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Molecular recognition. Design of new receptors for complexation and catalysis.

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INTRODUCTION

In recent years there has been intense activity in the design of synthetic molecules capable of enzyme-like recognition and binding of small substrates.[1] Two fundamental approaches have been taken. The first has generally involved non-directional binding forces (such as solvophobic, π-stacking and dispersion interactions) in water-soluble cyclophane frameworks.[2] This approach led to extremely important quantitative insights into the hydrophobic effect and the enthalpic and entropic contributions of solvent reorganization to binding.[3] However, the weakly oriented nature of the binding interactions has resulted in only moderate substrate selectivity beyond the shape recognition permitted by the cavity. In nature such selectivity is a prerequisite for the chiral recognition and catalytic activity of enzymes and is achieved by hydrogen bonding and electrostatic interactions. The second major approach to artificial receptors makes use of these more directional interactions by incorporating several hydrogen bonding groups into a cleft or cavity of defined geometry.[4] The resulting hosts form strong and selective complexes to those substrates with complementary shape and hydrogen bonding characteristics.[5] In these cases, however, the binding free energy is solvent dependent, diminishing to zero as the polarity of the medium increases, due to the strong solvation of the hydrogen bonding sites. A central goal in contemporary molecular recognition research must be to develop receptors that effectively use directed hydrogen bonding interactions in competitive solvents. Success will probably require combining strong (possibly charged) hydrogen bonding groups with hydrophobic sites capable not only of effective apolar association with the substrate but also of protecting the polar sites from full solvation.

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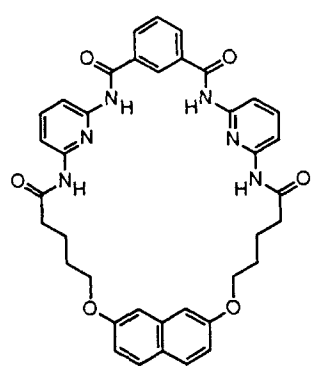
RECOGNITION OF BARBITURATE SUBSTRATES

Linking two 2,6-diaminopyridine units through an isophthalate spacer (as in **1**) creates a cavity that is complementary to both the shape and hydrogen bonding features of barbiturates. An X-ray structure of one receptor (**2**) shows a preorganized cavity with all six hydrogen bonding sites directed into the centre of the ring. Complexation can be easily followed using ^{1}H-NMR. Addition of one equivalent of diethyl barbituric acid to a $CDCl_3$ solution of **1** caused large downfield shifts of the amide proton resonances characteristic of intermolecular hydrogen bonding. A significant shift was also seen in the 2H-proton of the isophthaloyl spacer, indicating its position close to the bound substrate and confirming the structure of the complex shown in **3**. Monitoring the changes in the ^{1}H-NMR as a function of substrate concentration leads to a binding curve that can be analysed by a Scatchard plot or by non-linear regression analysis to give the association constant. The large values of K_a measured for **3** ($\sim 10^5$–10^6 M^{-1}) are indicative of strong complexation via six hydrogen bonds.[6] An X-ray structure (**4**) showed the position of the barbiturate in the centre of the cavity as well as details of the distances (2.9, 3.0 and 3.2 Å) and orientations of the three types of hydrogen bonds in the complex. By removing different functional groups in the receptor and substrate we have carried out a systematic investigation of the strength of different hydrogen bonds in the complex and have found an average value for $-\Delta G$ of 1.2–1.5 kcal mol^{-1}.

DICARBOXYLIC ACID RECOGNITION

An extremely simple receptor for dicarboxylic acid substrates can be prepared from the reaction of



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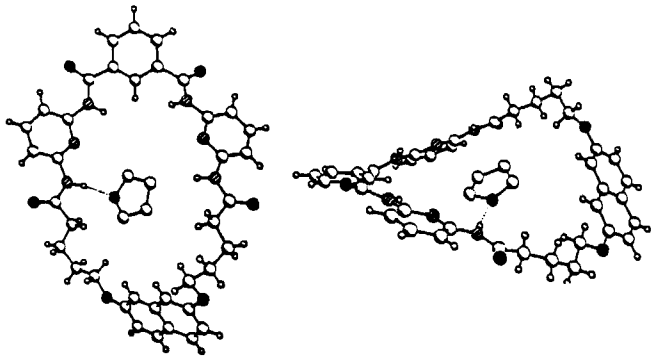

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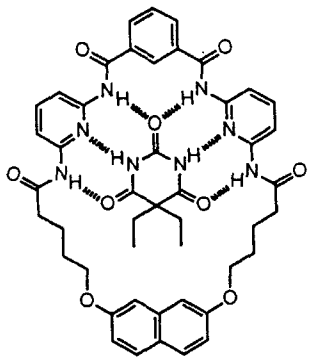

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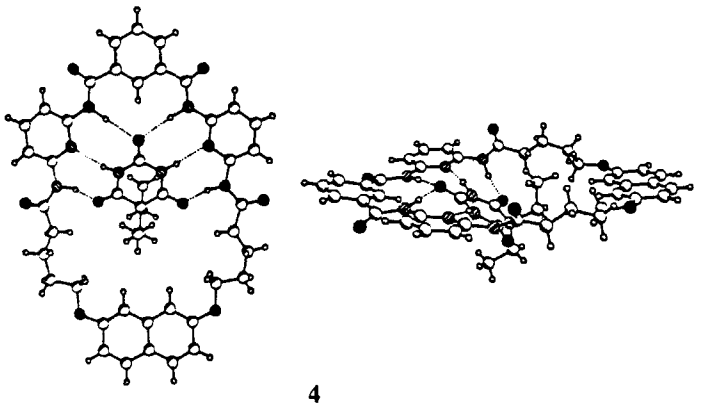

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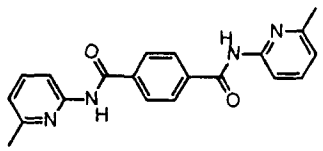

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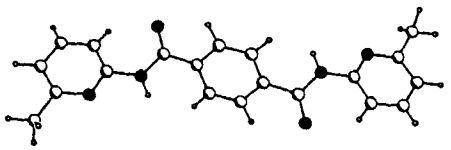

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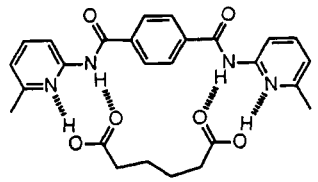
2-amino-6-methylpyridine groups with terephthaloyl dichloride. The resulting diamide **5** contains two amidopyridine groups linked by an easily variable, rigid spacer. An X-ray structure[7] of the uncomplexed host **6** shows an unproductive conformation with the two binding groups in a *trans* orientation due to intermolecular interactions in the crystal. However, there is a low barrier to rotation about the phenyl–CO bond and the host can readily undergo a conformational change to position the binding sites on the same side of the receptor. Again, ^{1}H-NMR is invaluable in the study of these simple diacid hosts. Addition of a complementary diacid to a $CDCl_3$ solution of **5** leads to large downfield shifts of the amide–NH resonances, consistent with the formation of a tetrahydrogen-bonded complex of the type shown in **7**. Selectivity is dependent on the spacer length and its fit to the length of the diacid; strongest complexes being formed between **5** and adipic or glutaric acid ($K_a \sim 10^4$–$10^5\ M^{-1}$). An X-ray structure of the complex to adipic acid is shown in **8** and supports the formation of four hydrogen bonds between receptor and substrate. That this conformation is also taken up in solution was confirmed by the observation of an intermolecular



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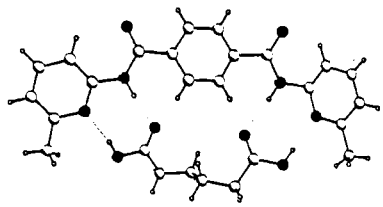


8

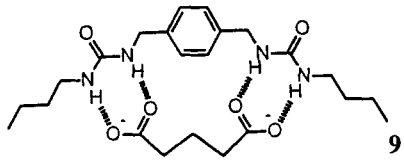
nuclear overhauser enhancement between the central CH_2 groups on the adipic acid guest and the aromatic-Hs on the terephthalic acid spacer in **5**.

DICARBOXYLATE RECOGNITION

The binding of dicarboxylic acids to **5** is strongly solvent dependent. In 5% THF/$CDCl_3$ binding decreases (at 295 K, $K_a = 6.4 \pm 1.4 \times 10^2$ M^{-1}, $\Delta G = -3.8$ kcal mol^{-1}) but measurement of thermodynamic parameters shows a strongly enthalpic driving force for binding ($\Delta H = -7.9$ kcal mol^{-1}, $\Delta S = -14$ cal mol^{-1} K^{-1}), with a substantial negative entropy term due to the loss of translational and rotational motion inherent in bimolecular association and also the freezing of bond rotations in the complex. (For recent discussions of solvent effects in hydrogen bonding see ref 8.) Addition of dimethylsulfoxide to **7** leads to strong solvation of the hydrogen bond donor sites and an almost complete disruption of the binding.

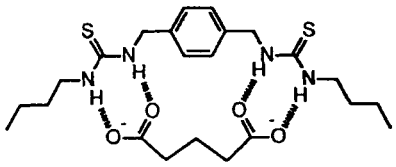
The binding site disposition in **5** can be improved by placing both hydrogen bond donors on the host to create a bis-urea receptor for dicarboxylate derivatives, as in **9**. This has the advantage of creating four favourable secondary hydrogen bonding interactions[9] in **9** (as opposed to four unfavourable ones in **7**) and of increasing the strength of the primary interaction through the use of charged hydrogen bond acceptors.[10]

The bis-urea receptor was soluble in d_6-DMSO and its interaction with the bis-tetrabutylammonium salts (TBA) of dicarboxylates was conveniently followed by ^{1}H-NMR. Addition of one equivalent of glutarate-TBA to a DMSO solution of the bis-urea (1.0×10^{-2} M) gave large downfield shifts of both the inner and outer urea-NH resonances (1.1 and 1.2 ppm), consistent with the formation of a tetrahydrogen-bonded complex, as in **9**. A Job's plot gave a maximum at mole ratio 0.5 confirming the 1:1 stoichiometry of the complex.[11] The association constant was measured by non-linear regression analysis of the binding curve[12] as $6.4 \pm 1.4 \times 10^2$ M^{-1} ($\Delta G_{293} = -3.7$ kcal mol^{-1}). In contrast to bis-amide complex **7**, efficient binding is seen between the bis-urea receptors and dicarboxylates in DMSO. The presence of two binding sites is critical, as seen by the weak association between *N,N'*-dimethylurea and tetramethylammonium acetate ($K_a = 45 \pm 3$ M^{-1}).



9

Insights into the origins of binding came from variable temperature measurements of thermodynamic parameters. The binding enthalpy ($\Delta H = -3.8$ kcal mol^{-1}) for **9** in DMSO is reduced (compared with **7** in 5% THF/$CDCl_3$) due to increased solvation, but is still significant enough to drive association (unlike **7** in DMSO). This underlines the advantage of positioning H-bond donor sites close together in the host where, for steric reasons, they are less effectively solvated than when widely spaced. (A similar proximity of H-bond donor sites is seen in the carboxylate binding pocket of the antibiotic vancomycin; see ref 13.) This effect is clearly seen in the shift of the NH resonances, on going from $CDCl_3$ to d_6-DMSO, which is smaller for the ureas (1.65 ppm) than for the 2-amidopyridines (2.33 ppm). The entropy of association ($\Delta S = -0.1$ cal mol^{-1} K^{-1}) for **9** in DMSO is close to zero despite the inherent entropic cost of bimolecular association and the greater flexibility of the xylylene spacer, compared with the terephthaloyl group in **7**. Binding must therefore involve an entropically favourable component to counterbalance these unfavourable factors. This may derive from two sources. The first is displacement by the dicarboxylate substrate of the two or more DMSO molecules solvating the urea-NH sites. The resultant randomization of solvent would lead to an increase in entropy and similar effects have been seen with aqueous solvation of H-bonding sites.[8] The second, related factor concerns the substrate which may be present as an ion pair in DMSO. Binding of the dicarboxylate dianion into the bis-urea cavity will lead to the entropically favourable dissociation of the two tetrabutylammonium cations. (For a discussion of related effects in cyclophane receptors, see ref 14.)



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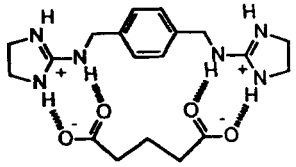

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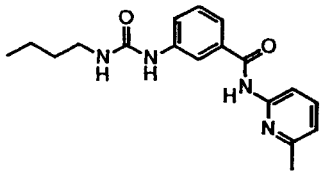

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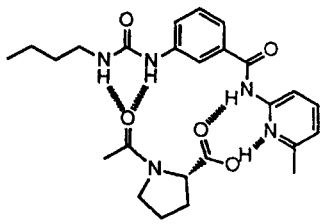

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Binding energy can be further improved by increasing the acidity of the H-bond donor sites in the receptor. Thiourea ($pK_a = 21.0$) is more acidic than urea ($pK_a = 26.9$)[15] and reaction of 1,4-bis(aminomethyl)-benzene with butyl isothiocyanate readily provides a bis-thiourea receptor capable of binding to glutarate, as in **10**. All NMR evidence is consistent with a complex of structure **10** and the K_a in d_6-DMSO ($1.0 \pm 0.2 \times 10^4$ M^{-1}) shows a 15-fold increase over **9**. Alkylguanidinium groups are even more acidic ($pK_a \sim 14$) and provide additional electrostatic stabilization from the complementary charge in the hydrogen bonding sites. Reaction of 1,4-bis(amino-methyl)benzene with methyl ethylenethiouronium iodide gave a bis-alkylguanidinium receptor[16] which can bind to glutarate, as in **11**. The association constant for the complex between the bis-guanidinium receptor (as its bis-iodide salt) and glutarate-TBA in d_6-DMSO was too large ($K_a > 5 \times 10^4$ M^{-1}) to be measured by ^{1}H-NMR. Addition of D_2O to the DMSO solution led to the expected decrease in K_a, due to increased solvation of the carboxylate groups. However, binding was still clearly observable at 12% D_2O/DMSO ($K_a = 8.5 \pm 1.5 \times 10^3$ M^{-1}) and even 25% D_2O/DMSO ($K_a = 4.8 \pm 2.5 \times 10^2$ M^{-1}). (For other examples of guanidinium-containing synthetic receptors, see ref 16.)

AMINO ACID CARBOXYLATE RECOGNITION

The diacid hosts discussed above can be readily modified to change their recognition properties. For example, receptors for acylamino acid carboxylates can be formed by positioning a urea substituent at the 3-position of a benzoate spacer linked to an acyl-aminopyridine, as in **12**. The urea-NH groups can form two hydrogen bonds to the peptide–CO while the 2-aminopyridine forms a bidentate interaction to the carboxylate terminus, as in **13**. ^{1}H-NMR experiments showed downfield shifts of the pyridine-NH and urea-NHs, on addition of *N*-acetyl-L-proline, indicating their involvement in hydrogen bonding to the substrate. Titration experiments in $CDCl_3$ gave a value of $K_a = 2.6 \times 10^3$ M^{-1} which corresponds to a binding free energy value $-\Delta G_{298} = 4.38$ kcal mol^{-1}. Increasing the temperature of the binding experiment led to a clear decrease in the curvature of the isotherm and a reduction in K_a (as seen in Fig 1). A van't Hoff plot of $-R \ln K_a$ vs. $1/T$ allows the dissection of this free energy term into its enthalpy and entropy components. Measurement for complex **13** in H_2O-saturated $CDCl_3$ gave $-\Delta H = 9.43$ kcal mol^{-1} and $-\Delta S = 16.9$ cal mol^{-1} K^{-1}.

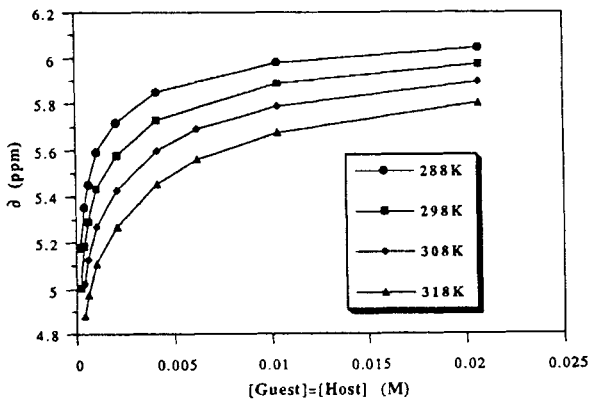
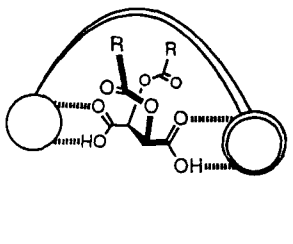


Figure 1 Variable temperature NMR dilution studies on complexation of *N*-Ac-proline and its receptor.

ENANTIOSELECTIVE COMPLEXATION

The design of receptors that differentiate between two enantiomers has been a very active part of molecular



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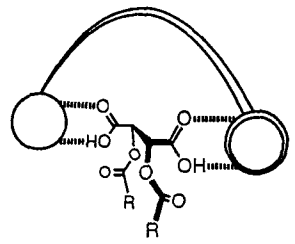

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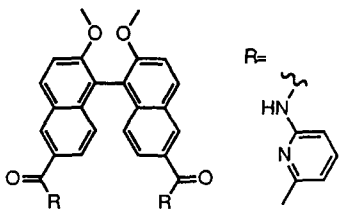

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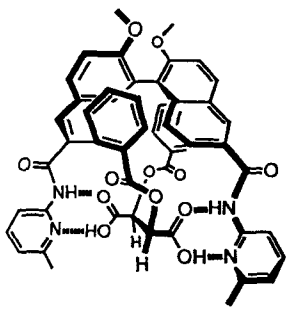

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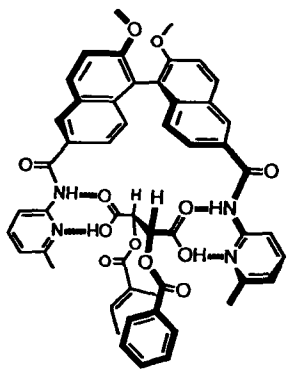

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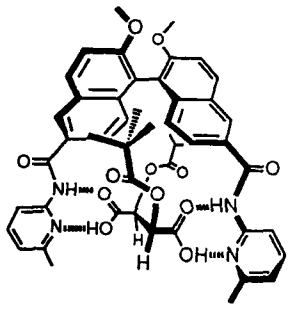

19

recognition research. Recent developments[17] have shown that directed hydrogen bonding groups within a chiral environment can lead to differences in binding between two enantiomers of >2 kcal mol^{-1}. Our own approach has been to use the diacid recognition strategy discussed above to develop receptors for tartaric acid derivatives.[18] For example, a receptor for diacyl tartrate derivatives in a *trans* conformation might contain two acylaminopyridine units linked through a chiral spacer such that the two acyloxy substituents of a bound tartaric acid will project into opposite open faces in the binding cavity. In this way, D-(−)-tartrate will bind as in **14** with the possibility of repulsive or attractive interactions between the ester groups and the chiral spacer, whereas L-(+)-tartrate will bind as in **15**. A simple receptor of this type is available from [2,2′-dimethoxy-1,1′-binaphthyl]-6,6′-dicarboxylic acid which can be converted to its diacid chloride followed by treatment with 6-methyl-2-aminopyridine to give receptor *R*-**16**. Addition of one equivalent of D(−)-dibenzoyl tartaric acid to a $CDCl_3$ solution of *R*-**16** gave large downfield shifts of the amide-NH resonance and upfield shifts of the benzoyl-2, -3, and -4 H resonances. These results, in addition to an intermolecular NOE between the 2-proton on the benzoyl group and the 8-proton on the naphthalene ring, indicate a complex structure as shown in **17** in which the benzoyl groups point towards the binaphthyl ring current. In contrast, the complex between *R*-**16** and L(+)-dibenzoyl tartaric acid shows a structure **18** in which the benzoyloxy substituents are directed out of the cavity. Substrate binding was followed by fluorescence spectroscopy in CH_2Cl_2 and gave association constant values for **17** of $3.0(\pm 0.3) \times 10^5$ M^{-1} and for **18** $3.6(\pm 0.4) \times 10^5$ M^{-1}.

Similar complex geometries are seen with the two enantiomers of dipivaloyl tartaric acid (DPTA) and *R*-**16**. However the association constant for the *R*-**16**: D-(−)-DPTA is higher ($K_a = 1.0 \times 10^6$ M^{-1}) than both the L-(+)-isomer ($K_a = 3 \times 10^5$ M^{-1}) and the D-(−)-dibenzoyl analogue. This increased chiral selectivity in the pivaloyl derivative may indicate a stabilizing of **19** by CH_3-π interactions.[19]

ACKNOWLEDGMENTS

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