Enantiomeric Recognition between Chiral Triazole-18-crown-6 Ligands and Organic Ammonium Cations Assessed by ^{13}C and ^{1}H NMR Relaxation Times

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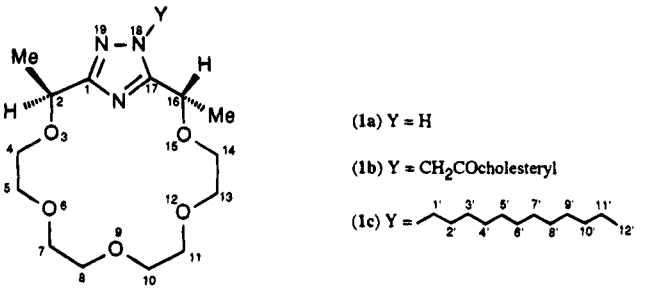
Enantiomeric recognition by a chiral triazole-18-crown-6 compound with the enantiomers of [1-(1-naphthyl)ethyl]ammonium cation ($HNEA^+$) has been investigated via ^{13}C and ^{1}H longitudinal relaxation time (T_1) measurements. The results reveal an interesting face selectivity of the organic ammonium cation for the planar triazole-crown ether host in solution. Steric interactions between the bulky aromatic group of the guest and the chiral centers of the host as well as at the connection end of the lipophilic side arm are clearly indicated by the substantial T_1 reductions in the diastereomeric complexes. These are probably responsible for the enantiomeric recognition observed.

Introduction

Not long ago, we reported enantiomeric recognition of chiral triazole-crown ethers **1a–c** for the enantiomers of [1-(1-naphthyl)ethyl]ammonium ($HNEA^+$) chloride and of 1-phenylethylammonium ($HPEA^+$) chloride in $CDCl_3$. These complexes were studied via binding constants and equilibrium competition using NMR spectroscopy.[1] For both triazole-substituted (*S,S*) chiral hosts, **1b** and **1c**, preferential binding with the *R*-enantiomers of the organic ammonium cations over the *S*-enantiomers was confirmed by the significant differences in K_a values, ranging from 2.9- to 3.4-fold. Although proton chemical shift changes upon complexation provided some information about the overall structures of the diastereomeric complexes, the structural basis responsible for enantiomeric recognition was not specifically identified. Davidson et al.[2] have reported the crystal structures of the diastereomeric complexes between dimethylpyridino-18-crown-6 (**2**) and [1-(1-naphthyl)ethyl]ammonium cation. The enantiomeric recognition in this analogous system has been attributed to the steric interaction between the methyl group of the host and a proton of the naphthyl group.[2,3] Although there are some similarities between **1** and **2**, two important structural differences must be stressed here. First, the chiral centers in **1** are directly bonded to the triazole ring and are thus more rigid. This is probably the reason for the better enantiomeric recognition ability of **1** versus **2**. The correlation between the enantiomeric recognition ability and the flexibility of the chiral centers in the crown ether derivatives has been recognized by Izatt et al.[4] in an analogous system containing a chiral pyridino-18-crown-6 molecule and its



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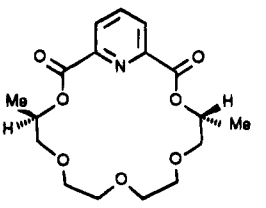

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2,16-diester derivative. The former displayed less enantiomeric recognition because its structure is flexible enough to adjust its conformation to relieve the strain energy caused by the steric repulsion during guest complexation. Second, in **1b** and **1c** the triazole NH proton present in **1a** is substituted by a lipophilic side arm. The sidearm attachment results in loss of the C2 symmetry of the macrocycle. These structural differences can lead to different steric interactions between the host and the guest and alter the recognition mechanism.

Longitudinal relaxation times (T_1) are a sensitive probe for investigating dynamic properties of organic molecules. ^{13}C T_1 has been used successfully to provide considerable information on ligand structural properties, binding strengths, and binding dynamics of crown ether molecules.[5–8] These parameters have not been extensively used to study enantiomeric recognition. In this report,

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Table 1. ^{13}C Longitudinal Relaxation Time T_1 (s) of 1c and Its Diastereomeric Complexes in $CDCl_3$

	carbons												
	Me2	Me16	C1	C17	C1′	C2′	C3′–C10′						
δ^b (ppm) comp/T_1	20.13	19.89	163.2	155.6	48.95	31.90	26.77	29.22	29.33	29.47	29.54	29.62	30.11
1c	0.83	0.89	5.56	9.68	0.54	3.74	0.88	1.08	2.16	1.26	1.31	1.93	0.66
1c/(*R*)-HNEA$^+$	0.44	0.80	1.75	6.00	0.46	3.86	0.78	0.91	2.20	1.07	1.34	1.63	0.60
1c/(*S*)-HNEA$^+$	0.41	0.92	*a*	5.03	0.47	2.69	0.76	1.04	2.44	1.17	1.28	1.64	0.54

	carbons										
	C11′	C12′		C2–C16							
δ (ppm) comp/T_1	22.68	14.10	68.01	68.28	70.18	70.23	70.43	70.56	70.63	70.81	71.50
1c	4.71	3.83	0.72	0.76	0.90	0.82	0.85	0.94	0.90	0.90	0.92
1c/(*R*)-HNEA$^+$	4.59	3.79	0.28	0.46	0.45	0.42	0.42	0.54	0.36	0.45	0.65
1c/(*S*)-HNEA$^+$	4.58	3.48	0.38	0.45	0.53	0.56	0.57	0.57	0.51	0.52	0.82

[a] Signals broaden and intensity of the signals were too low for T_1 calculation. [b] ^{13}C chemical shift of **1c** in the absence of enantiomeric guests.

the studies of both ^{13}C and ^1H longitudinal relaxation times (T_1) of **1c** in the absence and presence of the HNEA$^+$ enantiomers unambiguously revealed the specific interactions involved in the enantiomeric recognition process.

Results and Discussion

^{13}C NMR T_1 relaxation times for the free and the diastereomeric complexes of **1c** with (*R*)- and (*S*)-HNEA$^+$, determined in $CDCl_3$, are reported in Table 1. The molecular structure of **1c** along with the atomic assignments are shown in **1**. Individual carbon resonance assignments were made on the basis of chemical shifts. In the case of Me2 and Me16, the assignment was based on a heteronuclear correlation experiment (HETCOR), which correlated the carbons with the methyl proton signals previously assigned via NOESY experiments.[1]

The results clearly show that formation of the diastereomeric complexes reduces the T_1s of all of the methylene carbons of the macrocycle (C2–C16) considerably. This phenomenon is usually associated with increasing molecular size and/or reduced freedom of molecular motion at the site of the interaction. In the current system it is due to H-bond formation between the crown ether and the ammonium cation. In general, the T_1s of the methylene carbons in (*R*)-HNEA$^+$/**1c** are shorter when compared to those of the *S*-complex, especially those at 70.23, 70.43, 70.63, and 71.50 ppm. It is known from previous work[1] that **1c** binds (*R*)-HNEA$^+$ 3.4 times better than the *S*-isomer, i.e., K_a's were found to be 811 vs 239 cal/mol. Therefore, the shorter T_1s for the methylene carbons in the *R*-complex are consistent with the stronger H-bonding interactions.

The ^{13}C T_1 of C1′, the methylene carbon at the connection end of the side arm to the triazole ring, was reduced about 15% from that of the free host in both diastereomeric complexes. Interestingly, the T_1 of C2′ in the *S*-complex was reduced significantly, from 3.74 to 2.69 s, while the T_1 of the same carbon in the *R*-complex remained the same as the one in the free host. These data indicate that motion of the sidearm at the connection point is restrained in the complexes. The extent of the effect is more pronounced in the *S*-complex. It was previously noted that upon formation of these diastereomeric complexes, H1′ of **1c** exhibited some shifts, −3 and −21 Hz for the (*R*)- and (*S*)-HNEA$^+$ complexes, respectively.[1] Much larger shifts in this region were also observed in the case of the **1b** complexes. These observations indicated that the host–guest interactions extended beyond the triazole ring of the host to the connection end of the side arm. The host–guest interactions around this region are expected to be weak but they seem to be the origin of an unexpected face selectivity upon cation binding, *vide infra*. Getting back to the relaxation time results, the rest of the lipophilic sidearm carbons did not show significant deviations of their T_1 values upon complexation; see Table 1. Therefore, only the first two carbons in the chain are affected by the complexation process.

Substantial ^{13}C T_1 decreases were observed at C1 and C17. These two carbons connect the triazole ring and the macrocycle. They are much less flexible compared to the methylene carbons of the macroring. Binding enantiomeric guests significantly restrained the molecular movement at these two positions even further. The T_1's of C1 and C17 of the *R*-complex decreased from 5.56 and 9.68 s in the free host to 1.75 and 6.00 s, respectively. In the case of the *S*-complex, the decrease of T_1's was even more pronounced. The T_1 of C17 decreased to 5.03 s, while the T_1 of C1 decreased so much that it was below the limit of accurate measurement. These significant T_1 changes, together with the constrained molecular movement at the connection end of the dodecyl group (C1′, C2′) and also the observation of a negative chemical shift for H1′ in the diastereomeric complexes, indicate that the aromatic group of HNEA$^+$ is held on top of the triazole moiety of the host in the diasteromeric complexes. The restrained molecular movement at pivot positions C1 and C17 is probably caused by a parallel orientation of the triazole ring relative to the naphthyl ring required if there is a π–π interaction. A π–π interaction between the host and the guest was suggested from the binding constant study based on the observation of a stronger binding of **1c** with HNEA$^+$ than with HPEA$^+$.[1] The obvious differences in T_1 changes at C1 and C17 between the diastereomeric complexes, the more pronounced decrease of T_1 exhibited by C2′, and the more negative chemical shift at H1′ for the *S*-complex suggest that the naphthyl group of the guests could be spatially closer to the triazole ring in the *S*-complex than in the *R*-complex.

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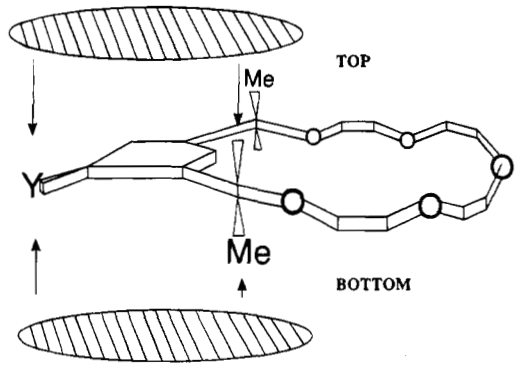

Figure 1. Schematic representation of the orientations of the naphthyl group relative to the macrocycle, illustrating the reason why there is face selectivity. The two-point interaction leads to two different faces for the macrocyclic host.

But the most interesting observation derived from these relaxation time studies is the face selectivity of these complexation reactions. Steric interactions between the host and the guest are clearly evident at position Me2, the methyl group at one of the chiral centers (on the top side of the molecular plane in **1**). Both complexes exhibit about a 50% reduction of the T_1 for Me2. On the other hand, the T_1 of Me16, the methyl group at the other chiral center (on the bottom side), remained essentially unchanged in the presence and absence of the ammonium substrates. This interesting observation indicates that the guests seem to be able to distinguish the two different sides of the host and selectively bind to one side, the top side, but not the other. This is surprising because based on a planar substituted triazole ring structure the two sides of the macrocycle itself should be equivalent. However, the two faces of the macrocycle can be different if, and only if, the chiral guests not only recognize the chiral centers of the host but also interact with the lipophilic sidearm connected to the triazole ring. If there is an interaction between the naphthyl group and the lipophilic side arm, the naphthyl group will prefer the orientation where the methyl group of the host points down from that side of the molecule. This would result in the top and bottom complexes with different energies. Figure 1 illustrates the orientation of the naphthyl group when the guest binds to the two different sides of the host. In the top configuration, Me16 is on the other side of where the guest binds. Obviously, less steric interactions would be involved in such a configuration when compared to the bottom configuration. Since both T_1 and chemical shift information discussed previously do indicate that the host–guest interaction extends beyond the triazole ring to the connection end of the side arm, it seems to explain consistently the observed face selective binding. In addition, the structural information obtained from the crystal structures of an analog system, that is, binding between **2** and HNEA+, reported by Davidson et al.,[2] also supports our observations. In the analog system, the naphthyl group of the guest is on top of the pyridino ring and part of the naphthyl group does extend beyond the pyridine ring, although in that case no side arm is attached to the pyridine ring. Kobayashi et al.[9,10] have reported that CH–π interactions are an important driving force for host–guest interactions in apolar organic media for binding of monools and acetylated compounds to resorcinol cyclic tetramer. Something similar may be present in the interaction between the naphthyl group and the side arm in the current case.

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Table 2. ^{1}H T_1 of 1c in $CDCl_3$ in the Presence and Absence of the Enantiomers of HNEA $^+Cl^-$

compound/T_1 (s)	H2	H16	H1′
1c	1.736	1.338	0.489
1c-(*R*)-HNEA+	1.172	0.594	0.413
1c-(*S*)-HNEA+	1.101	0.434	0.363

The aforementioned considerable T_1 reduction of Me2 clearly identifies a steric interaction between the methyl group and the enantiomeric guests. However, some difference of the T_1s of Me2 between the diastereomeric complexes was anticipated, but not observed. This suggests that the host–guest interactions at other regions of the host molecule should also be involved in the steric interactions and may be responsible for the chiral recognition process. This point is supported by the ^{1}H T_1 results obtained from these same samples.

Some interesting proton T_1 values are listed in Table 2. For protons, the T_1s of Me2 and Me16 could not be accurately measured for the free host and the *R*-complex due to signal overlap. For the same reason, proton signals of the macroring were not informative. Nevertheless, T_1 changes upon complexation for those well-separated signals, i.e., H2, H16, and H1′, revealed further steric interactions which were not revealed via ^{13}C T_1 studies.

The T_1 of H2 decreased about 30% upon complexation with both *R*- and *S*-guests, presumably caused by losing molecular freedom of the macroring upon binding. As observed for Me2, there is no obvious difference between diastereomeric complexes at this position. However, in the case of H16, the T_1 decreased pronouncedly upon complexation, 56% in the *R*-complex and 68% in the *S*-complex. It dropped 12% more in the *S*-complex. This observation is fully consistent with the face selectivity indicated by the ^{13}C T_1 study. The T_1 of H16, which is located on the top side of the molecule, is more strongly affected by cation binding. Although the T_1 of Me16 was not substantially affected by complexation, the hydrogen (H2) that is on the same side as Me16 was affected. This is probably a reflection of the fact that this proton is directly bonded to the crown ring, which surely becomes more rigid upon complexation.

For H1′, a similar situation was also observed. The T_1 of this proton in the *S*-complex decreases more than in the *R*-complex although the extent of the decrease at this position is much less when compared to that of H16. These complementary ^{1}H T_1 results strongly suggest that, in addition to Me2, H16 and H1′ are in the vicinity where the steric interactions between the host and the guests occur. The pronounced proton T_1 change of H16 as well as the obvious difference between the diastereomeric complexes indicate a relatively strong steric interaction close to this position. This could be a major cause for stereomercial bias in this particular system.

Similar ^{13}C T_1 experiments were also conducted for **1b** and its diastereomeric complexes with HNEA+. In this case, the cholesteryl signals overlap with those of other carbons around the binding site, rendering the T_1 study impossible. However, similar chemical shift changes to those of **1c** observed upon complexation suggested similarities in the recognition mechanism for the two chiral

hosts. Since the side arm of **1b** is rigid, and the connection end of the side arm to the macroring is also relatively more rigid, the interaction around this region could be more appreciable for this host molecule as indicated by the much larger chemical shift changes observed.[1]

Some structural features of the current system are similar to those observed for the crystals of the diastereomeric complexes between $HNEA^+$ perchlorate and **2**.[2] In the diastereomeric complexes of **2**, the guest naphthyl groups are adjacent to, and nearly parallel to, the host pyridino group. The distance between the two aromatic groups is 0.12 Å shorter in the less stable complex. The closer approach of the naphthyl to the pyridino moiety in the *S*-complex is partly responsible for bringing the hydrogen atoms of the naphthyl group closer to the substituent methyl group on the macrocycle ring compared to the corresponding distance in the *R*-complex, which result in the steric interactions between the host and the guest. Different from this system, the steric interactions between the enantiomeric $HNEA^+$ cations and **1c** not only involve the methyl group (Me2) but also the proton at the chiral center of the binding side (H16). The multiple points steric interactions in our system could be the result of the rigid chiral framework designed by direct attachment of the chiral centers to the triazole ring. This structural feature has generated an sensitive chiral receptor or a chiral matrix for the discrimination between enantiomers of $HNEA^+$ cation.

Experimental Section

The preparation of chiral macrocyclic compounds and the hydrochloride salts of (*R*)- and (*S*)-naphthylethylamine were reported previously.[1] Deuterated chloroform, $CDCl_3$ (Aldrich), was used directly as received. The experiments were conducted in $CDCl_3$ with a constant 1:1 host/guest ratio. NMR samples, consisting 0.6 mL of solution in 5 mm tubes, were degassed by at least four freeze–pump–thaw cycles and then sealed under vacuum.

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Varian VXR-400 spectrometer. Chemical shifts of the proton signals are referenced to the solvent signal and the chemical shifts of ^{13}C were referenced to the center peak of $CDCl_3$. All ^{13}C NMR measurements were performed under complete proton-noise decoupling conditions. The spectra were acquired with 48K data points and zero-filled to 128K. Sample concentrations were 10 and 20 mM for ^1H and ^{13}C T_1 studies, respectively. The sample concentration for ^{13}C T_1 measurement was limited by the solubility of the substrates in $CDCl_3$; hence, 1200–1600 scans were usually necessary for each τ value in order to obtain a reasonable signal to noise ratio. On the average, each run required 56–72 h to complete. A line broadening of 3.0 Hz was used for data processing to improve the signal to noise ratio. In the case of C1 and C17, a line broadening of 5.0 Hz was used because of their low intensity.

The inversion–recovery method was used. The pulse delay used for ^{13}C measurement was 10 s, which fully satisfied the requirement for complete relaxation for most of the carbons except C1, C17 as well as C11′ and C12′. The choice was limited by the practical time limit. However, since the same relaxation mechanisms should apply for the ^{13}C signals of the host molecules, given the presence or absence of the substrates, the partial relaxation data are valid and informative for the purpose of comparison between the complexes and the pure hosts as long as identical parameters are used for both cases. The pulse delay for ^1H T_1 measurement was 15 s. Eleven different pulse intervals, τ, were used for each individual measurement. T_1 values were calculated by the instrument automatically. Each experiment had a standard deviation for each signal of less than 10^{-2}.

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