Searching for Minimum Increments of Hydrophobic Collapse: Flexible Dinaphthyl Carboxylates

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Abstract: In an effort to identify minimal units of hydrophobically induced folding, we have examined flexible molecules containing two naphthyl moieties connected by a four-atom linker that also bears a carboxyl group. Crystallographic data show that the linkers allow intramolecular edge-to-face association of the naphthyl groups without excessive strain in the backbone. For the carboxylate forms of the dinaphthyl compounds, the occurrence of intramolecular naphthyl−naphthyl proximity in aqueous solution (24 °C) was detected via upfield shifts in the aromatic region ^{1}H NMR signals, relative to mononaphthyl control compounds. The naphthyl−naphthyl proximity does not appear to be strongly "hydrophobically driven", however, because similar upfield shifts (dinaphthyl vs mononaphthyl carboxylates) were observed in 8 M aqueous urea, and for the corresponding carboxylic acids in $CDCl_3$ and C_6D_6. We conclude that these upfield shifts largely reflect chance encounters between the naphthyl groups resulting from random conformational motion.

Introduction

The protection of nonpolar surfaces from aqueous solvation is widely believed to play a major role in determining the complexation behavior and conformational preferences of biopolymers[1] and small molecules.[2,3] There is still debate, however, on the extent to which hydrophobic clustering influences noncovalently controlled structural phenomena.[4] This uncertainty arises in part because of continued disagreement on the mechanism by which nonpolar−nonpolar interactions exert their energetically stabilizing effects, i.e., on the origin of the "hydrophobic effect". We have been trying to identify simple molecules (lowest possible molecular weight) in which hydrophobic forces influence conformation. Careful examination of folding processes in such systems should provide insight on the extent to which the hydrophobic effect determines structure and behavior in more complex systems. Further, the folding of small molecules in aqueous solution has become a subject of interest in its own right with the recent proposal that the biological activity of some drugs may be influenced by hydrophobically induced conformational preferences.[3f]

In this paper we describe the solution behavior of **1a**−**3a**, which contain two hydrocarbon aromatic moieties connected via a flexible tether; the tether segment also contains a carboxylate to confer water solubility. These molecules were chosen because the magnetic anisotropy induced by the aromatic π-electrons allows for sensitive detection of intramolecular proximity via ^{1}H NMR spectroscopy. Aromatic moieties are well-represented in proteins and their natural and synthetic ligands.

We will side-step much of the current debate on the nature of hydrophobicity by employing a strictly empirical definition: the term "hydrophobic" here refers to whatever makes hydrocarbons poorly soluble in water. According to this empirical definition, aromatic hydrocarbons are hydrophobic entities, although somewhat less so than aliphatic hydrocarbons. Thus, for example, the thermodynamic signatures for the transfer of benzene and cyclohexane from the pure liquid to dilute aqueous solution are qualitatively similar to one another.[4c] In both cases, at 25 °C, ΔG is positive, ΔH is negligible, ΔS is large and negative, and ΔC_p is large and positive. (According to ΔG, ΔS, and ΔC_p, cyclohexane is more hydrophobic than benzene, perhaps because of the ability of the aromatic π-electrons to engage in weak hydrogen bonds to water.[5]) Further evidence for the operational hydrophobicity of hydrocarbon aromatic moieties is found in the many reported scales of amino acid hydropathy: most scales rank phenylalanine among the most hydrophobic residues.[6,7]

[⊗] Abstract published in *Advance ACS Abstracts*, June 1, 1995.

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It has been suggested that aromatic amino acid side chains contribute to protein conformational stability via an intrinsic "weakly polar" attraction between the aromatic groups.[8] This proposal was based in part on the behavior of small aromatic hydrocarbons, which display "herringbone" or "edge-to-face" juxtapositions with their neighbors in the crystalline state.[9] The benzene dimer in the gas phase also appears to adopt a non-parallel arrangement.[10] This geometrical preference has been rationalized on the basis of polar interactions between the aromatic groups.[11] Two observations, however, indicate that the contribution of polar aromatic−aromatic interactions to protein stability is quite small. First, statistical surveys of aromatic−aromatic pairs in crystalline proteins reveal a nearly random orientation of the aromatic moieties relative to one another.[12] Second, a carefully constructed model system recently reported by Wilcox et al. shows that edge-to-face orientation of aromatic rings does not provide a significant conformation-directing force in solution.[13] Nevertheless, recent molecular dynamics calculations suggest that benzene molecules prefer to associate in edge-to-face rather than parallel fashion in aqueous solution.[14]

In a study related to the present one, we found that no intramolecular naphthyl−naphthyl stacking could be detected by ^{1}H NMR for **4** in aqueous solution (there were no upfield shifts of the aryl proton resonances of dinaphthyl **4** relative to a mononaphthyl reference compound).[15] In contrast, stacking could be detected by ^{1}H NMR for analogues of **4** in which one or both of the naphthyl groups was or were replaced by adenine.[15] The three-atom linker of **4** requires the naphthyl groups to associate intramolecularly in a parallel or near-parallel fashion. The four-atom linkers of **1a**−**3a**, on the other hand, are long enough to allow intramolecular edge-to-face approach. These longer linkers are of particular interest because of the computational prediction that the benzene dimer prefers an edge-to-face geometry in aqueous solution.[14] The results provided below suggest that the four-atom tethers do allow the linked aromatic groups to find one another in solution, but that there is little driving force, hydrophobic or otherwise, for this aromatic−aromatic proximity.

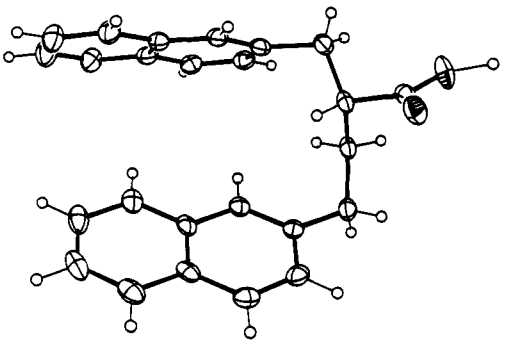

Figure 1. Crystal structure of carboxylic acid **1b**. The angle between the mean planes of the naphthyl units is 51°.

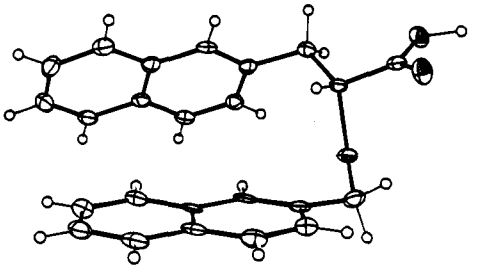

Figure 2. Crystal structure of carboxylic acid **2b**. The angle between the mean planes of the naphthyl units is 51°.

Results

Crystal Structures. The diaryl carboxylic acids **1b**−**3b**, their sodium salts **1a**−**3a**, and various reference compounds discussed below were prepared by standard methods, as described in the Experimental Section. The crystal structures of **1b** and **2b** are shown in Figures 1 and 2. These two dinaphthyl carboxylic acids adopt nearly identical conformations in the solid state, with an intramolecular edge-to-face orientation of the naphthyl moieties. In both cases, the angle between the planes of the linked naphthyl groups (51°) is nearly identical to the interplanar angle for neighboring molecules in crystalline naphthalene itself.[16] The conformations observed for these flexible molecules in the solid state do not provide any direct information on conformational preferences in solution, but the presence of these folding patterns in the crystals suggests that similar folded conformations are energetically accessible in solution.

Detection of Aromatic−Aromatic Proximity via ^{1}H NMR. Figure 3 shows aromatic region ^{1}H NMR data for dinaphthyl carboxylate **1a** and for a 1:1 mixture of mononaphthyl carboxylates **5a** and **6a**, both samples in D_2O at 24 °C. Qualitative comparison suggests that at least some of the resonances of the dinaphthyl carboxylate are shifted upfield relative to the corresponding resonances in the mixture of mononaphthyl carboxylates. (It is impossible to make assignments based upon these one-dimensional data.)

Before the ^{1}H NMR differences observed between **1a** and **5a** + **6a** (Figure 3) can be attributed to intramolecular naphthyl−naphthyl proximity, it must be demonstrated that aggregation does not occur under these conditions. Figure 4 shows the variation of the chemical shifts of two aromatic resonances of **1a** as a function of the logarithm of concentration. Since **1a** is composed largely of aromatic subunits, one expects self-

(5) It has long been known that π-systems can serve as hydrogen bond acceptors toward hydroxyl groups. For historical and leading references, see: (a) Schleyer, P. v. R.; Wintner, C.; Trifan, D. S.; Backskai, R. *Tetrahedron Lett.* **1959**, *14*, 1. (b) Oki, M.; Iwamura, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 427. (c) Bakke, J. M.; Chadwick, D. J. *Acta Chem. Scand.* **1988**, *B42*, 223. (d) Suzuki, S.; Green, P. G.; Bumgamer, R. E.; Dasgupta, S.; Goddard, W. A.; Blake, G. A. *Science* **1992**, *257*, 942.

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(7) It has been suggested that there are different molecular origins to the low aqueous solubilities of saturated and aromatic hydrocarbons (ref 4k), but this subtlety is beyond our focus on empirical behavior.

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(14) (a) Linse, P. *J. Am. Chem. Soc.* **1992**, *114*, 4366. (b) Linse, P. *J. Am. Chem. Soc.* **1993**, *115*, 8793.

(15) Newcomb, L. F.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4993.

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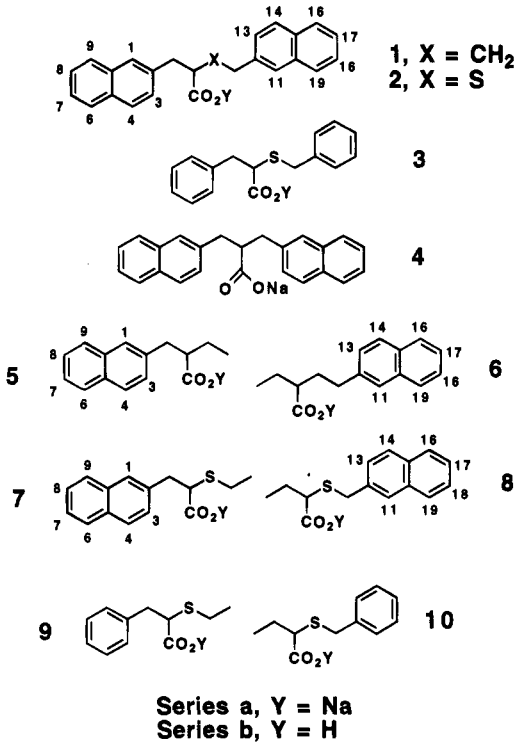
Chart 1



association to be signaled by upfield shifts in proton resonances. Indeed, slight upfield shifts are observed above ca. 0.5 mM, which suggests that self-association begins around this concentration. We conclude that the spectrum in Figure 3 represents monomeric **1a**, because these data were obtained at 0.2 mM, below the apparent onset of aggregation. Figure 5 shows the variation of the chemical shift of one aromatic resonance of mononaphthyl carboxylate **5a**. Aggregation is detectable only above 10 mM (we expect mononaphthyl carboxylate **6a** to behave similarly). This result suggests that aggregation is insignificant under the conditions used to obtain the spectrum of 1:1 **5a**:**6a** (2 mM each) in Figure 3. Therefore, we attribute the upfield shifts observed for **1a** relative to **5a** + **6a** in Figure 3 to intramolecular naphthyl−naphthyl proximity in the dinaphthyl compound.

The dinaphthyl system with a sulfur-containing linker, **2**, was examined because CS−CC torsional units have weaker conformational preferences than CC−CC units,[17] and we suspected that torsional strain opposing internal aromatic−aromatic association might be lower in **2** than in **1**. Figure 6 compares aromatic region ^{1}H NMR data for dinaphthyl carboxylate **2a** with analogous data for a 1:1 mixture of mononaphthyl carboxylates **7a** and **8a**, in D_2O at 24 °C. The upfield shifts for dinaphthyl carboxylate **2a** (relative to the reference compounds) are more substantial than was observed for **1a**, the analogue with the all-carbon tether (Figure 3). Figure 7 shows that there is no concentration dependence for several of the aromatic resonances of dinaphthyl carboxylate **2a** between 0.01 and 0.7 mM; all other aromatic resonances were also concentration independent over this concentration range.[18] The limited solubility of this salt precluded evaluation of higher concentrations. We conclude from these data that **2a** does not aggregate significantly up to its solubility limit in aqueous solution.[19]

An alternative interpretation of the concentration independence illustrated in Figure 7 is that **2a** is fully aggregated

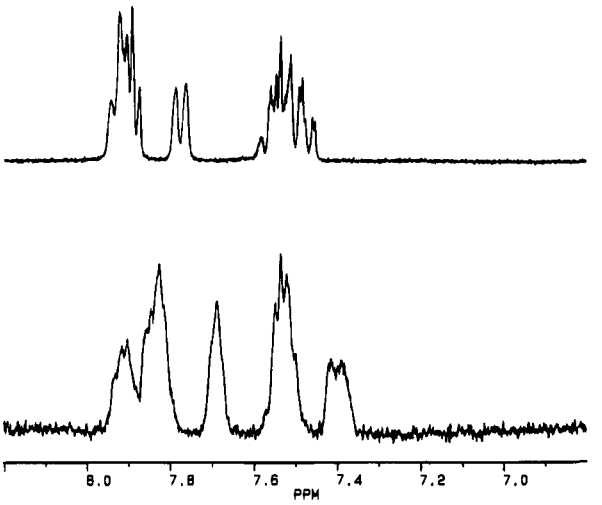


Figure 3. Aromatic region ^{1}H NMR (270 MHz) comparison between dinaphthyl carboxylate **1a** (0.2 mM; lower) and a 1:1 mixture of mononaphthyl carboxylates **5a** and **6a** (2 mM each; upper) in D_2O at 24 °C.

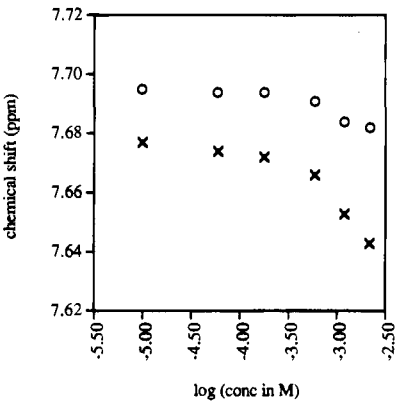


Figure 4. NMR chemical shifts of H1 (×) and H 11 (○) of dinaphthyl carboxylate **1a** in D_2O as a function of the logarithm of concentration, between 0.01 and 2.2 mM, at 24 °C. These data suggest that aggregation occurs gradually above 1 mM. NMR samples ≥1.2 mM were turbid. A nominally 1.7 mM solution of **1a** did not solubilize the hydrophobic dye orange OT.

even at 0.01 mM, but several lines of evidence argue against this possibility. First, analogue **1a** just barely begins to aggregate at 1 mM (Figure 4), and it seems unlikely that simply replacing one methylene group with a sulfur atom, to generate **2a**, would so dramatically increase self-association. Second, 0.7 mM **2a** fails to solubilize the hydrophobic dye orange OT. Solubilization of orange OT and related substances is commonly used to detect micelle formation,[20] and the lack of solubilization by **2a** suggests that this carboxylate is not in a micellar state at its solubility limit. Third, we know of no precedent for such avid aggregation in aqueous solution by a species of similar charge and molecular weight to **2a**.[19]

Concentration-dependent NMR studies of mononaphthyl carboxylates **7a** and **8a** indicate aggregation does not exert a significant effect on the data in Figure 6. Figure 8 shows the concentration-dependent variation in chemical shift of one aromatic proton resonance of mononaphthyl carboxylate **7a**.

(17) For leading references, see: Desper, J. M.; Gellman, S. H.; Wolf, R. E.; Cooper, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 8663.

(18) Data may be found in the supplementary material.

(19) The failure of carboxylate **2a** to aggregate up to its aqueous solubility limit is well precedented in the behavior of ionic surfactants. Most ionic surfactants have a characteristic "Krafft temperature", below which the solubility of the monomeric surfactant is smaller than the minimum concentration for aggregation. See: Myers, D. *Surfactant Science and Technology*, 2nd ed.; VCH Publishers: New York, 1992.

(20) Schott, H. *J. Phys. Chem.* **1966**, *70*, 2966.

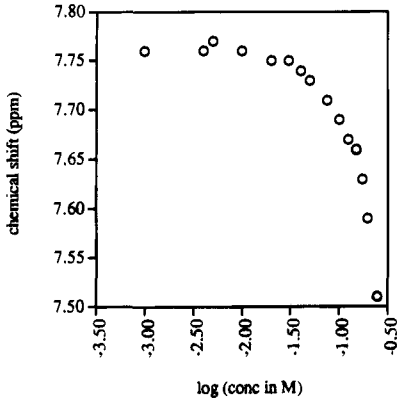


Figure 5. NMR chemical shift of H1 of mononaphthyl carboxylate **5a** in D_2O as a function of the logarithm of concentration, between 1 and 250 mM, at 24 °C. These data suggest that aggregation occurs gradually above 10 mM. NMR samples ≥200 mM were turbid. The behavior of the other aryl protons was similar (see supplementary material).

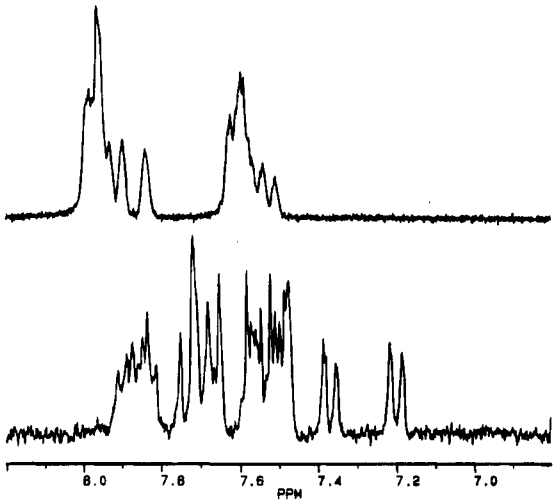


Figure 6. Aromatic ring ^1H NMR (270 MHz) comparison between dinaphthyl carboxylate **2a** (0.2 mM; lower) and a 1:1 mixture of mononaphthyl carboxylates **7a** and **8a** (5 mM each; upper) in D_2O at 24 °C.

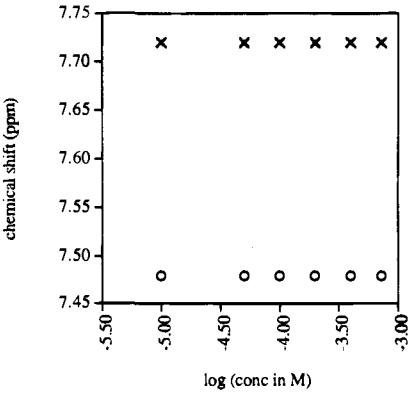


Figure 7. NMR chemical shifts of H1 (×) and H11 (○) of dinaphthyl carboxylate **2a** in D_2O as a function of the logarithm of concentration, between 0.01 and 0.7 mM, at 24 °C. These data show no sign of aggregation over this concentration range. NMR samples at 0.4 and 0.7 mM were turbid. A nominally 0.7 mM solution of **2a** did not solubilize the hydrophobic dye orange OT. The behavior of the other aryl protons was similar (see supplementary material).

These data suggest that little or no aggregation occurs up to 50 mM. Analgous data for mononaphthyl carboxylate **8a** (Figure 9) indicate that aggregation begins above 10 mM. These results

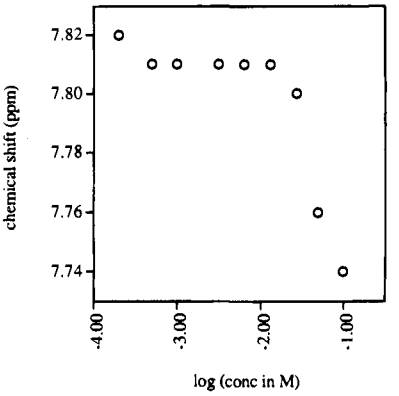


Figure 8. NMR chemical shifts of H1 of mononaphthyl carboxylate **7a** in D_2O as a function of the logarithm of concentration, between 0.2 and 98 mM, at 24 °C. These data suggest that aggregation occurs gradually above 10 mM. The sample of highest concentration slowly precipitated. The behavior of all six other aryl protons was similar (see supplementary material).

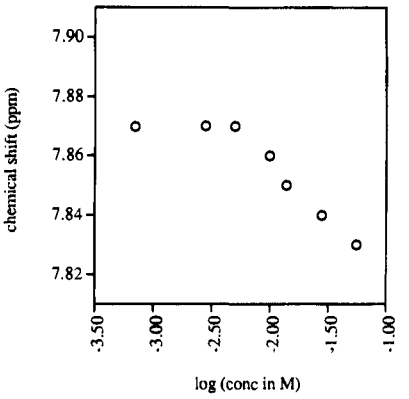


Figure 9. NMR chemical shifts of H11 of mononaphthyl carboxylate **8a** in D_2O as a function of the logarithm of concentration, between 0.7 and 56 mM, at 24 °C. These data suggest that aggregation occurs gradually above 5 mM. The behavior of the other aryl protons was similar (see supplementary material).

indicate that there should not be significant aggregation in the solution containing 1:1 **7a**:**8a**, 5 mM each. Therefore, we attribute the upfield shifts observed for **2a** relative to **7a** + **8a** in Figure 6 to intramolecular naphthyl−naphthyl proximity in the dinaphthyl compound.

Diphenyl carboxylate **3a**, which is analogous to **2a**, was also examined for intramolecular aryl−aryl proximity in aqueous solution. Figure 10 compares aromatic region ^1H NMR data for **3a** (2 mM) and for a 1:1 mixture of monophenyl carboxylates **9a** and **10a** (4 mM each) in D_2O at 24 °C. At least some of the aromatic resonances of the diphenyl compound appear to be shifted upfield relative to the controls. Figure 11 shows the concentration dependence of the chemical shift of one of the aromatic proton resonance for **3a**, which indicates that there is no significant aggregation up to 100 mM. Variable-concentration studies were not performed for **9a** and **10a**, but we assume that these monophenyl carboxylates will aggregate less avidly than their naphthyl analogues, **7a** and **8a**. We therefore conclude that the upfield shifts observed for **3a** relative to **9a** + **10a** arise from intramolecular phenyl−phenyl proximity in **3a**.

Solvent Effects. The ^1H NMR data presented above indicate that the covalently linked aromatic moieties of **1a**−**3a** spend some time near one another in aqueous solution. In order to determine whether this intramolecular proximity is hydrophobically induced, we carried out ^1H NMR comparisons of diaryl

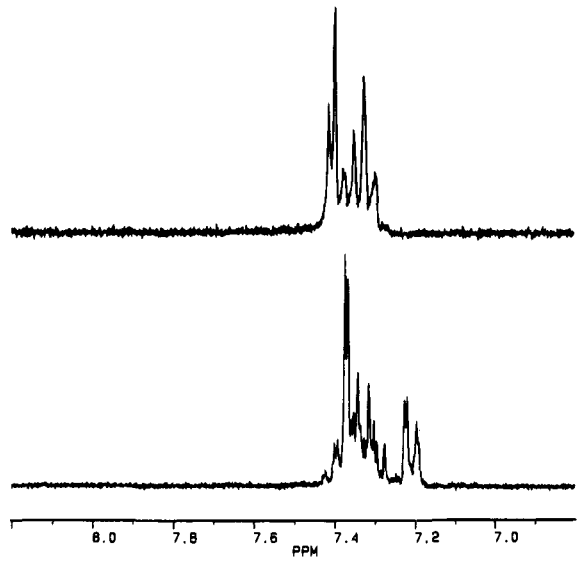


Figure 10. Aromatic region ^{1}H NMR (270 MHz) comparison between the diphenyl carboxylate **3a** (2 mM; lower) and a 1:1 mixture of monophenyl carboxylates **9a** and **10a** (4 mM each; upper) in D_2O at 24 °C.

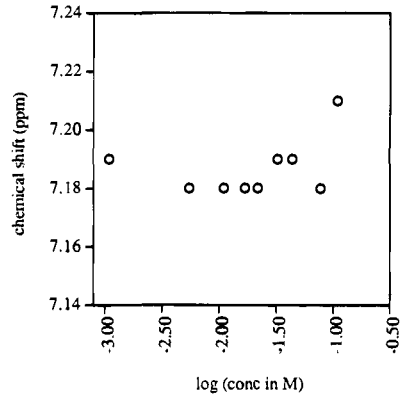


Figure 11. NMR chemical shifts of the most upfield proton resonance of diphenyl carboxylate **3a** in D_2O as a function of the logarithm of concentration, between 1.0 and 100 mM, at 24 °C. These data suggest that no aggregation occurs in this concentration range (the variation of ca. 0.03 ppm is within the uncertainty of the measurement).

carboxylic acids **1b**−**3b** with mixtures of the appropriate monoaryl carboxylic acids in C_6D_6. The hydrophobic effect is inoperative, by definition, in the absence of water, and we assume that there is no driving force for intramolecular naphthyl−naphthyl or phenyl−phenyl collapse in benzene solution. Therefore, the C_6D_6 results should represent chemical shift effects arising from random internal motions of one aryl group relative to the other.

Naphthyl proton NMR data for **2b** vs (**7b** + **8b**) in C_6D_6, shown in Figure 12, reveal significant upfield shifts for dinaphthyl carboxylic acid **2b** relative to the 1:1 mixture of mononaphthyl carboxylic acids. None of these three carboxylic acids displays concentration dependence in aryl proton chemical shifts in this solvent.[18] Qualitatively similar behavior was observed for **1b** and **3b** relative to their control compounds in C_6D_6.[18] NMR comparisons were conducted for dinaphthyl system **2** under two other sets of conditions expected to "turn off" the hydrophobic effect, **2b** vs (**7b** + **8b**) in $CDCl_3$, and **2a** vs (**7a** + **8a**) in 8 M aqueous urea. In both cases, substantial upfield shifts were observed for the dinaphthyl aromatic protons relative to the protons on the mononaphthyl reference compounds.[18]

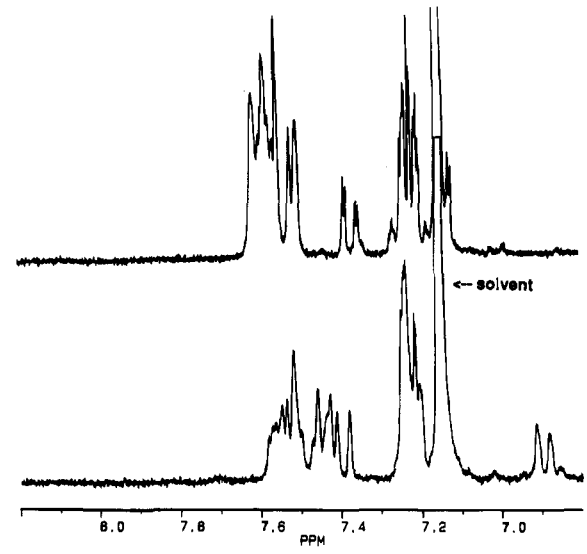


Figure 12. Aromatic region ^{1}H NMR (270 MHz) comparison between dinaphthyl carboxylic acid **2b** (0.5 mM; lower) and a 1:1 mixture of mononaphthyl carboxylic acids **7b** and **8b** (4 mM each; upper) in C_6D_6 at 24 °C.

Detailed Characterization of Naphthyl−Naphthyl Proximity. More complete comparison of diaryl folding behavior in aqueous and organic solvents required assignment of the aromatic proton resonances. The dinaphthyl compounds with the sulfur-containing linker (**2**) were selected for this in-depth study, because this system showed the greatest dispersion among aromatic proton resonances, the most dramatic upfield shifts relative to the mononaphthyl reference compounds, and the greatest dispersion among the proton resonances on the linking segment (this last point was crucial for assigning aromatic proton resonances to the proper naphthyl ring). Naphthyl proton NMR resonances were assigned via a combination of NOESY and TOCSY measurements, as described in the Experimental Section.

Table 1 provides a comparison of ^{1}H−^{1}H chemical shift differences, $\Delta\delta$ = dinaphthyl δ − mononaphthyl δ, for **2a** vs (**7a** + **8a**) in D_2O and for **2b** vs (**7b** + **8b**) in C_6D_6. The $\Delta\Delta\delta$ values in the rightmost column were obtained by subtracting the C_6D_6 $\Delta\delta$ from the D_2O $\Delta\delta$. The substantial $\Delta\delta$ values observed for some protons in both solvents indicate that there is significant population of conformers in which the naphthyl groups lie near their intramolecular neighbors in both water and benzene. As discussed above, we attribute the $\Delta\delta$ values observed for **2b** vs (**7b** + **8b**) in C_6D_6 exclusively to stochastic internal motions that periodically bring the tethered naphthyl groups near one another, because there should be no driving force for naphthyl−naphthyl association in benzene solution. (In other words, we assume that there is no significant energetic advantage for naphthyl−naphthyl interaction over naphthyl−benzene interaction.) Therefore, the fact that all of the $\Delta\Delta\delta$ values in Table 1 are small, with only a few values significantly different from zero, suggests that there is little hydrophobic driving force for pairwise naphthyl−naphthyl association in aqueous solution at room temperature.[21]

Table 2 shows coupling constant data that provide further support for the conclusion that there is little "hydrophobic collapse" in dinaphthyl carboxylate **2a** in aqueous solution. This

(21) In order to estimate the limiting secondary ^{1}H chemical shift for an "edge" aryl proton in an edge-to-face aromatic pair, we have examined a series of [4.4]thiocyclophanes that promote intramolecular edge-to-face juxtaposition. These studies suggest that these secondary ^{1}H chemical shifts are >1 ppm: Schladetzky, K. D.; Haque, T. S.; Gellman, S. H. *J. Org. Chem.*, in press.

Table 1. Upfield ^{1}H NMR Shifts of Aromatic Protons of Dinaphthyls **2a,b** Relative to Mononaphthyls **7a,b** and **8a,b**

proton[a]	$\Delta\delta(D_2O)$[b]	$\Delta\delta(C_6D_6)$[c]	$\Delta\Delta\delta$[d]
1	−0.34	−0.27	−0.07
3	−0.30	−0.25	−0.05
4	−0.25	−0.15	−0.10
6	−0.09	−0.04	−0.05
7	−0.05	−0.01	−0.04
8	−0.05	−0.01	−0.04
9	−0.28	−0.14	−0.14
11	−0.15	−0.13	−0.02
13	−0.22	−0.17	−0.05
14	−0.20	−0.15	−0.05
16	−0.04	−0.03	−0.01
17	0.00	0.00	0.00
18	0.00	0.00	0.00
19	−0.10	−0.08	−0.02

[a] Proton on **2a** or **2b**. [b] δ(**2a**) − δ(**7a** or **8a**); **2a** at 0.2 mM, **7a** and **8a** at 5 mM; uncertainty ±0.03 ppm. [c] δ(**2b**) − δ(**7b** or **8b**); **2b** at 1 mM, **7b** and **8b** at 5 mM; uncertainty ±0.03 ppm. [d] $[\delta(2a) - \delta(\mathbf{7a}\text{ or }\mathbf{8a})]_{D_2O} - [\delta(\mathbf{2b}) - \delta(\mathbf{7b}\text{ or }\mathbf{8b})]_{C_6D_6}$; uncertainty ±0.04 ppm.

Table 2. Vicinal Proton−Proton Coupling Constants from the Flexible Tethers of Dinaphthyls **2a,b** and Mononaphthyls **7a,b**

compd	solvent	$^3J_{HH}$ (Hz)
2a	D_2O	7.7
		8.4
7a	D_2O	7.7
		8.1
2b	C_6D_6	6.8
		8.6
7b	C_6D_6	6.7
		8.8

table compares the two vicinal proton−proton coupling constants ($^3J_{HH}$) from the tethers of **2a** and of reference compound **7a** in D_2O, and from the tethers of **2b** and of **7b** in C_6D_6. In each case, these vicinal coupling constants are consistent with random conformational averaging along the flexible carbon−carbon bond under scrutiny.

Table 3 shows NMR data that provide further insight on the origin of the upfield shifts of aromatic proton resonances for dinaphthyl system **2** relative to mononaphthyl reference compounds. This table contains $\Delta\delta$ data obtained in $CDCl_3$ for four variations on the **2** vs (**7** + **8**) theme, in which the branching substituent on the tether is varied from carboxylic acid [**2b** vs (**7b** + **8b**)] to methyl ester [**2c** vs (**7c** + **8c**)] or methoxymethyl [**2d** vs (**7d** + **8d**)], or eliminated [**2e** vs (**7e** + **8e**)]. Comparison of the results for **2b** vs (**7b** + **8b**) in $CDCl_3$ (first column in Table 3) and C_6D_6 (second column in Table 1) shows that the pattern of $\Delta\delta$ values is indistinguishable in these two solvents, within the uncertainty of these measurements. The similarity of behavior in C_6D_6 and $CDCl_3$ suggests that there is not a significant "polar" attraction between the naphthyl groups. This result is consistent with the recent demonstration by Wilcox et al. that there is little or no intrinsic attraction between aromatic rings juxtaposed in an edge-to-face manner.[13]

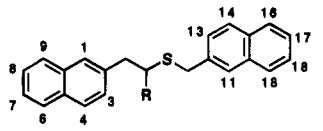
Comparison of the results in Table 3 for **2b** vs (**7b** + **8b**) with the results for **2c** vs (**7c** + **8c**) indicates that esterification has virtually no effect on the pattern of $\Delta\delta$ values. Conversion of the carboxylic acid group to a methoxymethyl substituent [**2d** vs (**7b** + **8b**)] leads to somewhat larger changes in the $\Delta\delta$ values, although only a few of these differences are beyond the level of uncertainty. The most significant effect on the pattern of $\Delta\delta$ values is observed when the carboxylic acid group is replaced by a proton [**2e** vs (**7e** + **8e**)]. This elimination of the branching substituent causes all eight of the $\Delta\delta$ values that were significant in **2b** to become substantially smaller; only three

Table 3.[a] Upfield ^{1}H NMR Shifts in $CDCl_3$ of Aromatic Protons of Dinaphthyls **2b−e** Relative to Mononaphthyls **7b−e** and **8b−e**

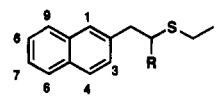
	R =			
proton[b]	CO_2H	CO_2Me	CH_2OCH_3	H
1	−0.22	−0.21	−0.15	−0.09
3	−0.22	−0.20	−0.16	−0.08
4	−0.14	−0.13	−0.07	−0.04
6	−0.04	−0.02	−0.02	−0.01
7	−0.03	−0.03	0.00	0.00
8	−0.03	−0.03	0.00	0.00
9	−0.17	−0.14	−0.11	−0.07
11	−0.10	−0.07	−0.13	−0.01
13	−0.14	−0.11	−0.12	−0.01
14	−0.14	−0.11	−0.12	−0.01
16	−0.03	−0.01	−0.02	−0.01
17	+0.01	0.00	+0.01	−0.02
18	+0.01	0.00	+0.01	−0.02
19	−0.10	−0.07	−0.11	−0.02

[a] Uncertainties ±0.03 ppm. [b] Proton on **2b−e**. The reported $\Delta\delta$ values are δ(**2**) − δ(**7** or **8**).

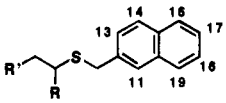
Chart 2



2a, R = CO_2Na
2b, R = CO_2H
2c, R = CO_2CH_3
2d, R = CH_2OCH_3
2e, R = H



7a, R = CO_2Na
7b, R = CO_2H
7c, R = CO_2CH_3
7d, R = CH_2OCH_3
7e, R = H



8a, R = CO_2Na, R' = CH_3
8b, R = CO_2H, R' = CH_3
8c, R = CO_2CH_3, R' = CH_3
8d, R = CH_2OCH_3, R' = CH_3
8e, R = H, R' = CH_2CH_3

naphthyl protons in **2e** show significant upfield shifts relative to the mononaphthyl reference compounds. These observations indicate that the pattern of $\Delta\delta$ values observed for **2a** vs (**7a** + **8a**) in aqueous solution and for **2b** vs (**7b** + **8b**) in nonpolar solutions is due largely to the presence of a branch point in the tether. This conclusion supports our contention that the intramolecular naphthyl−naphthyl proximity in **2a** in aqueous solution results predominantly from random internal motions, rather than from hydrophobic collapse.

Discussion

We have used aryl proton chemical shift effects to show that naphthyl and phenyl groups connected via flexible four-atom linkers spend time near one another in solution, but that this proximity is not strongly promoted by an aqueous environment relative to a nonpolar environment. Our experimental approach is based upon the fact that local magnetic anisotropy arising from aromatic π-electron systems can exert large effects on the chemical shifts of nearby protons. This type of secondary chemical shift has been widely used to detect intramolecular and intermolecular proximity of protons to aromatic rings.[3a−c,g,22]

One must be cautious in attempting to derive conformational information from secondary proton chemical shifts that arise

(22) (a) Detection of intramolecular heterocycle stacking via secondary ^{1}H NMR chemical shift effects: Constant, J. F.; Laugaa, P.; Roques, B. P.; Lhomme, J. *Biochemistry* **1988**, *27*, 3997 and references therein. (b) Host−guest chemistry examples: Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1994**, *116*, 2301. Zimmerman, S. C. *Top. Curr. Chem.* **1993**, *165*, 71.

from changes in molecular structure or solvent, because proton chemical shifts can be affected by multiple factors. We believe that analysis of secondary chemical shift effects for dinaphthyl compounds **2a**−**e** is valid because our quantitative comparisons are based *not* upon absolute chemical shifts but rather upon $\Delta\delta$ values, which are obtained from a given dinaphthyl ^1H chemical shift by subtracting the ^1H chemical shift for an analogous mononaphthyl compound. Thus, for example, comparison of the behavior of **2a** in aqueous solution with the behavior of **2b** in organic solvents involves a change from carboxylate to neutral carboxylic acid, and we assume that any effect of this change on absolute chemical shifts is accounted for in the $\Delta\delta$ values. Indeed, we have monitored the behavior of 14 aryl protons for dinaphthyl system **2a**,**b** (Table 1), and the internal consistency of the behavior of the secondary chemical shifts supports our conclusions. The lack of a substantial solvent effect on $\Delta\delta$ values between benzene and water indicates that this dinaphthyl system is not subject to a significant hydrophobic drive for folding. The absence of a solvent effect between benzene and chloroform supports the conclusion of Wilcox et al.[13] that polar interactions between hydrocarbon aromatic groups exert little or no conformational influence, because such a polar effect would have been expected to manifest itself in chloroform. (Calculations by Jorgensen and Severance suggest that there might be an intrinsic polar benzene−benzene attraction in chloroform solution.[11f])

It is common to use NOE or related two-dimensional measurements to detect spatial proximity between protons. ROESY[23] experiments were attempted for **2a** in D_2O, but no cross peaks could be clearly detected in the aromatic region, even between covalently adjacent protons. This difficulty stems from the very low aqueous solubility of **2a**. NOESY[24] cross peaks could be detected for covalently adjacent protons of ester **2c**, 45 mM in $CDCl_3$, but no cross peaks were observed between protons on different naphthyl groups within this molecule (1 s mixing time). This result for **2c** in $CDCl_3$, which displays $\Delta\delta$ values nearly identical to those for **2a** in D_2O, shows that secondary chemical shift effects provide more sensitive detection of intramolecular naphthyl−naphthyl proximity than do NOESY measurements. The NOESY data for **2c** suggest that the secondary chemical shift effects observed for **2a**−**d** in the various solvents arise from small populations of folded conformations.

The results reported here are important because aromatic hydrocarbon moieties (e.g., phenylalanine side chains) are commonly considered to be hydrophobic entities.[1d] The absence of significant hydrophobically driven folding in dinaphthyl system **2** is particularly interesting in the context of relatively large recent estimates of the thermodynamic gain associated with removal of nonpolar surfaces from contact with water.[1c] Comparison of the water-accessible surface area[25] of the crystallographically observed conformation of **2b** (568 Å^2) to the water-accessible surface area of the computationally minimized extended conformation of **2b** (656 Å^2) indicates that **2a** could bury at least 88 Å^2 of nonpolar surface by folding in aqueous solution. (Comparisons involving an isolated molecule of **2b** that has been minimized starting from the crystallographic conformation suggest that >100 Å^2 of nonpolar surface could be buried.)

(23) Bothner-By, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.

(24) Macura, S.; Ernst, R. R. *Mol. Phys.* **1980**, *41*, 95.

(25) Water-accessible surface areas were estimated with MacroModel v3.5 (1.4 Å probe radius); Mohamdi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Our findings are of interest also in the context of a recent hypothesis that hydrophobic collapse influences the solution conformations of low molecular weight medicinal agents.[3f] The lack of significant solvent-induced folding in water among the flexible diaryl carboxylates discussed here suggests that conformation-directing hydrophobic effects in drug molecules of similar size will be modest, at least when the "hydrophobic" moieties are aromatic.

Elucidation of basic chemical and biological processes and an enhanced ability to design molecules for specific functions (e.g., therapeutic agents, new catalysts) require an intimate understanding of the noncovalent interactions that control structure and function in flexible frameworks. Since many important events occur in aqueous solution, it is crucial that we learn the extent to which the hydrophobic effect can influence conformation and complexation. The results presented here provide intuitive calibration regarding the significance of hydrophobic effects involving hydrocarbon aromatic groups. These results should also be useful for quantitative calibration of computational tools that are intended to predict conformational preferences in aqueous solution. We are currently extending our experimental approach to systems containing aliphatic hydrophobic moieties.

Experimental Section

General. All melting points are uncorrected. THF was freshly distilled from sodium benzophenone ketyl under N_2. CH_2Cl_2 was freshly distilled from CaH_2 under N_2. CH_3CN was distilled from CaH_2 prior to use and stored over 4-Å sieves under N_2. Et_3N was distilled from CaH_2 prior to use and stored over KOH under N_2. Reagents were used as obtained from commercial suppliers. LDA was freshly prepared by adding 1.0 equiv of *n*-BuLi to a solution of 1.13 equiv of diisopropylamine in THF at 0 °C. NaH, a 60% dispersion in oil, was rinsed 1−3 times with dry pentane before use. Routine ^1H NMR spectra were obtained on either a Bruker WP-200, WP-270, or AC-300 spectrometer and referenced to residual protonated NMR solvent, or for spectra obtained in $CDCl_3$, to TMS. Routine ^{13}C NMR spectra were obtained on either a Bruker WP-270, AC-300, or AM-500 spectrometer and referenced to the NMR solvent. Routine FT-IR spectra were obtained on a Nicolet 740 spectrometer. High-resolution electron impact ionization mass spectrometry was performed on a Kratos MS-80. Elemental analyses were performed at Galbraith Laboratories. UV studies were performed on an HP 8452 diode array spectrophotometer. Column chromatography was carried out by using low N_2 pressure with either 230−400 mesh silica gel 60 from EM Science or reversed phase silica RP 18 (18−32) 60 A from ICN (this will be referred to as ODS, for octadecylsilyl).

Methyl 2-(Naphthyl)propionate. To a slurry of 15.3 g (37 mmol) of (carbomethoxymethyl)triphenylphosphonium bromide (Aldrich) in 100 mL of THF at 0 °C was added 14.1 mL (35 mmol) of *n*-BuLi (2.5 M in hexane) dropwise. The resulting solution was warmed to room temperature for 2 h, and then a solution of 5.0 g (32 mmol) of 2-naphthaldehyde (Aldrich) in 60 mL of THF was added *via* cannula. The solution was stirred at room temperature for 44 h, and then 50 mL of 1 N aqueous HCl was added. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the crude alkene was purified by SiO_2 column chromatography eluting with CH_2Cl_2 to give 6.4 g (94% yield) of a mixture of the *cis* and *trans* alkenes. The mixture of alkenes was dissolved in 150 mL of EtOAc, 0.64 g of 5% palladium on carbon was added, and the mixture was shaken under 40 psi of H_2 for 2.5 h and then filtered through Celite and rinsed well with EtOAc. Concentration of the filtrate gave 6.4 g (quantitative yield) of methyl 2-(naphthyl)propionate as a white solid that was recrystallized from hexane: mp 59.5 −60 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70 (t, J = 7.8 Hz, 2H), 3.10 (t, J = 7.8 Hz, 2H), 3.65 (s, 3H), 7.31 (dd, J = 1.4, 8.4 Hz, 1H), 7.40−7.45 (m, 2H), 7.62 (s, 1H), 7.73−7.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 173.24, 137.94, 133.53, 132.09, 127.88,

127.56, 127.45, 126.89, 125.96, 125.56, 125.06, 51.58, 35.55, 31.03; IR (KBr) 1729 cm^{-1}; EI MS *m/e* 214.0996, calcd for $C_{14}H_{14}O_2$ 214.0994.

2-(Naphthyl)propanoic Acid. A solution of 8.1 g (38 mmol) of methyl 2-(naphthyl)propionate in 190 mL of MeOH and 190 mL of 1 N aqueous NaOH was stirred at room temperature overnight. Most of the solvent was removed by rotary evaporation, and the resulting solution was diluted with H_2O and then washed with Et_2O. The aqueous phase was acidified to ca. pH 1 with concentrated HCl, causing formation of a white precipitate that was isolated by filtration. After recrystallization of the solid from EtOAc, 6.7 g (88% yield) of 2-(naphthyl) propanoic acid was isolated as a white crystalline solid: mp 133.5−135 °C (lit.[26] mp 137−138 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.76 (t, J = 7.7 Hz, 2H), 3.11 (t, J = 3.11 Hz, 2H), 7.33 (dd, J = 1.7, 8.5 Hz, 1H), 7.41−7.46 (m, 3H), 7.64, (s, 1H), 7.75−7.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 179.09, 137.61, 133.58, 132.20, 128.20, 127.62, 127.52, 126.86, 126.45, 126.06, 125.46, 35.48, 30.71; IR (KBr) 1693, 1708 cm^{-1}; EI MS *m/e* 200.0826, calcd for $C_{12}H_{12}O_2$ 281.9901.

2-(2-Mesylethyl)naphthalene. To a solution of 1.0 g (5.8 mmol) of 2-naphthylethanol (Aldrich) and 1.2 mL (8.7 mmol) of Et_3N in 30 mL of CH_2Cl_2 at 0 °C was added 0.67 mL (8.7 mmol) of methanesulfonyl chloride. The solution was stirred for 2 h, and then 1 N aqueous HCl was added to the cloudy yellow mixture. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the residue was purified by SiO_2 column chromatography eluting with CH_2Cl_2 to give 1.3 g (90% yield) of the desired mesylate as a white solid that was recrystallized from EtOAc and hexane to give large clear plates: mp 75−76 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.83 (s, 3H), 3.22 (t, J = 6.9 Hz, 2H), 4.54 (t, J = 6.9 Hz, 2H), 7.35 (dd, J = 1.8, 8.5 Hz, 1H), 7.45−7.50 (m, 2H), 7.69 (s, 1H), 7.77−7.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 133.65, 133.26, 132.18, 128.16, 127.46, 127.44, 127.34, 126.85, 126.07, 125.62, 70.05, 36.96, 35.45; IR (KBr) 1123, 1467 cm^{-1}; EI MS *m/e* 250.0667, calcd for $C_{13}H_{14}O_3S$ 250.0664.

2-(2-Iodoethyl)naphthalene. A mixture of 1.7 g (6.6 mmol) of 2-(2-mesylethyl)naphthalene and 6.0 g (40 mmol) of NaI in 35 mL of CH_3CN was stirred for 36 h, and then 20 mL of H_2O was added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the residue was purified by SiO_2 column chromatography eluting with CH_2Cl_2 to give 1.6 g (88% yield) of the desired iodide as an off-white solid that was recrystallized from hexane to give small off-white crystals: mp 77.5−79 °C (lit.[27] mp 81.5−83 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.29−3.49 (m, 4H), 7.31 (dd, J = 1.7, 8.4 Hz, 1H), 7.44−7.51 (m, 2H), 7.64 (s, 1H), 7.78−7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 134.51, 133.18, 132.60, 128.28, 128.21, 127.73, 127.70, 127.23, 126.21, 125.94, 43.59; IR (KBr) no major bands; EI MS *m/e* 155.0844, calcd for $C_{12}H_{11}$ ($M^+ - I$) 155.0861.

Compound 1b. To a solution of 2.0 g (10 mmol) of 2-(naphthyl)-propanoic acid in 30 mL of THF at 0 °C was added 22.7 mL of 1 M LDA (22.7 mmol) at 0 °C followed by 1.6 mL (13.1 mmol) of DMPU. The resulting dark solution was warmed to room temperature over 0.5 h, and then a solution of 5.7 g (20 mmol) of 2-(2-iodoethyl)naphthalene in 20 mL of THF was added. The reaction mixture, which immediately became a clear yellow solution, was stirred 2 h, and then 30 mL of 10% aqueous HCl was added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL); the aqueous phase was saturated with NaCl before the last extraction. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the residue was purified twice by SiO_2 column chromatography, eluting the first column with EtOAc and the second column with 1:1 EtOAc followed by EtOAc. Acid **1b** was isolated as a pale yellow solid, which was recrystallized from EtOAc and hexane to give 1.8 g (50% yield) of white crystals: mp 122−123 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.88−2.00 (m, 1H), 2.06−2.18 (m, 1H), 2.72−3.00 (m, 4H), 3.20 (dd, J = 7.3, 13.5 Hz, 1H), 7.23−7.29 (m, 2H), 7.37−7.46 (m, 4H), 7.55 (s, 1H), 7.59 (s, 1H), 7.71−7.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 181.80, 138.60, 136.16, 133.51, 133.42, 132.19, 132.00, 128.08, 127.94, 127.57, 127.54, 127.51, 127.41, 127.35, 127.20, 127.14, 126.51, 125.98, 125.88, 125.44, 125.20, 46.53, 38.21, 33.59, 33.01; IR (KBr) 1689, 1705 cm^{-1}; EI MS *m/e* 354.1606, calcd for $C_{25}H_{22}O_2$ 354.1620. Anal. Calcd for $C_{25}H_{22}O_2$: C, 84.71; H, 6.26. Found: C, 84.66; H, 6.33.

2-Naphthylmethyl Disulfide. To a solution of 15 g (68 mmol) of 2-(bromomethyl)naphthalene (Aldrich) in 180 mL of CH_3CN was added 5.2 g (68 mmol) of thiourea. The mixture was stirred for 2 h, during which time a substantial amount of white solid formed, and then the solvent was removed by rotary evaporation. The white solid was slurried with 200 mL of H_2O and 100 mL of 1 M aqueous NaOH, refluxed for 3 h, and then stirred at room temperature overnight. The solution was heated until the solid became an oil. After cooling, 200 mL of $CHCl_3$ were added. Iodine was added until a dark color persisted, and then $Na_2S_2O_3$ was added until the dark color was gone. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, 11.6 g (98% yield) of 2-naphthylmethyl disulfide was isolated as a pale yellow solid that was recrystallized from $CHCl_3$ and hexane: mp 127−128 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.71 (s, 4H), 7.33 (dd, J = 1.8, 8.5 Hz, 2H), 7.43−7.54 (m, 6H), 7.74−7.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 134.51, 133.18, 132.60, 128.28, 128.21, 127.73, 127.70, 127.23, 126.21, 125.94, 43.59; EI MS *m/e* 346.0850, calcd for $C_{22}H_{18}S_2$ 346.0850.

Compound 2c. A solid which contained acid **2b** was prepared from 2-(naphthyl)propanoic acid and 2-naphthylmethyl disulfide via a procedure analogous to that used for **1b**. The crude product was adsorbed onto SiO_2 and cleaned by SiO_2 column chromatography eluting with 2:1 EtOAc:hexane, EtOAc, 5% MeOH in EtOAc, and 35% MeOH in EtOAc. The middle fractions were collected, adsorbed onto SiO_2, and repurified by SiO_2 chromatography eluting with 2:1 EtOAc: hexane, 5% MeOH in EtOAc, 10% MeOH in EtOAc, and 50% MeOH in EtOAc. The middle fractions were concentrated to give 4.9 g of a crude solid containing acid **2b**. This material was dissolved in 50 mL of 1:1 MeOH:dioxane. Concentrated HCl (7 mL) was added, and the solution was stirred overnight. The reaction was quenched with water, some of the solvent was removed by rotary evaporation, and the remaining aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate the crude product was purified on five successive SiO_2 columns; the first was eluted with CH_2Cl_2 and the next four were eluted with toluene to give 1.15 g (21% yield from 2-naphthylpropanoic acid) of ester **2c** as a clear oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.02 (dd, J = 7.1, 14.1 Hz, 1H), 3.31 (dd, J = 8.5, 14.1 Hz, 1H), 3.52 (dd, J = 7.1, 8.5 Hz, 1H), 3.62 (s, 3H), 3.95 (ABq, J = 13.6, 2H), 7.12 (dd, J = 1.8, 8.4 Hz, 1H), 7.36 (dd, J = 1.8, 8.5 Hz, 1H), 7.40−7.42 (m, 2H), 7.43 (s, 1H), 7.44−7.46 (m, 2H), 7.62 (d, J = 7.7, 1H), 7.62−7.63 (m, 1H), 7.65 (s, 1H), 7.68 (d, J = 8.5, 1H), 7.71−7.72 (m, 1H), 7.74−7.75 (m, 1H), 7.77−7.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 171.57, 135.18, 134.53, 133.34, 133.14, 132.57, 132.27, 128.35, 127.95, 127.62, 127.52, 127.12, 127.00, 126.16, 125.93, 125.85, 125.52, 52.22, 47.18, 37.69, 36.62; IR (film) 1733 cm^{-1}; EI MS *m/e* 386.1334, calcd for $C_{25}H_{22}O_2S$ 386.1341.

Compound 2b. To a solution of 0.24 g (0.61 mmol) of ester **2c** in 3 mL of MeOH was added 3 mL of 1 N aqueous NaOH. The cloudy white mixture was stirred at room temperature overnight and then heated to reflux for 30 min. The resulting clear solution was cooled to room temperature, and concentrated HCl was added dropwise until the solution was ca. pH 1, causing formation of a white precipitate. This precipitate was isolated by filtration and dried under vacuum in the presence of P_2O_5 for 5 h to give 0.20 g (89% yield) of acid **2b** as a white solid that was recrystallized from EtOAc and hexane: mp 160−161 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.01 (dd, J = 7.5, 14.0 Hz, 1H), 3.32 (dd, J = 7.9, 14.0 Hz, 1H), 3.50 (t, J = 7.7, 1H), 3.99 (ABq, J = 13.6 Hz, 2H), 7.12 (dd, J = 1.6, 8.4 Hz, 1H), 7.34 (dd, J = 1.7, 8.5 Hz, 1H), 7.41−7.49 (m, 5H), 7.61−7.80 (m, 7H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 172.91, 135.95, 135.26, 132.85, 132.75, 132.01, 131.75, 128.04, 127.56, 127.50, 127.46, 127.41, 127.30, 127.26,

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127.21, 127.14, 126.21, 125.96, 125.83, 125.46, 47.53, 37.47, 35.36; IR (KBr) 1680, 1703 cm^{-1}; EI MS *m/e* 372.1189, calcd for $C_{24}H_{20}O_2S$ 372.1184.

Compound 3b was prepared from hydrocinnamic acid (Aldrich) and benzyl disulfide (Aldrich) via a procedure analogous to that used for **1b**. The crude product was purified by SiO_2 column chromatography eluting with 1:2 EtOAc:hexane and then 2:1 EtOAc:hexane containing a drop of AcOH to give 1.14 g (63% yield) of acid **3b** as a yellow oil that solidified upon standing. Recrystallization from hexane gave an off-white solid: mp 62.5−63.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.87 (dd, J = 6.9, 14.2 Hz, 1H), 3.16 (dd, J = 8.6, 14.1 Hz, 1H), 3.39 (dd, J = 6.9, 8.6 Hz, 1H), 3.84 (ABq, J = 13.4 Hz, 2H), 7.05−7.10 (m, 2H), 7.18−7.32 (m, 8H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 178.83, 137.50, 136.86, 129.05, 128.88, 128.40, 128.32, 127.16, 126.64, 47.05, 36.91, 36.23; IR (KBr) 1702, 1709 cm^{-1}; EI MS *m/e* 272.0864, calcd for $C_{16}H_{16}O_2S$ 272.0871.

Compound 5b was prepared from 2-(naphthyl)propanoic acid and ethyl iodide via a procedure analogous to that used for **1b**. The crude product was purified by SiO_2 column chromatography eluting with 1:1 EtOAc:hexane and then EtOAc to give 3.91 g (85% yield) of acid **5b** as a yellow oil that solidified upon standing. The product was repurified using bulb-to-bulb distillation: bp ca. 168−172 °C (0.20 mmHg); mp 49−50 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, J = 7.4 Hz, 3H), 1.55−1.75 (m, 2H), 2.67−2.76 (m, 1H), 2.90 (dd, J = 7.0, 13.7 Hz, 1 H), 3.14 (dd, J = 7.7, 13.7 Hz, 1H), 7.31 (dd, J = 1.8, 8.5 Hz, 1H), 7.42−7.45 (m, 2H), 7.63 (s, 1H), 7.74−7.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 182.24, 136.56, 133.44, 132.15, 127.95, 127.23, 125.92, 125.34, 48.70, 37.70, 24.70, 11.54; IR (KBr) 1702 cm^{-1}; EI MS *m/e* 228.1149, calcd for $C_{15}H_{16}O_2$ 228.1150. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.96; H, 7.20.

Compound 6b was prepared from butyric acid and 2-(2-iodoethyl)-naphthalene via a procedure analogous to that used for **1b**. The crude product was purified by SiO_2 column chromatography eluting with 5% acetone in $CHCl_3$ to give 0.18 g (13% yield) of the desired acid **6b** as a pale yellow oil. The oil was repurified by preparative scale TLC eluting with 1:2 acetone:$CHCl_3$ and then crystallized from hexane to give off-white crystals: mp 58−59.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, J = 7.5 Hz, 3H), 1.59−1.76 (m, 2H), 1.85−1.91 (m, 1H), 2.04−2.12 (m, 1H), 2.37−2.43 (m, 1H), 2.77−2.86 (m, 2H), 7.33 (dd, J = 1.7, 8.5 Hz, 1H), 7.37−7.46 (m, 2H), 7.63 (s, 1H), 7.75−7.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 182.81, 139.02, 133.56, 132.01, 127.93, 127.56, 127.41, 127.19, 126.47, 125.89, 125.17, 46.46, 33.71, 33.20, 25.19, 11.62; IR (KBr) 1703 cm^{-1}; EI MS *m/e* 242.1327, calcd for $C_{16}H_{18}O_2$ 242.1307.

Compound 7c. A mixture of the acid **7b** and 2-naphthylpropanoic acid was prepared from 2-(naphthyl)propanoic acid and ethyl disulfide via a procedure analogous to that used for **1b**. After several attempts at purification of **7b** on SiO_2 and ODS columns, the isolated material was still a mixture of these two acids. Ester **7c** was prepared from crude **7b** via a procedure analogous to that used for **2c**. The crude product was purified by SiO_2 column chromatography eluting with CH_2Cl_2. After purification on two more SiO_2 columns, each eluted with toluene, 0.36 g (13% yield based on 2-naphthylpropanoic acid) of the desired ester **7c** was isolated as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, J = 7.4 Hz, 3H), 2.63 (dq, J = 1.0, 7.4 Hz, 2H), 3.11 (dd, J = 6.3, 13.8 Hz, 1H), 3.36 (dd, J = 9.4, 13.8 Hz, 1H), 3.61 (s, 3H), 3.63 (dd, J = 6.3, 9.4 Hz, 1H), 7.30 (dd, J = 1.6, 8.3 Hz, 1H), 7.37−7.44 (m, 2H), 7.63 (s, 1H), 7.73−7.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 172.16, 135.25, 133.10, 132.00, 127.73, 127.26, 127.25, 127.20, 126.82, 125.67, 125.23, 51.65, 47.39, 37.62, 25.26, 14.05; IR (film) 1733 cm^{-1}; EI MS *m/e* 274.1017, calcd for $C_{16}H_{18}O_2S$ 274.1027.

Compound 7b was prepared from ester **7c** via a procedure analogous to that used for **2b**. The crude product was purified by preparative scale TLC eluting with EtOAc to give acid **7b** as a clear oil that solidified upon standing: mp 70.5−72.5 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.19 (t, J = 7.5 Hz, 3H), 2.64 (dq, J = 1.1, 7.5 Hz, 2H), 3.09 (dd, J = 6.6, 14.0 Hz, 1H), 3.34 (dd, J = 8.7, 14.0 Hz, 1H), 3.61 (dd, J = 6.7, 8.6 Hz, 1H), 7.31 (dd, J = 1.7, 8.5 Hz, 1H), 7.38−7.46 (m, 2H), 7.65 (s, 1H), 7.71−7.79 (m, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 178.31, 135.15, 133.36, 132.34, 128.14, 127.63, 127.60, 127.08, 126.04, 125.61, 47.59, 37.45, 25.96, 14.21; IR (film) 1706 cm^{-1}; EI MS *m/e* 260.0865, calcd for $C_{15}H_{16}O_2S$ 260.0871.

Compound 8b was prepared from butyric acid and 2-naphthylmethyl disulfide via a procedure analogous to that used for **1b**. The crude product was adsorbed onto SiO_2 and purified by SiO_2 column chromatography eluting with 1:1 EtOAc:hexane and then 4:1 EtOAc:hexane to afford 0.8 g (7% yield) of acid **8b** as a pale yellow solid that was recrystallized from $CHCl_3$ and hexane: mp 84.5−85 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.4 Hz, 3H), 1.61−1.70 (m, 1H), 1.82−1.92 (m, 1H), 3.07 (dd, J = 7.2, 7.9 Hz, 1H), 4.02 (ABq, J = 13.4 Hz, 2H), 7.44−7.51 (m, 2H), 7.52 (dd, J = 1.7, 8.4 Hz, 1H), 7.77 (s, 1H), 7.80−7.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 179.25, 134.62, 133.16, 132.59, 128.42, 127.78, 127.73, 127.65, 127.07, 126.19, 125.88, 46.99, 36.31, 24.05, 11.72; IR (film) 1703 cm^{-1}; EI MS *m/e* 260.0886, calcd for $C_{15}H_{16}O_2S$ 260.0871.

Compound 9b was prepared from hydrocinnamic acid (Aldrich) and ethyl disulfide via a procedure analogous to that used for **1b**. The crude product was purified by SiO_2 column chromatography eluting with 1:4 acetone:$CHCl_3$ to give 0.34 g (24% yield) of acid **9b** as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.4 Hz, 3H), 2.67 (dq, J = 1.9, 7.4 Hz, 2H), 2.95 (dd, J = 6.6, 13.9 Hz, 1H), 3.20 (dd, J = 8.9, 13.9 Hz, 1H), 3.52 (dd, J = 6.6, 8.9 Hz, 1H), 7.21−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 178.39, 137.62, 128.86, 128.40, 126.76, 47.62, 37.26, 25.85, 14.15; IR (film) 1705 cm^{-1}; EI MS *m/e* 210.0720, calcd for $C_{11}H_{14}O_2S$ 210.0714.

Compound 10b was prepared from butyric acid and benzyl disulfide (Aldrich) via a procedure analogous to that used for **1b**. The crude product was purified by SiO_2 column chromatography eluting with 1:1 acetone:$CHCl_3$ to give a crude mixture that contained the desired product. This mixture was purified twice more by SiO_2 column chromatography eluting successively with EtOAc and then $CHCl_3$ followed by 3% MeOH in $CHCl_3$ to give 0.22 g (15% yield) of acid **10b** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.59−1.69 (m, 1H), 1.79−1.89 (m, 1H), 3.10 (t, J = 7.4 Hz, 1H), 3.80 (ABq, J = 13.3 Hz, 2H), 7.19−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 178.92, 137.29, 129.07, 128.47, 127.22, 47.25, 36.05, 24.16, 11.74; IR (film) 1704 cm^{-1}; EI MS *m/e* 210.0712, calcd for $C_{11}H_{14}O_2S$ 210.0715.

Compound 8c was prepared from acid **8b** via a procedure analogous to that used for **2c**. The crude product was purified by preparative scale TLC eluting with CH_2Cl_2 to give ester **8c** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 7.3 Hz, 3H), 1.61−1.71 (m, 1H), 1.81−1.91 (m, 1H), 3.11 (dd, J = 6.8, 8.2 Hz, 1H), 3.69 (s, 3H), 3.95 (ABq, J = 13.4 Hz, 2H), 7.45−7.50 (m, 3H), 7.74 (s, 1H), 7.79−7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 173.07, 134.93, 133.19, 132.55, 128.33, 127.67, 127.63, 127.58, 127.08, 126.16, 125.81, 52.11, 47.66, 36.20, 24.58, 11.85; IR (film) 1734 cm^{-1}; EI MS *m/e* 274.1035, calcd for $C_{16}H_{18}O_2S$ 274.1027.

Compound 2d. A solution of 0.32 g (0.82 mmol) of ester **2c** in 3 mL of THF was added dropwise to a slurry of 48 mg (1.3 mmol) of $LiAlH_4$ in 2 mL of THF. The resulting slurry was stirred at room temperature for 1 h and then at reflux for 1 h. After this solution had cooled to room temperature, a freshly prepared solution of saturated aqueous Na_2SO_4 was added dropwise until no additional solid formed. The solids were removed by filtration and rinsed well with THF. Concentration of the filtrate gave 0.25 g of the slightly impure alcohol as a clear oil. This oil was dissolved in 3 mL of THF and added dropwise to a slurry of 34 mg (0.84 mmol) of NaH in 2 mL of THF at 0 °C, followed by 0.24 mL (3.8 mmol) of CH_3I. The resulting solution was stirred at room temperature for 6 h, and then 2 mL of 1% aqueous citric acid was added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the residue was purified by preparative scale TLC eluting with CH_2Cl_2. The desired product **2d** was isolated as 0.18 g (57% yield) of a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.86−2.99 (m, 2H), 3.13 (dd, J = 5.8, 12.7 Hz, 1H), 3.28 (s, 3H), 3.37−3.40 (m, 2H), 3.79 (ABq, J = 13.4 Hz, 2H), 7.19 (dd, J = 1.7, 8.5, 1H), 7.34 (dd, J = 1.8, 8.4 Hz, 1H), 7.37−7.44 (m, 4H), 7.49 (s, 1H), 7.54 (s, 1H), 7.63−7.67 (m, 4H), 7.72−7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 136.48, 135.62, 133.40, 133.14, 132.47, 132.15, 128.29, 127.80, 127.78, 127.68, 127.59, 127.30, 127.08, 126.10, 125.87, 125.71, 125.33, 76.54, 58.85, 45.56, 38.42, 36.30; EI MS *m/e* 372.1541, calcd for $C_{25}H_{24}OS$ 372.1548.

Compound 7d was prepared from ester **7c** via a procedure analogous to that used for **2d**. The crude product was purified by preparative scale TLC eluting with CH_2Cl_2 to afford 0.90 g (53% yield) of the desired product **7d** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, J = 7.4 Hz, 3H), 2.52 (q, J = 7.4, 2H), 2.97 (dd, J = 6.4, 12.6 Hz, 1H), 3.06−3.35 (m, 2H), 3.35 (s, 3H), 3.38−3.49 (m, 2H), 7.36 (dd, J = 1.6, 8.4 Hz, 1H), 7.38−7.47 (m, 2H), 7.66 (s, 1H), 7.75−7.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 136.58, 133.36, 132.11, 127.74, 127.67, 127.52, 127.47, 125.81, 125.26, 74.69, 58.74, 46.26, 38.50, 25.37, 14.79; EI MS *m/e* 260.1236, calcd for $C_{16}H_{20}OS$ 260.1235.

Compound **8d** was prepared from acid **8b** via a procedure analogous to that used for **2d**. The crude product was purified by SiO_2 column chromatography eluting with 1:5 EtOAc:hexane to afford 0.20 g (51% yield) of the desired product **8b** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7.0 Hz, 3H), 1.33−1.65 (m, 4H), 2.67−2.76 (m, 1H), 3.31 (s, 3H), 3.41−3.94 (m, 2H), 3.94 (ABq, J = 13.4, 2H), 7.43−7.47 (m, 2H), 7.51 (dd, J = 2.0, 8.6, 1H), 7.72 (s, 1H), 7.77−7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 136.04, 133.18, 132,43, 128.22, 127.59, 127.55, 127.19, 127.15, 126.03, 125.62, 76.27, 58.80, 44.13, 36.00, 33.86, 19.89, 13.91; EI MS *m/e* 274.1375, calcd for $C_{17}H_{22}OS$ 274.1391.

Compound 2e. A mixture of 0.47 g (2.7 mmol) of freshly prepared 2-naphthylmethanethiol,[28] 0.38 g (2.7 mmol) of K_2CO_3, and 0.56 g (2.2 mmol) of 2-(2-mesylethyl)naphthalene in 12 mL of CH_3CN was stirred at room temperature for 12 h, during which time a fluffy white solid formed. The mixture containing the starting mesylate was then heated at reflux for 4 h and stirred at room temperature for 20 h. After rotary evaporation of the solvent, the residue was partitioned between $CHCl_3$ and H_2O, and the solution was acidified with 8 mL of 10% aqueous HCl. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 8 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After concentration of the filtrate, the crude product was purified by SiO_2 column chromatography eluting with 3% EtOAc in hexane to give a mixture of the desired product and 2-naphthylmethyl disulfide. The mixture was dissolved in 1 mL of THF, and a few drops of *sec*-BuLi were added. The resulting solution was loaded onto preparative scale TLC plates, which were eluted with 1:2 CH_2Cl_2:hexane. The desired product **2e** was isolated as a white solid (19 mg, 3% yield) that was recrystallized from $CHCl_3$: mp 102−103.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71−2.76 (m, 2H), 2.96−3.02 (m, 2H), 3.87 (s, 2H), 7.24 (dd, J = 1.7, 8.4, 1H), 7.40−7.50 (m, 5H), 7.53 (s, 1H), 7.66 (s, 1H), 7.70−7.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 137.90, 135.68, 133.48, 133.21, 132.52, 132.13, 128.41, 127.98, 127.67, 127.58, 127.47, 127.27, 127.08, 127.04, 126.75, 126.17, 125.95, 125.74, 125.33, 36.80, 36.20, 32.59; EI MS *m/e* 328.1284, calcd for $C_{23}H_{20}S$ 328.1286.

Compound 7e was prepared from 2-(2-iodoethyl)naphthalene and ethanethiol via a procedure analogous to that used for **2e**. The crude product was purified by SiO_2 column chromatography eluting with 5% EtOAc in hexane to afford 0.24 g (32% yield) of the desired product **7e** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.4 Hz, 3H), 2.57 (q, J = 7.4 Hz, 2H), 2.83−2.88 (m, 2H), 3.01−3.07 (m, 2H), 7.33 (dd, J = 1.7, 8.4 Hz, 1H), 7.41−7.45 (m, 2H), 7.64 (s, 1H), 7.76−7.81 (m, 2H), 7.77 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 138.13, 133.52, 132.15, 128.02, 127.61, 127.47, 127.03, 126.65, 125.97, 125.33, 36.44, 33.07, 26.10, 14.76; EI MS *m/e* 216.0964, calcd for $C_{14}H_{16}S$ 216.0973.

Compound 8e was synthesized from freshly prepared 2-naphthylmethanethiol[28] and iodobutane via a procedure analogous to that used for **2e**. The crude product was purified twice by SiO_2 column chromatography eluting first with 2% EtOAc in hexane and then with hexane to give 0.57 mg (59% yield) of the desired product **8e** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 7.3 Hz, 3H), 1.31−1.39 (m, 2H), 1.50−1.57 (m, 2H), 2.40 (t, J = 7.4 Hz, 2H), 3.84 (s, 2H), 7.43−7.50 (m, 3H), 7.68 (s, 1H), 7.76−7.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 135.94, 133.17, 132.42, 128.24, 127.58, 127.52, 127.07, 126.03, 36.43, 31.21, 30.84, 21.91, 13.63; EI MS *m/e* 230.1124, calcd for $C_{15}H_{18}S$ 230.1129.

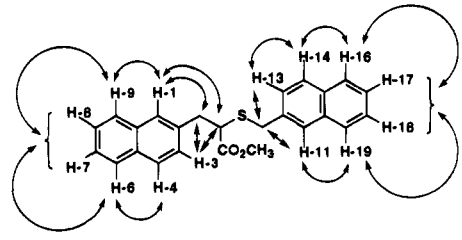
Preparation of Na Salts. To prevent contamination with divalent cations, all glassware was soaked for a minimum of 12 h in a Nochromix (Gooax Laboratories) acid bath and then rinsed three times with distilled H_2O and then three times with Millipore H_2O. Acids were dried at room temperature in the presence of P_2O_5 under vacuum and then weighed in air on a pre-tared balance. The acids were slurried in Millipore H_2O, and 1.02−1.20 equiv of a standardized solution of semiconductor grade NaOH in Millipore H_2O was added. The dinaphthyl salt solutions were stirred for 24 h. If undissolved material was present, it was removed by gravity filtration through filter paper. H_2O was removed by lyophilization.

Preparation of D_2O NMR Samples. All glassware was acid washed (see above). NMR tubes were soaked in either H_3PO_4 or HNO_3 for a minimum of 12 h and then rinsed multiple times with Millipore H_2O and dried under a stream of N_2. The salts were dried at room temperature or 100 °C in the presence of P_2O_5 under vacuum. All manipulations were performed in a N_2 glovebag. Salts were dissolved in D_2O, and the concentration of the solution was determined by UV spectroscopy (ϵ(276) = 4600 for 2-naphthyl, ϵ(258) = 200 for substituted phenyl), and then the stock solution was diluted to the desired concentration. For variable-concentration ^{1}H NMR studies, all dilutions were made from the stock solution.

Preparation of NMR Samples in Organic Solvents. The appropriate compound was dissolved in either $CDCl_3$, for studies in $CDCl_3$, or $CHCl_3$, for studies in other solvents, and the concentration of the solution was determined by UV spectroscopy (ϵ(276) = 4600 for 2-naphthyl, ϵ(258) = 200 for substituted phenyl). For studies performed in $CDCl_3$, the stock solution was diluted to the desired concentration. For studies performed in other solvents, a known amount of the stock solution was placed in a small round-bottom flask, the solvent was removed by evaporation, and the compound was placed under vacuum for 12 h. A known amount of the appropriate solvent was then added to the compound to make a solution of the desired concentration.

NMR Studies. The solubility of Na salts in D_2O was found to vary depending on the lot of D_2O, presumably because the amount of divalent counterions varies by lot. D_2O from Cambridge Isotope Laboratories (either 99.9% D in glass bottles, or 99.96% D that had been glass distilled and stored in plastic bottles) in which salt **2a** was soluble to at least 0.10 mM was used for these studies. Since an excess of NaOH was used in the preparation of the Na salts, solutions of the salts were basic; for example, a 200 mM solution of salt **5a** in Millipore-filtered H_2O was pH 11.9. Sequanal grade urea (from Pierce) was deuterated in an acid-washed flask (see above) by three lyophilizations from D_2O. The urea-d_4 was dried under vacuum in the presence of P_2O_5 for 48 h and then stored under N_2 in a desiccator containing $CaSO_4$ (Drierite).

Spectra obtained in D_2O or 8 M urea in D_2O were referenced to an external standard of a dilute solution of TSP (sodium 3-(trimethylsilyl)-propionate-*2,2,3,3-d*$_4$) in D_2O. The z and z^2 shims for the reference could be adjusted so that the TSP signal was a singlet without changing the absolute frequency of the TSP signal. Since the TSP signal is temperature sensitive (it changes 29.2 Hz over 5 °C), the temperature was controlled for all samples and the reference. Room temperature spectra were obtained at 24 °C. ^{1}H NMR studies of dilute D_2O solutions and all 2-D NMR studies were performed on a Varian Unity 500 spectrometer. All other ^{1}H NMR studies were performed on either a Bruker WP-270 or AM-500 spectrometer. All spectra for a concentration study of a specific compound were acquired on the same day. Due to line widths, instrument drift, and uncertainty associated with assigning the chemical shifts of peaks that are multiplets, the uncertainty in NMR assignments is ±0.02 ppm. All assignments were made from at least two independently referenced spectra.



NOE signals observed in 2c

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Two-Dimensional ^{1}H NMR Studies. All signals in ^{1}H NMR spectra of **2a−c** were assigned using both NOESY and TOCSY experiments. The spectra of **2a−c** are similar in all solvents examined, and the spectra of acid **2b** and ester **2c** in $CDCl_3$ are nearly identical. Since ester **2c** is substantially more soluble in $CDCl_3$, without apparent aggregation, than acid **2b**, a NOESY[24] experiment was performed on a 45 mM sample of ester **2c** in $CDCl_3$ using a sweep width of 5000 Hz and a mixing time of 1.0 s. The protons between which NOE enhancements were observed are shown above. The two naphthyl rings were differentiated by the NOE enhancements between the methylene protons on the linking chain and the aromatic protons H-1 and H-3, or H-11 and H-13. Further assignments were made by a TOCSY[29] experiment on the aromatic region using a sweep width of 1275 Hz. The TOCSY spectrum showed four coupled spin systems: (H-1, H-3, H-4); (H-11, H-13, H-14); (H-6, H-7, H-8, H-9); (H-16, H-17, H-18, H-19). The TOCSY spectrum allowed for assignment of most of the naphthyl proton resonances, but H-6 and H-9 could not be differentiated, nor could H-16 and H-19. The resonances of H-6 and H-9, and of H-16 and H-19, were assigned on the basis of NOE enhancements observed in the NOESY spectrum. All chemical shift assignments in D_2O at 24 °C, D_2O at 88 °C benzene-d_6, and $CDCl_3$ were made from TOCSY spectra of the appropriate mononaphthyl or dinaphthyl compound.

Dye Uptake Studies. An aqueous solution containing a carboxylate of known concentration and suspended orange OT [(1-*o*-tolylazo)-2-naphthol], was rocked for a minimum of 24 h. Solid dye was removed by filtration through cotton, and the filtrate was examined visually for the presence of color. If any color was present, the solution was checked by UV spectroscopy for absorbance at 500 nm.

(29) Braunschweiler, L.; Ernst, R. R. *J. Magn. Reson.* **1983**, *53*, 521.

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Supplementary Material Available: ^{1}H NMR comparisons involving dinaphthyl and diphenyl and appropriate monoaryl reference compounds, data from aggregation control studies, and crystallographic data for **1b** and **2b** (32 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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