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Chiral NMR Discrimination of Secondary Amines Using (18-Crown-6)-2,3,11,12-tetracarboxylic Acid

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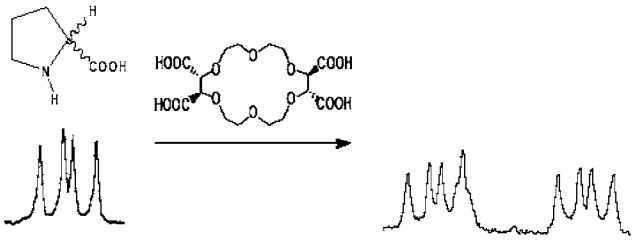
ABSTRACT



Enantiomeric discrimination is observed in the ^{1}H NMR spectra of chiral secondary amines in the presence of (*R*)-(+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid. Secondary amines are protonated by one of the carboxylic acid groups of the crown ether to produce the corresponding ammonium and carboxylate ions. The secondary ammonium ion likely forms two hydrogen bonds to crown ether oxygen atoms and an ion pair with the carboxylate anion.

Nuclear magnetic resonance spectroscopy is commonly used to determine the optical purity and to assign absolute configurations of chiral compounds.[1] Discrimination occurs when the addition of an optically pure chiral derivatizing or solvating agent reacts or associates with a pair of enantiomers to produce diastereomeric complexes that exhibit different shifts in the NMR spectrum.

Crown ethers are a widely studied family of chiral discriminating agents.[2] Those with an 18-crown-6 unit are effective reagents for the chiral discrimination of protonated primary amines, as the three hydrogen atoms are ideally aligned to form hydrogen bonds with three of the oxygen atoms of the crown. Several chiral crown ethers are available as liquid chromatographic stationary phases, but only (18-crown-6)-2,3,11,12-tetracarboxylic acid (**1**), which incorporates tartaric acid units as the chiral component, is commercially available for use in NMR applications (Figure 1).

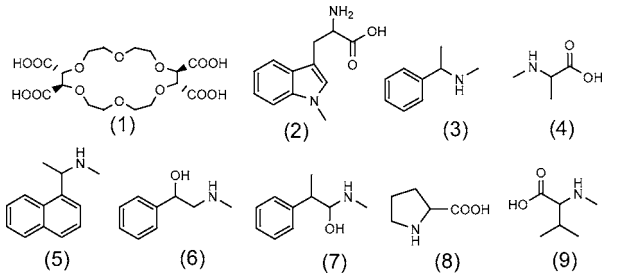


Figure 1. Structures of the crown ether and other substrates used in this study.

(1) (a) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256−270. (b) Wenzel, T. J. *Encyclopedia of Spectroscopy*; Academic Press: New York, 2000; Vol. 1, pp 411−421. (c) Webb, T. H.; Wilcox, C. S. *Chem Soc. Rev.* **1993**, *22*, 383−395. (d) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1447. (e) Pirkle, W. H.; Hoover, D. J. In Eliel, E. L., Wilen, S. H., Eds. *Top. Stereochem.* **1982**, *1*, 263−331. (f) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

(2) (a) Helgeson, R. C.; Timko, J. M.; Moreau, P.; Peacock, S. C.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 6762−6763. (b) Stoddart, J. F. In Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds. *Top. Stereochem.* **1988**, *17*, 207−288.

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Compound **1** has been shown to be an especially effective chiral NMR solvating agent for primary amines with aryl and alkyl substituent groups.[3,4]

The ^{1}H NMR spectra in Figure 2 provide an example of

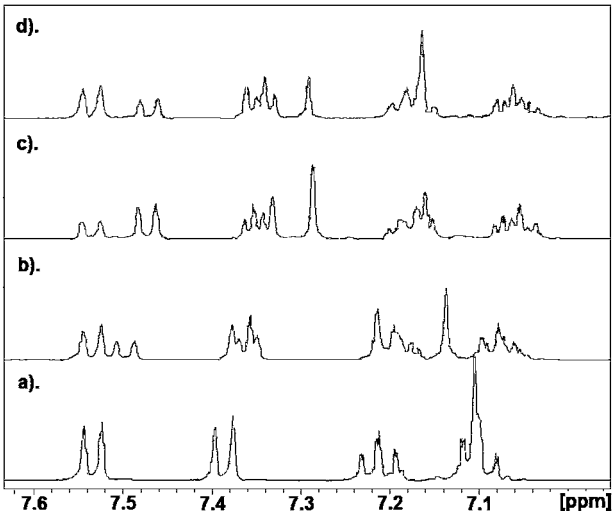

Figure 2. (a) Aromatic region of the ^{1}H NMR spectrum (400 MHz) of **2** (10 mM) in methanol-d_4 with (b) **1** (5 mM) mixture enriched in the L-enantiomer, (c) **1** (15 mM) mixture enriched in the D-enantiomer, and (d) **1** (15 mM) mixture enriched in the L-enantiomer.

the degree of enantiomeric discrimination that is commonly observed in mixtures of primary amines with **1**. The H_1, H_2, H_3, and H_4 aromatic resonances of the hydrochloride salt of 1-methyl tryptophan methyl ester hydrochloride (**2**) all exhibit some degree of enantiomeric discrimination (Table 1), although the separation of the H_1 resonance ($\delta = 7.538$ ppm) is especially pronounced and readily applicable to the determination of optical purity. The spectra in Figures 2c and 2d are of samples enriched in the D- and L-isomer, respectively, and unequivocally demonstrate that the splitting of the peaks is the result of enantiomeric discrimination. The spectra in Figures 2b and 2c demonstrate the beneficial effect of increasing the concentration of **1** relative to that of the substrate. This trend is consistent with other studies of chiral solvating agents in which increasing the concentration of the reagent promotes the formation of the diastereomeric complexes and enhances the extent of enantiomeric discrimination in the NMR spectrum.

Chiral 18-crown-6 ethers are generally regarded as ineffective for the analysis of secondary amines because the corresponding ammonium ions can only form two hydrogen

Table 1. Enantiomeric Discrimination (ppm) in the ^{1}H NMR Spectra (400 MHz) of Substrates with **1** in Methanol-d_4

substrate	proton	$\Delta\Delta\delta$	**1**:substrate
1-methyl tryptophan methyl ester HCl (**2**)	H_1	0.061	1:1
	H_2	0.009	0.5:1
	H_3	0.009	1:1
	H_4	0.010	1:1
dimethylbenzylamine (**3**)	*C*-CH_3	0.026	2:1
	N-CH_3	0.043	2:1
	C*H*CH_3	0.045	2:1
dimethylbenzylamine HCl (**3**)	*C*-CH_3	0.006	4:1
	C*H*CH_3	0.010	4:1
N-methyl alanine (**4**)	*C*-CH_3	0.006	4:1
	N-CH_3	0.005	4:1
N-methyl 1-(1-naphthyl)ethylamine (**5**)	*C*-CH_3	0.021	0.5:1
	N-CH_3	0.065	0.5:1
	C*H*CH_3	0.008	2:1
	H_2	0.073	1:1
	H_8	0.012	0.5:1
α-methylaminomethylbenzyl alcohol (**6**)	*N*-CH_3	0.025	0.5:1
	C*H*OH	0.035	1:1
ephedrine HCl (**7**)	*C*-CH_3	0.004	4:1
	N-CH_3	0.004	4:1
proline (**8**)	CH	0.099	4:1
N-methyl valine (**9**)	*N*-CH_3	0.008	4:1
	C*H*$(CH_3)_2$	0.006	1:1
	C*H*CH	0.004	4:1

bonds and the steric effects of the substituent groups of the amine hinder association with the crown ether. Larger macrocycles containing a pseudo-24-crown-8 ring do associate with secondary amines.[5] The pseudo-24-crown-8 ether is not commercially available for NMR applications, and the lengthy synthesis essentially precludes its use by many investigators. A chiral liquid chromatographic stationary phase that incorporates **1** has been shown to be effective for separating chiral secondary amines.[6] We now wish to report that **1** is a broadly effective chiral NMR solvating agent for secondary amines in methanol-d_4. It is preferable to add the secondary amine in its neutral form. A neutralization reaction between the amine and **1** forms the corresponding ammonium ion and carboxylate species. The (*R*)-(+) form of **1** was used for all of the studies described herein.

The spectra in Figure 3 for dimethylbenzylamine (**3**) demonstrate the effectiveness of **1** at causing enantiomeric discrimination in the ^{1}H NMR spectra of secondary amines. The series of spectra in Figure 3a result from the addition of **3** to **1**. The large shifts to higher frequency of the two methyl resonances indicate that a neutralization reaction has occurred to produce the corresponding ammonium salt of **3**

(3) (a) Wenzel, T. J.; Thurston, J. E. *J. Org. Chem.* **2000**, *65*, 1243−1248. (b) Wenzel, T. J.; Thurston, J. E. *Tetrahedron Lett.* **2000**, *41*, 3769−3772.

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(5) (a) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron Lett.* **2002**, *43*, 8539−8542. (b) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 555−566.

(6) Steffeck, R. J.; Zelechonok, Y.; Gahm, K. H. *J. Chromatogr., A* **2002**, *947*, 301−305.

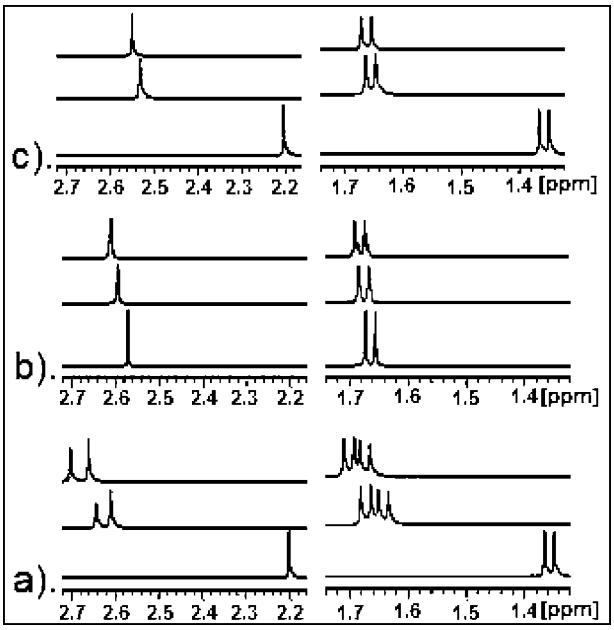

Figure 3. *C*-methyl and *N*-methyl resonances (400 MHz) of (a) **3** (10 mM) with increasing concentrations of **1** (0, 5, and 10 mM), (b) the hydrochloride salt of **3** (10 mM) with increasing concentrations of **1** (0, 20, and 40 mM), and (c) **3** (10 mM) with increasing concentrations of L-tartaric acid (0, 5, and 10 mM).

and the carboxylate form of **1**. Of more significance is the substantial enantiomeric discrimination that is observed for both the *C*-methyl (0.026 ppm) and *N*-methyl (0.043 ppm) resonances. Concentrations of **1** above a 2:1 crown/substrate ratio produce essentially no change in the NMR spectrum of **3**. Presumably, the neutralization between **1** and **3** has gone to completion by this ratio. Also, the relative shifts of the (*R*)- and (*S*)-isomers of **3** are different for the *C*-methyl and *N*-methyl resonances, indicating that the diastereomeric nature of the complexes causes the enantiomeric discrimination.

The series of spectra in Figure 3b show the resonances of the two methyl groups when increasing concentrations of **1** are added to the hydrochloride salt of **3**. The doublet for the *C*-methyl group exhibits a small amount of enantiomeric discrimination at a 4:1 crown/substrate ratio (0.006 ppm). The *N*-methyl resonance does not show any obvious enantiomeric discrimination. The larger shifts and enantiomeric discrimination that occur on adding a neutral amine rather than a protonated amine to **1** indicate the importance of an ion-pairing interaction in the associated species.

The series of spectra in Figure 3c show the *C*-methyl and *N*-methyl resonances of **3** with L-tartaric acid. The two resonances exhibit large shifts to higher frequencies, indicating that the tartaric acid does protonate **3**, but there is no enantiomeric discrimination in the NMR spectrum. Spectra of several other amines such as *N*-methyl alanine (**4**), *N*-methyl 1-(1-naphthyl)ethylamine (**5**), and α-methylaminomethylbenzyl alcohol (**6**) with **1** and tartaric acid showed the same trends. Addition of **1** to the amine causes large shifts to higher frequency and enantiomeric discrimination in the NMR spectrum, whereas addition of tartaric acid causes the large shifts but no enantiomeric discrimination. This unequivocally demonstrates the importance of the crown moiety in producing enantiomeric discrimination and the likely significance of hydrogen bonding between the hydrogen atoms of the ammonium ion and oxygen atoms of the crown.

With primary amines, the extent of enantiomeric discrimination caused in the spectrum by **1** was rather comparable whether the amine or its corresponding hydrochloride salt was added.[3] This suggests that the interaction of primary ammonium ions with **1** occurs via formation of three hydrogen bonds regardless of whether **1** is in its neutral (ammonium ion added) or monocarboxylate (neutral amine added) form (Figure 4a). This is consistent with earlier

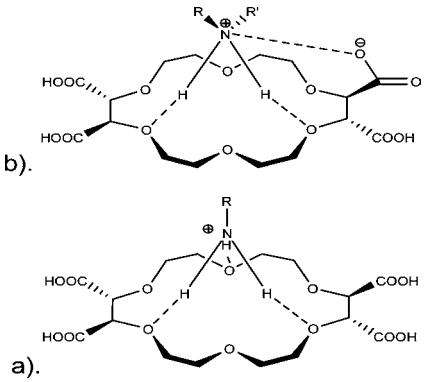

Figure 4. Proposed association geometries of the ammonium salts of (a) primary amines with neutral **1** and (b) secondary amines with the carboxylate anion of **1**.

conclusions on the association of protonated primary amines with 18-crown-6 ethers.[2] For secondary amines, it is more likely that the two hydrogen atoms of the ammonium group associate with oxygen atoms of the crown and that the cationic nitrogen pairs with the carboxylate oxygen atom as shown in Figure 4b, which is in agreement with the interaction that was proposed in the earlier study using **1** for liquid chromatographic separation of secondary amines.[6] Models show that the geometry in Figure 4b aligns the groups in favorable spatial proximity to each other to interact as proposed. Such an interaction accounts for the unusual ability of **1** compared to other 18-crown-6 ethers to associate with and enantiomerically discriminate secondary amines.

The ^{1}H NMR spectra in Figure 5 show the effect of adding small concentrations of **1** (1−5 mM) to a solution of a neutral amine (10 mM). In this case, raising the concentration of **1** converts more of the amine to its corresponding ammonium ion thereby causing larger shifts and enantiomeric discrimination of the *N*-methyl resonance.

The behavior of proline (**8**) and the two *N*-methyl amino acids (**4** and **9**) with **1** is different than that of the other secondary amines, as seen by the series of spectra for the

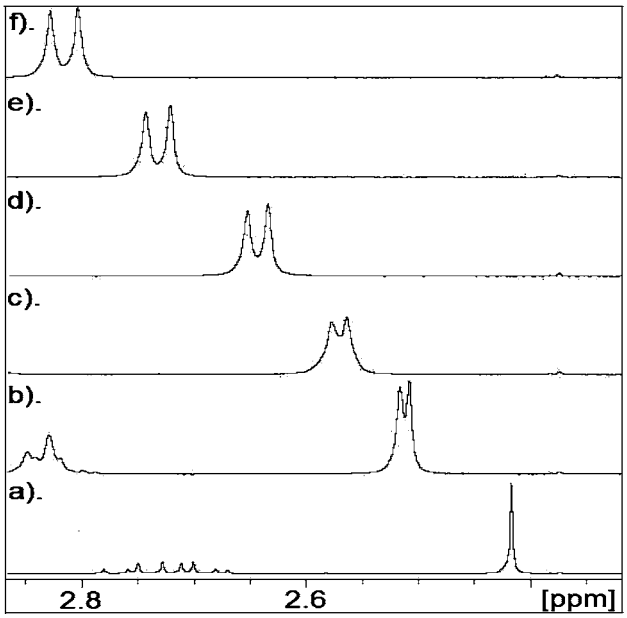

Figure 5. (a) ^{1}H NMR spectrum (400 MHz) of **6** (10mM) in methanol-d_4 with **1** at (b) 1 mM, (c) 2 mM, (d) 3 mM, (e) 4 mM, and (f) 5 mM.

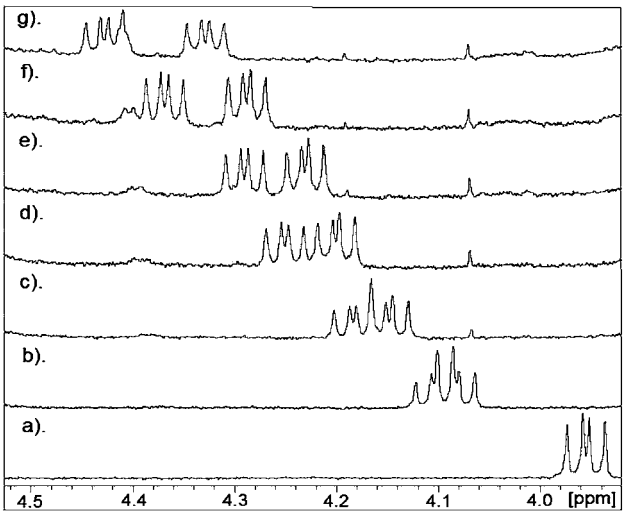

Figure 6. (a) ^{1}H NMR spectrum (400 MHz) of the methine resonance of **8** (10 mM) in methanol-d_4 with **1** at (b) 5 mM, (c) 10 mM, (d) 15 mM, (e) 20 mM, (f) 30 mM, and (g) 40 mM.

methine resonance of **8** in Figure 6. Unlike the other secondary amines, increasing the concentration of **1** relative to that of the amino acid above a 2:1 ratio causes larger shifts and greater enantiomeric discrimination. The likely explanation is that the amino acids exist as zwitterions in solution. Addition of **1** may lead to some protonation of the carboxylate group of the amino acid and to formation of a carboxylate group in **1**, but the pK_a values make it likely that this process is less favored than protonation of a secondary amine by **1**. Higher concentrations of **1** are therefore needed to protonate the amino acid, form the carboxylate group within **1**, and promote the association needed to cause the enantiomeric discrimination.

The enantiomeric discrimination observed in the ^{1}H NMR spectra of **2**−**9** with **1** is reported in Table 1. In almost every case, at least one resonance exhibits baseline separation that is suitable for the determination of enantiomeric purity. All of the substrates except **6** have the chiral center α to the secondary amine. The chiral center in **6** is β to the amine, but the spectrum still exhibits enantiomeric discrimination. It is noteworthy that the ^{1}H NMR spectra of **2** and **5** exhibit enantiomeric discrimination of resonances of aromatic hydrogen atoms that are rather remote from the chiral center.

The commercial availability of **1** makes this an especially suitable reagent for the analysis of the enantiomeric purity of secondary amines using NMR spectroscopy. Further studies of the general applicability of **1** for the analysis of secondary amines and of the structure of the amine−crown complexes are underway.

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