A Novel Receptor for Dicarboxylic Acid Derivatives

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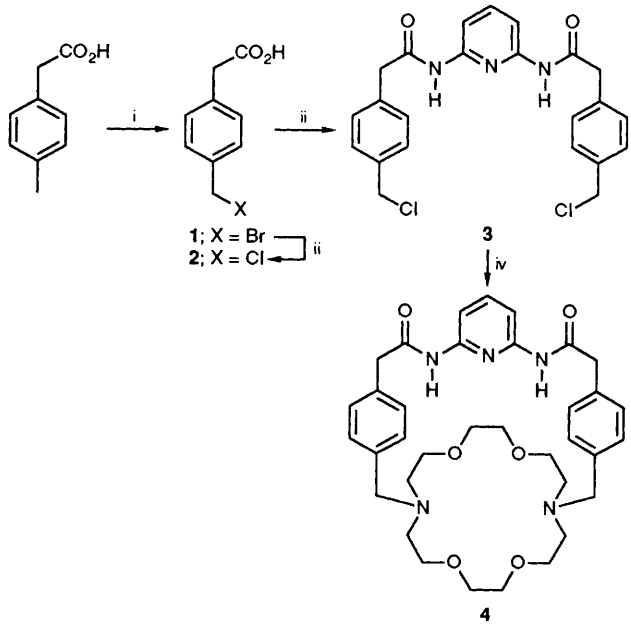
A novel receptor **4** has been prepared, which binds the monopotassium salts of various dicarboxylic acids in chloroform solution, using a combination of hydrogen bonding interactions and an electrostatic association between a carboxylate anion and a crown ether bound potassium cation, the crystal structure of the receptor is reported and evidence for the proposed binding interactions is provided by consideration of various extraction experiments, intermolecular NOEs (nuclear Overhausser effect), and FAB (fast atom bombardment) mass spectrometry, where a bimolecular species, held together by hydrogen bonds, can be detected in the negative ion mass spectrum.

As part of a programme of research to develop synthetic hosts for peptides and amino acids, we have synthesised a simple receptor **4** (Scheme 1), featuring a bis(amidopyridine) unit (known, from Hamilton's work,[1] to serve as a binding site for carboxylic acid functionality) and a diazacrown ether (well documented to bind to metal cations and to ammonium functionality[2]) in the anticipation that this might bind to the ammonium salts of amino acids.[3] We have found that this novel receptor does not bind to amino acid salts, but instead does serve as a receptor for the monopotassium salts of various dicarboxylic acids.

The synthesis of the receptor is straightforward (Scheme 1). Tolylacetic acid is brominated in reasonable yield and converted to the corresponding chloride **2**. Conversion to the acid chloride, and coupling with 2,6-diaminopyridine, gives dichloride **3**, which is then reacted with 1,10-diaza-18-crown-6,[4] in the presence of NaI and Na_2CO_3, to give the macrocyclic product **4** in an acceptable overall yield.

The ability of the receptor, in chloroform, to bind to a variety of guest substrates was assessed in a series of liquid–liquid and solid–liquid extraction experiments.† When hydrochloride or picrate salts of various amino acids were tried there was no evidence of uptake of the substrate into the organic chloroform phase. Instead it appears that the basic pyridine becomes protonated by transfer of acid from the ammonium of the amino acid. However, when the monopotassium salts of various dicarboxylic acids were used, they were taken up in variable amounts into $CDCl_3$ solution. The amount of uptake was determined, where possible, by comparing the integrals of relevant guest signals in the ^1H NMR spectrum against integrals of signals from the receptor. Significant shifts for the signal from the NH of the amidopyridine unit were also generally detected, although the signal frequently disappeared under the aromatic signals, so that the extent of this shift could not always be determined. The results of these studies are given in Table 1.

We believe that the potassium cation is held in the crown ether and the carboxylate functionality associates with it, while at the other end of the complex, the carboxylic acid



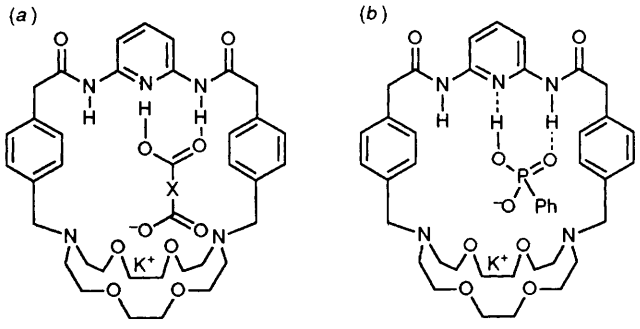
Scheme 1 *Reagents and conditions*: i, Br_2, AIBN, CCl_4, *hv*, 59%; ii, LiCl, acetone, reflux, 3 days, 91%; iii, a, $(COCl)_2$, CH_2Cl_2, cat. DMF; b, 2,6-diaminopyridine, Et_3N, THF, 25–33%; iv, 1,10-diaza-18-crown-6, NaI, Na_2CO_3, MeCN, reflux, 2 days, 28%; AIBN = azoisobutyronitrile; DMF = dimethylformamide, THF = tetrahydrofuran

† For liquid–liquid extraction experiments, 0.5 ml of a 0.095 mol dm^{-3} solution of the receptor in $CDCl_3$, and 0.5 ml of a 0.095 mol dm^{-3} solution of the guest in water, were vigorously stirred together, followed by separation of the two solutions and examining the $CDCl_3$ solution by ^1H NMR spectroscopy. For solid–liquid extraction experiments, 0.5 ml of a 0.095 mol dm^{-3} solution of the receptor in $CDCl_3$, was stirred with a finely powdered sample of the proposed guest, followed by filtration and examination of the resulting $CDCl_3$ solution by ^1H NMR spectroscopy.

Table 1

Entry	Substrate[a] Mono potassium salt of	Solid–Liquid Δδ N–H[b]	Solid–Liquid Extraction[c] (%)	Liquid–Liquid Δδ N–H[b]	Liquid–Liquid Extraction[c] (%)
1	Oxalic acid	0.48	—	—	—
2	Malonic acid	0.26	60	0.04	3
3	Methylmalonic acid	0.12	25	0.06	7
4	Benzylmalonic acid	0.24	65	0.20	54
5	Maleic acid	0.26	63	0.13	29
6	Fumaric acid	0	0	0	0
7	Succinic acid	0.18	27	0.06	<5
8	*Z*-Aminomalonic acid	0.40	29	0.44	42
9	*Z*-Aspartic acid	—	36	0.42	54
10	*Z*-Glutamic acid	—	42	0.52	50
11	Phenyl phosphinate	—	43	—	10
12	Phenyl phosphonate	—	11	—	10
13	Acetic acid	0.01	<10	0.02	<10

[a] All the substrates were insufficiently soluble in $CDCl_3$, in the absence of the receptor **4**, to be detected by ^1H NMR spectroscopy. [b] For the free receptor **4**, the NH signal, in the ^1H NMR spectrum ($CDCl_3$), comes at δ 7.38. For entries 9–12, in the solid–liquid extraction experiments, and for entries 11 and 12, in the liquid–liquid extraction experiments, the position of the NH signal could not be determined with any certainty. [c] Assessed (±5%) by integration of relevant signals in the ^1H NMR spectrum.



Scheme 2 Proposed mode of binding of receptor **4** with (*a*) monopotassium salts of dicarboxylic acids, and (*b*) the monopotassium salt of phenyl phosphonate

group is hydrogen bonded to the amidopyridine unit (Scheme 2).[5] The shifts of the NH signal, in the ^1H NMR spectrum, are good evidence for hydrogen bonding, but could be the result of protonation of the pyridine unit, and not of specific binding. That specific binding is taking place is supported by considering entries 5 and 6 (Table 1). The monopotassium salt (0.29 equiv.) of maleic acid (the *cis* isomer) is extracted into the organic solvent by the receptor in the liquid–liquid extraction experiment (and 0.63 equiv. in the corresponding solid–liquid extraction experiment), but none of the monopotassium salt of fumaric acid (the *trans* isomer) is taken up, in either the liquid–liquid or the solid–liquid extraction experiment. This is most readily interpreted by assuming that the *cis* maleic acid can fit into the cavity of the host, while the *trans* fumaric acid, with a greater separation of the two binding functionalities, cannot.‡ Interestingly, the relatively flexible succinic acid derivative (entry 7) is taken up to an intermediate extent. The relatively small uptake of potassium acetate (entry 13), also supports the notion that binding of both the carboxylate anion, and of the carboxylic acid, are important for efficient binding of the substrates (Scheme 2).

‡ Interpretation of these binding results is complicated by the fact that, for solid–liquid extractions, the lattice energy of the substrate, and the free energy of solvation of the substrate in chloroform, should be taken into account. Similarly for the liquid–liquid extraction experiments the relative solubility of substrates in water and chloroform should be considered. However, it is most improbable that differences in these terms for the monopotassium salt of fumaric acid, or of maleic acid, could, on their own, account for the observed results.

The macrocycle can also accommodate a range of malonate derivatives (entries 2–4 and 8), where the increasing degree of extraction into the organic phase, in liquid–liquid extraction experiments, presumably reflects the increasing hydrophobicity of the α-substituent. Similarly, a number of benzyl carbamate protected amino acids are extracted into the organic phase, which along with other results (entries 1, 2, 7–10), shows that the length of the flexible chain linking the two acid functionalities is relatively unimportant.

We looked also at the uptake of the monopotassium salt of phenyl phosphinate and of phenyl phosphonate (entries 11 and 12), since we felt that the phosphonate, particularly, might be able to establish a similar array of interactions, with the receptor and bound potassium (Scheme 2), as proposed for the dicarboxylic acid derivatives. Surprisingly, phenyl phosphinate is taken up to a considerably greater extent, in the solid–liquid extraction, than the corresponding phosphonate, despite the fact that it would seem to have one less binding functionality.

The above experiments provide good circumstantial evidence for binding as proposed, but we sought more conclusive proof. All our efforts to obtain crystals of a host–guest complex failed, but we were able to obtain crystals of the free host **4** from Me_2SO–H_2O. The crystal structure§ is presented in Fig. 1, and certainly indicates that the receptor possesses a large cavity with clear separation between the amidopyridine unit and the crown ether. The pyridine unit appears to be free to rotate about the CH_2–CO bonds, which may explain the ability to bind a range of substrates, with a flexible chain of variable length separating the two acid functionalities. Instead of using direct evidence from a crystal structure, the methylmalonic acid complex (entry 3, Table 1) gave good intermolecular NOE (nucelar Overhauser effect)

§ *Crystal data* for **4**: $C_{35}H_{45}N_5O_6 \cdot xH_2O$ [x = 1.59(1)], M = 631.77 + 18.01x, triclinic, space group $P\bar{1}$(no. 2), a = 10.367(3), b = 14.011(5), c = 14.371(4) Å, α = 117.61(1), β = 103.42(2), γ = 102.05(2)°, Z = 2, D_c = 1.29 (x = 1) g cm^{-3}, U = 1673.6 Å^3, F(000) = 676 + 20x, μ = 0.81 cm^{-1} (x = 1). The structure was solved by direct methods and refined by least-squares using 1665 observed data [$F_o > 4.0\sigma(F_o)$, $2\theta_{max}$ = 50°] out of a total of 7429, using an Enraf-Nonius FAST diffractometer with graphite monochromated Mo-Kα radiation, at −150 °C. The final R, R_w values were 0.052, 0.060 for 194 parameters (all atoms isotropic). Hydrogen atoms (bonded to carbon) were included in calculated positions. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

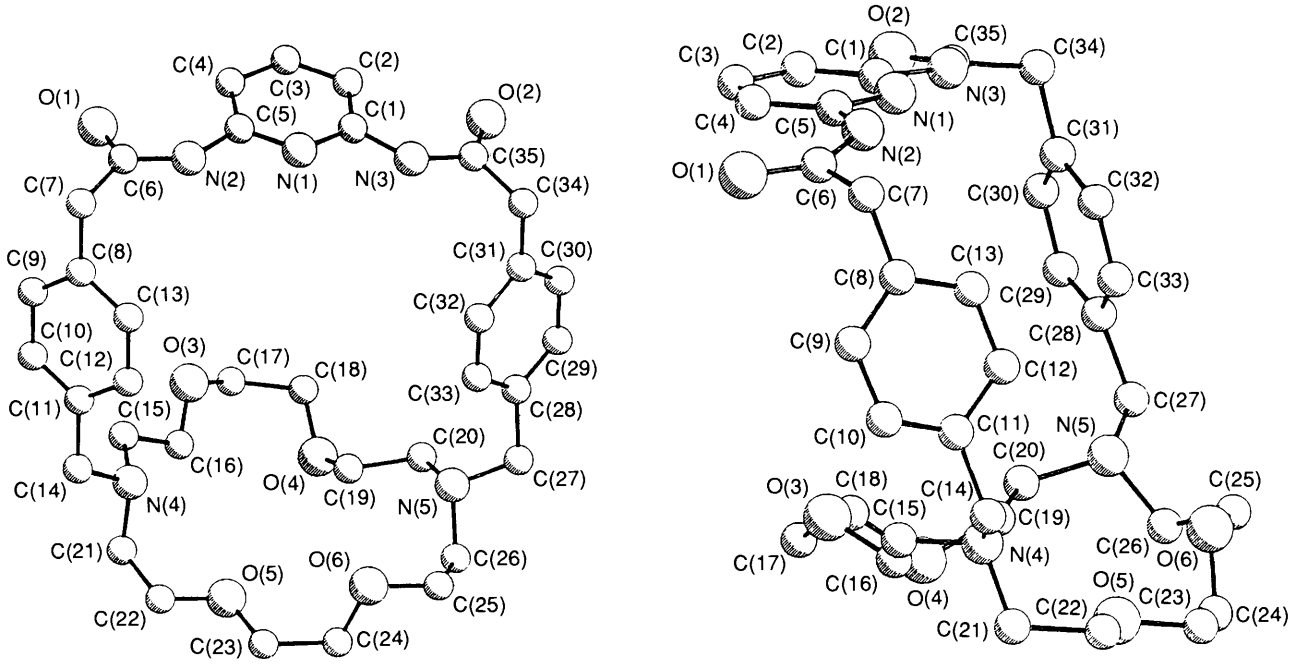


Fig. 1 The molecular structure of $C_{35}H_{45}N_5O_6 \cdot xH_2O$ showing the free host molecule **4**. H atoms excluded for clarity.

signals from both the methyl doublet, and the α-proton, of the substrate to the aromatic protons of the benzene rings forming the side wall of the cavity, using a ROESY pulse sequence.[6] The success of this experiment was very pleasing, following the initial failure of more conventional NOESY pulse sequences to provide a conclusive result, and given that only ~30% saturation of the host had been achieved. Furthermore it supports our contention that the substrates are held in the cavity in a 1 : 1 complex.

FAB mass spectrometry of samples of the chloroform solutions of the complex with the monopotassium salt of methylmalonic acid, of maleic acid and of phenyl phosphinate (entries 3, 5 and 11, Table 1) were also studied and in each case a peak corresponding to the macrocycle + potassium $(M + K)^+$, was observed in the positive ion FAB spectrum.[7] The negative ion FAB spectra, however, yield peaks corresponding to macrocycle + anion (carboxylate or phosphinate) complexes, $(M + A)^-$ with a daughter ion $(M - H)^-$, while under the same experimental conditions, the free macrocycle did not give any signal, and addition of the monopotassium salt of fumaric acid (which does not bind to the receptor according to the extraction experiments), to the FAB matrix, similarly led to no signal, confirming that we are not observing adduct ion formation in the ionisation of these samples. It therefore appears that, upon fast atom bombardment, the complex can lose the potassium cation but the resultant bimolecular species, held together by the interaction of the carboxylic acid with the amidopyridine, remains intact. As far as we are aware this is the first example of such an observation,[8] and also provides further evidence for the proposed mode of binding.

We thank the SERC for a studentship for S. S. F. and the ERASMUS scheme for supporting J.-L. C. (visiting from Rouen University, France). We also thank Dr N. H. Rees, of the NMR facility of the Southampton Molecular Recognition Centre, and Mrs J. Street, for carrying out the NMR experiments, and Professor M. B. Hursthouse, of the SERC Crystallographic Service Service (University of Wales, Cardiff) for collecting the crystallographic data.

Received, 29th October 1992; Com. 2/05768I

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