# Degree of Order of Lamellar and Hexagonal Mesophases with and without Cholesterol Additions

**F. Y. Fujiwara and L. W. Reeves***

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**Abstract:** Synthesis of specifically deuterated decylammonium salts has been followed by the preparation of nematic type II lyotropic phases of ternary and quaternary composition: (a) decylammonium salt, $D_2O$ plus an electrolyte, (b) and phases of type (a) but with added cholesterol. The type II phases are oriented in a magnetic field with the nematic axis perpendicular to the field. Deuterium, $^{11}B$, and $^{35}Cl$ magnetic resonance spectra of these oriented phases are of single crystal type with first order quadrupole splittings. The deuterium magnetic resonance spectra of $-CD_2-$, $-CD_3$, and $-ND_3^+$ segments have been studied in detail as a function of the composition of phases and temperature. The degree of order profile at constant temperature and composition along the C-D bond axes shows an alternating effect near the head group, a small decrease between carbon 5 and 8, and a rapid decrease at the final $-CD_2-CD_3$ group. The ratio of quadrupole couplings for deuterium at the head $-ND_3^+$ group to any other chain position remains constant when the water content is varied. These ratios are only slightly temperature dependent but are very sensitive to the nature of the counterion. There is a linear dependence between the $^2D$ quadrupole splittings in the aqueous $D_2O$ region and the $^{35}Cl$ splittings of the counterion to the head group $-ND_3^+$ quadrupole splittings. The addition of cholesterol has a stabilizing effect on the nematic phase and also produces a change in the ratios of the deuterium quadrupole splittings of the chain segments which is consistent with an increase in the population of the all-trans chains. The microdegrees of order of the hydrophobic chains can be linked to the macroscopic nematic order of the phase by considering the following motions: rapid rotation of the extended chain about the long axis; segmental rotations in the chain of the trans/gauche type; overall oscillatory motion of the extended chain about the perpendicular directrix to the electrical double layer; small oscillatory motions of the cylinders of the hexagonal nematic phase; rapid diffusion of the chain around the cylindrical superstructure surface; and partial or complete exit and insertion motions out of and into the cylindrical hydrophobic region. A satisfactory account of the effect of these rapid motions on the order parameters can be made in terms of the extensive experimental data presented here.

Lyotropic liquid crystals (mesophases) have been known since the end of the last century[1] but the lack of sophisticated tools to investigate their structure has retarded our knowledge of them compared to the better understood thermotropic liquid crystals.[2,3] Low-angle x-ray diffraction studies were not completed until the late 1950's and these have been extended in studies which continue to be made up to the present time.[4-8] Superstructure arrays of cylindrical or lamellar form are determined by the well known hydrophobic effect which has played an important role in the development of colloid chemistry.[9] All lyotropic liquid crystals can be divided into essentially three regions in the superstructure arrays: (a) an aqueous compartment which contains small counterions and may contain added balanced electrolytes, (b) an electrical or polar double layer interface with ionic or polar head groups which is structurally complex at the molecular and ionic level, (c) the hydrocarbon chains of the detergents or lipids. This last region can be shown to vary in local organization and crystallinity[3,10] by a variety of techniques. It is surprising that magnetic fields, which can order nematic type lyotropic liquid crystals,[11] have not been used in conjunction with low-angle x-ray studies.

Following an early study of motional effects in molecular solids by Gutowsky and Powles,[12] Phillips and co-workers[13] investigated the motion of single molecules in the liquid crystalline state of *p*-azoxyanisole by observing the deuterium resonance of specifically deuterated samples in both ring and methyl positions. The degree of orientation of a molecular axis was related to the deuterium quadrupole coupling constant of the labeled positions. It was assumed that the quadrupole coupling of deuterium nuclei in a C-D bond is described by a single electric field gradient along the C-D bond axis. In cases where the tensor has been measured,[14] the asymmetry parameter was not found to be large, though neglect of this does introduce a source of error. The use of deuterium substitution in hydrocarbon chains of lyotropic liquid crystals was first reported by Oldfield, Chapman, and Derbyshire[15] in a deuterium magnetic resonance study of phospholipid water mixtures in the randomly oriented lamellar phase regime. Later studies were reported for lyotropic systems by Charvolin and Rigny,[16] Seelig and co-workers,[17] and Reeves and co-workers.[18] In lamellar phases oriented between glass plates or hexagonal phases[17,19] oriented in a magnetic field the deuterium spectra can be of high resolution quality, if protons are decoupled during the experiment. A recent systematic study of the effect of counterions on the hydrocarbon chain motion[19] has revealed a strong dependence of the deuterium quadrupole coupling ratios on counterion and head group.[19]

The deuterium quadrupole splittings, in chain segments which in homogeneously ordered systems can be measured with considerable precision, show promise as a tool for studying the chemistry of the interface[18,19] in these phases. The purpose of the present study is to considerably enlarge the knowledge of these ratios with respect to the effect of ions and cholesterol additions. The present investigation seeks also to compare degree of order profiles in hydrocarbon chain regions for hexagonal and lamellar phases. The phases reported here are birefringent with the unique medium axis oriented perpendicular to the magnetic field. We have previously designated these phases as type II nematic phases.[20]

## Experimental Section

**Materials.** 1,1-Dideuteriodecylamine was prepared from nonylnitrile by lithium aluminum deuteride reduction.[21] 2,2-Dideuteriodecanal, which was obtained by refluxing decanal with $D_2O$ and pyridine, was converted to the oxime then reduced with sodium in ethanol to yield 2,2-dideuteriodecylamine.

2,2,3,3-Tetradeuteriodecylamine and 3,3,4,4-tetradeuteriodecylamine were prepared from 2-decyn-1-ol and 3-decyn-1-ol, respectively. The deuterated alcohols, obtained after reduction with deuterium over Adam's catalyst, were converted to the decylbromides[22] and then converted to the decylamines by means of the phthalimide complexes.[23]

10,10,11,11,11-Pentadeuterioundecanoic acid was prepared from 10-undecynoic acid by the following procedure. The acid was converted to the potassium salt and the acetylenic hydrogen was replaced with deuterium by a base-catalyzed exchange with $D_2O$.[24] The resulting 11-deuterio-10-undecynoic acid was reduced with deuterium

**Table I.** Ratios of the Deuterium Quadrupole Splittings for Various Positions in the Decylammonium Chains in Mesophases Containing the Decylammonium Chloride, Tetrafluoroborate, or Fluoride Salt

| Ratio | $Cl^-$ | $Cl^-$ with added cholesterol[a] | $BF_4^-$ | $F^-$ |
|---|---|---|---|---|
| $\Delta\nu_1/\Delta\nu_{ND}$ | 2.325 ± 0.015 | 2.42 ± 0.01 | 1.97 ± 0.05 | |
| $\Delta\nu_2/\Delta\nu_{ND}$ | 2.113 ± 0.016 | | | |
| $\Delta\nu_3/\Delta\nu_{ND}$[b] | 2.171 ± 0.017 | | | |
| $\Delta\nu_4/\Delta\nu_{ND}$[b] | 1.919 ± 0.039 | | | |
| $\Delta\nu_9/\Delta\nu_{ND}$ | 1.215 ± 0.020 | 1.57 ± 0.02 | 0.994 ± 0.008 | |
| $\Delta\nu_{10}/\Delta\nu_{ND}$ | 0.283 ± 0.006 | 0.309 ± 0.005 | 0.204 ± 0.004 | |
| $\Delta\nu_9/\Delta\nu^{10}$ | 4.296 ± 0.017 | 4.02 ± 0.01 | 4.63 ± 0.05 | 4.46 ± 0.01 |

[a] Mol % [cholesterol]/[DACl] = 9.20%. [b] Determined from the average value of $\Delta\nu_2$ and $\Delta\nu_3$ and of $\Delta\nu_3$ and $\Delta\nu_4$.

over Adams' catalyst in dioxane and part of the resulting undecanoic acid-$d_5$ was also labeled in the $\alpha$ position by exchange with $D_2O$.[25] The deuterium labeled undecanoic acids were converted to decylamine by the Schmidt reaction.[26]

The chloride, fluoride, and tetrafluoroborate decylammonium salts were prepared by neutralizing decylamine with the appropriate acid. The decylammonium chloride and fluoride salts were recrystallized twice from ethanol/petroleum ether; the tetrafluoroborate salt was recrystallized from ethyl acetate. All salts were dried for several days under vacuum.

Cholesterol, supplied by The British Drug House, was recrystallized from absolute ethanol and dried under vacuum.

**Composition of the Nematic Phases.** Lyotropic liquid crystalline phases, which were found to homogeneously orient in a magnetic field, were prepared with the following compositions. The decylammonium chloride phases contained, by weight, 37 parts decylammonium chloride, 4 parts ammonium chloride, and from 54 to 69 parts $D_2O$. The decylammonium tetrafluoroborate phases contained 49 parts decylammonium tetrafluoroborate, 4 parts ammonium tetrafluoroborate, and from 43 to 54 parts $D_2O$. Only two phases containing the fluoride salt were prepared with the following compositions: (a) 57.6 wt % $D_2O$, 37.7% decylammonium fluoride, and 4.7% ammonium fluoride; and (b) 57.1% $D_2O$, 37.9% decylammonium fluoride, and 5.0% ammonium fluoride. In most samples containing the decylammonium chloride and tetrafluoroborate salts, $D_2O$ containing 0.1 N HCl was used to slow down the exchange between $D_2O$ and the decylammonium and ammonium ions.

**NMR Measurements.** NMR spectra were obtained mainly on a Varian VF16 wide-line spectrometer equipped with a 10-kG magnet. A Schomandl ND30M frequency synthesisor was used to drive the rf unit of the VF 16 and spectra were calibrated by changing the frequency setting of the synthesisor at the termination of a spectrum while still sweeping the magnetic field in order to repeat the spectrum at a second or third calibrated frequency. The spectra were recorded as the derivative of the absorption mode on a Hewitt Packard Model 7004A X-Y recorder. Four to six spectra were obtained for each sample which was contained in 9 or 14 mm i.d. sample tubes.

Some $^2H$ and $^{11}B$ spectra were obtained on a Varian HR60 spectrometer at 7.95 and 15.1 MHz, respectively, when higher resolution or sample spinning was required. The audio frequency sideband technique was used to calibrate the spectra.

## Results

**(a) Studies of Deuterated Hydrocarbon Chains, $D_2O$, and Counterions.** The deuterium magnetic resonance spectra of the type II[20] nematic phases prepared for this study consist of a series of doublets originating from incompletely averaged nuclear quadrupole coupling constants. The decylammonium chloride mesophases were prepared with deuterium on carbons 1, 2, 2 and 3, 3 and 4; or 9 and 10 of the decylammonium chain in separate series. In this manner no ambiguity arose in assigning the doublets to specific $-CD_2-$ groups. Samples with deuterium on both carbons 2 and 3 or 3 and 4 could not be resolved and the average values were observed. The apparent line width of the deuterium signals is dominated by the direct intramolecular dipole-dipole couplings to the hydrogens[27] and for the $-CD_2-$ resonance at carbon 2 the line width between the inflection points was in the range 700 to 1000 Hz.

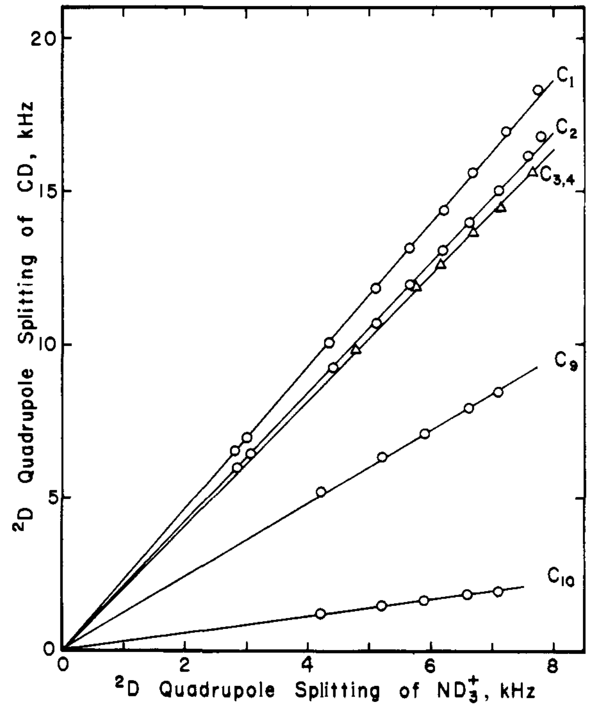

**Figure 1.** Deuterium nuclear quadrupole splittings $\Delta\nu_n$ for the $n$th carbon in decylammonium ion for nematic lyotropic phases as a function of the corresponding doublet splitting for the head group $-ND_3^+$. The results were obtained for decylammonium chloride/ammonium chloride/$D_2O$ mesophases measured at 30.3 ± 0.4 °C.

The mesophases had the same composition ranges and were all observed at the same temperature 30.3 ± 0.4 °C. The $D_2O$ component of the phase was acidified sufficiently with hydrochloric acid to place the chemical exchange rate between the $-ND_3^+$ head group and the $D_2O$ in the slow exchange region for NMR studies.

In Figure 1 the quadrupole splitting, $\Delta\nu$, for each $-CD-$ group studied is plotted against the quadrupole splitting for the head group $-ND_3^+$. Over the range of stable nematic type II behavior the plots are linear for each position studied in the chain. The ratios of all quadrupole couplings one to another are independent of the water content for a constant decylammonium chloride/ammonium chloride ratio. The extrapolation to zero splitting for each chain $-CD_2-$ group accurately reproduces zero splitting for the head $-ND_3^+$ group. In Table I, the ratios of the quadrupole splittings are presented and the errors quoted are the standard deviations determined from six to twelve samples. The ratios involving deuteriums on carbons

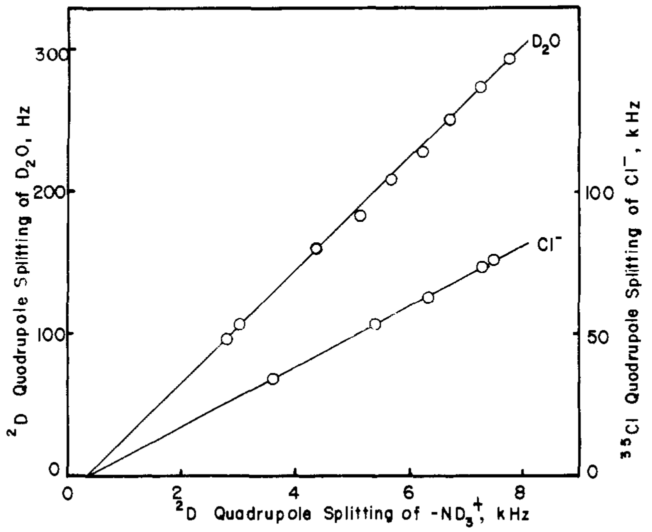

Figure 2. The dependence of the $^2$D quadrupole splitting of $D_2O$ and the $^{35}$Cl quadrupole splitting of $Cl^-$ on that of the ionic head group $-ND_3^+$. The $^{35}$Cl quadrupole splittings are taken as the separation of adjacent peaks in the triplet spectrum.

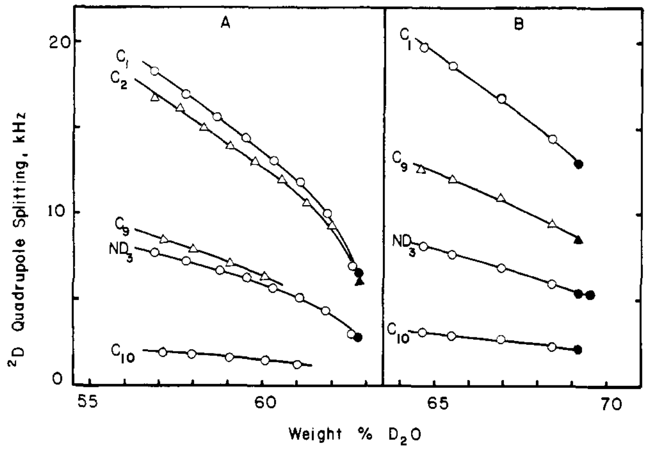

Figure 3. The dependence of the partially averaged deuterium quadrupole couplings on the weight percent of water in nematic phases. In part A the curves correspond to a ternary phase with decylammonium chloride/ammonium chloride/$D_2O$ and in part B the mesophases were modified by adding 9.20 mol % cholesterol to the detergent ratio. The solid points refer to samples containing a two-phase nematic–isotropic region.

3 and 4 were determined from the measured ratio of the average quadrupole splitting of deuteriums on carbons 2 and 3 to that of the $-ND_3^+$ group which was 2.142 ± 0.011 and the corresponding ratio for the average value of the quadrupole splitting of deuterium on carbons 3 and 4 which was 2.045 ± 0.014.

The dependence of the splitting of the water doublet on the $-ND_3^+$ deuterium quadrupole coupling for the phases reported in Figure 1 is shown in Figure 2. The least-squares straight line does not pass through zero coupling for the $-ND_3^+$ group, but an intercept of +0.4 kHz can be measured.

The $^{35}$Cl spectrum of the chloride ion consists of a triplet with intensity ratio 3:4:3 arising from an incompletely averaged quadrupole coupling constant. In Figure 2 the $^{35}$Cl nuclear quadrupole splitting, observed for the chloride ion in a set of the phases, is plotted versus the head group $-ND_3^+$ deuterium splitting. These quadrupole splittings for the $^{35}$Cl are taken as the separation of adjacent peaks of the triplet spectrum. It is interesting that (Figure 2) the $^{35}$Cl quadrupole coupling also becomes zero at an intercept of 0.4 kHz for the $-ND_3^+$ splitting. The division between hydrophobic and aqueous compartments of these phases is manifest in this extrapolated discontinuity in the ordering each side of the electrical double layer. In Figure 3A the dependence of each measured splitting in the chain is plotted against the water content of the phases. At lower $D_2O$ contents the dependence is linear on weight percent of water but a more rapid nonlinear fall of the splittings is seen on approaching the appearance of a two-phase isotropic/nematic system. At the temperature 30.3 ± 0.4 °C the two-phase region occurs at 62.7 wt % water.

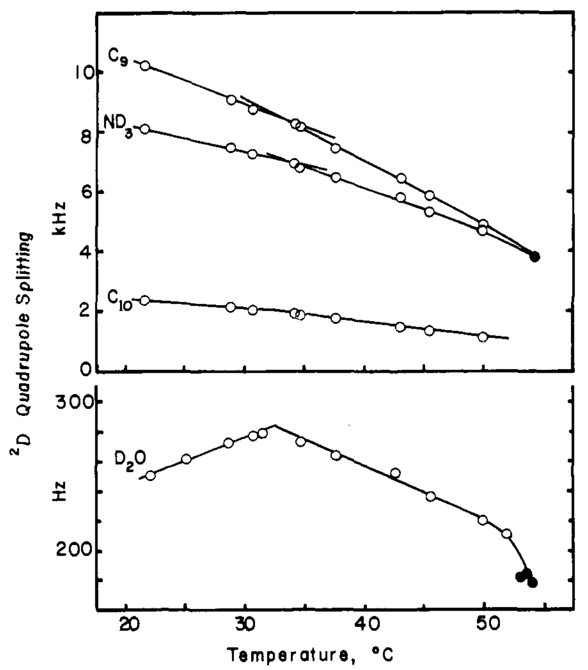

Figure 4. Deuterium quadrupole splittings from the detergent chains and from $D_2O$ as a function of temperature for a nematic phase whose composition is described in the text. The solid points refer to a two-phase nematic/isotropic region.

A phase prepared from 9,9,10,10,10-pentadeuteriodecylammonium chloride of the following composition—DACl 38.32 wt %, $D_2O$ 57.53%, and $NH_4Cl$ 4.14%—was carefully studied as a function of temperature. In Figure 4 the deuterium quadrupole couplings for the $-ND_3^+$, $-CD_2-$, and $-CD_3$ groups are represented as a function of temperature. The phase remained nematic up to 53 ± 0.5 °C. The dependence of the deuterium couplings in the detergent ion has two distinct linear regions. Below 32 ± 2 °C the linear dependence on temperature is less steep for all chain positions. The subtle break in the temperature dependence is indicative of a change in phase at 32 °C and this identifies all measurements reported in earlier figures as being made on the phase stable below this transition temperature. In Figure 4 a dramatic break can be observed for the dependence of the $D_2O$ doublet on temperature. In this case there is a change in the sign of the slope of the temperature dependence at 32 °C, the transition temperature. The phase change at 32 °C is not reflected in the ratios of the quadrupolar splittings in the decylammonium ion. The ratio $\Delta\nu_9/\Delta\nu_{10}$ remains constant, within the experimental uncertainty, over the complete temperature range studied while the ratio $\Delta\nu_9/\Delta\nu_{ND}$ decreases linearly from 1.26 ± 0.01 at 21.7 °C to 1.10 ± 0.01 at 45.4 °C and the ratio $\Delta\nu_{10}/\Delta\nu_{ND}$ decreases from 0.290 ± 0.002 to 0.255 ± 0.003 over the same temperature range.

A series of phases were prepared using decylammonium tetrafluoroborate with added ammonium tetrafluoroborate electrolyte. Measurements at 29.9 ± 0.1 °C of the quadrupole splittings of $-CD_2CD_3$, $-CD_2ND_3^+$, $D_2O$, $ND_4^+$, and $^{11}BF_4^-$ were made. The ratios of the splittings in the hydrocarbon chain were independent of the water content but were changed by a counterion effect, even down to the end groups. These ratios are presented in Table I. Deuterium quadrupole splittings in the range 4.48 to 8.15 kHz were observed for the $-ND_3^+$ group. A linear dependence with a positive slope was observed between the $^2D$ quadrupole splittings of the $-ND_3^+$ group and the $^2D$ quadrupole splittings of the $D_2O$ and $ND_4^+$ as well as the $^{11}B$ quadrupole splitting of $BF_4^-$. A comparison o the $^{11}B$ splittings with the boron-fluorine and fluorine-fluorine dipole-dipole spin couplings has been previously reported.[28] The range of values observed for the quadrupole splitting of $D_2O$ was from 141 to 293 Hz which is similar to that in the decylammonium chloride mesophase. However, the deuterium quadrupole splittings for the $ND_4^+$ ion in the tetrafluroborate mesophase were in the range 50 to 102 Hz compared with values of approximately 7 Hz for the decylammonium chloride mesophase.

The quadrupole splitting is observed for the $ND_4^+$ ion only if the ion is distorted from tetrahedral symmetry. Interactions with neighboring molecules will produce a net distortion along the nematic axis (the unique axis) because the ion is in an anisotropic environment. Consequently the differences in the quadrupole splittings of a given ion reflect the anisotropic motion of the surrounding molecules. The deuterium quadrupole splitting of the $ND_4^+$ ion in the decylammonium tetrafluoroborate mesophase is exceptionally large relative to that in the corresponding chloride mesophase. Since the average degree of order of the water is about the same in these two phases, the $ND_4^+$ ion must reside on the average in a region with a much higher microdegree of order.

Two phases prepared from decylammonium fluoride detergent gave a ratio $(\Delta\nu_9/\Delta\nu_{10}) = 4.46 \pm 0.01$ further illustrating an effect on the chain motions which accompanies the change in counterion. In this case acidification of the phase results in the formation of HF and separate measurement of the $D_2O$ and $-ND_3^+$ doublets was not possible.

**(b) The Effect of Added Cholesterol.** Cholesterol can be added to the nematic phase produced from decylammonium chloride/electrolyte/$D_2O$ without inducing phase transitions up to a mole ratio of cholesterol/detergent ~0.09-0.12, depending on water content. These amounts of a neutral molecule are not usually incorporated into this phase. Less than 0.5 wt % of decanol, for instance, induces a phase change to an extremely viscous birefringent material, which does not orient in the magnetic field. The addition of cholesterol increases all deuterium quadrupole splittings that have been observed for this phase including the $D_2O$ signal. The phases containing cholesterol will sustain the addition of more $D_2O$ before the appearance of a second isotropic phase. This neutral lipid has an important effect in man and forms part of most living membrane material. Experiments have been designed to quantify the effect of varying water and cholesterol content in terms of the partially averaged nuclear quadrupole coupling constants.

A sample containing 1.1098 g of decylammonium-*1,1,9,9,10,10,10-$d_7$* chloride, 0.1199 g of ammonium chloride, and 1.9890 g of $D_2O$ was subjected to five separate cholesterol additions containing mole ratios of [cholesterol]/[detergent] × 100 = 1.04, 1.79, 2.76, 3.65, and 4.65%. The deutrium quadrupole couplings for the detergent chain for these five samples and the uncontaminated phase are plotted against the mole ratios above, in Figure 5. Apart from a short nonlinear dependence at the lowest cholesterol contents the effect of the neutral lipid is to increase all doublet splittings in a linear fashion with added cholesterol.

The effect of water content on samples containing cholesterol was investigated with phases of 0.1967 g of cholesterol, 1.1098 g of decylammonium-$d_7$ chloride, 0.1199 g of ammonium chloride, and $D_2O$ weighings of 2.6067, 2.7067, 2.8813, 3.0872, and 3.3016 g. The mol % [cholesterol]/[detergent] × 100 = 9.2 for these phases. The lowest water content of the above series did surpass the point at which an isotropic phase appears and the following deuterium quadrupole splittings were observed for this sample: $\Delta\nu_{D_2O} = 121 \pm 1$ Hz, $\Delta\nu_{ND} = 5.35 \pm 0.02$ kHz, $\Delta\nu_1 = 12.95 \pm 0.02$ kHz, $\Delta\nu_9 = 8.40 \pm 0.01$ kHz, and $\Delta\nu_{10} = 2.10 \pm 0.02$ kHz. These results have been plotted in Figure 3B in order to compare them with the cholesterol-free phases. The ratios of the quadrupole splittings of the deuteriums on the decylammonium chain in these samples with a constant cholesterol:detergent ratio were found to be independent of the water content and are tabulated in Table I.

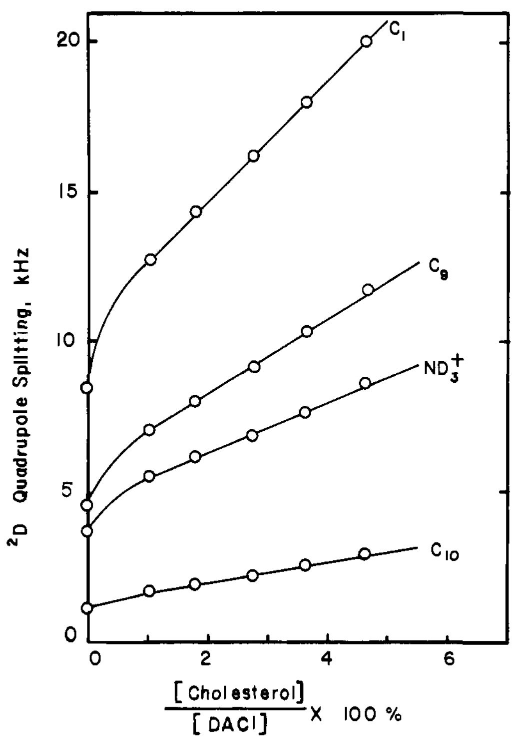

**Figure 5.** The effect of adding cholesterol to a decylammonium chloride mesophase. The quadrupole splittings from some decyl chain and the $-ND_3^+$ positions as a function of the mole percent [cholesterol]/[detergent]. Only the amount of cholesterol in each sample was varied.

Continuing the addition of cholesterol leads to the formation of a different mesophase which is probably a lamellar phase. These phases register spectra of powder pattern form for all signals. A sample of the following composition formed two layers of approximately equal volume at 30.8 °C, one isotropic, the lower layer, and the other lamellar: $D_2o$ 68.73 wt %, cholesterol 5.67%, decylammonium chloride 23.1%, and ammonium chloride 2.5%. The lamellar phase had the following NMR spectral parameters: $\Delta\nu_{D_2O} = 291 \pm 4$ Hz, $\Delta\nu_{ND} = 10.25 \pm 0.2$ kHz, $\Delta\nu_1 = 25.75 \pm 0.2$ kHz, $\Delta\nu_9 = 17.15 \pm 0.10$ kHz, and $\Delta\nu_{10} = 4.55 \pm 0.2$ kHz. The doublet separations were determined from the maxima and minima in the derivative spectrum. The separations were corrected according to an empirical formula used by Johansson and Drakenberg.[29]

$$\Delta\nu_c = \Delta\nu_{exp} - (0.36 \pm 0.05)\delta$$

where $\Delta\nu_c$ = corrected doublet separation, $\Delta\nu_{exp}$ = measured doublet separation, and $\delta$ = width at half-height of the largest peaks in the derivative spectrum. Corrections were of the order 0.25 kHz for the chain deuterium signals with a $\delta$ = 700 Hz. The powder pattern splittings represent those obtainable with the 90°, i.e. perpendicular, alignment of the optic axis to the magnetic field. In a later argument these figures for the lamellar phase can be related to those for the hexagonal phase.

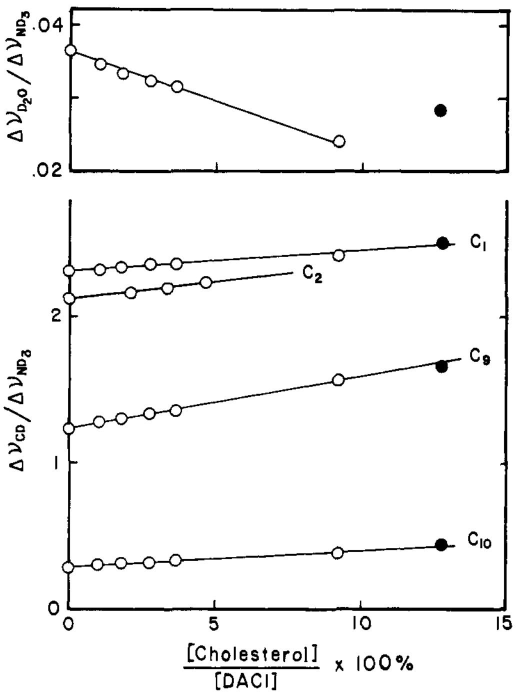

Figure 6. Ratios of deuterium quadrupole doublet separations for hydrocarbon chain segments and $D_2O$ to the head group $-ND_3^+$ splitting for mesophases with added cholesterol. The filled points correspond to a lamellar phase. Temperature of the experiment was 30.8 ± 0.4 °C.

In Figure 6 the ratios of the deuterium quadrupole splittings are plotted against the mole percent of [cholesterol]/[detergent]. In all cases there is little departure from a linear dependence; furthermore the composition of the lamellar phase is also included. The filled points fall on the extrapolated straight lines for the hexagonal phases except for the case of the $D_2O$ signal. It is possible to conclude that the hydrocarbon chains in hexagonal phases do not greatly modify their motions in passing to the lamellar phase. More substantial arguments for this result will be considered in the Discussion section.

## Discussion

**(a) The Motion of Hydrocarbon Chains in Hexagonal and Other Lyotropic Liquid Crystals. General Aspects.** The following motions form the basis of a model to define the relative or overall microdegrees of order measurable from NMR studies in lyotropic hexagonal phases.

(1) Overall rotation of hydrocarbon chains about their long axes in the extended form including independent rotation of end methyl groups.

(2) Segmental motions of the trans gauche type arising from rotations about specific or several carbon-carbon bonds.

(3) Overall movement of the long axis of the chain in an oscillatory fasion about the perpendicular to the electrical double layer interface and/or actual oscillation of the whole cylinder of the superstructure which represents an oscillation of the perpendicular directrix to the magnetic field direction. Both of these may occur but are indistinguishable in their effect of NMR spectra.

(4) Diffusion of the head group in the hydrophobic/water interface. This introduces the possibility of motions of the head group along a direction parallel to the cylindrical superstructure of the hexagonal phase and in a direction perpendicular to the cylinder axis, i.e., a rotation of the head group around the cylinder.

(5) Partial or complete exit and insertion motions of the chain out of and into the cylindrical hydrophobic region. This is a motion parallel to the extended chain axis, perpendicular to the interface in both positive and negative senses. This motion for any extensive exit of the head group from the surface must be accompanied by additional chain buckling in terms of motions of type (2). Complete exit, as may be possible for short chain molecules dissolved in a long chain bilayer matrix, would mean an equilibrium between random and isotropic coiling in the aqueous layer and some ordering in the hydrophobic region.

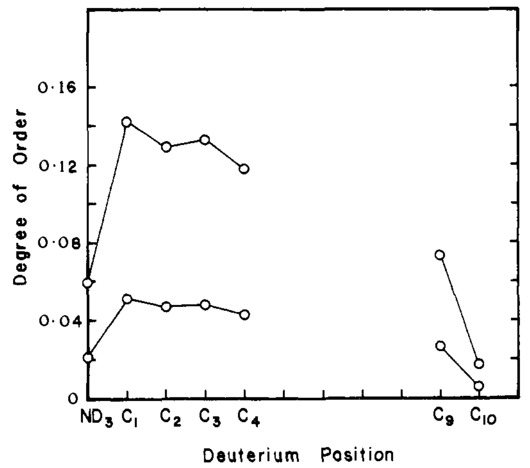

Figure 7. The degree of order of deuterium bonds in the decylammonium ion in hexagonal phases determined from $^2D$ quadrupole splittings. The upper points joined by straight lines correspond to the maximum values and the lower points refer to the minimum values observed in the nematic region for the decylammonium chloride mesophase (without cholesterol) at 30.3 ± 0.4 °C.

The principal axis of the electric field gradient at the deuterium nucleus in a C-D bond is close to the C-D bond axis and will be assumed here to be along it.[30,31] With the assumption that the asymmetry parameter "$\eta$" for this coupling is zero, the doublet separation "$\Delta\nu_i$" in hertz observed in spectra is given by:[32]

$$\Delta\nu_i = \frac{3}{2}\frac{e^2qQ}{h}S_i\tfrac{1}{2}(3\cos^2\Omega - 1) \qquad (1)$$

where $(e^2qQ/h)$ is the deuterium quadrupole coupling constant and $S_i = \frac{1}{2}(3\cos^2\alpha - 1)$. "$\alpha$" is the angle between the symmetry axis (the director) direction of the phase and the C-D bond axis which becomes averaged over the inter- and intramolecular motions. The subscript "$i$" refers to a labeled deuterium site in the chain, and $\Omega$ is the angle between the director and the magnetic field direction.[33]

In Figure 7, the maximum and minimum values of $S_i$ observed for the deuterium positions on the decylammonium chloride chain are shown. Deuterium quadrupole coupling constants of 170 and 176.7 kHz were used for the C-D[30,31] and N-D[35] bonds, respectively. The starting point for discussing the motional types (1) to (5) listed above is the position of the extended chain with the ionic head group in the interface and the cylinder axis on the average perpendicular to the applied field.

**Type (1) Motions.** The rotation of hydrocarbon chains about their extended long axes is known to have a very short correlation time on a time scale appropriate to the Larmor frequency.[34] $S_i$ can be resolved into various contributions when the C-D vector rotates simultaneously about several axes with correlation times $\tau < \frac{1}{2}\pi\Delta\nu$.[12] For the methylene groups the degree of order of the C-D bond can be expressed as

$$S_i = \tfrac{1}{2}(3\,\overline{\cos^2}\,\gamma_i - 1)S_{zz} \qquad (2)$$

where $\gamma_i$ is the angle between the C-D vector and the $zz$ axis shown in Figure 8A which joins the midpoints of the C–C bonds in an extended chain. $S_{zz} = \frac{1}{2}(3\,\overline{\cos^2\beta} - 1)$ and $\cos^2\beta$, where $\beta$ is the angle between the $zz$ axis and the director is averaged over the molecular motions of the $zz$ axis.

The terminal $-CD_3$ and $-ND_3^+$ groups have an additional independent rotational motion and the associated deuteriums are always distinguished by having a smaller quadrupole splitting than the rest of the chain. The degree of order of the deuterium bonds in the $-ND_3^+$ terminal group can be expressed as[12]

$$S_{ND} = \tfrac{1}{2}(3\cos^2\theta - 1)\tfrac{1}{2}(3\,\overline{\cos^2\gamma} - 1)S_{zz} \qquad (3)$$

where $\theta$ is the C–N–D bond angle and $\gamma$ is the angle between the C–X bond and the $zz$ axis.

In an extended chain, both C–D bond axes in a methylene group are perpendicular to the $zz$ axis and $S_i = -\frac{1}{2}S_{zz}$. Assuming that all bonds are at the tetrahedral angle, $S_{ND_3} = -\frac{1}{6}S_{zz}$. This ratio of 3 for $S_9/S_{10}$ or $S_1/S_{ND}$ is rarely found experimentally, as we have pointed out before, because other relative motions occur[36,18] which result in a departure from the extended chain conformation.

**Type (2) Motions.** For a free chain the number of possible conformations from three rotamer positions on each C–C bond for ten carbons is extremely large. Seelig and co-workers[17,37] have postulated that only a few conformational "defects" in the extended phospholipid and detergent chains in lameller systems actually occur. The limitations on many possible conformers arise because the excessive creation of free volume would increase the free energy of the system. Consequently the probable conformations are restricted to those which do not excessively perturb the parallel packing of the hydrocarbon chains. The following conformational defects are thought to be present in dipalmitoyl lecithin chains of 16 carbon length: 2g1 kink, 2g2 jog, 3g2, 2g3 jog, 3g3, and 4g3. The notation "$AgB$" implies $A$ gauche rotations with shortening of the chain length by $B$ units of 1.54 cos 35.26° = 1.26 Å. The notation is that of Pechhold.[38] These conformational defects are in dynamic equilibrium with extended chains and lead to a shortening of the average bilayer thickness.[37]

As the equilibrium population of such defects increases the degree of order of the C–D bonds decreases. The extended chain leaves all C–D axes, except for the terminal groups discussed above, perpendicular to $zz$. If rotamers such as $g^+g^+$, which bend the chain at right angles, are neglected there are only two possible orientations of the C–D axes of a methylene group with respect to the $zz$ axis: one at 90° and the other 35.26°, which gives values of $\frac{1}{2}(\cos^2\theta - 1)$ of $-\frac{1}{2}$ and $+\frac{1}{2}$, respectively. If only odd numbers of trans rotamers occur between gauche conformers as in 2g1, 2g2, and 3g2 then for $-CD_2-$ groups between a pair of gauche positions one C–D bond has a degree of orientation $-\frac{1}{2}$ and the other $+\frac{1}{2}$. Because, for example, 2g1 kink defects occur in pairs, $g^+\,tg^-$ and $g^-tg^+$, the net contribution to the degree of order for such $-CD_2-$ groups is zero. If the formation of gauche rotamers is equally probable for all the possible combinations of 2g1, 2g2, 3g2, 2g3, 3g3, and 4g3 defects, then the net effect is to reduce the degree of order of $CD_2$ groups from C-2 to C-8 equally. If all other contributions to the degree of order were known, then the absolute population or probability of a gauche rotation occurring at given carbons could be evaluated. The profiles of the degree of order for $-CD_2-$ groups in the present study indicate quite small changes from $C_2$ to $C_8$. Near the head of the chain there is a small alternation effect in the degree of order profile, which suggests some preference for certain conformations. It is evident that single gauche rotamers have higher probability at the $C_7$–$C_8$ and $C_8$–$C_9$ bonds leading to a fall off in segmental order at the terminal carbons.

**Type (3) and (4) Motions.** The value of $S_{zz}$, the degree of order of the $zz$ axis, is determined by the type (3) and (4) motions. Type (3) motions are partly inclusive in the degree of order of the cylinder axes, which might be measured macroscopically by other techniques.[39] While there are many measurements of the macroscopic degree of order, by several independent techniques, of thermotropic nematic phases[40] there are no measurements of the degree of order of hexagonal lyotropic phases. The cylinder axes if perfectly ordered would have a degree of orientation $S_{cyl} = -\frac{1}{2}$. The oscillation of the hydrocarbon chains in the cylindrical superstructure about the perpendicular directrix to the surface is an independent motion probably of much shorter correlation time. The effects of these two motions on the deuterium quadrupole splittings are indistinguishable.

The lateral diffusion of the amphiphilic molecule or ion in phospholipid and detergent mesophases, in which the head group remains in the interface region, is known to be fast.[16,34,41] In our assumed model of the type II phases only the tangential perpendicular motion affects the degree of order parameter and this motion around the circumference of the cylinder is sufficiently fast as to result in a single averaged quadrupole splitting at each deuterium position. This averaging motion in the plane parallel to the magnetic field direction and perpendicular to the average cylinder orientation will reduce $S_{zz}$ by a factor $\frac{1}{2}$. The degree of order corrected for this averaging motion will be designated as $S_{zz}{}^0$ and defined by

$$S_{zz} = \tfrac{1}{2}S_{zz}{}^0 \qquad (4)$$

**Type (5) Motion.** These exit and insertion motions are unlikely to be important for C-10 chains since the long-range stability of the electrical double layer, which depends on the structural stability of the head groups and water, is a prerequisite of hexagonal phase formation.

**(b) Application of the Model to Experimental Results.** Quantitative and reasonable estimates for some of the various motions of types (1) to (4), which affect the degree of order of hydrocarbon chains in hexagonal phases, are in good accordance with experimental results, recorded here. Variation of the water content for any of the mesophases studied does not change the relative magnitudes of the quadrupole splittings of deuterium on the decylammonium chain even though the absolute quadrupole splittings change over a wide range. The ratios of the deuterium quadrupole splittings of the $-CD_2-$ groups in the central part of the hydrocarbon chain are insensitive to changes in the populations of the trans-gauche conformers. The presence of these conformers does not drastically change the ratio from unity, the value for a frozen all-trans configuration.

The number of reasonable conformations of the ionic head group are rather limited. The deviations from the ratio of 3 for $S_1/S_{ND}$ in an extended chain can be assigned to the presence of conformers containing a single gauche C–C bond near the head of the decylammonium chain as shown in Figure 8. Rapid exchange between these conformers results in a population weighted average quadrupole splitting for each deuterium position. If $\theta$ and $\phi$ in Figure 8 are equal to 109.5 and 35.26°, respectively (assuming tetrahedral bond angles), then from eq 3 the degree of order of the head group would be $-\frac{1}{6}S_{zz}$ for conformer 8A and 8C and $+\frac{1}{6}S_{zz}$ for conformer 8B. Since both C–D axes of the adjacent methylene in conformer 8A are perpendicular to the $zz$ axis, the degree of order for these axes is $-\frac{1}{2}S_{zz}$. In conformers 8B and 8C one C–D axis is perpendicular and the other at an angle $\phi$ to the $zz$ axis and therefore the degrees of order of these bonds are $-\frac{1}{2}S_{zz}$ and $+\frac{1}{2}S_{zz}$, respectively. Since both $g^+$ and $g^-$ rotamers are equally probable, the average degree of order for the C–D bonds in the methylene group adjacent to the terminal group would be zero in conformers 8B and 8C. If only the three conformers shown

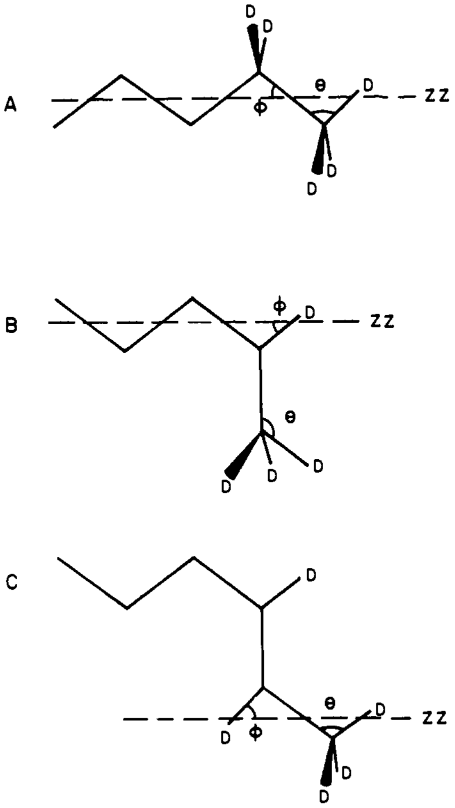

**Figure 8.** Conformations of the terminal segments of the decylammonium ion. Part A shows the geometry of the extended chain and parts B and C show the geometry for chains containing a single gauche carbon–carbon bond.

in Figure 8 are considered the average degrees of order for the deuteriums in the -$CD_2ND_3$ groups will be given by:

$$\langle S_{ND_3}\rangle = -\tfrac{1}{6}(1-2x)S_{zz} \qquad (5)$$

$$\langle S_{CD_2}\rangle = -\tfrac{1}{2}(1-x-y)S_{zz} \qquad (6)$$

were $x$ and $y$ are the fraction of the chains in conformers 8B and 8C, respectively.

The observed ratio of the quadrupole splittings $\Delta\nu_1/\Delta\nu_{ND}$ for the decylammonium chloride mesophase is 2.325 ± 0.015. Applying eq 1, $S_1/S_{ND} = 2.42$ using 170 and 176.7 kHz for the CD[55,56] and ND[35] deuterium quadrupole coupling constants. In this model the equilibrium population of 8C must be greater than that of 8B to account for the experimental ratio. In order to determine the populations of the conformers in this three-site model, a knowledge of $S_{zz}$ which contains the contributions from averaging motions of types 3 and 4 would be required. An alternate approach which does not require a knowledge of $S_{zz}$ would be to assume that the population of conformer 8B is negligible since in this conformer the ionic head group is rotated out of the highly ordered interface region. In this two-site model ($x = 0$ in eq 5 and 6) the experimental ratio requires an 81% population of the trans and 19% population of the gauche conformer shown in Figure 8C.

$S_1/S_{ND}$ remains a constant experimental quantity because only a limited number of conformers contribute and their relative populations appear to be unaltered.

The alternation in the degree of order of the C–D bonds on carbons 1 to 4 reflects the equilibrium population of various conformers. The relative proportions of these conformers appear to depend on the interactions of the head group in the interface layer. A similar effect was observed for the first four -$CD_2$- positions of the decyl sulfate ion in a type II mesophase. However, in this mesophase the alternating effect was in the opposite sense; the degree of order of the C–D bonds on carbons 1 and 3 was less than those on carbons 2 and 4. For decanol in the same phase there was o difference in the degree of order for the deuterium bonds on carbons 1 and 2.

Motions of type (3) may be estimated in the following manner. The most rigid part of the chain is the -$ND_3^+$ head group which builds into the structure of the electrical double layer interface. It is therefore taken as a reference to estimate chain order, outside of segmental motions. The deuterium quadrupole splittings for the -$ND_3^+$ head group of 2.82 to 7.80 kHz were observed in the decylammonium chloride mesophase without cholesterol. Larger values were observed at low temperatures (see Figure 4) and for samples containing less water than those reported here but these mesophases are probably of a different type and the model assumed here may not be appropriate. The minimum and maximum values of the degree of order of the N–D bond computed from eq 1 are ±0.0212 and ±0.0588. Combining the effects of eq 3 and overall chain rotation about the long axis and diffusion of the headgroup around the cylinders of the superstructure yields ±0.255 and +0.706 for the range of values. The positive sign can be assigned because the magnitude is greater than 0.5.

A positive sign is consistent with a model of parallel alignment of the extended chain to the magnetic field direction and perpendicular orientation of the cylinder axis to the magnetic field. The range of values of $S_{zz}{}^0$ within the stable nematic type II behavior is surprisingly large. The degree of order of all C–D and N–D bond axes is necessarily negative, to account for the overall positive values.

In the decylammonium tetrafluoroborate mesophases the range of values for $S_{zz}{}^0$ computed from the observed deuterium quadrupole splittings of the -$ND_3^+$ group is from +0.406 to +0.738. These macroscopic degrees of order estimated here compare with those measured for thermotropic nematic crystals over the stable range of nematic behavior.[40] A solid/nematic or smetic/nematic transition occurs with a maximum of about $S = +0.85$ for the nematic phase and transitions to isotropic liquids occur around $S = 0.44$. These values are very similar to the range estimated in the present study for hydrocarbon chains in lyotropic liquid crystals. The behavior of both types of nematic medium depends on the degree of alignment of adjacent chains no matter by what means it is achieved.

(c) **The Effect of Cholesterol and of the Counterion.** The addition of cholesterol to the decylammonium chloride mesophase has two effects. First, the presence of cholesterol tends to stabilize the nematic phase. The dramatic increase in the degrees of order of the deuterium bond along the decylammonium chain on the addition of cholesterol is shown in Figure 5. This effect can also be seen in Figure 3 which compares the deuterium quadrupole splittings observed over the nematic region of a mesophase containing cholesterol (Figure 3B) with those in the same mesophase without cholesterol (Figure 3A). While the rnge of values of the quadrupole splittings is similar, the mesophase containing cholesterol can incorporate much more water before undergoing a phase change into an isotropic micellar solution. This effect may be primarily due to the presence of the 3-OH group of cholesterol which presumably resides in the electrical double layer region, since long-chain *n*-alkanols have a similar effect on detergent mesophases. Unfortunately decanol could not be added to the decylammonium chloride mesophase without resulting in a phase change but the effect of decanol has been studied for the cesium decylsulfate-decanol-water system which also forms a type II nematic phase. It was found that increasing the decanol:detergent ratio from 1:25 to 3.5:25 (by weight) increased the maximum amount of water which could be present without destroying the mesophase from 39.5 to 67.8 wt %.[42] X-ray diffraction studies of both the hexagonal and lamellar mesophases, observed in potassium soap-alcohol-water systems, have shown that long-chain alcohols affect the electrical double layer region.[8] The alcohols were found to decrease the area per hydrophilic head group at the amphiphile/water interface which is consistent with a stabilizing effect.

This stabilizing or condensing effect of cholesterol has been observed in lamellar mesophases composed of membrane lipids.[43]

The second effect of cholesterol is shown in Figure 6. The ratios of the quadrupole splittings of deuterium at various positions on the decylammonium ion, which are independent of the water content, are changed by a small but significant amount by the presence of cholesterol. All of these changes are consistent with an increase in the equilibrium population of the extended chain. For example the ratios $S_1/S_{\mathrm{ND}}$ and $S_9/S_{10}$ approach the value of 3 expected for an extended chain. If the two-site model used above to describe the $\text{-}CD_2ND_3^+$ segment is applied, the addition of cholesterol at a concentration of 9.2 mol % of the detergent concentration results in an increase from 80.6 to 83.8% for the population of the extended form for this segment.

The increase in the population of the extended chain caused by cholesterol may be due to the presence of the large planar region in the cholesterol molecule, but the indirect effect on the chain conformations arising from the effect of the 3-OH group on the interface region cannot be ruled out. This sensitivity of the relative populations of the chain conformers to changes in the electrical double layer is demonstrated by changing the counterion. The results in Table I clearly show that the nature of the counterion has a marked effect on the chain conformation even at the end of the hydrocarbon chain.

**(d) Comparison of the Hexagonal and Lamellar Phases.** On increasing the mole percent of cholesterol to detergent from 9.2 to 12.7% a phase change occurred which resulted in an isotropic phase in equilibrium with a mesophase which had a texture characteristic of a lamellar phase. A similar phase change has also been observed in the sodium caprylate system.[44] The quadrupole splittings observed in the lamellar phase can be compared with those in the hexagonal phase containing 9.2% cholesterol also at maximum hydration (i.e., at the nematic-isotropic transition). The lamellar phase orients randomly to the field direction and thus the major deuterium doublet splittings are ½ that of a phase homogeneously ordered with the optic axis parallel to the magnetic field (i.e., the bilayers perpendicular to the field). Thus multiplying all quadrupole doublet splittings measured for the lamellar phase by a factor 2 leads to values comparable to the homogeneously oriented hexagonal phase values (the latter values will be uncorrected for diffusion around the cylindrical superstructure). A ratio of 4 according to eq 1 and 4 at all positions in the chain would indicate that the degree of order profile for chains in lamallae do not differ from those ordered in cylinders. The experimental ratio's are: $\text{-}D_2O$ 4.81; $\text{-}ND_3^+$ 3.83; $C_1D_2$ 3.98; $C_9D_2$ 4.08; and $C_{10}D_2$ 4.33. The figures are close to 4 but do show the influence of the increase in cholesterol ratio from 9.2 to 12.7% (see Figure 6). The water content of the two phases is quite different, consequently the departure from a ratio 4 for the water doublet is not significant.

The degrees of order determined from the quadrupole splittings of deuterium on the hydrocarbon chain in lamellar mesophases containing potassium laurate,[45] sodium decanoate,[17] or dipalmitoyllecithin[37] are also in the range observed in this study when the additional averaging motion is taken into consideration. Also the profile of the degree of order along the hydrocarbon chain in lamellar phases is very similar to those observed in hexagonal phases in this and other studies[19] which shows that the geometry of the molecular aggregations has little or no effect on the anisotropic motion of the amphiphilic molecule. Studies of the rates of molecular motion in the potassium laurate-water system by relaxation and diffusion measurements have also shown that there is very little difference in the local behavior of the soap molecule in lamellar, cubic, or hexagonal phases.[16,41]

## Conclusions

For mesophases formed using decylammonium salts the following general conclusions are indicated:

1. The relative values of the deuterium quadrupole splittings of the decylammonium chain are sensitive to the nature of the counterion and to the presence of cholesterol in the hydrophobic region. The presence of cholesterol tends to stabilize the cylindrical micelles with respect to water addition and to decrease the flexibility of the hydrocarbon chain.

2. The ratios of the chain deuterium splittings, for a given mesophase, are independent of the water content which strongly indicates that the relative populations of the various gauche-trans conformers are constant. This is consistent with the results of the x-ray study of binary soap-water hexagonal mesophases in which practically no change in the cylinder diameters was observed.[5] On the other hand, significant changes in the ratios of the quadrupole splittings were observed with changes in temperature.

3. Consequently the large change in the absolute values of the quadrupole splittings with variation of the water content must be due to the type (3) motions: oscillatory motion of the chain axes about the perpendicular to the interface and/or oscillatory motions of the cylinder axes about the average orientation direction perpendicular to the magnetic field direction. While these two motions are indistinguishable in the present study, large changes in the motion of the chain axes about the perpendicular to the interface would be unexpected since the results indicate that the packing of the hydrocarbon region remains unchanged. Therefore the variation of about a factor of 3 in the quadrupole splitting in a given position must be attributed to changes in the motion of the cylinders themselves. This is consistent with the phase change at the liquid crystalline-isotropic transition; the isotropic phase contains rod-shaped micelles[46] which can undergo isotropic rotation. The additional averaging motion caused by the diffusion of the hydrocarbon chains at the ends of the cylinders will become significant when the length of the cylinders is decreased.

4. The fact that the degree of order of the head group and the water are proportional indicates that the variation in the average degree of order of the water and other ions or molecules in the aqueous region basically reflects the change in the degree of order of the interfacial region. The variation observed with changes in the water concentration is therefore not primarily due to the changes in the distribution of molecules between the highly ordered region near the interface and the less highly ordered regions. However, the changes in the relative populations of molecules between regions of different degrees of order are not negligible and probably account for the nonzero intercept in Figure 2.

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# Conformational Analysis. 118. Application of the Molecular-Mechanics Method to Alcohols and Ethers[1,2]

**N. L. Allinger* and D. Y. Chung**

*Contribution from the Department of Chemistry, University of Georgia, Athens, Georgia 30601.* *Received March 2, 1976*

**Abstract:** Force-field calculations previously described for hydrocarbons and other compounds have been extended to include oxa compounds—alcohols and ethers. It was found necessary to explicitly include lone pairs in the calculations. The structures and energies of oxa compounds can be calculated fairly well, although the agreement with experiment is not as good as with hydrocarbons.

The force-field or molecular-mechanics method has been extensively applied to hydrocarbons during the last few years, and it is now clear that for most such compounds it is possible to calculate the structures and energies (and sometimes other properties such as vibrational spectra, and thermodynamic functions) with an accuracy that is usually competitive with the best that can be done experimentally.[3]

While the calculations have been highly successful for hydrocarbons and a number of classes of compounds that do not differ very much from hydrocarbons, such as silanes, carbonyl compounds, alkenes, and a few other classes,[3] very little has so far been reported on compounds containing ether (or alcohol) oxygen. Some preliminary studies[4] showed that most simple oxa compounds could be handled without difficulty, but further work has not been forthcoming. We will report here our calculational studies on this important class of compounds.

As is well known, hydrogen bonding is extremely important with alcohols and similar compounds in condensed phases. Our calculations are strictly for isolated molecules in the gas phase. While these calculations can be used as good approximations for molecules at low concentrations in inert solvents, we have not taken hydrogen bonding into account, and hence extrapolations of the calculations to polar solutions must be made with caution. In addition, for compounds which contain two or more polar groups, there are problems to be expected from the electrostatics of the situation.

The force field for hydrocarbons previously described (our 1973 force field[5]) was used unchanged. To extend the force field to alcohols, one needs to introduce the specific parameters which pertain to bond lengths, bond angles, torsional angles, dipoles, and energetics which involve oxygen. We originally chose dimethyl ether, methyl ethyl ether, methanol, and 1,3-dioxane as the key compounds to fit. Good structural data (microwave) are available for the first three of these compounds. As will be subsequently discussed, 2-methoxypyran was also studied to supply a needed torsional barrier which is missing in the above compounds.

The initial parameterization was carried out and then the parameters deduced from the above compounds were applied to a number of more complex compounds. A serious discrepancy was immediately noted, which involved the 5-alkyl-1,3-dioxanes. Many studies on alkyl-1,3-dioxanes have been recently reported and a large amount of conformational and isomerization equilibrium data are available for these systems. It is known that the 5-methyl compound has the methyl group preferentially equatorial, with the axial conformation being some 0.8 kcal/mol higher in energy. The preliminary force