

# Differential Incorporation of L- and D-N-Acyl-1-phenyl-*d*<sub>5</sub>-2-aminopropane in a Cesium N-Dodecanoyl-L-alaninate Cholesteric Nematic Lyomesophase

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Deuterium quadrupole splittings from two series of optical isomers, L- and D-N-acyl-1-phenyl-*d*<sub>5</sub>-2-aminopropane, with linear acyl chains ranging from 1 to 10 carbon atoms, were measured using <sup>2</sup>H NMR spectroscopy. Both series of molecules were dissolved in anionic nematic cholesteric lyotropic liquid crystals prepared with cesium N-dodecanoyl-L-alaninate. With these values, the two order parameters that completely characterize the average alignment of the aromatic ring were calculated. Differential incorporation of both series of isomers into the aggregate is observed for intermediate size molecules, as evidenced by the values of the order parameters of the ring. Our results indicate that the first two derivatives in both series, L- and D-C<sub>1</sub> and L- and D-C<sub>2</sub>, are located near the interface, possibly forming a H bond between the NH and/or CO groups and the interstitial water molecules. Increasing the hydrophobicity of the chain by adding one carbon atom induces a decrease in the overall alignment. Intermediate acyl chain length molecules progressively incorporate sufficiently into the aggregate for both asymmetric carbons, from the surface and the guest molecule, to approach each other, introducing differences in the average alignment of the aromatic ring between both series of isomers. Longer acyl chain derivatives incorporate deeper into the micelle and do not show this differentiation, possibly because the asymmetric carbons are located far away from each other.

## Introduction

Interactions between biologically interesting molecules and molecular assemblies, such as micelles, vesicles, bilayers, liposomes, and liquid crystals, are a subject of current research interest.<sup>1–7</sup> The molecular composition of living matter is essentially chiral, and specific interactions between chiral molecules are known to be crucial in most biological processes. With this in mind it seems reasonable that specific interactions between chiral centers might influence the distribution as well as diffusion of chiral biologically active molecules across natural membranes.

Only during the past few decades the pharmacological importance of chirality has been widely recognized. For instance, the D-isomer of amphetamine is a potent central nervous system stimulant, while the L-isomer is less active. The existence of stereospecific binding sites of D-amphetamine in membrane preparations from rat brain has been demonstrated.<sup>8</sup> L-Epinephrine is 10 times more active as a vasoconstrictor than the corresponding D-isomer. The L-isomer of propoxyphene shows antitussive activity

whereas the D-isomer is analgesic. Perhaps the most dramatic example of this is thalidomide, a sedative commonly used in the 1950s and early 1960s, which was ingested in racemic form. It is now known that the right-handed form of thalidomide is teratogenic; however, the drug may have no adverse effects if only the left-handed molecule is administered. Aside from drug–receptor interactions, drug metabolism occurs at different rates for different stereoisomers. There are many examples of this behavior, and for this reason the pharmaceutical industry shows an increasing interest in developing asymmetric synthesis and chiral resolution technology.<sup>9</sup>

Drug transport through cell membranes, regardless of its mechanism, may also be expected to depend on the stereochemistry of the drug molecules in view of the intrinsic chirality of biomembrane components. Unfortunately, such effects are difficult to demonstrate in vivo because they are obscured by the possibly different enantioselectivity of blood plasma protein binding and metabolic processes. Consequently, little is known about the importance that enantioselective membrane permeation may have in such fundamental phenomenon as drug absorption, transport, and excretion.

For more than 30 years it has been observed that different optical isomers may display different NMR spectra in chiral anisotropic media, such as cholesterics. More recently, it has become one of the most promising techniques for the evaluation of enantiomeric enrichment and specific recognition interactions.<sup>10–17</sup> Lately, experimental and theoretical efforts have been also devoted to understanding the role of chiral interactions and recogni-

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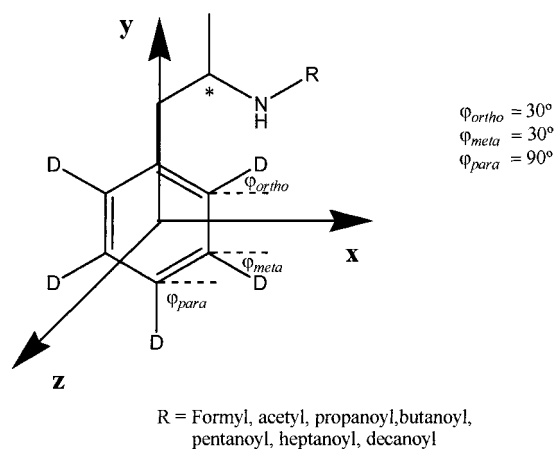
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tion in chromatographic applications oriented to the resolution of racemic mixtures.<sup>18</sup>

Discotic cholesteric lyotropic liquid crystals,  $Ch_D$ , provide a magnetic field oriented bilayer with a chiral interface. This type of liquid crystal has been prepared before, and a number of NMR and laser pitch studies oriented to elucidate the mechanism of generation of the macroscopic twist have been published.<sup>19–25</sup> Two different origins for the twisted structure have been proposed: the first involves interactions between pairs of molecules in adjacent micelles, and the second implicates interactions between molecules in the same micelle which should induce an asymmetry that is transmitted to the interactions between micelles. An X-ray study showed that, for a fixed molar concentration of chiral dopant in a mixed system, the cholesteric pitch of the micellar system decreases with the increase in micellar shape anisotropy.<sup>26</sup>

One of the simplest methods to estimate the average alignment of ions and molecules in anisotropic media, such as an oriented bilayer, is by using order parameters derived from the <sup>2</sup>H NMR spectra of specifically labeled molecules. In the past, we have studied the solubilization process of a number of ions and molecules in cationic and anionic nematic lyotropic liquid crystals, using deuterium quadrupole splittings of deuterated aromatic rings.<sup>3,27–29</sup> In this work, we have employed <sup>2</sup>H NMR spectroscopy to measure the deuterium quadrupole splittings from the fully deuterated aromatic ring of two series of seven optical isomers each, L- and D-*N*-acyl-1-phenyl-2-aminopropane, 40% *d*<sub>5</sub>. Both series contain linear acyl substituents ranging from 1 to 10 carbon atoms and were dissolved in a nematic cholesteric lyomesophase prepared using cesium *N*-dodecanoyl-L-alaninate (CsD-L-Ala) as the main surfactant component, providing the chiral interface. The nomenclature used to identify the different molecules is related to the number of carbons in the linear acyl substituent: the formyl derivative is named C<sub>1</sub>; C<sub>2</sub> corresponds to *N*-acetyl; C<sub>3</sub> is *N*-propanoyl, and so on. Figure 1 shows the basic structure of the studied molecules including the designation of the symmetry axis and structural parameters of the aromatic ring. From the quadrupole splittings of the deuterium nuclei at the ortho, meta, and para positions we have calculated the two order parameters that completely describe the average alignment of the aromatic ring. Using this information, we



**Figure 1.** Structure of the studied molecules and designation of the symmetry axis of the aromatic ring. The principal axis of the electric field gradient is assumed to be along the direction of the C–D bond.

have postulated a possible mechanism of incorporation of the guest molecules into the mesophase. Differences in the alignment attributable to chirality were first observed by Tracey and Radley in the proton–proton dipolar couplings of L- and D-alanine dissolved in potassium dodecanoyl-L-alaninate mesophase.<sup>25</sup> The effect of the added molecules on the integrity of the aggregate was studied by adding 20% decanol- $\alpha$ -*d*<sub>2</sub> to the decanol necessary to form the mesophase. The interaction between the interstitial water molecules and the bilayer interface was studied measuring the quadrupole splitting from HDO, including 0.05% D<sub>2</sub>O in the water used to dissolve the mesophase components.

## Experimental Section

**Synthesis of (±)-1-Phenyl-*d*<sub>5</sub>-2-aminopropane.** The racemic mixture (±)-1-phenyl-2-aminopropane, 40%-*d*<sub>5</sub>, was prepared from a 40/60 mixture of benzyl alcohol-*d*<sub>5</sub>, 99% enrichment, and benzyl alcohol p.a.. This mixture of benzyl alcohols was treated with pyridinium chlorochromate, PCC (50% mol excess), and oxidized quantitatively to benzaldehyde. The 40%-*d*<sub>5</sub> benzaldehyde was transformed into  $\beta$ -methyl- $\beta$ -nitrostyrene by reaction with nitroethane, also used as solvent, catalyzed by *n*-butylamine. The reaction mixture was refluxed for 6 h, and the crude product, a yellow oil, crystallized from methanol.  $\beta$ -Methyl- $\beta$ -nitrostyrene, 40%-*d*<sub>5</sub>, was reduced to the racemic 1-phenyl-2-aminopropane by reaction with LiAlH<sub>4</sub> in anhydrous ether. The suspension was refluxed for 12 h, excess of LiAlH<sub>4</sub> was eliminated by careful treatment with an ethanol/water mixture, the pH of the crude product was adjusted to 11, and the aqueous fraction was extracted with ether. The ether from the reaction and the extraction was dried with MgSO<sub>4</sub> and evaporated. The product is obtained as an oil.

**Enantiomeric Resolution of (±)-1-Phenyl-2-aminopropane.** The racemic mixture of amines was resolved by using di-*p*-toluoyl-L-tartaric acid and di-*p*-toluoyl-D-tartaric acid. Equivalent molar parts of (±)-1-phenyl-2-aminopropane and di-*p*-toluoyl-D-tartaric acid were separately dissolved in the minimum amount of 2-propanol. Both solutions were mixed, and the 1:1 salt precipitated. The solid was filtered and dried. 4 g of dry salt was dissolved in 250 mL of methanol and allowed to crystallize at room temperature. The crystals were filtered and recrystallized from methanol. After the second crystallization the precipitate was hydrolyzed with ammonium hydroxide, the pH was adjusted to 11, and the solution was extracted with ether. The organic phase was washed several times with a 10% solution of Na<sub>2</sub>CO<sub>3</sub>, to completely eliminate the acid, washed with water, and dried with MgSO<sub>4</sub>. The ether was evaporated, and the product was obtained as an oil. The optical rotation was measured in methanol (1 g/100 mL) giving a value between +20° and +22°, which compared with the reported value +22° indicates a highly pure

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enantiomeric product.<sup>30</sup> The mixture of mother liquors of both crystallizations was evaporated to dryness, and the residue worked up in the same way as the pure di-*p*-toluoyl-D-tartrate. The ether from the extraction was dried and evaporated, and the remaining oil, now free amine enriched in the L-isomer, was treated in the same way as described before, except that now di-*p*-toluoyl-L-tartaric acid was used to crystallize the mixture from 2-propanol. The free amine obtained showed an optical rotation between  $-20^\circ$  and  $-22^\circ$  in methanol solution (1 g/100 mL).

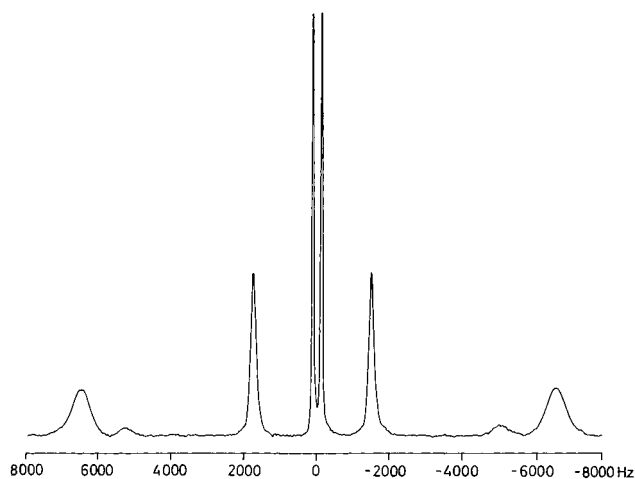
**Synthesis of L- and D-N-Acyl-1-phenyl-*d*<sub>5</sub>-2-aminopropane.** All chiral amides, except the formyl derivative, were obtained from the reaction between the chiral free amine and the corresponding acid chloride with drops of pyridine. For the formyl derivative the amine was made to react with formic acid in glacial acetic acid. All the products were purified by column chromatography using silica gel 60 as stationary phase and different chloroform/ethyl acetate mixtures, depending on the polarity of the product.

**Sample Preparation.** Cesium *N*-dodecanoyl-L-alaninate was prepared using a method described before, except that we used CsOH in the neutralization of the acid.<sup>20,22</sup> To prepare the sample, 264 mg of CsDD-L-Ala and 25 mg of KCl were dissolved in 0.48 mL of H<sub>2</sub>O (0.05% D<sub>2</sub>O) and 60  $\mu$ L of decanol (30% decanol- $\alpha$ -*d*<sub>2</sub>). The decanol- $\alpha$ -*d*<sub>2</sub> was synthesized by reduction of the ethyl ester with LiAlD<sub>4</sub>. Between 5 and 8 mg of amide, depending on its molecular weight, was dissolved in 0.6 mL of mesophase, and transferred to the NMR tube. A volume of approximately 15 mL of liquid crystal was obtained from one preparation to avoid differences in mesophase composition.

**NMR Experiments.** All NMR spectra were obtained at 300 K on a Bruker AMX-300 spectrometer belonging to the Centro de Equipamiento Mayor (CEM) Facultad de Ciencias, Universidad de Chile. Proton spectra were obtained from the <sup>1</sup>H channel of a broad-band probe, and deuterium spectra were recorded employing the X channel tuned to the <sup>2</sup>H frequency. A 30 kHz spectral window, 32 kB file size and 10  $\mu$ s pulse length (30° flip angle), at a rate of 30 pulses/s, were employed when measuring the <sup>2</sup>H spectra. More than 10 000 transients were acquired to obtain a signal/noise ratio greater than 20 for the smallest peak. The experimental errors in the measured quadrupole splittings were  $\pm 2$  Hz for HDO,  $\pm 10$  Hz for the ortho and meta deuterium nuclei,  $\pm 40$  Hz for decanol- $\alpha$ -*d*<sub>2</sub>, and  $\pm 70$  Hz for the para deuterium nucleus. These errors have been propagated to the values of the order parameters and the standard deviations calculated.

## Results and Discussion

Figure 2 shows the <sup>2</sup>H NMR spectrum of D-C<sub>7</sub> dissolved in the CsD-L-Ala lyomesophase. <sup>2</sup>H quadrupole splittings from decanol- $\alpha$ -*d*<sub>2</sub>, HDO, and the ortho, meta, and para positions of the aromatic ring can be measured directly from the spectrum. Only one set of splittings was observed for each experiment, a clear evidence that the *E*/*Z*-conformational equilibrium around the peptide linkage, observed in micelles of sodium *N*-dodecanoyl-L-prolinate and sodium *N*-dodecanoyl-*N*-methylglycinate, is not detected in our system.<sup>31,32</sup> The fact that the splittings from the ortho and meta positions were never resolved suggests a rapid rotation around the ring torsion angle of the guest molecules. The splittings from the para positions in L-C<sub>10</sub> and D-C<sub>10</sub> were not observed. It was assumed that the signal is completely overlapped by the peak from decanol- $\alpha$ -*d*<sub>2</sub> and that value was used in the order parameter calculations. All the experimental results obtained in this work, including the splittings of the mesophase components without any dissolved guest molecule, are listed in Tables 1 and 2. As may be seen from these tables, the



**Figure 2.** <sup>2</sup>H NMR spectrum of D-*N*-heptanoyl-1-phenyl-2-aminopropane dissolved in CsD-L-Ala mesophase. The central doublet arises from HDO, the next external doublet comes from the ortho and meta positions of the aromatic ring, the smallest pair of signals arises from the para position and the external splitting corresponds to decanol- $\alpha$ -*d*<sub>2</sub>.

**Table 1.** L-Amide Splittings

no. of carbons	$\Delta\nu_{\text{HDO}}$	$\Delta\nu_{\text{DeOH}}$	$\Delta\nu_{\text{ortho}}$	$\Delta\nu_{\text{meta}}$	$\Delta\nu_{\text{para}}$
1	183.1	10 518	1323	1323	-6645
2	173.7	10 426	1304	1304	-6679
3	176.4	10 660	1375	1375	-5643
4	210.0	11 760	1776	1776	-6280
5	212.4	12 100	2153	2153	-6789
7	226.6	12 744	2488	2488	-10043
10	226.6	12 375	2655	2655	-12375
pure phase	178.3	10 643			

**Table 2.** D-Amide Splittings

no. of carbons	$\Delta\nu_{\text{HDO}}$	$\Delta\nu_{\text{DeOH}}$	$\Delta\nu_{\text{ortho}}$	$\Delta\nu_{\text{meta}}$	$\Delta\nu_{\text{para}}$
1	175.5	10 529	1394	1394	-6233
2	169.8	10 128	1360	1360	-6063
3	186.2	10 904	1529	1529	-5596
4	182.5	10 750	1745	1745	-5729
5	204.5	11 760	2218	2218	-7055
7	237.6	12 967	3234	3234	-10259
10	237.6	12 850	2660	2660	-12850
pure phase	178.3	10 643			

quadrupole splitting from DHO for the short chain derivatives remains constant, about 180 Hz, practically the same value as in the absence of added guest molecule. However, for intermediate and long chain derivatives it increases to about 220 Hz. The same behavior is observed for the quadrupole splitting of decanol- $\alpha$ -*d*<sub>2</sub>. This phenomenon is observed in both series of amide isomers. It may be attributed to two factors: the incorporation of the added molecule either induces modifications in the aggregate size or produces modifications in the internal dynamics of the interface, or both. The fact that the amount of added guest molecule is rather low, 5 mg in about 300 mg of amphiphilic molecules, suggests that this observation could arise mainly from modifications in the internal dynamics of the aggregate.

The quadrupole splittings from the ortho, meta, and para positions of the aromatic rings reveal that both series of molecules are significantly attached to the aggregate. From these experimental splittings it is possible to calculate the two order parameters,  $S_{xx}$  and  $S_{yy}$ , necessary to completely describe the average orientation of the aromatic ring.  $S_{zz}$  can be evaluated from the traceless condition of the order parameter matrix. Using previously reported values for the aromatic deuterium quadrupole

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**Table 3.** L-Amide Order Parameters

no. of carbons	$S_{xx}$ (st dev $\times 10^5$ )	$S_{yy}$ (st dev $\times 10^4$ )	$S_{zz}$ (st dev $\times 10^4$ )	$S_{yy}/S_{xx}$
1	0.016 28 (9.5)	-0.026 29 (2.3)	0.010 00 (3.3)	-1.6144
2	0.016 38 (9.6)	-0.026 65 (2.3)	0.010 27 (3.3)	-1.6274
3	0.014 93 (9.4)	-0.022 07 (2.3)	0.007 14 (3.2)	-1.4784
4	0.016 19 (8.5)	-0.022 30 (2.1)	0.006 10 (3.0)	-1.3769
5	0.018 06 (8.3)	-0.023 46 (2.0)	0.005 40 (2.8)	-1.2989
7	0.022 40 (7.9)	-0.032 86 (1.9)	0.010 46 (2.7)	-1.4671
10	0.026 61 (8.1)	-0.041 63 (1.9)	0.015 02 (2.7)	-1.5645

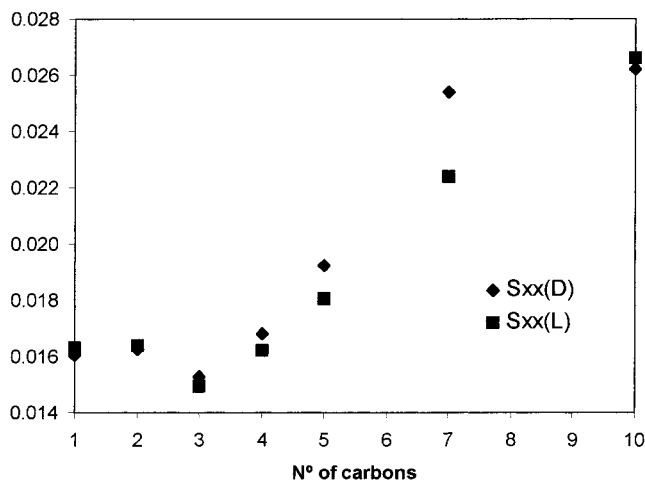
**Table 4.** D-Amide Order Parameters

no. of carbons	$S_{xx}$ (st dev $\times 10^5$ )	$S_{yy}$ (st dev $\times 10^4$ )	$S_{zz}$ (st dev $\times 10^4$ )	$S_{yy}/S_{xx}$
1	0.016 05 (9.5)	-0.024 66 (2.2)	0.008 61 (3.2)	-1.5364
2	0.016 25 (9.9)	-0.024 93 (2.3)	0.008 68 (3.3)	-1.5342
3	0.015 30 (9.2)	-0.021 42 (2.2)	0.006 12 (3.1)	-1.4000
4	0.016 79 (9.3)	-0.022 27 (2.2)	0.005 48 (3.1)	-1.3264
5	0.019 22 (8.5)	-0.025 08 (2.0)	0.005 86 (2.9)	-1.3049
7	0.025 39 (7.7)	-0.033 08 (1.8)	0.007 69 (2.6)	-1.3029
10	0.026 20 (7.8)	-0.041 62 (1.8)	0.015 42 (2.6)	-1.5885

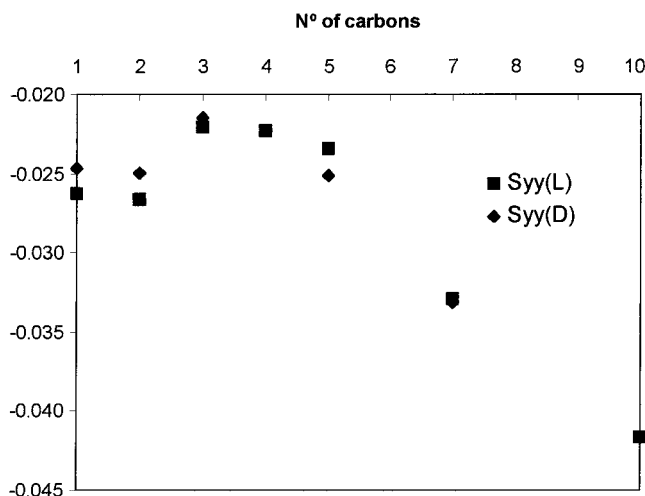
coupling constant ( $Q=185$  kHz) and electric field gradient at the deuterium nucleus ( $\eta=0.05$ ), we have calculated the order parameters of the ring.<sup>28,33</sup> Geometrical information necessary for the evaluation of these parameters was obtained from AM1-MO full geometry optimization of all derivatives.<sup>34</sup> The AM1 calculated angles differ by less than 0.06% from the ideal values, and since the order parameters are practically insensitive to these differences, the ideal values were used. With this information, a detailed picture about the reorientational dynamics of the aromatic ring in the aggregate can be obtained. As noticed before, there is a significant effect of the added guest molecule on the size and/or dynamics of the aggregate. For this reason, the calculation of order parameters using the measured splittings directly may not reveal clearly the process of incorporation. Instead, with the purpose of obtaining order parameters that provide information in the absence of this particular effect, we have first normalized the experimental quadrupole splittings from the ortho, meta, and para positions, dividing these values by the splitting of decanol and multiplying them by the average value of the decanol splitting along the series. From these normalized splittings, independent from the particular effect of each added guest molecule on the integrity of the aggregate, the order parameters  $S_{xx}$  and  $S_{yy}$  were calculated. All the calculated values and their standard deviations are shown in Tables 3 and 4, and graphic representations of these results are shown in Figures 3 and 4. To distinguish a true reorientational process from an overall increase in order parameters, resulting from the molecular mass increment, Tables 3 and 4 also include a column to display the  $S_{yy}/S_{xx}$  ratio.  $S_{xx}$  mainly represents the reorientational behavior of the torsional coordinate of the ring, whereas  $S_{yy}$  mostly represents the average alignment of its  $C_2$  local symmetry axis. An order parameter may range from  $-0.5$ , for an axis oriented perpendicular to the magnetic field, to  $+1.0$ , for an axis oriented parallel to the magnetic field. The value 0.0 corresponds to a freely rotating axis or an axis oriented at the magic angle. Further evidence for the fast rotational dynamics of the ring torsion is obtained by comparing the absolute values of  $S_{xx}$  and  $S_{zz}$ , affected by the torsional dynamics, with the absolute value of  $S_{yy}$ . The latter is significantly larger.

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**Figure 3.** Normalized order parameters along the X molecular axis of the aromatic ring of L-N-acyl-1-phenyl-2-aminopropanes (■) and D-N-acyl-1-phenyl-2-aminopropanes (◆), dissolved in CsD-L-Ala mesophase as a function of the acyl chain.



**Figure 4.** Normalized order parameters along the Y molecular axis of the aromatic ring of L-N-acyl-1-phenyl-2-aminopropanes (■) and D-N-acyl-1-phenyl-2-aminopropanes (◆), dissolved in CsD-L-Ala mesophase as a function of the acyl chain.

From the  $S_{yy}/S_{xx}$  ratio it is clear that there exists a significant modification of the alignment among the different samples, in both series of isomers. Moreover, from Tables 3 and 4 it may be seen that the first two derivatives, D- and L-C<sub>1</sub> and D- and L-C<sub>2</sub>, have very similar sets of order parameters in both series. This result strongly suggests that these molecules are located in the same region of the mesophase, not in close proximity to the asymmetric carbons, but possibly near the interface forming H bond between the amino and/or carbonyl groups and the interstitial water molecules. Attractive dipolar and van der Waals interactions between similar groups, present in the guest molecule and in the interface of the mesophase, cannot be discarded. The small differences observed in the  $S_{yy}$  values for some derivatives can be partly attributed to the large error in the quadrupole splittings from the para position, due to the poor signal-to-noise ratio because of the greater line width. As the acyl chain increases in length, the hydrophobic effect of the guest molecule increases, and the H bond with the interstitial water molecules is disrupted by the tendency of the acyl chain to become more incorporated into the superstructure of the aggregate. These two processes should be competitive for C<sub>3</sub>, and the result is a decrease

in the overall alignment due to a reorientational phenomenon induced by the acyl chain hydrophobicity. As the acyl chain increases, the molecule is progressively more incorporated into the aggregate and for C<sub>4</sub> and longer chain derivatives there is an increasing differentiation in the incorporation process. This phenomenon is fundamentally manifested in the increasing difference in the values of  $S_{xx}$  between both series of isomers. This difference increases up to C<sub>7</sub>, suggesting that these molecules should be located such that the asymmetric carbons are close in space. Effects attributed to molecular chirality are found to be short distance range phenomena.<sup>35</sup> Further increase in the hydrophobicity of the guest molecule forces the structure to become more incorporated in the hydrophobic region of the aggregate, in a position where both asymmetric carbons no longer lie close to each other. In this location there is no differentiation between both isomers, as observed for the order parameters of C<sub>10</sub>. The same differentiation process is not clearly observed for  $S_{yy}$ , where the values are similar for both isomers along the complete series. This parameter  $S_{yy}$  mainly reflects the behavior of the quadrupole splitting from the para position, the one

(35) Olsson, U.; Wong, T. C.; Söderman *J. Phys. Chem.* **1990**, *94*, 5356.

with the largest experimental error. Our results indicate that the torsional coordinate of the ring is clearly more sensitive to the chiral nature of the interface, showing that this motion is more restricted in the D-series than in the L-series. Since the order parameters are composite properties, these results could also be interpreted in terms of a difference in the average orientation of the X symmetry axis of the ring with respect to the direction of the magnetic field. Particularly for intermediate chain derivatives, the average angle between the X axis of the ring and the magnetic field direction should be closer to the magic angle in the L-series than in the D-series. The small differences between the  $S_{yy}$  order parameters suggest that the reorientational motion or the average orientation of the symmetry axis of the ring is very similar for both series of isomers. Finally, an inspection of Table 2 reveals that the  $S_{yy}/S_{xx}$  ratio keeps changing for the long-chain derivatives. This reveals that the overall alignment of the ring is still being modified by the increase of the acyl chain.

**Acknowledgment.** The authors are pleased to acknowledge financial assistance from FONDECYT, Grant 1980838.