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^{1}H NMR studies of enantioselective host–guest complexation by modified β-cyclodextrins and their europium(III) complexes

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Abstract—The enantioselectivity of mono-substituted β-cyclodextrins 6^A-[bis(carboxylatomethyl)amino]-6^A-deoxy-β-cyclodextrin, 6βCDidaH$_2$, (2^AS,3^AS)-3^A-[bis(carboxylatomethyl)amino]-3^A-deoxy-β-cyclodextrin, 3βCDidaH$_2$, 6^A-[tris(carboxylatomethyl)(2-aminoethyl)amino]-6^A-deoxy-β-cyclodextrin, 6βCDedtaH$_3$, and their Eu^{3+} complexes in the formation of host–guest complexes with six enantiomeric guests in D_2O have been studied by ^{1}H NMR 600 MHz spectroscopy. The guests are D/L-tryptophanate, D/L-Trp$^-$, D/L-4hydroxyphenylglycinate, D/L-4HOPhg$^-$, D/L-histidinate, D/L-His$^-$, D/L-pheniramine, D/L-Phm/D/L-PhmH$^+$, D/L-phenylglycinate, D/L-Phg$^-$, and D/L-β-phenylserinate, D/L-βPhs$^-$. Enantioselective host–guest complexation occurs between [Eu(3βCDida)]$^+$, [Eu(6βCDida)]$^+$, and [Eu(6βCDedta)] and D/L-Trp$^-$, [Eu(3βCDida)]$^+$ and [Eu(6βCDida)]$^+$ and D/L-4HOPhg$^-$, and βCD, 3βCDida^{2-}, 6βCDida^{2-}, 6βCDedta^{3-}, [Eu(3βCDida)]$^+$, [Eu(6βCDida)]$^+$, and [Eu(6βCDedta)] and D/L-Phm/D/L-PhmH$^+$. While host–guest complexation occurs for D/L-His$^-$ and D/L-Phg$^-$, no enantioselectivity is apparent. Host–guest complexation occurs in the D/L-βPhs$^-$ systems but their spectra are too complex for reliable analysis. The preparation of 3βCDidaH$_2$ and 6βCDedtaH$_3$ and the determination of their pK_as are also reported.

1. Introduction

Homochiral β-cyclodextrin, βCD, consists of seven D-glucopyranose units joined in a macrocycle through α(1→4) linkages (Fig. 1).[1] The wider end of the annulus is defined by seven secondary hydroxyl groups on the C2 carbons and seven on the C3 carbons of the glucopyranose units; the narrower end is defined by seven primary hydroxyl groups on the C6 carbons. The interior of the macrocyclic annulus is lined with ether oxygens and methine hydrogens and is hydrophobic.

Consequently, βCD has a well-explored ability to act as a host for hydrophobic guests in water.[1–3] Due to its homochirality, βCD may selectively complex enantiomeric guests. This has been exploited through chromatographic[4] and electrophoretic[5] procedures, and explored in calorimetric,[2,3,6] X-ray diffraction,[7] NMR,[8] and computational studies.[9] However, because of the regularity of the βCD annulus, the magnitude of the enantioselectivity is usually small and the effect of the substitution of one or more hydroxyl groups to increase the annular asymmetry has been studied for a range of substituents.[10] Some substituents act as ligands for metal ions and result in the formation of metallo-β-cyclodextrins in which the metal ion may also complex a guest in the βCD annulus.[11] This may be exploited to form chiral shift reagents when the metal ion is dysprosium(III) and europium(III).[12]

This study explores the effect of substituents on βCD on the selective host–guest complexation of six enantiomeric guests. The substituted βCDs are 6^A-[bis(carboxylatomethyl)amino]-6^A-deoxy-β-cyclodextrin, 6βCDidaH$_2$,[13] (2^AS,3^AS)-3^A-[bis(carboxylatomethyl)amino]-3^A-deoxy-β-cyclodextrin, 3βCDidaH$_2$, 6^A-[tris(carboxylatomethyl)(2-aminoethyl)amino]-6^A-deoxy-β-cyclodextrin, 6βCDedtaH$_3$ (Fig. 1) and their Eu^{3+} complexes. While 3βCDidaH$_2$ and 6βCDidaH$_2$ obviously differ through bearing the bis(carboxylatomethyl)amino substituents on $C3^A$ and $C6^A$ carbons, respectively, they also differ through the inversion of the $C2^A$ and $C3^A$ carbons of 3βCDidaH$_2$ lowering the βCD annular symmetry. The guests are D/L-tryptophanate, D/L-Trp$^-$, D/L-4-hydroxyphenylglycinate,

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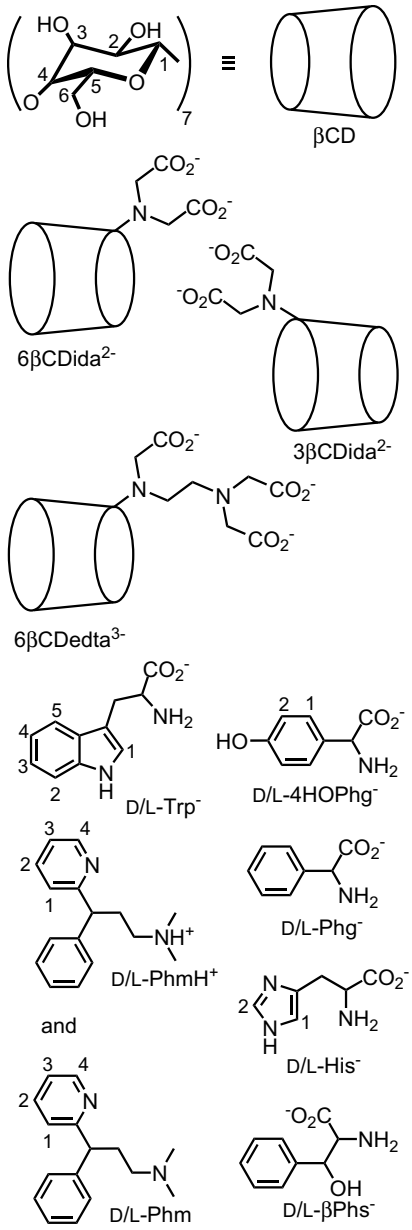

Figure 1. Structures of the substituted βCDs and enantiomeric guests at pD 10.

D/L-4HOPhg^{-}, D/L-histidinate, D/L-His^{-}, D/L-pheniramine in its neutral and protonated forms, D/L-Phm/D/L-PhmH^{+}, D/L-phenylglycinate, D/L-Phg^{-}, and D/L-β-phenylserinate, D/L-βPhs^{-} (Fig. 1). Both 1D and 2D ^{1}H NMR studies of these systems are reported. The preparations of 3βCDidaH$_2$ and 6βCDedtaH$_3$ and the determination of their pK_as are also reported.

2. Results and discussion

2.1. Syntheses of the substituted βCDs

6^{A}-[Bis(carboxylatomethyl)amino]-6^{A}-deoxy-β-cyclodextrin, 6βCDidaH$_2$, was prepared as previously described,[13] and 3βCDidaH$_2$, and 6βCDedtaH$_3$ were prepared from (2^{A}S,3^{A}S)-3^{A}-amino-3^{A}-deoxy-β-cyclodextrin,[14] 3βCDNH$_2$, and 6^{A}-(2-aminoethyl)amino-6^{A}-deoxy-β-cyclodextrin,[15] 6βCDen, respectively, as shown schematically in Figure 2.

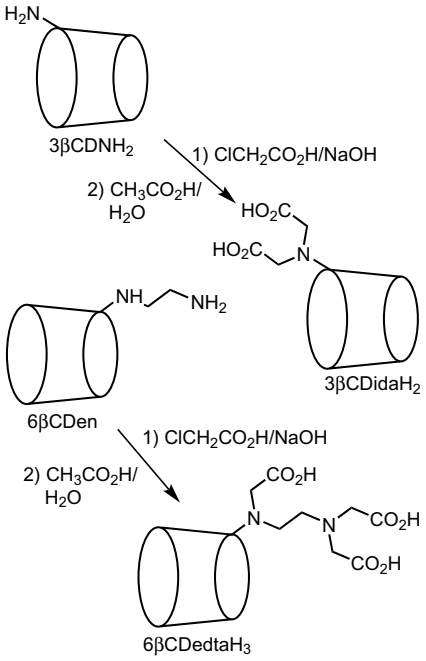

Figure 2. The preparation of 3βCDidaH$_2$, and 6βCDedtaH$_3$.

2.2. pK_as of the substituted βCDs

The pK_as of 3βCDidaH$_2$ (4.55 ± 0.05 and 8.03 ± 0.04), 6βCDidaH$_2$ (4.08 ± 0.09 and 8.75 ± 0.09), and 6βCDedtaH$_3$ (2.89 ± 0.08, 4.28 ± 0.05 and 9.48 ± 0.03), which compare with those for iminodiacetic acid, idaH$_2$ (2.61 and 9.35),[16] and ethylenediaminetetraacetic acid, edtaH$_4$ (2.00, 2.68, 6.11, and 10.17),[16] were determined in aqueous solution at $I = 0.10$ mol dm^{-3} (HClO$_4$/NaClO$_4$) by potentiometric titration with 0.10 M NaOH at 298.2 K. The differences between the pK_as of 3βCDidaH$_2$ and 6βCDidaH$_2$ are probably due to a combination of the inversion of C2^{A} and C3^{A} of 3βCDidaH$_2$ causing the acetate groups to be closer to the secondary hydroxyl groups of βCD than are those of 6βCDidaH$_2$ to the primary hydroxyl groups of βCD, as discussed below, and the differing numbers of hydroxyl groups at either end of the βCD and the consequent local differences in hydration. The differences between the pK_as of the substituted βCDs and those of idaH$_2$ and edtaH$_3$ are attributable to electron density changes introduced into the substituents of the substituted βCDs and also to changes in their hydration due to their close proximity to the hydroxyl groups of βCD. To ensure that 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-} were the dominant forms of the substituted βCDs available to complex Eu^{3+} in D$_2$O in the ^{1}H NMR experiments described below, the solution pD was adjusted to 10 with NaOD.

2.3. Molecular modeling

Molecular models of 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-} were energy minimized (MM2) in the gas

phase using the Cambridge Chem3D Ultra 8.0 protocol[17] (Fig. 3). It can be seen that the acetate groups of 3βCDida^{2-} are close to the center of the wider end of the βCD annulus as a consequence of the inversion of C2^{A} and C3^{A} while those of 6βCDida^{2-}and 6βCDedta^{3-} are more distant from the narrower end of the βCD annulus. These differences may affect the host–guest complexation if they persist in aqueous solution.

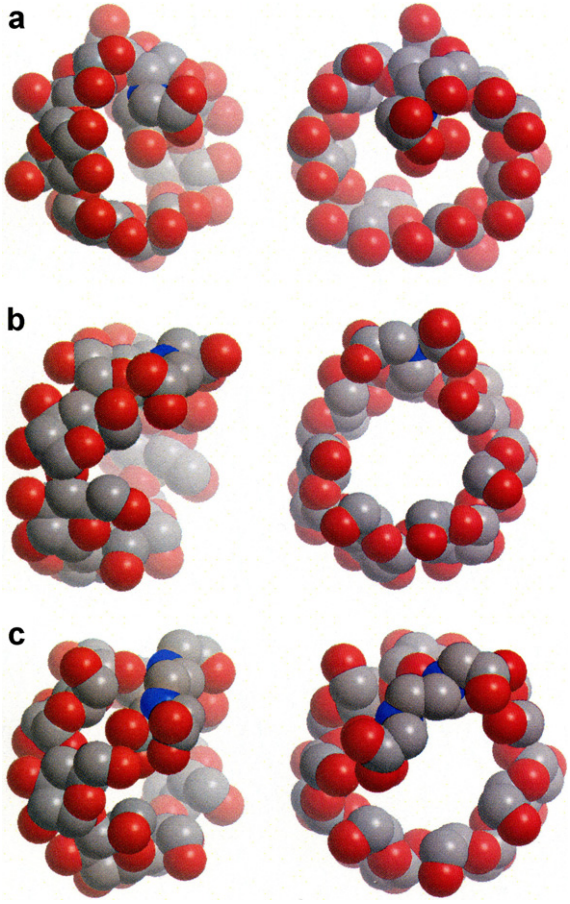

Figure 3. Molecular models of (a) 3βCDida^{2-}, (b) 6βCDida^{2-}, and (c) 6βCDedta^{3-}. Hydrogens and lone pairs are omitted for clarity and carbon, oxygen, and nitrogen atoms are shown in gray, red, and blue, respectively.

2.4. Solution equilibria

The equilibria anticipated for the host–guest complexation in the 6βCDida^{2-}/D/L-Trp^{-}/Eu^{3+} system are shown in Figure 4, and similar equilibria are expected to apply for the other two D/L-Trp^{-} systems. In principle there are two isomers, (a) and (b), of the host–guest complex [(6βCDida)(D/L-Trp)]$^{3-}$ in which the orientations of D/L-Trp^{-} are reversed within the βCD annulus. The relative isomeric proportions depend on the balance of the complexing forces. While the orientation of D/L-Trp^{-} in isomer (a) appears likely to produce the greater electrostatic repulsion between host and guest, it also appears more likely to lead to the formation of [Eu(6βCDida)(D/L-Trp)]. However, there is an alternative path to [Eu(6βCDida)(D/L-Trp)] through [Eu(6βCDida)]$^{+}$, which may be electrostatically favored.

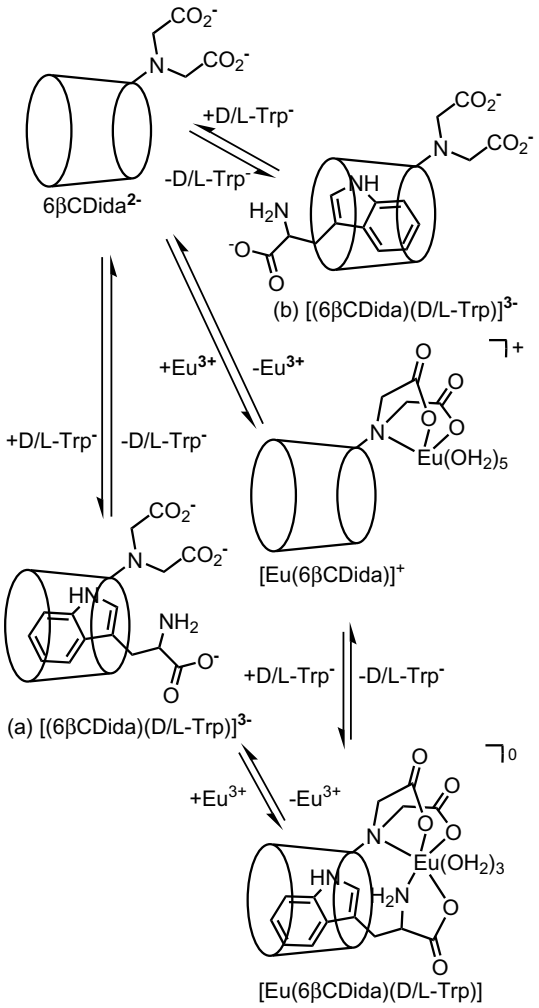

Figure 4. The formation of the metallo-β-cyclodextrin exemplified by [Eu(6βCDida)]$^{+}$, and host–guest complexes exemplified by isomers (a) and (b) of [(6βCDida)(D/L-Trp)] and [Eu(6βCDida)(D/L-Trp)].

2.5. ^{1}H NMR studies of the D/L-Trp^{-} system

A series of 1D ^{1}H NMR spectra of D/L-Trp^{-} alone and in the presence of equimolar βCD, substituted βCDs, and substituted βCDs and Eu^{3+} are shown in Figure 5a. While βCD and the substituted βCDs induce small changes in the D/L-Trp^{-} spectrum, thus indicating host–guest complexation, they are insufficient for enantioselectivity to be discerned. The chemical shifts of all guests alone and in the presence of 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-} appear in Table 1, and in the presence of [Eu(3βCDida)]$^{+}$, [Eu(6βCDida)]$^{+}$, and [Eu(3βCDedta)] appear in Table 2. However, in the presence of equimolar 6βCDida^{2-} and Eu^{3+}, the D/L-Trp^{-} H2 doublet resolves into two narrow doublets (Fig. 5d) consistent with D-Trp^{-} and L-Trp^{-} exchange between their free and complexed states being in the fast exchange limit of the ^{1}H NMR timescale.[18] When the D/L-Trp^{-} ratio is adjusted to 4:1 by the addition of D-Trp^{-}, the area of the upfield doublet increases proportionately consistent with it characterizing D-Trp^{-} with the

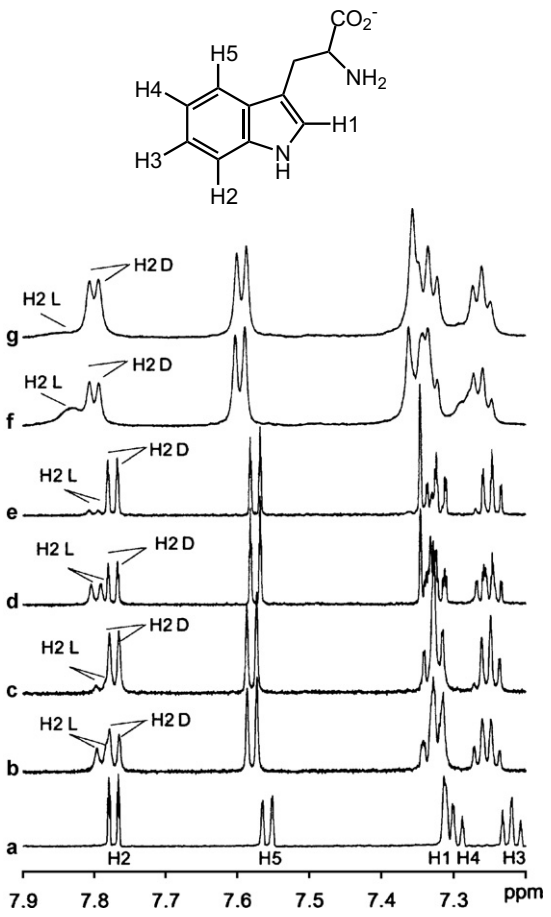

Figure 5. 1D ^{1}H NMR (600 MHz) spectra of pD 10 D_2O solutions of (a) 0.005 mol dm^{-3} racemic D/L-Trp$^-$ in the presence of (b) equimolar 3βCDida^{2-} and Eu^{3+}, (c) equimolar 3βCDida^{2-} and Eu^{3+} but with a D/L-Trp$^-$ ratio of 4:1, (d) equimolar 6βCDida^{2-} and Eu^{3+}, (e) equimolar 6βCDida^{2-} and Eu^{3+} but with a D/L-Trp$^-$ ratio of 4:1, (f) equimolar 6βCDedta^{3-} and Eu^{3+}, and (g) equimolar 6βCDedta^{3-} and Eu^{3+} but with a D/L-Trp$^-$ ratio of 4:1. In (b)–(g) the H2 resonances of L-Trp$^-$ appear downfield from those of D-Trp$^-$.

downfield doublet arising from L-Trp$^-$ (Fig. 5e). A partial resolution of the H3 triplet and some lesser changes in the H1 and H4 multiplets also occur. This is consistent with the formation of [Eu(6βCDida)]$^+$ and the subsequent enantioselective formation of the [Eu(6βCDida)(D/L-Trp)] diastereomeric host–guest complexes. Under similar conditions, smaller chemical shift changes and some resonance broadening (consistent with the exchange rate of D/L-Trp$^-$ between their free and complexed states not quite reaching the ^{1}H NMR fast exchange limit[18]) are seen in Figure 5b and c consistent with the formation of diastereomeric [Eu(3βCDida)(D/L-Trp)] host–guest complexes with the L-Trp$^-$ H2 doublet appearing downfield. The formation of diastereomeric [Eu(6βCDedta)(D/L-Trp)]$^-$ host–guest complexes is evidenced by the changes seen in the D/L-Trp$^-$ spectrum shown in Figures 5f and g. However, the resonances are substantially broadened and consistent with the exchange of D/L-Trp$^-$ between the free and host–guest complexed environments being in the intermediate exchange rate regime of the ^{1}H NMR timescale.[18] This results from either the chemical shift difference between the D/L-Trp$^-$ and [Eu(6βCDedta)(D/L-Trp)]$^-$ environments being greater than the analogous differences in the two preceding systems, or the exchange process being slower than in the two preceding systems. Differentiation between these possibilities cannot be made on the basis of the present data, as is also the case where broadening occurs in the other systems discussed below.

A 2D ^{1}H ROESY NMR spectrum (Fig. 6a) shows a cross-peak arising from dipolar through-space interaction between H3 and H5 of [Eu(6βCDida)]$^+$ and H2 of D-Trp$^-$, which is replaced by the one arising from the interaction between H3 and H5 of [Eu(6βCDida)]$^+$ and H4 of L-Trp$^-$ (Fig. 6b). This indicates a significant difference of orientation of D-Trp$^-$ in [Eu(6βCDida)(D-Trp)] by comparison with that of L-Trp$^-$ in [Eu(6βCDida)(L-Trp)] as the observation of significant ROESY cross-peaks requires interacting protons to be within 400 pm of each other. This difference probably results from the combined effects of the bidentate coordination of Trp$^-$ to Eu^{3+} through carboxylate and amine groups and the differing interactions of homochiral [Eu(6βCDida)(D/L-Trp)] with the opposite chiralities of the D/L-Trp$^-$ guests. Neither the [Eu(3βCDida)(D/L-Trp)] nor the [Eu(3βCDedta)(D/L-Trp)]$^-$ systems show analogous ^{1}H NMR ROESY cross-peaks probably because the resonance broadening evident in their 1D ^{1}H NMR spectra depresses the cross-peak amplitudes.

2.6. ^{1}H NMR studies of the D/L-4HOPhg$^-$ system

The 1D ^{1}H NMR spectrum of D/L-4HOPhg$^-$ (Fig. 7a and Table 1) shows no evidence of enantioselectivity occurring in the presence of either equimolar βCD or any of the three substituted βCDs, although substantial downfield shifts occur indicating host–guest complexation. In the presence of equimolar amounts 3βCDida^{2-} and Eu^{3+}, the H2 doublet almost resolves into two broadened doublets with that downfield characterizing the [Eu(3βCDida)(L-4HOPhg)] host–guest complex, but the H1 doublet only shows broadening probably arising from partially superimposing doublets (Fig. 7b and c). In contrast, in the presence of equimolar 6βCDida^{2-} and Eu^{3+} the H1 doublet resolves into two sharp doublets with that of the [Eu(3βCDida)(L-4HOPhg)] host–guest complex being upfield with the H2 doublet showing no sign of enantioselectivity (Fig. 7d and e).

These contrasting data are consistent with either D/L-4HOPhg$^-$ entering opposite ends of the [Eu(3βCDida)]$^+$ and [Eu(6βCDida)]$^+$ annuli to allow bidentate coordination to Eu^{3+} and to accommodate the phenyl ring inside the annuli, or with the inversion at $C2^A$ and $C3^A$ in [Eu(3βCDida)]$^+$ inducing significantly different orientations of D/L-4HOPhg$^-$ within the annuli, or a combination of these effects. The H1 and H2 doublets are broadened in the presence of equimolar 6βCDedta^{3-} and Eu^{3+} consistent with the exchange of 4HOPhg$^-$ between the free and complexed environments being in the intermediate rate range of the NMR timescale (Fig. 7f and g).

The 2D ^{1}H ROESY NMR spectra of the [Eu(3βCDida)(D/L-4HOPhg)] system show strong cross-peaks between D/L-

Table 1. Chemical shifts, δ (ppm), for the 600 MHz ^{1}H NMR spectra of the free guests and their host–guest complexes with βCD, 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-} in D_2O solution at pD 10 and 298.2 K

Guest	Guest proton[a]	Guest δ ppm[b]	βCD guest δ ppm[b]	3βCDida^{2-} guest δ ppm[b]	6βCDida^{2-} guest δ ppm[b]	6βCDedta^{3-} guest δ ppm[b]
D/L-Trp$^-$	H2	d 7.72	d 7.72	d 7.72	d 7.72	d 7.72
	H5	d 7.51	d 7.50	d 7.52	d 7.51	d 7.51
	H1	s 7.26	d 7.26	s 7.30	*s L 7.28*	s 7.28
					s D 7.27	
	H4	t 7.26	t 7.24	t 7.26	t 7.26	s 7.25
	H3	t 7.17	t 7.16	t 7.18	t 7.17	t 7.17
D/L-4HOPhg$^-$	H1	d 7.19	d 7.20	d 7.31	d 7.31	d 7.28
	H2	d 6.76	d 6.77	d 6.93	d 6.93	d 6.99
D/L-His$^-$	H1	s 7.65	s 7.66	s 8.63	s 8.44	s 7.71
	H2	s 6.91	s 6.92	s 7.37	s 7.30	s 7.01
D/L-Phm/ D/L-PhmH$^+$	H4	d 8.45	m 8.57	*d 8.62*	t 8.58	*d 8.64*
				d 8.60		*d 8.61*
	H2	t 7.85	m 7.88	*t 8.33*	q 8.07	*t 8.28*
				t 8.29		*t 8.23*
	H1	d 7.48	d 7.38	*d 7.84*	d 7.59	*d 7.77*
				d 7.84		*d 7.75*
	H3	t 7.39	t 7.40	p 7.72	*t 7.55*	*t 7.70*
					t 7.54	*t 7.67*
D/L-Phg$^-$	Ar	m 7.37	m 7.39	m 7.46	m 7.40	m 7.48
	Protons					m 7.44
D/L-βPhs$^-$	Ar	m 7.38	m 7.39	m 7.47	m 7.43	m 7.47
	Protons		m 7.35	m 7.40	m 7.35	m 7.40

(s—singlet, d—doublet, t—triplet, q—quartet, p—pentuplet, m—multiplet, br—broad, Ar—aromatic).
The values in italic characterize enantiomers.
[a] Protons labeled as in Figure 1.
[b] Values for singlets or the center of multiplets.

Table 2. Chemical shifts, δ (ppm), for the 600 MHz ^{1}H NMR spectra of the free guests and their host–guest complexes with [Eu(3βCDida)]$^+$, [Eu(6βCDida)]$^+$, and [Eu(6βCDedta)] in D_2O solution at pD 10 and 298.2 K

Guest	Guest proton[a]	Guest δ ppm[b]	[Eu(3βCDida)]$^+$ δ ppm[b]	[Eu(6βCDida)]$^+$ guest δ ppm[b]	[Eu(6βCDedta)] guest δ ppm[b]
D/L-Trp$^-$	H2	d 7.72	*br d L 7.75*	*d L 7.75*	*br s L 7.78*
			d D 7.72	*d D 7.72*	*d D 7.75*
	H5	d 7.51	d 7.53	d 7.52	d 7.54
	H1	s 7.26	s 7.53	s 7.29	s 7.54
	H4	t 7.26	br t 7.28	t 7.28	s 7.31
	H3	t 7.17	*t L 7.21*	*t L 7.20*	*t L 7.22*
			t D 7.19	*t D 7.19*	*t D 7.20*
D/L-4HOPhg$^-$	H1	d 7.19	d 7.29	*d D 7.29*	br d 7.30
				d L 7.28	
	H2	d 6.76	*d L 6.95*	d 6.93	d 6.94
			d D 6.94		
D/L-His$^-$	H1	s 7.65	s 8.65	s 8.52	br s 7.71
	H2	s 6.91	s 7.37	s 7.32	br s 6.98
D/L-Phm/ D/L-PhmH$^+$	H4	d 8.45	d 8.57	t 8.58	t 8.60
	H2	t 7.85	q 8.46	q 8.28	t 8.47
	H1	d 7.48	t 8.02	d 7.84	d 8.02
	H3	t 7.39	t 7.83	t 7.70	t 7.84
D/L-Phg$^-$	Ar	m 7.37	m 7.49	m 7.47	m 7.48
	Protons		br 7.41	m 7.42	m 7.42
D/L-βPhs$^-$	Ar	m 7.38	m 7.45	m 7.46	m 7.48
	Protons			m 7.40	m 7.42

(s—singlet, d—doublet, t—triplet, q—quartet, p—pentuplet, m—multiplet, br—broad, Ar—aromatic).
The values in italic characterize enantiomers.
[a] Protons labeled as in Figure 1.
[b] Values for singlets or the center of multiplets.

4HOPhg$^-$ H2 and the 3βCDida^{2-} H3, H5, and –NCH_2- protons but no analogous cross-peaks with D/L-4HOPhg$^-$ H1. This suggests that D/L-4HOPhg$^-$ is coordinated to Eu^{3+} through its amino and carboxylate groups such that H1 is positioned outside the annulus while H2 resides inside it. Cross-peaks arising from both H1 and H2 of D/L-

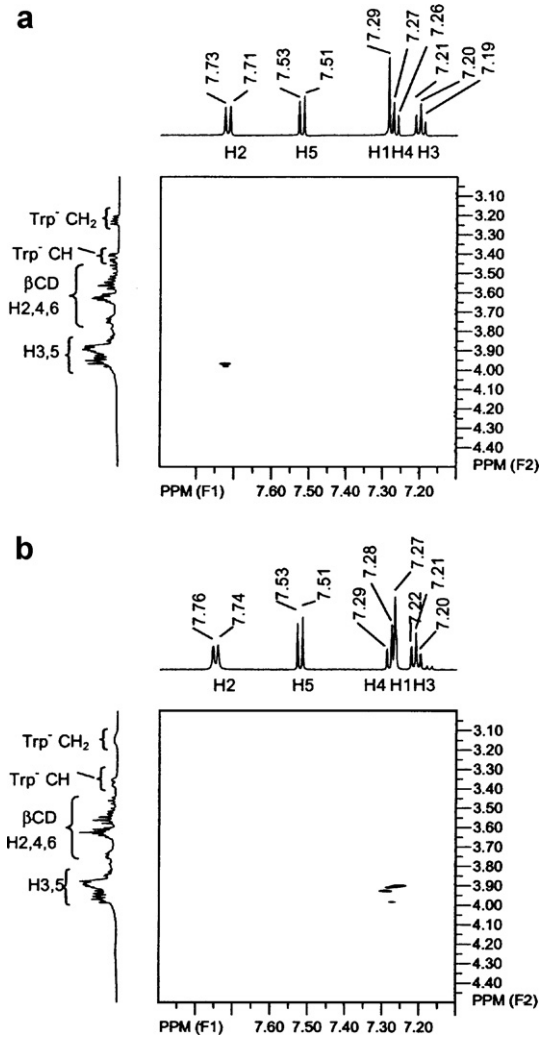

Figure 6. 2D ^{1}H ROESY NMR (600 MHz) spectra of pD 10 D_2O solutions of (a) equimolar 0.005 mol dm^{-3} D-Trp$^-$, 6βCDida^{2-}, and Eu^{3+} and (b) equimolar 0.005 mol dm^{-3} L-Trp$^-$, 6βCDida^{2-}, and Eu^{3+}.

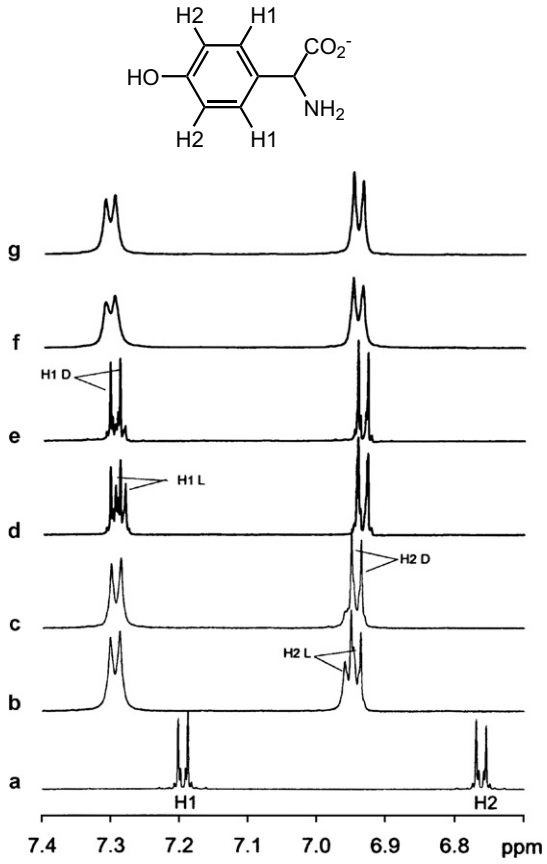

Figure 7. 1D ^{1}H NMR (600 MHz) spectra of pD 10 D_2O solutions of (a) 0.005 mol dm^{-3} racemic D/L-4HOPhg$^-$ in the presence of (b) equimolar 3βCDida^{2-} and Eu^{3+}, (c) equimolar 3βCDida^{2-} and Eu^{3+} but with a D/L-4HOPhg$^-$ ratio of 4:1, (d) equimolar 6βCDida^{2-} and Eu^{3+}, (e) equimolar 6βCDida^{2-} and Eu^{3+} but with a D/L-4HOPhg$^-$ ratio of 4:1, (f) equimolar 6βCDedta^{3-} and Eu^{3+}, and (g) equimolar 6βCDedta^{3-} and Eu^{3+} but with a D/L-4HOPhg$^-$ ratio of 4:1.

4HOPhg$^-$ interacting with H3 and H5 of 6βCDida^{2-} in the [Eu(6βCDida)(D/L-4HOPhg)] and system are consistent with the phenyl ring residing well inside the annulus of 6βCDida^{2-}. The [Eu(6βCDedta)(D/L-4HOPhg)]$^-$ system shows no analogous ^{1}H NMR ROESY cross-peaks probably because the resonance broadening evident in the 1D ^{1}H NMR spectra depresses the cross-peak amplitudes.

2.7. ^{1}H NMR studies of the D/L-Phm/D/L-PhmH$^+$ system

The series of 1D ^{1}H NMR spectra of D/L-Phm/D/L-PhmH$^+$ alone and in the presence of either equimolar βCD, substituted βCDs, or substituted βCDs and Eu^{3+} (Fig. 8) shows interesting contrasts with those of the D/L-Trp$^-$ and D/L-4HOPhg$^-$ systems. These probably arise because at pD 10 in D_2O approximately equimolar amounts of neutral D/L-Phm and positively charged D/L-PhmH$^+$ ($pK_a = 9.9$ in D_2O) exist as opposed to the negatively charged D/L-Trp$^-$ and D/L-4HOPhg$^-$. Consequently differing electrostatic interactions between these guests and their βCD, substituted βCDs and substituted βCDs and Eu^{3+} hosts exist as has also been observed in other systems in which the cyclodextrin charge varies.[19] While βCD induces some significant chemical shift changes and overlapping doubling of the H1, H2, and H4 resonances (Fig. 8b, Table 1), 3βCDida^{2-} induces a well-resolved doubling of the H1-H4 resonances consistent with D/L-Phm/D/L-PhmH$^+$ being in fast exchange between the free state and the [(3βCDida)(D-Phm)]$^{2-}$/[(3βCDida)(D-PhmH)]$^-$ and [(3βCDida)(L-Phm)]$^{2-}$/[(3βCDida)(L-Phm)]$^-$ diastereomeric host–guest complexes (Fig. 8c). This is echoed by the [(6βCDida)(D/L-Phm)]$^{2-}$/[(6βCDida)(D/L-PhmH)]$^-$ host–guest diastereomer complexes, although their chemical shift differences are smaller (Fig. 8d) and probably reflect the structural differences between the 3βCDida^{2-} and 6βCDida^{2-} hosts. The trinegatively charged 3βCDedta^{3-} shows substantial chemical shift differences between the H1–H4 doublets of the [(6βCDedta)(D/L-Phm)]$^{3-}$/[(6βCDedta)(D/L-PhmH)]$^{2-}$ host–guest complexes (Fig. 8e) probably because of the increased electrostatic attraction between the host and guest species. This may coincide with the phenyl group entering from the wider annular end of 3βCDida^{2-} and the narrower end of 6βCDida^{2-} and 6βCDedta^{3-} as electrostatic attraction is maximized. (In

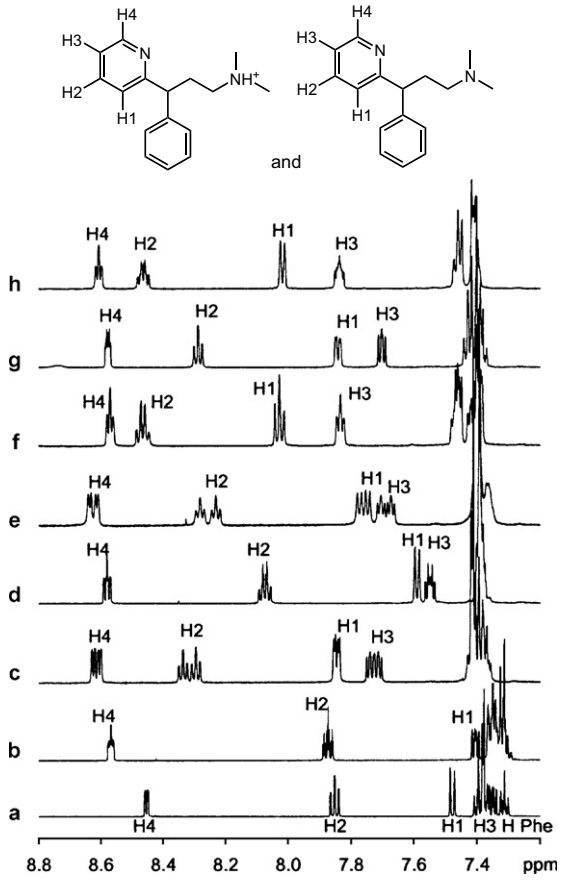

Figure 8. 1D ^{1}H NMR (600 MHz) spectra of pD 10 D_2O solutions of (a) 0.005 mol dm^{-3} racemic D/L-Phm/D/L-PhmH$^+$ in the presence of (b) equimolar βCD, (c) equimolar 3βCDida^{2-}, (d) equimolar 6βCDida^{2-}, (e) equimolar 6βCDedta^{2-}, (f) equimolar 3βCDida^{2-} and Eu^{3+}, (g) equimolar 6βCDedta^{3-} and Eu^{3+}, (h) equimolar 6βCDedta^{3-} and Eu^{3+}.

the absence of separate D and L enantiomers of D/L-Phm/D/L-PhmH$^+$, it is not possible to assign ^{1}H resonances to the D and L enantiomers.)

In the presence of equimolar Eu^{3+}, the substituted βCD induces a similar or lesser enantioselectivity than the substituted βCDs alone as judged from the extent of duplication of the H1–H4 D/L-Phm/D/L-PhmH$^+$ resonances (Fig. 8f–h). It is probable that the positive charges of [Eu(3βCDida)]$^+$ and [Eu(6βCDida)]$^+$ and the neutrality of [Eu(6βCDedta)] decrease the electrostatic attraction by comparison with 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-} and thereby host–guest complexation. This is unlikely to be compensated for by the significant complexation of Eu^{3+} as D/L-Phm/D/L-PhmH$^+$ cannot complex Eu^{3+} in the bidentate manner of the amino acid anions as exemplified by D/L-Trp$^-$ shown in Figure 4.

The 2D ^{1}H ROESY NMR spectra of the βCD and the three substituted βCD systems only show strong cross-peaks for the D/L-Phm/D/L-PhmH$^+$ phenyl group consistent with its complexation inside their βCD annuli and with the pyridine group residing in the vicinity of the hydroxyl groups to which its nitrogen may hydrogen bond.

2.8. ^{1}H NMR studies of the D/L-Phg$^-$, D/L-βPhs$^-$, and D/L-His$^-$ systems

The aromatic resonances of D/L-Phg$^-$ and D/L-βPhs$^-$ are complex. While the 1D ^{1}H NMR spectral changes induced by equimolar amounts of βCD, substituted βCDs, and substituted βCDs and Eu^{3+} (Tables 1 and 2) are consistent with the formation of host–guest complexes, their complexity precludes a reliable analysis in terms of enantioselectivity. Equimolar 6βCDida^{2-}, 3βCDida^{2-}, and 6βCDedta^{3-} induces large downfield shifts for the sharp singlet H^1 and H^2 resonances of D/L-His$^-$ consistent with host–guest complexation, but no duplication of resonances indicative of enantioselectivity occurs. A similar situation prevails in equimolar 6βCDida^{2-} and Eu^{3+}, 3βCDida^{2-} and Eu^{3+}, and 6βCDedta^{3-} and Eu^{3+} solutions. In the latter case, the resonances are substantially broadened consistent with an exchange of D/L-His$^-$ between the free and host–guest complex environments being in the intermediate exchange regime of the NMR timescale[18] (Tables 1 and 2). It appears that D/L-His$^-$ may be too small by comparison with the βCD annulus for enantioselective host–guest complexation to occur.

3. Conclusions

The hosts 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-}, and their Eu^{3+} complexes form host–guest complexes with all six of the enantiomeric guests studied in accordance with the complexation equilibria shown in Figure 4. However, significant enantioselectivity only occurs within the host–guest complex if one or both of (i) an optimal combination of the relative sizes of the host's βCD annulus and the guest occurs, and (ii) the electrostatic host–guest interactions are appropriate. While these criteria are met for some component combinations in the D/L-Trp$^-$, D/L-4HOPhg$^-$, and D/L-Phm/D/L-PhmH$^+$ systems, D/L-His$^-$ appears to be too small to satisfy (i), and the ^{1}H NMR spectra of the D/L-Phg$^-$ and D/L-βPhs$^-$ systems are too complex to be reliably interpreted in terms of enantioselectivity. The effect of Eu^{3+} on enantioselectivity in host–guest complexation where the guest has a bidentate Eu^{3+} complexing group ranges from increasing enantioselectivity as shown for the D/L-Trp$^-$ and D/L-4HOPhg$^-$ systems to having no readily distinguishable effect in the D/L-Phg$^-$, D/L-βPhs$^-$, and D/L-His$^-$ systems (Figs. 5 and 7 and Tables 1 and 2). In the first two systems, bidentate complexation of the guest to Eu^{3+} (Fig. 4) orients the D and L guest to accentuate differences in their stereochemical interactions within the homochiral βCD annulus such that they experience sufficiently different magnetic environments for them to display different chemical shifts in their ^{1}H NMR spectra. This orientating effect of Eu^{3+} may be greater than that of the host modified βCD alone and may either reinforce or diminish differences in the ^{1}H NMR spectra of complexed guests arising from this second effect. A combination of these competing effects probably contributes to the lack of reliably distinguishable resonances attributable to D and Lenantiomer appearing in the ^{1}H NMR spectra of D/L-Phg$^-$, D/L-βPhs$^-$, and D/L-His$^-$. Although D/L-Phm/D/L-PhmH$^+$ has no significant metal ion complexing group, the presence of Eu^{3+} de-

creases the enantiomeric discrimination caused by 3βCDida^{2-}, 6βCDida^{2-}, and 6βCDedta^{3-}, which suggests that the electrostatic guest orientating effect of Eu^{3+} on host complexation opposes that of the modified βCDs alone such that differences in the enantiomeric ^{1}H NMR chemical shifts are decreased.

4. Experimental

4.1. Reagents

All aqueous solutions were prepared in boiled deionized water using a MilliQ Reagent system to give a resistivity of >15 MΩ cm. Standard reagents were of good commercial grade and were not further purified. β-Cyclodextrin was donated by Nihon Shokuhin Kako Co. The amino acids and pheniramine maleate (Sigma) and europium triflate, $Eu(CF_3SO_3)_3$ (Aldrich), were used as received. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} on aluminum-backed sheets. For the analysis of cyclodextrin derivatives, TLC plates were developed with 7:7:5:4 v/v ethyl acetate/propan-2-ol/ammonium hydroxide/water. The cyclodextrins were visualized by drying the TLC plate and then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat gun. To visualize amino substituted cyclodextrins, TLC plates were dried prior to dipping into 0.5% ninhydrin in ethanol and heated with a heat-gun, before dipping in 1% sulfuric acid in ethanol. For the preparations described below, R_c represents the R_f of a modified cyclodextrin relative to the R_f of the parent cyclodextrin.

4.2. Instrumental

Routine ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini ACP-300 spectrometer operating at 300.145 MHz and 75.4 MHz, respectively. The 2D ^{1}H ROESY and NOESY NMR spectra were recorded on a Varian Inova 600 spectrometer operating at 599.957 MHz, using a standard sequence with a mixing time of 0.3 s. Chemical shifts were determined against external trimethylsilylpropiosulfonic acid in D_2O. LC-Q Mass spectrometry was carried on a Finnigan LCQ instrument. Potentiometric titrations were carried out with a Metrohm Dosino 800 titrimator, a Metrohm Titrando 809 potentiometer, and an Orion 81-03 combination electrode filled with aqueous 0.10 mol dm^{-3} $NaClO_4$ solution. The electrode was soaked in a 0.10 mol dm^{-3} $NaClO_4$ solution for at least three days prior to use. Titrations were performed in a water-jacketed 2 cm^3 titration vessel held at 298.2 ± 0.1 K. A continuous gentle stream of nitrogen bubbles (previously passed through aqueous 0.10 mol dm^{-3} KOH to remove any CO_2 traces and then aqueous 0.10 mol dm^{-3} $NaClO_4$) was passed through the titration solutions, which were magnetically stirred. Solutions were equilibrated in the titration vessel for 30 min before commencement of the titration to allow them to become nitrogen saturated at 298.2 K. For each system, 0.10 NaOH was titrated against the species of interest (0.001 mol dm^{-3}) in 0.010 mol dm^{-3} in $HClO_4$ and 0.09 mol dm^{-3} in $NaClO_4$ solutions. The pK_as were derived from the titration data using the program Hyperquad 2003.[20] Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand.

4.3. Preparation of substituted β-cyclodextrins

6^A-Bis(carboxymethyl)amino-6^A-deoxy-β-cyclodextrin,[13] 6βCDidaH$_2$, (2^A*S*,3^A*S*)-3^A-amino-3^A-deoxy-β-cyclodextrin,[14] 3βCDNH$_2$, and 6^A-(2-aminoethyl)amino-6^A-deoxy-β-cyclodextrin,[15] 6βCDen, were prepared as previously described. The general methods for the preparation of (2^A*S*,3^A*S*)-3^A-bis(carboxylmethyl)amino-3^A-deoxy-β-cyclodextrin, 3βCDidaH$_2$, and 6^A-[tris(carboxylmethyl)(2-aminoethyl)amino]-6^A-deoxy-β-cyclodextrin, 6βCDedtaH$_3$ were as follows. Solutions containing chloroacetic acid (0.5 g, 5 mmol) in 2 cm^3 H_2O and NaOH (0.2 g, 0.5 mmol) in 2 cm^3 H_2O were cooled to 0 °C and then combined. The mixture was added to either 3βCDNH$_2$ or 6βCDen (0.68 g and 0.71 g, respectively, 0.6 mmol) in 5 cm^3 H_2O at 0 °C. After adjusting the pH to 10–11 with aqueous NaOH, the reaction mixture was heated at 80 °C for 24 h. During this time, aqueous NaOH (10 cm^3) equivalent to the HCl produced from the reaction was very slowly added with a perfuser. The reaction was monitored by TLC until neither 3βCDNH$_2$ nor 6βCDen was detected, respectively. The reaction mixture was cooled to room temperature and was then slowly added to ethanol (200 cm^3). The resulting precipitate was filtered, washed with ethanol (50 cm^3), and dissolved in water (10 cm^3) and loaded onto a Dowex 50w x2 cation exchange column (1.5 × 15 cm). The column was washed with water (500 cm^3) and 1.0 mol dm^{-3} aqueous acetic acid (500 cm^3). The eluate was collected in 20 cm^3 fractions. Fractions containing the product were combined and evaporated to dryness under vacuum. The residue was freeze-dried to give the products as white solids.

4.3.1. (2^A*S*,3^A*S*)-3^A-Bis(carboxylmethyl)amino-3^A-deoxy-β-cyclodextrin. Yield: 382 mg (51%); $R_c = 0.46$. ^{1}H NMR (D_2O, 300 MHz): δ_H (ppm) 5.08–5.01 (m, 7H, H1); 4.2 (s, 4H, CH_2); 4.09–3.61 (m, 42H, H2–H6). ^{13}C NMR (D_2O, 75.4 MHz) δ_C 173.05 (acid C=O), 104.5–103.2 (C1), 102.1 (C1A), 85.6–83.6 (C4), 82.1 (C4^A), 78.2–73.5 (C2, C3, C5), 63.1–62.1 (C6^{B-G}), 59.2 (C6A), 53.8 (C3A), 49.7 (CH_2). LCQ-MS *m*/*z* (M+H$^+$) 1249; (M+Na$^+$) 1272. Elemental Anal. Calcd for $C_{46}H_{75}NO_{38}\cdot 11H_2O$: C, 38.15; H, 6.75; N, 0.96. Found: C, 38.10; H, 6.66; N, 0.92.

4.3.2. 6^A-[Tris(carboxylmethyl)(2-aminoethyl)amino]-6^A-deoxy-β-cyclodextrin. Yield: 535 mg (66%); $R_c = 0.31$. ^{1}H NMR: δ_H(D_2O, 300 MHz) 5.08–5.06 (m, 7H, H^1); 4.7, 4.2 (m, 6H, acid CH_2); 4.0–3.35 (m, 42H, H^2–H^6). ^{13}C NMR: δ_C (D_2O, 75.4 MHz) 176.7 (acid C=O), 104.5 (C1), 102.5 (C1^A), 85.6–83.7 (C4), 81.7 (C4^A), 75.7–71.2 (C2, C3, C5), 63.2–62.1 (C6^{B-G}), 58.8 (C6^A), 47.5 (CH_2). LCQ-MS *m*/*z* (M+H$^+$) 1350; (M+Na$^+$) 1373. Elemental Anal. Calcd for $C_{50}H_{82}N_2O_{40}\cdot 11H_2O$: C, 38.76; H, 6.76; N, 1.80. Found: C, 38.99; H, 6.78; N, 1.62.

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