), 7.07 (d, 1 H, J = 1.8 Hz, Xan), 5.28 (s, 2 H, Bn), 3.92 (s, 3 H, Me), 1.62 (s, 6 H, Me), 1.34 (s, 18 H, *t*-Bu); HRMS (EI) calcd for $C_{33}H_{39}N_1O_5$ 529.2831, found 529.2831.

Xanthene Amino Acid (7). Xanthene carbamate ester **6** (9.73 g, 18.38 mmol) and KOH (15.0 g) were suspended in ethylene glycol (250 mL) and refluxed under an Ar atmosphere for 3.5 h. The solution was acidified *with 1.0 N HCl, diluted with H_2O (300 mL), and filtered.* The wet solid was washed well with H_2O, yielding a white solid (7.20 g, 100%): mp 258–259 °C; IR (KBr) 3378, 2963, 2904, 2869, 2592, 1702, 1587, 1460, 1363, 1281, 1242, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 2.1 Hz, Xan), 7.65 (d, 1 H, J = 2.1 Hz, Xan), 6.81 (d, 1 H, J = 1.8 Hz, Xan), 6.73 (d, 1 H, J = 1.8 Hz, Xan), 3.4 (br s, 2 H, $–NH_2$), 1.63 (s, 6 H, Me), 1.35 (s, 9 H, *t*-Bu), 1.30 (s, 9 H, *t*-Bu); HRMS (EI) calcd for $C_{24}H_{31}N_1O_3$ 381.2304, found 381.2301.

C- and S-Perylene Diamine (9). Xanthene diamine **8**[6] (0.203 g, 0.58 mmol) was dissolved in 10 mL of quinoline with perylene dianhydride (0.113 g, 0.29 mmol) and zinc acetate dihydrate (0.44 g, 0.15 mmol). The solution was stirred and heated to 200 °C for 20 h, then allowed to cool. Most of the quinoline was removed by distillation under high vacuum, leaving a red solid. This solid was dissolved in CH_2Cl_2, extracted with 1.0 M HCl, and dried over $MgSO_4$. Rotary evaporation gave a dark red solid which was column chromatographed on silica gel (0.5–0.75% MeOH/CH_2Cl_2). From this column was isolated a mixture of C- and S-shaped diamino clefts. These were separated further with another silica gel column (1.0–1.5% acetone/CH_2Cl_2). The individual fractions were compared by ^1H NMR and TLC to confirm that the two isomers were separate. Some contaminants which exhibited ^1H NMR peaks at 2.0–2.5 ppm were presumably from the condensation of acetone with the free xanthene amines of the clefts. S-isomer: ^1H NMR ($CDCl_3$) δ 8.80 (d, 4 H, J = 8.0 Hz), 8.73 (d, 4 H, J = 8.0 Hz), 7.58 (d, 2 H, J = 1.8 Hz), 7.25 (d, 2 H, obscured), 6.84 (d, 2 H, J = 2.1 Hz), 6.55 (d, 2 H, J = 1.90 Hz), 3.31 (br s, 4 H), 1.71 (s, 12 H), 1.40 (s, 18 H), 1.26 (s, 18 H); mp >330 °C; IR (KBr) 3378, 2961, 1709, 1673, 1594, 1479, 1356, 1252, 851, 809, 746, 674 cm^{-1}; HRMS (EI) calcd for $C_{70}H_{68}N_4O_6$ 1060.5139, found 1060.5129. C-isomer: ^1H NMR ($CDCl_3$) δ 8.78 (d, 4 H, J = 7.9 Hz), 8.68 (d, 4 H, J = 8.1 Hz), 7.57 (d, 2 H, J = 2.2 Hz), 7.28 (d, 2 H, 2.2 Hz), 6.83 (d, 2 H, J = 2.1 Hz), 6.55 (d, 2 H, J = 2.1 Hz), 3.29 (br s, 4 H), 1.70 (s, 12 H), 1.38 (s, 18 H), 1.26 (s, 18 H); mp >330 °C; IR (KBr) 3372, 2960, 1709, 1672, 1594, 1480, 1357, 1254, 852, 810, 746, 675 cm^{-1}; HRMS (EI) calcd for $C_{70}H_{68}N_4O_6$ 1060.5139, found 1060.5124.

C-Perylene Diamide Cleft (10). The acid chloride was prepared by dissolving the C-isomer of the diacid cleft **4** (87 mg, 0.0777 mmol) in 10 mL of CH_2Cl_2 and 1.0 mL of $SOCl_2$. The solution was refluxed for 1.5 h and then concentrated *in vacuo* to a red solid.

The diacid chloride was taken up in 15 mL of CH_2Cl_2, treated with 1 mL of concentrated NH_3 solution, and stirred for 1 h. The reaction mixture was washed with 1.0 N HCl (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL). The organic layer was concentrated by rotary evaporation and column chromatography on silica gel (2% MeOH/CH_2Cl_2) to yield a red solid (71.6 mg, 82%): mp >330 °C; IR (KBr) 3492, 3399, 2961, 1709, 1673, 1594, 1449, 1357, 1253, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 18 H, *t*-Bu), 1.33 (s, 18 H, *t*-Bu), 1.74 (s, 12 H, Me), 4.77 (br s, 2 H, NH), 6.67 (br s, 2 H, NH), 7.47 (d, 2 H, J = 2.2 Hz, Xan), 7.56 (d, 2 H, J = 2.1 Hz, Xan), 7.58 (d, 2 H, J = 2.6 Hz, Xan), 7.80 (d, 2 H, J = 2.4 Hz, Xan), 8.45 (d, 4 H, J = 8.2 Hz, Per), 8.66 (d, 4 H, J = 7.9 Hz, Per); HRMS (EI) calcd for $C_{71}H_{65}N_4O_8$ ($M - CH_3$) 1101.4802, found 1101.4798.

S-Perylene Diamide (10). The preparation of the S-isomer is identical to that of C-isomer (above) using S-diacid **4** (77 mg, 0.0688 mmol) to yield the a red solid (70.4 mg, 92%): mp >330 °C: IR (KBr) 3433, 2962, 1705, 1673, 1592, 1451, 1355, 1274, 1252, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.81 (d, 4 H, J = 8.7 Hz), 8.77 (d, 4 H, J = 7.2 Hz), 7.81 (d, 2 H, J = 2.4 Hz), 7.62 (d, 2 H, J = 2.7 Hz), 7.59 (d, 2 H, J = 2.4 Hz), 7.29 (d, 2 H, J = 2.1 Hz), 6.86 (br s, 2 H), 4.84 (br s, 2 H), 1.76 (s, 12 H), 1.41 (s, 18 H), 1.32 (s, 18 H); HRMS (EI) calcd for $C_{71}H_{65}N_4O_8$ ($M - CH_3$) 1101.4802, found 1101.4798.

C- and S-Perylene Dibenzyl Diester (11). The diacid chloride (1.31 mmol) was prepared by refluxing diacid cleft **4** (a mixture of C- and S-isomers) in 200 mL of CH_2Cl_2 with 12.0 mL of $SOCl_2$ for 1 h. The solution was concentrated *in vacuo* and taken up in 100 mL of CH_2Cl_2. Benzyl alcohol (740 μL, 7.14 mmol) and $(Et)_3N$ (995 μL, 7.14 mmol) were added and then heated at reflux for 2 h. The solution was diluted with 100 mL of CH_2Cl_2 and extracted with 1.0 N HCl (2 × 150 mL). The organic layer was evaporated *in vacuo* to a red solid. Column chromatography on silica gel (0.0–0.25% MeOH/CH_2Cl_2) separated the two isomers as red solids. S-isomer (0.831 g, 49%): mp >330 °C; IR (KBr) 2960, 1709, 1673, 1594, 1451, 1358, 1256, 1179, 1179, 810, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (d, 4 H, 8.0 Hz, Per), 8.54 (d, 4 H, 8.1 Hz, Per), 7.63 (d, 2 H, J = 2.2 Hz, Xan), 7.60 (d, 2 H, J = 2.5 Hz, Xan), 7.58 (d, 2 H, J = 2.0 Hz, Xan), 7.29 (d, 2 H, J = 2.1 Hz, Xan), 7.09 (d, 2 H, J = 7.0 Hz, Ph), 7.03 (dd, 4 H, J = 7.0 Hz, J = 7.5 Hz, Ph), 6.76 (d, 4 H, J = 7.2 Hz, Ph), 4.38 (s, 4 H, $–CH_2–$), 1.74 (s, 12 H, Me), 1.41 (s, 18 H, *t*-Bu), 1.30 (s, 18 H, *t*-Bu); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{86}H_{79}N_2O_{10}$ ($M + H$) 1299.5734, found 1299.5721. C-isomer (0.702 g, 41%): mp >330 °C; IR (KBr) 2960, 1708, 1673, 1594, 1451, 1357, 1256, 1177, 1111, 810, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (d, 4 H, 7.8 Hz, Per), 8.28 (d, 4 H, 8.4 Hz, Per), 7.58 (s, 4 H, Xan), 7.53 (s, 2 H, Xan), 7.48 (s, 2 H, Xan), 7.01 (d, 2 H, J = 7.2 Hz, Ph), 6.92 (dd, 4 H, J = 7.2 Hz, J = 7.2 Hz, Ph), 6.52 (d, 4 H, J = 7.0 Hz, Ph), 4.13 (s, 4 H, $–CH_2–$), 1.72 (s, 12 H, Me), 1.33 (s, 18 H, *t*-Bu), 1.28 (s, 18 H, *t*-Bu); HRMS (EI) calcd for $C_{86}H_{78}N_2O_{10}$ 1298.5656, found 1298.5645. Anal. Calcd for $C_{86}H_{78}N_2O_{10}$: C, 79.48; H, 6.05; N, 2.16. Found: C, 79.28; H, 5.85; N, 2.24.

C-Perylene Diamide Hexol (12). The diacid chloride (0.0474 mmol) was prepared (see **10**) and taken up in 10 mL of CH_2Cl_2. The amino triol, TRIS (120 mg, 0.991 mmol), was added neat and the solution stirred for 16 h. The reaction mixture was washed with 1.0 N HCl (1 × 50 mL) and saturated $NaHCO_3$ (1 × 50 mL). Column chromatography on silica gel (4% MeOH/CH_2Cl_2) yielded a red solid (24 mg, 38%): mp >330 °C; IR (KBr) 3394, 3167, 2960, 1708, 1671, 1594, 1449, 1403, 1360, 1257, 810 cm^{-1}; ^1H NMR ($CDCl_3$/MeOD-d_4) δ 8.54 (d, 4 H, J = 8.1 Hz, Per), 8.32 (d, 4 H, J = 8.4 Hz, Per), 7.59 (d, 2 H, J = 2.1 Hz, Xan), 7.47 (d, 2 H, J = 2.7 Hz, Xan), 7.46 (d, 2 H, J = 1.8 Hz, Xan), 7.01 (d, 2 H, J = 2.7 Hz, Xan), 6.57 (s, 2 H, –NH), 2.62 (s, 12 H, $–CH_2–$), 1.67 (s, 12 H, Me), 1.24 (s, 18 H, *t*-Bu), 1.20 (s, 18 H, *t*-Bu); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{80}H_{85}N_4O_{14}$ ($M + H$) 1325.6062, found 1325.6056.

C-Perylene Diamide Tetrol (13). The diacid chloride (0.0188 mmol) was prepared (see **10**) and taken up in 15 mL of CH_2Cl_2. The amino diol, (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (54 mg, 0.323 mmol), was added neat and the solution stirred for 16 h. The reaction mixture was washed with 1.0 N HCl (1 × 50 mL). Column chromatography on silica gel (4% MeOH/CH_2Cl_2) yielded a red solid (20 mg, 75%): mp >330 °C; IR (KBr) 3407, 2959, 1707, 1671, 1594, 1449, 1358, 1257, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (d, 4 H, J = 7.8 Hz, Per), 8.68 (d, 2 H, J = 8.4 Hz, Per), 8.47 (d, 2 H, J = 9.0 Hz, Per), 7.52 (d, 2 H, J = 1.5 Hz, Xan), 7.45 (d, 2 H, J = 1.2 Hz, Xan), 7.43 (d, 2 H, J = 2.7 Hz, Xan), 7.05–7.15 (m, 6 H, Xan and Ph), 6.90–7.00 (m, 4 H, Ph), 6.83 (d, 2 H, J = 0.9 Hz), 6.17 (d, 2 H, J = 6.3 Hz, –NH), 4.40–4.48 (m, 2 H), 3.65–3.78 (m, 2 H), 3.30–3.42 (m, 2 H), 2.85–2.97

(m, 2 H), 2.55–2.70 (m, 2 H), 2.28–2.40 (m, 2 H), 1.70 (s, 6 H, –Me), 1.68 (s, 6 H, –Me), 1.33 (s, 18 H, *t*-Bu), 1.83 (s, 18 H, *t*-Bu); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{90}H_{89}N_4O_{12}$ (M + H) 1417.6477, found 1416.6383.

C-Perylene Bridged $(CH_2)_7$ Diamide (14). The diacid chloride (0.0168 mmol) was prepared (see **10**) and taken up in 20 mL of CH_2Cl_2. The diamine, 1,7-diaminoheptane (4.4 mg, 0.0335 mmol), and pyridine (2.7 μL, 0.0336 mmol) in 15 mL of CH_2Cl_2 were added dropwise. The reaction was stirred for 1 h. The reaction mixture was washed with 1.0 N HCl (1 × 50 mL), and then column chromatography on silica gel (2% MeOH/CH_2Cl_2) yielded a red solid (15.1 mg, 74%): mp >330 °C: IR (KBr) 3435, 2960, 1710, 1673, 1594, 1446, 1357, 1254, 810, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.76 (d, 4 H, *J* = 8.1 Hz, Per), 8.62 (d, 4 H, *J* = 8.4 Hz, Per), 7.93 (d, 2 H, *J* = 2.4 Hz, Xan), 7.58 (d, 2 H, *J* = 2.4 Hz, Xan), 7.54 (d, 2 H, *J* = 2.4 Hz, Xan), 7.37 (d, 2 H, *J* = 2.1 Hz, Xan), 7.13 (t, 2 H, *J* = 5.7 Hz, –NH), 2.05–2.18 (m, 4 H, $-CH_2-$), 1.73 (s, 12 H, Me), 1.34 (s, 18 H, *t*-Bu), 1.31 (s, 18 H, *t*-Bu), 1.55–1.70 (m, 4 H, $-CH_2-$), 0.20–0.40 (m, 6 H, $-CH_2-$); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{79}H_{81}N_4O_8$ (M + H) 1213.6054, found 1213.6061.

C-Perylene Bridged Fluorene Diamide (15). The diacid chloride (0.00894 mmol) was prepared (see **10**) and taken up in 15 mL of CH_2Cl_2. The diamine, 2,7-diaminofluorene (2.1 mg, 0.0107 mmol), and pyridine (1.7 μL, 0.0214 mmol) in 5 mL of CH_2Cl_2 were added dropwise. The reaction was stirred for 1 h and then washed with 1.0 N HCl (1 × 50 mL). Column chromatography (2% MeOH/CH_2Cl_2) yielded a red solid (10.2 mg, 90%): mp >330 °C; IR (KBr) 3408, 2959, 1708, 1673, 1593, 1445, 1366, 1259, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.33 (s, 18 H, *t*-Bu), 1.34 (s, 18 H, *t*-Bu), 1.78 (s, 12 H, Me), 3.23 (s, 2 H, $-CH_2-$), 6.18 (d, 2 H, *J* = 8.0 Hz, Fl), 6.53 (d, 2 H, *J* = 8.0 Hz, Fl), 7.31 (d, 2 H, *J* = 1.8 Hz, Xan), 7.45 (s, 2 H, Fl), 7.60 (d, 2 H, *J* = 2.0 Hz, Xan), 7.63 (d, 2 H, *J* = 2.4 Hz, Xan), 7.93 (d, 2 H, *J* = 2.3 Hz, Xan), 8.34 (d, 4 H, *J* = 8.0 Hz, Per), 8.54 (d, 4 H, *J* = 7.5 Hz, Per), 8.55 (s, 2 H, NH); HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{85}H_{75}N_4O_8$ (M + H) 1279.5585, found 1279.5574.

C-Perylene Biphenyl Bridged Diamide (16). The lower R_f isomer of the diamine cleft **9** (42.0 mg) was combined with 4,4′-biphenyldicarboxylic acid dichloride (11.5 mg) in CH_2Cl_2 (5 mL) with 5 drops of pyridine. The reaction mixture was brought to reflux for 3 h and cooled overnight with a drying tube, and the solvent was removed *in vacuo*. Column chromatography on silica gel (0.5–0.75% MeOH/CH_2Cl_2) gave as the major product (24 mg) a red solid: ^1H NMR ($CDCl_3$) δ 8.62 (d, 4 H, *J* = 7.9 Hz), 8.36 (d, 4 H, *J* = 7.9 Hz), 8.21 (d, 2 H, *J* = 2.1 Hz), 8.08 (d, 2 H, obscured), 7.63 (d, 2 H, *J* = 2.2 Hz), 7.33 (d, 2 H, *J* = 2.0 Hz), 7.27 (d, 4 H, *J* = 8.2 Hz), 6.67 (d, 4 H, *J* = 8.2 Hz), 1.76 (s, 12 H), 1.39 (s, 18 H), 1.35 (s, 18 H); mp >330 °C; IR (KBr) 3434, 2959, 1709, 1674, 1593, 1438, 1356, 1251, 809, 756 cm^{-1}; HRMS (FAB in 3-nitrobenzyl alcohol) calcd for $C_{84}H_{75}N_4O_8$ (M + H) 1267.5585, found 1267.5577.

Acknowledgment. This work was funded by a NIH training grant (CA09112) and by other NIH grants.

Supplementary Material Available: Text describing experimental procedure, tables listing experimental details, intramolecular bond angles, intermolecular distances, positional parameters and B(eq) values, torsion and conformation angles, U values, and least-squares planes, and ORTEP drawings (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.