

## Enantiomeric and Enantiotopic Analysis of Cone-Shaped Compounds with $C_3$ and $C_{3v}$ Symmetry Using NMR Spectroscopy in Chiral Anisotropic Solvents

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**Abstract:** We describe the enantiomeric and enantiotopic analysis of the NMR spectra of compounds derived from the functionalized cone-shaped core, cyclotriveratrylenes (CTV), dissolved in weakly oriented lyotropic chiral liquid crystals (CLCs) based on organic solutions of poly- $\gamma$ -benzyl-L-glutamate. The CTV core lacks prostereogenic as well as stereogenic tetrahedral centers. However, depending on the pattern of substitution, chiral and achiral compounds with different symmetries can be obtained. Thus, symmetrically nonasubstituted CTVs ( $C_3$  symmetry) are optically active and exhibit enantiomeric isomers, while symmetrically hexasubstituted ( $C_{3v}$  symmetry) derivatives are prochiral and possess enantiotopic elements. In the first part we use  $^2\text{H}$  and  $^{13}\text{C}$  NMR to study two nonasubstituted ( $-\text{OH}$  or  $-\text{OCH}_3$ ) CTVs, where the ring methylenes are fully deuterated, and show for the first time that the observation of enantiomeric discrimination of chiral molecules with a 3-fold symmetry axis is possible in a CLC. It is argued that this discrimination reflects different orientational ordering of the M and P isomers, rather than specific chiral short-range solvent-solute interactions that may affect differently the magnetic parameters of the enantiomers or even their geometry. In the second part we present similar measurements on hexasubstituted CTV with flexible side groups ( $-\text{OC}(\text{O})\text{CH}_3$  and the, partially deuterated bidentate,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ), having on the average  $C_{3v}$  symmetry. No spectral discrimination of enantiotopic sites was detected for the  $-\text{OC}(\text{O})\text{CH}_3$  derivative. This is consistent with a recent theoretical work (*J. Chem. Phys.* **1999**, *111*, 6890) that indicates that in  $C_{3v}$  molecules no chiral discrimination between enantiotopic elements, based on ordering, is possible. In contrast, a clear splitting was observed in the  $^2\text{H}$  spectra of the enantiotopic deuterons of the side groups in the tri(dioxyethylene)-CTV. It is argued that this discrimination reflects different ordering characteristics of the various, rapidly (on the NMR time scale) interconverting conformers of this compound. Assuming two twisted structures for each of the dioxyethylene side groups, four different conformers are expected, comprising two sets of enantiomeric pairs with, respectively,  $C_3$  and  $C_1$  symmetries. Differential ordering and/or fractional population imbalance of these enantiomeric pairs leads to the observed spectral discrimination of sites in the side chains that on average form enantiotopic pairs.

### Introduction

Functionalized cyclotriveratrylenes (CTV), also referred to as tribenzocyclononene (TBCN), can exist in two geometrical isomers, crown and saddle, as shown in Figure 1.<sup>1-7</sup> The saddle

form is highly flexible and, in solution, it undergoes fast pseudorotation between its various conformations, leading to an average nonchiral species.<sup>5</sup> The crown form, on the other hand, is rigid and, depending on the mode of substitution, can exhibit  $C_1$ ,  $C_s$ ,  $C_3$ , or  $C_{3v}$  symmetry. From a stereochemical point of view, the latter two symmetries are of interest with regard to their chiral (or prochiral) properties. Thus, although the crown core lacks prostereogenic or stereogenic tetrahedral centers, symmetrically nonasubstituted CTVs ( $C_3$  symmetry) are chiral, exhibiting enantiomeric isomers (see compounds **1** and **2** in Figure 2). According to their stereochemical helicity, these are

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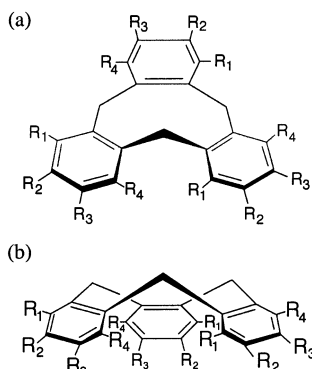
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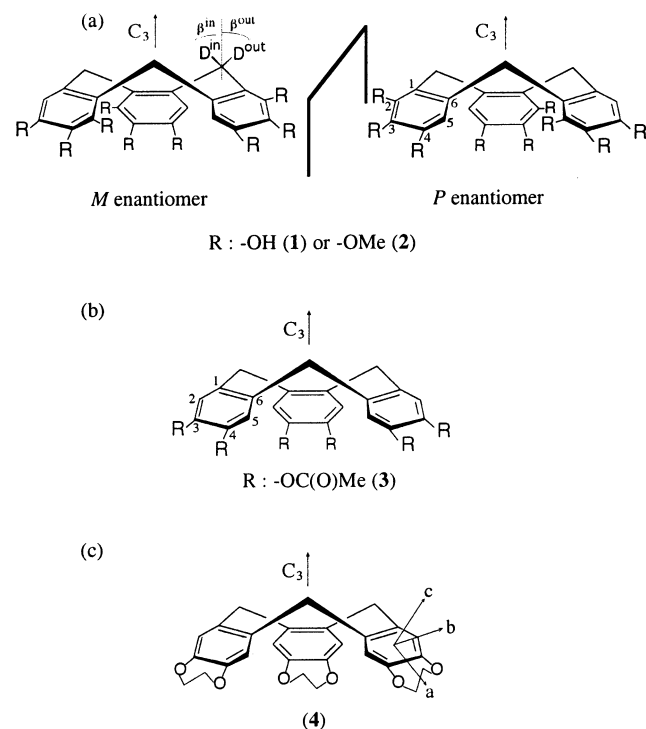
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**Figure 1.** Structure of substituted cyclotrimeratrylene (CTV) derivatives in the saddle (a) and in the crown conformation (b).



**Figure 2.** Structure of four CTV derivatives investigated in this work: (a) nonahydroxy- and nonamethoxy-CTV (**1** and **2**; the two enantiomeric structure are shown), (b) hexaacetyloxy-CTV (**3**) with average  $C_{3v}$  symmetry, and (c) tri(dioxyethylene)-CTV (**4**) with average  $C_{3v}$  symmetry.

labeled using the *M* or *P* descriptors.<sup>5,6</sup> On the other hand, symmetrically hexasubstituted CTVs ( $C_{3v}$  symmetry; see compound **3** in Figure 2) are prochiral and possess enantiotopic elements. According to IUPAC nomenclature, enantiotopic elements are “constitutionally identical atoms or groups in molecules, which are related by symmetry elements of the second kind only (mirror plane, inversion center, or rotation-reflection axis)”. Such elements can in principle be discriminated by spectroscopic methods, such as NMR, in a chiral environment. These two classes of CTV derivatives of the crown form, therefore, merit special attention, and in the present work we investigate the NMR spectra of some selected nona- and hexasubstituted derivatives of this core in chiral liquid crystalline solvents. Such studies are possible because the crown and saddle forms of CTV are long-lived and do not interconvert in solution, even on the time scale of many months at room temperature.<sup>3,5</sup>

In principle, any isotropic chiral solvent could lead to NMR spectral discrimination of enantiomeric solutes through specific

chiral, short-range solute–solvent interactions that may affect differently the magnetic parameters (for example, differential electronic shielding) or even the geometry of the chiral centers (vibrations). In practice, however, except for very special cases,<sup>8</sup> the spectral resolution is often too low to exhibit separated signals for the different enantiomers. An alternative approach is to employ a chiral liquid crystal as a solvent.<sup>9–11</sup> In such solutions, in addition to (the negligible) specific solute–solvent interactions, orientational ordering of the solute also contributes to the chiral discrimination. As it turns out, in many situations it is the dominant discrimination mechanism providing the doubling of peaks, where the conventional approach of using isotropic solvents failed. In the present work, we apply this method by using as solvent a lyotropic liquid crystalline solution of poly- $\gamma$ -benzyl-L-glutamate (PBLG) in organic solvents, such as chloroform ( $\text{CHCl}_3$ ) or dimethylformamide (DMF).<sup>10,11</sup> Under proper experimental conditions of concentration and temperature, such solutions form a cholesteric phase with a relatively long pitch. Under the effect of the strong magnetic field ( $B_0$ ) of the NMR spectrometer, the cholesteric pitch in these solutions unwinds, yielding well-aligned chiral-nematic phases with the director parallel to  $B_0$ .<sup>12</sup> For comparative purposes, similar solutions containing racemic (compensated) mixtures of PBLG and PBDG (poly- $\gamma$ -benzyl-D-glutamate), which are nematic but not chiral, have also been used. In the following we denote such solutions as PBG. In these solutions the solute molecules exchange rapidly between the PBLG and PBDG vicinities, resulting in identical average magnetic interactions for the two enantiomers.<sup>11,13</sup>

Solutes dissolved in PBLG or PBG solutions become aligned and, although this alignment is usually rather small,<sup>10,11</sup> they often exhibit characteristic NMR features of partially ordered systems. These features are the extra splittings or shifts due to anisotropic interactions, such as dipolar couplings, quadrupolar couplings (for spin  $I > 1/2$ ), and chemical shift anisotropies (CSA).<sup>14</sup> For our purpose, carbon-13 and deuterium NMR are particularly useful in this respect.<sup>10</sup> The  $^{13}\text{C}$ – $^1\text{H}$  dipolar interaction over a single bond is on the order of 30 kHz, the deuterium quadrupole coupling in a C–D bond is about 180 kHz, while the  $^{13}\text{C}$  CSA for aromatic carbons is about 100 ppm (translated to  $\sim 10$  kHz in commonly used spectrometers). Thus, even if the orientational order parameter of the solutes is only about  $10^{-2}$  to  $10^{-4}$ , extra splitting and shifts (compared with NMR in isotropic solvent) may be observed in their high-resolution NMR spectra. The special chiral discrimination power of CLC, such as the PBLG solutions, results from selective effects on the ordering parameter of chiral solutes.<sup>15</sup> Due to the large effect of orientational ordering on the NMR spectra (compared to that induced by specific solute–polymer interac-

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tions), even small differences in the ordering of corresponding chiral elements may result in sufficient spectral discrimination to be observed in particular using deuterium NMR. This is manifested in doubling (or partial doubling) of the NMR spectra of the chiral solutes in comparison with those recorded in a corresponding racemic PBG solution.

The discrimination effect can be divided into two categories. The first one concerns optically active compounds. In this case the two enantiomers will in general have slightly different orientational order parameters resulting, in favorable situations, in doubling of the NMR spectrum due to the two optical isomers. In the first part of the Results and Discussion, we examine the case of nonasubstituted CTV derivatives ( $C_3$  symmetry) with side chains  $R = OH$  and  $OCH_3$  (compounds **1** and **2** in Figure 2). Both compounds were deuterated in the ring methylenes and as spectroscopy tools we use proton-decoupled deuterium and carbon-13 NMR ( $^2H-\{^1H\}$  and  $^{13}C-\{^1H\}$ ).<sup>10,16,17</sup> The NMR spectra of the *M* and *P* isomers in PBLG/DMF solutions are indeed well-resolved, while no such discrimination is observed in chiral isotropic solvents. We argue that this chiral discrimination is due to selective ordering rather than specific, short-range chiral solute–solvent interactions such those that can differently affect the magnetic parameters of two enantiomers in chiral isotropic solvents.

The second category of chiral discrimination relates to prochiral molecules.<sup>18,19</sup> In this case the stereochemical discrimination concerns enantiotopic elements and is brought about by reducing the symmetry of the orientational distribution function (eliminating symmetry elements of the second kind) compared to their symmetries in achiral solvents.<sup>20</sup> This reduction in symmetry may, depending on the original molecular symmetry, partially lift the restrictions on the orientation of the principal coordinate system of the ordering tensors in the molecular frame. This, in turn, will cause enantiotopic elements to become nonequivalent in the CLC solution, resulting in doubling of their NMR spectra. In a recent paper a comprehensive theoretical analysis of this effect was given, including a full classification of all molecular point groups into those whose symmetries are, or are not, affected by a uniaxial CLC.<sup>20</sup> Thus, for example, the principal directions of the ordering tensor in molecules with  $C_{2v}$  symmetry are fixed to lie along the  $C_2$  ( $z$ ) axis and perpendicular to the two mirror planes ( $x$ ,  $y$ ). The effective symmetry of such molecules in a CLC reduces to  $C_2$  and only the  $z$ -direction of the ordering tensor remains fixed (parallel to the  $C_2$  axis), while the  $x$  and  $y$  axes are undetermined by any symmetry consideration. Pairs of enantiotopic sites in such molecules become nonequivalent in CLC solutions, because they are not symmetry related anymore in the principal

axes frame of the ordering tensor.<sup>21</sup> Thus, enantiotopic sites in such molecules will, in general, exhibit resolved NMR signals in CLC solutions, purely by ordering, even in the absence of specific chiral, short-range solute–solvent interactions. Similar situations apply to molecules with  $C_s$ ,  $S_4$ , or  $D_{2d}$  symmetry.<sup>20–23</sup> In contrast, in molecules with  $C_{3v}$  symmetry (or other point groups with  $C_3$  or higher order symmetry axes) the ordering tensor is axially symmetric with the unique principal direction ( $z$ ) parallel to the molecular  $C_3$  (or  $C_n$ ,  $n > 3$ ) axis. Thus, even though the effective symmetry of such a molecule, when dissolved in a CLC, reduces to  $C_3$  (or  $C_n$ ), the orientational ordering tensor remains axially symmetric with  $z$  still parallel to the unique axis. Consequently, on the basis of ordering considerations alone, enantiotopic sites in such molecules will not become nonequivalent in CLC solutions. Regarding discrimination due to specific chiral, short-range solute–solvent interactions as unlikely, we therefore expect no discrimination in the NMR spectra of such sites in chiral liquid crystalline solutions. In the second part of the Results and Discussion we test this conclusion by studying two examples of hexasubstituted CTV derivatives, i.e. hexaacetyloxy-CTV (compound **3**) and tri(dioxyethylene)-CTV (compounds **4**, 10% deuterated in the ethylene groups). In both compounds the side chains are highly flexible, rapidly (NMR wise) interconverting between different conformations, leading to an average  $C_{3v}$  symmetry. Indeed, no discrimination was found between the enantiotopic sites of compound **3** in the PBLG solutions. However, somewhat unexpectedly, well-resolved signals were observed for the enantiotopic ethylene deuterons in the dioxyethylene side groups of compound **4**. We argue that this discrimination reflects selective ordering of the various (chiral) conformers in the oriented PBLG system.

## Experimental Section

**Synthesis.** The synthesis of isotopically normal nonahydroxy-, nonamethoxy- and hexaacetyloxycyclotrimeratrylenes (**1**, **2**, and **3**) was as described earlier.<sup>2,3</sup> Compounds **1** and **2** deuterated in the crown-ring methylenes were prepared as reported in ref 1. Compound **4** was prepared both in the normal form as well as statistically deuterated (~10%) in the dioxyethylene side groups. The latter was prepared according to the five-step reaction shown in Scheme 1. The normal compound was obtained by trimerization of normal 1,4-benzodioxane-6-methanol, which was prepared by reduction of the commercially available 1,4-benzodioxane-6-carboxaldehyde (Aldrich). In the following we describe the synthetic steps leading to the deuterated compound **4**.

**1,2-Ethanediol** (~10% Deuterated). A solution of 65 g of diethyl-oxalate (Aldrich) in 100 mL of dry ether was slowly added to a slurry of  $LiAlH_4$  (18 g) and  $LiAlD_4$  (2 g) in 1300 mL of ether. The mixture was refluxed for 3 h, followed by hydrolysis with water containing 10% deuterium and saturated with  $Na_2SO_4$ . The slurry was filtered, and the residue was boiled with 300 mL of THF and filtered. This process was repeated twice. The filter cake was then treated with  $H_2SO_4$  (2 N) for complete hydrolysis, and then extracted again with THF. The combined filtrates were evaporated under vacuum and the oily residue purified by vacuum distillation to yield 24.0 g of 1,2-ethanediol (~10% deuterated).

**1,2-Dibromoethane** (~10% Deuterated). The 24.0 g of the above glycol and 5.3 g of red phosphorus were heated and stirred at 140 °C,

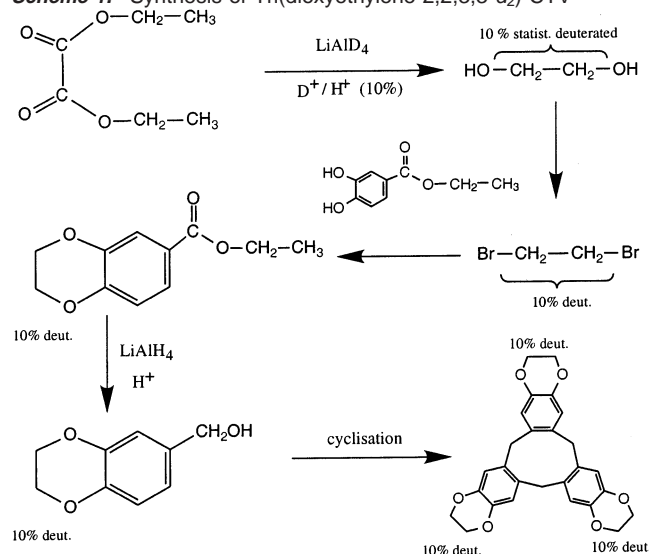
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**Table 1.** Compositions of Liquid-Crystalline NMR Samples Investigated

solute	sample	polymer	DP <sup>a</sup> (PBLG/PBDG)	cosolvent	solute/mg <sup>b</sup>	polymer/mg <sup>b</sup>	cosolvent/mg <sup>b</sup>	% of polymer by wt
<b>1</b> <sup>c</sup>	1	PBLG	562	DMF	3.6	129.2	301.0	29.8
<b>2</b> <sup>c</sup>	2	PBLG	562	DMF	4.2	129.9		29.8
<b>1</b> <sup>c</sup>	3	PBG	562/914	DMF	3.4	65.4/65.4	306.0	29.7
<b>2</b> <sup>c</sup>	4	PBG	562/914	DMF	4.2	66.2/66.2	313.6	29.4
<b>3</b>	5	PBLG	562	CHCl <sub>3</sub>	25.0	100.1	475.1	16.7
<b>4</b>	6	PBLG	562	CHCl <sub>3</sub>	5.4 <sup>d</sup>	102.0	450.1	18.3
<b>4</b>	6	PBG	562/914	CHCl <sub>3</sub>	5.4 <sup>d</sup>	51.2/51.2	450.3	18.3

<sup>a</sup> DP: degree of polymerization. <sup>b</sup> The accuracy of the weights is  $\pm 0.5$  mg. <sup>c</sup> The solutes **1** and **2** are dideuterated on the three methylene bridges. <sup>d</sup> To eliminate residual solid particles, 12.0 mg of solute **4** have been dissolved in 1 g of CHCl<sub>3</sub> and then filtered; 450 mg of this solution was added to the polymer.

**Scheme 1.** Synthesis of Tri(dioxyethylene-2,2,3,3-*d*<sub>2</sub>)-CTV



while dropwise adding 20.0 g of bromine. The reaction mixture was kept at this temperature for another hour and then cooled to room temperature. The reaction mixture was diluted with water and ether, the solid residues were filtered, the ether layer was separated, and the solvent was evaporated. After distillation, 23 g of the 1,2-dibromoethane (~10% deuterated) was obtained.

**1,4-Benzodioxane-6-carboxylic Acid Ethyl Ester** (~10% Deuterated). To 11.5 g of 3,4-dihydroxybenzoic acid ethyl ester (Aldrich) in 60 mL of ethanol (95%) was added 9.2 g of solid KOH while being stirred. The mixture was slowly heated while 23 g of the 1,2-dibromoethane (~10% deuterated) was dropwise added and the mixture refluxed for 6 h. The hot mixture was filtered, the residue was boiled with ethanol and filtered again, and the combined filtrates were evaporated. An oil was obtained that was subject to column chromatography (silica, CH<sub>2</sub>-CH<sub>2</sub>/*n*-hexane 8/2) to yield 4.7 g of pure (one spot on TLC) 1,4-benzodioxane-6-carboxylic acid ethyl ester (~10% deuterated in the dioxyethylene side chains).

**1,4-Benzodioxane-6-methanol** (~10% Deuterated). A solution of 4.5 g of the above ester in 50 mL of dry ether was slowly added to a slurry of 1 g of LiAlH<sub>4</sub> in 200 mL of ether. After refluxing for 2 h the compound was hydrolyzed using 10% H<sub>2</sub>SO<sub>4</sub>. After the usual workup, 3.2 g of 1,4-benzodioxane-6-methanol (~10% deuterated) was isolated (TLC: one spot, silica/CH<sub>2</sub>Cl<sub>2</sub>).

**Tri(dioxyethylene)-CTV** (~10% Deuterated). A 3 g portion of the above compound was heated and stirred with 60 mL of 10% H<sub>2</sub>SO<sub>4</sub> for 6 h. The resulting solid was filtered, washed with water, and dried under vacuum. The solid was tritiated with 80 mL of benzene overnight and isolated. The mass spectrum and <sup>1</sup>H NMR were consistent with the desired product and showed approximately 10% statistical deuteration in the dioxyethylene side chains. (<sup>1</sup>H NMR, 500 MHz,

CDCl<sub>3</sub>/TMS: aromatic singlet at  $\delta = 6.81$  ppm; crown-ring methylenes; two doublets (AX spin system) at  $\delta = 4.52$  and 3.46 ppm,  $J_{AX} = 13.8$  Hz; hydrogens in the dioxyethylene side chain, a symmetrical multiplet at  $\delta = 4.13$  ppm.)

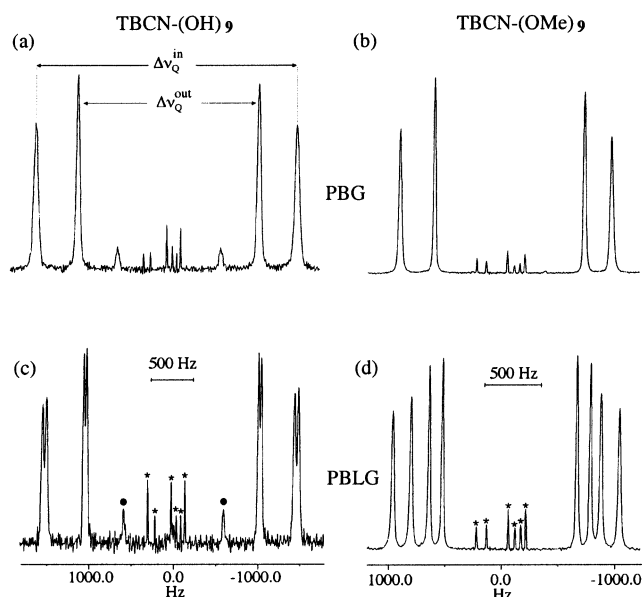
As indicated above, isotopically normal tri(dioxyethylene)-CTV was prepared by trimerization of normal 1,4-benzodioxane-6-methanol, which was obtained by reduction of the commercially available 1,4-benzodioxane-6-carboxaldehyde. The procedure was as follows: 10 g of the latter dissolved in dry ether (200 mL) was slowly added under stirring to a slurry of 3 g of LiAlH<sub>4</sub> in ether at room temperature. The mixture was refluxed overnight and then hydrolyzed with H<sub>2</sub>O, acidified, and separated by repeated extractions. The ether extracts were dried and the solvent finally removed, resulting in 8 g of a colorless oil (TLC: one spot, no traces of the aldehyde, silica/CH<sub>2</sub>Cl<sub>2</sub>). This product was then trimerized using the same procedure described for the synthesis of the tri(dioxyethylene)-CTV (~10% deuterated).

**Sample Preparation.** The various liquid-crystalline NMR samples investigated in this work were prepared using a standard procedure described elsewhere.<sup>10</sup> Note that all homopolymers used are commercially available from Sigma and all 5 mm o.d. NMR tubes were sealed to avoid solvent evaporation and centrifuged back and forth until an optically homogeneous birefringent phase was obtained. The exact composition of each oriented NMR sample (sample 1–7) is shown in Table 1. Except for compound **3**, the amount of CTV derivatives used in the oriented sample studied does not exceed 1% in weight due to the rather low solubility of this kind of solute in organic solutions of PBLG. For the PBLG/DMF system, it was necessary to heat the mixture slightly in order to dissolve the polypeptide during sample preparation more easily.<sup>10</sup>

**NMR Spectroscopy.** Deuterium and carbon-13 NMR spectra in oriented solvents were collected at 9.4 T on a high-resolution Bruker DRX 400 spectrometer equipped with a standard variable-temperature unit (BVT 3000) and using either a selective deuterium probe operating at 61.4 MHz for deuterium or inverse multinuclear probe (BBI) operating at 100.13 MHz for carbon-13. The proton-decoupled deuterium and carbon-13 spectra were recorded with 8  $\mu$ s pulse duration (90° pulse) and 6  $\mu$ s pulse duration (ca. 70°), respectively. For <sup>13</sup>C-<sup>1</sup>H and <sup>2</sup>H-<sup>1</sup>H experiments, the protons were decoupled using the broadband composite pulse sequence WALTZ-16. For the carbon-13 spectra, proton irradiation was applied during the relaxation delay period so as to benefit from the nuclear Overhauser effect. Other experimental NMR parameters or details are given in the legend of the figures.

## Results and Discussion

**Chiral Discrimination of Enantiomers in Nonasubstituted CTV with C<sub>3</sub> Symmetry.** In this subsection we discuss the NMR spectra of compounds **1** and **2** (perdeuterated in the ring methylene; see Figure 2) dissolved in PBLG solutions. Both derivatives are chiral (C<sub>3</sub> symmetry) and thus, as synthesized, they consist of a racemic mixture of two enantiomers, *M* and *P*. Before recording their NMR spectra in the CLC solvents,



**Figure 3.** 61.4 MHz  $^2\text{H}\{-^1\text{H}\}$  spectrum of the hexadeuterated nonahydroxy-CTV (left) and hexadeuterated nonamethoxy-CTV (right), at 310 K in the achiral PBG/DMF phase (a and b) and in the chiral PBLG/DMF phase (c and d). The spectra c, d, a, and b (samples 1, 3, 2, and 4 in Table 1) were recorded by adding 21 000, 7200, 30 000, and 5200, scans, respectively. For all spectra, zero-filling to 32K data points was used to increase the digital resolution, and a Gaussian filtering was also applied to improve the spectral appearance. Peaks marked with solid circles are tentatively assigned to the saddle conformer. The natural abundance deuterium signals of DMF are labeled by asterisks.

we tried to see whether any chiral discrimination is observed in their NMR spectra when dissolved in isotropic chiral solvents. To that end, we used solutions of compound **1** in the enantiomerically pure solvent 3-methyl-2-butanol with 10% acetone, as well as in a chloroform solution of an optically pure chiral-lanthanide shift reagent.<sup>8</sup> No extra splitting was observed in the proton and carbon-13 spectra in both these solvents.

For the measurements in the CLC solutions we used proton-decoupled deuterium and carbon-13 NMR in two solvents, PBLG/ $\text{CHCl}_3$  (18%) and PBLG/DMF (29.8%). No discrimination was observed in the chloroform solutions, but both compounds exhibited clear chiral discrimination in the proton-decoupled deuterium and carbon-13 spectra in the DMF solutions (samples 1 and 2 in Table 1). For comparison, we also performed measurements in PBG/DMF solutions for which no chiral differentiation is expected. These samples contain a racemic mixture of PBLG and PBDG with the same total concentration of the polymer as in the chiral PBLG solutions (samples 3 and 4 of Table 1). Examples of the deuterium spectra, recorded at 310 K, in both the racemic and chiral solvents are shown in Figure 3.

We first discuss the top traces in the figure, which correspond to the racemic solution. Each spectrum consists of two intense quadrupolar doublets ascribed to the diastereotopic inner and outer deuterons, which we label  $\text{D}^{\text{in}}$  and  $\text{D}^{\text{out}}$  in Figure 2. This result is fully consistent with that recorded in nonchiral, thermotropic nematic solvents.<sup>1</sup> Some weak peaks at the center region of the spectra are assigned to natural abundance deuterons of the DMF solvent (namely three quadrupolar doublets centered on three distinct chemical shifts) and, for compound **1**, also to a small amount of the saddle isomer, as indicated in the caption of the figure. The width of the lines ( $\sim 30$  Hz) is somewhat

larger than usually observed for proton-decoupled deuterons in lyotropic PBG solutions. We attribute the extra broadening to unresolved geminal  $\text{D}^{\text{in}}\text{--}\text{D}^{\text{out}}$  dipolar interactions. The full quadrupolar splittings,  $\Delta\nu_{\text{Q}}^i$ , of these doublets are directly related to the orientational order parameter,  $S_{zz}$ , of the molecular  $\text{C}_3$ -symmetry axis by

$$\Delta\nu_{\text{Q}}^i = \frac{3}{2} S_{zz} Q_{\text{C-D}} \left( \frac{3 \cos^2 \beta^i - 1}{2} \right) \quad (1)$$

where  $\beta^i$  is the angle between the  $\text{C}\text{--}\text{D}^i$  bond direction and the molecular  $\text{C}_3$  axis, and  $Q_{\text{C-D}}$  is the deuterium quadrupole coupling constant,  $Q_{\text{C-D}} = e^2 q Q / h$ . For aliphatic deuterons this constant is  $\sim 170$  kHz. In eq 1 the quadrupolar coupling tensor is assumed to be axially symmetric with the unique axis parallel to the  $\text{C}\text{--}\text{D}$  bond direction. The angles  $\beta^{\text{in}}$  and  $\beta^{\text{out}}$  for the inner and outer deuterons were estimated earlier from X-ray and NMR measurements, in various substituted CTV derivatives to be approximately  $38^\circ$  and  $66^\circ$ , respectively.<sup>1</sup> Hence, from eq 1, we can identify the larger and smaller splittings with  $\text{D}^{\text{in}}$  and  $\text{D}^{\text{out}}$ , respectively as shown in Figure 3. Moreover, it follows that  $\Delta\nu_{\text{Q}}^{\text{in}}$  and  $\Delta\nu_{\text{Q}}^{\text{out}}$  have opposite signs, but on the basis of the deuterium NMR spectra shown in this figure alone, we cannot decide which is positive and which is negative. In the next section we show (on the basis of the proton-coupled  $^{13}\text{C}$  NMR spectrum) that the sign of  $S_{zz}$  for compound **3** dissolved in PBLG/ $\text{CHCl}_3$  is negative, indicating that it prefers to align with its  $\text{C}_3$  axis perpendicular to the director of the liquid-crystalline phase. It is safe to assume that the same preference applies also to other CTV derivatives dissolved in such solvents. Thus, assuming a negative sign for  $S_{zz}$  of compounds **1** and **2** in the PBG/DMF solutions, it follows that  $\Delta\nu_{\text{Q}}^{\text{in}}$  is negative and  $\Delta\nu_{\text{Q}}^{\text{out}}$  is positive, as indicated in Table 2. Using the above quoted value for  $Q_{\text{C-D}}$ , we can use the values of  $\Delta\nu_{\text{Q}}^i$  to calculate the molecular order parameters,  $S_{zz}$  of the solutes in these racemic solutions. The average values (over  $\text{D}^{\text{in}}$  and  $\text{D}^{\text{out}}$ ) obtained at 310 K are  $-0.030$  and  $-0.019$  for compounds **1** and **2**, respectively. These values are quite large for PBG solutions and reflect the strong tendency of the CTV core to align in such solvents. A close examination of the spectra in the racemic solvent shows that the centers of the quadrupolar doublets, due to  $\text{D}^{\text{in}}$  and  $\text{D}^{\text{out}}$ , do not exactly coincide. Rather, the center of the  $\text{D}^{\text{in}}$  doublet is slightly shifted ( $\sim 0.58$  ppm) to low field compared to that of  $\text{D}^{\text{out}}$ , indicating that the inner hydrogen of the ring methylenes is less shielded than the outer ones. Within the experimental errors due to the line width and considering a small solvent effect induced by the phase, the shift observed in CLC is essentially identical to that measured in high-resolution proton NMR in isotropic solvents (e.g.,  $\text{CHCl}_3$ ).

Referring next to the spectra in the PBLG/DMF solutions (bottom traces in Figure 3), we note that each of the doublets splits into two, corresponding to the two enantiomers, which become inequivalent in a chiral environment. The splittings are small but quite apparent and reflect the chiral discrimination power of the CLC solvent with respect to the CTV enantiomers. The degree of discrimination can be quantified using the “differential ordering effect” (DOE) parameter. For an axially symmetric molecule for which the signs of  $(\Delta\nu_{\text{Q}}^i)^{\text{M}}$  and  $(\Delta\nu_{\text{Q}}^i)^{\text{P}}$  are identical and assuming that the chiral discrimination is

**Table 2.** Quadrupolar Splittings in Hz Associated with D<sup>in</sup> and D<sup>out</sup> in the Compounds **1-d**<sub>6</sub> and **2-d**<sub>6</sub> in the PBLG/DMF and PBG/DMF Phase

solute	sample	solvent	inner deuterons		outer deuterons	
			$\Delta\nu_Q^{M \text{ or } P}/\text{Hz}$	DOE/%	$\Delta\nu_Q^{M \text{ or } P}/\text{Hz}$	DOE/%
1	1	PBLG/DMF	$-2928 \pm 19$ $-3018 \pm 19$	$3.0 \pm 1.5$	$+2030 \pm 15$ $+2090 \pm 15$	$2.9 \pm 1.4$
	3	PBG/DMF	$-3076 \pm 35$ $(-2973.1)^a$	0.0	$+2131 \pm 30$ $(+2059.8)^a$	0.0
2	2	PBLG/DMF	$-1678 \pm 14$ $-2005 \pm 16$	$17.7 \pm 1.6$	$+1188 \pm 11$ $+1425 \pm 12$	$18.1 \pm 1.8$
	4	PBG/DMF	$-1916 \pm 15$ $(-1841)^a$	0.0	$+1359 \pm 11$ $(+1306)^a$	0.0

<sup>a</sup> The values in parentheses correspond to the average of quadrupolar splittings measured in the PBLG/DMF phase.

entirely due to ordering, the expression for the DOE is

$$\begin{aligned} \text{DOE}_i &= 2 \times \left| \frac{(\Delta\nu_Q^i)^M - (\Delta\nu_Q^i)^P}{(\Delta\nu_Q^i)^M + (\Delta\nu_Q^i)^P} \right| \times 100 \\ &= 2 \times \left| \frac{(S_{zz}^i)^M - (S_{zz}^i)^P}{(S_{zz}^i)^M + (S_{zz}^i)^P} \right| \times 100 \end{aligned} \quad (2)$$

The results are 2.9% and 18.1% for compounds **1** and **2**, respectively (see Table 2). The figures can safely be compared, since they are derived from spectra taken under the same experimental conditions (solvent, concentration, temperature). It is noteworthy that the DOE parameter for **1** is considerably smaller than that for **2**, even though the quadrupole splittings in the latter are smaller. This indicates that the factors determining the chiral discrimination and the ordering are not necessarily the same. The smaller DOE in CTV–OH compared with CTV–OCH<sub>3</sub> seems surprising at first glance. In fact, similar relations were found earlier for chiral solutes such as ethers or esters, compared to their hydroxy analogues in PBLG/DMF, while the opposite relations were found in PBLG/CHCl<sub>3</sub> or PBLG/CH<sub>2</sub>-Cl<sub>2</sub> solutions.<sup>24</sup> The effect could be explained in terms of molecular affinity. In the present case we may argue that the stronger affinity between the (achiral) DMF solvent and the polar CTV–OH solute, compared with that of CTV–OCH<sub>3</sub>, reduces the affinity of the former with the chiral polypeptide, thus decreasing its DOE in comparison with that of the nonhydroxylic CTV derivative.

It is interesting to note that for both compounds, within the experimental accuracy (line width), the DOE values for D<sup>in</sup> and D<sup>out</sup> are essentially identical, differing by less than 3%. This fact lends support to the conclusion that the chiral discrimination is predominantly due to differential ordering.<sup>15</sup> If, instead, it were due to selective, chiral short-range solute–solvent interaction on, for example, the quadrupolar coupling, the inner and outer deuterons would be expected to exhibit completely different degrees of enantioselectivity. Thus, we conclude that the discrimination is brought about by small but different changes in  $S_{zz}$  of the two isomers in the chiral solvent. This conclusion also allows us to identify the outer doublets of D<sup>in</sup> and D<sup>out</sup> with one enantiomer and likewise the two inner doublets with the other enantiomer. It is noteworthy that the average splitting of the corresponding quadrupolar doublets for a given deuteron is almost identical to its splitting in the racemic solution. This indicates that in the chiral solution  $S_{zz}$  for one

isomer increases by the same amount as its decrease for the other. This is expected on the basis of similar observation in other chiral systems, but it is not required by any symmetry considerations.

Encouraged by the positive results (enantioselectivity) of the deuterium spectra, we looked for chiral discrimination in the <sup>13</sup>C–{<sup>1</sup>H} NMR of compounds **1** and **2**.<sup>10,17</sup> For this nucleus the useful order-dependent interaction is the CSA, which is particularly large for doubly and triply bonded, as well as aromatic, carbons. In practice, the spectral enantiodiscrimination is manifested by peak doubling in CLC solution as in the deuterium spectra. If we assume that the discrimination is entirely due to the orientational dependent anisotropic part of the chemical shift tensors, a line splitting between the *M* and *P* enantiomers of

$$|\nu_i^M - \nu_i^P| = \nu_L |(\delta_{\text{aniso}}^i)^M - (\delta_{\text{aniso}}^i)^P| \quad (3)$$

is expected, where  $\delta_{\text{aniso}}^i$  is the anisotropic chemical shift for a given carbon *i* (see below) and  $\nu_L$  is the carbon-13 Larmor frequency.

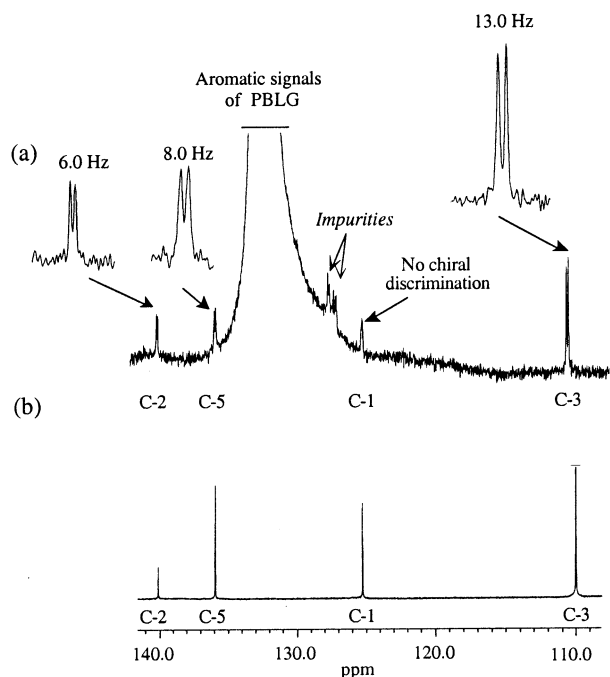
For the measurements we used samples 1 and 2 (PBLG/DMF), for which the enantiomeric discrimination in the deuterium spectra was apparent. No spectral differentiation was found for compound **1**, but very pronounced doubling of some of the aromatic carbon signals was observed for compound **2**. Examples of spectra for this compound are shown in Figure 4.

The upper and lower traces were recorded at 310 K in a PBLG/DMF solution (sample 2) and at room temperature in chloroform, respectively. Only the spectral range 110–140 ppm, including four (out of the six) aromatic peak, is shown. The strong background signal in the 125–135 ppm range of the CLC solution is due to the natural abundance aromatic carbon-13 in the flexible side chains of the PBLG molecule.<sup>17,25</sup> Some impurity lines are also observed. The signals of the CTV solute are quite weak, due to its low solubility (about one weight percent), but they are apparent and can readily be identified by comparison with those in the chloroform solution. The labeling of these peaks is according to the numbering system of Figure 2. Their assignment is tentative and is based on additive rules for benzene substituents.<sup>26</sup> The assignment of the C–H carbon (C-5) was confirmed by the appearance of a doublet in the uncoupled C-13 spectrum of the chloroform solution. Well-resolved, albeit small, splittings of 6, 8, and 13 Hz are measured

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**Figure 4.** 100.6 MHz  $^{13}\text{C}\{-^1\text{H}\}$  signals of the aromatic C-1, C-2, C-3, and C-5 carbons of the hexadeuterated nonamethoxy-CTV (sample 2) at 310 K in the PBLG/DMF phase (a) and at room temperature in an isotropic solution of  $\text{CHCl}_3$  (b). Signals of carbons C-4 and C-6 located at around 152 ppm are not shown, because they do not exhibit enantiomeric discrimination. Spectra a and b were recorded by adding 27 000 and 10 000 scans, respectively. For both a recycle delay of 1.8 s was used. No filtering was employed. The peak assignment corresponds to the numbering system shown in Figure 2.

for carbons 2, 3, and 5, but none are measured for the other aromatic carbons. The chemical shift differences evidently reflect the discrimination of the CTV- $\text{OCH}_3$  enantiomers in the chiral liquid-crystalline solvent. An exact analysis of the chemical shifts is not as straightforward as for the quadrupolar splittings in the deuterium spectra. This is because the carbon-13 results are quite sensitive to the CSA parameters (principal values and principal directions). While the principal values of the chemical shift tensors can often readily be obtained from magic angle spinning (MAS) measurements,<sup>27</sup> the accurate determination of the principal axis system (PAS) in the molecular frame is more involved and as a rule requires single-crystal measurements as a function of the magnetic field orientation. We shall therefore reverse the procedure and attempt to calculate the expected enantiomeric discrimination in the carbon-13 spectra from the earlier analysis of the deuterium results and crude estimates of the CSA for the aromatic carbons. For a solute molecule with a  $C_3$  (or higher) symmetry axis,  $\delta_{\text{aniso}}^i$  is given by<sup>28</sup>

$$\delta_{\text{aniso}}^i = S_{zz} \left[ \frac{2}{3} \left( \delta_{cc}^i - \frac{1}{2} (\delta_{aa}^i + \delta_{bb}^i) \right) \left( \frac{3 \cos^2 \beta^i - 1}{2} \right) + \frac{1}{2} (\delta_{aa}^i - \delta_{bb}^i) (\sin^2 \beta^i) \cos 2\alpha^i \right] \quad (4)$$

where  $\delta_{aa}^i$ ,  $\delta_{bb}^i$ , and  $\delta_{cc}^i$  are the principal components of the carbon-13 anisotropic chemical shift tensors in their respective principal axis system (PAS<sup>i</sup>) with  $\delta_{aa}^i > \delta_{bb}^i > \delta_{cc}^i$  and  $\delta_{aa}^i +$

$\delta_{bb}^i + \delta_{cc}^i = 0$ , and  $\alpha^i$  and  $\beta^i$  are the azimuthal and polar angles of the molecular symmetry axis ( $C_3$ ) in the PAS<sup>i</sup>. For aromatic carbons, the  $c$  direction (most shielded) is usually normal to the molecular plane. Moreover, its value is often quite different from the in-plane components, while  $\delta_{aa}^i$  and  $\delta_{bb}^i$  are often quite close in magnitude.<sup>29</sup> For a rough estimate of the order-dependent chemical shifts of the aromatic carbons, we can therefore assume that the tensor is approximately axially symmetric ( $\delta_{aa}^i = \delta_{bb}^i = -\delta_{cc}^i/2$ ), so that

$$\delta_{\text{aniso}}^i = \frac{2}{3} S_{zz} \Delta \delta^i \left( \frac{3 \cos^2 \beta^i - 1}{2} \right) \quad (5)$$

where  $\Delta \delta^i = [\delta_{cc}^i - (\delta_{aa}^i + \delta_{bb}^i)/2]$ . For the CTV core, the angle  $\beta$  is about  $43^\circ$ ,<sup>1</sup> while the  $\Delta \delta^i$  values depend somewhat on the substituents, ranging from about  $-150$  ppm for the C-H atoms, through ca.  $-130$  ppm for the ternary (C-C) atoms to ca.  $-80$  ppm for oxygen-substituted (C-O) carbons.<sup>29</sup> Taking the  $S_{zz}$  value from the deuterium results yields, respectively, 0.9, 0.8, and 0.6 ppm for  $\delta_{\text{aniso}}^i$  of the three types of carbons, respectively.

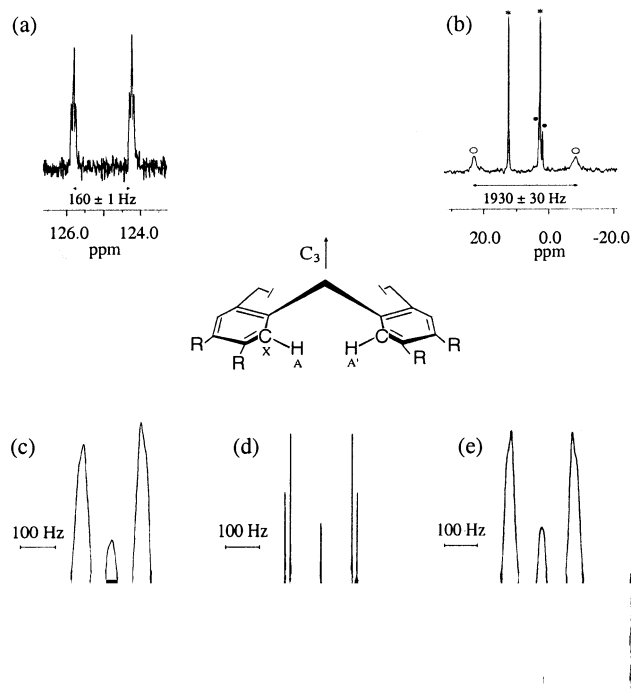
This corresponds to overall shifts of 90–60 Hz (for a spectrometer frequency of 100 MHz) compared with their respective isotropic values. Finally, assuming that the chiral discrimination results entirely from ordering, we can use the DOE value determined from the deuterium spectra (18%) to calculate chiral discriminations of about 16 Hz for the C-H carbons, 14 Hz for the ternary carbons, and 11 Hz for the C-O carbons. Considering the crudeness of the approximation made, the comparison with the experimental results (Figure 4) is not unsatisfactory. The order of magnitude agreement, in fact, strongly supports the conclusion that the chemical shift discrimination in the PBLG solution is driven by differential ordering. Also, the lack of chiral discrimination in the carbon-13 spectrum of sample 1 (compound 1) is not surprising. A similar order of magnitude calculation predicts a maximum splitting (for the C-H carbon) of  $\sim 3$  Hz, which is well within the experimental line width (6–8 Hz). On the other hand, the discussion above also shows that the application of carbon-13 NMR for quantitative analysis of the discrimination, for example, determining the degree of selective ordering, is more subtle than for deuterium, because it requires an exact knowledge of the chemical shift tensors, which are in general not simply related to the molecular structure.

**Spectral Discrimination of Enantiotopic Elements in Hexasubstituted CTV with  $C_{3v}$  Symmetry.** In this section we explore possible spectral discrimination of enantiotopic elements of hexasubstituted CTV with  $C_{3v}$  symmetry in PBLG liquid-crystalline solutions. These molecules possess equivalent groups of atoms related only by the mirror planes in the molecule (enantiotopic elements), for example, the pairs of aromatic carbons 1/6, 2/5, and 3/4, or groups linked to these atoms (see Figure 2). These pairs become nonequivalent in chiral circumstances and in principle should be distinguished in NMR spectroscopy using chiral solvents.<sup>18</sup> However, as indicated in the Introduction, specific chiral, short-range solute-solvent interactions are usually too weak to exhibit a measurable enantiotopic discrimination, while discrimination by orienta-

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**Figure 5.** Series of NMR spectra associated with the aromatic C–H carbon (2/5) of compound **3**, recorded at 300 K. (a) 100.6 MHz  $^{13}\text{C}$ – $\{^1\text{H}\}$  spectrum (2900 scans) in  $\text{CDCl}_3$ . The large doublet originates from the scalar couplings  $^1J_{\text{C–H}}$ , while the triplet structure is due to scalar couplings with the nearby methylene protons  $^3J_{\text{C–H}}$ . (b) 61.4 MHz  $^2\text{H}$ – $\{^1\text{H}\}$  signals at natural abundance (160 000 scans) in PBLG/ $\text{CHCl}_3$ . The chloroform signals are labeled with asterisks. The quadrupolar doublet associated with the deuterons of the methyl and aromatic groups are labeled by solid and open circles, respectively. No signals are observed for the deuterons of the ring methylenes. (c) 100.6 MHz  $^{13}\text{C}$ – $\{^1\text{H}\}$  (30 000 scans) in the PBLG/ $\text{CHCl}_3$  phase. An exponential filtering (LB = 4 Hz) was applied to reduce the spectral noise. (d) Simulated proton-coupled carbon-13 spectrum obtained with the spectral data reported in the text. The spectrum is displayed using a line width of 2 Hz. (e) Same as d, calculated with a line width of 25 Hz.

tional order is not possible for molecules with  $C_{3v}$  symmetry.<sup>20</sup> The latter law applies to rigid molecules with fixed symmetry. The question posed here, however, is whether it also applies to “flexible” molecules, namely molecules undergoing rapid interconversion between several, not necessarily symmetric, conformations, even though their ensemble average has a  $C_{3v}$  symmetry. The question is relevant to the substituted CTV derivative, since although the core is rigid, the substituents are usually flexible. We have studied two hexasubstituted CTV compounds with (average)  $C_{3v}$  symmetry, hexaacetyloxy-CTV (compound **3**) and tri(dioxyethylene)-CTV (compound **4**), partially deuterated to  $\sim 10\%$  in the dioxyethylene groups. No chiral discrimination was detected in the proton-decoupled deuterium and carbon-13 (both in natural abundance) of a solution of compound **3** in a PBLG/ $\text{CHCl}_3$  solution. However, a clear spectral enantiodistinction was observed for the enantiotopic deuterons in the ethylene groups of the dioxane chain in compound **4**. In section II(a) we discuss this effect in terms of differential ordering of the various conformers of this compound. Before doing so, however, we briefly describe the spectra obtained for compound **3** in the lyotropic PBLG/ $\text{CHCl}_3$  solution. As mentioned earlier, this allowed us to determine the magnitude and sign of the order parameter of this solute in the PBLG mesophase.

**NMR Spectra and Order Parameter of Hexaacetyloxy-CTV in PBLG/ $\text{CHCl}_3$ .** In Figure 5 is shown a set of spectra

related to the aromatic C–H carbons (carbons 2/5) of compound **3**. Trace a, exhibiting a doublet of triplets, is an undecoupled carbon-13 spectrum recorded in a  $\text{CDCl}_3$  solution at room temperature. The larger doublet splitting is due to scalar coupling with the adjacent proton,  $^1J_{\text{C–H}} = +160$  Hz, where the positive sign is the commonly accepted sign for  $^1J_{\text{C–H}}$ .<sup>17,26</sup> The smaller splitting is due to scalar interaction with the nearby ring methylene,  $^3J_{\text{C–H}} = 6.0$  Hz. Spectrum b is a natural abundance deuterium spectrum of compound **3** dissolved in PBLG/ $\text{CHCl}_3$  (sample 5) at 300 K.<sup>30</sup> The outer doublet (open circles) corresponds to the aromatic C–D deuterium and exhibits a splitting of  $|\Delta\nu_Q^{\text{C–D}}| = 1930 \pm 30$  Hz. The other doublets in the spectrum are due to natural abundant deuterons in the side chain methyls (solid circles) and the chloroform solvent (asterisks). From the structure of the CTV (crown) core (Figure 2) it follows that the aromatic C–D bonds are perpendicular to the molecular  $C_3$  axis ( $\beta^{\text{C–D}} = 90^\circ$ ). We can thus use eq 1 to calculate the magnitude of the order parameter, yielding  $|S_{zz}| = 0.015$ . The more interesting spectrum is that shown in part c. It is the proton-coupled carbon-13 spectrum of carbons 2/5 in the same PBLG/ $\text{CHCl}_3$  solution (sample 5) and recorded at the same temperature (300 K) as the deuterium spectrum of b. The structure of this spectrum can be interpreted in terms of the following three-spin system,  $^{13}\text{C}$ – $^1\text{H}_A$ – $^1\text{H}_{A'}$  (see drawing in Figure 5), where the C– $\text{H}_A$  pair belongs to one benzene ring and  $\text{H}_{A'}$  to the nearby ring. A quantitative analysis of this spectrum in terms of the dipolar and scalar interactions between the three nuclei allows us to determine both the magnitude and sign of the molecular order parameter,  $S_{zz}$ .

The spin Hamiltonian of this three-spin system for a molecule that dissolves in a nematic solvent is

$$\hat{\mathcal{H}} = -\nu_L^{13\text{C}} S_z - \nu_L^1\text{H} (I_z^A + I_z^{A'}) + ({}^1J_{\text{C–H}} - 2D_{\text{C–H}}) S_z I_z^A - 2D_{\text{H–H}} \left[ I_z^A I_z^{A'} - \frac{1}{4} (I_+^A I_-^{A'} + I_-^A I_+^{A'}) \right] \quad (6)$$

where the first two terms correspond to the Zeeman energies of the carbon-13 and hydrogen nuclei, respectively, and the next two terms are the C– $\text{H}_A$  and  $\text{H}_A$ – $\text{H}_{A'}$  interactions. We have neglected long-range scalar and dipolar couplings (over more than a single bond). Recalling the 3-fold molecular symmetry of CTV and that the dipolar tensor is axially symmetric, the dipolar couplings in eq 7 are given by an expression similar to eq 1,

$$D_{\text{M–N}} = S_{zz} \frac{K_{\text{M–N}}}{r_{\text{M–N}}^3} \left( \frac{3 \cos^2 \beta^{\text{M–N}} - 1}{2} \right) \quad (7)$$

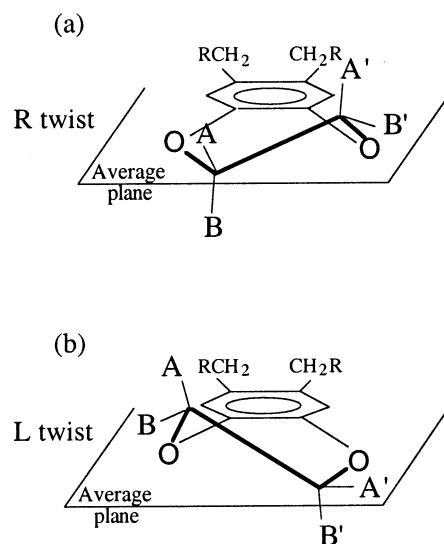
where  $r_{\text{M–N}}$  is the M to N distance (in Å),  $\beta^{\text{M–N}}$  is the angle between the  $r_{\text{M–N}}$  direction and the molecular  $C_3$  axis, and  $K_{\text{M–N}}$  is a constant proportional to the magnetic dipoles of the M and N nuclei,  $K_{\text{C–H}} = 30\,188 \text{ Hz} \cdot \text{Å}^3$  and  $K_{\text{H–H}} = 120\,060 \text{ Hz} \cdot \text{Å}^3$ . Since  $\beta^{\text{M–N}}$  is the same for both pairs of interacting nuclei ( $\beta^{\text{M–N}} = 90^\circ$ ), it follows that both interactions have the same sign. The Hamiltonian in eq 6 can be solved analytically. For the carbon-13 spectrum it yields a symmetric five-line spec-

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trum centered around  $\nu_L^{13C}$ , featuring (a) an inner doublet at  $\pm 1/2(^1J_{C-H} - 2D_{C-H})$ , each with the relative intensity 1, (b) an outer doublet located at  $\pm 1/2[(^1J_{C-H} - 2D_{C-H})^2 + 4D_{H-H}^2]^{1/2}$ , each with the relative intensity  $(^1J_{C-H} - 2D_{C-H})^2 / [(^1J_{C-H} - 2D_{C-H})^2 + 4D_{H-H}^2]$  (smaller than 1), and (c) a central singlet with relative intensity  $8D_{H-H}^2 / [(^1J_{C-H} - 2D_{C-H})^2 + 4D_{H-H}^2]$ . Despite the poor resolution, the main features of the expected spectrum can readily be recognized in trace c of Figure 5. To facilitate the analysis, we first estimate the magnitude of the  $D_{C-H}$  from the measured quadrupolar splitting of the corresponding C–D deuteron (trace b of Figure 5). From eqs 1 and 7 it follows that for the aromatic C–H/C–D fragment the ratio  $\Delta\nu_Q^{C-D}/D_{C-H}$  is fixed by the quadrupolar and dipolar constants at  $(3/2)Q_{C-D}/(K_{C-H}/r_{C-H}^3) \approx 12$ .<sup>31</sup> Thus, from the measured  $|\Delta\nu_Q^{C-D}|$  (1930 Hz),  $|D_{C-H}|$  is estimated to be about 170 Hz. Referring next to trace c, we can readily recognize the two (unresolved) doublets (a and b) and the center peak (c). From the splitting of the inner doublet we calculate  $|^1J_{C-H} - 2D_{C-H}| \approx +150$  Hz. Since we know that  $^1J_{C-H} = +160$ ,  $D_{C-H}$  must be ca. +150 Hz. The alternative solution of  $|D_{C-H}| \sim 0$  Hz is ruled out by a comparison with  $|\Delta\nu_Q^{C-D}|$ . From this value of  $D_{C-H}$ , using  $r_{C-H} = 1.09$  Å, we obtain  $S_{zz} \approx -0.013$ . Thus, both dipolar couplings,  $D_{C-H}$  and  $D_{H-H}$  as well are positive, while  $S_{zz}$  is negative. This means that the molecular  $C_3$ -symmetry axis of compound **3** prefers to be aligned perpendicular, rather than parallel, to the director in the PBLG/CHCl<sub>3</sub> phase. We assume that the same applies to the other CTV derivatives in the lyotropic PBLG solutions. Finally a best-fit analysis was carried out on the experimental spectrum, yielding  $D_{C-H} = +159 \pm 2$  Hz and  $D_{H-H} = +49 \pm 1$  Hz. The calculated best-fit spectrum, using an effective line width of 25 Hz, is shown in trace e of Figure 5. When the same parameters are used with a line width of only 2 Hz, the calculated spectrum shown in d is obtained. We believe that at least some of the broadening is due to dipolar interaction with remote protons in the molecule. Using the final result  $D_{C-H}$  and eq 7, we obtain  $S_{zz} = -0.0146$ , which is essentially identical to the absolute value calculated above from  $\Delta\nu_Q^{C-D}$  ( $|S_{zz}| = 0.015$ ).

**Deuterium NMR Spectra and Order Parameter of Tri-(dioxyethylene)-CTV in PBLG/CHCl<sub>3</sub>.** Tri(dioxyethylene)-CTV (compound **4**) consists of the rigid CTV core to which three dioxyethylene bridges are symmetrically linked. The dioxyethylene bridges can acquire two states, corresponding to a right twist and a left twist, as displayed in Figure 6, which we label hereafter R and L, respectively. From the high-resolution NMR spectra of this compound we know that these states rapidly interconvert, so that hydrogens A and A' are on average equivalent and likewise hydrogens B and B'. When all possible twisted states are considered, four types of conformers for the tri(dioxyethylene)-CTV molecules are obtained. Two of them, labeled RRR and LLL, have  $C_3$  symmetry, where the triplets of letters indicate the twist of the dioxyethylene groups sequentially around the CTV core. The two other conformers are RLL and LRR with  $C_1$  symmetry. The latter two are structurally 3-fold degenerate, RLL, LRL and LLR, and similarly, LRR, RLR, and RRL. Each conformer is chiral with



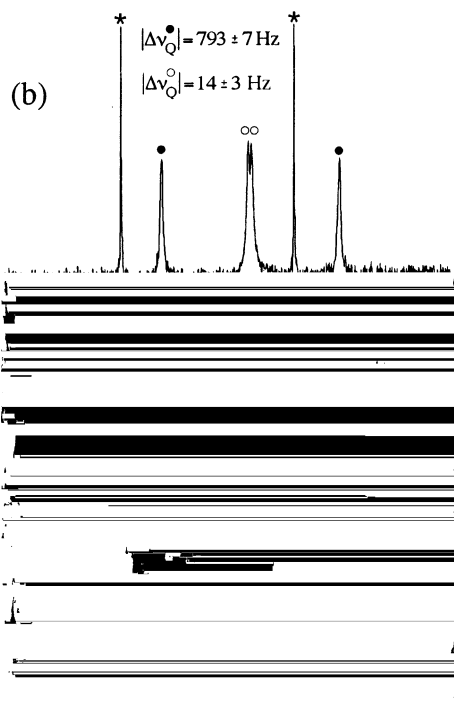
**Figure 6.** Schematic representation of twisted dioxyethylenebenzene fragments of compound **4**. The right twist (a) and a left twist (b) are shown.

RRR and LLL comprising an enantiomeric pair (which will be denoted arbitrarily *M* and *P*) and likewise RLL and LRR. In a nonchiral liquid-crystalline solution there is no discrimination between enantiomeric pairs. The *M* and *P* conformers have the same fractional population, the same order parameter, and, from the NMR point of view, the same magnetic parameters for corresponding nuclei. Moreover, the fast interconversion between the various conformations results in an average  $C_{3v}$  symmetry. This statement applies, in fact, to each class of conformers ( $C_3$  and  $C_1$ ) separately. Hence, sites in the molecule that are related by the average  $C_{3v}$  symmetry are chemically equivalent (as in isotropic medium), but if they are related by reflection, they are also enantiotopic. In a chiral liquid-crystalline solvent the chemical equivalence of such sites is not preserved. This is because, in principle, neither the fractional population nor the ordering of the *M* and *P* enantiomeric conformers need to be the same, nor even the magnetic parameters of their corresponding nuclei. These effects may lead to chiral spectroscopic discrimination of enantiotopic sites, as we have indeed observed in the case of compound **4** embedded in the PBLG solvent.

In Figure 7 are shown deuterium NMR spectra of solutions of tri(dioxyethylene)-CTV enriched to 10% deuterium in the ethylene side groups (compound **4**), recorded at 300 K in achiral PBG/CHCl<sub>3</sub> (top) and chiral PBLG/CHCl<sub>3</sub> (bottom) solutions (samples 6 and 7, respectively). We first discuss the spectrum observed in the racemic solution, which exhibits three quadrupolar doublets. The more intense one, centered at 6.5 ppm (labeled by asterisks), is due to the natural abundant deuterons in the chloroform solvent. The two weaker doublets (open and solid circles), centered at 3.5 ppm are ascribed to the A(A') and B(B') deuterons in the enriched dioxyethylene groups (see Figure 6). This spectrum is consistent with the average  $C_{3v}$  symmetry of the compound, according to which sites A and A' are equivalent, and likewise B and B'.

To quantitatively analyze the spectrum in the racemic solution it is sufficient to consider the average over a single pair of R and L conformations and assume an overall  $C_{3v}$  symmetry for the tri(dioxyethylene)-CTV molecule. Thus, the average quad-

(31) Sarfati, M.; Courtieu, J.; Lesot, P. *Chem. Commun.* **2000**, 1113.



**Figure 7.** 61.4 MHz  $^2\text{H}\{-^1\text{H}\}$  spectra of compound **4**, with statistically ( $\sim 10\%$ ) deuterated dioxyethylene side chains, recorded at 300 K. (a) In the chiral solvent PBLG/ $\text{CHCl}_3$ , (b) In the achiral solvent PBG/ $\text{CHCl}_3$ . The spectra a and b were recorded by adding 20 000 and 10 000 scans, respectively. For both spectra, zero-filling to 32K data points was used to increase the digital resolution and a Gaussian filtering was applied to improve the spectral appearance. The quadrupolar doublets associated with (A and A') and (B and B') deuterons are labeled with open and solid circles, respectively. Peaks with asterisks correspond to the natural abundance deuterium signals of chloroform.

rupole splittings of the A (or B) deuterons can be written as<sup>32,33</sup>

$$\Delta\nu_Q^{(i)} = \sum_n f^n S_{zz}^n \left(\frac{3}{2}\right) Q_{\text{C-D}}^{n(i)} F^n(i) \quad (8)$$

where

$$F^n(i) = \frac{3 \cos^2 \beta^n(i) - 1}{2} \quad (9)$$

In these equations the index,  $i$ , labels the deuterons A and A' (or B and B'), the summation index,  $n$ , indicates whether the twist of the dioxyethylene bridge is R or L,  $f^n$  is the fractional population of the two twists, and  $\beta^n(i)$  the angle between the  $C_3$  axis and the C–D bond direction of the  $i$ th deuteron in the  $n$ th conformer. In eq 8 we included the possibility that  $Q_{\text{C-D}}$  may, in principle, depend on the deuterium site (A or B) and conformation (R or L), hence the superscript  $n(i)$ . On the basis of the discussion above we consider this effect too small to be of importance here, and in the following we will drop the superscript and use the quadrupolar coupling constant at 170 kHz for all deuterons. To proceed we need to estimate the  $\beta^n(i)$  values. This we have done in two steps. First, we calculated the geometry of the twisted dioxyethylene-benzene fragments (R and L of Figure 6) using the Gaussian 98 DFT (density

**Table 3.** Geometrical Parameters Related to the C–D Bonds in the Dioxyethylene Side Groups, in the R and L Conformations of Compound **4**<sup>a</sup>

C–D bond	A	A'	B	B'
$\theta^{\text{R}}(i)^a$	74.7	8.59	171.4	104.9
$\varphi^{\text{R}}(i)$	−34.9	−86.5	83.1	34.8
$\theta^{\text{L}}(i)$	8.59	74.7	104.9	171.4
$\varphi^{\text{L}}(i)$	86.5	34.9	−34.8	−83.1
$\beta^{\text{R}}(i)$	110.3	44.2	(−)137.3 <sup>b</sup>	136.8
$F^{\text{R}}(i)$	−0.3197	0.2709	0.3112	0.2984

<sup>a</sup> All angles are in degrees.  $\theta$  and  $\varphi$  are the polar and azimuthal angles of the indicated C–D bonds in the frame of the dioxyethylenebenzene fragment (Figure 6). In this frame,  $c$  is perpendicular to the benzene plane,  $b$  is in the direction linking the two aromatic C–H bonds, and  $a$  completes the frame to a right-handed system (Figure 2).  $\beta$  is the angle between the indicated C–D bond and the molecular  $C_3$  axis and  $F$  is the second-order Legendre function (eq 9). In the calculation of the  $\beta$  values, an angle of  $43^\circ$  between  $C_3$  and  $Z$  was assumed. Only values for the R conformation are given. Those for the L conformation are related to the latter by  $\beta^{\text{L}}(\text{A}) = \beta^{\text{R}}(\text{A}')$  and  $\beta^{\text{L}}(\text{A}') = \beta^{\text{R}}(\text{A})$  and similar relations apply for the B and B' deuterons.

functional theory) program.<sup>34</sup> The angular orientations of the ethylene C–D bonds,  $\theta$  and  $\varphi$  in these fragments are summarized in Table 3. Note that the calculations do not yield a perfect symmetric twist, but the deviations are minute. Perfect symmetry would require that  $\theta^n(\text{A}, \text{A}') = 180^\circ - \theta^n(\text{B}', \text{B})$  and  $\varphi^n(\text{A}, \text{A}') = -\varphi^n(\text{B}', \text{B})$ . Using these results, the angles  $\beta^n(i)$  between the C–D bond directions and the molecular  $C_3$  axis were computed assuming that the latter is inclined by  $43^\circ$  to the benzene ring normal ( $c$  in Figure 2).<sup>1</sup> The results for the various  $\beta^n(i)$  values and corresponding  $F^n(i)$  functions are also given in Table 3. Only the  $\beta^n(i)$  values for the  $n = \text{R}$  conformation are included. Those for the L conformation are related to the former, by  $\beta^{\text{L}}(\text{A}) = \beta^{\text{R}}(\text{A}')$ ,  $\beta^{\text{L}}(\text{A}') = \beta^{\text{R}}(\text{A})$  and a similar relation exists for the B and B' deuterons.

For the calculations it is sufficient to consider the enantiomeric pair, RRR (say  $M$ ) and LLL ( $P$ ), both of which have  $C_3$  symmetry. Identical conclusions would be reached if the  $C_1$  isomers were included in the analysis, since the average over RLL, LRL, and LLR also corresponds to  $C_3$  symmetry and likewise the average over LRR, RLR, and RRL. Considering first the results for the PBG solution, where the  $M$  and  $P$  conformation have the same ordering ( $S_{zz}^M = S_{zz}^P = S_{zz}$ ), the same fractional populations ( $f^M = f^P = 1/2$ ) and using the entries from Table 3, we obtain from eq 9

and

This result immediately allows us to identify the doublets with the larger and smaller splittings (solid and open circles in Figure 7) with the deuterons A(A') and B(B'), respectively. To proceed we use eq 10b for  $\Delta\nu_Q^{(\text{B})}$ . The corresponding equation for  $\Delta\nu_Q^{(\text{A})}$  is quite unreliable, since the numerical coefficient in it results as a small differences between similarly large numbers

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(33) Emsley, J. W.; Luckhurst, G. R. *Mol. Phys.* **1980**, *41*, 19.

(34) *Gaussian 98*, Revision A.7; Gaussian Inc., Pittsburgh, PA, 1998.

and is therefore subject to a very large uncertainty. Thus, taking  $|\Delta\nu_Q^{(B)}| = 793$  Hz yields  $|S_{zz}| \approx 0.010$ , where, based on the earlier results, the sign is most likely negative.

We next discuss the spectrum of tri(dioxyethylene)-CTV in the chiral solvent (bottom trace in Figure 7), where both the A,A' and B,B' enantiotopic deuterons exhibit chiral discrimination with  $\Delta\nu_Q^{(A)} \neq \Delta\nu_Q^{(A')}$  and  $\Delta\nu_Q^{(B)} \neq \Delta\nu_Q^{(B')}$ . Although this discrimination is not forbidden by symmetry, its origin is puzzling. To discuss the mechanism of this discrimination and estimate its extent, we use again eq 9. Here too it is sufficient to consider the enantiomeric conformer pair RRR (*M*) and LLL (*P*). Thus, the difference in the quadrupolar splittings between deuterons A and A' can be written as

$$\begin{aligned} \Delta\Delta\nu_Q^{(A-A')} &= \Delta\nu_Q^{(A)} - \Delta\nu_Q^{(A')} \\ &= (3/2)\{[f^M S_{zz}^M Q_{C-D} F^M + f^P S_{zz}^P Q_{C-D} F^P(A)] - \\ &\quad [\phi^M S_{zz}^M Q_{C-D} F^M(A') + f^P S_{zz}^P Q_{C-D} F^P(A')]\} \quad (11) \end{aligned}$$

and similarly for  $\Delta\Delta\nu_Q^{(B-B')} = \Delta\nu_Q^{(B)} - \Delta\nu_Q^{(B')}$ . From eq 11 the discrimination can result from a selective effect on the fractional population ( $f^M \neq f^P$ ) and/or the ordering ( $S_{zz}^M \neq S_{zz}^P$ ). In principle, the discrimination can also result from chiral, short-range solute–solvent interactional effects on the magnetic and geometrical parameters ( $Q_{C-D}$  and  $\beta^{(i)}$ ), but as before, we reject this possibility as unlikely. By symmetry we set  $\beta^M(A) = \beta^P(A')$ ,  $\beta^M(A') = \beta^P(A)$  (see Figure 6 and Table 3). Equation 11 thus becomes

$$\Delta\Delta\nu_Q^{(A-A')} = 255(f^M S_{zz}^M - f^P S_{zz}^P)[F^M(A) - F^M(A')] \quad (\text{in kHz}) \quad (12)$$

with a similar equation for  $\Delta\nu_Q^{(B-B')}$ . Substituting the  $F^i(i)$  values from Table 3 yields

$$\Delta\Delta\nu_Q^{(A-A')} = \pm 150(f^M S_{zz}^M - f^P S_{zz}^P) \quad (\text{in kHz}) \quad (13a)$$

and

$$\Delta\Delta\nu_Q^{(B-B')} = \pm 3.26(f^M S_{zz}^M - f^P S_{zz}^P) \quad (\text{in kHz}) \quad (13b)$$

where the sign is undetermined because we did not commit ourselves to the absolute configuration of the *M* and *P* enantiomers. The calculations suggest that  $\Delta\Delta\nu_Q^{(A-A')}$  and  $\Delta\Delta\nu_Q^{(B-B')}$  have opposite signs, but this conclusion depends very delicately on the difference  $[F^M(B) - F^P(B')]$ , which is minute compared to the magnitude of each element separately (see Table 3). For this reason we continue the analysis with the less vulnerable eq 13a for  $\Delta\nu_Q^{(A-A')}$ . Assuming that the dominant effect on the discrimination is due to selective ordering, rather than an imbalance in the population distribution ( $S_{zz}^M \neq S_{zz}^P$ ,  $f^M = f^P = 1/2$ ), eq 13a becomes  $|\Delta\Delta\nu_Q^{(A-A')}| = 75|(S_{zz}^M - S_{zz}^P)|$  (in kHz). The two quadrupolar doublets of the A and A' deuterons in Figure 7 have splittings of 40 and 10 Hz. If both splittings have the same sign,  $|\Delta\Delta\nu_Q^{(A-A')}| = 30$  Hz, while if their sign is opposite,  $|\Delta\Delta\nu_Q^{(A-A')}| = 50$  Hz. Substituting these values (with  $|S_{zz}| = 0.011$ , calculated from the average of B and B' splittings) yields  $|(S_{zz}^M - S_{zz}^P)/S_{zz}| = 0.037$  and 0.060, respectively. Both values are on the order found for the

enantiomers of compounds 1 and 2 (see DOE values in Table 2). We cannot rule out, however, the possibility that the discrimination is due to imbalance in the population of the *M* and *P* enantiomers or to a combined effect of the latter and selective ordering. The mechanism discussed above can only affect the flexible part of the molecule. In the approximation used to derive eq 12, the geometrical factor vanishes for atoms in the rigid part of the molecule, and therefore, no discrimination based on this mechanism is expected in the NMR spectra of nuclei from this part. In principle, other mechanisms could lead to discrimination of enantiotopic elements. For example, the twisted side chains can induce magnetic nonequivalence of the substituted aromatic carbons (3,6) that could lead to NMR spectroscopic discriminations.

Finally, the question may be asked, why was there no discrimination observed in the carbon-13 and deuterium spectra of hexaacyloxy-CTV (compound 3) in the chiral solvent PBLG/CHCl<sub>3</sub> (sample 5). After all, here too the side chains are flexible and can lead to many, including chiral, conformations. We believe that the effect certainly exists, but it is simply too small to be experimentally observed. As we saw in the discussion above, the spectral discrimination reflects small differences in the ordering and/or the population distribution of the conformers. Apparently these effects tend to cancel when a large number of conformers is involved in the averaging.

## Summary and Conclusions

In the present work we extend earlier studies of chiral discrimination, by NMR spectroscopy, in the lyotropic chiral nematic mesophases of PBLG to solutes derived from the crown form of CTV. This core does not possess stereogenic tetrahedral centers, but depending on the substitution pattern, its derivatives can be chiral, prochiral, or achiral. In the present work we concentrated on two types of substituted CTV derivatives having *C*<sub>3</sub> and *C*<sub>3v</sub> symmetries. In the first part of the paper we discuss the (proton decoupled) deuterium and carbon-13 NMR spectra of nonasubstituted CTV derivatives with *C*<sub>3</sub> symmetry. Depending on the nature of the cosolvent, in particular its polarity, very significant chiral discrimination could be obtained, demonstrating the power of the method for studies of such chiral compounds and its potential for analytical application to these systems.

In the second part of the paper we discuss substituted CTV with flexible side chains having on average *C*<sub>3v</sub> symmetry. In solution these compounds consist of mixtures of rapidly (NMR wise) interconverting conformers, with in general lower symmetries than *C*<sub>3v</sub>, including chiral enantiomeric pairs. Nonstatistical distribution or selective ordering of these enantiomeric conformers may result in spectral discrimination of some sites, which on the average are enantiotopic. It is important to point out that, based on population or ordering selectivity alone, only sites in the flexible part of the molecule can be spectrally discriminated. No discrimination of enantiotopic elements in the rigid part is possible by this mechanism alone. The question of whether the discrimination observed in the flexible part is predominantly due to selective ordering and/or deviation from statistical population distribution of enantiomeric isomers remains open. On the basis of comparison with the results for the *C*<sub>3</sub> compound in the first part of the paper, it appears that the former mechanism dominates the discrimination. If indeed

this is so, the example discussed in the second part of the paper is the first direct observation of conformation dependent ordering in a CLC. Until now the arguments of an orientation–conformation dependence have been invoked to explain some unexpected deviations between theoretical and experimental results (after fastidious calculations involving various elaborated models),<sup>33,37</sup> but to the best of our knowledge, a direct experimental evidence has not been reported so far. Conclusively, NMR in PBLG solutions should provide an interesting tool for investigating the orientation–conformation correlation in flexible molecules.

Contrary to simple stereochemical considerations, we have shown that all elements (nuclei, groups, internuclear directions) defined as enantiotopic, according to the symmetry or substitution criteria customary employed as a test,<sup>18,19</sup> cannot be experimentally differentiated using NMR in a CLC system as far as selective ordering is only concerned. From an NMR in CLC point of view, it now becomes possible to divide solutes exhibiting enantiotopic elements in three classes according to

the possibility to differentiate between them. The first class contains all nonplanar rigid derivatives of  $C_s$ ,  $C_{2v}$ ,  $S_4$ , and  $D_{2d}$  symmetry. Typical examples of enantiotopic distinction for this molecular class can be found in refs 20, 21, and 23. The second one contains all flexible derivatives exhibiting one of these symmetries on average on the NMR time such as benzyl alcohol or ethyl alcohol reported in refs 22 and 23. The third and the last one contain all flexible molecules (such as compound **4**) of which the average symmetry differs from  $C_s$ ,  $C_{2v}$ ,  $S_4$ , and  $D_{2d}$  but exhibit a sufficiently large differential ordering for their enantiomeric conformers in the course of their stereochemical dynamic.

The next step of this work will consist of quantifying the molecular orientational ordering dependence on molecular conformation in the case of two flexible enantiomers embedded in a chiral oriented solvent. This research is currently underway.

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