A new macrocycle demonstrates ditopic recognition properties†

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The synthesis and binding properties of a new macrocycle is reported. The host, comprised of three basic pyridines, four hydrogen bond accepting carbonyls, and two hydrogen bond donating amide groups, binds mono-alkyl ammonium salts in a manner that is dependent on the counter-ion of the ammonium guest.

The design and synthesis of ditopic receptors,[1–4] in particular receptors that can simultaneously bind cationic and anionic species, is an emerging area of supramolecular chemistry. These types of host often exhibit cooperative and allosteric effects, but the precise rules governing when positive/negative cooperativity or non-cooperativity is observed are still unclear. Recent work has led to a number of ditopic receptors for inorganic salts,[5–14] zwitterionic amino acids[15–18] and tetra-alkyl ammonium salts.[19–25] However, relatively few examples of ditopic hosts for mono-alkyl ammonium guests have been described.[26–28] We report here the synthesis and binding properties of host **1** (Fig. 1). This dish-shaped, relatively rigid macrocycle has an array of both hydrogen-bond donors and acceptors that engenders binding sites for both mono-alkyl ammoniums and their counter ions.

The synthesis of macrocycle **1** began with known dibromide **2** (Scheme 1).[29] Treatment with CuCN gave the corresponding dicyanide, which upon hydrolysis gave diacid **3**. Monoester **4** was subsequently obtained *via* Fischer esterification of **3** followed by hydrolysis with 1 equivalent of NaOH. Treatment of **4** with diphenylphosphoryl azide (DPPA) in *t*-BuOH led to a Curtius rearrangement and, after removal of the Boc group, isolation of amine **5**. Standard peptide bond forming techniques, followed by base and then acid hydrolysis, led to **6**. Cyclization, using DPPA to generate an acyl azide active ester intermediate, gave macrocycle **1** under high dilution.

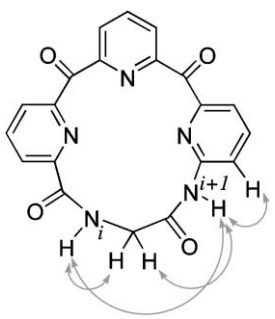

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Fig. 1 Macrocycle **1** highlighting observed NOE interactions.

NMR analysis of macrocycle **1**, which exists as a pair of inverting enantiomers, reveals a number of NOE signals (Fig. 1). The *i* and *i* + 1 N–H groups are proximal to each other and the glycine methylene. In addition, the *i* + 1 N–H shows a NOE with the H-atom *ortho* to the aniline nitrogen. These results, in combination with calculations (see below) and IR data (supporting information†), suggest that **1** does not form a γ-turn conformation with a hydrogen bond between the *i* + 1 N–H and the *i* − 1 carbonyl.

The converging pyridine moieties of **1** make for a rather narrow complexation site ill-suited for binding tetra-alkyl ammonium (TBA) ions. Hence, various TBA salts were complexed with **1** to evaluate how 'isolated' anions bound to the host (Table 1). Addition of aliquots of the salts caused a significant downfield shift (>0.5 ppm) of the NMR signals from the amide groups; both are involved in binding the anion. Only the binding of TBA fluoride resulted in slight shifts of the signals from the tris(pyridyl) moiety. These observations suggest that by-and-large the ammonium component of the TBA guests interact minimally with the host.

In general, associations were relatively weak, with the strongest binding observed with the strongest hydrogen bond accepting fluoride ion. In contrast, PF_6^-, a weak hydrogen bond acceptor, showed no affinity with **1**. Overall, there appears to be no simple relationship between ion basicity or size and the binding data. Presumably, the observed trend is a result of an amalgamation of these factors and the extent to which the different ion pairs dissociate.

The mono-alkyl ammonium salt binding properties of **1** were examined with salts of L-phenylalanine methyl ester (Table 1). Binding of these chiral guests was fast on the NMR timescale and therefore it was not possible to observe individual diastereomeric complexes. Rather, complexation led to downfield shifts of both amide (>0.5 ppm) and pyridyl (0.1–0.2 ppm) signals. All the amino acid salts bound more strongly than their TBA counterparts did. For example, the binding constant for the association of host **1** with the nitrate salt of the amino acid was 18,400 M^{-1}, whereas the corresponding association constant for the TBA salt was only 70 M^{-1}. These differences, along with the NMR shift data, suggest that the mono-alkyl ammonium ion binds much more strongly to the tris(pyridyl) array. However, similar trends for both series of salts were observed: $NO_3^- > Cl^- > CF_3CO_2^- > Br^- \approx TsO^- > I^-$.

The differences between mono-alkyl ammonium and TBA salt binding confirm the notion that when both components of the guest can bind, association is stronger. Equally as informative are the cooperativity factors,[6] the K_a ratio for binding the two salts

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b414923h/

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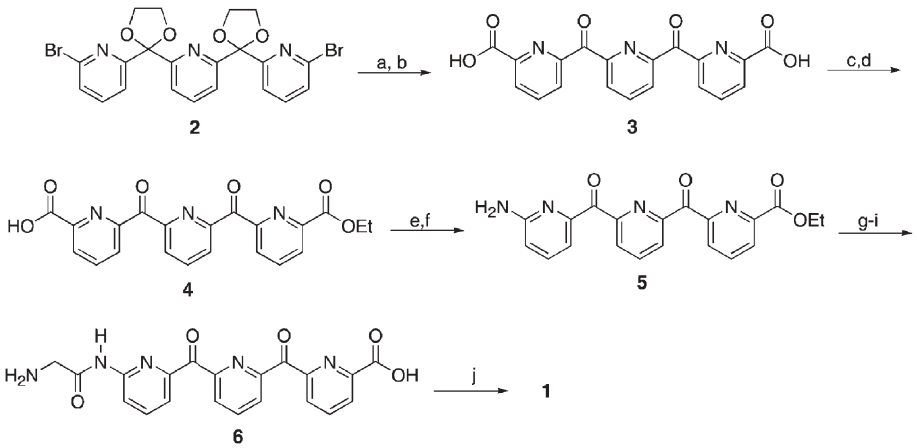

Scheme 1 Synthesis of **1**. *Reagents and Conditions*: a) CuCN, pyridine, reflux (98%); b) conc. HCl, reflux (90%); c) EtOH/HCl, (75%); d) 1 eq. NaOH (65%); e) DPPA/*t*-BuOH, reflux (60%); f) TFA/CH_2Cl_2, (95%); g) Boc-Gly-OH, HBTU, HOBt (60%); h) 1.1 eq. NaOH (85%); i) 10% HCl (80%); j) DPPA/DMF (32%).

Table 1 Association constants[a] between **1** and various ammonium salts

$^+NBu_4$ salt	K_a (M^{-1})	$^+H_3NCH(Bn)CO_2Me$ salt	K_a ($\times 10^3$ M^{-1})	Cooperativity factor[b]
F^-	110	F^-	—[c]	—[c]
Cl^-	63	Cl^-	12.1	190
Br^-	40	Br^-	1.9	48
I^-	32	I^-	0.4	13
PF_6^-	—[d]	PF_6^-	—[c]	—[c]
NO_3^-	70	NO_3^-	18.4	257
$CF_3CO_2^-$	52	$CF_3CO_2^-$	6.3	121
TsO^-	42	TsO^-	1.5	36

[a] At 298 K, initial [**1**] = 1.0 mM in $CDCl_3$. Errors are $\pm 10\%$. [b] $(K_{a(\text{amino acid})}/K_{a(\text{TBA})})$. [c] Guest insoluble in $CDCl_3$. [d] No binding observed.

(Table 1). These demonstrate that when both ions of the guest bind, overall binding is enhanced when the anionic component is a better guest. Thus, strongly binding nitrate ion leads to a cooperativity factor of 257, while weakly binding iodide results in a cooperativity factor of 13.

Modelling provides some insight into binding. MMFF94 calculations demonstrated that the free host preferentially adopts a conformation in which the central pyridine ring is antiparallel to the other two (supporting information†). In this conformation only one minimized structure, with the *i* N–H pointing towards the ammonium binding site, could be identified. In contrast, constraining the host to an idealized conformer so that all three pyridine rings can potentially hydrogen bond with an ammonium guest, resulted in two stable conformers with the *i* or the $i+1$ N–H pointing towards the binding site (supporting information†). Both allow same-side, ion-pair binding in which the amide N–H forms a hydrogen bond to the anion lying adjacent to the cation. However, the conformer with the inward pointing $i+1$ N–H was preferred by *ca.* 5 kJ mol^{-1}. NMR shift data also suggests that this conformer predominates; it is the signal from the $i+1$ N–H that undergoes the largest shift upon salt binding. Consequently, we used this conformer as a starting point for *ab initio* calculations of the $MeNH_4^+F^-$ complex. The result of these Hartree–Fock calculations (6-31G** basis set) is shown in Fig. 2. The (again) unconstrained host is calculated to move back towards its minimum conformation in the free state, while the guest is seen to partially decomplex. However, although two $N_{pyr}\cdots H\text{–}N^+R_3$ distances are calculated to lengthen, in compensation the $i-1$ carbonyl and the F^- ion are within hydrogen bonding distance of one of the ammonium hydrogens. Hence, these calculations suggest that the tris(pyridyl) array lacks some preorganization, but guest complexation is strengthened by the other donor and acceptors on the host. Current studies are focused on further analysis of host **1** and the synthesis of chiral, ditopic macrocycles for enantiomeric recognition of ammonium salts.

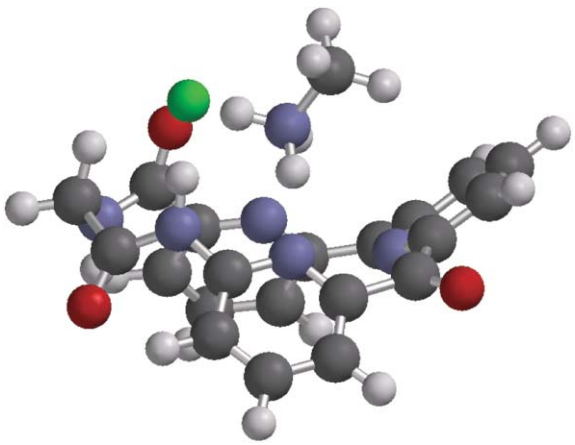

Fig. 2 Calculated structure of **1** binding $MeNH_3^+F^-$.

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