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FUNCTIONAL GROUPS POSITIONED IN UNUSUAL ASYMMETRIC MICROENVIRONMENTS

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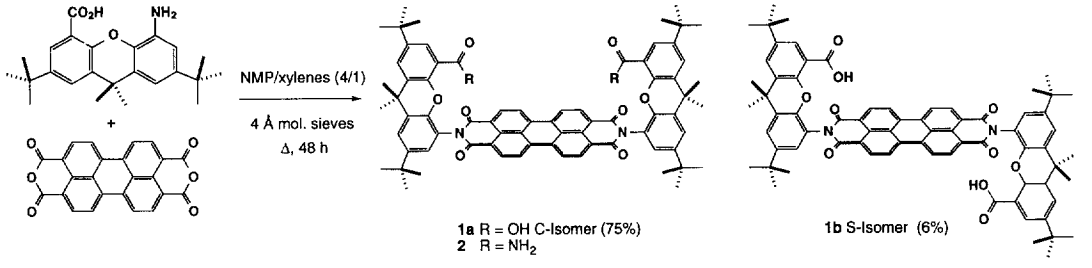
Abstract: Selective functionalization of a rigid, C-shaped molecular cleft containing two convergent carboxylic acid groups has led to the preparation of molecules which bear a reaction site within a well-defined asymmetric region. Copyright © 1996 Elsevier Science Ltd

Asymmetric recognition and its applications to reagent or catalyst design are the goals of much effort in modern organic chemistry. While progress has been made toward rational development of enantioselective reactions,[1] the search process has, nonetheless, been likened to a fishing expedition.[2] A reasonable starting point is to position a reactive group within an asymmetric microenvironment, and we describe here our recent progress in directing the carboxylic acid function into such a region.

Molecules containing convergent functionality fit in naturally with this goal, and our earlier efforts using Kemp's triacid modules generated a number of small molecular clefts.[3] The C-shaped perylene diimide cleft **1a** was recently introduced and offers an attractive scaffold with a sizable capacity.[4] Restricted rotation about the N(imide)-C(aryl) bonds of **1** leads to the existence of stable, chromatographically separable C- and S-shaped isomers.

Scheme 1



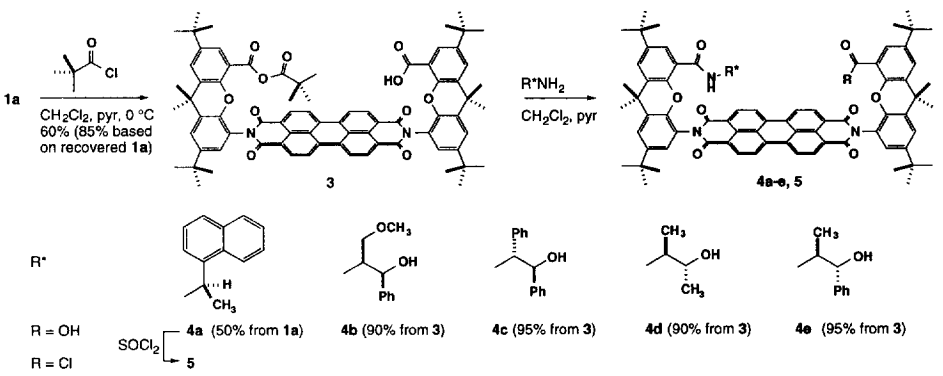
The binding of various guest species by diamide derivative **2** confirmed that the interior functional groups in the C-shaped **1a** are indeed convergent and are able to chelate complementary functions.[4,5] The perylene spacer provides a cleft wide enough for the incorporation of an asymmetric element via one of the carboxyl groups, while leaving the other intact as an incipient reaction site.

Our previous procedure for the preparation of the brilliantly red **1** (hot quinoline, catalytic zinc acetate) had provided a modest overall yield (50%) that was evenly divided between the C-and S-shaped forms.[4] Unexpectedly, the use of a mixture of N-methyl-2-pyrrolidinone (NMP) and xylenes[6] as the solvent in the condensation reaction, effected selective formation of the desired C-shaped isomer (**1a/1b** = 12/1).[7] The C and S forms of **1** equilibrate in refluxing toluene to an approximately 1/1 mixture, so it is difficult to imagine how—in NMP/xylenes at ca 200 °C—a C to S ratio significantly different from unity results. It seems more likely that the

favorable proportion of C-shaped cleft results as the reaction mixture cools, perhaps due to differing solubilities of the C- and S-isomers in NMP/xylenes.

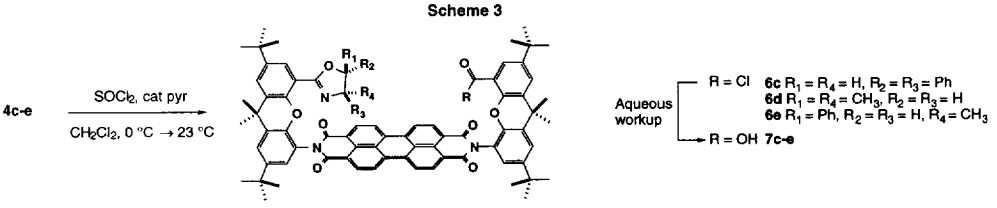
Selective functionalization of **1a** was also initially a problem: attempts to exploit the sterically demanding intermediates involved in carbodiimide-promoted coupling reactions or to differentially protect one carboxyl as its triisopropylsilyl ester failed. Instead, both carboxyl groups of **1a** were affected, as in the conversion to diamide **2**. Treatment of a suspension of the sparingly soluble **1a** with a stoichiometric amount of pivaloyl chloride (CH_2Cl_2, pyr, 0 °C) successfully generated the mono mixed anhydride **3**, contaminated with only traces of the undesired dianhydride (not shown). Happily, we found **3** robust enough to be separated from the dianhydride and remaining **1a** via column chromatography on silica gel (3→4% THF/CH_2Cl_2). The pivaloyl group of the mono mixed anhydride apparently fills enough of the cleft to discourage the formation of a second anhydride.

Scheme 2



The activated species **3** reacted with scalemic amines—including a variety of β-hydroxyamines[8]—at the less hindered, aryl-substituted anhydride carbonyl, providing mono amide derivatives of **1a** that incorporated asymmetry into the C-shaped cleft (Scheme 2).[9,10] Cyclization of the β-hydroxyamides **4c-e** to the corresponding oxazolines occurred on exposure to thionyl chloride (Scheme 3). The concomitantly formed acid chloride could be hydrolyzed back to the carboxylic acid via aqueous workup, although it was more conveniently used directly in further coupling reactions. The carboxylic acids **7c** and **7d** are unique: they are directed into a chiral space of almost C_2 symmetry, the shape so very much admired for catalytic applications (Figure 1). Less symmetry but two asymmetric centers confront the acid function of **7e**, while the carboxyl **4a** "sees" the large, medium and small groups of a conventional asymmetric center.

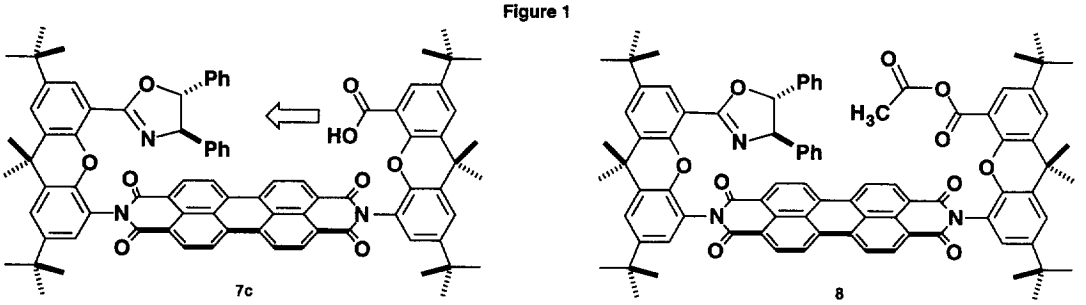
Scheme 3



Our functionalized clefts exhibited good solubility in chlorinated organic solvents, but characterization was complicated by markedly concentration-dependent ^1H NMR spectra. Even relatively small changes in

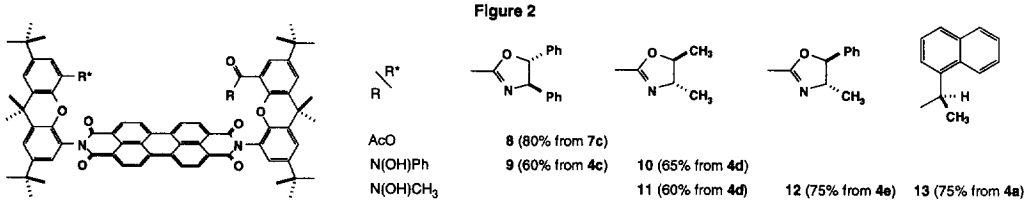
concentration (e.g., 19 mg **4a**/500 μL $CDCl_3$ → 670 μL) led to readily discernible differences in chemical shifts for the perylene and aromatic xanthene hydrogen resonances as well as for the signals corresponding to the naphthyl group. Chemical shift changes were observed for the upfield resonances as well. This behavior also occurred in systems without a free carboxylic acid function, and we attribute it to concentration-dependent aggregation via aryl-aryl interactions between the large surfaces.

Figure 1



Introduction of various reactive functions on the face of the C-cleft framework opposing the asymmetric elements was explored. Treatment of oxazoline-acid **7c** with acetyl chloride provided anhydride **8** which was stable to silica gel chromatography (3% $MeOH/CH_2Cl_2$) yet efficiently transferred the acyl group to a variety secondary amines. The positioning of the acyl donor in its peculiar surroundings (Figure 1) raises the possibility of using **8** for the kinetic resolution of racemic mixtures of chiral amines.

Figure 2



Formation of the acyl chlorides from either amide **4a** or oxazolines **7c-e** or directly from the β-hydroxyamides **4c-e** allowed for reactions with methyl or phenylhydroxylamine, leading to the corresponding hydroxamic acid derivatives **9-13**. These functions are known to chelate a variety of metal ions, including iron (III), vanadium (V) and copper(II),[11] and their incorporation within such clefts offers access to a metal center in a most unconventional asymmetric environment.

In summary, the greatly improved synthesis of the C-shaped diacid **1a** and an effective procedure for selectively activating one of its two carboxyl groups have led to the synthesis of various entities bearing asymmetric elements within a well-defined molecular cleft. Efforts to realize enantioselective processes within the context of these systems are ongoing.

Acknowledgments. We thank Dr. Takashi Oi for preliminary investigations on the synthesis of oxazoline **6c**.

References and Notes

1. For some recent examples and leading references, see: (a) Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 356. (c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.
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3. For a review, see: Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.
4. Shimizu, K. D.; Dewey, T. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 5145.
5. Rebek, J., Jr.; Heagy, M. D, unpublished.
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7. Preparation of C- and S-diacids **1**: A suspension of the xanthene aminoacid (0.73 g, 1.9 mmol)[4] and 3,4,9,10-perylenetetracarboxylic dianhydride (0.37 g, 0.95 mmol) in N-methyl-2-pyrrolidinone/xylenes (20 mL/5 mL) was heated at reflux through a column of 4 Å molecular sieves. After 48 h the mixture was allowed to cool, and solvent was removed by vacuum distillation. The residue was chromatographed (4→5% THF/CH_2Cl_2→5% $MeOH/CH_2Cl_2$ gradient, 100 g SiO_2), providing first the S-isomer **1b** (0.060 g, 6%) then the C-isomer **1a** (0.78 g, 75%), identical to the materials previously described.[4]
8. The amines were commercially available with the exception of the 1,2-dimethyl-β-hydroxyamine used in the synthesis of **4d** which was prepared according to: Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
9. Preparation of **4a**: To a 0 °C solution of the C-diacid **1a** (0.50 g, 0.45 mmol) and pyridine (0.50 mL, 6.2 mmol) in CH_2Cl_2 (25 mL) was added pivaloyl chloride (0.067, 0.54 mmol). After 3 h solvent and volatiles were removed in vacuo and the residue was suspended in CH_2Cl_2 (20 mL) at 0 °C. Pyridine (0.18 mL, 2.3 mmol) was added, followed by R-(+)-1-(1-naphthyl)ethylamine. After 30 min the cold bath was removed and the mixture was stirred overnight. Solvent and volatiles were removed in vacuo, and the residue was chromatographed (5% THF/CH_2Cl_2), providing amide **4a** (0.27 g, 50%) and recovered C-diacid **1a** (0.22g). R_f = 0.43 (5% THF/CH_2Cl_2); mp >300 °C; IR (thin film) 3420, 3060, 2960, 1705, 1670, 1590, 1580, 1445, 1355, 1260 cm^{-1}; ^1H NMR (300 MHz, 0.018M in $CDCl_3$) δ 8.67 (d, *J* = 8.0 Hz, 1H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 8.41 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.58 (overlapping doublets, *J* = 2.2 Hz, 2H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 5.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 7.1 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.91 (d, *J* = 7.1 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.50 (t, *J* = 7.6 Hz, 1H), 4.82 (apparent pentet, *J* = 6.7 Hz, 1H), 1.87 (s, 3H), 1.76 (s, 3H), 1.75 (s, 3H), 1.67 (s, 3H), 1.36 (s, 9H), 1.30 (s, 9H), 1.29 (s, 9H), 1.28 (s, 9H), 0.95 (d, *J* = 6.5 Hz, 3H); HRMS (FAB) *m/e* calcd for $C_{84}H_{77}N_3O_9Cs$ $(M+Cs)^+$ 1404.4714, found 1404.4763.
10. Preparation of **4e**: To a 0 °C solution of the C-diacid **1a** (0.36 g, 0.32 mmol) and pyridine (0.52 mL, 6.4 mmol) in CH_2Cl_2 (50 mL) was added pivaloyl chloride (0.059 mL, 0.48 mmol). After 3 h the mixture was concentrated in vacuo and the residue was chromatographed (3→4% THF/CH_2Cl_2), affording the mono mixed anhydride **3** (0.22 g, 57%) and recovered C-diacid **1a** (0.12 g). To a portion of mixed anhydride **3** (0.076 g, 0.063 mmol) and pyridine (0.060 mL, 0.74 mmol) in CH_2Cl_2 (6 mL) at 23 °C was added (1R, 2S)-(−)-norephedrin. The mixture was stirred overnight and solvent and volatiles were removed in vacuo. The residue was chromatographed (2→3% $MeOH/CH_2Cl_2$, 8 g SiO_2), providing amide **4e** (0.075 g, 95%). R_f = 0.25 (5% $MeOH/CH_2Cl_2$); mp >300 °C; IR (thin film) 3425, 2965, 1705, 1665, 1595, 1575, 1450, 1405, 1360, 1260 cm^{-1}; ^1H NMR (300 MHz, 0.011M in $CDCl_3$) δ 8.65 (m, 4H), 8.45 (m, 2H), 8.33 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 6.82 (m, 3H), 6.69 (m, 2H), 6.25 (d, *J* = 6.9 Hz, 1H), 4.13 (br s, 1H), 2.99 (m, 1H), 1.75 (br s, 9H), 1.71 (s, 3H), 1.35 (s, 9H), 1.32 (s, 9H), 1.30 (s, 9H), 1.29 (s, 9H), 0.36 (d, *J* = 6.9 Hz, 3H); HRMS (FAB) *m/e* calcd for $C_{81}H_{77}N_3O_{10}Cs$ $(M+Cs)^+$ 1384.4663, found 1384.4679.
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