

# Benzoylated and Benzylated Cyclodextrins: A New Class of Chiral Solvating Agents for Chiral Recognition of 3,5-Dinitrophenyl Derivatives by $^1\text{H}$ -NMR Spectroscopy

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Benzoylated and benzylated cyclodextrins give rise to non-equivalence in the  $^1\text{H}$ -NMR spectra of racemates of 3,5-dinitrophenyl derivatives of chiral amines, amino alcohols, alcohols, carboxylic acids and amino acids in  $\text{CDCl}_3$  solution, suggesting their potential use as  $\text{CDCl}_3$ -soluble cyclodextrinic chiral solvating agents (CSAs) in NMR

spectroscopy. Cyclodextrins bearing aromatic substituents at the primary or secondary sites only are more efficient CSAs compared to exhaustively substituted ones. NMR investigations based on NOE measurements or complexation shift determinations strongly suggest non-inclusive interaction mechanisms for these selector/selectand systems.

## Introduction

The structural preorganization of cyclodextrins makes them selective complexing agents through inclusion processes and the chirality of the individual glucosidic units can render the complexation enantioselective.<sup>[1]</sup> However, one of their most interesting and attractive features is that it is possible to modulate all recognition mechanisms by selective or non-selective modification of the network of primary and secondary hydroxy functions. For this purpose, a great deal of work has been devoted to the synthesis of derivatized cyclodextrins,<sup>[1][2]</sup> which have found widespread application in catalysis,<sup>[1][3]</sup> asymmetric synthesis,<sup>[1][2a][4]</sup> analytical and preparative separation of enantiomers by chromatography,<sup>[5]</sup> and in NMR, mainly as chiral solvating agents (CSAs).<sup>[6]</sup>

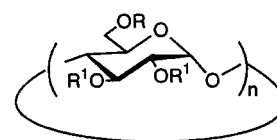
In the last area mentioned, modified and unmodified cyclodextrins have enabled a very broad range of analyses to be performed. The earliest applications of native cyclodextrins as CSAs were concerned with water-soluble chiral analytes.<sup>[6d][6e]</sup> More recently, alkylated cyclodextrins have been evaluated as efficient CSAs for non-polar substrates<sup>[6l][6o][6s][6t][6u][6v][6w]</sup> and, in particular, permethylated cyclodextrins have been shown to have general utility in determining the enantiomeric purities of trisubstituted alkenes<sup>[6s][6t][6v][6w]</sup> and aromatic hydrocarbons.<sup>[6u][6v][6w]</sup>

Moreover, selectively or exhaustively benzoylated cyclodextrins, such as hexakis(2,3-di-*O*-benzoyl)- $\alpha$ -cyclodextrin (**1**) or hexakis(2,3,6-tri-*O*-benzoyl)- $\alpha$ -cyclodextrin (**2**) (Scheme 1), have been proposed as  $\text{CDCl}_3$ -soluble CSAs for 3,5-dinitrophenyl derivatives of organic compounds.<sup>[6x]</sup>

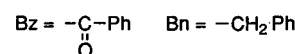
On this basis, various kinds of cyclodextrin derivatives bearing benzoyl [hexakis(6-*O*-benzoyl)- $\alpha$ -cyclodextrin (**3**) and heptakis(2,3,6-tri-*O*-benzoyl)- $\beta$ -cyclodextrin (**4**)] or

benzyl [hexakis(2,3-di-*O*-benzyl)- $\alpha$ -cyclodextrin (**5**)] or both groups [hexakis(6-*O*-benzoyl-2,3-di-*O*-benzyl)- $\alpha$ -cyclodextrin (**6**)] (Scheme 1) are now evaluated as potential CSAs in NMR analyses of the 3,5-dinitrophenyl derivatives **7–12** (Scheme 2). Their efficiencies are compared to those of **1** and **2**.

Scheme 1



R=H	R <sup>1</sup> =Bz	n=6	<b>1</b>
R=R <sup>1</sup> =Bz		n=6	<b>2</b>
R=Bz	R <sup>1</sup> =H	n=6	<b>3</b>
R=R <sup>1</sup> =Bz		n=7	<b>4</b>
R=H	R <sup>1</sup> =Bn	n=6	<b>5</b>
R=Bz	R <sup>1</sup> =Bn	n=6	<b>6</b>

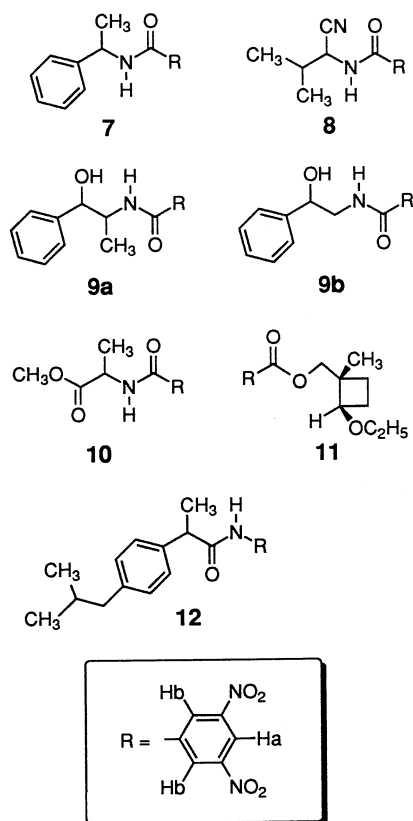


## Results and Discussion

In order to probe the efficiencies of **3–6** as CSAs for the determination of the enantiomeric compositions of chiral analytes by NMR spectroscopy, mixtures of each cyclodextrin and racemates of different classes of underivatized or derivatized organic compounds were analyzed in  $\text{CDCl}_3$  solution. For all compounds, non-equivalences were detected only when the substrates contained a 3,5-dinitrophenyl moiety.

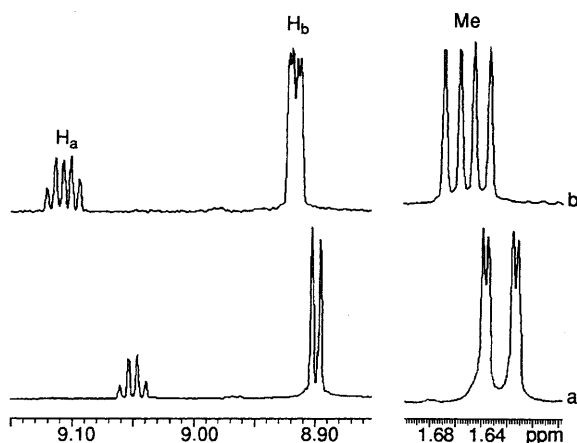
The cyclodextrin **3**, benzoylated at its primary hydroxy functions, induces non-equivalence in the protons of com-

Scheme 2



pound **7** (Figure 1a): the  $H_a$  proton signal underwent a splitting of 2.0 Hz and the non-equivalences measured for the amide and methyl protons were 10.7 and 1.1 Hz, respectively.

Figure 1.  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ) spectral regions corresponding to the 3,5-dinitrobenzoyl and methyl protons of **7** (28 mM) in mixtures containing equimolar amounts of the cyclodextrins **3** (a) or **1** (b)



Detectable non-equivalences were also induced in the case of compound **8**: its 3,5-dinitrobenzoyl protons  $H_b$  were resolved into two doublets centered at  $\delta = 8.97$  and  $\delta = 8.96$  ( $\Delta\delta = 1.8$  Hz). The proton  $H_a$  of the same compound showed a splitting of 3.0 Hz, but its diastereotopic methyl resonances were not differentiated. As far as the alkyl moi-

ety was concerned, only a small but detectable (0.8 Hz) splitting of the methine absorptions of the isopropyl group was observed. The resonances of the amide proton and of the adjacent methine group were obscured by the cyclodextrin signals.

The effect of the presence of **3** on the proton signals of **9a** and **9b** was completely different in that the line broadening induced by the CSA on the **9b** protons prevented any observation of non-equivalence. A small change in the linewidth of the proton signals of **9a** was produced and non-equivalences of 1.8 Hz, 7.0 Hz and 7.1 Hz were measured for the protons  $H_b$ , NH, and the adjacent CH, respectively. The 3,5-dinitrobenzoyl absorptions of **10** showed a small splitting (0.8 Hz) for  $H_a$ , but a more significant separation of the NH signals (6.3 Hz) was observed. The addition of **3** resulted in non-equivalence in the 3,5-dinitrophenyl moiety of **12** and in its amide group (4.0 Hz for both  $H_a$  and  $H_b$  and 8.7 Hz for NH). The alcohol derivative **11** was the only substrate not discriminated by **3**.

In Table 1, all the aforementioned non-equivalence data are summarized and compared to the results obtained in the presence of the cyclodextrins **1** and **2**. The cyclodextrin **1**, underivatized at its primary hydroxy groups, produced signal differentiation in almost all compounds, as did the chiral auxiliary **3**, in which the secondary hydroxy groups are unprotected. As an example, in Figure 1 the spectral regions featuring the resonances of the 3,5-dinitrobenzoyl and methyl protons of **7** in the presence of either **3** or **1** are compared. Applications of the exhaustively benzoylated cyclodextrin **2** are more limited owing to the fact that in some cases the line broadening produced by the CSA on the analyte signals prevents evaluation of the magnitude of the non-equivalences. In the presence of **2**, the separation between the diastereotopic signals of **9b** is so large that a separate integration of the absorptions due to the two enantiomers could be performed, in spite of the remarkable perturbation of the lines: non-equivalences of 18.0 Hz and 29.0 Hz were measured for the 3,5-dinitrobenzoyl protons  $H_a$  and  $H_b$ , respectively, with a line width greater than 5.0 Hz.

It is noteworthy that **9b** also underwent a similar line broadening in the presence of cyclodextrin **3**, as already discussed.

The perbenzoylated  $\beta$ -cyclodextrin **4** was able to resolve some proton signals of the compounds **8**, **9a**, **10** and **12**, whereas no enantiodiscrimination was observed for **7**, **9b** and **11** (Table 1). Therefore, **4** showed a more limited applicability than the analogous perbenzoylated  $\alpha$ -cyclodextrin.

Finally, the efficiencies as CSAs of the cyclodextrins **5** and **6** towards **9a** and **9b** were compared. The benzylated cyclodextrin **5** discriminated the 3,5-dinitrobenzoyl protons  $H_a$  and  $H_b$  of both substrates and the resulting non-equivalences ranged between 2.3 and 4.0 Hz (Table 2). Slightly smaller non-equivalences were produced by the cyclodextrin **6**, although it also led to differentiation of the methyl resonances of **9a** (Table 2).

As reported previously,<sup>[6x]</sup> NMR investigations by 2D ROESY (Rotating-frame Overhauser Enhancement Spec-

Table 1. Non-equivalences ( $\Delta\Delta\delta^{[a]}$ , 300 MHz,  $\text{CDCl}_3$ ) of the protons of **7–12** in the presence of equimolar amounts of cyclodextrins **1–4**

		1	2	3	4
7	H <sub>a</sub>	6.1	2.0	2.0	
	H <sub>b</sub>	1.5			
	CH <sub>3</sub>	6.9		1.1	
	CH	n.d.	n.d.		
	NH	n.d.	n.d.	10.7	
8	H <sub>a</sub>			3.0	
	H <sub>b</sub>			1.8	2.4
	CH <sub>3</sub> ( <i>i</i> Pr)	7.1	2.7		
9a	CH ( <i>i</i> Pr)	n.d.	n.d.	0.8	2.7
	H <sub>a</sub>	7.1	1.3		1.6
	H <sub>b</sub>	2.9	1.8	1.8	
	CH <sub>3</sub>	2.4	4.4		4.0
	CH			7.1	
9b	NH			7.0	
	H <sub>a</sub>		18.0	n.d.	
	H <sub>b</sub>	1.9	29.0	n.d.	
	CH <sub>3</sub>		n.d.	n.d.	
10	H <sub>a</sub>		n.d.	0.8	2.1
	H <sub>b</sub>	2.1			
	CH <sub>3</sub>	2.6			
	CH	n.d.		n.d.	
11	NH		n.d.	6.3	
	H <sub>a</sub>		n.d.		
	H <sub>b</sub>		n.d.		
12	CH <sub>3</sub> CH <sub>2</sub>	3.1			
	H <sub>a</sub>			4.0	2.0
	H <sub>b</sub>	1.9		4.0	
	CH <sub>3</sub>	4.2			
	CH <sub>2</sub> ( <i>i</i> Bu)	2.3	2.5		
	CH ( <i>i</i> Bu)		2.5		
	CH <sub>3</sub> ( <i>i</i> Bu)				1.4
	CH*				2.2
	NH			8.7	

<sup>[a]</sup>  $\Delta\Delta\delta$  is the difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of the CSA; n.d.: not determined.

Table 2. Non-equivalences ( $\Delta\Delta\delta^{[a]}$ , 300 MHz,  $\text{CDCl}_3$ ) of the protons of **9a** and **9b** in the presence of equimolar amounts of cyclodextrins **5** and **6**

	H <sub>a</sub>	9a H <sub>b</sub>	CH <sub>3</sub>	H <sub>a</sub>	9b H <sub>b</sub>	CH <sub>3</sub>
5	4.0	3.9		2.7	2.3	
6	1.3		2.6	2.4	2.4	

<sup>[a]</sup>  $\Delta\Delta\delta$  is the difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of the CSA.

troscopy) techniques on mixtures **2/9b** allow the detection of superficial analyte–cyclodextrin interactions and a significant conformational variation of the host. This represented one of the most favourable cases encountered, because the association constants involved were probably high, as indicated by the remarkable complexation shifts measured in the mixtures compared to the free compounds. As an example, the 3,5-dinitrobenzoyl protons H<sub>a</sub> and H<sub>b</sub> of **9b** were high-frequency shifted by 41.9 and 52.5 Hz, respectively, for (*S*)-**9b** and by 12.6 and 34.5 Hz, respectively, for (*R*)-**9b**.

In contrast, for the mixtures containing each cyclodextrin **3–6** and the analytes **7–12**, non-equivalences were measured but were accompanied by small complexation shifts

for each enantiomer, thus indicating the formation of remarkably labile diastereoisomeric adducts with the CSA. In fact, no dipolar interactions were detected in the mixtures by NOE methods. Only in the case of the cyclodextrin **3** could some information be gleaned concerning the mechanism of the interaction from analysis of the complexation shifts (Table 3) for the cyclodextrin protons in different mixtures. In all cases, only the benzoyl and hydroxy protons of **3** showed detectable chemical shift variations in the presence of the analytes, whereas its internal protons were almost unaffected.

Table 3. Complexation shifts ( $\Delta\delta^{[a]}$ , 300 MHz,  $\text{CDCl}_3$ , 25 °C) measured for the cyclodextrin protons of **3** in the presence of **7–10** and **12**

	7	8	9a	9b	10	12
H <sub>o</sub> , 6-OBz	−5.2	−3.0	−5.6	−1.6	−2.7	−5.6
H <sub>m</sub> , 6-OBz	−4.2	−2.2	−4.2	+3.1	−2.6	−4.4
H <sub>p</sub> , 6-OBz	−3.6	−1.9	−3.6	+3.5	−2.8	−3.8
3-OH	−15.3	−6.8	−15.3	−36.0	−9.5	−12.9
2-OH	−7.8	−3.4	−8.8	−7.2	−5.4	−5.6

<sup>[a]</sup>  $\Delta\delta = \delta_{\text{mixture}} - \delta_{\text{free}}$  (Hz).

Therefore, in these cases no inclusion occurs and the interaction probably takes place at the external surface by means of  $\pi$ – $\pi$  attractive interactions involving the aromatic moieties, and by formation of hydrogen bonds with the secondary hydroxy functions. A non-inclusive interaction mechanism is also in keeping with the lack of selectivity towards the dimensions of the analyzed substrates.

## Conclusion

Benzoylation and benzylation render cyclodextrins soluble in  $\text{CDCl}_3$ , making them more suitable CSAs for water-insoluble chiral organic compounds. In fact, a very large range of substrates can be analyzed, with the sole requirement being the presence of a 3,5-dinitrophenyl moiety. This group can be easily introduced and represents an optimal probe group for enantiomer composition determinations, as its absorptions are usually very sharp and are located in generally otherwise free spectral regions. Collectively, derivatized (both by aromatic or alkyl groups) and underivatized cyclodextrins constitute a very interesting and versatile class of auxiliaries for NMR analyses of both polar and non-polar chiral substrates.

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## Experimental Section

**General:** NMR measurements were performed with a Varian VXR-300 spectrometer in  $\text{CDCl}_3$  solution, unless otherwise stated; the temperature was controlled by a Varian control unit ( $\pm 0.1$  °C). Synthetic procedures for preparing cyclodextrins **3**, **5** and **6** have been reported elsewhere.<sup>[7]</sup> Derivative **4** was prepared according to the procedure described in ref.<sup>[8]</sup>. Compounds **7–12** were prepared according to the literature.<sup>[6x]</sup>

*Hexakis(6-O-benzoyl)- $\alpha$ -cyclodextrin (3):* <sup>1</sup>H NMR:  $\delta$  = 3.55 (6 H, 4-H), 3.75 (6 H, 2-H), 4.12 (6 H, 3-H), 4.24 (6 H, 5-H), 4.38 (6

H, 6-H), 4.76 (6 H, 6-H), 4.97 (6 H, 1-H), 5.24 (6 H, 2-OH), 6.67 (6 H, 3-OH), 7.33 (12 H,  $H_m$ , 6-OBz), 7.45 (6 H,  $H_p$ , 6-OBz), 7.91 (12 H,  $H_o$ , 6-OBz). —  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ ):  $\delta$  = 63.4 (C-6), 69.4 (C-5), 71.6 (C-2), 72.9 (C-3), 82.3 (C-4), 102.1 (C-1), 128.5 ( $C_o$ , 6-OBz), 129.0 ( $C_m$ , 6-OBz), 129.2 ( $C_p$ , 6-OBz), 133.2 ( $C_{\text{quat}}$ ), 165.2 (CO). —  $\text{C}_{78}\text{H}_{84}\text{O}_{36}$  (1597.5): calcd. C 58.63, H 5.30; found C 58.67, H 5.26.

**Heptakis(2,3,6-tri-O-benzoyl)- $\beta$ -cyclodextrin (4):**  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ ,  $140^\circ\text{C}$ ):  $\delta$  = 3.93 (7 H, 4-H), 4.19 (7 H, 5-H), 4.37 (7 H, 6-H), 4.43 (7 H, 6-H), 4.63 (7 H, 2-H), 5.10 (7 H, 1-H), 5.41 (7 H, 3-H), 6.55 (28 H,  $H_m$ , 2-OBz, and  $H_m$ , 3-OBz), 6.81–6.85 (14 H,  $H_p$ , 2-OBz, and  $H_p$ , 3-OBz), 6.93–6.99 (28 H,  $H_o$ , 2-OBz, and  $H_o$ , 3-OBz), 7.06 (14 H,  $H_m$ , 6-OBz), 7.14 (7 H,  $H_p$ , 6-OBz), 7.58 (14 H,  $H_o$ , 6-OBz). —  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): glucosidic carbon atoms:  $\delta$  = 63.4 (C-6), 69.9 (C-5), 71.3 (C-2 and C-3), 77.6 (C-4), 97.4 (C-1); proton-bearing aromatic carbon atoms:  $\delta$  = 127.5, 127.6, 129.5, 129.8, 132.1, 132.5, 133.2; quaternary aromatic carbon atoms:  $\delta$  = 128.0, 128.6, 129.3; carbonyl carbon atoms:  $\delta$  = 164.3, 165.8, 165.9. —  $\text{C}_{189}\text{H}_{154}\text{O}_{56}$  (3321.3): calcd. C 68.34, H 4.68; found C 68.36, H 4.70.

**Hexakis(2,3-di-O-benzyl)- $\alpha$ -cyclodextrin (5):**  $^1\text{H}$  NMR:  $\delta$  = 3.43 (6 H, 2-H), 3.59 (6 H, 4-H), 3.65 (6 H, 6-H), 3.87 (6 H, 6-H), 3.99 (6 H, 5-H), 4.04 (6 H, 3-H), 4.38 [6 H, 2-(PhCHH)], 4.54 [6 H, 2-(PhCHH)], 4.77 [6 H, 3-(PhCHH)], 4.97 (6 H, 1-H), 5.06 [6 H, 3-(PhCHH)], 6.95–7.25 (60 H, PhCH<sub>2</sub>). —  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ ): glucosidic carbon atoms:  $\delta$  = 60.2 (C-6), 71.7 (C-5), 71.9 (C-2), 74.3 (C-3), 80.5 (C-4), 96.5 (C-1); benzylic carbon atoms:  $\delta$  = 77.5, 78.8; proton-bearing aromatic carbon atoms:  $\delta$  = 127.0, 127.2, 127.8, 127.9; quaternary aromatic carbon atoms:  $\delta$  = 138.2, 139.0. —  $\text{C}_{120}\text{H}_{132}\text{O}_{30}$  (2054.4): calcd. C 70.15, H 6.48; found C 70.13, H 6.50.

**Hexakis(6-O-benzoyl-2,3-di-O-benzyl)- $\alpha$ -cyclodextrin (6):**  $^1\text{H}$  NMR:  $\delta$  = 3.50 (6 H, 2-H), 4.01 (6 H, 4-H), 4.23 (6 H, 5-H), 4.25 (6 H, 3-H), 4.44 [6 H, 2-(PhCHH)], 4.53 [6 H, 2-(PhCHH)], 4.59 (6 H, 6-H), 4.64 (6 H, 6-H), 4.88 [6 H, 3-(PhCHH)], 5.19 [6 H, 3-(PhCHH)], 5.14 (6 H, 1-H), 6.99–7.23 (60 H, PhCH<sub>2</sub>), 7.37 (12 H,  $H_m$ , 6-OBz), 7.46 (6 H,  $H_p$ , 6-OBz), 7.98 (12 H,  $H_o$ , 6-OBz). —  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ ): glucosidic carbon atoms:  $\delta$  = 64.0 (C-6), 69.6 (C-2), 72.0 (C-5), 74.8 (C-3), 80.2 (C-4), 97.9 (C-1); benzylic carbon atoms:  $\delta$  = 78.6, 78.9; proton-bearing aromatic carbon atoms:  $\delta$  = 127.1, 127.8, 128.6, 129.3; quaternary aromatic carbon atoms:  $\delta$  = 133.3, 138.3, 138.8; carbonyl carbon atoms:  $\delta$  = 165.3. —  $\text{C}_{162}\text{H}_{156}\text{O}_{36}$  (2679.0): calcd. C 72.62, H 5.87; found C 72.66, H 5.83.

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Benzoylated and Benzylated Cyclodextrins: A New Class of Chiral Solvating Agents for Chiral Recognition of 3,5-Dinitrophenyl Derivatives by  $^1\text{H}$ -NMR Spectroscopy

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