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Chiral NMR discrimination of pyrrolidines using (18-crown-6)-2,3,11,12-tetracarboxylic acid

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Abstract—The compound (18-crown-6)-2,3,11,12-tetracarboxylic acid is shown to be an effective chiral NMR solvating agent for determining the enantiomeric excess of chiral pyrrolidines. Enantiomeric discrimination is observed in both the ^{1}H and ^{13}C NMR spectra. The neutral amine is mixed with the crown ether in an NMR tube and a neutralization reaction between the two produces the corresponding ammonium and carboxylate ions. An association of these ions accounts for the chiral recognition. Pyrrolidines with one or two substituent groups α to the nitrogen atom are not inhibited from binding to the crown ether. Chiral discrimination was observed in the NMR spectra of pyrrolidines that have a stereogenic center α or β to the nitrogen atom. Dibasic substrates are likely converted to their diprotonated form in the presence of the crown ether, and both ammonium sites appear to associate with the crown ether moiety.

1. Introduction

NMR spectroscopy is one of the most common methods employed for the analysis of chiral compounds.[1] Enantiomerically pure derivatizing reagents can be used to prepare diastereomeric compounds that have differences in their NMR spectra. Alternatively, enantiomerically pure or enriched compounds can be used as chiral solvating agents to form diastereomeric complexes that associate through non-covalent interactions. Chiral solvating agents avoid the potential for kinetic resolution or racemization that sometimes occurs with chiral derivatizing agents.

Cyclodextrins and crown ethers are two important families of cavity compounds that have found rather widespread application as chiral NMR solvating agents. Cyclodextrins, which can be used in their native form or derivatized to analogues that are soluble in a variety of NMR solvents, have the potential to function for a variety of classes of substrates.[2] Crown ethers, which usually involve compounds with an 18-crown-6 unit, are known for their ability to bond to protonated primary amines.[3] The ammonium ion associates with the 18-crown-6 unit through the formation of three hydrogen bonds, as shown in Figure 1a. Compound **1**, which is the only commercially available chiral crown ether for use in NMR applications, has been shown to be an especially effective reagent for determining the enantiomeric excess of chiral primary amines.[4]

Crown ethers with an 18-crown-6 unit are generally ineffective at bonding to secondary amines. The ability to only form two hydrogen bonds coupled with unfavorable steric interactions from the substituent groups on the amine accounts for the poor association with 18-crown-6 ethers. The use of a pseudo-24-crown-8 ether provided a larger cavity that did associate with protonated secondary amines, but this reagent is not commercially available and its synthesis is rather involved.[5] We have recently shown that **1** is an effective chiral NMR solvating agent for secondary amines.[6] The addition of a neutral secondary amine to **1** in methanol results in a neutralization reaction that forms the corresponding ammonium and carboxylate ions. The ammonium ion and **1** exhibit favorable association that presumably involves two hydrogen bonds and an ion pairing interaction, as shown in Figure 1b.[6,7] Enantiomeric discrimination was not observed using only tartaric acid, the template on which the chirality of **1** is based.[6] In this report, we show that **1** is an especially effective reagent for determining the optical purity of chiral pyrrolidines (Fig. 2) using NMR spectroscopy.

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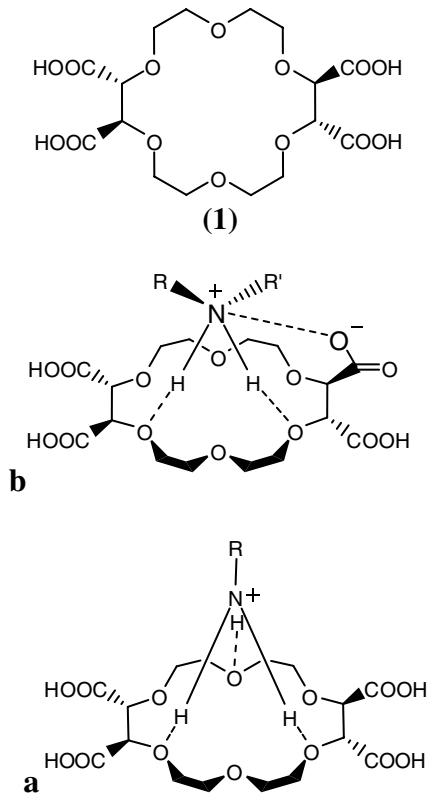

Figure 1. Association geometries of the ammonium salts of (a) protonated primary amines with neutral **1** and (b) protonated secondary amines with the carboxylate ion of **1**.

Table 1. Enantiometic discrimination ($\Delta\Delta\delta$) in ppm in the NMR spectra (400 MHz) of substrates (10 mM) with **1** (20 mM) in MeOH-d_4

Substrate	Proton	$\Delta\Delta\delta$
α,α-Di(2-naphthyl)-2-pyrrolidinemethanol **2**	H_3	0.068
	H_5	0.041
	H_6	0.025
α,α-Diphenylpyrrolidinemethanol **3**	H_5	0.005
	H_9	0.026
2-(Diphenylmethyl)pyrrolidine **4**	H_5	0.137
	H_7	0.019
	H_{14}	0.019
3-Aminopyrrolidine **5**	C*H*–NH_2	0.056
	CH*H′*–CH	0.057
	C*H*H′–CH	0.123
3-Pyrrolidinol **6**	C*H*–OH	0.039
2-Methoxymethylpyrrolidine **9**	O–CH_3	0.007
2-Methylpyrrolidine **10**	CH_3	0.083
2-Methylindoline **11**	H_1	0.240
	H_2	0.002
	H_3	0.191
	H_3'	0.039
	H_4	0.014
	H_5	0.072
	H_6	0.067
2,2,5,5-Tetramethyl-3-pyrrolidine carboxylate **12**	CH_2	0.018

2. Results and discussion

Compounds **2**, **3**, and **4** are similar in structure and the effect of **1** on their spectra is interesting to compare. The enantiomeric discrimination measured for the ^{1}H and ^{13}C resonances of **2**, **3**, and **4** with **1** is provided in Tables 1 and 2, respectively. The ^{1}H resonances of all three shift to higher frequencies in the presence of **1**, indicating that a neutralization reaction has occurred to produce the corresponding ammonium and carboxylate ions. The ^{1}H and ^{13}C NMR spectra of **2**–**4** show a substantial degree of enantiomeric discrimination that produces more than one baseline resolved resonance in either the ^{1}H or ^{13}C NMR spectrum. In the case of **2**, even with the steric bulk of the two naphthyl rings, the pyrrolidinium nitrogen is still able to associate with the crown ether. In fact, the enantiomeric discrimination in the H1′ resonances of **2** is larger than those of the corresponding *ortho*-positions of **3** and **4**. The ^{13}C resonances of the pyrrolidine rings of **2** and **3** are strikingly similar in their behavior in the presence of

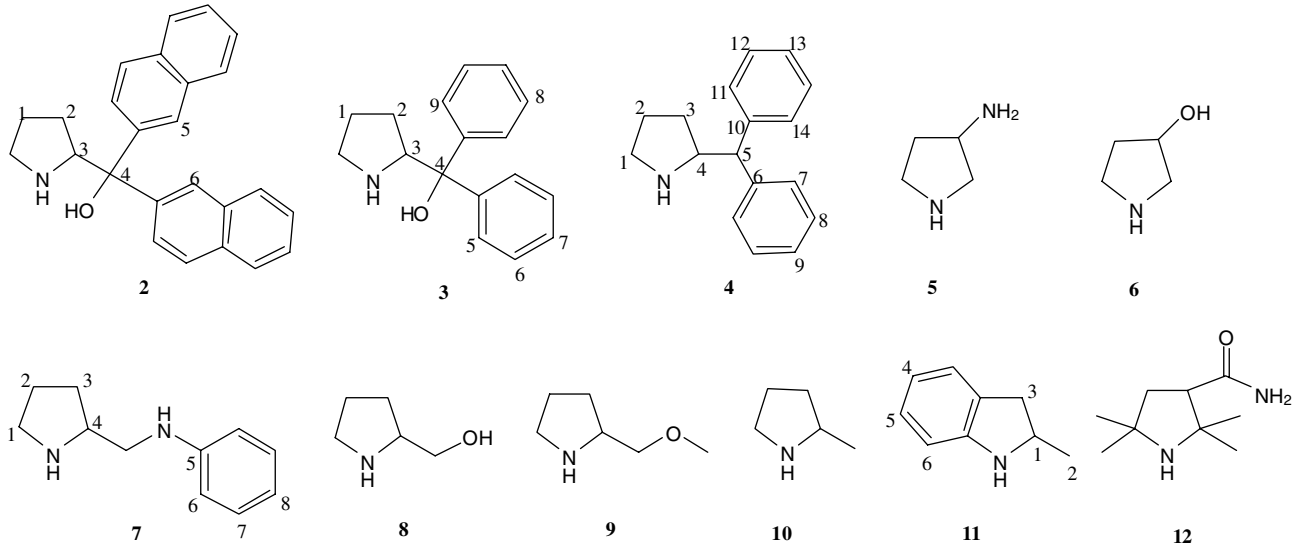

Figure 2. Structures of the substrates examined in this study.

Table 2. Enantiomeric discrimination ($\Delta\Delta\delta$) in ppm in the ^{13}C NMR spectra (100 MHz) of substrates (10 mM) with **1** (20 mM) in methanol-d_4

Substrate	Carbon	$\Delta\Delta\delta$	Substrate	Carbon	$\Delta\Delta\delta$
α,α-Di(2-naphthyl)-2-pyrrolidinemethanol **2**	C_1	0.494	2-(Anilinomethyl)pyrrolidine **7**	C_1	0.145
	C_2	0.238		C_2	0.354
	C_3	0.806		C_3	0.575
	C_4	0.205		C_4	0.376
α,α-Diphenylpyrrolidinemethanol **3**	C_1	0.510		C_5	0.220
	C_2	0.230		C_6	0.028
	C_3	0.730		C_7	0.167
	C_4	0.210		C_8	0.127
	C_5	0.160	2-Pyrrolidinemethanol **8**	CH_2–NH	0.374
	C_6	0.141		CH_2CH_2NH	0.132
	C_7	0.145		CH_2CHNH	0.328
	C_8	0.097		$CHNH$	0.354
2-(Diphenylmethyl)pyrrolidine **4**	C_1	0.432		CH_2OH	0.096
	C_2	0.082	2-Methoxymethylpyrrolidine **9**	CH_2CH_2NH	0.130
	C_3	0.377		CH_2CHNH	0.555
	C_4	0.313		$CHNH$	0.098
	C_5	0.143		CH_2O	0.061
	C_6	0.172		CH_3O	0.054
	C_7	0.065	2-Methylpyrrolidine **10**	CH_2–NH	0.415
	C_8	0.042		CH_2–CH_2NH	0.494
	C_9	0.107		CH_2–CHNH	0.594
	C_{10}	0.265		CH	0.161
	C_{11}	0.136		CH_3	0.324
	C_{12}	0.247	2-Methylindoline **11**	C_1	0.030
	C_{13}	0.141		C_2	0.150
3-Aminopyrrolidine **5**	CH_2CH	0.632		C_5	0.065
3-Pyrrolidinol **6**	$NHCH_2CH_2$	0.050		C_6	0.271
	CH_2CHOH	0.136			
	$CHCH_2CH$	0.022			

1, which is not surprising given the structural similarity of the two compounds. The identical nature of the ^{13}C spectra of **2** and **3** in the presence of **1** further indicates that the naphthyl rings of **2** do not inhibit association of the substrate with **1**.

The pattern of the enantiomeric discrimination of the ^{13}C resonances of the pyrrolidine ring of **4** is different than that observed for **2** and **3**. The differences imply that the hydroxyl group β to the nitrogen atom in **2** and **3** is involved in the association of these substrates with **1**, and is likely involved in hydrogen bonding with either the oxygen atoms of the crown moiety or more likely with one or more of the carboxylic acid groups.

The aryl groups of **2**, **3**, and **4** are diastereotopic and the resonances of hydrogen atoms exhibit different degrees of diastereotopic resolution in the spectrum of the substrates without the crown. For **2**–**4**, the diastereotopic resolution is greatest for the *ortho*-position and smallest for the *para*-position. Two singlets at about 8.1 and 8.2 ppm were observed for the diastereotopic H1′ hydrogen atoms of **2**, as seen in the spectrum in Figure 3a. The addition of **1** causes both of these to split, as seen by the spectrum in Figure 3b. The mixture shown in the spectrum was enriched in the (*R*)-enantiomer of **2**, confirming that the splitting of the two signals is the result of enantiomeric discrimination. The reversal in shift order for the two enantiomerically resolved H1′ resonances is particularly noteworthy. A similar reversal in shift order was observed for some of the ^{13}C resonances of **2**, **3**, and **4** with **1**. This suggests that differences

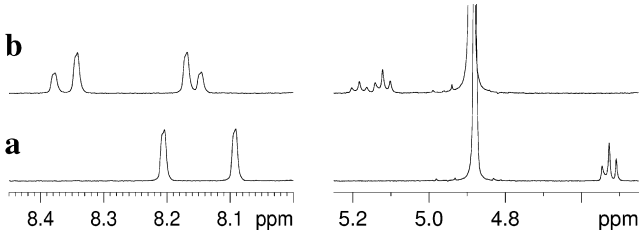

Figure 3. ^1H NMR spectrum (400 MHz) of the (a) diastereotopic H1′ and methane resonances of **2** (10 mM) in methanol-d_4 (b) with **1** at 20 mM.

in the two diastereomeric complexes between these substrates and **1** are more responsible for the enantiomeric discrimination than differences in the association constants of the two enantiomers with **1**. The spectra in Figure 3 show the chiral discrimination of the methine resonance of **2**. The *ortho*-hydrogens of **3** and **4** are diastereotopically resolved in the NMR spectrum of the substrate and enantiomerically discriminated in the presence of **1**.

Substrates **5** and **7** are dibasic, raising the question of whether one or both amine sites are protonated in the presence of **1**. If a diprotic cation is formed, it is also important to consider whether one or both of the ammonium sites associate with **1**. Figure 4 shows Job plots for mixtures of **2** and **5** with **1**.[8–10] There are two processes to consider in interpreting these plots. One is the neutralization of the amine by **1**. The other is association of the protonated amine with the carboxylate form of **1**. The magnitudes of the shifts of resonances of the substrate are dominated by

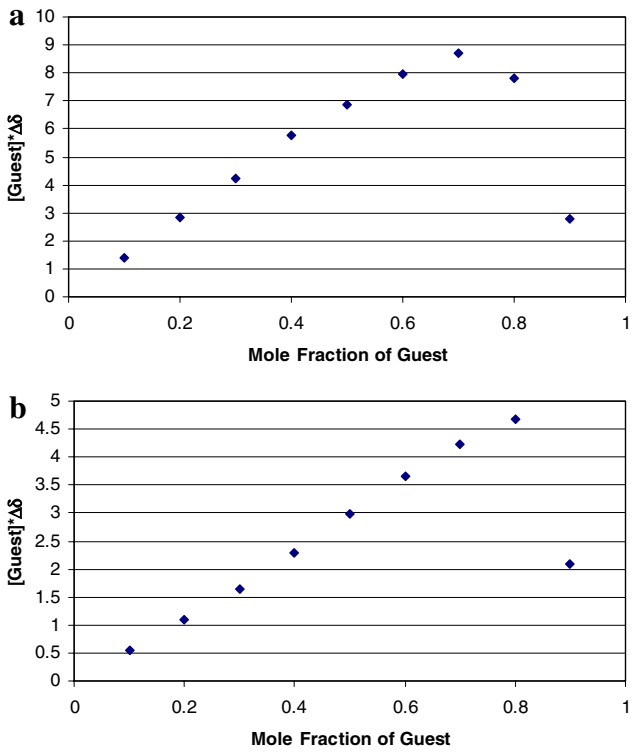

Figure 4. (a) Job plot of the CH resonance of **2** with **1**; (b) Job plot of the $NHCH_2CH_2$ resonance of **5** with **1**.

the effect of protonation versus the effect of association with **1**. With this system, the Job method shows the stoichiometry of the neutralization reaction rather than the stoichiometry of the association of the substrate with **1**. For **2**, a monobasic pyrrolidine, the Job plot in Figure 4a has a peak at 0.8, indicating that a single equivalent of **1** protonates four equivalents of the substrate. For **5**, a dibasic pyrrolidine, the Job plot in Figure 4b has a peak at 0.67, indicating that a single equivalent of **1** protonates two equivalents of the substrate, and that both nitrogen atoms of **5** are protonated. Spectral evidence supports this latter conclusion as well.

A comparison of **5** and **6**, which differs only by virtue of having a hydroxyl group in **6** in place of the amino group in **5**, provides evidence for the formation of a diprotic cation. The enantiomeric discrimination in the ^1H and ^{13}C resonances of **5**, **6**, and **7** with **1** is provided in Tables 1 and 2. Figure 5 shows a portion of the ^1H NMR spectra of **5** and **6** (10 mM) in mixtures with **1** at concentrations of 5 and 10 mM.

The results with **6** are typical of monobasic secondary amines. The addition of **1** at sufficient concentrations to create a crown–substrate ratio of 0.5:1 (Fig. 5b) causes the resonances of the hydrogen atoms α to the pyrrolidine nitrogen to shift significantly to higher frequencies. For example, the resonances of the hydrogen atoms α to the nitrogen atom in **6**, which are not shown in the spectra because they overlap with the resonances of **1**, shift by as much as 0.6 ppm. The resonances of the three hydrogen atoms β to the nitrogen, which are shown in the spectra in Figure 5a–c, also shift to higher frequencies, but to a lesser extent than those α to the nitrogen atom. Increasing the concentration of **1** above a 0.5:1 crown–substrate ratio with **6** causes relatively minor changes in the shifts of the resonances of the substrate, as seen in Figure 5b and c. This supports the conclusion that a single equivalent of **1** protonates two equivalents of the amine in methanol. At a crown–substrate ratio of 0.5:1, compound **6** is protonated and a high proportion of a 1:2 crown–substrate complex, as shown in Figure 6, likely occurs. The spectra at a crown–substrate ratio of 0.5:1 often show a broadening of both the crown and substrate resonances, and the resonances sharpen as the concentration of **1** is increased. Presumably, the 1:1 crown–substrate complex is favored at higher concentrations of **1** and faster exchange occurs. The reduction in broadening and small changes in chemical

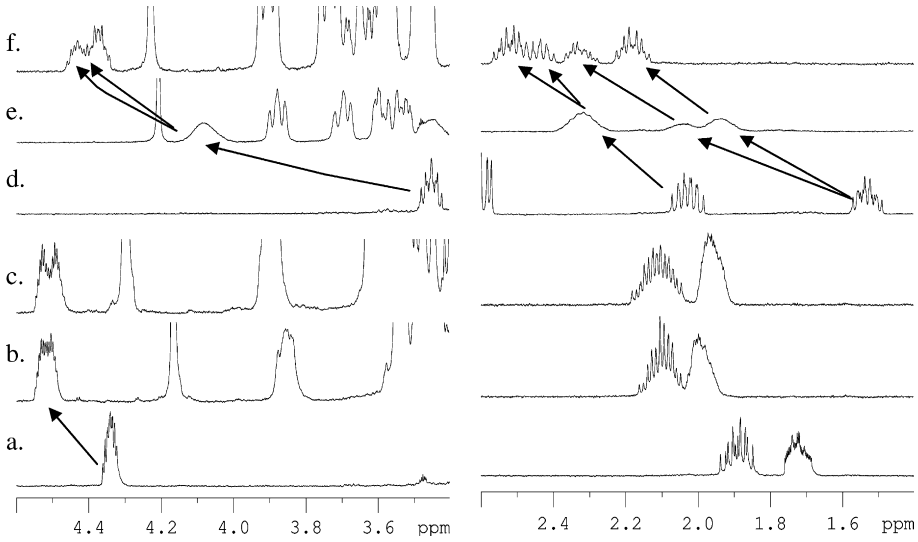

Figure 5. Portions of the ^1H NMR spectrum (400 MHz) of (a) **6** (10 mM) in methanol-d_4 with **1** at (b) 5 mM and (c) 10 mM, and (d) **5** (10 mM) in methanol-d_4 with **1** at (e) 5 mM, and (f) 10 mM.

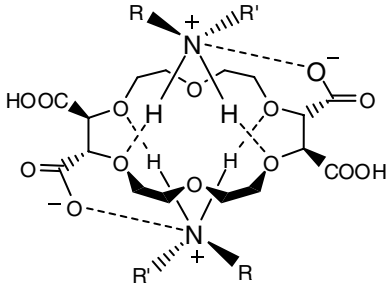

Figure 6. Structure of the association complex of two protonated secondary amines with the dicarboxylate ion of **1**.

shifts usually results in a significant improvement in the enantiomeric discrimination, such that spectra with a crown–substrate ratio of 1:1 or 2:1 are preferable when measuring enantiomeric excess as seen for the resonance at about 4.5 ppm in Figure 5c.

The spectra of mixtures of **5** and **1**, which are shown in Figure 5e and f, are substantially different than those of **6** and **1**. With **5**, larger shifts of the resonances in the ^{1}H NMR spectrum occur as the crown–substrate ratio is raised from 0.5:1 to 1:1, indicating that further protonation of **5** occurs. Furthermore, in contrast to what has been observed with **6**, all of the hydrogen resonances of **5** shift significantly to higher frequencies in the presence of **1**. The differences in shifts for the hydrogens at the C3 and C4 positions of **5** and **6** are apparent by comparing the spectra in Figure 5b and c to those in e and f. Another important distinction between **5** and **6** in the presence of **1** is the pronounced enantiomeric discrimination of the H4 resonances of **5**, whereas the H4 resonances of **6** exhibit no obvious enantiomeric discrimination. The reverse sense of nonequivalence observed for the H4 resonances in **5** in Figure 5f is also worth noting. These observations strongly suggest that both of the nitrogen atoms of **5** are protonated in the presence of **1**, and that both ammonium sites probably associate with the crown. The relative magnitude of the shifts and enantiomeric discrimination in the spectrum of **5** may mean that a 2:1 crown–substrate complex forms, when the concentration of **1** is higher than that of **5**. Compounds **5** and **6** are chiral at positions β to the pyrrolidine nitrogen atom, yet both exhibit substantial enantiomeric discrimination in the presence of **1**.

The ^{13}C resonances of **5** in the presence of **1** shift much further than those of **6** such that many overlap with the methanol resonance and the extent of enantiomeric discrimination cannot be assessed. The unusually large enantiomeric discrimination for the C3 position of **5** compared to the same carbon in **6** is a further evidence that both amine sites are protonated and likely associate to some degree with **1**.

Compound **7** is also a dibasic substrate. The resonances of all five of the hydrogen atoms at positions α to a nitrogen atom in **7** shift substantially to higher frequencies in mixtures with **1**. Therefore, both amine sites of **7** are likely protonated by **1**. Resonances in the ^{1}H NMR either did not show enantiomeric discrimination or overlapped with other substrate or crown resonances, such that the ^{1}H NMR spectrum was not suitable for an analysis of the enantiomeric excess of **7**. Resonances of the carbon nuclei in the pyrrolidine and aniline ring did exhibit enantiomeric discrimination. Chiral discrimination of the *para*-position of the aniline ring, which is rather remote from the stereogenic center, implies that the anilinium nitrogen atom associates either with the crown ether oxygen atoms or with the carboxylic acid functionalities of the crown.

Compounds **8** and **9** differ only in the substitution of a methoxy group for the hydroxyl group. The enantiomeric discrimination observed in the ^{1}H and ^{13}C resonances of **8** and **9** is provided in Tables 1 and 2. The pyrrolidine resonances in the ^{1}H NMR spectra of **8** and **9** with **1** either did not show significant enantiomeric discrimination or could not be assessed due to overlap with other peaks. Only the methoxy resonance of **9** showed obvious enantiomeric discrimination. The ^{13}C NMR spectra of **8** and **9** did show significant chiral discrimination in the presence of **1**. The pattern of the discrimination is different for the two compounds, especially at the C2 and C3 positions. Presumably the presence of the methyl group in **9** alters the binding to the crown and the nature of the interactions of the substituent group of the substrate with the carboxylic acid groups of **1**.

The enantiomeric discrimination in the ^{1}H and ^{13}C resonances of **10**, **11** and **12** is provided in Tables 1 and 2. The resonances of the methyl group and one of the α-hydrogen atoms of **10** exhibit pronounced enantiomeric discrimination in the presence of **1**, as seen by the spectrum in Figure 7b and c. As with other monobasic amines, the chemical shifts of the resonances of **10** do not show much additional shift at crown–substrate ratios greater than 0.5:1. This is in contrast to the behavior of **11** with **1** (Fig. 7d–g). Now the ^{1}H resonances of the pyrrolidine ring shift to higher frequencies as the crown–substrate ratio is raised to 1:1 and 2:1. Presumably the phenyl ring lowers the basicity of the nitrogen atom in **11** such that higher concentrations of **1** are needed to protonate it. Whereas the methyl resonance of **10** exhibits greater enantiomeric discrimination than the methyl resonance of **11**, the reverse is true for one of the resonances of a hydrogen atom α to the nitrogen atom. Significant enantiomeric discrimination was observed for several of the aromatic hydrogen resonances of **11**, as well as for many of the ^{13}C resonances of both **10** and **11**. Compound **11** is substituted at both carbons α to the nitrogen atom, yet is still able to associate with **1** in spite of this steric hindrance.

Compound **12**, which has four substituent groups α to the nitrogen atom, behaves quite differently than any of the other substrates already examined in this study. The ^{1}H resonances of the four diastereotopic methyl groups of **12** all shift significantly to higher frequency (about 0.25 ppm) in the presence of **1**, which indicates that a neutralization reaction occurs. However, only the most minimal enantiomeric discrimination is observed in the ^{1}H NMR spectrum of **12** in the presence of **1**. No chiral discrimination was observed in the ^{13}C NMR spectrum. Presumably, the steric hindrance of the four methyl groups α

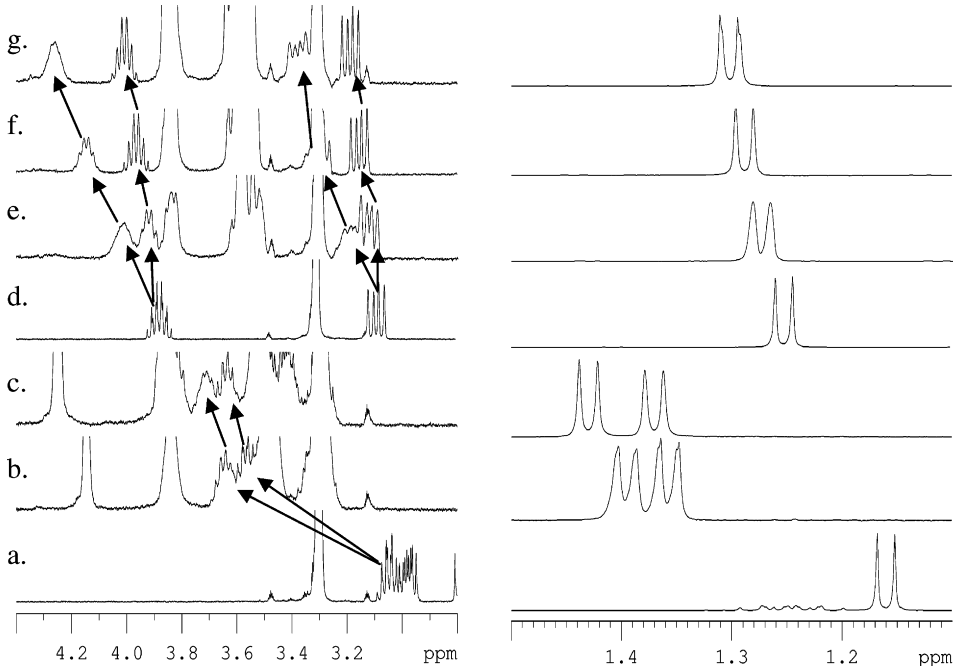

Figure 7. Portions of the ^{1}H NMR spectrum (400 MHz) in methanol-d_4 (a) of **10** (10 mM) with **1** at (b) 5 mM and (c) 10 mM, and (d) of **11** (10 mM) with **1** at (e) 5 mM, (f) 10 mM, and (g) 20 mM.

to the pyrrolidine nitrogen atom in **12** inhibits binding of the pyrrolidinium nitrogen to **1**.

Several of the substrates examined in this study were available in enantiomerically pure form. An analysis of the order of shifts in the ^{1}H and ^{13}C NMR spectra of enantiomerically enriched mixtures of these substrates with **1** indicated that there was no consistent trend among all of the substrates. Compounds of very similar structures such as **2**, **3**, and **4** did show consistent trends in the ^{13}C NMR spectra, but certain of the ^{13}C resonances of the pyrrolidine ring carbon atoms of **7**, **8**, and **9** varied by comparison. Using empirical trends in the shift order in mixtures with **1** to assign absolute configurations of pyrrolidines may only be possible with closely related substrates. General trends among the family of pyrrolidines will likely require the analysis of the spectra of many more substrates than examined in this study. The utilization of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) derivatives is the method of choice for assigning the absolute configurations of pyrrolidines.[11] The utilization of **1** is warranted as a straightforward and broadly applicable way in order to determine the enantiomeric excess of pyrrolidines.

The design of other chiral solvating agents specifically for the analysis of secondary amines is limited in scope.[5,12] A pseudo-24-crown-8 ether exhibited chiral recognition for secondary amines as evidenced by different association constants for enantiomers, but it was not evaluated as a chiral NMR discriminating agent.[5] A chiral pybox ligand, 2,6-bis(4,5-dihydro-4-phenyloxazol-2-yl)pyridine, was shown to cause enantiomeric discrimination in the ^{1}H NMR spectra of two alkyl aryl amines, one pyrrolidine (proline methyl ester hydrochloride), and three piperidines.[12] As such, the chiral recognition of the pybox species cannot be directly compared to the values reported herein with **1**, but the nonequivalence observed in the spectra of amines with both species is rather comparable. Unlike **1**, the pybox ligand is not commercially available.

3. Conclusions

Crown ether **1** is an effective reagent for determining the enantiomeric excess of pyrrolidines using NMR spectroscopy. The neutral amine is mixed with **1** and a neutralization reaction produces the corresponding ammonium and carboxylate ions. Pyrrolidines with the stereogenic center α or β to the nitrogen atom exhibit enantiomeric discrimination in their ^{1}H and ^{13}C NMR spectra in mixtures with **1**. The presence of one or two substituent groups on the carbon atoms α to the nitrogen atom does not inhibit association of the substrate with **1**.

4. Experimental

4.1. Reagents

All substrates and deuterated NMR solvents were obtained from major commercial suppliers. The (−)-isomer of **1** was obtained from Sigma–Aldrich (Milwaukee, WI) and used as received.

4.2. Instrumentation

All ^{1}H (16 scans) and ^{13}C spectra (4096 scans) were collected on a Bruker Avance 400 MHz NMR spectrometer. The spectra were run in methanol-d_4 at ambient probe temperature and calibrated using tetramethylsilane as an inter-

nal reference. When necessary, assignments were confirmed using 2D-COSY spectra.

4.3. Procedures for chiral discrimination studies

Solutions of the chiral substrates (10 mM) in methanol-d_4 with 0.05% TMS were prepared, and enriched with one of the enantiomers when available. Increments of **1** were added to the sample by appropriately sized aliquots of a 0.3 M stock solution in methanol-d_4.

4.4. Determination of stoichiometry

Stoichiometries of the protonation of secondary amine by **1** were determined using Job's method.[8–10] The concentrations of **1** and the substrate were continuously varied throughout the series while maintaining a total concentration of 20 mM.

Acknowledgements

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