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Improved Receptors for Dibutylmalonic Acid

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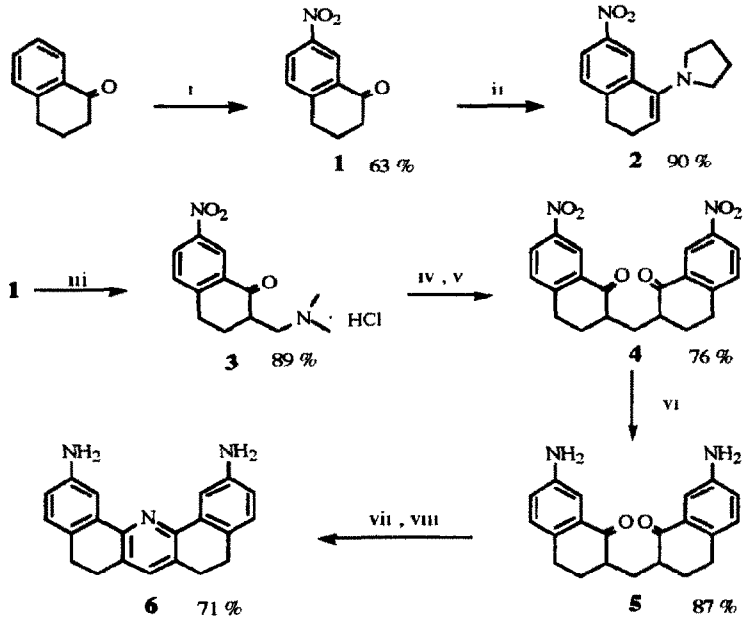
Abstract: *New molecular receptors with a dibenz[c,h]acridine skeleton bearing functional groups complementary to dibutylmalonic acid have been developed.*

Following the initial study of synthetic hosts with complexation properties for dibutylmalonic acid via hydrogen bonding, new improved receptors based on a 5,6,8,9-tetrahydrodibenz[c,h]acridine structure have now been prepared. Molecular recognition of these compounds is interesting due to their potential to mimic enzyme-like catalysis.

Previously, simple complexating agents for dibutylmalonic acid have been prepared using 3,3'-diaminobenzophenone as a spacer carrying different functional groups, suitable for binding by hydrogen bonds with this guest.[1] The catalytic decarboxylative activity was studied and the results were published.[2] Afterwards, receptors with a relatively rigid molecular framework and higher association constants were developed.[3] We now report the synthesis and complexation properties of new receptors with a better defined geometry that improve the association of dibutylmalonic acid derivatives.

Synthesis of the receptors **7** - **10** was achieved from the accessible α-tetralone (scheme 1), which was functionalized with a nitro group at C-7, followed by its transformation in the required amine group in that position. For the preparation of diamino acridine **6**,[4] the basic structure of these receptors, a convergent synthesis was performed by condensation of enamine **2** with Mannich-base **3**.[5] In the preparation of enamine, trimethylsilylpyrrolidine[6] was used to avoid 7-nitro-α-tetralone decomposition due to heating and water removal, which is necessary if pyrrolidine is used. The Mannich-base hydrochloride was prepared in the treatment of **1** with Eschenmoser's salt in equimolecular amounts at room temp. yielded the hydrochloride **3** as a white crystalline solid (yield 89%, m.p. 161°C), while when the α,β-unsaturated ketone was formed this rapidly dimerizes. The ^{1}H NMR spectra of **4** shows a diastereomeric mixture which is unnecessary to resolve for our purpose. The nitro groups of **4** were reduced to the diaminodicarbonyl compound **5**, the cyclization[7] of which with ammonium acetate in acetic acid for 3h under reflux conditions provided a diacetamide which treated with KOH in ethanol at reflux for 4h afforded the dibenz[c,h]acridine **6**.[8]



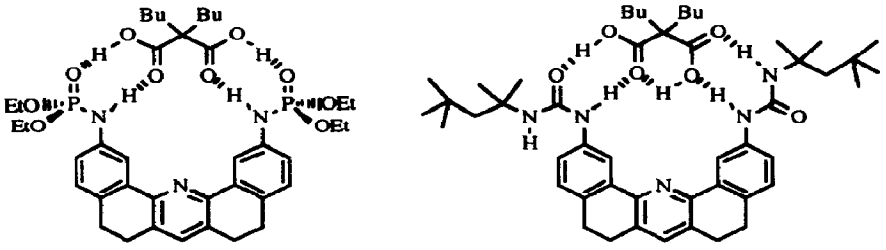
Scheme 1 Reagents and Conditions: i) HNO_3/H_2SO_4; ii) trimethylsilylpyrrolidine/pTsOH, 12h, r.t.; iii) $H_2C=^+N(CH_3)_2Cl^-$ /AcCl, 12h, r.t.; iv) 2, EtOH, 3h, r.t. ; v) HCl; vi) $SnCl_2$/HCl, 10 min., 60°C; vii) $AcO^-NH_4^+$/AcOH, 3h reflux ; viii) KOH/EtOH, 4h reflux.

Reaction of **6** with two molar amounts of diethyl chlorophosphate in pyridine at room temp., yielded the symmetric phosphoramide **7** (74%),[9] which has a 1,3-relationship between donor and acceptor hydrogen bonds well suited for binding with the acid linkages of the guest.

Due to the poor solubility of malonic acid in chloroform, quantitative binding studies were carried out with dibutylmalonic acid (DBMA) as guest which showed better solubility. Bindings were evaluated by NMR titrations in this solvent at 293K by adding increasing amounts of the guest.[10] From the ^1H NMR spectra, it was observed that the NH resonance of **7** moves to a lower field upon addition of the guest over a 2.2 ppm range. Analysis of these data using a non-linear least squares regression led to the determination of an association constant of $\mathbf{1.5 \times 10^5\ M^{-1}}$ for DBMA.

This association constant is amazingly high because the intramolecular malonic acid hydrogen bond must [11] apparently be broken in the complex. However, ureas can act either as a hydrogen bond donor-acceptor or as double hydrogen bond donor. This effect confers to an urea , as **8**, the possibility of binding the malonic acid maintaining its intramolecular hydrogen bond in the complex. Treatment of **6** with a excess of phosgene followed by treatment with *tert*-octylamine afforded the symmetric diurea **8** in 73% yield.[12]

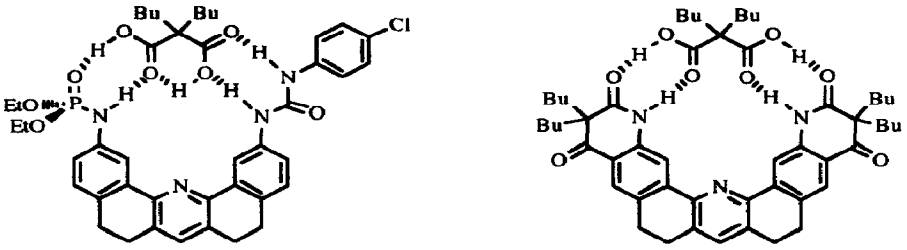
The effect of addition of DBMA to the receptor **8** led to a progressive deshielding of the host NH resonance of 1.8 ppm.[13] Analysis of these data led to an association constant of $\mathbf{2.6 \times 10^4\ M^{-1}}$.This association constant, however, is smaller than with the phosphoramide **7**. In receptor **8**, the urea function shows a twisted geometry due to steric hindrance with the receptor ortho hydrogens. This torsion makes the cleft



7 8

Figure 1 Complexes between diphosphoramide **7** and diurea **8** with dibutylmalonic acid.

wider and prevents the formation of completely linear hydrogen bonds with the guest, which seems to reduce the association constant, despite the fact that the malonic acid intramolecular hydrogen bond does not have to be broken in the complex. To assess how important the intramolecular DBMA hydrogen bond is, receptor **9** was prepared (61%, m.p. 135°C, CH_2Cl_2/hex), in which both possible binding arms, urea and phosphoramide, are combined. The association constant obtained for **9** was **1.3 x 10^5 M^{-1}**. In our opinion, the similar value of DBMA association constants with receptors **7** and **9** can be best explained if the malonic acid intramolecular hydrogen bond is kept in the receptor **9** complex. However, this kind of intramolecular hydrogen bond seems to be weak. Once the reduced importance of the intramolecular hydrogen bond had been assessed, a more rigid receptor **10** was prepared. The amine groups of **6** were acylated with the chloride of dibutylmalonic acid monoethylester, hydrolysis of the ester groups, and final treatment with Eaton's reagent (phosphorus pentoxide, 7.5 wt % in methanesulfonic acid) [14] to produce the symmetric bilactam **10** (56.5% total yield).[15]



9 10

Figure 2 Complexes between asymmetric receptor **9** and cyclic diamide **10** with dibutylmalonic acid.

The association constant of this receptor with DBMA has a value of **2.8 x 10^5 M^{-1}**, which indicates that this more organized structure is a better receptor for complexing malonic acids despite the lack of the intramolecular hydrogen bond.

In summary, we have prepared a dibenz[c,h]acridine framework incorporating two amine groups, easily functionalizable to other interesting groups to complex malonic acid derivatives. Future efforts will be aimed

at attaining catalytic activity for the decarboxylation of amidomalonic acids[16] as a way to produce enantioselective amino acid synthesis.

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8. Physical and spectroscopic data of **6**: m.p. 224°C (CH_2Cl_2/MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.87 (m, 8H), 6.66 (dd, J=8.0 Hz, J=2.4 Hz, 2H), 7.03 (d, J=8.0 Hz, 2H), 7.29 (s, 1H), 7.87 (d, J=2.4 Hz, 2H). ^{13}C NMR and DEPT (50 MHz, DMSO-d_6): δ = 26,54 (CH_2), 27.57 (CH_2), 109.94 (CH), 114.76 (CH), 125.42 (C), 127.90 (CH), 130.08 (C), 134.62 (C), 134.96 (CH), 146.96 (C), 149.75 (C). MS m/z (%) 313 (M^+, 100). Analysis calcd for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.29; H, 6.20; N, 13.22%.

9. Physical and spectroscopic data of **7**: m.p. 207°C (CH_2Cl_2/hex). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, J=7.0 Hz, 12H), 2.87 (m, 8H), 4.19 (m, 8H), 6.13 (d, J=9.0 Hz, 2H, NH), 7.09 (d, J=8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 7.30 (s, 2H), 8.11 (s, 2H). ^{13}C NMR and DEPT (50 MHz, $CDCl_3$): δ = 18.15 (CH_3), 18.31 (CH_3), 27.48 (CH_2), 28.17 (CH_2), 62.85 (CH_2), 62.95 (CH_2), 114.45 (CH), 114.64 (CH), 117.70(CH), 128.59 (CH), 131.01 (C), 131.38 (C), 135.41 (CH), 135.88 (C), 138.90 (C), 150.11(C). MS m/z (%) 585 (M^+, 50). Analysis calcd for $C_{29}H_{37}N_3O_6P_2$: C, 59.48; H, 6.37; N, 7.18. Found: C, 59.69; H, 6.16; N, 6.92%

10. The ^1H NMR spectra were taken for a series of solutions containing the host at a fixed concentration of $1x10^{-3}$ mol dm^{-3} $CDCl_3$ and varying concentrations of the guest over the range 0-2 mol equiv., and the changes in the chemical shifts of the host were monitored by a specially adapted Monte Carlo curve fitting program.

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12. Physical and spectroscopic data of **8**: ^1H NMR (200 MHz, $CDCl_3$): δ = 0.98 (s, 18H), 1.42 (s, 12H), 1.78 (s, 4H), 2.84 (m, 8H), 4.87 (s, 2H, NH), 6.68 (s, 2H, NH), 7.11 (d, J=8.0 Hz, 2H), 7.27 (s, 1H), 7.46 (dd, J=8.0 Hz, J=2.4 Hz, 2H), 8.07 (d, J=2.4 Hz, 2H). Analysis calcd for $C_{39}H_{53}N_5O_2$: C, 75.08; H, 8.56; N, 11.22. Found: C, 74.80; H, 8.37; N, 11.03%.

13. Carbon protons undergo smaller shifts (0.13 ppm). However similar association constants have been found following these protons, which allows comparison of the validity of monitoring.

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15. Physical and spectroscopic data of **10**: m.p. 310°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.67 (t, J=6.7 Hz, 12H), 1.12 (m, 16H), 2.02 (m, 8H), 2.99 (m, 8H), 7.45 (s, 1H), 7.85 (s, 2H), 8.18 (s, 2H), 9.39 (s, 2H, NH). ^{13}C NMR and DEPT (50 MHz, $CDCl_3$): δ = 13.73 (CH_3), 22.99 (CH_2), 27.17 (CH_2), 27.35 (CH_2), 27.81 (CH_2), 40.18 (CH_2), 61.85 (C), 112.31 (CH), 119.79 (C), 126.47 (CH), 132.93 (C), 133.75 (C), 136.20 (CH), 140.35 (C), 141.91 (C), 149.13 (C), 175.18 (C), 198.11 (C). MS m/z (%) 673 (M^+, 28). Analysis calcd for $C_{43}H_{51}O_4N_3$: C, 76.64; H, 7.63; N, 6.23. Found: C, 76.44; H, 7.79; N, 5.99%.

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