

$\nu(\text{CO})$ 1995 (w), 1872 (vs), 1851 (s), 1797 (s) cm^{-1} .

Bis(triphenylphosphine)iminium Pentacarbonyl(2-phenylethyl)tungstenate(0) (9). Analogous to the preparation of **4a**, this derivative was obtained from **1a** (0.9542 g, 2.5797 mmol), $\text{PhCH}_2\text{CH}_2\text{OTs}$ (0.7841 g, 2.8377 mmol), and $[\text{PNP}][\text{Cl}]$ (1.6290 g, 2.8377 mmol): yield (with some impurities of **5**), 1.7973 g; $^1\text{H NMR}$ ($\text{THF}-d_8$) δ 7.40 (m, 35 H, PNP, Ph), 3.05, 0.95 (AA'XX', 2 H, 2 H, $\text{H}_2\text{C}-\text{Ph}$ and $\text{H}_2\text{C}-\text{W}$, respectively). $^{13}\text{C}\{^1\text{H}\}$ NMR ($\text{THF}/\text{THF}-d_8$) δ 208.1 (s, $^1J_{\text{CW}} = 146.2$ Hz, *trans*-CO), 207.4 (s, $^1J_{\text{CW}} = 126.2$ Hz, *cis*-CO), 153.2-123.2 (m, PNP, Ph), 47.1 (s, CH_2-Ph), -2.5 (s, $^1J_{\text{CW}} = 48.2$ Hz, CH_2-W); IR (THF) $\nu(\text{CO})$ 2028 (w), 1883 (s), 1839 (m) cm^{-1} .

Silver 3-Phenylpropionate (10a). To $\text{PhCH}_2\text{CH}_2\text{CO}_2\text{H}$ (3.0024 g, 19.976 mmol), suspended in 50 mL of H_2O , KOH (1.1208 g, 19.976 mmol) dissolved in 12 mL of H_2O was added. To the resulting clear solution of $\text{K}[\text{O}_2\text{CCH}_2\text{CH}_2\text{Ph}] \text{AgNO}_3$ (3.3902 g, 19.976 mmol) dissolved in 4 mL of H_2O was added dropwise with stirring. After 15 min, the white precipitate which formed was separated and washed 3 times with 10 mL of H_2O , 10 mL of MeOH, and 10 mL of ether followed by drying in vacuo over P_2O_5 : yield, 4.7239 g (92%); mp 269-271 °C dec.

Silver threo-2,3-Dideuterio-3-phenylpropionate (10b). This salt was prepared in a completely analogous manner as **10a** from 1.740 g (17.889 mmol) of *threo*- $\text{PhCHDCHDCO}_2\text{H}$,^{8b} 1.0037 g (17.889 mmol) of KOH, and 3.0388 g (17.889 mmol) of AgNO_3 : yield, 4.2169 g (91%); mp 261-264 °C dec.

Bis(triphenylphosphine)iminium Pentacarbonyl(3-phenylpropionylato)tungstenate(0) (12a). A mixture of **10a** (0.2571 g, 1.0004 mmol) and **11** (0.6910 g, 0.7695 mmol) in 30 mL of THF was stirred for 80 min in the dark. The precipitate of AgCl and excess **10a** (0.1683 g) was separated by centrifuging. The clear, yellow solution of **12a** was evaporated in vacuo. Redissolving the remaining oil in 15 mL of THF, adding 30 mL of hexane, and washing the separated oil 4 times with 10 mL of hexane, followed by drying in vacuo afforded 0.6120 g (78%) of yellow, microcrystalline **12a**: $^1\text{H NMR}$ ($\text{THF}-d_8$) δ 7.50 (35 H, PNP, Ph), 2.90, 2.43 (AA'BB', 2 H, 2 H, $\text{H}_2\text{C}-\text{Ph}$ and $\text{H}_2\text{C}-\text{CO}_2$, respectively). $^{13}\text{C}\{^1\text{H}\}$ NMR ($\text{THF}/\text{THF}-d_8$) δ 205.4 (s, $^1J_{\text{CW}} = 159.2$ Hz, *trans*-CO), 201.2 (s, $^1J_{\text{CW}} = 132.1$ Hz, *cis*-CO), 176.3 (s, OC(O)), 143.9-125.0 (m, PNP, Ph), 38.6, 33.4 (s, s, CH_2 , CH_2); IR (THF) $\nu(\text{CO})$ 2058 (w), 1911 (vs), 1850 (m) cm^{-1} .

Bis(triphenylphosphine)iminium threo-Pentacarbonyl(2,3-dideuterio-

3-phenylpropionylato)tungstenate(0) (8a). This derivative was obtained by the methodology of **12a** from 0.7215 g (0.8035 mmol) of **11** and 0.2617 g (1.0043 mmol) of **10b**: yield, 0.7412 g (91%).

Bis(triphenylphosphine)iminium Tetracarbonyl(trimethylphosphine)-(3-phenylpropionylato)tungstenate(0) (12b). A solution of **12a** (0.6940 g, 0.6860 mmol) and Me_3P (0.1044 g, 1.3720 mmol) in 25 mL of THF was heated to 50 °C for 40 min. The clear yellow solution was then evaporated in vacuo to a yellow oil, which was redissolved in 10 mL of THF. Addition of 30 mL of hexane led to the separation of 0.5234 g (72%) of yellow, powdery **12b** from 0.0362 g (12%) of **6**. **12b**: $^1\text{H NMR}$ ($\text{THF}-d_8$) δ 7.50 (m, 35 H, PNP, Ph), 2.95, 2.50 (AA'BB', 2 H, 2 H, H_2CPh and H_2CCO_2 , respectively), 1.52 (d, $^2J_{\text{HCP}} = 7.1$ Hz, 9 H, H_3CP); $^{13}\text{C}\{^1\text{H}\}$ NMR ($\text{THF}/\text{THF}-d_8$) δ 213.1 (d, $^2J_{\text{CWP}} = 38.5$ Hz, CO_{eq} , *trans* to Me_3P), 212.5 (d, $^2J_{\text{CWP}} = 8.3$ Hz, CO_{eq} *cis* to Me_3P), 206.8 (d, $^2J_{\text{CWP}} = 8.3$ Hz, CO_{ax}), 176.0 (d, $^3J_{\text{COWP}} = 1.8$ Hz, OC(O)), 144.2-124.9 (m, PNP, Ph), 39.2, 33.4 (s, s, CH_2 , CH_2), 18.17 (d, $^2J_{\text{CHP}} = 21.9$ Hz, CH_3P). $^{31}\text{P}\{^1\text{H}\}$ NMR ($\text{THF}/\text{THF}-d_8$) δ 227.4 (s, $^1J_{\text{PW}} = 224.2$ Hz, PW), 25.86 (s, PNP); IR (THF) $\nu(\text{CO})$ 1995 (w), 1872 (vs), 1851 (s), 1797 (s) cm^{-1} .

Bis(triphenylphosphine)iminium threo-Tetracarbonyl(2,3-dideuterio-3-phenylpropionylato)(trimethylphosphine)tungstenate(0) (8b). This complex was prepared in an analogous manner to **12b** from 0.6040 g (0.5959 mmol) of **8a** and 0.0907 g (1.1917 mmol) of Me_3P : yield, 0.5314 g (84%).

Bis(triphenylphosphine)iminium Pentacarbonyl(3-phenyl-2,3-dideuterio-3-phenylpropionylato)tungstenate(0) (13). A solution of **4a** (0.4410 g, 0.4548 mmol) in 50 mL of THF was pressurized with 400 psi of CO at 25 °C in a stainless steel Parr reactor. After 2.5 h of rapid stirring, the reaction mixture was brought to atmospheric pressure and the yellow solution was evaporated to a yellow oil. Recrystallization from THF/toluene at -10 °C provided 0.3981 g (88%) of yellow crystalline **13**: $^1\text{H NMR}$ ($\text{THF}-d_8$) δ 7.55 (m, 35 H, PNP, Ph), 2.98, 2.80 (AB, $^3J_{\text{HCCH}} = 4.3$ Hz, 1 H, 1 H, HDC, HDC); IR (THF) $\nu(\text{CO})$ 2039 (w), 1895 (vs), 1864 (m), $\nu\text{C(O)}$ 1558 (w) cm^{-1} .

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Convergent Functional Groups: Synthetic and Structural Studies

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Abstract: The synthesis of new molecular systems in which carboxyl groups are directed at well-defined microenvironments is described. The structures are obtained by condensation of suitable aromatic diamines with triacid **4a**. Crystallographic studies establish the structural details of the systems and lead to the design and preparation of systems featuring a molecular cleft. These new molecules resemble enzymes in which carboxyl groups converge at the active sites.

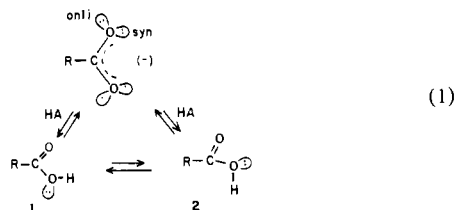
It was on account of our foundering in olefin epoxidation¹ that we became involved with molecules in which carboxyl groups are imbedded in rigid, well-defined microenvironments. The intent was to exploit the high selectivity anticipated for reactions of such systems, as is the case when the carboxyl function is found in enzyme interiors. After considerable screening we have devised a new molecular scaffold on which carboxyl groups are arranged in the desired sense. Here we report the development and characterization of these systems; in the sequel, their binding properties as molecular receptors and their application to the Prilashajew reaction are described.

Stereoelectronics

The specific issue concerns the trajectory, i.e., the stereoelectronics of reactions involving carboxyl oxygen. Unlike carbonyl carbon, which enjoys ample attention in acyl transfer and aldol reactions, the carboxyl oxygen has been ignored as a relatively colorless entity, about which little could be done, anyway. An exception to this ignorance is the thoughtful analysis provided by Gandour² on the subject of general base catalysis by carboxylate. While his cases involve proton transfers, the conclusions, summarized in eq 1, are relevant to the reactions of carboxylate with electrophiles in general. Gandour points out that proton transfers

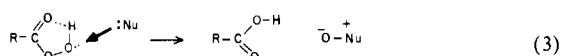
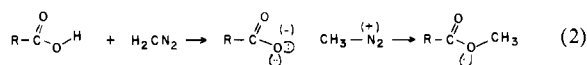
(1) Rebek, J., Jr. *Heterocycles* 1981, 15, 517-545.

(2) Gandour, R. *Bioorg. Chem.* 1981, 10, 169-176.



to carboxylate will be favored when they result in the syn acid **1**, rather than the less stable anti form **2**, i.e., the syn lone pairs are more basic than the anti ones.

One consequence of this character is expressed in the reaction of carboxylic acids with CH_2N_2 . After proton transfer, the $\text{S}_{\text{N}}2$ reaction occurs in such a way as to produce the syn ester (eq 2). Since this process involves the rectilinear arrangement shown, it is easy to see why all conventional carboxylic acids react "instantly" with CH_2N_2 . A structure of R which could exert steric hindrance to either the proton transfer or the $\text{S}_{\text{N}}2$ reaction is hard to image.

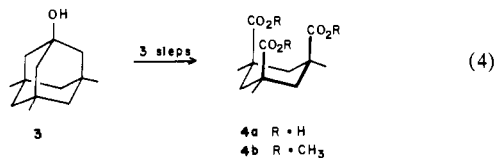


The reaction of peracids with nucleophiles (:Nu) provides similar reaction trajectories (eq 3). The intramolecular hydrogen bond fixes the orientation of the O-O bond and determines the approach of the reducing agent as shown.³ As a result, peracids derived from typical carboxylic acids cannot be expected to show stereoselectivity, since little opportunity exists for interactions between the R and the :Nu components.

The viability of the anti lone pairs of the carboxylate as nucleophiles has also been established by a number of ring-forming reactions such as haloactonizations.⁴ Comparison of the nucleophilicity of syn vs. anti lone pairs of a carboxylate is not a simple matter, as syn electrons are generally involved in bimolecular reactions whereas anti electrons will be restricted to unimolecular (i.e., cyclization) processes. Systems in which the microenvironment of the syn lone pairs can be controlled are, therefore, necessary for studies of general acid/base catalysis, nucleophilic substitution, and olefin epoxidation.

Structure and Synthesis

The foundation for the molecular scaffold was provided by the remarkable triacid **4a** (eq 4) first prepared by Kemp⁵ from the trimethyladamantanol **3**. The conformation shown was originally



deduced by Kemp from NMR data; the chemical shift differences observed between the equatorial and axial protons ($\Delta\delta \geq 1$ ppm) were best accommodated by the triaxial orientation of the carboxyl groups as shown. This structure was confirmed by x-ray crystallographic analysis (Figure 1). The striking features of this structure are the loss of symmetry in the crystalline state (Figure 1A) and the *intermolecular* hydrogen bonding (Figure 1B). The U shape that exists between any two carboxyl groups in the molecule cannot be due to *intramolecular* hydrogen bonding. (Such bonding would require the less stable anti form of a carboxylic acid as in **2**.) Moreover, the trimethyl ester **4b** also shows the NMR characteristics of the triaxial orientation. Its crystal

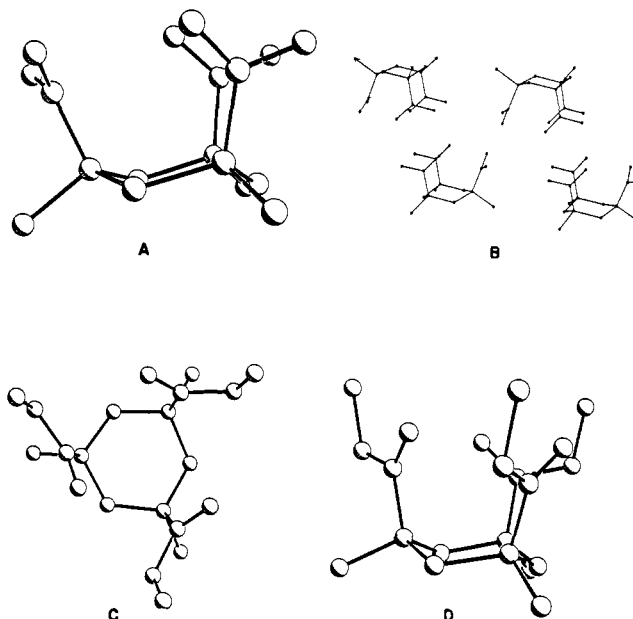
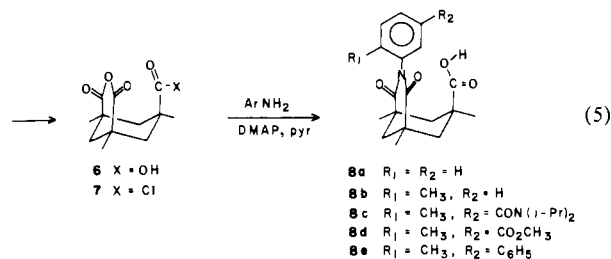


Figure 1.

structure was also solved and revealed the C_3 symmetry shown in C and D.

The anhydride **6** is readily prepared from **4a** by mere sublimation, while the action of SOCl_2 gives the acid chloride anhydride⁵ **7** in high yield (eq 5). The latter condenses readily with amines in hot pyridine containing catalytic amounts of 4-(dimethylamino)pyridine (DMAP). The imides **8** are obtained in 90–95% yield from **4a**.



A number of imides derived from alkyl or aryl amines could be prepared in this manner, and dynamic NMR spectral characteristics could be used to deduce conformational features. Specifically, the acid chloride of **8a** showed an exchange broadened signal for the ortho protons of the aromatic ring at ambient temperature. Cooling to 266 K gave the coalescence spectrum from which an activation barrier, ΔG^\ddagger , of 12.8 kcal/mol could be calculated for rotation about the $\text{C}_{\text{aryl}}-\text{N}$ bond. The corresponding derivative of *o*-toluidine, **8b**, showed no such temperature dependence, from which it could be concluded that the methyl group drastically reduces rotation about the bond in question. The best conformation should feature the methyl function directed away from, rather than toward, the carboxylic acid, i.e., the methyl may be considered an effective lock that limits the internal rotations of the molecule. In consequence, substituents meta to the nitrogen of the aniline (R_2 of **8**) are *suspended above the carboxylic acid when $\text{R}_1 \neq \text{H}$* .

Crystallography was again used to confirm these surmises. Specifically, the diisopropyl amide **8c** was obtained in suitably crystalline form and its structure revealed that the methyl group was indeed directed away from the carboxyl. Unlike the triacid **4a**, only slight distortions are present in the cyclohexyl portion of **8c** and, as is evident in the perspective of Figure 2, the plane defined by the atoms of the imide function and that of the carboxyl group are nearly parallel. These planes are roughly perpendicular to that of the aromatic ring.

(3) For a discussion with leading references, see: Sharpless, K. B. *Alldrichim. Acta* **1979**, *12*, 63–74.

(4) Bartlett, P. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, Chapter 6.

(5) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140–5143.

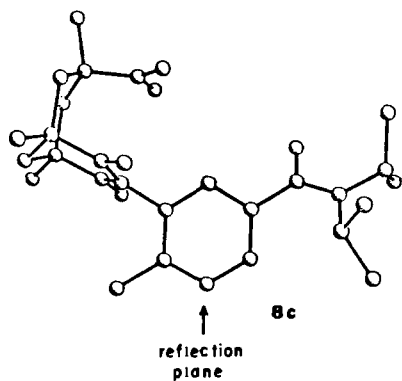


Figure 2.

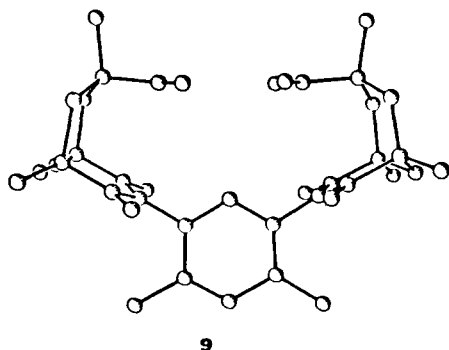


Figure 3.

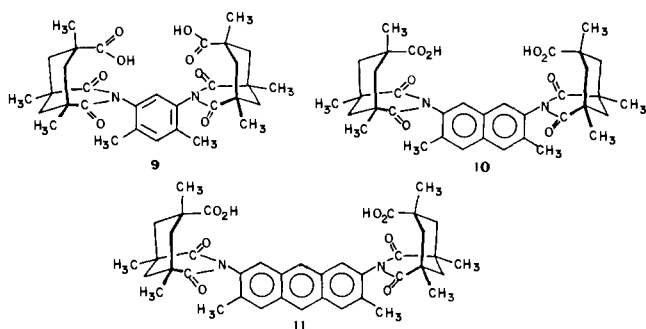


Figure 4.

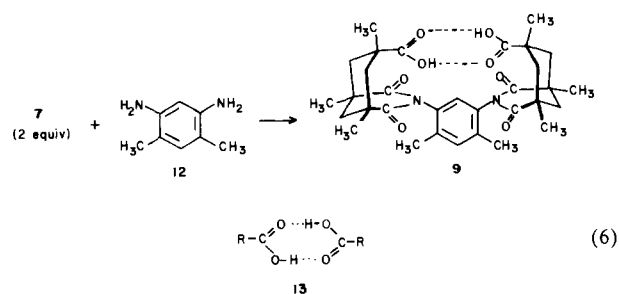
Since these structural features are expected to be quite independent of the nature of the meta substituent and the fractional coordinates for the aliphatic portion were in hand, we used the computer to construct molecules of promising size and shape. Merely reflecting the coordinates across the plane indicated in Figure 2 gave the computer-generated diacid **9** (Figure 3), then successive insertion of aromatic rings gave **10** and **11** (Figure 4). In this sense, the computer was used in its molecular graphics modality. Coupled with molecular mechanics calculations,⁷ these graphics can provide an alternative conceptualization to the unforgiving volume of CPK models and the seductive, spacious gaps that characterize Dreiding models.

In the laboratory, the diacid **9** was constructed in >90% yield by the condensation of the *m*-xylylene diamine⁸ **12** with two molecules of **7** (eq 6) when the same conditions as before were used. In this unique structure, the two carboxyl groups are constrained to *confront* each other in the manner of a typical H-bonded dimer **13**. The molecular scaffolding permits very little rotational motion in **9**, and the IR spectrum (ν acid CO) = 1705 cm^{-1}) is consistent with the intramolecular hydrogen bonds shown.⁹

(6) Steitz, A., Jr. *J. Org. Chem.* **1968**, *33*, 2978–2979.

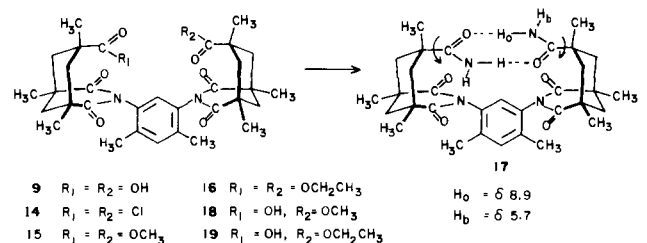
(7) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134. No attempt was made to deal with an intramolecular hydrogen bond in the structure calculated for **9**. The distance between opposing carboxyl oxygens in this calculation was 3.0 Å.

(8) Noelting, E.; Thesmar, G. *Chem. Ber.* **1902**, *35*, 628–650.



(6)

Even though such H bonding is likely, there is enough room available *between* the two carboxyls of **9** to permit some conventional chemical reactions (eq 7). For example, the diacid chloride **14** is readily generated with SOCl_2 and subsequent reaction with alcohols or NH_3 gives the respective diesters **15** or **16** and the diamide **17**.



(7)

Striking evidence for intramolecular hydrogen bonding was found in the NMR spectrum of **17**. Two widely separated N–H signals are observed at δ 8.9 and δ 5.7. The downfield resonance shows only a small change in chemical shift with temperature ($\Delta\delta/T = 2.35 \times 10^{-3}$ ppm/°C) while the upfield resonance shows a larger change: $\Delta\delta/T = 4.5 \times 10^{-3}$ ppm/°C. These trends are in reasonable agreement with those observed for intra- and intermolecular H-bonded amides in peptides.¹⁰ In addition, the two downfield equatorial protons of the cyclohexyl ring were involved in a temperature-dependent exchange process for which $\Delta G^\ddagger_c = 11.5 \pm 0.4$ kcal/mol could be calculated at 248 °K (T_c). The event most likely responsible for this exchange is the coupled rotation of the two amides as depicted in eq 8. We cannot rule out sequential rotation of the amide functions although breaking both hydrogen bonds, as required by such a process, should result in a higher activation barrier than that observed.

The acyl transfer reactions involved in eq 8 are unexceptional because nucleophiles enter and depart along a trajectory¹¹ unhindered by the presence of the second acyl function (eq 8A). In other ways the chemistry of **9** is unique. *Its reaction with CH_2N_2 is relatively slow!* With excess CH_2N_2 the monomethyl ester can be readily detected by NMR, and with Me_3O^+ or Et_3O^+ and Hunig's base, the mono esters **18** and **19** are cleanly generated.¹² These results are exceptional because electrophiles approach the carboxyl oxygen along a trajectory hindered by the presence of a second carboxyl function, i.e., this behavior is just that anticipated for a system in which the syn lone electron pairs are shielded by a hindered microenvironment (eq 8B).

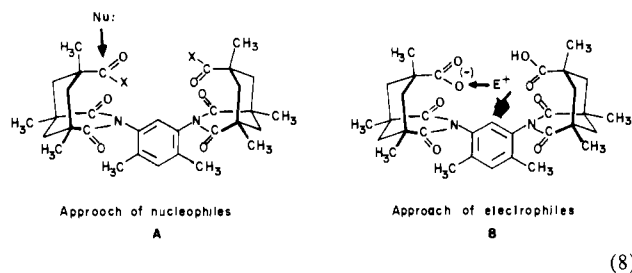
What other structures are accessible in this series? The laboratory counterpart to the computer-drawn **11** was provided by the inexpensive dye acridine yellow **20** (eq 9). Its condensation

(9) A long-chain (flexible) diacid has also been reported to show the intramolecular hydrogen-bonded structure: Vogtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753–776. In addition, such a structure was determined for a crown ether derivative: Goldberg, I. *Acta Crystallogr.* **1981**, *B37*, 102. For a discussion see: Cram, D. J.; Trueblood, K. N. *Top. Current Chem.* **1981**, *98*, 58.

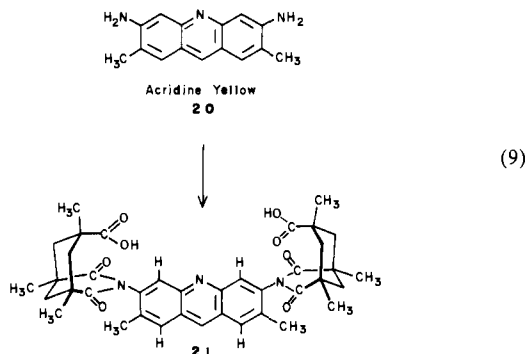
(10) Ovchinnikov, Y. A.; Ivanov, V. T. *Tetrahedron*, **1975**, *31*, 2177.

(11) Baldwin, J. J. *Chem. Soc., Chem. Commun.* **1976**, 738–740. Burgi, H. B.; Dunitz, J. D.; Shefter, W. *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067.

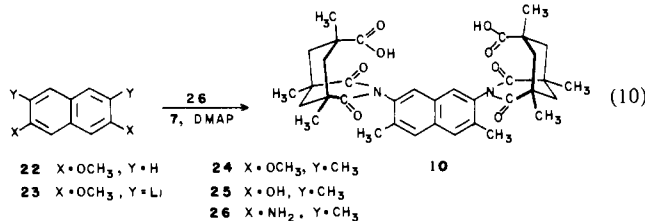
(12) Raber, D. J.; Gariano, P., Jr.; Broad, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149–1154. A referee has offered the excellent suggestion that the mono functionalization is a consequence of a ΔpK_a between the two carboxylic acid functions. We are investigating this possibility through the appropriate measurements.



with 2 equiv of **4a** was effected by fusing the two solids, and excellent yields of **21** were obtained.



The naphthalene version could be prepared as well, although the diamine component was not as readily available (eq 10). Starting from 2,7-dimethoxynaphthalene (**22**), the best sequence involved dilithiation¹³ with BuLi/TMEDA to give **23** followed by methylation. Compound **24** so obtained could be dealkylated to **25** with ether BBr₃¹⁴ or HI. The diol, under the conditions of the Bucherer¹⁵ reaction, gave the required diamine **26** from which the corresponding diacid **10** was prepared by fusion with **4a**, or condensation with **7**.



Outlook

This series of diacids provides a unique group of structures incorporating a molecular cleft. The carboxyl groups in these systems converge to provide a cavity which may act as a receptor to molecules of complementary size, shape, and hydrogen-bonding capabilities. Moreover, in the naphthalene or acridine versions sufficient space exists in the cleft for constructing, say, a monoamide from an optically active amine. In such structures a chiral microenvironment exists *between* functional groups in the same sense that such groups converge on an enzyme's active site. Our initial studies of these molecules as *receptors*, reported elsewhere, support this analogy.

The series of diacids having benzene, naphthalene, or acridine spacer groups provide three points, rather than a continuously variable system. Unfortunately, this problem of discontinuity appears to be a general one in mechanistic organic chemistry. Whether stated as a need for an element between carbon and nitrogen or a ring size of more than 3 but less than 4 members, the problem of "fine tuning" is characteristic of small molecules. One wonders if enzyme structure is, in part, nature's response to this problem. A microenvironment complementary to transition

(13) Sunthanker, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8–16.

(14) Vickery, E. H.; Pahler, L. F.; Eisenbraun, J. *J. Org. Chem.* **1979**, *44*, 4444–4445.

(15) Drake, N. L. In "Organic Reactions"; John Wiley and Sons: New York, 1942; Vol. I, Chapter 5.

Lysozyme

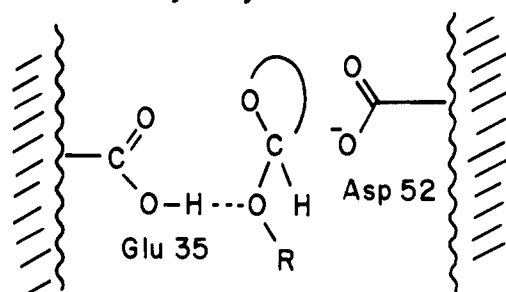


Figure 5.

states,¹⁶ rather than to ground states, may be accessible only with the tremendous synthetic investment represented by macromolecules. It would be fortunate to find such perfect fits with much smaller structures. For example, the active site of lysozyme¹⁷ is characterized by two convergent carboxyls (Figure 5) separated by 5–6 Å, a distance quite similar to that presented by the naphthalene **10**. Perhaps this molecule can function as a catalyst for glycoside hydrolysis, or even an aspartic proteinase;¹⁸ however, if it fails in this capacity, there is precious little that might be done about it. Aromatic diamines representing intermediate distances exist, but their relative orientations differ from the ideal. The lack of ortho substituents also reduces the rigidity of such systems. At least the appropriate stereoelectronics of the diacids described here, compared to other models,¹⁹ are cause for sanguinity, as are the results of our preliminary studies on their binding capacities.²²

Experimental Section

General Procedures for Preparation of Imide Acids **8**. Procedure A.

Anhydride acid chloride **7** (1 equiv), the appropriate amine (1 equiv), and a catalytic amount of DMAP (4-(dimethylamino)pyridine) were heated overnight at 90 °C in 3–5 mL of pyridine under N₂. The reaction solution was then evaporated and the product was purified by column chromatography on silica with EtOAc/hexane as eluent. Alternatively, the product was extracted into saturated NaHCO₃, acidified with 3 N HCl, and extracted into CHCl₃. Purified yields ranged from 60 to 100%.

Procedure B. Anhydride acid chloride **7** (1 equiv), the amine (1 equiv), a catalytic amount of DMAP, and poly(4-vinylpyridine)¹⁹ (same weight as amine) were refluxed in 3–5 mL of toluene under N₂ overnight. The polymer was removed by filtration, and workup and isolation followed the methods in A above. All NMR values refer to protons.

General Procedure for Preparation of Imide Acid Chlorides. The imide acid was refluxed overnight in neat SOCl₂ or oxalyl chloride under a CaCl₂ drying tube. Evaporation of the volatiles and flash chromatography through a silica plug (EtOAc/hexanes) then afforded the stable imide acid chlorides as tan or white solids. Yields were in the range 90–100%.

Anilide Imide **8a.** **8a** was prepared from aniline in 70% yield as a white solid: mp 243–245 °C; NMR (300 MHz, CDCl₃) δ 1.29 (s, 3 H), 1.36 (s, 6 H), 1.35 (d, *J* = 14 Hz, 2 H), 1.45 (d, *J* = 14 Hz, 1 H), 2.11 (dt, *J* = 14 Hz, 2 H, 1 H), 2.85 (d, *J* = 14 Hz, 2 H), 6.9–7.15 (br s, 2 H), 7.25–7.4 (m, 3 H); IR (CDCl₃) 1680, 1700, 1725 cm⁻¹. The acid chloride was prepared as a white solid in quantitative yield with SOCl₂: mp 180–183 °C; NMR (300 MHz, CDCl₃) δ 1.35 (s, 6 H), 1.42 (s, 3 H), 1.42 (d, *J* = 14 Hz, 2 H), 1.52 (d, *J* = 14 Hz, 1 H), 2.17 (dt, *J* = 14, 2 Hz, 1 H), 2.91 (d, *J* = 14 Hz, 2 H), 7.1 (br s, 2 H), 7.4–7.6 (m, 3 H); IR (CDCl₃) 1690, 1735, 1760, 1785, 1800 cm⁻¹; mass spectrum, *m/e* 335, 333, 298, 270, 242, 188.

Toluide Imide **8b.** **8b** was prepared as a white solid, mp 303–304 °C, in 50% yield with *o*-toluidine: NMR (300 MHz, acetone-*d*₆) δ 1.29 (s,

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6 H), 1.30 (s, 3 H), 1.38 (d, $J = 14$ Hz, 2 H), 1.64 (d, $J = 13$ Hz, 1 H), 1.94 (s, 3 H), 2.15 (dt, $J = 13$, 2 Hz, 1 H), 2.76 (d, $J = 13$ Hz, 2 H), 7.10 (m, 1 H), 7.19 (dd, $J = 5.5$, 1 Hz, 2 H), 7.24 (d, $J = 7.8$ Hz, 1 H); mass spectrum, m/e 329, 314, 283. The acid chloride was quantitatively prepared as a white solid, mp 190–193 °C, with SOCl_2 : NMR (300 MHz, CDCl_3) δ 1.35 (s, 6 H), 1.42 (s, 3 H), 1.42 (d, $J = 14$ Hz, 2 H), 1.54 (d, $J = 13.5$ Hz, 1 H), 1.96 (s, 3 H), 2.16 (d, $J = 13.5$ Hz, 1 H), 2.92 (d, $J = 14$ Hz, 2 H), 7.15 (m, 1 H), 7.25 (m, 3 H); IR (CHCl_3) 1690, 1740, 1760, 1780, 1790, 1810 (s) cm^{-1} ; mass spectrum, m/e 349, 347, 284, 283, 256.

2-Amino-3-methylbenzoic Acid Diisopropyl Amide. To 2-nitro-3-methylbenzoic acid (2.2 g) was added 3 mL of SOCl_2 and the resulting solution was heated under reflux for 3 h under a CaCl_2 drying tube. The volatiles were evaporated, and the resulting solid was suspended in 45 mL of benzene. To this was added diisopropylamine (4 mL) and THF (5 mL). The resulting solution was heated at 60 °C for 5 h. After the solution was cooled, the solvents were removed in vacuo and the crude product was dissolved in EtOAc and washed with H_2O (2×30 mL), 3 N HCl (2×30 mL), and 10% NaOH (2×30 mL). The organic phase was dried over MgSO_4 and concentrated to afford the 2-nitro compound as a white solid (2.5 g, 78%): mp 87–89 °C; NMR (90 MHz, CDCl_3) δ 1.32 (br d, $J = 6$ Hz, 12 H), 2.62 (s, 3 H), 3.70 (sep, $J = 6$ Hz, 2 H), 7.5 (m, 2 H), 8.02 (s, 1 H); mass spectrum, m/e 264, 249, 221, 207, 164. Catalytic reduction of this substance in AcOH/MeOH (1/1) with 300 mg of 10% Pd/C gave the amine as a tan solid. Recrystallization from benzene afforded a pure white solid: mp 183–183.5 °C (1.54 g, 96%); NMR (90 MHz, CDCl_3) δ 1.27 (br d, $J = 6$ Hz, 12 H), 2.10 (s, 3 H), 3.65 (br, 4 H), 6.65 (m, 2 H), 7.05 (d, $J = 7$ Hz, 1 H); mass spectrum, m/e 234, 219, 191, 134, 107.

Diisopropyl Amide Imide 8c. **8c** was prepared in 75% yield as a white solid, mp 252–254 °C, with amine above: NMR (300 MHz, CDCl_3) δ 1.17 (br, 6 H), 1.24 (d, $J = 14$ Hz, 2 H), 1.29 (s, 3 H), 1.33 (s, 6 H), 1.49 (br, 6 H), 1.51 (d, $J = 13$ Hz, 1 H), 1.99 (s, 3 H), 2.11 (d, $J = 13$ Hz, 1 H), 2.86 (d, $J = 14$ Hz, 2 H), 3.50 (br, 1 H), 4.03 (br, 1 H), 7.12 (d, $J = 7$ Hz, 1 H), 7.21 (d, $J = 7$ Hz, 1 H), 7.52 (s, 1 H); IR (CHCl_3) 1600, 1685, 1710, 1725 cm^{-1} ; mass spectrum, m/e 456, 441, 412, 356. The acid chloride was obtained in quantitative yield with SOCl_2 : mp 209–214 °C; NMR (300 MHz, CDCl_3) δ 1.35 (s, 6 H), 1.42 (s, 3 H), 1.15–1.45 (br, 14 H), 1.55 (d, $J = 13$ Hz, 1 H), 1.97 (s, 3 H), 2.16 (d, $J = 13$ Hz, 1 H), 2.91 (d, $J = 14$ Hz, 2 H), 3.70 (br, 2 H), 7.06 (s, 1 H), 7.28 (m, 2 H); IR (CHCl_3) 1610, 1680, 1725, 1750, 1775, 1795 (s) cm^{-1} ; mass spectrum, m/e 476, 474, 461, 459, 433, 431, 376, 374, 339, 310.

Methyl Ester Imide 8d. **8d** was prepared in 68% yield as a pale tan solid, mp 260–261 °C, with the corresponding amine:²¹ NMR (300 MHz, acetone- d_6) δ 1.29 (s, 6 H), 1.32 (s, 3 H), 1.44 (d, $J = 14$ Hz, 2 H), 1.69 (d, $J = 13.5$ Hz, 1 H), 2.03 (s, 3 H), 2.22 (dt, $J = 13$ Hz, 2 H), 2.75 (d, $J = 14$ Hz, 2 H), 3.86 (s, 3 H), 7.37 (d, $J = 8$ Hz, 1 H), 7.86 (dd, $J = 8$, 1.5 Hz, 1 H), 7.94 (d, $J = 1.5$ Hz, 1 H); mass spectrum, m/e 387, 372, 356, 355, 327. The acid chloride was prepared as a pale tan solid, mp 185–190 °C, with SOCl_2 : NMR (300 MHz, CDCl_3) δ 1.35 (s, 6 H), 1.43 (s, 3 H), 1.45 (d, $J = 14$ Hz, 2 H), 1.56 (d, $J = 13.5$ Hz, 1 H), 2.01 (s, 3 H), 2.15 (d, $J = 13.5$ Hz, 1 H), 2.92 (d, $J = 14$ Hz, 2 H), 3.89 (s, 3 H), 7.31 (d, $J = 8$ Hz, 1 H), 7.89 (s, 1 H), 7.96 (d, $J = 8$ Hz, 1 H); IR (CDCl_3) 1690, 1720, 1735 (s), 1765, 1790 cm^{-1} ; mass spectrum, m/e 407, 405, 370, 369, 341, 297.

Biphenyl Imide 8e. **8e** was prepared in 78% yield as a white solid, mp 294–296 °C, with 3-amino-4-methylbiphenyl:¹⁹ NMR (300 MHz, acetone- d_6) δ 1.30 (s, 6 H), 1.32 (s, 3 H), 1.44 (d, $J = 14$ Hz, 2 H), 1.69 (d, $J = 14$ Hz, 1 H), 1.99 (s, 3 H), 2.21 (dt, $J = 14$, 2 Hz, 1 H), 2.76 (d, $J = 14$ Hz, 2 H), 7.31 (d, $J = 8$ Hz, 1 H), 7.35 (dt, $J = 7$, 1.5 Hz, 1 H), 7.43 (dt, $J = 7$, 1.5 Hz, 2 H), 7.54 (dd, $J = 8$, 2 Hz, 1 H), 7.64 (d, $J = 2$ Hz, 1 H), 7.66 (dd, $J = 7$, 1.5 Hz, 2 H); mass spectrum, m/e 405, 361, 359, 210. The acid chloride was prepared in 97% yield as a white solid, mp 178–180 °C, with SOCl_2 : NMR (300 MHz, CDCl_3) δ 1.37 (s, 6 H), 1.44 (s, 3 H), 1.44 (d, $J = 14$ Hz, 2 H), 1.56 (d, $J = 14$ Hz, 1 H), 2.00 (s, 3 H), 2.19 (d, $J = 14$ Hz, 1 H), 2.95 (d, $J = 14$ Hz, 2 H), 7.18 (d, $J = 7$ Hz, 1 H), 7.26 (t, $J = 7$ Hz, 1 H), 7.31 (t, $J = 7$ Hz, 1 H), 7.41 (t, $J = 7$ Hz, 1 H), 7.45 (d, $J = 2$ Hz, 1 H), 7.53 (dd, $J = 7$, 2 Hz, 1 H), 7.63 (dd, $J = 7$, 1.5 Hz, 2 H); mass spectrum, m/e 425, 423, 359, 332.

Diacid 9. **9** was prepared in quantitative yield as a white solid, mp >355 °C from *m*-xylylidine diamine⁸ **12** and 2 equiv of **7**: NMR (300 MHz, CDCl_3) δ 1.24 (d, $J = 14.3$ Hz, 4 H), 1.30 (s, 12 H), 1.32 (s, 6 H), 1.50 (d, $J = 13.3$ Hz, 2 H), 1.93 (s, 6 H), 2.09 (d, $J = 13.3$ Hz, 2 H), 2.80 (d, $J = 13.8$ Hz, 4 H), 6.62 (s, 1 H), 7.11 (s, 1 H); IR (CHCl_3) 1690, 1730, 1705 (s), 3000 (br) cm^{-1} . Anal. Calcd for $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_8 \cdot \text{CH}_3\text{OH}$: C, 64.68; H, 7.23. Found: C, 64.72; H, 7.32. The diacid chloride **14** was prepared in 97% yield as a pale tan solid, mp 297–303 °C with SOCl_2 : NMR (300 MHz, CDCl_3) δ 1.33 (s, 12 H), 1.38 (s, 6

H), 1.38 (d, $J = 14.6$ Hz, 4 H), 1.51 (d, $J = 13.3$ Hz, 2 H), 1.91 (s, 6 H), 2.13 (d, $J = 13.3$ Hz, 2 H), 2.92 (d, $J = 13.8$ Hz, 4 H), 7.01 (s, 1 H), 7.07 (s, 1 H); IR (CHCl_3) 1690, 1730, 1760, 1785, 1805 cm^{-1} ; mass spectrum, m/e 616, 580, 552, 524, 488; high-resolution MS calcd for $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_6\text{Cl}_2$ 616.2107, obsd 616.2098.

Diamide 17. Ammonia gas was bubbled into a solution of diacid chloride **14** (60 mg) in 5 mL of dry THF under a CaCl_2 drying tube. After 10 min the reaction mixture became milky. The solvent was removed in vacuo and the residue was taken up in CHCl_3 , washed with H_2O (2×10 mL), dried over MgSO_4 , and concentrated to afford the diamide in quantitative yield as a white solid: mp 340–342 °C; NMR (300 MHz, CDCl_3) δ 1.26 (s, 6 H), 1.31 (s, 12 H), 1.2–1.3 (axial doublet, 4 H), 1.48 (d, $J = 13.2$ Hz, 2 H), 1.91 (s, 6 H), 2.10 (d, $J = 13.5$ Hz, 2 H), 2.61 (br d, $J = 13.8$ Hz, 4 H), 5.69 (br s, 2 H), 7.00 (s, 1 H), 7.09 (s, 1 H), 8.92 (br s, 2 H); IR (CHCl_3) 1670, 1690 (s), 1730, 3100–3250 cm^{-1} ; mass spectrum, m/e 578, 534, 357, 236; high-resolution MS calcd for $\text{C}_{32}\text{H}_{42}\text{N}_4\text{O}_6$ 578.3104, obsd 578.3107.

Methyl Ester Acid 18. To $\text{Me}_3\text{O}^+\text{BF}_4^-$ (15.5 mg, 0.105 mmol) in 5 mL CH_2Cl_2 was added diacid **9** (55.3 mg, 0.095 mmol) and Hunig's base¹¹ (18.5 μL , 0.105 mmol). The stoppered flask was allowed to stand at room temperature overnight. The resulting solution was washed with 1 N HCl (3×5 mL) and then dried over MgSO_4 . Evaporation of the solvent gave the monoester **18** in quantitative yield (57 mg) as a whiter solid: mp 331–333 °C; NMR (300 MHz, CDCl_3) δ 1.24 (s, 3 H), 1.24 (d, $J = 13.5$ Hz, 4 H), 1.31 (s, 9 H), 1.32 (s, 6 H), 1.46 (d, $J = 13.1$ Hz, 1 H), 1.48 (d, $J = 13.1$ Hz, 1 H), 1.92 (s, 6 H), 2.09 (d, $J = 11.1$ Hz, 2 H), 2.85 (d, $J = 13.5$ Hz, 4 H), 3.59 (s, 3 H), 6.93 (s, 1 H), 7.07 (s, 1 H); mass spectrum, m/e 594, 550; high-resolution MS calcd for $\text{C}_{33}\text{H}_{42}\text{N}_2\text{O}_8$ 594.2941, obsd 594.2942. The corresponding acid chloride was prepared in 90% yield with SOCl_2 : mp 266–268 °C; NMR (300 MHz, CDCl_3) δ 1.24 (s, 3 H), 1.32 (s, 6 H), 1.33 (s, 6 H), 1.38 (s, 3 H), 1.15–1.45 (axial doublet, 4 H), 1.50 (d, $J = 13.5$ Hz, 2 H), 1.91 (s, 3 H), 1.92 (s, 3 H), 2.10 (d, $J = 13.5$ Hz, 1 H), 2.13 (d, $J = 13.5$ Hz, 1 H), 2.87 (d, $J = 13.5$ Hz, 2 H), 2.92 (d, $J = 13.5$ Hz, 2 H), 3.65 (s, 3 H), 7.07 (s, 1 H), 7.19 (s, 1 H); IR (CHCl_3) 1690, 1730, 1760, 1780 cm^{-1} ; mass spectrum, m/e 612, 548, 520, 489.

Ethyl Ester Acid 19. The procedure of Raber and Guida was used.¹¹ To diacid **9** (162 mg) in 5 mL of CH_2Cl_2 were added 54.3 mg of $\text{Et}_3\text{O}^+\text{BF}_4^-$ in 5 mL of CH_2Cl_2 and 50 μL of diisopropylethylamine. The reaction flask was stoppered and left standing overnight. After the solution was washed with 1 N HCl (2×5 mL) and dried over MgSO_4 , evaporation of the solvent afforded the monoethyl ester **19** (164 mg, 97%) as a white solid: mp 277–278 °C; NMR (300 MHz, CDCl_3) δ 1.11 (t, $J = 7.1$ Hz, 3 H), 1.18–1.2 (axial doublet, 4 H), 1.24 (s, 3 H), 1.30 (s, 3 H), 1.31 (s, 6 H), 1.32 (s, 6 H), 1.47 (d, $J = 13.1$ Hz, 1 H), 1.45 (d, $J = 13.1$ Hz, 1 H), 1.92 (s, 6 H), 2.08 (d, $J = 12.1$ Hz, 2 H), 2.86 (d, $J = 14.3$ Hz, 4 H), 4.01 (q, $J = 7.1$ Hz, 2 H), 6.93 (s, 1 H), 7.06 (s, 1 H); mass spectrum, m/e 608, 590, 564, 534; high-resolution MS calcd for $\text{C}_{34}\text{H}_{44}\text{N}_2\text{O}_8$ 608.3098, obsd 608.3092. The corresponding acid chloride was prepared in 90% yield as a tan solid, mp 233–237 °C, with SOCl_2 : NMR (300 MHz, CDCl_3) δ 1.02 (t, $J = 7.1$ Hz, 3 H), 1.12 (d, $J = 14.1$ Hz, 2 H), 1.16 (s, 3 H), 1.24 (s, 6 H), 1.26 (s, 6 H), 1.30 (s, 3 H), 1.30 (d, $J = 14.8$ Hz, 2 H), 1.38 (d, $J = 13.3$ Hz, 1 H), 1.43 (d, $J = 13.3$ Hz, 1 H), 1.83 (s, 3 H), 1.85 (s, 3 H), 2.02 (d, $J = 13.5$ Hz, 1 H), 2.06 (d, $J = 13.5$ Hz, 1 H), 2.81 (d, $J = 13.0$ Hz, 2 H), 2.84 (d, $J = 13.0$ Hz, 2 H), 4.06 (q, $J = 7.1$ Hz, 2 H), 6.99 (s, 1 H), 7.10 (s, 1 H); IR (CHCl_3) 1690, 1720, 1730, 1760, 1785 cm^{-1} .

Synthesis of the Acridine Diacid 21. Commercially available acridine yellow¹⁵ was liberated from HCl by stirring with 2.5 N NaOH and vacuum drying the resulting yellow solid at 50 °C. The free amine (0.40 g, 1.68 mmol) was ground with **4a** (0.87 g, 3.36 mmol), placed in a sealed tube, and heated at 200 °C for 4 h in an aerated sand bath. After cooling, the contents of the tube were dissolved in 500 mL of CH_2Cl_2 and filtered. Concentration of the solution followed by chromatography on silica (15% MeOH/EtOAc) afforded 0.85 g (60% yield) of **21** as an orange solid: mp >330 °C; NMR (CD_3OD) δ 1.21 (s, 6 H), 1.26 (s, 12 H), 1.35 (d, $J = 14$ Hz, 4 H), 1.60 (d, $J = 13.5$ Hz, 2 H), 2.10 (s, 6 H), 2.15 (d, $J = 13.3$ Hz, 2 H), 2.76 (d, $J = 13$ Hz, 4 H), 7.28 (s, 2 H), 7.90 (s, 2 H), 8.7 (s, 1 H); IR (CHCl_3) 3250 (br), 1718, 1680, 1180 cm^{-1} .

Because varying amounts of H_2O and other solvents were found present in samples of **21**, this substance was further characterized as its dimethyl ester (CH_2N_2). This material showed the following: ^1H NMR (300 MHz, $\text{CDCl}_3/\text{Me}_4\text{Si}$) δ 8.55 (s, 1 H), 8.15 (s, 2 H), 7.78 (s, 2 H), 3.85 (s, 6 H), 3.69 (d, $J = 14.5$ Hz, 4 H), 2.95 (d, $J = 14.5$ Hz, 4 H), 2.24 (d, $J = 14.5$ Hz, 2 H), 2.19 (s, 6 H), 1.55 (d, $J = 14.5$ Hz, 2 H), 1.39 (s, 12 H), 1.33 (s, 6 H); mp >300 °C dec; high-resolution MS calcd for $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_8$ 709.3363, obsd 709.3357.

2,7-Dimethoxy-3,6-dimethylnaphthalene (24). A modification of Gilman's procedure¹³ for the lithiation of **22** was used. Dimethoxy-naphthalene (1.88 g, 0.01 mol) was dissolved in 100 mL of ether and

TMEDA (5.8 g, 7.55 mL, 0.5 mol) was added. The solution was chilled in an ice bath and *n*-butyllithium (31.4 mL of a 1.6 M solution in hexane, 0.05 mol) was added dropwise. The turbid solution was allowed to warm up to room temperature and then heated under reflux overnight (20 h). During this lithiation period a tannish-yellow precipitate formed. The mixture was again cooled in an ice bath and quenched by dropwise addition of a solution of dimethyl sulfate (6.94 g, 5.2 mL, 0.55 mol) in 50 mL of ether. The precipitate became more dense and turned white. After being stirred for 3 h, the mixture was poured over ice-water, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with 2 N NH₄OH, 2 N HCl, water, and brine and then dried (MgSO₄) and concentrated. The yellow residue was recrystallized from pentane: mp 168–169 °C; ¹H NMR δ 2.312 (s, 6 H, CH₃), 3.877 (s, 6 H, OCH₃), 6.956 (s, 2 H, aromatic H's at C₄ and C₅), 7.374 (s, 2 H, aromatic H's at C₁ and C₈); mass spectrum, *m/e* 216, 202, 188 and 173. Anal. Calcd for C₁₄H₁₆O₂: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.54.

2,7-Dihydroxy-3,6-dimethylnaphthalene (25). A 1.0 M solution of BBr₃ in CH₂Cl₂ (27 mL) was placed in a flame-dried flask and cooled to -78 °C. A solution of **24** (1 g, 0.082 mmol) in 20 mL of dry CH₂Cl₂ was added dropwise. The resulting mixture was warmed to 25 °C and stirred for 4.5 h. Next, 100 mL of water was added causing the formation of a white precipitate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The organic phases were pooled and dried (MgSO₄) and then evaporated, giving 0.85 g of tan solid (97%): mp 248–249 °C; ¹H NMR (Me₂SO/CDCl₃) δ 7.45 (s, 2 H), 6.96 (s, 2 H), 3.5 (br s, H), 2.35 (s, 6 H); mass spectrum, *m/e* 188, 173, 159 and 145; *m*, 174. Anal. Calcd for C₁₂H₁₂O₂: C, 76.57; H, 6.43. Found: C, 76.43; H, 6.51.

2,7-Diamino-3,6-dimethylnaphthalene (26). A classic Bucherer¹⁵ synthesis was employed. The diol **25** (4.2 g) was placed in a 350-mL pressure reactor along with a solution made by passing sulfur dioxide for 30 min into 150 mL of cooled ammonium hydroxide. The vessel was sealed and heated to 170 °C and stirred for 7 h. The reaction was cooled and the resulting brown solution was filtered. The solids were taken up in ethyl acetate and then extracted into 1 N HCl. The HCl extracts were made basic with solid KOH giving a tan precipitate which was filtered and vacuum dried at 40 °C. The crude brown solid (4.15 g, 96%) was used without further purification: mp 215–218 °C; ¹H NMR (acetone-*d*₆) δ 7.35 (s, 2 H), 6.85 (s, 2 H), 2.9 (br s, 4 H), 2.20 (s, 6 H); mass spectrum, *m/e* 186 (m), 172.

Preparation of 10. Condensation of the diamine **26** and 2 equiv of the triacid **4a** was accomplished by fusion as described for **21**. The yield was 96.5% of an off-white solid: mp >330 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.10 (s, 6 H), 1.98 (d, *J* = 14.5 Hz, 4 H), 1.30 (s, 12 H), 1.36 (d, *J*

= 13.0 Hz, 2 H), 2.05 (s, 6 H), 2.08 (d, *J* = 13.4 Hz, 2 H), 2.75 (d, *J* = 14.3 Hz), 4.75 (br, 4 H), 7.44 (s, 2 H), 7.65 (s, 2 H); IR (CDCl₃) 1180, 1718 (s), 3100 (br) cm⁻¹. Anal. Calcd for C₃₆H₄₂N₂O₈·H₂O: C, 66.65; H, 6.84; N, 4.32. Found: C, 66.44; H, 6.55; N, 4.24.

Crystallography. Complete details will be published elsewhere. Data for **4a**, **4b**, and **9** were collected with a Nicolet R3m diffractometer with Mo Kα radiation. Unique reflections with *I* > 2.5σ(*I*)—1571 for **4a**, 2038 for **4b**, and 3030 for **9**—were used in the structure solution (Direct Methods) and least-squares refinement. After anisotropic thermal parameters were used for all non-hydrogen atoms, convergence was reached at *R* = 0.047 for **4a**, *R* = 0.064 for **4b**, and *R* = 0.096 for **9**.

Data for **8c** were collected with a Nicolet R3m diffractometer with Cu Kα radiation. Unique reflections with *I* > 2.5σ(*I*), 3229 for **8c**, were used in the structure refinement with use of Direct Methods and least-squares refinement. Following the use of anisotropic thermal parameters for all non-hydrogen atoms, convergence was reached at *R* = 0.064.

All crystallographic calculations were carried out on a Data General Eclipse 5/140 computer. The principal programs used were the SHELXTL series supplied with the diffractometer. Crystals of **4c** were obtained from the slow evaporation of a pyridine solution. Crystal data for C₁₂H₁₈O₆: *M*_r, 258.0, space group *P*2₁/*n*, *a* = 8.471 (2) Å, *b* 12.138 (3) Å, *c* = 12.902 (3) Å, β = 101.80 (2)°, volume = 1298.7 (5) Å³, *Z* = 4, ρ(calcd) = 1.32, μ = 1.1.

Crystals of **4b** were obtained from the evaporation of an ethyl acetate/hexane solution. Crystal data for C₁₅H₂₄O₆: *M*_r, 300.0, space group *P*2₁/*n*, *a* = 9.020 (3) Å, *b* = 18.930 (7) Å, *c* = 10.106 (3) Å, β = 110.47 (3)°, volume = 1616.7 (9) Å³, *Z* = 4, ρ(calcd) = 1.23, μ = 1.0.

Crystals of **8c** were obtained after considerable trial and error involving many solvent systems. Crystal data for C₂₆H₃₅O₅N₂·H₂O·C₆H₁₂: *M*_r, 557.0, space group = *P*-1, *a* = 8.153 (2) Å, *b* = 12.577 (3) Å, *c* = 15.019 (3) Å, α = 88.145 (2)°, β = 87.675 (2)°, γ = 70.739 (2)°, volume = 1452.4 (0) Å³, *Z* = 2, ρ(calcd) = 1.28, μ = 6.62.

Crystals of **9** were obtained from the slow evaporation of an equal volume mixture of HCCl₃, MeOH, and EtOAc as solvents. Crystal data for C₃₂H₄₀N₂O₈·H₂O·C₄H₈O₂: *M*_r, 686.0, space group = *P*2₁/*n*, *a* = 14.313 (6) Å, *b* = 13.448 (6) Å, *c* = 19.03 (1) Å, β = 92.18 (4)°, volume = 3661 (3) Å³, *Z* = 4, ρ(calcd) = 1.25, μ = 0.86.

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Allosteric Effects in Organic Chemistry: Binding Cooperativity in a Model for Subunit Interactions

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Abstract: Experimental details are presented for the synthesis, structure, and dynamics of the first nonenzymatic system to show allosteric binding cooperativity in solution. The system involves two crown ether binding sites connected through a biphenyl skeleton. Binding of mercury derivatives at one ethereal site reduces the conformational freedom of the remote site in a manner favorable to binding. The structures of the Hg complexes are established by crystallography, and the thermodynamics of binding are studied by NMR. The relevance of these findings to biochemical systems is briefly addressed.

For the past several years we have been concerned with the construction of molecules capable of *allosteric* behavior. In biochemical systems, allosteric effects provide a means by which the catalytic activity of enzymes may be regulated. Binding of

an *effector* to a remote, allosteric site induces conformational changes at the active site and alters the binding affinity of the enzyme for its substrate. In general, such effects involve systems composed of identical subunits, and binding information is passed between subunits through intermolecular contacts. When the effector is also the substrate, as in the binding of O₂ to hemoglobin, the system is termed *homotropic*, and the phenomenon is *coop-*

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