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Enantioselective recognition of a chiral quaternary ammonium ion by C_3 symmetric cyclic hexapeptides

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Received (in Columbia, MO, USA) 25th February 2003, Accepted 24th March 2003
First published as an Advance Article on the web 23rd April 2003

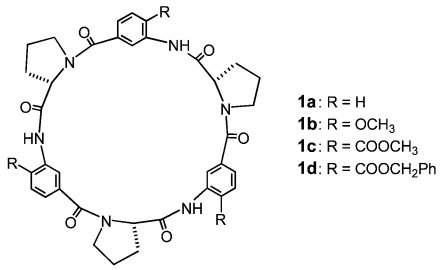
C_3 Symmetric cyclic hexapeptides containing alternating L-proline and 3-aminobenzoic acid derivatives as subunits possess different affinities towards the two enantiomers of the *N*,*N*,*N*-trimethyl-1-phenylethyl ammonium cation.

Artificial receptors that differentiate between the two enantiomers of a given substrate not only mimic a key feature of biological systems but can also serve as chiral catalysts or carriers. Such receptors are therefore of great interest in bioorganic and supramolecular chemistry. After pioneering work by Cram who showed that a chiral crown ether preferentially binds one enantiomer of an amino acid derivative,[1] numerous other C_1 or C_2 symmetric crown ether derivatives with improved chiral recognition properties have been described.[2] Initial attempts to achieve enantioselective binding with receptors of higher symmetry, particularly C_3 or D_3, were unsuccessful, however, and it was concluded that such systems are not capable of chiral recognition at all.[3] The contrary could be demonstrated, for example, with C_3 symmetrical receptors binding peptides selectively[4a] and, more recently, for a tris(oxazoline) based host.[4b]

We have reported some time ago that cyclic hexapeptides containing L-proline and 3-aminobenzoic acid or derivatives of this non-natural aromatic amino acid in an alternating sequence form complexes with quaternary ammonium ions in chloroform.[5] These peptides are, of course, chiral and possess C_3 symmetry, which raised the question if they interact with chiral quaternary ammonium ions enantioselectively. To the best of our knowledge, only one other group has addressed the stereoselective recognition of chiral quaternary ammonium ions with artificial receptors so far. Although the homoazacalix[4]arene hosts used in these studies form diastereomeric complexes with racemic cations, almost no difference in complex stabilities could be detected.[6] Here, we show that, depending on their structure, our cyclopeptides bind the two enantiomers of the *N*,*N*,*N*-trimethyl-1-phenylethyl ammonium cation with appreciable selectivity.

Four different cyclopeptide derivatives were chosen to evaluate the influence of the cyclopeptide structure on chiral recognition. Peptide **1a** is composed of alternating L-proline and unsubstituted 3-aminobenzoic acid subunits. In the other cyclopeptide derivatives, methoxy (**1b**) or ester (**1c,d**) groups in the 4-position of the aromatic subunits restrict the orientation of the secondary amide groups thus causing a better receptor preorganisation for cation binding.[5b] In addition, we expected that contributions of the cyclically arranged aromatic substituents in **1c,d** to the chiral environment inside the cyclopeptide cavity affect chiral recognition favourably, and that the phenyl groups in the periphery of **1d** assist in cation binding by cation–π interactions. As guests we used the picrate salts of the *R*, *S*, and the racemic *N*,*N*,*N*-trimethyl-1-phenylethylammonium cation (**2*S***, **2*R***, **2*rac***). Picrate was chosen as counterion because it does not bind to the NH groups of **1a**,[5a] and only weakly interferes in interactions between artificial receptors and cations in non-polar solvents.[7]

We have shown that the interaction between our cyclopeptides and quaternary ammonium ions induces an upfield shift of the guest signals in the ^{1}H-NMR spectrum.[5] The same effect was also observed upon binding of **1a–d** to **2**, allowing us to use the established methodology also for the characterisation of the cyclopeptide complexes of the chiral cation. In Fig. 1, the ^{1}H-NMR spectra of **2*R***, and those of the complexes between **1b** and **2*R***, **2*S***, and **2*rac*** in 0.1% d_6-DMSO–$CDCl_3$ are depicted.



The upfield shifts of the guest CH and $N(CH_3)_3$ signals caused by complex formation are clearly visible. Interestingly, these shifts are larger in the complex of **2*R***. Moreover, the interaction of **1b** with **2*rac*** causes a splitting of the guest signals, clearly illustrating the formation of diastereomeric complexes. Under the chosen conditions, the distances of the pairs of $N(CH_3)_3$ and CH signals amount to 0.06 ppm and 0.22 ppm, respectively, which made us confident that, in spite of their C_3 symmetry, our cyclopeptides are well suited for enantioselective interactions with quaternary ammonium ions.

In order to confirm this assumption we determined the association constants of the complexes between **1a–d** and the two enantiomers **2*R*** and **2*S*** individually with the help of NMR titrations.[8] The non-linear regressions of the saturation curves

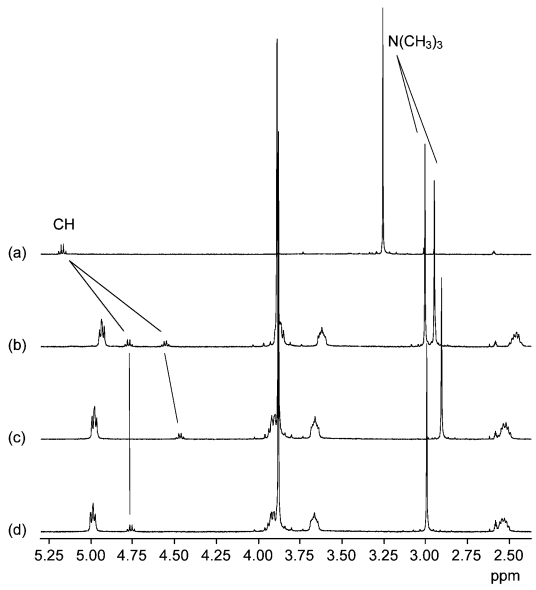


Fig. 1 ^{1}H-NMR spectra of **2*R*** (1 mM) (a) and of the complexes between **1b** (1 mM) and **2*rac*** (1 mM) (b), **2*R*** (0.5 mM) (c), and **2*S*** (0.5 mM) (d) in 0.1% d_6-DMSO–$CDCl_3$.

DOI: 10.1039/b302092d

obtained were based on the mathematical treatment of 1:1 complex formation, a stoichiometry that was validated by Job-plots for the complexes of **2*R*** with **1b** and **1c**. The results of these binding studies are summarised in Table 1.

Consistent with our previous findings, **1c** forms the most stable complexes with the quaternary ammonium ion.[5b] The complex of **1d** is somewhat less stable, indicating that the additional aromatic sites in the periphery of the cyclopeptide cavity are not involved in cation binding. The stability constants of the complexes of **1a** and **1b** are of the same order of magnitude, which could be due to the size of the guest because **1b** binds a smaller, non-chiral *N*,*N*,*N*-trimethylbutyl ammonium ion *ca*. twice as well than **1a**.[5b] Important with respect to enantioselective recognition is that we observed different stability constants for the diastereomeric complexes of each cyclopeptide, and that in every case, the complexes of **2*R*** are more stable than the ones of **2*S***. Enantioselectivity is best for the substituted cyclopeptides **1b** and **1c**, both of which almost equally well differentiate between the two enantiomers of **2**. As expected, **1a** is somewhat less suited for chiral recognition, but the combination of the bulky substituents in the periphery of **1d** and the large guest also seems to be disadvantageous.

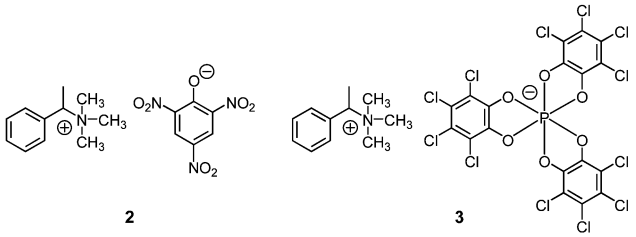
Although association constants determined by NMR titrations are generally well reproducible, the differences in K_a we observed for each pair of diastereomeric complexes is close to the error limit of the measurement. Therefore, we also carried out competitive NMR titrations, with which the ratio of the stability constants of two complexes can be determined directly. In such a titration, the shifts of both $N(CH_3)_3$ signals observed in the ^{1}H NMR spectrum upon complexation of **2*rac*** by a cyclopeptide are followed simultaneously, and the ratio $K_a(R)/K_a(S)$ is calculated from the resulting two saturation curves.[9] Table 1 shows that the ratios k_{exp} thus determined are all in very good agreement with the results of the individual titrations, and it is therefore safe to say that the investigated cyclopeptides are indeed able to enantioselectively interact with the chiral quaternary ammonium ion used. The de's determined for **1b** and **1c**, although admittedly low, are the largest ones reported for the chiral recognition of this cation by an artificial host so far.

A number of investigations have shown recently that the stabilities of complexes between cations and artificial receptors such as calixarenes and cyclophanes are strongly affected by the counterion.[5b,7] In general, higher stability constants are observed in the presence of larger, more lipophilic anions. In the context of chiral recognition, one could expect that the nature of the anion not only influences the strength of the interactions between an artificial receptor and its substrate but the enantioselectivity as well. We therefore also tested the affinity of one cyclopeptide (**1b**) towards the racemic TRISPHAT salts of the *N*,*N*,*N*-trimethyl-1-phenylethyl ammonium cation (**3*R***, **3*S***, **3*rac***). TRISPHAT was chosen because of its weak effect on the NMR spectrum of this ammonium ion.[10a] In the enantiopure form, TRISPHAT is an efficient chiral shift reagent for cationic metallo-organic and organo-metallic substrates.[10b,c]

Table 1 Stabilities of the *N*,*N*,*N*-trimethyl-1-phenylethyl ammonium complexes of **1a–d**[a]

Peptide	Salt	K_a	$\Delta\delta_{max}$	$\Delta\Delta G$	k_{calcd}	k_{exp}	de
1a	**2*R***	1580	0.66	0.43	1.19	1.12	8
	2*S*	1330	0.66				
1b	**2*R***	1550	0.65	1.01	1.50	1.41	21
	2*S*	1030	0.67				
	3*R*	4410	0.69	0.98	1.49	1.52	20
	3*S*	2980	0.71				
1c	**2*R***	4550	0.54	0.99	1.49	1.41	20
	2*S*	3050	0.54				
1d	**2*R***	3620	0.55	0.34	1.15	n.d.	7
	2*S*	3150	0.56				

[a] T = 298 K; K_a = stability constants in M^{-1}, error limits of K_a < 15%; $\Delta\delta_{max}$ = maximum chemical shift of the $N(CH_3)_3$ signal in ppm; $\Delta\Delta G$ in kJ mol^{-1}; de = diastereomeric excess in %; k_{exp}, k_{calcd} = experimental and calculated ratios $K_a(R)/K_a(S)$.



2 **3**

As expected, our NMR titrations revealed an increase in cation complex stability upon replacement of picrate by the more lipophilic TRISPHAT anion (Table 1). An effect on enantioselectivity could not be detected, however.

In conclusion, we could demonstrate the potential of our cyclopeptides in the chiral recognition of quaternary ammonium ions. Future work will now deal with the influence of the absolute configuration of the anion on chiral recognition. Such binding studies could reveal interesting new aspects of the anion effect on cation binding in non-polar solvents. Furthermore, we will also elucidate the structure of the complexes to reveal the origin of enantioselectivity, and analyse the influence of the cation structure on complex stability. In this context, the complexation of biologically relevant quaternary ammonium ions such as carnitine or methacholine is of special interest.[11]

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