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Matched/Mismatched Interaction of a Cyclic Hexapeptide with Ion Pairs Containing Chiral Cations and Chiral Anions

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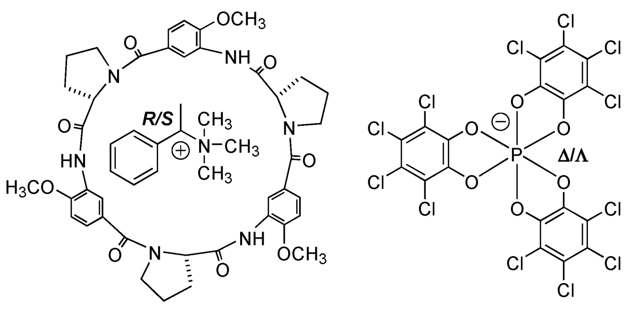

Complex Stability: ***R*Δ > *R*Λ > *S*Δ > *S*Λ**

The binding of a chiral quaternary ammonium ion to a cyclopeptide containing aromatic amino acid subunits is affected not only by the configuration of the cation but also by the configuration of the chiral counterion. Analysis of the binding equilibria shows that complex formation involves interaction of the whole ion pair with the host indicating that steric requirements of the anion influence complex geometry and stability.

The recognition of cations by synthetic receptors in nonpolar solvents is strongly affected by the counterion causing the unusual effect, for example, that an interaction of a receptor with the cation of an ion pair can be completely suppressed by the choice of the anion.[1] Although an influence of anions on the affinity of cation hosts was noticed some time ago,[2–4] systematic investigations into the nature of this effect were carried out only recently by Dalla Cort et al.[5] and, in particular, Roelens and co-workers.[1] Both groups showed that variation of the anion causes an increase in the association constants of calixarene and cyclophane complexes with quaternary ammonium ions in chloroform in the order acetate < tosylate < chloride < iodide < picrate. This sequence is essentially independent of the receptor and also applies to the interaction of quaternary ammonium ions with the cyclic hexapeptides investigated by us.[6a,b] It can change, however, if the receptor binds both components of an ion pair simultaneously,[6c,d,7] or if interactions with the anion change the electronic properties of the receptor.[8]

One way to rationalize the influence of the anion on cation binding is based on the assumption that charge polarization in the ion pair causes a nonsymmetrical charge distribution in the cation that is the more pronounced the higher the anion's charge density.[1b,c] This interpretation is consistent with the observations that anions with a more dispersed negative charge inhibit cation binding to a lesser extent and that each anion possesses a characteristic inhibiting effect independent of host structure.[1d] The interpretation ascribing the anion effect to ion pair formation competing with cation/receptor interactions[5] is supported by results indicating that, at least for cation-π interactions, anions do not affect the intrinsic interaction between a cation and a host but compete with the cation for binding sites in the complex.[9] Here we show that steric requirements of the anion can also have an effect on cation binding in nonpolar solvents. Previous investigations such as the characterization of complexes formed between a cyclophane and various acetylcholine salts only provided indirect evidence for this aspect of the anion effect so far.[1c]

The work described in this paper is based on our finding that cyclic hexapeptides containing alternating L-proline and 3-aminobenzoic acid derived subunits, for example, the methoxy-substituted derivative **1**, can dis-

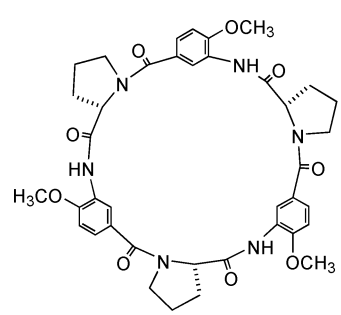

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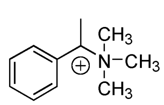
TABLE 1. Association Constants K_a of the *N,N,N*-Trimethyl-1-phenylethylammonium Complexes of 1 in the Presence of Various Anions in 0.1% d_6-DMSO/CDCl$_3$[a]

guest	K_a	$-\Delta\delta_{max}$	k_{calcd}	k_{exp}	$\Delta\Delta G$
[(*R*)-**2**][**3**][b]	1550	0.646	1.50	1.41	1.01
[(*S*)-**2**][**3**][b]	1030	0.666			
[(*R*)-**2**][(Δ)-**4**]	5210	0.736	1.96	1.69	1.60
[(*S*)-**2**][(Δ)-**4**]	2660	0.795			
[(*R*)-**2**][(Λ)-**4**]	2890	0.692	1.39	1.35	0.82
[(*S*)-**2**][(Λ)-**4**]	2080	0.715			

[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*-methyl signal; $\Delta\Delta G$ in kJ mol^{-1}; k_{exp}, k_{calcd} are the experimental and calculated ratios $K_a(R)/K_a(S)$. [b] Cited from ref 10.

tinguish the enantiomers of chiral cations such as the *N,N,N*-trimethyl-1-phenylethylammonium ion in salt [**2**][**3**].[10] The ability of **1** or structurally related cyclopeptide derivatives to interact with quaternary ammonium ions in chloroform has previously been demonstrated by us.[6a,b] Binding occurs inside a cavity lined by the aromatic peptide subunits, which causes the resonance of the cation protons in the ^{1}H NMR to shift to lower frequencies upon complex formation thus allowing the complex stability to be determined by means of NMR titrations.[11,12]

Such titrations clearly demonstrated that the affinity of **1** toward both enantiomers of the cation in the picrate salt [**2**][**3**] differs slightly with [(*R*)-**2**][**3**] being somewhat better bound than [(*S*)-**2**][**3**]. The ratio $k_{calcd} = K_a(R)/K_a(S)$ thus determined could be verified experimentally by means of competitive NMR titrations by using [*rac*-**2**][**3**] as guest.[10] The results of these investigations are summarized in Table 1.



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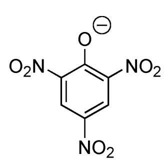

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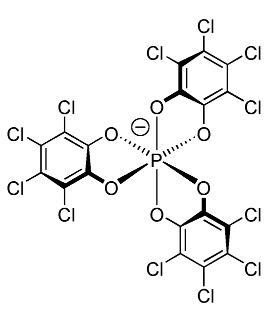
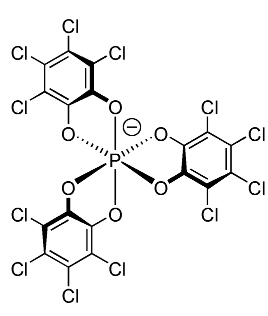


Δ-**4**



Λ-**4**

To address the question of whether the configuration of a chiral anion can also affect cation binding of **1** we subsequently turned our attention to guests that contain a combination of enantiomerically pure cations and anions. With respect to the anions we concentrated on the lipophilic TRISPHAT anion **4**,[13a,b] which is readily available in the Δ-form and the Λ-form.[13c] The four salts [(*R*)-**2**][(Δ)-**4**], [(*S*)-**2**][(Δ)-**4**], [(*R*)-**2**][(Λ)-**4**], and [(*S*)-**2**][(Λ)-**4**] containing all possible combinations of (*R*)- and (*S*)-**2** as well as (Δ)- and (Λ)-**4** were thus prepared according to previously published procedures[13d,e] and binding of these salts to **1** was studied by means of NMR titrations following the shift of the *N*-methyl signal of the cation.

Complex formation between **1** and **2** has previously been shown to proceed with 1:1 stoichiometry.[10] The saturation curves resulting from NMR titrations involving a neutral host and the ion pair of a charged guest can only be evaluated on the basis of the simple mathematical model of 1:1 binding, however, if the host binds to the undissociated ion pair. The analysis becomes more complicated if ion pair dissociation precedes complex formation, but methods to evaluate the parameters that fully describe such coupled equilibria have recently been developed.[14] According to this work, a way to test whether ion pair dissociation has to be considered in the analysis of NMR titrations or not involves inspection of the concentration dependency of the binding constants. If K_a is invariant with concentration, whole ion pairs are bound to the host, whereas variation of K_a at different concentrations of either host or guest indicates that ion pair dissociation cannot be neglected.[14b] Application of this method to the titration of **1** with [(*R*)-**2**][(Δ)-**4**] is presented in Table 2. The binding constants were calculated from $K_a = (\Delta\delta/\Delta\delta_{max})/[1 - (\Delta\delta/\Delta\delta_{max})]\{[H]_0 - (\Delta\delta/\Delta\delta_{max})[G]_0\}$, where $[H]_0$ and $[G]_0$ are the initial concentrations of respectively the cyclopeptide and the salt, $\Delta\delta$ is the chemical shift of the *N*-methyl signal of the cation with respect to the resonance of the uncomplexed species $\delta_0 - \delta$, and $\Delta\delta_{max}$ is the maximum shift $\delta_0 - \delta_{max}$ resulting from an extrapolation of the experimental data.[15] $\Delta\delta_{max}$ amounts to -0.736 in this case.

TABLE 2. Association Constants K_a Calculated for Different Initial Concentrations of 1[a]

$[H]_0$	$[G]_0$	$-\Delta\delta$	$\Delta\delta/\Delta\delta_{max}$	K_a
0.20	0.20	0.291	0.396	5430
0.40	0.20	0.437	0.594	5190
0.60	0.20	0.516	0.702	5120
0.80	0.20	0.565	0.769	5140
1.00	0.20	0.596	0.811	5110
1.20	0.20	0.619	0.841	5140
1.40	0.20	0.635	0.863	5140
1.60	0.20	0.648	0.882	5230
1.80	0.20	0.660	0.897	5360
2.00	0.20	0.668	0.908	5450

[a] K_a = stability constants in M^{-1}, concentrations in mM, $\Delta\delta_{max} = -0.736$.

Table 2 clearly shows that K_a is practically independent of the initial concentration of **1** for this host/guest pair. Since we obtained similar results for all complexes we

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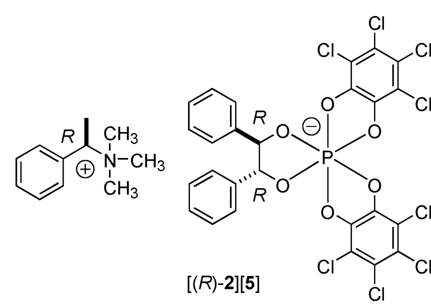
investigated (see the Supporting Information), dissociation of the TRISPHAT salts prior to complex formation is unlikely. Three additional independent results support this assumption. First, concentration-dependent ^{1}H NMR spectroscopy showed that the resonances of the cation signals are almost unaffected by varying the concentration of, for example, [(*R*)-**2**][(Δ)-**4**] between 2.00 and 0.01 mM (see the Supporting Information) indicating that the same species are present in solution in this concentration range. Second, the results of the NMR titrations are independent of whether the concentration of the cyclopeptide is varied or the salt. Thus, titration of [(*R*)-**2**][(Δ)-**4**] with **1** and assuming a 1:1 complex formation yielded a K_a of 5210 M^{-1} and the reverse titration a K_a of 5120 M^{-1}. Finally, diffusion NMR spectroscopy demonstrated that TRISPHAT salts of quaternary ammonium ions form contact ion pairs in chloroform.[16] Taken together, these results strongly indicate that complex formation involves interactions between **1** and undissociated ion pairs. Consequently, the saturation curves of the NMR titrations can be treated on the basis of 1:1 binding and the association constants thus obtained describe the stability of the ternary complexes formed between **1** and both components of the guest. These constants are also included in Table 1. Again, competitive NMR titrations with the salts [*rac*-**2**][(Δ)-**4**] and [*rac*-**2**][(Λ)-**4**] as guests essentially confirmed the ratios $K_a(R)/K_a(S)$ calculated from the individual titrations.

Table 1 demonstrates that, independent of the cation, replacing the picrate anion with TRISPHAT in the guests causes an increase in complex stability, an effect that is consistent with the more dispersed charge over the larger anion.[1b,c] In addition, complex stability is not only affected by the configuration of the cation but by that of the anion as well, which causes the ion combination in [(*R*)-**2**][(Δ)-**4**] to give rise to the most stable complex and that in [(*S*)-**2**][(Λ)-**4**] to the least stable one. The remaining two salts form complexes of intermediate stability. Comparison of the binding constants of complexes differing only in cation configuration shows that the configuration of the anion has no effect on the preference of **1** for the *R*-cation indicating that it is most probably an intrinsic property of the host. Anion configuration does, however, affect diastereoselectivity, which is larger in the presence of the Δ-anion ($K_a(R)/K_a(S) = 1.96$) than in the presence of the Λ-anion ($K_a(R)/K_a(S) = 1.39$). As a consequence, inversion of the anion configuration in complexes containing the same cation can cause a difference in complex stability up to a factor of almost 2 (K_a([(*R*)-**2**][(Δ)-**4**])/K_a([(*R*)-**2**][(Λ)-**4**])).

Considering the size and the charge density of TRISPHAT anions it seems unlikely that differences in charge polarization of the diastereomeric salts could be responsible for such a large effect. Since **1** also does not contain a specific binding site for an anion, particularly not for a TRISPHAT anion, it is more likely that steric reasons account for the effect of the anion on complex stability. Thus, the arrangement of the partners in the ion pair of [(*R*)-**2**][(Δ)-**4**] obviously allows tight interactions of the cation with **1**, whereas the anion in [(*R*)-**2**][(Λ)-**4**] prevents a similarly favorable complex geometry. This interpretation is consistent with the diastereomeric nature of the complexes of **1** with the four TRISPHAT salts. It also implies, however, that these complexes possess well-defined structures in which the positions of the cation and the anion are controlled by the mutual arrangement of the oppositely charged ions in the close ion pair and by the structure of the host. Unfortunately, our attempts to gain a deeper insight into the structural causes responsible for the different stabilities of complexes of **1** with diastereomeric ion pairs failed. Neither did NOESY NMR spectroscopy provide conclusive information on complex structure in solution nor could we obtain crystals of the complexes that would allow a structural assignment in the solid state. We are therefore currently unable to precisely specify whether the observed diastereoselectivity in complex formation is due to the different structures of the diastereomeric guests alone or whether there is an additional effect of host structure on the arrangement of the oppositely charged ions in the complexes. Important information supporting our interpretation can still be derived from the results of the NMR titrations and the respective NMR spectra.

First, we observed unequal maximum chemical shifts of the cation protons in the diastereomeric complexes of **1** with the shift of, for example, the *N*-methyl protons of (*R*)-**2** generally smaller that that of (*S*)-**2**. These shift differences account for differences in the inclusion geometries of the cations into the cavity of **1** and they show that, independent of the anion, the inclusion geometries of cations with the same absolute configuration are probably similar. Interestingly, a larger maximum chemical shift does not correlate with a larger complex stability.

Second, an upfield shift of the picrate signal in the NMR upon binding of [**2**][**3**] to **1** demonstrates the tight association of the anion with the other components of the complex. A similar shift has been observed during complex formation between picrate salts and calixarenes[5] or aromatic group-containing crown ethers.[17] In these cases, the shift was attributed to a close proximity of the anion to the outer faces of the aromatic subunits of the hosts and we assume a similar arrangement also for the complexes between **1** and [**2**][**3**]. Since TRISPHAT anions are ^{1}H NMR silent the spectra of the NMR titrations provide no information on the location of this anion in the complexes. We therefore included another salt in our investigations, namely [(*R*)-**2**][**5**] containing a 70:30 ratio



[(*R*)-**2**][**5**]

of diastereomeric (*R*,*R*,Δ)- and (*R*,*R*,Λ)-HYPHAT anions whose characteristic structural feature is the presence

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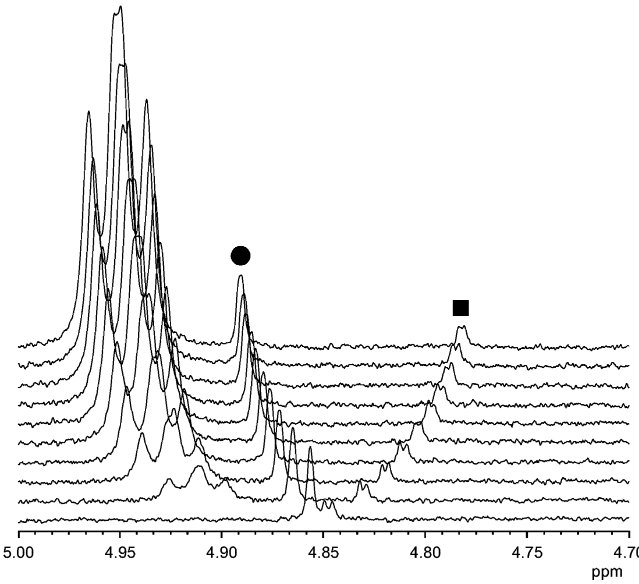

FIGURE 1. Effect of an addition of increasing amounts of **1** to a 0.2 mM solution of [(*R*)-**2**][**5**] in 0.1% d_6-DMSO/$CDCl_3$ on the resonances of the benzylic protons of the HYPHAT anion in the ^{1}H NMR. The bottom trace represents the spectrum of [(*R*)-**2**][**5**] in the absence of cyclopeptide and the top one the spectrum in the presence of 18 equiv of **1**. The circle and the square mark the signals of respectively the major and the minor HYPHAT diastereomer. The third signal in the spectrum originates from the cyclopeptide.

of a hydrobenzoin ligand.[18] Interestingly, our NMR spectroscopic characterization of the interaction between [(*R*)-**2**][**5**] and **1** not only demonstrated that chiral phosphate anions are an integral part of the complexes between the peptide and ion pairs, it also showed that the arrangement of the (*R*,*R*,Δ)-HYPHAT anion in the complexes distinctly differs from that of the (*R*,*R*,Λ)-anion.

Figure 1 shows the region of the ^{1}H NMR spectrum of the benzylic signals of the HYPHAT anion in [(*R*)-**2**][**5**] and the effect of an addition of increasing amounts of **1**. As in the case of picrate, significant shifts of the anion signals occur but whereas the signal of the major HYPHAT diastereomer shifts downfield with increasing concentration of the cyclopeptide, that of the minor diastereomer shifts upfield indicating that the benzylic proton of one anion is located in a more deshielding environment in the complex and that of the other in a more shielding one. The opposite shift changes can therefore be regarded as clear evidence for different overall structures of the ternary complex between **1** and [(*R*)-**2**][**5**] that are induced by the stereochemistry of the anion. We therefore conclude that, even if the primary target of a host is a cation and the counterion is only indirectly involved in complex formation as part of an ion pair in nonpolar media, the shape of the anion can affect the overall structure of the ternary complexes formed and, as a consequence, also complex stability.

This work thus provides direct evidence that not only electronic properties but also the shape of anions can account for their influence on the interaction between a cation and a synthetic host. In addition, the anion effect detected in our system represents an example for a matched/mismatched relationship in the formation of supramolecular complexes. The matched case is obviously represented by the complex between **1** and [(*R*)-**2**][(Δ)-**4**], which is the most stable one. Inversion of the configuration of either the cation or the anion of the guest causes a reduction in complex stability, and the corresponding salts can thus be regarded as mismatched guests. The least stable complex is, however, formed if both the configuration of the cation and the anion are inverted with respect to [(*R*)-**2**][(Δ)-**4**].

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Supporting Information Available: Results of all NMR titrations including the evaluation of the concentration dependence of K_a and the concentration dependence of the resonance of the *N*-methyl protons of [(*R*)-**2**][(Δ)-**4**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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