

Determination of the Dihedral Angle of the Monoanion of Succinic Acid in Aprotic Media

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A value of $74(\pm 4)^\circ$ was determined from NMR-observed dipolar couplings for the rotational dihedral angle of the monosuccinate anion in an aprotic liquid-crystal solution of the gauche conformation of tetraoctylammonium monosuccinate. This value is in reasonable agreement with other, somewhat less definitive, evidence gleaned from isotropic vicinal proton–proton couplings of the essentially completely gauche preference of the monosuccinate anion in *tert*-butyl alcohol and aprotic solvents, such as DMSO and THF, and quantum computations for the monoanion in THF.

Introduction

Nuclear magnetic resonance spectroscopy (NMR) may be used to evaluate the geometry of solutes by analysis of potentially observable internuclear dipolar couplings in solutions, as in liquid crystals, where molecular motions are directionally restricted by a magnetic field.¹ A dipolar coupling between a pair of magnetic nuclei is a function of the internuclear distance and the average angle between the vector connecting the nuclei and the magnetic field vector. If several dipolar couplings are known for a particular molecule, it may be possible to determine bond distances and bond angles of that molecule in the solution. Matters become much more complicated when one desires structural information from dipolar couplings for rapidly interconverting conformational mixtures, such as of the monosuccinate anion, which in water is estimated to have little, if any, conformational preference other than statistical (one-third trans and two-thirds gauche).^{2–5} With any such system, typified here by a 1,2-disubstituted ethane, the pertinent molecular parameters determining the dipolar couplings are the bond angles, bond distances, and dihedral angles for each conformer, along with the magnetic properties of the nuclei involved, the conformational equilibrium constant and the average orientational preferences of each conformer with respect to the magnetic field axis of the liquid-crystal or other oriented medium. As a first approximation, the bond angles and bond distances in such conformational systems may be assigned their conventional tetrahedral values. It is possible to go further to measure many of the other needed parameters for a three-conformer system but it is generally useful to assume values for some of the desired parameters. Usually, it is not practical to measure enough dipolar couplings to determine a geometry completely.^{6,7} It is also found by a simple simulation that conformational preference and the dihedral angles can be obtained from dipolar couplings simultaneously; however, the accuracy of results obtained this way deteriorates quickly with the accuracy of the dipolar couplings. Chidichimo and co-workers have used dipolar couplings determined for ethylene glycol and for succinic acid and its anions in lyotropic solutions to estimate the dihedral angles of these entities by the artifice of assuming that the different conformational mixtures are effectively for practical purposes in aqueous solution consisting of 100% of a single conformer.^{8,9} Thus, ethylene glycol, succinic acid, and monosuccinate were taken

to be exclusively gauche, while the succinate dianion was taken to be only trans. This assumption simplifies the calculation of the dihedral angle. The general approach is a valid one, as we will attempt to show, but Chidichimo's assumption that the different samples to be all of this or all of that is simply not congruent with the scalar vicinal proton–proton data obtained on the same materials in either isotropic^{3,4,10} or lyotropic solutions.^{8,9}

If the Chidichimo approach to determining dihedral angles from dipolar couplings is to have credibility, one needs to at least know by NMR or other possible spectroscopic or dipole moment measurements what the actual equilibrium concentrations are of the conformers. These can be estimated approximately for 1,2-disubstituted ethanes, but the calculations to do that, with the aid of Altona procedures for estimating the three-bond couplings of the vicinal protons,^{11,12} require average values of the dihedral angles of the individual conformers. We start here with a much simpler process where the key is to have strong arguments based on experimental results for assigning particular sets of conformational preferences to compounds of interest.

For this purpose, the best candidate we have so far is the monosuccinate anion, which has proton–proton vicinal couplings that indicate a very strong preference for the gauche conformation as the result of strong intramolecular hydrogen bonding, not at all in water, but in *tert*-butyl alcohol, DMSO, and THF.^{3,4} Further support for the gauche preference comes from calculations that suggest that the gauche hydrogen-bonded conformation in THF is 11 kcal more stable than any of the other possible conformations.⁵

In this and other work, estimation of the conformational preferences for 1,2-substituted ethanes has been achieved by comparison of the averaged vicinal proton–proton scalar couplings $^3J_{\text{HH}}$ observed in ^1H NMR spectra in combination with $^3J_{\text{HH}}$ couplings predicted for each conformer by the semiempirical Altona equation, which is similar to the Karplus equation,¹³ but which takes into account substituent effects.^{11,12} This equation uses assigned dihedral angles between pairs of protons, viewed down the central C–C bond, and λ_1 and λ_2 , which are parameters corresponding to substituent effects on $^3J(\text{HH})$ couplings of the molecule of interest. The Altona equation for a single conformation of a substituted ethane is shown in eq 1, where the dihedral angle between the protons of the calculated coupling constant is given by ϕ (Figure 1),

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$${}^3J(\text{HH}) = 14.63 \cos^2(\varphi) - 0.78 \cos(\varphi) + 0.60 + \sum_i \lambda_i \{0.34 - 2.31 \cos^2[s_i(\varphi) + 18.4|\lambda_i|]\} \quad (1)$$

Equation 1 gives predicted values of the two observable proton–proton vicinal scalar couplings (J_{13} , J_{14}) for each conformer (it should be noted that the two energetically equivalent gauche conformers have different J_{13} , J_{14} values). The values of λ_1 and λ_2 and assigned magnitudes of θ_t and θ_g (the respective dihedral angles between the substituents for the gauche and trans conformers, most often assumed to be 60° and 180° , respectively) allow one to predict the couplings of any gauche and trans mixture. Simple algebra with $f_g + f_t = 1$, where f_g is the fraction of gauche and f_t the fraction of trans, using predicted and experimentally measured J_{13} , J_{14} couplings for 1,2-disubstituted ethanes, affords two independent estimations of the conformational preferences. When this procedure is used for the monoanion dissolved in *tert*-butyl alcohol, dimethyl sulfoxide (DMSO), or tetrahydrofuran (THF), on the assumptions that θ_g is 60° and θ_t is 180° (Figure 2b), values for f_g result that are greater than 1. This is not unreasonable, because as pointed out early on, models indicate that $\theta_g = 60^\circ$ is not likely to correspond to the most stable conformation for an intramolecularly hydrogen-bonded succinate monoanion.⁵ If one keeps $\theta_t = 180^\circ$ and opens θ_g to 65 – 75° , the structure not only looks more favorable, but f_g approaches unity as expected for the calculations for the monoanion in THF.⁵ The reasonableness of this approach is seen for the monoanion in water, where Westheimer and Benfey have shown that intramolecular hydrogen bonding is not significant for the monophthalate ion and, if monosuccinate is assigned $\theta_g = 60^\circ$ and $\theta_t = 180^\circ$, the estimated and experimental couplings also indicate very little if any such bonding.²

Because there is no experimental evidence for the magnitudes of dihedral angles for rapidly equilibrating conformers of 1,2-disubstituted ethanes in solution and despite the rather strong inferences that the monoanion of succinic acid is essentially a single gauche conformer with a dihedral angle greater than 60° , it is important to have an experimental test of these inferences, because they underlie almost all conformational analysis made through the agency of NMR. X-ray crystallography gives no hint of what to expect in solution, because the crystals are intermolecularly hydrogen bonded in linear arrays.^{14–17} Quantum calculations for THF solutions are among the strong inferences suggestive of a dihedral angle greater than 60° ,⁵ but again these computations need experimental support to be taken as truly creditable.

The most plausible way to try to settle this question is with the use of dipolar couplings (D), which can be observed in NMR spectra taken of solutions of the molecules of interest in oriented media as follows.

Theory

Dipolar couplings between two magnetic nuclei accord with the formulas (2).

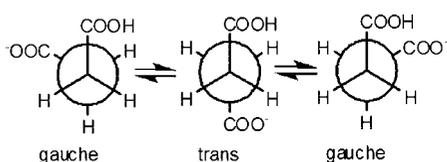


Figure 1. Conformers of monosuccinate.

$$D_{ij} = \frac{h\gamma_i\gamma_j}{4\pi^2 r_{ij}^3} \frac{1}{2} S_{ij} \quad S_{ij} = \langle 3 \cos^2 \phi - 1 \rangle \quad (2)$$

γ_i , γ_j are the gyromagnetic ratios of nuclei i and j , r_{ij} is the distance between nuclei i and j , and $\langle 3 \cos^2 \phi - 1 \rangle$ is given by taking an average over ϕ , the angle between the magnetic field

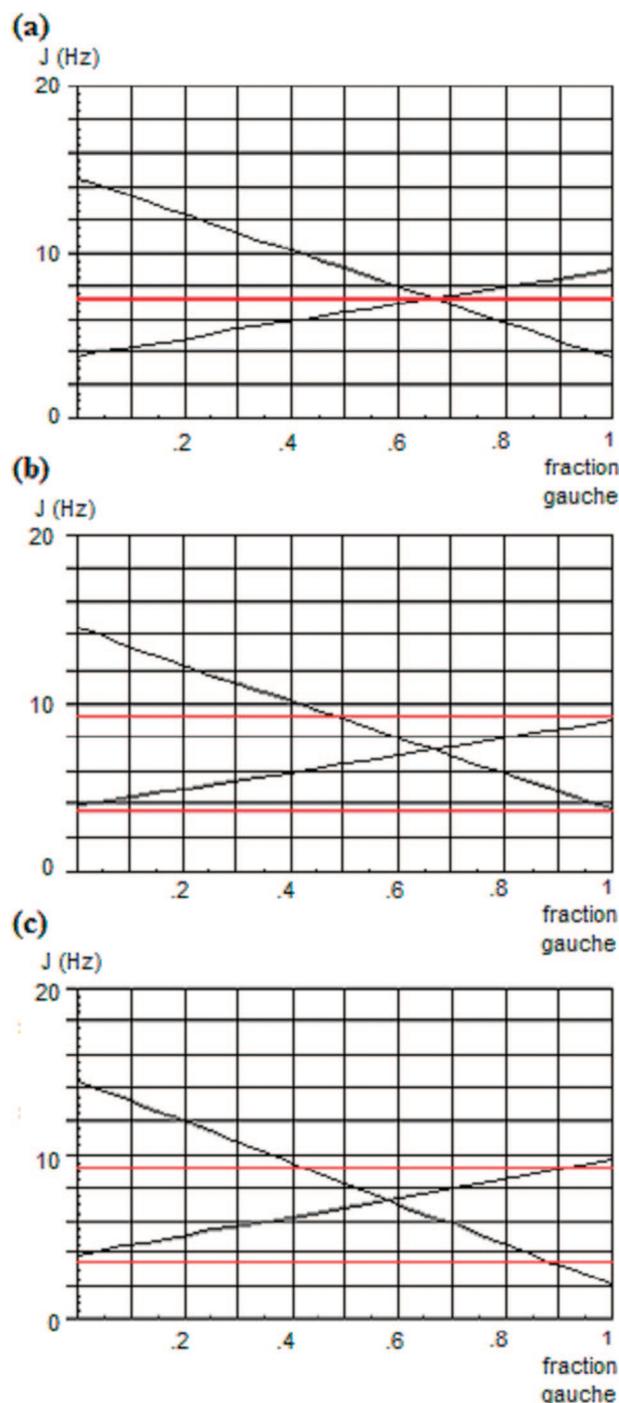


Figure 2. Altona equation graphs. The theoretical values of J_{13} and J_{14} are plotted against f_g (black), where $\lambda_1 = 0.41$, $\lambda_2 = 0.39$. The experimental values of J_{13} and J_{14} are also shown (red). (a) Experimental values of J_{13} and J_{14} for monosuccinate in D_2O are shown against theoretical values, assuming $\theta_g = 60^\circ$, $\theta_t = 180^\circ$.⁴ f_g is determined to be equal to 0.66. (b) Experimental values of J_{13} and J_{14} for monosuccinate in THF are shown against theoretical values, assuming $\theta_g = 60^\circ$, $\theta_t = 180^\circ$. f_g is determined to be equal to 1.04, which is unreasonable.⁴ (c) Experimental values of J_{13} and J_{14} for monosuccinate in THF are shown against theoretical values, assuming $\theta_g = 70^\circ$, $\theta_t = 180^\circ$. f_g is determined to be equal to 0.90, which is reasonable.⁴

vector and the vector connecting nuclei i and j . For several dipolar couplings, it is convenient to have a relationship between the terms S_{ij} , where S_{ij} gives the orientational dependence of the dipolar couplings, of each dipolar coupling. If Cartesian coordinates are assigned to a molecule, it becomes possible to define Saupe order parameters which are constant for any one molecule in solution.¹⁸ The nine-order parameters make up the second rank tensor

$$\begin{bmatrix} S_{xx} & S_{xy} & S_{xz} \\ S_{yx} & S_{yy} & S_{yz} \\ S_{zx} & S_{zy} & S_{zz} \end{bmatrix}$$

$$S_{\alpha\beta} = \langle 3 \cos \phi_\alpha \cos \phi_\beta - \delta \rangle$$

$$\delta = 1 \text{ if } \alpha = \beta, \delta = 0 \text{ otherwise} \quad (3)$$

where ϕ_α is the angle between the magnetic field vector and axis α (x , y , or z). Only five of these order parameters are independent, because $S_{xy} = S_{yx}$, $S_{xz} = S_{zx}$, $S_{yz} = S_{zy}$, and $S_{xx} + S_{yy} + S_{zz} = 0$. Using this definition for the order parameters, the following relationships are true.^{8,9}

$$D_{ij} = \gamma_i \gamma_j \hbar^2 \sum_{\alpha\beta} S_{\alpha\beta}(k) F_{ij}^{\alpha\beta}$$

$$F_{ij}^{\alpha\beta}(k) = \frac{r_{ij}^2 \delta_{\alpha\beta} - 3 \Delta\alpha_{ij}(k) \Delta\beta_{ij}(k)}{r_{ij}^5(k)} \quad (4)$$

Here γ_i , r_{ij} , $S_{\alpha\beta}$, and $\delta_{\alpha\beta}$ are defined as previously, and $\Delta\alpha_{ij}$ is the length of the projection of the vector between nuclei i and j onto the α axis (the formula actually used multiplies this formula by a factor of $2 \times 3^{-1} h^{-1}$). For a molecule, such as monosuccinate, which has C_2 symmetry, if the z -axis of the Cartesian coordinates is set on the C_2 axis of symmetry, then the terms S_{xz} and S_{yz} become zero, reducing the number of independent order parameters to three.

A Fortran program, Dipolar, was written for the purpose of correlating the observed dipolar couplings of disubstituted ethanes with their molecular geometries. In this program, bond lengths and angles were assumed. For monosuccinate, these are given to be those measured by Levie and co-workers.¹⁹ Also, a dihedral angle is assumed. From this, coefficients to the order parameters $F^{\alpha\beta}$ in eq 4 are calculated, and the order parameters $S_{\alpha\beta}$ are calculated such that eq 4 produces theoretical dipolar couplings (D) that are as close as possible to the observed dipolar couplings by rms error. Using this procedure, iteration is performed where the dihedral angle is changed from 0° to 180° . The dihedral angle that allows calculation of theoretical dipolar couplings closest to the experimental dipolar couplings, determined by rms error, is reported as the best fit value of the dihedral angle.

Results

To observe dipolar couplings of a solute in NMR spectra, the solvent must restrict the motion of the solute (anisotropic solution). If the motion is not restricted (isotropic solution), then the value of S_{ij} in eq 2 averages to zero. A liquid-crystal solution of monosuccinate was used to achieve the orientation of the solute, relative to the magnetic field axis.

Previous work with monosuccinate in aprotic solvents suggests that its equilibrium is found at essentially 100% gauche.^{4,5,20} Because liquid crystals are also aprotic, the assumption that the fraction of gauche is equal to 1 is reasonable. If the fraction of gauche is not assumed to be 1, then it becomes necessary to calculate the fraction of gauche simultaneously with the dihedral

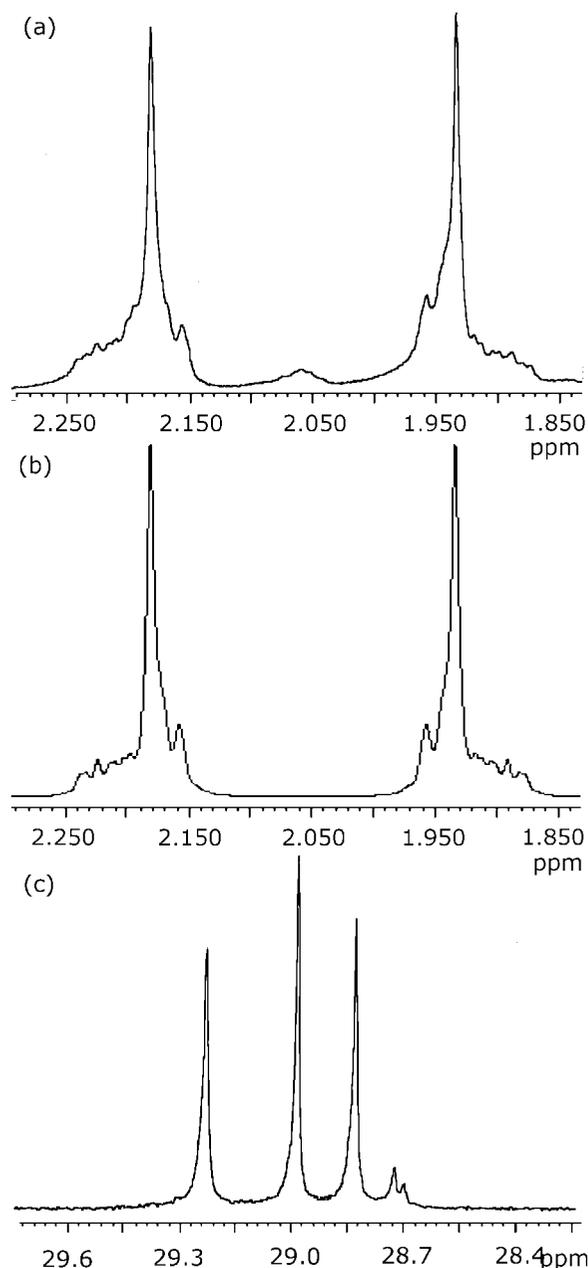


Figure 3. Isotropic spectrum of tetraoctylammonium monosuccinate in liquid crystal. (a) Isotropic ^1H spectrum of tetraoctylammonium monosuccinate (^{13}C labeled at the 2 and 3 carbons), taken at 70°C . (b) gNMR fit of *a*, which allows the determination of all the scalar coupling constants, except the carbon–carbon coupling constant, which is obtained from part *c*. (c) Isotropic ^{13}C proton decoupled spectrum of monosuccinate, taken at 70°C . A gNMR fit is not necessary for this spectrum because only the peaks at 29.0 and 29.2 ppm are significant. These peaks allow determination of the carbon–carbon coupling constant simply by finding their shift difference.

angle, and also it becomes necessary to calculate the dihedral angle of the trans conformer, further complicating the analysis.

Liquid-crystal spectra of tetraoctylammonium monosuccinate-2,3- ^{13}C were obtained by using a 1:1 molar mixture of 4'-(pentyloxy)-4-biphenyl carbonitrile and 4'-(heptyloxy)-4-biphenyl carbonitrile. A ^1H NMR spectrum and a ^{13}C NMR decoupled spectrum were taken at 70°C (Figure 3a,c). At this temperature, the liquid-crystal solution is in the liquid state, which is isotropic, hence dipolar couplings are not observed at this temperature, simplifying the determination of the scalar couplings (J). These spectra were then simulated with gNMR

4.1 to determine values of the scalar coupling constants (Figure 3b).²¹ The values of the vicinal scalar couplings are similar to those measured by Kent et al. in tetrahydrofuran (2.22 Hz, 9.85 Hz).²⁰ A ¹³C coupled spectrum and a ¹H NMR spectrum were then taken at 50 °C (Figure 4a,c). At this temperature, the liquid-crystal solution is in the liquid-crystal state, which is anisotropic. Assuming the scalar couplings were the same as at 70°, the dipolar couplings (*D*) were also determined by fitting with gNMR 4.1 (Figure 4b,d). The values of the obtained coupling constants are given in Table 1. It should be noted that by determining the scalar couplings from spectra taken at isotropic conditions and assuming these values for anisotropic conditions, the accuracy to which the dipolar couplings can be determined is improved. Allowing all 12 couplings to be variables in the anisotropic spectra will lead to apparently good spectral fits which in fact are the results of errors in the values of the dipolar couplings being countered by errors in the scalar couplings. In some cases, the geminal couplings (*J*₁₂) do not affect the isotropic spectrum, making their determination impossible from the isotropic spectrum; however, in this case, they do affect the spectrum, so this potential problem is avoided.

Discussion

From the calculated dipolar couplings, the dihedral angle was determined with Dipolar. The order parameters so obtained were *S*_{xx} = 0.0389, *S*_{yy} = -0.0216, *S*_{zz} = -0.0173, *S*_{xy} = 0.0587, and the dihedral angle was determined to be 74(±4)°. This fit was obtained with an rms error of 5.9 Hz. The corresponding *D* values are given in Table 2. The degree of error was determined to be ±4° because it is possible to change the values of the dipolar couplings slightly and obtain simulated spectra which still are a reasonably good fit to the observed spectra. These dipolar couplings correspond with dihedral angles ranging from 72° to 79°. At this point, the initial assumption of the fraction gauche being 1 was tested by using the Altona equation.¹² When using a dihedral angle of 79° in the Altona equation, the fraction gauche is 0.94, contradicting the assumption that the fraction gauche is 1. If it is assumed that the dihedral angle is a weighted average of the trans and gauche dihedral angles and also that the trans angle is 180°, then the gauche angle is calculated to be 73°. A smaller trans angle gives a larger gauche angle, although the variation is easily within the ±4° range of error. Thus, it is reasonable to report that the dihedral angle is 74(±4)°. This finding suggests that hydrogen bonding in monosuccinate stabilizes the molecule most when the dihedral angle is near 74°. Although the resulting dihedral angle is not highly precise, the original objective of justifying the use of 70° as the gauche dihedral angle in the Altona equation is accomplished, since the present results show this angle to be very reasonable.

It is important to note that a dihedral angle of 74° is a significant departure from the classical angle of 60°. This can be attributed to the strong affects of intramolecular hydrogen bonding. Because the solvent is aprotic, strong hydrogen bonding to the solvent does not dominate the acidic proton's interactions with electronegative centers. As a result, monosuccinate is stabilized by an intramolecular hydrogen bond. The resulting geometry of monosuccinate is then largely determined by having an optimal distance and angle for the hydrogen bond. Although geometry optimizations are beyond the scope of this paper, it should be noted that potential conformations of monosuccinate with a 74° bond angle include what is categorized by Desiraju and Steiner as a strong hydrogen bond.^{22,23}

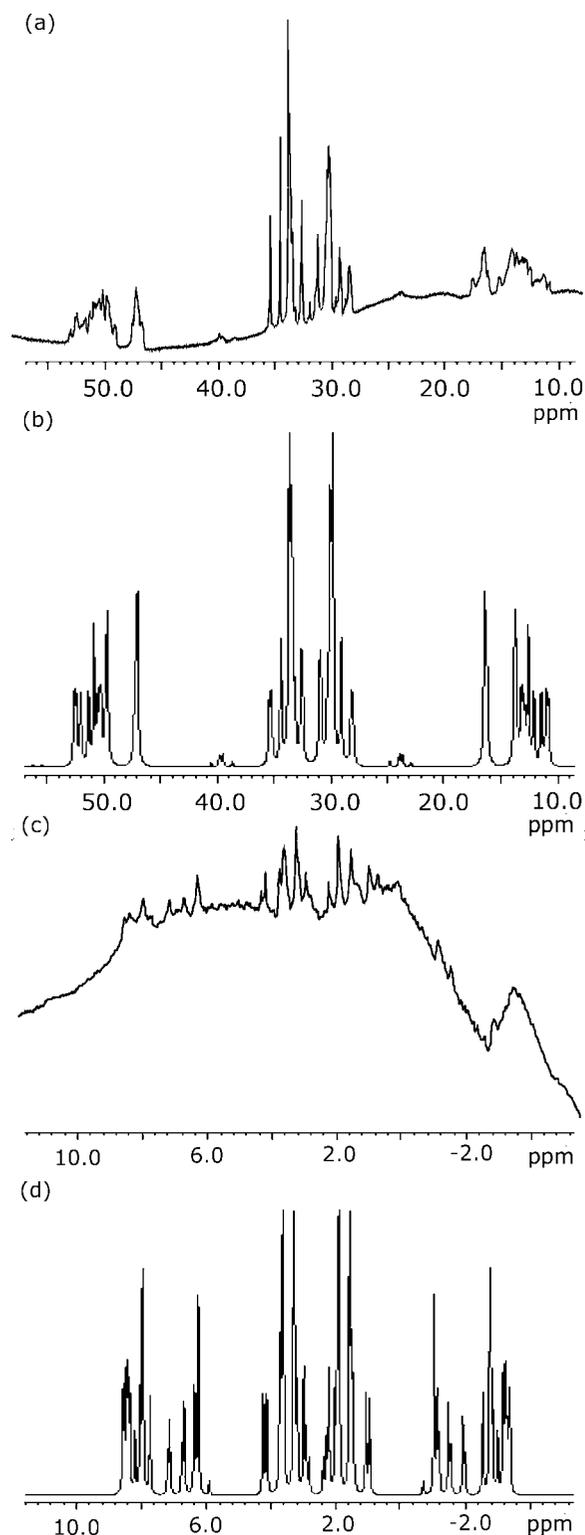
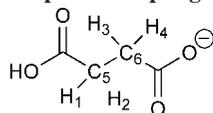


Figure 4. Anisotropic spectra of tetraoctylammonium monosuccinate in nematic phases of the liquid-crystal solutions (all at 50 °C). (a) Anisotropic ¹³C coupled spectrum of tetraoctylammonium monosuccinate (¹³C labeled at the 2 and 3 carbons). (b) gNMR fit of part a. (c) Anisotropic ¹H spectrum of monosuccinate. (d) gNMR simulation of the ¹H spectrum using the same dipolar and scalar couplings as the ¹³C spectrum. The visible peaks in part c are seen in part d and therefore serve as verification of the accuracy of the fit in part b.

Methods

Tetraoctylammonium Monosuccinate Synthesis. Succinic acid (20 mg, 2,3 ¹³C labeled) was dissolved in a minimal amount of water in a round-bottomed flask, then 0.51 mL of

TABLE 1: Observed Dipolar Couplings



J	units, Hz	D	units, Hz
J_{12}	-5.41	D_{12}	881.79
J_{13}	2.01	D_{13}	-17.74
J_{14}	9.73	D_{14}	-370.39
J_{15}	128.45	D_{15}	1074.47
J_{16}	-4.45	D_{16}	-53.81
J_{56}	30.16	D_{56}	-161.16

TABLE 2: Calculated Dipolar Couplings

D	units, Hz
D_{12}	878.55
D_{13}	-20.40
D_{14}	-362.78
D_{15}	1078.15
D_{16}	-63.13
D_{56}	-167.14

20% tetraoctylammonium hydroxide was added, which resulted in a phase separation in the form of a liquid–liquid emulsion. Methanol was added until the emulsion cleared. This was stirred and rotovapored until a very small amount of liquid tetraoctylammonium monosuccinate remained.

NMR Sample Preparation. A solution of 9 mg of tetraoctylammonium monosuccinate was made up with 370 mg of an equimolar mixture of 4'-(pentylxy)-4-biphenylcarbonitrile and 4'-(heptylxy)-4-biphenylcarbonitrile.

Procedure for Obtaining NMR Spectra. The sample was heated to 70 °C in the 500 MHz spectrometer tuned for ^{13}C NMR and ^1H NMR, at which temperature the sample is visibly homogeneous. Shimming was performed manually by viewing the spectrum and shimming until the line shape appeared most correctly. ^1H NMR, proton-decoupled ^{13}C NMR, and proton-coupled ^{13}C NMR spectra were taken. The sample was then cooled to 50 °C at a rate of -1 deg/3 min. The spectrometer was retuned for ^{13}C NMR and ^1H NMR. Proton-coupled ^{13}C NMR and ^1H NMR spectra were taken. All spectra were taken over a period of 5–15 min, as appropriate for obtaining resolved spectra, except the proton-coupled ^{13}C NMR spectrum taken at 50 °C, which was allowed to scan for 8 h. The signals were not locked on any of these samples, because there is no strong solvent peak to lock on when working with liquid crystals.

It may be noted that the anisotropic ^1H spectrum (Figure 4c) could afford significant improvement. This may be possible with modern NMR technology. However, the anisotropic ^1H spectral simulation (Figure 4d) presented offers verification of the fit of the anisotropic ^{13}C spectrum (Figure 4b), since it is simulated

by using the same scalar and dipolar couplings as the ^{13}C fit, and the observable peaks in the ^1H spectrum are seen in this simulation.

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