Molecular Receptor Design for the Complexing of Dibutylmalonic Acid

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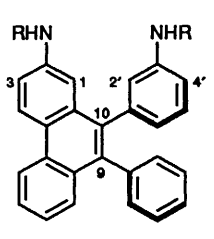
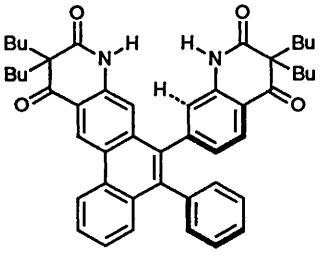
The synthesis and binding properties of compounds with the basic structure of 2-amino-10-(3-aminophenyl)-9-phenylphenanthrene **1** are described. The key steps were the formation of the tetrasubstituted alkene **9** and its photocyclization to a diphenylphenanthrene skeleton. The more rigid bilactam **2** and the bis-diethylaminophosphonate **3** are good receptors for binding malonic acid derivatives in chloroform, *via* four-point hydrogen-bonding interactions.

Since molecular recognition, the specific interaction of substrates with receptors,[1] is of great importance in enzymatic catalysis,[2] the development of artificial receptors for neutral molecules representing an important synthetic challenge. Recent reports have shown that molecules containing several hydrogen-bonding groups directed into a cleft can effectively recognize their complementary substrates.[3] We have developed a relatively rigid molecular framework that organizes hydrogen bonding sites for effective complexation of malonic acid derivatives which can form at least four hydrogen bonds. Malonic acid is a good target guest because it has a well defined geometry; moreover, malonic acid selective hosts may be applied to amino acid synthesis if amidomalonic acid derivatives are used.[4]

Complexation Properties.—The selected semirigid receptor presents functional groups that, according to Corey–Pauling–Koltun (CPK) models, converge on a well-defined molecular cleft. This structure has a basic skeleton of 9,10-diphenylphenanthrene **1**, with two amino groups in appropriate positions (synthesis is discussed below). By varying the R substituents on the N atoms, several hydrogen-bonding receptors become readily available, the one with amide functions being one of the most attractive. Dibutylmalonic acid (DBMA) was chosen as the guest because of its solubility in chloroform.



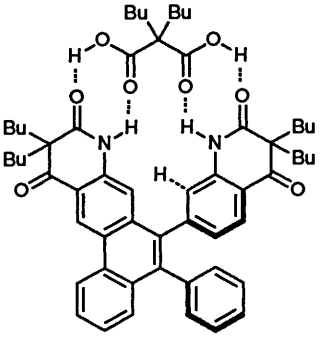


2

1 R = H
3 R = P(O)(OEt)$_2$
4 R = CO_2CH_2Ph

We have synthesized the symmetric cyclic bilactam **2** in order to confer a more rigid structure to both sides and to cancel rotational degrees of freedom. The 1:1 complex of dibutylmalonic acid with the cleft **2** can be viewed as a four-point hydrogen-bonded complex **5**.

The complexation properties of the receptor were studied by ^{1}H NMR spectroscopy. Titration experiments in $CDCl_3$ between the receptor and the malonic substrate led to characteristic changes in the receptor spectra showing downfield shifts mainly for NH, 1-H and 2′-H. The 2-H of the receptor, which is *ortho* to the NH, is shifted from δ 6.537 to δ 6.731 at saturation binding ($\Delta\delta_{sat}$ 0.194). We monitored this chemical shift change as a function of the malonic derivative concentration and obtained a value† of $K_s = (3.2 \pm 0.7) \times 10^3$ dm^3 mol^{-1}.



5

As expected, with DBMA the bis-benzyloxycarbonyl derivative **4** shows a smaller association constant, $K_s = (5.2 \pm 0.4) \times 10^2$ dm^3 mol^{-1}, due to the freezing of conformational degrees in the complex and the consequent loss of entropy. However, the bis-diethylaminophosphonate **3**, which also shows a high chain mobility, presents $K_s = (3.0 \pm 0.5) \times 10^3$ dm^3 mol^{-1}, close to that of complex **5**. Probably the strong degree of polarization of the P–O bond makes this oxygen a very good hydrogen bond acceptor.

Owing to our parallel interest in research into complexing agents for urea and urea derivatives,[5] we checked the association properties of **2** with the cyclic urea 5,5-dibutyltetrahydropyrimidin-2-one in $CDCl_3$, plotting the chemical shifts of the methylenes of this substrate. The results point to a loss of association with a value of $K_s = (1.7 \pm 0.5) \times 10^2$ dm^3 mol^{-1} in agreement with the reported data for unidentate binding.[6] Therefore, structure **2** is a better spacer for malonic acid than for urea derivatives.

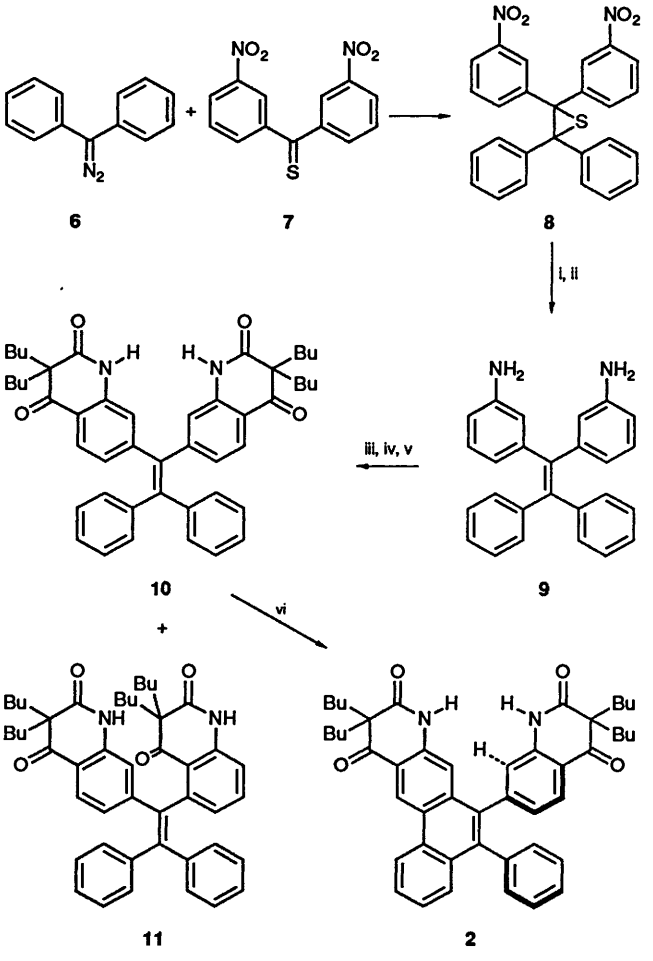
Syntheses of Receptors.—Substrate **2** was prepared from benzophenone. The key steps of the synthesis were formation of the tetrasubstituted alkene and cyclization to a diphenylphenanthrene skeleton.

The synthesis of the thione **7** was carried out starting

† Association constants (K_s) are apparent (calculation does not include host or guest self-association). They were measured using a 200 MHz ^{1}H NMR spectrometer at 20 °C, employing a specially adapted Montecarlo curve-fitting computer program.

from 3,3'-dinitrobenzophenone by reaction with Lawesson's reagent.[7] The deep blue product obtained was unstable and was used directly in the next step. Therefore, a small portion of the reaction mixture was dissolved in $CDCl_3$; the ^{13}C NMR spectra showed shifts at δ 231.6 for C=S in compound **7** and δ 191.8 for C=O in dinitrobenzophenone, in full agreement with the relation described between both in the literature.[8]

Compound **7** reacted quickly with the diphenyldiazomethane **6** at room temperature, with nitrogen elimination and decolourization to afford the crystalline episulfide **8** in 75% yield (Scheme 1). Its ^{13}C NMR shows two quaternary carbons bonded to the S atom at δ 67.5 and 63.8.



Scheme 1 *Reagents and conditions:* i, Ph_3P; ii, Fe–AcOH; iii, $ClCOC(Bu)_2CO_2Et$; iv, Na^+EtO^-; v, polyphosphoric acid; vi, *hv*, I_2, $MeCHCH_2O$

Desulfurization with triphenylphosphine gave the alkene in 85% yield; the quaternary carbons are shifted to δ 146.0 and 144.2 (alkenic).

Cyclization of the aromatic rings was achieved through the reduction of nitro groups to amines **9** (80% yield), acylation with the chloride of the monomethyl ester from dibutylmalonic acid, and acid ring closure (57% total yield). In this last step, two compounds were obtained by cyclization of different sides. The likely target **10** and the unlikely cyclized product **11** are at a ratio 3:1.

In its ^1H NMR spectrum compound **10** shows signals of a symmetric molecule with a 1,2,4-substituted aromatic system. On the other hand, the minor isomer shows a 1,2,3-substituted benzene ring in addition to the preceding system. The assignments were made by double irradiation experiments.

The tetraphenylethylene system of compound **10** was converted photochemically into a 9,10-diphenylphenanthrene system. Toluene solutions were irradiated with UV light for 1 h with iodine as oxidant[9] in the presence of propylene oxide to remove the HI generated. The ^1H NMR showed characteristic signals of a phenanthrene where protons 4-H and 5-H of this system had displacements at δ 9.48 (s) and 8.85 (d, J 8.4 Hz), respectively. The yield of compound **2**, based on the transformed product, was 95%. The same photocyclization reactions of compounds **3** and **4** were complete.

A second ring closure did not occur even on prolonged irradiation under similar conditions. The diamine **9** underwent only a single photocyclization, as described in the literature, because of the presence of the phenanthrene system.[10]

The synthesis of 5,5-dibutyltetrahydropyrimidin-2-one was achieved from malononitrile by alkylation with butyl chloride and later treatment with $LiAlH_4$ and phosgene.

We conclude that the molecular architecture of structure **1** effectively preorganizes hydrogen bonding sites for complexing malonic acids. Current efforts are directed toward the development of an artificial amidomalonic acid decarboxylase in an approach to an enantioselective amino acid synthesis using this molecular model receptor.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60, 230–400 mesh, and TLC on silica gel Merck 60, F_{254}. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 and 50.3 MHz respectively. Chemical shifts (δ) are reported with Me_4Si as internal standard; J values are recorded in Hz. IR spectra were determined on a Beckman 33-IR spectrophotometer. Mass spectra were measured on a VG-TS-250 spectrometer (electron impact 70 eV). Elemental analyses were carried out using a Perkin-Elmer 240 B Analyser. The photoirradiations were made with a Hanovia 450-W high-pressure quartz Hg-vapour lamp.

1,2-Epithio-1,1-bis(3-nitrophenyl)-2,2-diphenylethylene **8**.—*3,3'-Dinitrobenzophenone.* A mixture of nitric acid (*d* 1.5; 3 cm^3) and concentrated sulfuric acid (7.5 cm^3) was added dropwise to a solution of benzophenone (5 g, 27.4 mmol) in concentrated sulfuric acid (30 cm^3) at room temperature; the mixture was then slowly heated to 75 °C, and kept at this temperature for 30 min. The solution was cooled and poured over crushed ice. The pasty mass, washed free of acid, gave 3,3'-dinitrobenzophenone (6.7 g, 90%), m.p. 152 °C (from acetone).

3,3'-Dinitrothiobenzophenone **7**. The above ketone (3.5 g, 12.8 mmol) and the dimer of *p*-methoxyphenylthionophosphine sulfide (3.5 g, 8.6 mmol) in anhydrous toluene (15 cm^3) were kept under N_2 at 110 °C until all the ketone had been consumed (TLC); moisture was strictly excluded. The mixture was then allowed to cool and subsequently passed down a silica gel column (hexane–EtOAc, 9:1) to give a deep blue solution of the thioketone **7**, used directly in the next step.

Diphenyldiazomethane **6**. Lead tetraacetate (8.8 g, 19.8 mmol) in dichloromethane (50 cm^3) was added dropwise over 45 min to a stirred solution of benzophenone hydrazone (3 g, 15.3 mmol) in dichloromethane (40 cm^3) and triethylamine (50 cm^3) at −20 °C, with the immediate appearance of the crimson diazo compound. The solution was allowed to warm to 20 °C when the solid was removed by filtration through Celite, and the organic layer was washed with water and dried. Evaporation of the solvent gave the diazomethane **6** (2.8 g, 95%) as a crimson solid (m.p. 32 °C).

A solution of the diazomethane **6** was added to a stirred solution of the thioketone **7** to give immediate decolourization;

solvent removal and recrystallisation afforded the episulfide **8** (75%) as colourless crystals, m.p. 178–180 °C (from EtOAc) (Found: C, 68.7; H, 3.9; N, 6.1. $C_{26}H_{18}N_2O_4S$ requires C, 68.8; H, 4.0; N, 6.2%); δ_H 7.05–7.25 (10 H), 7.20 (2 H, t, *J* 8), 7.45 (2 H, dt, J_1 8, J_2 2.2), 7.93 (2 H, ddd, J_1 8, J_2 2.3, J_3 2.2) and 8.01 (2 H, t, *J* 2.2); δ_C 63.8 (1 C, s), 67.5 (1 C, s), 122.3, 125.6, 126.5, 127.5, 127.7, 128.4, 130.6, 136.4 (18 C, d), 138.3 (2 C, s), 141.4 (2 C, s) and 147.6 (2 C, s); *m/z* 455 (M^+ + 1, 49%), 454 (18), 423 (100), 289 (18), 252 (43), 165 (88), 121 (25) and 96 (9).

1,1-*Bis*(3-*aminophenyl*)-2,2-*diphenylethylene* **9**.—1,1-*Bis*(3-*nitrophenyl*)-2,2-*diphenylethylene*. Ph_3P (4.5 g, 17.2 mmol) was added to a solution of episulfide **8** (3 g, 6.6 mmol) in anhydrous THF (45 cm^3) and heated at 80 °C under nitrogen for 16 h. Evaporation of the solvent followed by flash chromatography of the residue (hexane–EtOAc, 95:5) afforded 1,1-bis(3-nitrophenyl)-2,2-diphenylethylene (2.5 g, 85%), colourless, m.p. 185–186 °C (from MeOH) (Found: C, 74.0; H, 4.1; N, 6.6. $C_{26}H_{18}N_2O_4$ requires C, 74.0; H, 4.3; N, 6.6%); δ_H 6.86–7.04 (10 H), 7.16 (2 H, t, *J* 8), 7.24 (2 H, dt, J_1 8, J_2 2), 7.74 (2 H, t, *J* 2) and 7.87 (2 H, dt, J_1 8, J_2 2); δ_C 122.1, 125.9, 127.8, 128.3, 129.1, 131.0, 137.2 (18 C, d), 136.2 (2 C, s), 141.7 (2 C, s), 144.2 (1 C, s), 146.0 (1 C, s) and 148.2 (2 C, s); *m/z* 422 (M^+, 100%), 327 (17), 252 (28), 150 (18) and 77 (13).

The dinitro compound (2.2 g, 5.2 mmol) was dissolved in absolute ethanol (100 cm^3) and glacial acetic acid (4 cm^3) and reduced iron (2 g, 35.8 mmol) was added to the solution which was then stirred and refluxed in ethanol for 3 h. Collection by filtration of the solid was followed by evaporation of the organic solvent and addition of aqueous $NaHCO_3$. After extraction with EtOAc, the organic solution as dried (Na_2SO_4) and concentrated to afford a white solid **9** (1.5 g, 80%), m.p. 210–211 °C (from $CHCl_3$–hexane) (Found: C, 86.1; H, 6.1; N, 7.7. $C_{26}H_{22}N_2$ requires C, 86.3; H, 6.1; N, 7.7%); δ_H 3.20 (4 H), 6.38 (2 H, d, *J* 1.5), 6.40 (2 H, dt, J_1 8, J_2 1.5), 6.44 (2 H, dt, J_1 8, J_2 1.5), 6.86 (2 H, dt, J_1 8, J_2 0.6) and 7.01–7.11 (10-H); δ_C 113.5, 118.2, 122.2, 126.3, 127.6, 128.4, 131.2 (18 C, d), 141.0 (2 C, s), 141.7 (2 C, s), 143.9 (1 C, s), 144.8 (1 C, s) and 145.7 (2 C, s); *m/z* 362 (M^+, 100%), 344 (27), 327 (10), 269 (100), 252 (57), 181 (83), 165 (50) and 93 (51).

7,7′-(*Diphenylvinylidene*)*bis*(3,3-*dibutyl*-1H-*quinoline*-2,4-(1H,3H)-*dione*) **10**.—Treatment of the ethylene **9** (1 g, 2.7 mmol) with methyl hydrogen dibutylmalonate (1.5 g, 5.7 mmol) in triethylamine (0.58 g) gave the diester, which was treated with ethanolic NaOH (10%) and maintained at reflux for 0.5 h. The mixture was placed in water and extracted with chloroform; the aqueous layer was treated with HCl (2 mol dm^{-3}) (to isoelectric point) and then extracted with chloroform. The combined organic layers were dried (Na_2SO_4) to give, after evaporation of the solvent, a brown solid (1 g) which was dissolved in polyphosphoric acid; phosphorus pentoxide was then added and the mixture heated at 90 °C for 1.5 h. Addition of aqueous hydrogencarbonate and extraction with ethyl acetate gave a mixture which was flash chromatographed (hexane–EtOAc, 9:1) to give the dione **10** (474 mg, 45%); m.p. 135 °C (from MeOH) (Found: C, 79.65; H, 7.5; N, 3.7. $C_{48}H_{54}N_2O_4$ requires: C, 79.85; H, 7.5; N, 3.9%); δ_H 0.82 (6 H, t, *J* 7.2), 0.86 (6 H, t, *J* 7), 1.0–1.3 (16 H, m), 1.8–2.1 (8 H, m), 6.63 (2 H, d, *J* 1.4), 6.79 (2 H, dd, J_1 8, J_2 1.4), 6.96–7.2 (10 H) and 7.70 (2 H, d, *J* 8); δ_C 13.7 (4 C, q), 22.9, 27.1, 39.3 (12 C, t), 61.8 (2 C, s), 118.6, 126.3, 127.1, 128.0, 130.9 (16 C, d), 137.5 (2 C, s), 140.7 (2 C, s), 142.0 (2 C, s), 146.0 (2 C, s), 150.5 (2 C, s), 175.2 (2 C, s) and 197.3 (2 C, s); *m/z* 722 (M^+, 52%), 666 (74), 637 (29), 624 (80), 581 (38), 567 (100), 525 (74), 279 (55), 263 (100), 167 (58).

Elution with hexane–EtOAc (8:2) yielded the isomer **11** (126 mg, 12%); m.p. 263 °C (from MeOH) (Found: C, 79.7; H, 7.5; N, 3.8. $C_{48}H_{54}N_2O_4$ requires C, 79.85; H, 7.5; N, 3.9%); δ_H 6.57 (1 H, d, *J* 1.4), 6.62 (1 H, dd, J_1 8, J_2 1.4), 6.84 (1 H, d, *J* 8), 6.85 (1 H, d, *J* 8); 7.04–7.16 (10 H), 7.31 (1 H, t, *J* 8) and 7.60 (1 H, d, *J* 8); δ_C 13.5, 13.7, 14.0, 14.2 (4 C, q), 20.9, 22.7, 22.9, 26.4, 26.9, 27.1, 27.5, 38.2, 39.0, 39.5, 40.3, (12 C, t), 60.3, 61.6 (2 C, s), 115.8, 119.3, 125.6, 126.1, 127.3, 127.5, 127.7, 128.8, 130.3, 131.2, 134.8 (16 C, d), 117.9, 139.6, 141.9, 142.2, 143.1 (8 C, s), 144.4 (1 C, s), 149.6 (1 C, s), 174.4 (1 C, s), 174.9 (1 C, s) and 197.1 (2 C, s).

10,10-*Dibutyl*-6-(3,3-*dibutyl*-2,4-*dioxo*-1,2,3,4-*tetrahydroquinolin*-7-*yl*)-5-*phenylnaphtho*[1,2-g]*quinoline*-9,11(8H,10H)-*dione* **2**.—A mixture of the dione **10** (200 mg, 0.27 mmol) and iodine (298.6 mg, 1.17 mmol) was dissolved in anhydrous toluene (200 cm^3). Nitrogen was bubbled through the stirred solution for 20–30 min before an excess of propylene oxide (10 cm^3) was added. After photoirradiation for 1 h, the resulting colourless solution was evaporated to leave a light yellow solid which, after chromatography (hexane–EtOAc 9:1) yielded the title compound **2** (145 mg) and starting material **10** (50 mg); **2**: m.p. 305–306 °C (from MeOH) (Found: C, 79.9; H, 7.2; N, 3.85. $C_{48}H_{52}N_2O_4$ requires: C, 80.1; H, 7.3; N, 3.9%); δ_H(DMSO) 6.66 (1 H, s), 6.97 (1 H, dd, J_1 8, J_2 1.2), 7.23 (1 H, s), 7.09–7.32 (5 H), 7.40 (1 H, d, *J* 8), 7.56 (1 H, br t, *J* 8), 7.65 (1 H, d, *J* 8), 7.76 (1 H, br t, *J* 8.2), 8.91 (1 H, d, *J* 8.2), 9.08 (s, NH), 9.24 (s, NH) and 9.31 (1 H, s); δ_C 13.7 (4 C, q), 22.9, 26.6, 27.3, 27.4, 37.9, 39.6, 39.9, 41.1 (12 C, t), 61.8 (2 C, s), 112.2, 119.1, 122.7, 123.7, 126.4, 126.9, 127.3, 127.6, 128.2, 128.4, 130.3, 130.5 (14 C, d), 101.1, 118.6, 118.9, 131.0, 134.4, 136.2, 138.0, 138.2, 140.7, 142.0, 147.4 (12 C, s), 174.4 (1 C, s), 175.3 (1 C, s), 197.5 (1 C, s) and 198.4 (1 C, s); *m/z* 720 (M^+, 60%), 664 (62), 647 (31), 635 (38), 622 (100), 579 (28), 565 (52), 537 (15) and 524 (51).

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