Partially versus Exhaustively Carbamoylated Cyclodextrins: NMR Investigation on Enantiodiscriminating Capabilities in Solution

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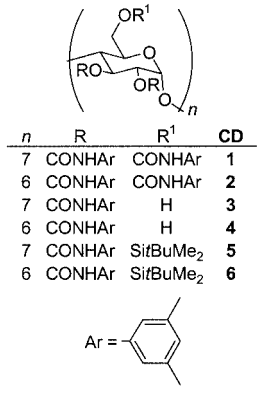
Keywords: Chiral resolution / Cyclodextrins / Enantiodiscrimination / NMR spectroscopy

The enantiodiscriminating efficiency of exhaustively carbamoylated, mixed carbamoylated/silylated, and partially carbamoylated cyclodextrins in solution has been compared by NMR spectroscopy. Investigation of the origin of the observed chiral discrimination was also carried out.

Introduction

The effectiveness of carbamoylated cyclodextrins as chiral selectors for HPLC has been extensively exploited[1−13] and their potential as chiral auxiliaries for NMR spectroscopy − with the aim of making the enantiotopic nuclei of enantiomeric species distinguishable − has also been suggested.[5,6] In particular, per(3,5-dimethylphenylcarbamoyl)cyclodextrins seemed to be promising chiral solvating agents (CSAs),[5] due to their good solubility in chloroform, allowing their application for enantiodiscrimination of chiral substrates with poor solubilities in protic solvents, for which underivatized cyclodextrins cannot be employed.

Here we have focused our attention on the exhaustively carbamoylated cyclodextrins heptakis[2,3,6-tri-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (**1**) and hexakis-[2,3,6-tri-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (**2**) and on the partially carbamoylated heptakis[2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (**3**) and hexakis[2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (**4**) (Scheme 1), comparing their capabilities to induce non-equivalence in the NMR spectra, recorded in $CDCl_3$, of several classes of chiral compounds including alcohols, amines, carboxylic acids, amino acids, and their simple derivatives (Scheme 2). Heptakis[6-*O*-(*tert*-butyldimethylsilyl)-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (**5**) and hexakis[6-*O*-(*tert*-butyldimethylsilyl)-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (**6**) (Scheme 1), intermediates in the syntheses of the partially substituted chiral selectors **3** and **4**, have also been examined.



n	R	R^1	CD
7	CONHAr	CONHAr	**1**
6	CONHAr	CONHAr	**2**
7	CONHAr	H	**3**
6	CONHAr	H	**4**
7	CONHAr	$SitBuMe_2$	**5**
6	CONHAr	$SitBuMe_2$	**6**

Scheme 1

Results and Discussion

Synthesis of Cyclodextrins 1−6

The preparation of exhaustively carbamoylated cyclodextrins **1** and **2** involves the treatment of well-dried β- and α-cyclodextrins with excess 3,5-dimethylphenyl isocyanate in pyridine at 80 °C for 20 h (Scheme 3).[11] The selective modification of the secondary sites of the cyclodextrins was carried out by use of a general procedure (Scheme 3), involving the preliminary protection of the primary hydroxy groups as *tert*-butyldimethylsilyl (TBDMS) ethers,[14] followed by carbamoylation of the secondary sites and final deprotection of the primary sites.

The cleavage of the protecting groups on the primary sites does not proceed as easily as their introduction. Attempts to *O*-desilylate **5** and **6** through the use of tetrabutylammonium fluoride (TBAF) in dioxane at reflux[15] (3 h) afforded mixtures of partially *O*-desilylated and *O*-decarbamoylated compounds, as shown by ^1H NMR analysis of the crude products.

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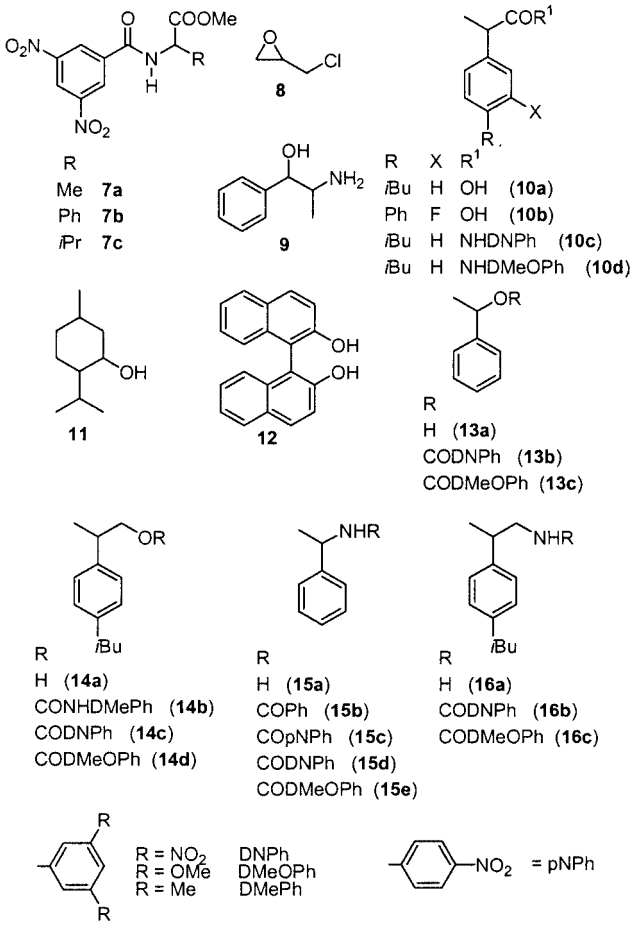
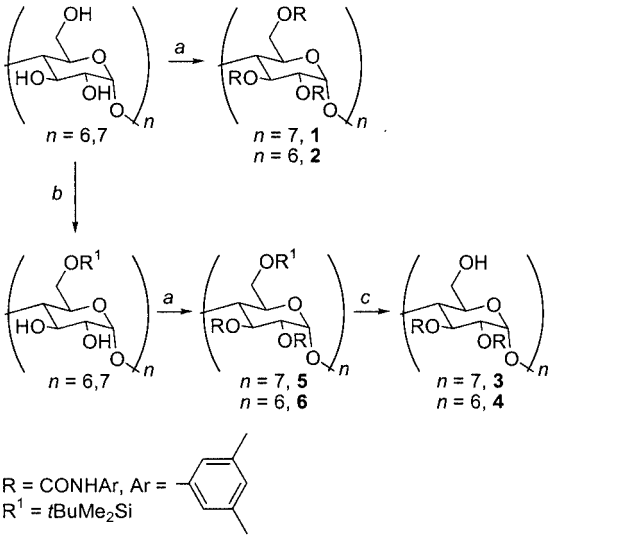


Scheme 2



Scheme 3

Among the many methods reported for the deprotection of TBDMS ethers, we have focused our attention on those involving mild conditions.[16−19] The use of LiCl/H_2O in DMF at 90−120 °C[16] constitutes a general method for the cleavage of primary and secondary TBDMS ethers under neutral conditions. A variety of TBDMS ethers can be cleaved with ceric ammonium nitrate (CAN) in methanol at 0 °C in a short reaction time (1−3 h).[17] An alternative method reported for the efficient deprotection of polyhydroxy compounds involves the use of a 1% solution of iodine in methanol at reflux temperature,[18] the TBDMS ether being removed within 90−120 min. *O*-Desilylated cyclodextrins containing acetyl substituents were obtained by employment of $BF_3{\cdot}Et_2O$,[19] which allowed the selective removal of the silyl groups without loss of the acetyl moieties. We therefore carried out cleavage reactions of **5** by employing the above procedures, the efficiency of the deprotection being evaluated by ^1H NMR spectroscopy. In the presence of LiCl/H_2O, no decarbamoylation occurred, but **5** was only partially desilylated (70%) after 72 h. CAN produced partial desilylation (75%) after 1 h, but with a large number of by-products. Complete desilylation, but also concomitant partial decarbamoylation (15%), was observed in a solution of iodine in methanol. Treatment of **5** and **6** with $BF_3{\cdot}Et_2O$ in dichloromethane at room temperature, however, resulted in the cleavage of the silyl groups (after 8 h) without loss of carbamoyl functions.

The CSAs **1**−**6** were fully characterized by ^1H and ^{13}C NMR spectroscopy. The proton resonances were assigned by comparative analysis of scalar homonuclear (DQF-COSY) and dipolar (ROESY) correlations. ^1H-^{13}C heteronuclear chemical shift correlation spectroscopy (HETCOR) was employed to attribute carbon signals.

Enantiodiscrimination Experiments

All the derivatized β-cyclodextrins **1**, **3**, and **5** (Scheme 1) are capable of inducing relevant non-equivalence in the nuclei of *N*-(3,5-dinitrobenzoyl)amino acid methyl esters **7** (Scheme 2), giving rise to non-equivalence ranging from 3 to 40 Hz. With particular regard to the 3,5-dinitrophenyl protons of **7a** (Table 1), similar non-equivalences are obtained by using the exhaustively carbamoylated β-cyclodextrin **1**, the mixed silylated/carbamoylated **5**, and the deprotected cyclodextrin **3**, bearing the carbamoyl functions on the secondary sites but possessing free primary hydroxy groups (Figure 1).

Table 1. Non-equivalence data ($\Delta\delta = \delta_R - \delta_S$ [Hz], 300 MHz, $CDCl_3$, 25 °C) of the proton nuclei of **7a** (10 mM) in the presence of equimolar amounts of **1**−**6** (the chiral auxiliary **4** produces signals so broad and extended that it cannot be employed as a CSA)

	1	**2**	**5**	**6**	**3**
Me	13.0	18.0	13.0	21.7	n.d.[a]
CH	15.1	n.d.[a]	10.3	n.d.[a]	n.d.[a]
OMe	5.2	16.6	–	n.d.[a]	10.1
NH	29.5	n.d.[a]	n.d.[a]	n.d.[a]	n.d.[a]
H_{ortho}	5.7	4.4	5.6	9.9	9.2
H_{para}	16.6	26.0	20.8	38.0	29.0

[a] n.d. = not determined (signals of the chiral substrate are partially superimposed by cyclodextrin resonances).

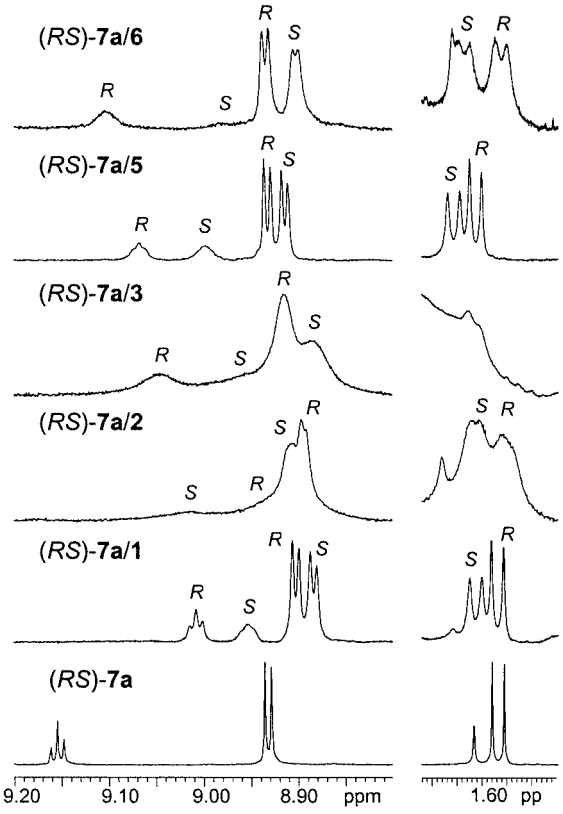


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) spectral regions corresponding to the 3,5-dinitrophenyl and the methyl protons of (*RS*)-**7a** (10 mM) in the pure compound and in the presence of equimolar amounts of **1**−**3**, **5**−**6**

A peculiarity of the mixtures containing the *N*-(3,5-dinitrobenzoyl)amino acid methyl esters **7** is that the resonances due to the (*S*) enantiomers of the amino acid derivatives have linewidths markedly broader than those of the analogous signals of the (*R*) enantiomers, as shown in Figure 1 for **7a**. This line-broadening is not observed in the enantiodiscrimination of the other substrates **8**−**16**, at least through the use of **1**, **2**, **5**, and **6**.

The non-equivalence data for the analyzed samples are collected as Supporting Information.

The percarbamoylated cyclodextrin **1** showed relevant versatility, allowing us to obtain detectable separations of signals of free carboxylic acids (**10a**−**b**) or, better, their derivatives **10c** and **10d**, containing either an electron-deficient (**10c**) or an electron-rich (**10d**) aromatic substituent. As an example, non-equivalence of up to 15 Hz was measured for **10d**, with a 3,5-dimethoxyphenyl group directly bound to the NH group.

In the presence of **1**, doublings of the resonances of free alcohols (**11**, **12**, **13a**) are observed, but not of their ester derivatives (**13b**−**c**).

Free amines (**15a**, **16a**) are not enantiodiscriminated, whereas good separations are obtained for their amide derivatives containing phenyl (**15b**), 3,5-dimethoxyphenyl (**15e**, **16c**), *p*-nitrophenyl (**15c**), or 3,5-dinitrophenyl (**15d**) moieties.

Some splittings of small entities are also observed for the amino alcohol **9** and the epoxide **8**.

In the majority of cases considered, the cyclodextrin **5**, with silyl groups on its primary sites and carbamoyl functions on its secondary ones, has similar enantiodiscriminating efficiency and versatility, enabling us to induce non-equivalence of alcohols (**11**−**13a**), carboxylic acids (**10a**−**b**) and their derivatives (**10c**−**d**), amides (**15b**−**c**, **16b**), and also the amino alcohol **9** and the epoxide **8**.

The analogous desilylated cyclodextrin **3** shows good efficiency with the amino acid derivatives **7**, but no enantiodiscrimination at all with the underivatized carboxylic acids or amines. Some alcohols are enantiodiscriminated (**12**, **13a**). The presence of an electron-deficient substituent (*p*-nitrophenyl or 3,5-dinitrophenyl) in the chiral enantiomeric substrates seems to be a prerequisite for their differentiation (**10c**, **15c**−**d**) in the presence of **3**. However, we should comment that both the cyclodextrin **3** and the enantiodiscriminated substrates produce signals so broad that the results are in many cases difficult to analyze and, overall, no reliable quantitative determinations of the enantiomeric excesses can be performed.

The use of the percarbamoylated α-cyclodextrin **2** as a chiral solvating agent was evaluated towards the selected substrates **7a** (Table 1), **10c**−**d**, **12**, **13a**, **14b**, and **15b**. It showed efficiency similar to that of the corresponding β system, with a remarkably enhanced line-width broadening effect for the amino acid derivatives **7** (Figure 1). Among the analyzed substrates, the silylated/carbamoylated chiral auxiliary **6** is mainly effective only towards derivatized substrates (**10c**−**d**, **15b**). The widths of the resonances of **4** are so large that this compound cannot be usefully employed as chiral solvating agent.

Chiral Discrimination Mechanism

The relevant non-equivalence measured in mixtures containing the amino acid derivative **7a** and both the percarbamoylated β-cyclodextrin **1** and the mixed silylated/carbamoylated β-cyclodextrin **5** prompted us to carry out NMR investigations by 2D ROESY analyses on the interaction mechanism of the two enantiomers of the chiral substrate and the two cyclodextrins.

No such investigations were carried out on the mixtures containing the cyclodextrin **3**, with the carbamoyl functions on the secondary sites and free primary hydroxy groups, due to the fact that the resonances both of the chiral substrates and of the cyclodextrin are so broad that extensive resonance superimposition occurs in several spectral regions, making the analysis of the NOE data very difficult.

The 2D-ROESY map of the cyclodextrin **1** does not show reciprocal dipolar interactions between the carbamate groups at the secondary and primary sites, thus indicating that the aromatic moieties on the wider rim are far away from those on the narrower one. The exhaustive carbamoylation must therefore mainly generate an extension of the truncated cone shape. This conformational preference is also retained in the mixtures containing one or the other

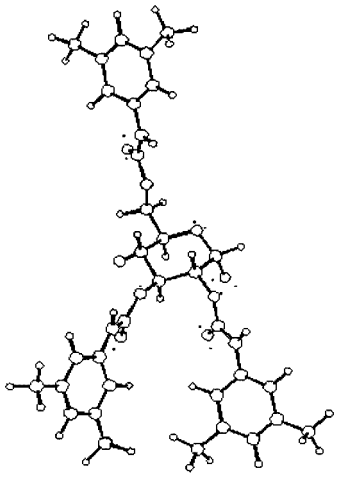


Figure 2. Stereochemistry of **1**: representation of one cyclodextrin unit

enantiomer of the amino acid derivative **7a**. Figure 2 represents one unit of the cyclodextrin.

No intermolecular dipolar interactions with internal protons of the cyclodextrin were found in the mixtures. Both the 3,5-dinitrobenzoyl and the methyl (Figures 3 and 4) protons of (*S*)-**7a** generate dipolar interactions with all the carbamate functions on the 2, 3, and 6 sites. In the case of (*R*)-**7a**, NOEs were mainly detected between its 3,5-dinitrophenyl protons and the primary 3,5-dimethylphenyl groups of the cyclodextrin (Figures 3 and 4).

Therefore, we can assess that the interaction between the (*R*) enantiomer and the cyclodextrin only involves the π-π attraction between the 3,5-dinitrophenyl and 3,5-dimethylphenyl moieties on the primary sites. In the mixture containing the (*S*) enantiomer, the 3,5-dinitrophenyl protons interact with all the three kinds of carbamate groups: the proximity between the methyl function of the amino acid and the same carbamoyl groups also suggests the possibility that hydrogen-bonding interactions between the NH groups of the cyclodextrin and the ester function of the amino acid could be involved in the formation of the (*S*)-**7a/1** complex, producing a greater degree of immobilization of the (*S*) enantiomer than of its (*R*) counterpart. For the (*R*) enantiomer, the same kind of interaction probably generates steric hindrance involving groups of the amino acid derivative bound to the chiral center and cyclodextrin substituents. A schematic picture of the interactions detected is given in Figure 4, showing the complexation modes between one unit of the cyclodextrin and one or the other enantiomer of the substrate, the arrows indicating the proximity correlations found by the NOE measurements.

Such a major stabilization of the (*S*)-**7a/1** complex with respect to the (*R*)-**7a/1** pair is well reflected in the values of the association constants: 35.7 M^{-1} and 14.1 M^{-1}, respectively. Their determination was carried out by fitting of Equation (1), which gives the dependence on the concen-

$$c = \frac{(\delta_{obsd.} - \delta_f)(\delta_b - \delta_f)}{K(\delta_b - \delta_{obsd.})^2} \quad (1)$$

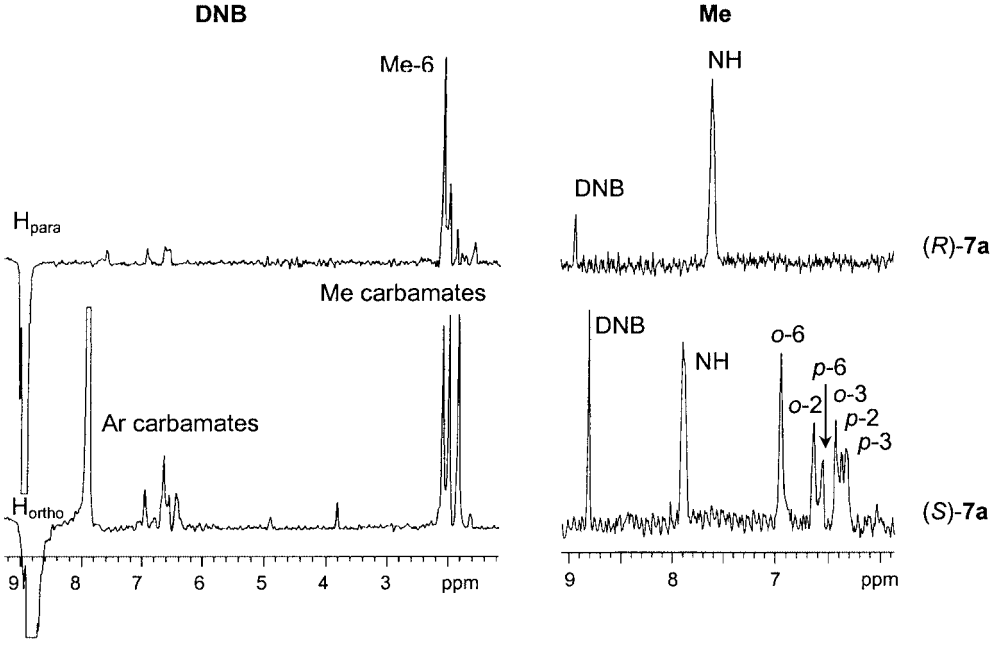


Figure 3. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, τ = 0.3 s) analyses of mixtures of (*S*)-**7a/1** and (*R*)-**7a/1** (3:1, c_{CSA} = 20 mM); traces of the 3,5-dinitrobenzoyl and methyl protons

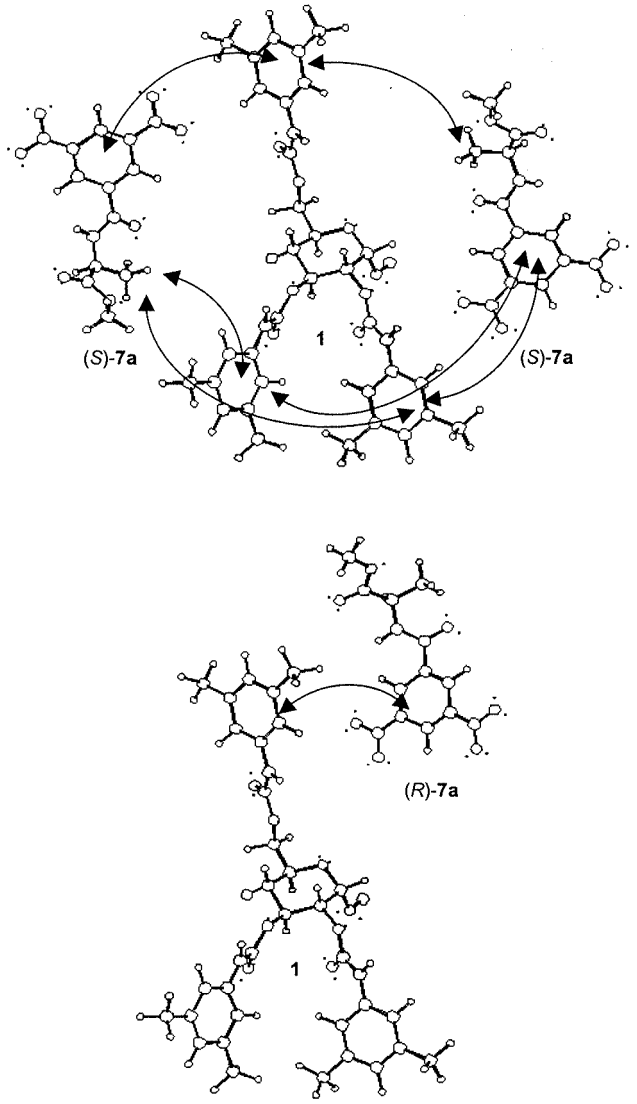


Figure 4. Representation of the NOE interactions in the two diastereoisomeric complexes (*S*)- and (*R*)-**7a/1** detected by ROESY analyses; only one cyclodextrin unit is represented

tration of the proton chemical shifts of progressively more dilute equimolar substrate/cyclodextrin solutions (180−2 mM),[20] and where K is the association constant, c is the concentration, $\delta_{obsd.}$ is the observed chemical shift, and δ_f and δ_b are the chemical shifts of the free and the bound species, respectively.

Since the nature of the NOEs detected and the differences found in the linewidths of the two enantiomers in the presence of the cyclodextrin (Figure 1) strongly suggest a greater degree of immobilization for the (*S*) enantiomer than for the (*R*) enantiomer in the complex, we also investigated the dynamic features of the amino acid derivative in the complexes by proton-selective relaxation rate (R^s) measurements, analyzed in the initial rate approximation.[21] Selective relaxation rates are measured by selective inversion of one spin in the molecule, leaving the other spins unperturbed, and by monitoring its recovery to equilibrium. Such selective determinations were preferable to nonselective measurements (R^{ns}), in which all the spins are inverted simultaneously, since the proton-selective relaxation rates undergo a sharp increase in the slow-motion regime ($\omega^2\tau_c^2 >> 1$) characteristic of the systems under investigation, which allow us to detect significant differences in the relaxation parameters of the uncomplexed and the complexed systems.[22,23] No such comparably high differences are detected for the nonselective relaxation rates. It is also noteworthy that we had already previously[24] employed selective measurements to detect differences of motional features arising from enantioselective interactions.

We have compared the monoselective relaxation rates of the *p*-(3,5-dinitrophenyl) protons of (*S*)- and (*R*)-**7a** in the free state and in the mixtures with **1** and have obtained the values reported in Table 2.

Taking into account that the measured parameters in the mixtures are the means of the values in the bound and free states, we calculated the bound fractions at the concentration and molar ratios employed in the mixtures from the association constants and extracted the monoselective relaxation rates in the bound state for the two enantiomers, the differences of which can be attributed to the different degree of immobilization.

In fact, the bound-state values of the relaxation rates for the (*S*) enantiomer of the amino acid derivative were higher than those of the (*R*) enantiomer.

As far as the diastereoisomers (*S*)-**7a/5** and (*R*)-**7a/5** are concerned, the complex formed by (*S*)-**7a** is once again stronger (K = 14.7 M^{-1}) than that formed by (*R*)-**7a** (K = 9.0 M^{-1}), while the proton-selective relaxation rates measurements also demonstrated an analogous higher degree of immobilization for the (*S*) enantiomer (Table 2). NOE measurements revealed the presence of external superficial interactions between the enantiomeric substrates and the cyclodextrin, indicating proximity both to the silyl and the 3,5-dimethylphenyl groups of the macrocycle, but no detect-

Table 2. Observed ($R^s_{obsd.}$ [s^{-1}]) and calculated (R^s_b [s^{-1}]) proton-selective relaxation rates of the *para*-proton of the 3,5-dinitrophenyl group of **7a** in the free state and in the mixtures (*S*)- and (*R*)-**7a/1** and (*S*)- and (*R*)-**7a/5** [**7a**/CSA (3:1), CSA concentration 20 mM, $CDCl_3$, 25 °C]

	7a	(*S*)-**7a/1**		(*R*)-**7a/1**		(*S*)-**7a/5**		(*R*)-**7a/5**	
	R^s_{free}	$R^s_{obsd.}$	R^s_b	$R^s_{obsd.}$	R^s_b	$R^s_{obsd.}$	R^s_b	$R^s_{obsd.}$	R^s_b
H_{para}	0.18±0.01	0.38±0.01	0.50	0.27±0.01	0.39	0.31±0.02	0.48	0.23±0.02	0.33

able differences were obtained in the proximity constraints imposed to the two enantiomers.

Conclusion

Carbamoylated cyclodextrins show relevant enantiodiscriminating capabilities, inducing anisochrony in the proton nuclei of chiral alcohols, acids, and their derivatives, as well as derivatized primary amines and amino acids. Of the derivatized cyclodextrins, the carbamoylated forms are more versatile than the previously reported benzoylated and benzylated compounds,[25] the applicability of which is limited to substrates endowed with a 3,5-dinitrophenyl moiety. $CDCl_3$-soluble carbamate cyclodextrins therefore constitute a very good complement to alkylated cyclodextrins,[20,26−28] which are efficient towards apolar substrates devoid of polar functionalities (trisubstituted allenes and hydrocarbons), and to underivatized cyclodextrins,[29] the use of which is mainly limited to water-soluble substrates. Furthermore, the comparable efficiencies of systems **1** and **5** suggest the possibility of expanding their versatility and efficiency by modulation of the nature of the functional groups present on the primary sites.

The introduction of the carbamate functions on the primary and secondary sites generates new, extended structures, in which, as in the cases of benzylated and/or benzoylated cyclodextrins,[25,30] no inclusion phenomena are detected, the interactions with the chiral substrates being mainly addressed towards the polar substituents lying on the external surface. This is also confirmed by the fact that the dimensions of the cyclodextrin do not affect its enantiodiscriminating efficiency significantly, as the two percarbamoylated systems **1** and **2** show similar performances.

The presence of functional groups situated on the primary sites − silyl in **5** and carbamoyl in **1** − seems to be fundamental, as the cyclodextrin **3**, with free primary hydroxy groups, shows significantly lower enantiodiscriminating versatility and efficiency, whereas the enantiodiscriminating efficiencies of the two cyclodextrins **1** and **5** are similar.

In spite of the complexity of the systems under investigation, some insight into the nature of the enantiodiscriminating interactions has been gained for the β-percarbamate chiral auxiliary **1** and *N*-(3,5-dinitrobenzoyl)alanine methyl ester (**7a**), showing the capabilities of the percarbamate cyclodextrin to involve either all three kinds of carbamate functions or only one in the interaction with the enantiomeric mixtures. The attractive interactions stabilizing the diastereoisomeric pairs formed in solution are therefore very different and produce significantly different degrees of immobilization of the two enantiomers on the cyclodextrin surface. This phenomenon could afford a reasonable basis for interpretation of the differences found in the retention of enantiomeric mixtures on chiral chromatographic supports based on percarbamate cyclodextrins.[3,5−8,11−13]

Experimental Section

General Methods: NMR measurements were performed with a spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C, respectively and the temperature was controlled to within ±0.1 °C. All ^1H and ^{13}C NMR chemical shifts are referenced to TMS as external standard. The 2D NMR spectra were obtained by use of standard sequences. The double-quantum-filtered (DQF) COSY experiments were recorded with the minimum spectral width required; 512 increments of 8 scans and 2 K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2 K × 1 K and a Gaussian function was applied for processing in both dimensions. The HETCOR spectra were acquired with the minimum spectral width required in F_2 and in F_1 in 2 K data points by use of 64 scans of the 512 increments. The relaxation delay was 1 s. The data were zero-filled to 2 K × 1 K data points and a Gaussian function was applied for processing in both dimensions. The ROESY spectra were recorded in the phase-sensitive mode, with use of mixing times ranging from 0.2 to 0.6 s. The spectral width used was the minimum required in both dimensions. The pulse delay was maintained at 5 or 10 s; 512 hypercomplex increments of 8 scans and 2 K data points each were collected. The data matrix was zero-filled to 2 K × 1 K data points and a Gaussian function was applied for processing in both dimensions. The selective relaxation rates were measured in the initial rate approximation by employment of a selective π pulse with the proton decoupler at the selected frequency for 25 ms. After the delay τ, a non-selective π/2 pulse was employed to detect the longitudinal magnetization. For the biselective measurements, the two protons were inverted consecutively. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck, Silica G-60 0.2 mm) and compounds were viewed by use of iodine or by examination under UV light. Chromatography was carried out on Silica Gel 60 (70−230 mesh ASTM). Melting points were determined with a Kofler hot-stage apparatus.

Materials: The α- and β-cyclodextrins were purchased from Fluka, as were *tert*-butyldimethylsilyl chloride (TBDMSCl) and boron trifluoride−diethyl ether ($BF_3{\cdot}Et_2O$). 3,5-Dimethylphenyl isocyanate was obtained from Aldrich. The α- and β-cyclodextrins were dried (8 h) at 110 °C/0.1 Torr, in the presence of P_2O_5. Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin were prepared as described elsewhere.[14]

Heptakis[2,3,6-tri-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (1):[11] Anhydrous β-cyclodextrin (0.9 mmol) was treated under N_2 with 3,5-dimethylphenyl isocyanate (27 mmol) in dry pyridine (17 mL) at 80 °C for 20 h. The pyridine was evaporated under reduced pressure, and the residue was dissolved in THF and centrifuged to eliminate the insoluble fraction. After chromatographic purification (SiO_2; benzene/MeOH, 85:15), **1** was obtained (3.6 g, 94%) as a solid, with m.p. 236−239 °C. ^1H NMR ([D$_6$]DMSO, 60 °C): δ = 1.88 (s, 42 H, Me-2), 1.99 (s, 42 H, Me-3), 2.16 (s, 42 H, Me-6), 4.29 (dd, $J_{45} = J_{43} = 9.7$ Hz, 7 H, H^4), 4.38 (d, $J_{54} = 9.7$ Hz, 7 H, H^5), 4.58 (d, $J_{6'6} = 11.5$ Hz, 7 H, H$^{6'}$), 4.72 (d, $J_{66'} = 11.5$ Hz, 7 H, H^6), 5.01 (dd, $J_{23} = 10.3$, $J_{21} = 2.8$ Hz, 7 H, H^2), 5.35 (d, $J_{12} = 2.8$ Hz, 7 H, H^1), 5.43 (dd, $J_{32} = 10.3$, $J_{34} = 9.7$ Hz, 7 H, H^3), 6.39 (s, 7 H, H$_p$-2), 6.48 (s, 7 H, H$_p$-3), 6.54 (s, 14 H, H$_o$-3), 6.59 (s, 7 H, H$_p$-6), 6.82 (s, 14 H, H$_o$-2), 7.11 (s, 14 H, H$_o$-6), 7.74 (br. s, 7 H, NH-3), 8.99 (br. s, 7 H, NH-2), 9.32 (br. s, 7 H, NH-6) ppm. ^{13}C NMR ([D$_6$]DMSO, 25 °C): δ = 20.7 (Me-2), 20.8 (Me-3), 21.0 (Me-6), 63.3 (C^6), 69.5 (C^5), 71.0 (C^2), 72.0 (C^3), 77.7 (C^4), 98.6 (C^1), 116.3 (C$_o$-6), 116.9 (C$_o$-3), 117.4 (C$_o$-2), 124.1 (C$_p$, 21 C);

quaternary C: 136.9, 137.3, 137.7, 138.2, 138.8; CO: 152.5, 152.7, 153.3 ppm. $C_{231}H_{259}N_{21}O_{56}$ (4225.69): calcd. C 65.66, H 6.18, N 6.96; found C 65.35, H 6.13, N 6.94.

Heptakis[6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (5): Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (1.0 mmol) was treated under N_2 with 3,5-dimethylphenyl isocyanate (20.0 mmol) in dry pyridine (20 mL) at 80 °C for 20 h. The pyridine was evaporated under reduced pressure, and the residue was dissolved in THF and centrifuged to eliminate the insoluble fraction. After chromatographic purification (SiO_2; hexane/EtOAc, 8:2), **5** was obtained (3.2 g, 80%) as a solid, with m.p. 150−152 °C. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.06 (s, 21 H, MeSi), 0.07 (s, 21 H, MeSi), 0.87 (s, 63 H, *t*Bu), 1.84 (s, 42 H, Me-2), 2.01 (s, 42 H, Me-3), 3.82 (d, $J_{6'6}$ = 11.2 Hz, 7 H, H$^{6'}$), 4.00 (d, J_{54} = 9.4 Hz, 7 H, H^5), 4.11 (d, $J_{66'}$ = 11.2 Hz, 7 H, H^6), 4.14 (dd, J_{43} = 10.3, J_{45} = 9.4 Hz, 7 H, H^4), 5.06 (dd, J_{23} = 10.3, J_{21} = 3.4 Hz, 7 H, H^2), 5.23 (d, J_{12} = 3.4 Hz, 7 H, H^1), 5.50 (dd, J_{32} = J_{34} = 10.3 Hz, 7 H, H^3), 6.37 (s, 7 H, H$_p$-2), 6.46 (s, 21 H, H$_p$-3 and H$_o$-3), 6.67 (s, 21 H, H$_o$-2 and NH-3), 6.81 (s, 7 H, NH-2) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = −5.3 (MeSi), −5.0 (MeSi), 18.3 (Me$_3$*C*), 20.8 (Me-2), 21.0 (Me-3), 25.9 (*t*Bu), 61.9 (C^6), 71.5 (C^2), 72.6 (C^5), 74.2 (C^3), 76.4 (C^4), 98.2 (C^1), 116.7 (C$_o$-3), 117.5 (C$_o$-2), 124.6 (C$_p$), 125.4 (C$_p$); quaternary C: 137.1, 137.3, 137.7, 138.6; CO: 152.7, 153.5 ppm. $C_{210}H_{294}N_{14}O_{49}Si_7$ (3995.30): calcd. C 63.13, H 7.42, N 4.91; found: C 62.98, H 7.37, N 4.93.

Heptakis[2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-β-cyclodextrin (3): Compound **5** (1.0 mmol) was treated under N_2 with BF_3·Et_2O (8.2 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 20 h and was then poured into ice-cold water. The organic layer, having been washed with H_2O, $NaHCO_3$ (10%), and H_2O, was dried (Na_2SO_4). The solvent was evaporated under reduced pressure. After filtration through silica ($CHCl_3$/MeOH), **3** was obtained (2.5 g, 77%) chemically pure as a solid, with m.p. 225−230 °C. ^{1}H NMR ([D$_6$]DMSO, 25 °C): δ = 1.88 (s, 42 H, Me-2), 1.97 (s, 42 H, Me-3), 3.87 (d, $J_{6'6}$ = 11.2 Hz, 7 H, H$^{6'}$), 3.95 (d, $J_{66'}$ = 11.2 Hz, 7 H, H^6), 4.07 (m, 14 H, H^4 and H^5), 4.85 (dd, J_{23} = 9.4, J_{21} = 3.3 Hz, 7 H, H^2), 4.95 (s, 7 H, OH), 5.36 (m, 14 H, H^1 and H^3), 6.34 (s, 7 H, H$_p$-2), 6.44 (s, 7 H, H$_p$-3), 6.60 (s, 14 H, H$_o$-3), 6.83 (s, 14 H, H$_o$-2), 8.37 (s, 7 H, NH-3), 9.26 (s, 7 H, NH-2) ppm. ^{13}C NMR ([D$_6$]DMSO, 25 °C): δ = 20.7 (Me-2), 20.8 (Me-3), 60.1 (C^6), 71.1 (C^5), 71.2 (C^2), 72.7 (C^3), 74.4 (C^4), 96.5 (C^1), 116.7 (C$_o$-3), 117.1 (C$_o$-2), 123.9 (C$_p$, 14 C); quaternary C: 136.8, 137.1, 137.9, 138.2; CO: 152.4, 152.5 ppm. $C_{168}H_{196}N_{14}O_{49}$ (3195.46): calcd. C 63.15, H 6.18, N 6.14; found: C 62.95, H 6.26, N 5.97.

Hexakis[2,3,6-tri-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (2):[11] Anhydrous α-cyclodextrin (1.2 mmol) was treated under N_2 with 3,5-dimethylphenyl isocyanate (30 mmol) in dry pyridine (17 mL) at 80 °C for 20 h. The pyridine was evaporated under reduced pressure and the residue was dissolved in THF and centrifuged to eliminate the insoluble fraction. After chromatographic purification (SiO_2; benzene/MeOH, 85:15), **2** was obtained (3.7 g, 85%) as a solid with m.p. 241−245 °C. ^{1}H NMR ([D$_6$]DMSO, 60 °C): δ = 1.89 (s, 36 H, Me-2), 1.99 (s, 36 H, Me-3), 2.15 (s, 36 H, Me-6), 4.26 (dd, J_{45} = J_{43} = 9.1 Hz, 6 H, H^4), 4.49 (d, J_{54} = 9.1 Hz, 6 H, H^5), 4.59 (d, $J_{6'6}$ = 9.3 Hz, 6 H, H$^{6'}$), 4.86 (d, $J_{66'}$ = 9.3 Hz, 6 H, H^6), 5.00 (d, J_{23} = 9.1 Hz, 6 H, H^2), 5.37 (br. s, 6 H, H^1), 5.45 (dd, J_{32} = J_{34} = 9.1 Hz, 6 H, H^3), 6.40 (s, 6 H, H$_p$-2), 6.47 (s, 6 H, H$_p$-3), 6.52 (s, 12 H, H$_o$-3), 6.60 (s, 6 H, H$_p$-6), 6.84 (s, 12 H, H$_o$-2), 7.12 (s, 12 H, H$_o$-6), 7.64 (br. s, 6 H, NH-3), 9.16 (br. s, 6 H, NH-2), 9.34 (br. s, 6 H, NH-6) ppm. ^{13}C NMR ([D$_6$]DMSO, 25 °C): δ = 20.7 (Me-2), 20.8 (Me-3), 21.0 (Me-6), 63.2 (C^6), 69.5 (C^5), 70.8 (C^2), 72.7 (C^3), 77.5 (C^4), 98.2 (C^1), 116.2 (C$_o$-6), 116.7 (C$_o$-3), 117.1 (C$_o$-2), 124.0 (C$_p$, 18 C); quaternary C: 137.0, 137.3, 137.5, 137.6, 138.3, 138.8; CO: 152.4, 152.7, 153.3 ppm. $C_{198}H_{222}N_{18}O_{48}$ (3622.02): calcd. C 65.66, H 6.18, N 6.96; found: C 65.20, H 6.05, N 6.90.

Hexakis[6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (6): Hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (1.3 mmol) was treated under N_2 with 3,5-dimethylphenyl isocyanate (22 mmol) in dry pyridine (25 mL) at 80 °C for 72 h and at 110 °C for 48 h. The pyridine was evaporated under reduced pressure and the residue was dissolved in THF and centrifuged to eliminate the insoluble fraction. After chromatographic purification (SiO_2; hexane/EtOAc, 8:2), **6** was obtained (3.5 g, 78%) as a solid with m.p. 135−137 °C. ^{1}H NMR ($CDCl_3$, 25 °C) δ = 0.09 (s, 36 H, MeSi), 0.90 (s, 54 H, *t*Bu), 1.88 (s, 36 H, Me-2), 1.99 (s, 54 H, Me-3), 3.80 (d, $J_{6'6}$ = 11.2 Hz, 6 H, H$^{6'}$), 4.05 (d, J_{54} = 9.0 Hz, 6 H, H^5), 4.10−4.23 (m, 12 H, H^4 and H^6), 4.98 (dd, J_{23} = 10.6, J_{21} = 3.4 Hz, 6 H, H^2), 5.14 (d, J_{12} = 3.4 Hz, 6 H, H^1), 5.60 (dd, J_{32} = J_{34} = 10.6 Hz, 6 H, H^3), 6.36 (s, 12 H, H$_o$-3), 6.39 (s, 6 H, H$_p$-2), 6.44 (s, 12 H, H$_p$-3), 6.55 (br. s, 6 H, NH-2), 6.62 (s, 12 H, H$_o$-2), 7.14 (br. s, 6 H, NH-3) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = −5.2 (MeSi), −4.9 (MeSi), 18.2 (Me$_3$*C*), 20.9 (Me-2), 21.0 (Me-3), 25.9 (*t*Bu), 62.1 (C^6), 72.1 (C^2), 72.6 (C^5), 73.9 (C^3), 78.3 (C^4), 99.6 (C^1), 116.4 (C$_o$-3), 117.5 (C$_o$-2), 124.6 (C$_p$), 125.3 (C$_p$); quaternary C: 136.9, 137.2, 137.7, 138.5; CO: 152.9, 153.1 ppm. $C_{180}H_{252}N_{12}O_{42}Si_6$ (3424.54): calcd. C 63.13, H 7.42, N 4.91; found: C 62.90, H 7.45, N 4.85.

Hexakis[2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]-α-cyclodextrin (4): Compound **6** (1.0 mmol) was treated under N_2 with BF_3·Et_2O (7.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 20 h and was then poured into ice-cold water. The organic layers, having been washed with H_2O, $NaHCO_3$ (10%), and H_2O, were dried (Na_2SO_4). The solvent was evaporated under reduced pressure. After filtration through silica, **4** was obtained (2.0 g, 74%) chemically pure as a solid with m.p. 208−210 °C. ^{1}H NMR ([D$_6$]DMSO, 25 °C): δ = 1.89 (s, 36 H, Me-2), 1.99 (s, 36 H, Me-3), 3.81 (br. s, 6 H, H$^{6'}$), 3.93−4.15 (m, 12 H, H^6 and H^5), 4.22 (dd, J_{45} = J_{43} = 8.0 Hz, 6 H, H^4), 4.92 (m, 12 H, H^2 and OH), 5.25 (br. s, 6 H, H^1), 5.28 (dd, J_{32} = 10.3, J_{34} = 8.0 Hz, 6 H, H^3), 6.39 (s, 6 H, H$_p$-2), 6.46 (s, 6 H, H$_p$-3), 6.59 (s, 12 H, H$_o$-3), 6.85 (s, 12 H, H$_o$-2), 8.11 (s, 6 H, NH-2), 9.31 (s, 6 H, NH-3) ppm. ^{13}C NMR ([D$_6$]DMSO, 25 °C): δ = 20.7 (Me-2), 20.8 (Me-3), 60.2 (C^6), 71.0 (C^5), 71.8 (C^2), 73.1 (C^3), 76.4 (C^4), 97.5 (C^1), 116.7 (C$_o$-3), 117.1 (C$_o$-2), 123.9 (C$_p$), 124.1 (C$_p$); quaternary C: 137.0, 137.3, 137.9, 138.4; CO: 152.5, 152.7 ppm. $C_{144}H_{168}N_{12}O_{42}$ (2738.97): calcd. C 63.15, H 6.18, N 6.14; found: C 63.40, H 6.00, N 6.18.

Acknowledgments

This work was supported by the Ministero della Ricerca Scientifica e Tecnologica (MURST) and CNR, Italy.

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Received September 9, 2002

