Enantiotopic Group Recognition: Direct Evidence for Selective Complexation of Enantiotopic Groups by a Chiral Host

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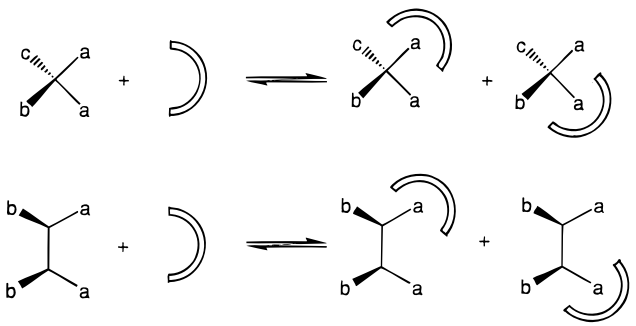
An important motivation for research in the area of synthetic host/guest chemistry is the desire to mimic natural biological systems in order to understand them better.[1] Many kinds of host molecules capable of distinguishing between two or more guest molecules have been the subject of extensive studies. Simple in concept but often most difficult in practice is enantioselective molecular recognition in which a chiral host molecule selectively binds one of two enantiomers in a racemic mixture.[2] In contrast to these phenomena, a different type of recognition event can be envisioned in which a chiral host distinguishes between two enantiotopic groups *in one and the same guest molecule* (Scheme 1).

A variety of reactions in synthetic organic chemistry using enzymes[3] or synthetic chiral reagents and catalysts[4] involve the stereoselective transformation of enantiotopic groups with the formation of chiral products. In some cases it has been postulated that selective complexation of one of the enantiotopic groups by the enzyme or chiral reagent occurs prior to the actual reaction, but to date no direct spectroscopic evidence for such enantiotopic group recognition has been presented. Here we describe our efforts at illuminating this type of phenomenon. Since it was known that certain chiral crown ethers bind chiral ammonium ions enantioselectively *via* hydrogen bonding,[1,2] we prepared the *bis*-ammonium triflates **1**−**3** to examine whether proper chiral hosts such as **4**[5] complex one of the H_3N^+ groups selectively (Scheme 2).

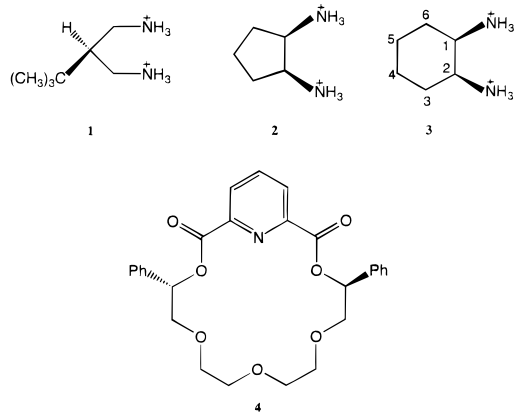
Job plots obtained by ^{1}H NMR spectroscopy confirmed that the stoichiometry of the relevant host/guest complexes is in all cases 1:1. For each of the *bis*-ammonium salts **1**−**3**, two diastereomeric complexes with **4** can be expected, each providing a set of NMR signals. However, in all cases just one set of signals was observed in the ^{1}H and ^{13}C NMR spectra at room temperature. While this would occur if the enantiotopic group selectivity were 100%, a second and more likely explanation is that rapid exchange of the guest molecules takes place, so that the observed shifts are weighted averages. The observation of two signals for, for example, the NH_3^+ protons is not itself evidence of *preferential* complexation of one of these groups, since these on time average become diastereotopic if any complexation with the chiral host molecule occurs. Under these conditions, splitting of the signals of the guest could be expected even if there were no selective complexation whatsoever. For this reason, in the case of the *bis*-ammonium salt **1** no conclusions could be reached as to whether enantioselective group recognition complexation was taking place even at low temperature. In contrast, upon reacting the *cis*-configurated *bis*-ammonium salts **2** and **3** with an equivalent amount of the chiral crown **4**, the presence of two diastereomeric 1:1 complexes was clearly demonstrated by NMR spectroscopy (Scheme 3).

Although the planar representation of **3** implies that it has a *meso*-configuration, the compound is in fact a racemic mixture of enantiomeric chair conformers undergoing rapid interconversion.[6] A detailed study of the complexation of **3** to **4** showed the existence of two diastereomeric complexes. At room temperature in CD_3CN/CD_2Cl_2 the ratio **6a**:**6b** is *ca.* 5:1 (or 1:5), indicating a significant preference of the host molecule

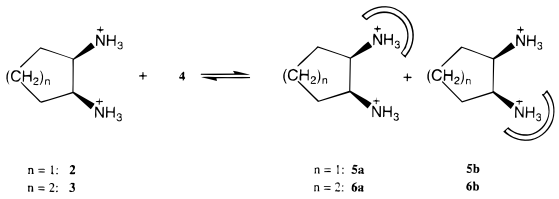
Scheme 1



Scheme 2



Scheme 3



(1) (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995. (b) Vögtle, F. *Supramolecular Chemistry*; Wiley: Chichester/England, 1991.

(2) (a) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383. (b) Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823.

(3) (a) Terradas, F.; Teston-Henry, M.; Fitzpatrick, P. A.; Klibanov, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 390. (b) Jones, J. B. *Aldrichimica Acta* **1993**, *26*, 105. (c) Faber, K. *Biotransformations in Organic Chemistry*; Springer: Berlin, 1992.

(4) Typical examples: (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (c) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (d) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (e) Paetow, M.; Ahrens, H.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323. (f) Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1989**, *54*, 2599. (g) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793. (h) Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566. (i) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477. (j) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1994**, 611. (k) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Cañas, F.; Pierson, A.; van Basten, A. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (l) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem.* **1995**, *107*, 2605; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395.

(5) Izatt, R. M.; Zhu, C. Y.; Dolley, N. K.; Curtis, J. C.; Kou, X.; Bradshaw, J. S. *J. Phys. Org. Chem.* **1992**, *5*, 656.

(6) (a) The same situation pertains to such molecules as *cis*-1,2-dimethylcyclohexane, which has been described by Eliel and Wilen as being an example of a molecule whose "averaged symmetry (C_{2v}) is higher than the symmetry of the contributing conformers (C_1)": Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 703. See also the earlier discussion by Jaffé, H. H.; Orchin, M. *Symmetry in Chemistry*; Wiley: New York, 1965; p 25. (b) It should be noted that even such molecules as *n*-butane have chiral conformations. See also discussion on chiramers of ethane: Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993**, *115*, 8278.

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for one of the enantiomeric conformers of **3**. The temperature dependence of the NMR spectra reveals that the ratio shifts to 7:1 when the temperature is lowered to −80 °C. At room temperature a rapid exchange on the NMR time scale is observed involving **6a**, **6b**, and small amounts of the uncomplexed host **4** and guest molecules **3**, such that the observed chemical shifts are weighted averages. Below −40 °C the rate of exchange is reduced sufficiently (at 9.4 T) to allow the spectra of the individual complexes to be observed. The ^{1}H and ^{13}C NMR signals at room temperature and those of the major component at low temperature were assigned using COSY, TOCSY, ^{1}H and ^{13}C shift-correlated 2D NMR (HSQC) and HSQC-TOCSY spectra.[7] All the NMR experiments were carried out on a Bruker AMX-400 spectrometer.

Above −40 °C, in the range in which rapid dissociation and recomplexation occurs, the recomplexation of the guest can take place either above or below the plane of the crown ether ring. On time average the same number of signals for the crown ether is observed as for the uncomplexed host molecule. At low temperature the exchange rate is slow, and all atoms in the crown ether ring are inequivalent. In the complex the guest molecule retains the chair conformation. One of the NH_3^+ signals, shown by detailed study and signal assignment to be from the equatorial NH_3^+, is shifted strongly downfield on complexation (1.96 ppm relative to the shift in the uncomplexed guest).[8] This shift, consistent with hydrogen bonding, indicates that the main interaction with the host involves the equatorial NH_3^+ group of **3**. Little or no interaction occurs between the axial NH_3^+ group and the crown ether.

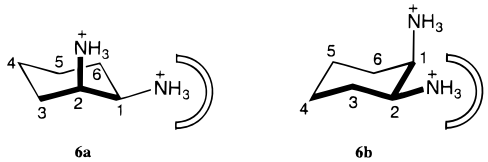
The chemical shifts of C-4 and C-5 in the cyclohexane ring are a useful probe of the conformation in the cyclohexane ring. At low temperature the rate of ring inversion of the free guest molecule **3** is slow on the NMR time scale, and six signals are observed in the ^{13}C NMR spectrum. For the 1-*eq*,2-*ax*-conformer the chemical shift difference between C-4 and C-5 is 6.1 ppm (see Table 1), since C-4 is γ to the axial NH_3^+ group and C-5 is γ to the equatorial one. At room temperature in the region of rapid inversion just three signals are observed, resulting from rapid exchange between two equally weighted conformations; C-4 and C-5 give a single exchange-averaged resonance. Also for the complexes **6a** and **6b** we can safely assume that the major factor in the shift difference (δ_{4-5}) is the conformation of the cyclohexane ring (Scheme 4). Remarkably, in the presence of the host molecule at 30 °C not only are *six* signals observed for the guest molecule in the ^{13}C NMR spectrum but the magnitude of the time-averaged difference between the chemical shifts of C-4 and C-5 (δ_{4-5}) is large; this shift difference results largely from different weightings of the complexes **6a** and **6b**. In **6a** C-4 is γ to the axial NH_3^+ group and C-5 is γ to the equatorial one while in **6b** C-4 is γ to the equatorial NH_3^+ group and C-5 is γ to the axial NH_3^+ group. If there were no preference for either complex, then the weighted average shift difference δ_{4-5} should be small. However, at 30 °C in the presence of an excess of **4** (added to reduce the contribution from uncomplexed guest molecules in the weighted average shifts) (δ_{4-5}) is 4.2 ppm as compared with 6.1 ppm in the free guest at low temperature. This corresponds to an enantioselectivity of *ca.* 5:1.

Table 1. ^{13}C NMR Chemical Shifts of Cyclohexyl Carbon Atoms in **3** and **6a**/**6b**

compound	temp (K)	C-1	C-2	C-3	C-4	C-5	C-6	(δ_{4-5})
3[a]	300	51.4[d]	51.4[d]	27.0[e]	21.5[f]	21.5[f]	27.0[e]	0.0
	189	51.4	50.0	28. 8	18.6	24.5	24.5	5.9
6a/**6b**[b]	300	51.1	51.1	27.4	19.1	22.4	25.8	3.3
	190	49.1	49.6	27.0	16.4	22.6	24.1	6.2
6a/**6b**[c]	300	51.0	51.0	27.0	18.5	22.7	25.6	4.2

[a] Solvent CD_3OD, δ_C rel. solvent [CD_3: ^{13}C (TMS) ≡ 49.00]. [b] Signals of major component. **4**/**3** in ratio 1:1. Solvent CD_2Cl_2/CD_3CN, δ_C rel. CD_3CN [CD_3: ^{13}C (TMS) ≡ 1.30]. [c] **4** in 7.6-fold excess. [d, f, e] Averaged signals.

Scheme 4



6a **6b**

We next turned our attention to the *meso*-configurated *bis*-ammonium salt **2** having two enantiotopic NH_3^+ groups. The dynamic behavior of **5a**/**5b** as shown by the ^{1}H and ^{13}C NMR spectra is analogous to that of **6a** and **6b**, with dissociation and rapid exchange occurring at room temperature, leading to averaged spectra. When an equivalent amount of **4** is used at −83 °C, two signals for the NH_3^+ groups bound in the host molecule were recorded in the NMR spectrum at 8.93 and 8.46 ppm in the intensity ratio *ca.* 2.5:1. Other signals in the ^{1}H and ^{13}C NMR spectra also reveal the presence of two complexes. Thus the chiral host binds one of the enantiotopic groups of the guest **2** selectively. As in the previous case, the results do not allow it to be established whether the major complex is **5a** or **5b**.

In summary, we have presented the first direct spectroscopic evidence for enantiotopic group recognition in a *meso*-compound and enantioselective molecular recognition involving rapidly interconverting enantiomers as guests.

Supporting Information Available: Temperature dependent ^{1}H NMR spectra of **5a**/**5b** and ^{13}C NMR spectra of **6a**/**6b** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(7) (a) Mynott, R. unpublished results. (b) Rudolph, J. Dissertation, Universität Bochum, 1995.

(8) To establish whether the complexed NH_3^+ group is equatorial or axial it is necessary to assign the carbon and proton signals in the complexed guest molecule at 190 K; at this temperature all the cyclohexyl protons and carbons are inequivalent. The assignment was achieved using data from 2D NMR spectra. Cross peaks in the COSY spectrum allowed the methine protons vicinal to the NH_3^+ groups to be identified. The ^{1}H and ^{13}C signals of each CH_2 group were identified in the C,H shift-correlated spectrum. Finally, the signal assignment was completed by determining the connectivities of the methine and methylene groups using the HSQC-TOCSY and COSY spectra. The ^{13}C chemical shifts, which are similar to those of 1,2-diammoniumcyclohexane at low temperature, are fully consistent with the ring having a chair conformation and reveal that the complexed NH_3^+ group is equatorial.