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Carboxymethylated cyclodextrins and their paramagnetic lanthanide complexes as water-soluble chiral NMR solvating agents

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ABSTRACT

Cyclodextrins that are indiscriminately carboxymethylated at the 2-, 3-, and 6-position are used as chiral NMR solvating agents for cationic aromatic amines and aromatic hydroxy amines. Enantiomeric discrimination with the α-, β-, and γ-cyclodextrin derivatives is compared. The carboxymethylated derivatives are consistently more effective as chiral NMR discriminating agents for cationic substrates than native cyclodextrins. The most effective cyclodextrin varies for different substrates, although the β-cyclodextrin derivative is usually the best for the phenyl-containing compounds examined herein. Addition of paramagnetic praseodymium(III) or ytterbium(III) to mixtures of the carboxymethylated cyclodextrin and substrate often causes enhancements in enantiomeric discrimination and facilitates measurements of enantiomeric purity. The lanthanide ion bonds to the carboxymethyl groups and shifts the NMR spectra of substrate molecules in the cyclodextrin cavity.

1. Introduction

NMR spectroscopy is often used in the analysis of chiral compounds.[1–6] Enantiomerically pure chiral derivatizing agents undergo a covalent reaction with a pair of enantiomers to form diastereomers that may exhibit different chemical shifts. When using chiral derivatizing agents for determining enantiomeric purity, kinetic resolution or loss of configuration in the derivatization step is a potential concern.

Chiral solvating agents are mixed with the compound under study in the NMR tube and interact through non-covalent interactions. Hydrogen bonding, other dipole–dipole interactions, π-stacking, and steric effects are often important in the association of chiral solvating agents with substrates. Unlike chiral derivatizing agents, kinetic resolution or loss of configuration is not observed with chiral solvating agents. Enantiomeric discrimination with chiral solvating agents can occur in the NMR spectrum because of two mechanisms. First, complexes of a pair of enantiomers with a chiral solvating agent are diastereomeric and may have different chemical shifts. The second is that the association constants of the enantiomers with the chiral solvating agent are often different. Under conditions of fast exchange between bound and unbound forms, this can lead to different time-averaged solvation environments. In many cases, both mechanisms likely contribute to the enantiomeric discrimination. Many different compounds have been employed as chiral NMR solvating agents.[1–6]

Cavity compounds that form host–guest complexes with suitable substrates are often used as chiral NMR solvating agents. Cyclodextrins, which are cyclic oligosaccharides formed from glucose units, are an important family of cavity compounds.[7] The most common cyclodextrins have six (α), seven (β), and eight (γ) glucose units. Each glucose ring has one primary (6-position) and two secondary (2- and 3-position) hydroxyl groups. Derivatization of the hydroxyl groups facilitates the preparation of a wide variety of cyclodextrin derivatives with different solubility properties and different attributes as chiral NMR solvating agents.[1,8–34]

One important property of the native, underivatized cyclodextrins is that they are water-soluble. Water-soluble organic compounds, and especially those with hydrophobic aromatic rings, form host–guest complexes with cyclodextrins that usually involve insertion of the aromatic ring into the cavity. Since many pharmaceuticals are purposefully designed to be water-soluble, and water-soluble systems are of growing interest in green chemistry, the availability of water-soluble chiral NMR solvating agents is necessary. Cyclodextrins represent one of the few water-soluble systems suitable for chiral NMR applications.

We described the preparation of carboxymethylated cyclodextrins and their preliminary application as chiral NMR solvating agents in an earlier report.[32] By varying the reaction conditions, it was possible to prepare α-, β- and γ-cyclodextrins selectively carboxymethylated at the 2- (CDCM-2) or 6-position (CDCM-6). Other reaction conditions led to cyclodextrin derivatives with the carboxymethyl groups indiscriminately substituted at the 2-, 3-, and 6-position (CDCM-Ind).[32] The carboxymethylated cyclodextrins were examined with cationic substrates. The highly

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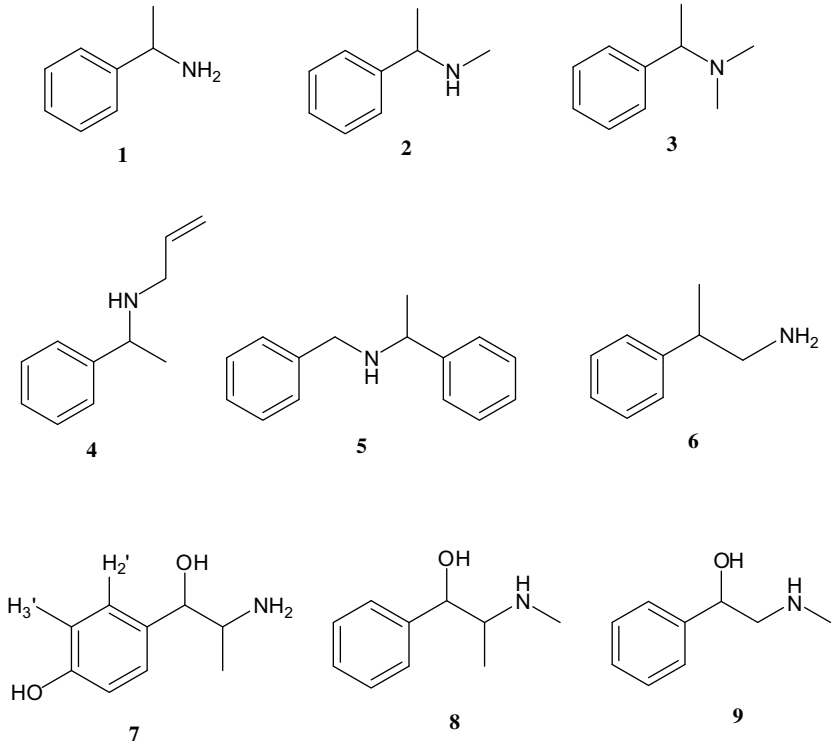
substituted CDCM-Ind derivatives were more effective than those with the carboxymethyl groups at only the 2- or 6-position. The CDCM-Ind derivatives described in the earlier report were also better than commercially available carboxymethylated cyclodextrins with lower degrees of substitution.[28,30,32]

Herein, we report the further utilization of α-, β-, and γ-CDCM-Ind as chiral NMR discriminating agents for a series of cationic aromatic amines and aromatic hydroxy amines. We also discuss the utility of adding paramagnetic lanthanide species to mixtures of CDCM-Ind derivatives and substrates.[17,28,30,31] The lanthanide ion binds to the carboxymethyl group of the cyclodextrin derivatives and frequently causes differential chemical shifts of the two enantiomers. In such cases, the enantiomeric discrimination in the ^{1}H NMR spectrum of the substrate is often enhanced by the addition of the lanthanide ion.

2. Results and discussion

2.1. Comparison of different cyclodextrins

A series of aromatic-containing amines and hydroxylamines including 1-phenylethylamine **1**, *N*,α-dimethylbenzylamine **2**, dimethylphenethylamine **3**, *N*-allyl-α-methylbenzylamine **4**, *N*-benzyl-α-methylbenzylamine **5**, β-methylphenethylamine **6**, α-(1-aminoethyl)-4-hydroxybenzyl alcohol **7**, ephedrine **8**, and α-methylaminomethyl benzyl alcohol **9** are examined in this study. These substrates are rendered water-soluble by conversion to their hydrochloride salts. The hydrochloride salt can be prepared by dissolving the neutral amine in methanol saturated with hydrogen chloride gas, and then isolating the solid product by rotary evaporation. Alternatively, the hydrochloride salt can be prepared directly in the NMR tube through the addition of an appropriate amount of hydrochloric acid.



It is well known that upfield shifts for the H_3 and H_5 resonances of cyclodextrin, which are inside the cavity, occur upon insertion of an aromatic ring.[35–37] The NMR spectra of **1**–**9** with β-cyclodextrin show upfield shifts of the H_3 and H_5 resonances in the order of 0.1–0.15 ppm, indicating the formation of host–guest complexes by insertion of the aromatic ring into the cavity. The spectra of the CDCM-Ind derivatives are broadened because the synthetic scheme leads to a variety of substitution patterns of the carboxymethyl groups. As such, it is not possible to accurately monitor the chemical shifts of the H_3 and H_5 resonances of the CDCM-Ind derivatives in the presence of a substrate as it is with the native cyclodextrins. However, it is still clear that the H_3 and H_5 resonances of β-CDCM-Ind show substantial upfield shifts in the presence of **1**–**9**. Binding of **1**–**9** with the CDCM-Ind derivatives involves insertion of the aromatic ring into the cavity, rather than association at one of the external faces.

Enantiomeric discrimination in the ^{1}H NMR spectra of **1**–**9** (10 mM) in the presence of α-, β-, and γ-CDCM-Ind (20 mM) is reported in Table 1. Data are not reported for the underivatized native α-, β-, and γ-cyclodextrins, since none of these produce enantiomeric discrimination in the ^{1}H NMR spectra of **1**–**9** under the conditions employed. The anionic carboxymethyl groups are essential in causing enantiomeric discrimination with these cationic substrates. Enantiomeric discrimination in the ^{1}H NMR spectrum of several of the substrates with the CDCM-2 derivatives is never as large as that with the corresponding CDCM-Ind derivatives and is not reported as well. The aromatic resonances of **1**–**9** generally do not exhibit large shifts in the presence of the CDCM-Ind derivatives. With the exception of **7**, no observable enantiomeric discrimination occurs for the aromatic resonances of the substrates. All of the substrates have methyl resonances that exhibit enantiomeric discrimination in the presence of one or more of the CDCM-Ind derivatives. The location of these methyl groups on the aliphatic side chain likely places them in the proximity of the hydroxyl and carboxymethyl substituents on the secondary face of the cavity. In all likelihood, ion pairing between the ammonium group of the substrate and carboxymethyl group of the cyclodextrin enhances the association of the substrate and the cyclodextrin, and provides additional points of interaction that can contribute to enantiodifferentiation.

Table 1
Enantiomeric discrimination ($\Delta\Delta\delta$) in ppm in the ^{1}H NMR spectra (400 MHz) of **1**–**9** (10 mM) with α-, β-, and γ-CDCM-Ind (20 mM) in D_2O

Substrate	Resonance	α-CDCM-Ind	β-CDCM-Ind	γ-CDCM-Ind
1	CH	0.010	0.010	0.005
2	CCH_3	0	0.008	0
	NCH_3	0.006	0.013	0
3	CCH_3	0	0.010	0
4	CH_3	0.010	0.004	0
5	CH_3	0.017	0	0
6	CH_3	0	0.007	0
7	H_2'	0	0.021	0.009
	H_3'	0	0.014	0.008
	CH_3	0.008	0.005	0
8	NCH_3	0	0.010	0
9	CH_3	0	0.015	0

The influence of the size of the cyclodextrin cavity on enantiomeric discrimination is well known from prior studies.[1,9,15,16,32,35] Complementarity in the fit between the substrate and cavity size is beneficial in promoting chiral recognition. Phenyl-containing compounds such as **1**–**9** tend to fit best into β-cyclodextrin. The large upfield shifts of the H_3 and H_5 resonances of β-cyclodextrin and β-CDCM-Ind in the presence of **1**–**9** are an indication of the complementary sizes. It is not surprising that β-CDCM-Ind is the most effective of the CDCM-Ind derivatives and causes enantiomeric discrimination in the ^{1}H NMR spectra for eight of the nine substrates. While **1**–**9** likely enter the cavity of γ-CDCM-Ind, the larger size does not constrain the substrate as well as β-CDCM-Ind, and such a constraint appears to be important in promoting enantiomeric discrimination.[1] The H_3 and H_5 resonances of γ-cyclodextrin and γ-CDCM-Ind shift only slightly, if at all in the presence of **1**–**9**, indicating that the substrates are not tightly constrained in the cavity. Resonances in the ^{1}H NMR spectra of only three of the substrates exhibit enantiomeric discrimination in the presence of γ-CDCM-Ind. Phenyl rings insert to a lesser degree in α-cyclodextrin than in β-cyclodextrin, generally not fitting as deeply into the cavity.[1] Not surprisingly, the H_3 and H_5 resonances of α-cyclodextrin and α-CDCM-Ind shift only slightly, if at all, in the presence of **1**–**9**. Resonances in the ^{1}H NMR spectra of five of the nine substrates show enantiomeric discrimination with α-CDCM-Ind.

While γ-CDCM-Ind never causes the largest enantiomeric discrimination among the three cyclodextrin derivatives, the most effective of α- or β-CDCM-Ind varies with substrate or the particular resonance of a substrate. For example, larger enantiodifferentiation of the methyl resonances of **4** and **5** occurs with α-CDCM-Ind compared to β-CDCM-Ind. Figure 1 shows the methyl resonance of **4** in the presence of α-, β-, and γ-CDCM-Ind, and the larger discrimination of this resonance with α-CDCM-Ind is apparent. Another interesting observation is the reversal in order of the chemical shifts of the (*R*)- and (*S*)-isomers of **4** with α- and β-CDCM-Ind. Enantiomeric discrimination in the ^{1}H NMR spectra of **2**, **3**, **6**, **8**, and **9** is best with β-CDCM-Ind. Figure 2 shows a comparison of the *N*-methyl resonance of **9** in mixtures with α-, β-, and γ-CDCM-Ind. The larger magnitude of the enantiomeric discrimination in the *N*-methyl resonance of **9** with β-CDCM-Ind (Fig. 2c) compared to α- and γ-CDCM-Ind is apparent. The *N*-methyl resonance of **9** in the presence of β-CDCM-Ind has a large enough enantiodifferentiation to allow accurate measurements of the enantiomeric purity. For **7**, enantiomeric discrimination of the methyl resonance occurs in the order α-CDCM-Ind > β-CDCM-Ind > γ-CDCM-Ind. However, for the two aromatic resonances of **7**, the order of enantiomeric discrimination is β-CDCM-Ind > γ-CDCM-Ind > α-CDCM-Ind.

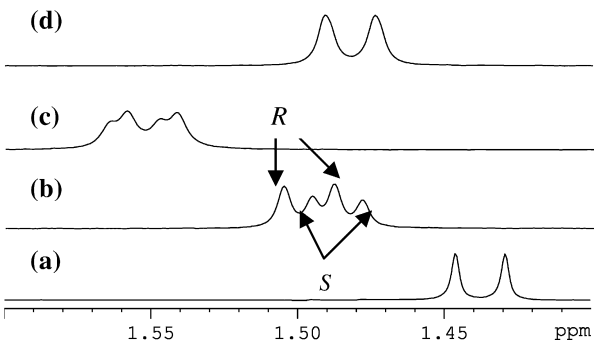


Figure 1. ^{1}H NMR spectrum (400 MHz, D_2O) of the methyl group of (a) **4** (10 mM, 2/3-(*R*), 1/3-(*S*)) with 20 mM, (b) α-CDCM-Ind, (c) β-CDCM-Ind, and (d) γ-CDCM-Ind.

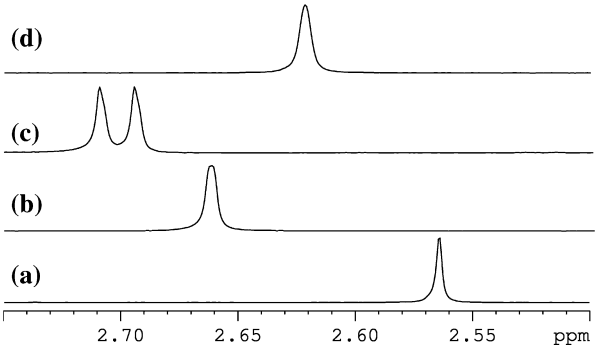


Figure 2. ^{1}H NMR spectrum (400 MHz, D_2O) of the methyl group of (a) **9** (10 mM) with 20 mM, (b) α-CDCM-Ind, (c) β-CDCM-Ind, and (d) γ-CDCM-Ind.

Substrates **1**–**9** are similar in that each has a phenyl ring and a stereogenic carbon directly attached to the ring. The differences in effectiveness of α-, β-, and γ-CDCM-Ind for **1**–**9** demonstrate the significance of interactions between the aliphatic group of the substrates and the hydroxyl and carboxymethyl groups of the cyclodextrin. Enantiomeric discrimination in the ^{1}H NMR spectra of **1**–**9** in the presence of α-, β-, and γ-CDCM-Ind is only a few thousandths to a couple of hundredths of a ppm. These values are often sufficient enough to assess whether or not a compound is enantiomerically pure. In a few cases, the enantiodifferentiation is large enough that integrated areas of the resonances (Fig. 2c provides one such example) can be used to accurately determine enantiomeric purity. A strategy for enhancing the enantiomeric discrimination and thereby expanding the utility of the CDCM-Ind derivatives as chiral NMR solvating agents is to add paramagnetic lanthanide ions to the samples.

2.2. Effect of adding paramagnetic lanthanide ions

Lanthanide ions bond to the anionic carboxymethyl groups of the CDCM-Ind derivatives and perturb the NMR spectra of substrate molecules in the cavity. If the lanthanide-induced changes in chemical shifts are different for the two enantiomers, then there is the potential to enhance the enantiomeric discrimination in the ^{1}H NMR spectrum. The addition of lanthanide ions to mixtures of native cyclodextrins and cationic substrates is not effective at enhancing enantiodifferentiation, since there are no suitable moieties for lanthanide binding. Pronounced broadening of the resonances of the CDCM-Ind derivatives, especially those for the methylene hydrogen atoms of the carboxymethyl group, provides evidence that the lanthanide ions bind to the carboxymethyl groups.

Selection of the appropriate lanthanide ions is a balance of shift and broadening effects.[38] Chemical shift perturbations caused by

paramagnetic lanthanide ions can be a combination of dipolar (through-space), contact (through-bond) and complexation effects. Complexation shifts are generally quite small with lanthanide shift reagents. Contact shifts are usually negligible with lanthanide ions because the unpaired electrons are in shielded f-orbitals, and do not become involved in covalent bonding with the substrate. Since the lanthanide ion associates with the carboxymethyl groups of the CDCM-Ind derivatives instead of the substrate, complexation and contact effects from the lanthanide ion in the ^{1}H NMR spectrum of the substrate should be non-existent.

Dipolar shifts are described by Eq. 1 in which $\Delta\delta$ is the lanthanide-induced shift, K is a constant that varies for the different lanthanide ions, r is the distance between the lanthanide ion and the nucleus of interest, and θ is the angle between the line that defines r and the principle magnetic axis of the lanthanide–cyclodextrin–substrate complex.[38] Irrespective of whether the simplified form of the dipolar shift equation represented in Eq. 1 rigorously applies to the CDCM-Ind systems, the values of K, r, and θ are important. The K term includes magnetic susceptibility values and is either positive (downfield shifts) or negative (upfield shifts) for a particular lanthanide ion. The larger the absolute value of K, the larger the changes in chemical shifts caused by the lanthanide ion. If the distance dependency ($1/r^3$) is dominant, the closer a nucleus is to the lanthanide ion, and the larger the change in chemical shift. The angle term ($3\cos^2\theta - 1$) can be significant as this expression equals zero at 54.7°. Usually, θ values are all less than 54.7° for a substrate, such that the changes in chemical shifts of the resonances are all in the same direction. There are examples where so-called 'wrong-way' shifts occur with substrates that have one or more hydrogen nuclei with θ values greater than 54.7°[39–42]

$$\Delta\delta = K(3\cos^2\theta - 1)/r^3 \quad (1)$$

Lanthanide ions that produce larger changes in chemical shifts also cause greater broadening in the spectrum. Severe broadening of the resonances can compromise the determination of the enantiomeric purity. Praeseodymium(III) and ytterbium(III) induce shift changes of intermediate magnitude without causing too much line broadening. Chemical shift perturbations with an ion such as europium(III), which is commonly used with organic-soluble lanthanide shift reagents, are generally too small to be of much utility with these carboxymethylated cyclodextrins.[38]

Pr(III) and Yb(III) have K values that are opposite in sign, and therefore they induce chemical shift changes that are opposite in direction. Also, the perturbations with Yb(III) are larger than those with Pr(III). While the scheme used to carboxymethylate the cyclodextrins leads to indiscriminate substitution at the 2-, 3-, and 6-position, a prior report found that substitution of the carboxymethyl groups at the 2-position is substantially greater than that at the 3- and 6-position.[43] Therefore, binding of the Pr(III) and Yb(III) to the CDCM-Ind derivatives predominately occurs at the 2-position.

The direction of the lanthanide-induced changes in chemical shifts caused in the ^{1}H NMR spectra of substrates with CDCM-Ind derivatives shows some interesting behavior. For example, the *N*-methyl resonance of **8** (Fig. 3) and methyl resonance of **4** (Fig. 4) move to a higher frequency when Pr(III) is added to mixtures with β-CDCM-Ind, whereas the aromatic resonances in the same mixtures move to lower frequencies. The spectra in Figure 5 for **7** show the same trend as the aromatic resonances shift to lower frequencies when Pr(III) is added to mixtures with β-CDCM-Ind. Similarly, for mixtures of **1**–**3** with α-CDCM-Ind, the addition of Yb(III) causes the resonances of the aromatic hydrogen atom *ortho* to the substituent group and methyl resonances to move to lower frequencies, whereas the resonances of the hydrogen atoms at the *meta* and *para* positions move to higher frequencies. With β- and γ-CDCM-Ind, all of the aromatic resonances of **1**–**3** move to higher frequencies upon addition of Yb(III), whereas the methyl resonances move to lower frequencies. The addition of Yb(III) to mixtures of **6** and **7** with α-, β-, and γ-CDCM-Ind causes all of the aromatic resonances to move to higher frequencies, whereas the methyl resonances shift to lower frequencies. The observation that lanthanide-induced changes in chemical shifts for different resonances of the same substrate move in opposite directions most likely involves changes in the sign of the ($3\cos^2\theta - 1$) term. The principal magnetic axis of the substrate–CDCM-Ind–lanthanide complex must be positioned in such a way that a θ value of 54.7° bisects the substrate molecule.

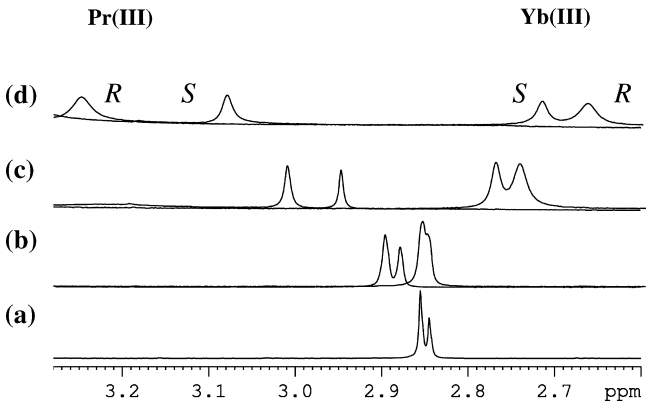


Figure 3. ^{1}H NMR spectrum (400 MHz, D_2O) of the *N*-methyl group of **8** (10 mM, 2/3-(*R*), 1/3-(*S*)) with β-CDCM-Ind (20 mM) and increasing concentration of Pr(III) and Yb(III), respectively, at (a) 0 mM, 0 mM, (b) 4 mM, 2 mM, (c) 8 mM, 6 mM, and (d) 16 mM, 8 mM.

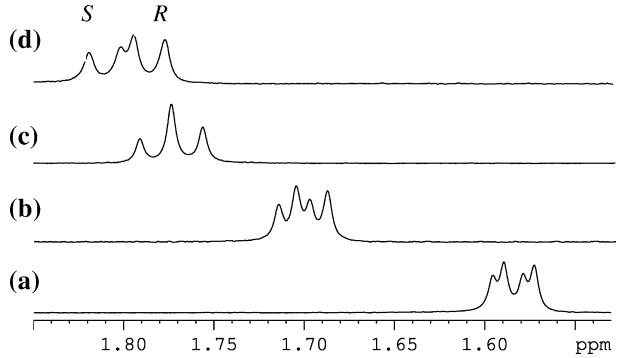


Figure 4. ^{1}H NMR spectrum (400 MHz, D_2O) of the methyl group of **4** (10 mM, 2/3-(*R*), 1/3-(*S*)) with β-CDCM-Ind (20 mM) and Pr(III) at (a) 0 mM, (b) 8 mM, (c) 14 mM, and (d) 20 mM.

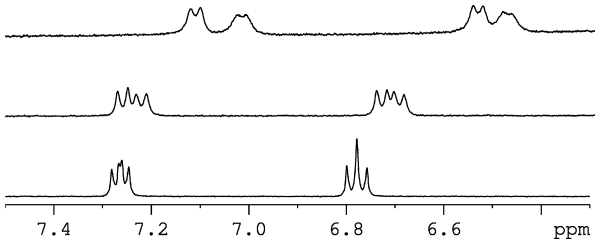


Figure 5. ^{1}H NMR spectrum (400 MHz, D_2O) of the aromatic region of **7** (10 mM) with β-CDCM-Ind (20 mM) and Pr(III) at (a) 0 mM, 8 mM, and (c) 14 mM.

A more important consideration is whether addition of Pr(III) or Yb(III) enhances the enantiomeric discrimination in the ^{1}H NMR spectra of the substrates. Tables 2–4 provide enantiomeric discrimination in the spectra of substrates in the presence of α-, β-, and γ-CDCM-Ind, respectively, on the addition of Pr(III) or Yb(III). Figure 6 provides graphical representations of the data provided in Tables 2–4 that show the significant enhancements in enantiomeric discrimination that frequently occurs when Yb(III) or Pr(III) is added to the samples. Data are provided for only those resonances where lanthanide-induced enhancements occur.

Table 2
Enantiomeric discrimination ($\Delta\Delta\delta$) in ppm in the ^{1}H NMR spectra (400 MHz) of substrates (10 mM) in D_2O in the presence of α-CDCM-Ind (20 mM) with either Yb(III) or Pr(III)

Substrate	Resonance	α-CDCM-Ind	Yb(III)	Pr(III)
1	CH_3	0	0.016 (6 mM)	0.020 (12 mM)
2	CCH_3	0	—	0.015 (12 mM)
	NCH_3	0.006	0.039 (12 mM)	0.011 (12 mM)
6	CH_3	0	—	0.016 (12 mM)
7	H'_2	0	—	0.040 (14 mM)
	H'_3	0	—	0.020 (14 mM)
	CH_3	0.008	—	0.016 (14 mM)
8	CCH_3	0	—	0.040 (20 mM)

The concentration of the lanthanide ion is shown in parentheses.

Table 3
Enantiomeric discrimination ($\Delta\Delta\delta$) in ppm in the ^{1}H NMR spectra (400 MHz) of substrates (10 mM) in D_2O in the presence of β-CDCM-Ind (20 mM) with either Yb(III) or Pr(III)

Substrate	Resonance	β-CDCM-Ind	Yb(III)	Pr(III)
1	CH_3	0	0.009 (12 mM)	0.009 (14 mM)
2	CCH_3	0.008	—	0.029 (20 mM)
4	CH_3	0.004	0.006 (12 mM)	0.025 (12 mM)
6	CH_3	0.007	0.053 (8 mM)	0.048 (22 mM)
7	H'_2	0.021	—	0.067 (16 mM)
	H'_3	0.014	—	0.108 (16 mM)
	CH_3	0.005	—	0.047 (16 mM)
8	NCH_3	0.010	0.178 (16 mM)	0.183 (18 mM)
	CCH_3	0	0.006 (6 mM)	0.062 (26 mM)

The concentration of the lanthanide ion is shown in parentheses.

Table 4
Enantiomeric discrimination ($\Delta\Delta\delta$) in ppm in the ^{1}H NMR spectra (400 MHz) of substrates (10 mM) in D_2O in the presence of γ-CDCM-Ind (20 mM) with either Yb(III) or Pr(III)

Substrate	Resonance	γ-CDCM-Ind	Yb(III)	Pr(III)
1	CH	0.005	—	0.011 (14 mM)
2	CCH_3	0	0.003 (8 mM)	0.003 (2 mM)
	NCH_3	0	0.010 (16 mM)	0.003 (2 mM)
6	CH_3	0	—	0.017 (14 mM)
7	H'_2	0.009	—	0.023 (18 mM)
	H'_3	0.008	—	0.020 (18 mM)
	CH_3	0	0.040 (12 mM)	—
8	NCH_3	0	0.012 (14 mM)	0.014 (18 mM)
	CCH_3	0	0.007 (14 mM)	—

The concentration of the lanthanide ion is shown in parentheses.

For a variety of reasons, not all resonances of the substrates show enhancements when lanthanide ions are added. Broadening or overlap with other resonances sometimes restricts the ability to observe enantiodifferentiation. In other cases, the differential shifts caused by the lanthanide ion can actually diminish the enantiomeric discrimination caused by the CDCM-Ind alone. Finally, some hydrogen atoms in the two enantiomers can have similar *r* and θ values in the diastereomeric complexes, such that their lanthanide-induced chemical shift changes are essentially identical.

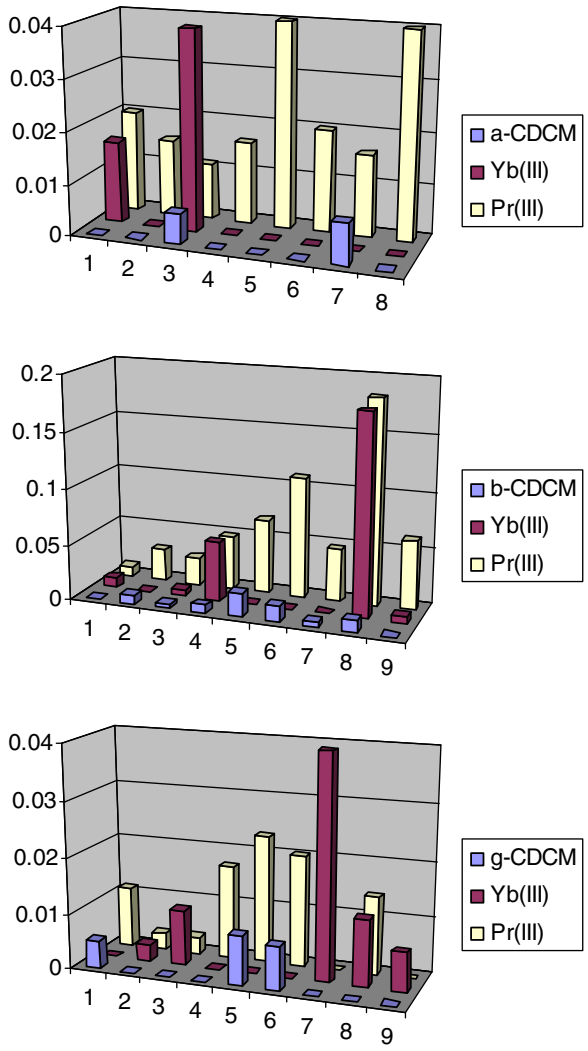


Figure 6. Graphical presentation of the lanthanide-induced enhancements in enantiomeric discrimination provided in Tables 2–4 with α-CDCM-Ind (top), β-CDCM-Ind (middle) and γ-CDCM-Ind (bottom). Numbers on the *x*-axis follow the order of resonances reported in Tables 2–4.

NMR spectra are best collected as a series with increasing concentration of the lanthanide ion in order to follow the resonances and find conditions where enantiomeric discrimination occurs, without too much broadening or interference from other resonances. The values listed in Tables 2–4 are reported for the optimal lanthanide concentration for each resonance. Addition of Pr(III) and Yb(III) to mixtures of several of the substrates with the CDCM-2 derivatives does not produce enhancements in enantiodifferentiation as large as those with CDCM-Ind and is not reported.

The addition of Yb(III) or Pr(III) causes pronounced enhancements in enantiomeric discrimination for many of the substrates with α-, β-, and γ-CDCM-Ind. As discussed earlier, β-CDCM-Ind causes enantiomeric discrimination in the ^{1}H NMR spectra of more of the substrates than does α- or γ-CDCM-Ind. As seen in Table 3 and Figure 6, the addition of Pr(III) is especially effective at enhancing the enantiomeric discrimination with β-CDCM-Ind. Whereas $\Delta\Delta\delta$ values are in the range of a few thousandths to a couple hundredths of a ppm with only β-CDCM-Ind, the addition of Pr(III) leads to enantiodifferentiation as high as 0.183 ppm. Several resonances that do not exhibit enantiomeric discrimination in the presence of β-CDCM-Ind do so when Pr(III) is added. While

Yb(III) causes larger shifts than Pr(III), the greater broadening in the spectrum detracts from the utility of Yb(III) in many cases.

The spectra in Figure 3 represent a composite of the results for the *N*-methyl signal of **8** on adding either Pr(III) or Yb(III). The resonance exhibits a small degree of enantiomeric discrimination in the presence of β-CDCM-Ind (Fig. 3a). The addition of Pr(III) causes the chemical shift of the resonance of the (*R*)-enantiomer to move to higher frequency more than that of the (*S*)-enantiomer, thereby enhancing the enantiodifferentiation. Yb(III) shifts the resonances to lower frequencies. The greater change in chemical shift of the (*R*)-enantiomer with Yb(III) initially causes the resonances to coalesce and then to reverse their sense of non-equivalence. For both Pr(III) and Yb(III), the greater broadening of the resonance of the (*R*)-enantiomer, which experiences more perturbation from the lanthanide ion, is apparent. It should also be noted that the concentration of Pr(III) is higher than that of Yb(III). Other examples with β-CDCM-Ind include enhancement of the methyl signal of **4** in the presence of Pr(III) (Fig. 4), aromatic signals of **7** with Pr(III) (Fig. 5), and methyl signal of **6** with Yb(III) (Fig. 7). In each case, enantiomeric discrimination with the lanthanide ion is large enough that integration of appropriate peaks can be used to accurately determine enantiomeric purity.

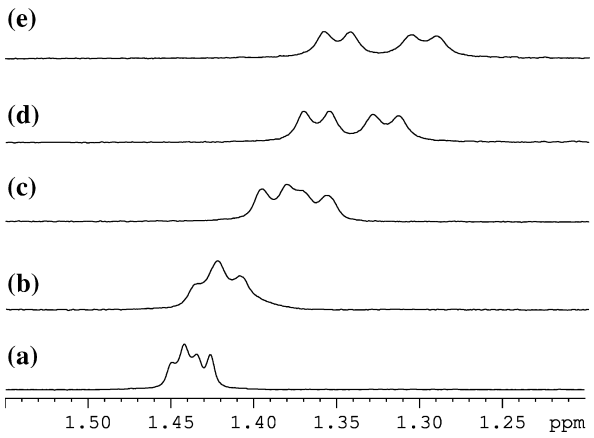


Figure 7. ^{1}H NMR spectrum (400 MHz, D_2O) of the methyl group of **6** (10 mM) with β-CDCM-Ind (20 mM) and Yb(III) at (b) 2 mM, (c) 4 mM, (d) 6 mM, and (e) 8 mM.

The addition of Pr(III) or Yb(III) also causes significant enhancements in the enantiomeric discrimination for resonances of several substrates with α-CDCM-Ind (Table 2) and γ-CDCM-Ind (Table 4); although generally not as large as those with β-CDCM-Ind, they are significant enhancements nonetheless. There are a few cases such as the methyl resonance of **1** with α-CDCM-Ind and Pr(III), methine resonance of **1** with γ-CDCM-Ind and Pr(III), and methyl resonance of **2** with α-CDCM-Ind and Yb(III) or Pr(III), where the enantiodifferentiation with α- or γ-CDCM-Ind is better than that with β-CDCM-Ind.

The spectra in Figures 8 and 9 compare the enantiomeric discrimination of the *C*-methyl resonance of **8** when Pr(III) is added to α-CDCM-Ind and β-CDCM-Ind, respectively. Neither show any enantiodifferentiation in the absence of Pr(III). An especially interesting observation is the difference in direction of the Pr(III)-induced changes in chemical shifts with the α- and β-CDCM-Ind. In both cases, the (*R*)-enantiomer experiences greater changes in chemical shift. While the enhancement in discrimination is greater when Pr(III) is added to β-CDCM-Ind, the broadening is larger as well. The larger broadening with β-CDCM-Ind compromises its utility, and the combination of Pr(III) and α-CDCM-Ind is more suitable for determining enantiomeric purity.

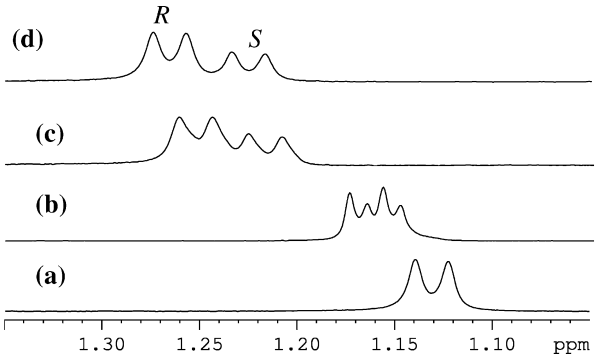


Figure 8. ^{1}H NMR spectrum (400 MHz, D_2O) of the *C*-methyl group of 8 10 mM, 2/3-(*R*), 1/3-(*S*)) with α-CDCM-Ind (20 mM) and Pr(III) at (a) 0 mM, (b) 4 mM, (c) 10 mM, and (d) 14 mM.

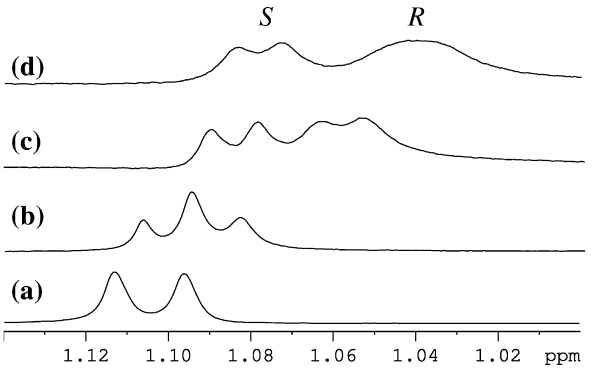


Figure 9. ^{1}H NMR spectrum (400 MHz, D_2O) of the *C*-methyl group of 8 (10 mM, 2/3-(*R*), 1/3-(*S*)) with β-CDCM-Ind (20 mM) and Pr(III) at (a) 0 mM, (b) 12 mM, (c) 16 mM, and (d) 22 mM.

3. Conclusions

Indiscriminately carboxymethylated α-, β-, and γ-cyclodextrins are more effective water-soluble chiral NMR solvating agents for cationic aromatic amines and aromatic hydroxy amines than the corresponding native cyclodextrins. The most effective carboxymethylated cyclodextrin depends on the particular substrate, although β-CDCM-Ind is generally the most effective with the phenyl-containing substrates examined herein. In cases where the enantiomeric discrimination with the CDCM-Ind derivatives is too small for measurements of enantiomeric purity, addition of paramagnetic Pr(III) and Yb(III) often leads to substantial enhancements in enantiodifferentiation. The lanthanide ions bind at the carboxymethyl groups of the CDCM-Ind derivatives, which cause changes in the chemical shifts in the NMR spectra of the enantiomers in the cyclodextrin cavity. The shifts in the NMR spectrum are larger with Yb(III) than Pr(III), although the results are generally better with Pr(III) because of reduced peak broadening.

4. Experimental

4.1. Reagents

All reagents were obtained from commercial suppliers. CDCM-Ind derivatives were prepared as previously described.[32]

4.2. NMR spectra

All ^{1}H NMR spectra (8 scans) were obtained at 400 MHz. Samples were run in D_2O at ambient probe temperature and ^{1}H NMR spectra were calibrated using the HOD peak at 4.79 ppm.

4.3. Sample preparation

Solutions of the chiral substrates were prepared in D_2O and enriched in one of the enantiomers when available. Substrates were either purchased as hydrochloride salts or the neutral amine (10 mM) was converted to its hydrochloride salt by dissolution in a solution of hydrochloric acid (12 mM) in D_2O. An appropriate weight of the cyclodextrin was added to the NMR tube. Spectra with lanthanide ions were obtained by adding the appropriate volume of a stock solution (0.20 M) of either praseodymium(III)nitrate or ytterbium(III)nitrate in D_2O. Spectra with the lanthanide ions were usually run as a series with concentrations that increased in 2 mM increments.

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