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Aromatic Stacking in Folded Architectures through Hydrogen Bonding

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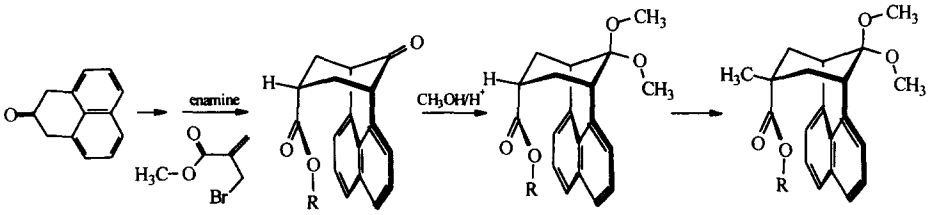
Abstract: The α, α′-annelation of the enamine of 1,3-dihydro-2-phenalenone with methyl α-(bromomethyl)acrylate affords an aromatic bicyclic framework, methyl 8,9,10,11-tetrahydro-7,11-methano-12-keto-7H-cyclooocta(*de*)naphthalene-9-*endo*-carboxylate having the ester function positioned over the aromatic ring. The acid derivatives of this framework dimerize affording a "sandwich" structure with the H-bonded carboxyl groups between parallel naphthalene rings. The dimeric association can be easily probed using both NMR and fluorescence techniques. © 1997 Elsevier Science Ltd.

Chemical investigations of molecular recognition processes depend upon the construction of molecular architectures which position both the attractive and repulsive attributes of the structure(s) so that one molecule may strongly associate with another.[2] To define these interactions in solution, it is necessary for the structure(s) to contain elements which provide a mechanism for documenting that contact and association.[3-6] Carboxylic acid functions, through dimer formation, allow the assembly of molecular units. These units, because of their architecture, usually position themselves in a linear or sheet-like fashion.[7] To create 3-dimensional aggregation, these functions have been placed on scaffolds which constrain the associating elements in specific directions[8] and the most popular architectures are derived from Kemp's triacid.[9] The α, α′-annelation, a reaction studied by our group over many years[10,11] provides a simple ability to fabricate bicyclic architectures (folded or U-shaped structures[12]) having constrained carboxylic acid functions and aromatic rings.[13]



1 **2** **3** **4** R=CH_3, **5** R=H **6** R=CH_3, **7** R=H

Scheme 1

The basic frameworks for this study were constructed in a single step from the enamine of 1,3-dihydro-2-phenalenone[14-17][**1**] and methyl α-(bromomethyl)acrylate [**2**] to produce bicyclic methyl 8, 9, 10, 11-tetra-hydro-7, 11-methano-12-keto-7H-cycloocta(*de*)naphthalene-9-*endo*-carboxylate[18][**3**]. The framework is fashioned through consecutive alkylation, intramolecular Michael addition and kinetic protonation[10] affording

the consequent *axial* (*endo*) ester group positioned directly over the naphthalene π system [**3**]. The 12,12-dimethyl ketal[19] [**4**] of the strained ketone was rapidly and easily formed using methanol and a trace of *p*-TSA. Basic hydrolysis of the highly hindered keto esters [either **3** or **4**] results in concomitant isomerization with formation of both equitorial and axial acids [**5** *axial & equitorial*]. Acidic hydrolysis also results in isomerization. To avoid this problem, the α-anion of ketal ester **4** was produced and alkylated with methyl iodide to give the corresponding 9-α-substituted *axial* ester[20] **6** (99%) which was then hydrolyzed [KOH/ethylene glycol, reflux] to the corresponding acid[21] [**7**].

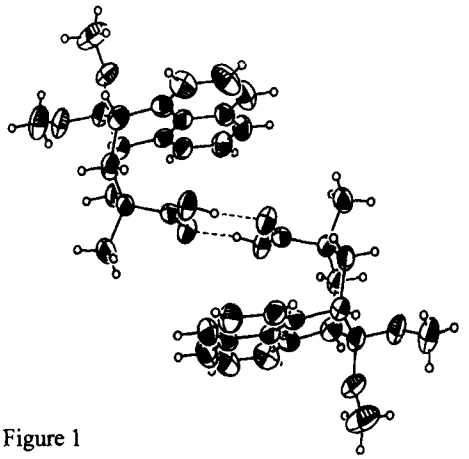
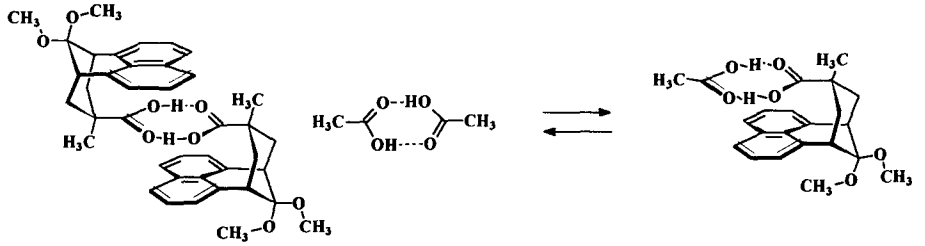


Figure 1

The initial clue that the architecture of the acid was dimeric and "stacked" came from a comparison of the NMR characteristics of the ester **6** and acid **7**. The aromatic ring protons of the acid **7** (H-6, 7.12 δ; H-7, 7.26 δ; H-8, 7.41 δ) showed a considerable shielding compared to that of the ester **6** (H-6, 7.28 δ; H-7, 7.43 δ; H-8, 7.65 δ) suggesting the "stacked" dimeric acid structure **8** with each naphthalene ring shielding the other.

An X-ray crystallographic study confirmed the dimeric assemblies and that the structure has stacked aromatic rings and a "sandwiching" of the dimer carboxyl groups between those rings in the solid state[Figure 1, X-ray].[22] The equilibrium character of carboxylic acid H-bonding allows an exchange of one partner for another and, combined with the positioned aromatic rings, provides for a variety of physical and chemical techniques for defining the solution assembly and associations in these molecules. The 3 Å proximity of the aromatic naphthalene ring and the carboxyl function generates other remarkable chemical interactions.[23]



8 **9** **10**

Scheme 2

The parallel naphthalene rings are about 6 Å from one another. That the solution NMR shielding effects were due to dimer formation was tested by incremental addition of d^4-acetic acid to the NMR sample solution ($CHCl_3$) of the dimer acid **8**. The equilibrium formation [Scheme 2, **8** + **9** ⇄**10**] of a mixed-dimer acid **10** (H-6,

7.23 δ; H-7, 7.35 δ; H-8, 7.59 δ) resulting in loss of the corresponding shielding effect was easily recognized (compare symmetrical dimer **8**, H-6, 7.12 δ; H-7, 7.26 δ; H-8, 7.41 δ with mixed-dimer **10** or ester **6**). The equilibrium constant for the dimer/acetic acid ⇄ mixed-dimer **10** is 1.0 as determined by NMR titration measuring the shift of the protons [becoming less shielded] on C-3 as well as the proton shift of the methyl of non-deuterated acetic acid titrant [becoming more shielded]. Interestingly, the acidic protons of the dimer **8** could not be observed in the NMR (search range from +20 to -10 δ) though the proton was easily observed when the spectrum of **8** was taken in DMSO(δ = 10.68), this solvent causing dis-aggregation. The equilibrium exchange effect was also observed in the fluorescence spectra of **8**. Addition of acetic acid [**9**] to a CH_2Cl_2 solution of the acid dimer [**8**] results in an enhancement (~35%) of the fluorescence as the quenching effect of the neighboring naphthalene is removed. These spectroscopic elements suggest potential applications to the design of "molecular switches".

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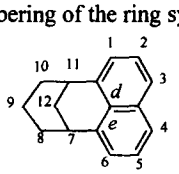
18 Compound **3**: 76% yield as a pale yellow microcrystalline solid; mp 131-133°C; FT IR (KBr) 3037, 2930, 2853, 1762, 1735, 1721, 1596, 1250, 1200, 821, 780; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, *J* = 8,4, 1.0 Hz, 2 H), 7.50 (dd, *J* = 8.4, 7.5 Hz, 2 H), 7.27 (dd, *J* = 7.5, 1.0 Hz, 2 H), 3.88 (t, *J* = 2.6 Hz, 2 H), 3.07-3.02 (m, 2 H), 2.63-2.59 (m, 1 H), 2.61 (s, 3 H), 2.53-2.47 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 210.8, 172.0, 136.6, 132.4, 129.1, 126.4, 126.3, 124.2, 52.3, 50.82, 37.7, 34.2; Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.25; H, 5.74· The CA numbering of the ring system is:



19 Compound **4**: white crystalline solid; mp 113-114°C; FT IR (KBr) 2937, 1729, 1209, 1150, 1052; ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, *J* = 8.3, 1.0 Hz, 2 H), 7.43 (dd, *J* = 8.3, 6.8 Hz, 2 H), 7.28 (dd, *J* = 6.8, 0.9 Hz, 2 H), 3.53 (t, *J* = 2.6 Hz, 2 H), 3.39 (s, 3 H), 3.02 (s, 3 H), 2.54-2.50 (m, 2 H), 2.52 (s, 3 H), 2.43 (t, *J* = 2.8 Hz, 1 H), 2.37-2.32 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 137.5, 132.4, 129.9, 125.9, 124.5, 100.0, 50.7, 47.29, 47.26, 41.0, 33.7, 30.1; MS: 326 (M+), 295, 263, 203, 165; HRMS Calcd. for $C_{20}H_{22}O_4$ (M)+: 326.1518. Found: 326.1523.

20 Compound **6**: Methyl 12,12-dimethoxy-9-*exo*-methyl-8,9,10,11-tetrahydro-7,11-methano-7H-cycloocta-[*de*]naphthalene-9-*endo*-carboxylate. mp 72°C; FT IR (KBr) 2934, 1720, 1312, 1214, 1126, 1112, 1054; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, *J* = 8.3, 1.0 Hz, 2 H), 7.41 (dd, *J* = 8.3, 6.9 Hz, 2 H), 7.25 (dd, *J* = 6.9, 0.9 Hz, 2 H), 3.51 (t, *J* = 2.5 Hz, 2 H), 3.38 (s, 3 H), 3.00 (s, 3 H), 2.59-2.54 (m, 2 H), 2.43 (s, 3 H), 2.03-1.98 (m, 2 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.0, 137.8, 132.6, 129.9, 126.05, 126.0, 124.5, 100.4, 50.9, 47.6, 47.4, 41.8, 38.7, 38.6, 30.3; MS: 340 (M+), 309, 277, 217, 165; HRMS Calcd. for $C_{20}H_{22}O_4$ (M)+: 340.1675. Found: 340.1658; Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.71; H, 7.19.

21 Compound **7**: mp 253°C; FT IR (KBr) 3200-2400, 2928, 1694, 1321, 1114, 1072, 1062, 776; ^{1}H NMR ($CDCl_3$) d 7.41 (dd, *J* = 8.3, 1.0 Hz, 2 H), 7.26 (dd, *J* = 8.3, 6.9 Hz, 2 H), 7.12 (dd, *J* = 6.9, 0.9 Hz, 2 H), 3.45-3.41 (m, 2 H), 3.35 (s, 3 H), 2.97 (s, 3 H), 2.41-2.35 (m, 2 H), 1.95-1.91 (m, 2 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) d 180.4, 137.3, 132.3, 129.8, 125.95, 125.91, 100.3, 47.6, 47.4, 41.7, 38.43, 38.39, 30.0; MS: 326 (M+), 295, 263, 217, 165; HRMS Calcd. for $C_{20}H_{22}O_4$ (M)+: 326.1518. Found: 326.1522.

22 Structure confirmed by Xray crystallographic structure. See supplemental experimental.

23 Intermediates in the electrophilic attack on the naphthalene ring can be captured by the neighboring carboxylic acid anion. Results to be published.

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