was also isolated which had the following spectroscopic properties: ir spectrum (CH_2Cl_2) showed absorptions characteristic of sulfinates, 1128 (s) and 952 (s), and of sulfinamides, 1085 (s), 1057 (s), 1016 (m), 868 (m); nmr ($CDCl_3$) δ 1,39 (d, 3, J = 7.0 Hz), 2.38 (s, 3), 2.41 (s, 3), 3.70 (quintet, 1, J = 7.0 Hz), 5.24 (d, 1, J = 7.0 Hz), 7.2–7.61 (m, 13). This material was presumably *l*-ephedrine *O*-(*p*-toluenesulfinyl)-*p*-toluenesulfinamide.

Methylmagnesium Bromide. A solution of methylmagnesium bromide (based on 40 mg (1.64 mmol) of magnesium) and 190 mg of (1.64 mmol) TMEDA in 15 ml THF was added dropwise with stirring to a soluton of 250 mg (0.82 mmol) of (*R*)-*l*-ephedrine *p*-toluenesulfinate [(*R*)-**7a**] in 20 ml of THF at −25°. The reaction was allowed to continue for 1.5 hr. The usual work-up followed by thick-layer chromatography using 20% methylene chloride and acetonitrile solvent mixture as the eluent afforded 63 mg (51%) of pure methyl *p*-tolyl sulfoxide: mp 75–76° (lit.[3,36] mp 74–75.5°); $[\alpha]^{25}_{546}$ +182.5° (c 2.13, acetone) (lit.[36] $[\alpha]^{25}_{546}$ +180.5° (c 1.61, acetone)). No *l*-ephedrine *p*-toluenesulfinamide (**3a**) could be detected or isolated.

A similar result was obtained when this reaction was carried out in the absence of TMEDA.

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Electric Field Effects in the ^{13}C Nuclear Magnetic Resonance Spectra of Unsaturated Fatty Acids. A Potential Tool for Conformational Analysis[1a]

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Abstract: The source of nonequivalence in the ^{13}C chemical shifts of unsaturated carbons in fatty acids is shown to arise from a linear electric field effect. The behavior of the nonequivalence is in accord with predictions of direction, magnitude, distance, and solvent dependence. The effect is larger than previously reported for protons and fluorine and is discernible at least eight C–C bonds away from the head group dipole. We predict that this linear electric field effect, which is dependent both on distance and orientation factors, will play an important part in future cmr conformational studies.

Conformational data on molecules which are large or members of complex structures are essential to our understanding of many problems of chemical and biological interest. Proton magnetic resonance spectroscopy has in the past been a principle source of this type of data, and for most molecules it will continue to be so. However, as the molecules of interest become larger and more complex, line broadening and spectral overlap tend to detract from the ease with which information can be obtained by this technique. In these cases, carbon-13 magnetic resonance (cmr) offers potential advantages in the form of great dispersion of ^{13}C chemical shifts, smaller line broadening, and the consequent improved resolution.[2] Before cmr can be applied to conformational studies a number of conformationally dependent parameters must be identified. One such parameter, the γ-carbon contribution to chemical shift, has been identified[3] and applied to the analysis of hydrocarbon chain conformation in a model membrane system.[4] However, progress in such cmr studies has in general been restricted by the small number of parameters, such as the γ effect, known to be conformationally dependent, and the accuracy of any conformational interpretations, particularly those of cmr shift data, has been limited by uncertainties in the contributions from other, unknown, effects.

The present study provides evidence for the existence of a significant electric field dependent contribution to ^{13}C chemical shift, which should be useful in conformational analysis and describes in detail the dependence of this contribution on molecular geometry and functionality. The existence of such an effect has been suggested by Horsley and Sternlicht[5a] and by McFarlane[5b] but their papers have received surprisingly little attention and, to our knowledge, no application to conformational problems has been suggested. This linear field dependent contribution can be interpreted on the basis of polarization of the bonds between carbon and adjacent atoms by an electric field originating at a molecular dipole, point charge, or other intra- or intermolecular source and, as for analogous effects in fluorine and proton magnetic resonance,[6,7] the contribution to chemical shift can be represented as a sum of terms with linear and second-order de-

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(1) (a) Support for this work by the National Institute of General Medical Sciences, U. S. Public Health Service GM 19035, and by the Biotechnology Resources Branch of the National Institutes of Health (RR00356) is gratefully acknowledged. (b) Department of Chemistry.

(2) A. Allerhand, D. Doddrell, V. Glushko, D. Cochran, E. Wenkert, P. Lawson, and F. Gurd, *J. Amer. Chem. Soc.*, 93, 544 (1971).

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(6) J. Feeney, L. H. Sutcliffe, and L. H. Walker, *Mol. Phys.*, 11, 117 (1966).

(7) A. D. Buckingham, *Can. J. Chem.*, 38, 300 (1960).

pendence on the electric field. The electric field squared term, which will dominate at short distances from point charges or molecular dipoles, has been considered previously.[6] However, the linear term which is our principal concern here should prove to be the more useful analytical parameter in future cmr conformational studies.

The linear electric field effect will be discussed in the light of data on olefinic carbons in a series of fatty acid esters having their sites of unsaturation at positions varying from the 5 carbon to the 15 carbon. These molecules are of special interest to us because of their importance as widespread constituents of biological membrane systems. They also offer a reasonably good system for the analysis of the electric field effect, despite their flexibility, because they lack any distinguishable functionality for large distances on either side of the double bond site. This allows us to discount σ-inductive and magnetic anisotropic contributions to chemical shift which might otherwise complicate the analysis.

The electric field effect appears particularly large for the unsaturated carbons of the esters and, in this case, manifests itself as a nonequivalence in chemical shift of the two carbons at the double bond. This nonequivalence is very large (3.20 ppm) at the 5,6 position in *cis*-5-tetradecenoic acid and is still discernible (0.10 ppm) at the 11–12 position in tri-*cis*-11-eicosaenoylglycerol. The rate of decrease of the nonequivalence as the unsaturated bond moves down the chain is consistent with the expected decrease of the resolved component of the dipole field along the unsaturated bond. The value of the computed linear electric field coefficient, although about 45 times larger than that of the C–H case[7] and about 5 times larger than that of the C–$^{13}CH_2$–C case,[8] can be rationalized in terms of the results of molecular orbital calculations on a model system. The size of the effect holds particular promise for application to conformational problems because it can produce significant and resolvable shifts at interaction distances where other contributions to chemical shift become negligible for unsaturated systems. The manifestations of the effect as a nonequivalence of two carbons in the same spectrum is also useful because it eliminates errors due to referencing when comparing results from different spectra.

Experimental Section

Fatty acids, methyl esters, and triglycerides were purchased from the Hormel Institute (Austin, Minn.), Nu Chek Prep (Elysian, Minn.), Farchan Laboratories (Willoughby, Ohio), and Analabs (North Haven, Conn.).

Methyl esters, ^{13}C enriched at odd carbons, were obtained by biosynthetic incorporation of sodium [1-^{13}C]acetate (Merck Sharp and Dohme, Canada, Ltd.) into a double mutant of *E. coli* (CY2 *aceF, gltA*) which uses acetate almost exclusively as a fatty acid carbon source. Methyl esters were prepared from the cell lipids and purified by argentation silica gel column chromatography and glc on a diethylene glycol succinate column. Because only small quantities were prepared, the ^{13}C enriched samples were run in much more dilute solution than the natural abundance spectra. Except where noted, natural abundance samples were prepared using 500 mg of the compound under investigation, 0.15 ml of hexamethyldisilane (HMDS) as internal ^{13}C standard, and 1.35 ml of chloroform and were run in 10-mm sample tubes. Hexafluorobenzene contained in a 5-mm tube mounted coaxially provided a heteronuclear field-frequency lock.

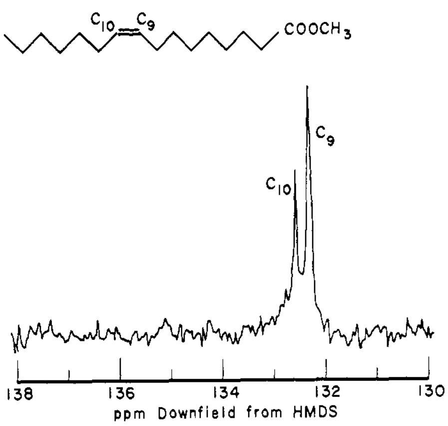

Figure 1. Unsaturated carbon region of the cmr spectrum of 3% ^{13}C odd carbon enriched methyl palmitoleate. This 16K spectrum was obtained on a Bruker HX-90-E spectrometer courtesy of Bruker Scientific Inc., Elmsford, N. Y. 10523.

The spectra were obtained at ~45° by a proton noise decoupled ^{13}C Fourier transform operation using a computer-controlled system based on a Bruker 21.5 Kgauss spectrometer.[9] An 8K data set was used where not otherwise indicated. Under these conditions, measured chemical shifts are correct to ±0.05 ppm and narrow peaks as close as 0.10 ppm can be resolved. Chemical shifts were measured with reference to the $\omega - 1$ carbon of the hydrocarbon chain and converted to an HMDS scale by the relationship $\delta_c = \delta_c^{\omega-1} + 25.20$ ppm.

Results and Discussion

Assignments. The assignment of the carbon resonances of fatty acids and their methyl esters is a prerequisite to the understanding of the origin of chemical shift differences in these systems. Some preliminary work has been reported[10–12] which assigns several of the resonances in the spectra to specific saturated carbons and assigns resonances in the region about 132 ppm downfield from HMDS collectively to the unsaturated carbons. Complete assignments of the chemical shifts of the common monounsaturated fatty acids will be published elsewhere,[8] but as we will be considering differences in the chemical shifts of the two olefinic carbons in the present study, the assignment of each peak in the unsaturated region to a specific carbon must be pursued at this point.

The assignment is most easily accomplished by the selective biosynthetic enrichment of all odd numbered carbons as described in the Experimental Section. Figure 1, which displays the unsaturated region of the spectrum of a methyl palmitoleate (methyl *cis*-9-hexadecenoate) sample prepared in this manner with about 3% enrichment, clearly shows the enriched (C-9) peak to lie upfield of the natural abundance (C-10) peak. Table I shows the shifts of the vinyl carbons of a series of monounsaturated methyl esters, some at natural abundance and some enriched at odd carbon positions, together with a parent alkene. We see in the data for 60% ^{13}C odd carbon enriched methyl *cis*-7-tetradecenoate that the resonance position

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[8] J. G. Batchelor, R. J. Cushley, J. H. Prestegard, and S. R. Lipsky, *J. Org. Chem.*, submitted for publication.

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[12] K. Kanohta, *Eisei Shikenjo Hokoku*, **89**, 1 (1971).

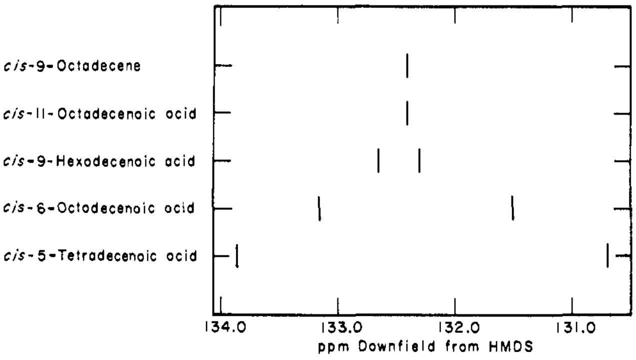

Figure 2. Olefinic ^{13}C chemical shifts of an alkene and a series of monounsaturated fatty acids with varying head group-double bond separations.

Table I. ^{13}C Shifts of Unsaturated Carbon Resonances in Long Chain Methyl Esters

Compd	Position	Shift, ppm	Position	Shift, ppm
cis-9-Tetradecene	C-9	132.40	C-10	132.40
Methyl *cis*-15-tetracosaenoate (methyl nervonate)	C-15	132.4[e]	C-16	132.4[e]
Methyl *cis*-11-octadecenoate (methyl vaccenate)	C-11	132.30	C-12	132.30
Methyl *cis*-9-hexadecenoate (methyl palmitoleate)	C-9	132.35	C-10	132.55
Methyl *cis*-9-hexadecenoate[a] (methyl palmitoleate)	C-9	132.40	C-10	
Methyl *cis*-7-tetradecenoate[b]	C-7	132.05	C-8	
Methyl *cis*-6-octadecenoate (methyl petroselinate)	C-6	131.6[e]	C-7	133.0[e]
Methyl *cis*-6-octadecenoate[c]	C-6	131.90	C-7	132.80
Methyl *cis*-6-octadecenoate[d]	C-6	131.45	C-7	132.60

[a] 60% ^{13}C-9 enriched, 20 mg/ml. [b] 60% ^{13}C-7 enriched, 2 mg/ml. [c] Acetone solution. [d] Cyclohexane solution. [e] 4K data set used.

of the enriched (C-7) olefinic carbon also lies well upfield from the average position of the unsaturated peaks in any of the spectra. This suggests that the upfield peak of this and all other methyl esters can be assigned to the double bond carbon closest to the head group. In line with this suggestion, assignments of all fatty acids and related compounds, as presented in Figure 2 and Tables I and II, have been made assuming that the most upfield resonance in the olefinic region of the spectrum corresponds to the unsaturated carbon nearest the carboxy end of the chain. This assumption will be shown to be consistent with our interpretation of the origin of the chemical shift differences in these compounds.

Table II. ^{13}C Shifts in Various 9-Unsaturated Compounds

Compd	C-9, ppm	C-10, ppm
9-Octadecynoic acid (stearolic)	82.45	82.70
cis-9-Hexadecenoic acid (palmitoleic)	132.30	132.55
Oleic acid (*cis*-9-octadecenoic)	132.2[a]	132.5[a]
Trioleoylglycerol	132.1[a]	132.4[a]
1-Monooleoylglycerol	132.2[a]	132.5[a]
Oleoyl alcohol	132.35	132.45
Octadecyl oleate	132.15	132.45
Oleoyl methyl sulfonate	132.20	132.55
trans-9-Octadecenoic acid (elaidic)	132.70	133.05

[a] 4K data points used.

Nonequivalence of Chemical Shifts. Figure 2 shows the shifts of the vinyl carbons in a series of monounsaturated fatty acids with varying sites of unsaturation and a parent alkene for comparison. The salient feature of the chemical shifts is that the two peaks for the double bond shift in opposite directions, increasing the nonequivalence of the unsaturated carbons as they are moved from the 11–12 position to the 5–6 position in the fatty acid chain. This nonequivalence ranges from less than 0.05 ppm for 11-*cis*-octadecenoic acid to 3.20 ppm for 5-*cis*-tetradecenoic acid. Comparable nonequivalencies are observed for the methyl esters, alcohols, and triglycerides.

In view of the widely adopted formalism for explaining shifts in hydrocarbons and related molecules,[13-16] which is based on a sum of, at most, four empirical terms attributed to α, β, γ, and δ substituents, the observed nonequivalence is surprising. Oleic acid, for example, which has an observed nonequivalence of 0.3 ppm has not only equivalent methylene substituents at the α, β, γ, and δ positions on either side of the double bond, but it has three additional equivalent methylenes beyond these points.

Although the shifts for the unsaturated carbons in the compounds of Table II are apparently insensitive to changes in head group and although the head groups are in all cases separated from the unsaturated site by eight C–C bonds, the observed nonequivalences are clearly linked to the C-1 functional group. This fact is demonstrated by the dependence of the shifts on bond position and by the absence of nonequivalence in parent hydrocarbons. However, considering the distances involved and the relatively slow decrease in nonequivalence with bond position, σ-inductive effects can be ruled out as a mechanism of transmission.[17] Likewise, distance and local symmetry of the site make differential solvent effects unlikely. Anisotropic magnetic susceptibility effects associated with the head groups can be ruled out even in 5-*cis*-tetradecenoic acid since resonances of the C-5 and C-6 carbons in saturated acids differ in chemical shift by less than 0.2 ppm.[8] Steric explanations based on molecular association are also unlikely because of the similarity of the effect in acids, esters, and alcohols which are expected to have vastly different associative properties.

With most common sources of chemical shift perturbation eliminated, we propose that the observed effects are a result of polarization of the bonds by the electric field associated with the dipolar head groups. The experimental values for the dipole moments of the molecules considered are sufficiently similar to explain the apparent insensitivity to functionality and we will demonstrate in the following paragraphs that the direction, the dependence on bond position, the solvent dependence, and the magnitude of the effect are all consistent with the electric field interpretation.

(13) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, 86, 2984 (1964).

(14) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

(15) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7107 (1970).

(16) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, 36, 2757 (1971).

(17) A. Streitweiser, Jr., "Molecular Orbital Theory," Wiley, New York, N. Y., 1961, p 128.

Theory of Electric Field Shift Dependence. Buckingham[7] has presented a general expression for electric field contributions to the rotationally averaged shielding constant of a nucleus in a molecular environment in terms of a power series in the electric field, E. An equivalent statement for the contribution to chemical shift δ_{el} is the following

$$\delta_{el} = E_i A_{ij} dR_j + E_i E_j B_{ijk} dR_k \qquad (1)$$

Here E_i are components of the field vector, dR_k are components of a unit vector fixed in the molecular framework, A_{ij} are components of a second rank tensor, and B_{ijk} are components of a third rank tensor.

The linear component can be viewed as originating largely *via* polarization of a molecular bond by an electric field. In the case of a nucleus involved in one axially symmetric bond, where the $\bar{z}$ axis of the coordinate system and the unit vector $d\vec{R}$ have been chosen along the bond, all elements of the tensor A_{ij} except A_{zz} can be shown to be zero and the linear term reduces to the familiar expression for X–H[7] and X–F[6] shifts.

$$\delta = A_{zz} E_z \qquad (2)$$

In the case of a multivalent atom, such as carbon, one seldom finds axial symmetry, and simplification to this degree is not, in general, possible. The sp^2 bonding of an olefinic carbon has planar symmetry and hence we would expect no contributions to the linear term from a field perpendicular to this plane. Thus, if we choose $d\vec{R}$ and $\bar{z}$ along the double bond, $\bar{y}$ perpendicular to it and $\bar{x}$ perpendicular to $\bar{y}$ and $\bar{z}$, as shown in Figure 3, all A_{yj} and A_{iy} become zero. If the hydrogen atom were replaced by a carbon atom, the symmetry would be sufficient for the tensor A_{ij} to reduce to a single nonzero term, A_{zz}. Now, since the polarizabilities of C–H and C–C bonds are similar (see Table III) we shall consider that only one term is necessary to describe the linear field dependence of the unsaturated carbons. In fact, CNDO calculations suggest that the error involved in this assumption is no more than 6%. The electric fields at points far from a dipole, such as pairs of unsaturated carbons at carbon numbers 5–6 and above will be very similar. We therefore expect the linear electric field contribution to provide almost equal and opposite shifts of the two carbons.

Table III. Longitudinal Bond Polarizabilities[a]

Bond	$b_{11} \times 10^{+23}$ cm^3
C—H	0.064
C—C	0.099
C═C	0.280
C≡C (terminal)	0.35

[a] R. J. W. Le Fevre, *Advan. Phys. Org. Chem.*, **3**, 1 (1965).

The second-order term can be attributed to the mixing of excited states into the wave function. This causes a downfield shift in sp^3 hybridized systems.[6] Now, any point charge or dipole field arising within a molecule will fall off rapidly with distance so that, at points far removed from the polar group, the second-order terms will become negligible compared to terms linear in E. From its form, we also expect the E^2 term to be unchanged on inversion. E^2 contributions to shift would then be small and cause both carbons in an unsaturated bond to be shifted in the same direction. We will ignore, then, second-order effects in our application of the electric field description. Any residual contribution of the E^2 term can be minimized by confining our discussion to the difference, $\Delta\delta$, between the shifts of a pair of unsaturated carbons.

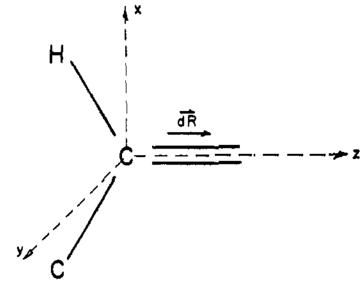

Figure 3. Coordinate system used for the description of linear electric field effects of unsaturated carbons.

Assuming the field to be uniform over the dimensions of the unsaturated fragment, we can express the shift difference as follows

$$\Delta\delta = 2E_z A_{zz} \qquad (3)$$

where E_z is the component of the electric field resolved along the double bond and A_{zz} is the linear electric field coefficient for one of the unsaturated carbons. Our anticipated nonequivalence of olefinic carbon shifts should depend, then, both on the molecular geometry, through E_z, and on the electronic structure of the sp^2 carbon atom through A_{zz}. We now wish to compare theoretical predictions with experiment in order to justify the electric field interpretation.

Dependence of the Shifts on Double Bond Position. Let us first consider geometric effects and attempt to calculate an average field value E_z as a function of bond position on the basis of a model for methyl ester behavior. This will be applicable to other molecules with changes in the dipole moment. We will assume the functional group to be represented adequately by a point dipole $\vec{\mu}$ of magnitude 1.7 debye (the value for methyl acetate[18]) centered at the first carbon and oriented parallel to the first bond of a hydrocarbon chain. The hydrocarbon chain will be represented by a random walk of N steps on a diamond lattice. For ease of computation we will depart from the exact geometry of the unsaturated site and represent it as the bond between the N and $N + 1$ carbon atoms on the diamond lattice. For a given chain conformation the vector to the Nth carbon atom will be $\vec{R}(N)$ and the unit vector along the double bond from the N to the $N + 1$ carbon will be $d\vec{R}$. In this notation, the component of the field *in vacuo* at carbon atom N, resolved along the double bond, is given by

$$E_z(N) = \frac{3(\vec{\mu}\cdot\vec{R}_N)(\vec{R}_N\cdot d\vec{R})}{R_N^5} - \frac{\vec{\mu}\cdot d\vec{R}}{R_N^3} \qquad (4)$$

Now, because the field is not uniform in this descrip-

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(18) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963, p 86.

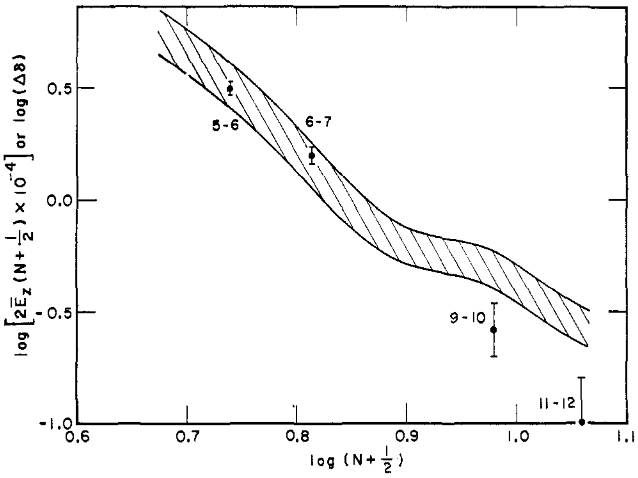

Figure 4. Comparison of shift and electric field dependences on double bond position (N + 0.5). Experimental points for $\Delta\delta$ are taken from Figure 2. $\bar{E}_z(N + 0.5)$ is the average field calculated for a weighted average of chain conformations. The width of the cross hatched area indicates the range of $\bar{E}_z(N + 0.5)$ values so obtained.

tion and we wish to simplify our notation, we shall consider

$$\Delta\delta = [E_z(N) + E_z(N + 1)]A_{zz} = 2E_z(N + 0.5)A_{zz} \quad (5)$$

by analogy with eq 3.

The magnitude of $E_z(N + 0.5)$ and, therefore, $\Delta\delta$ is expected to decrease with increasing separation of the dipole and double bond because of both distance and orientation effects. If the chain were rigid, the orientation of the double bond relative to the dipole would remain fixed (at least within an odd or even series of unsaturates) and only distance would contribute to a decrease in $E_z(N + 0.5)$. It would drop in proportion to N^{-3}. If the chain conformation were highly labile we would have to average $E_z(N + 0.5)$ over many conformations. For a completely random chain conformation, R would increase[19] as $N^{0.5}$, and the distance contribution to the drop in $E_z(N + 0.5)$ would be proportional to $N^{-1.5}$. However, in this case, orientation of the double bond relative to the dipole also becomes random forcing $E_z(N + 0.5)$ very quickly to zero. Since there is some preference for trans conformers, the actual rate of decrease with bond–dipole separation must be somewhere between these extremes. In an attempt to predict the decrease of $E_z(N + 0.5)$ with bond position more accurately, we used a FOCAL program run on a PDP 8/E computer which generates random conformations, calculates $E_z(N)$ for each, weights each with respect to a Boltzmann factor calculated using a temperature of 300°K and an energy of 0.5 kcal for each gauche bond in the carbon chain, and prints an average value for $E_z(N)$. The results of calculations based on 1000 or more points are presented in Figure 4 in the form of a log–log plot. Errors based on the standard deviations of a series of calculations are indicated by the width of the theoretical line. Certain systematic errors will also exist because of failure to include gauche (+)/gauche (−) interactions and to exclude chain overlap. If we wish to express our predicted fall off rate in terms of some power of N, the best value is −3.5. It is interesting to note that this is very near to the value expected for an all-trans, rigid chain.

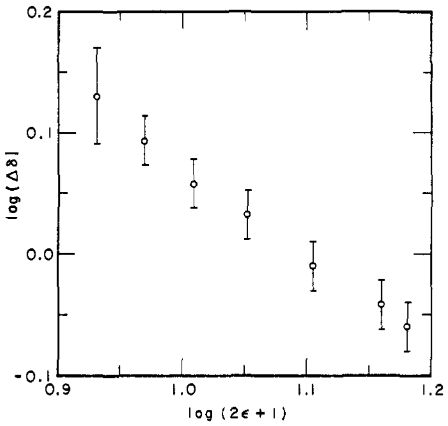

Figure 5. Shift nonequivalence, $\Delta\delta$, observed for methyl petroselinate in a series of chloroform–acetone solvent mixtures as a function of (2ϵ + 1) for the solution.

The experimental points for a series of fatty acids in chloroform, with which we wish to compare our predictions, are also shown in Figure 4. The scales for electric field and chemical shift have been chosen so that the points for the calculated value of $2E_z(6 + 0.5)$ and the observed shift for petroselinic acid are superimposed. The experimental slope is −4.0, a value which we believe to be close enough to the predicted value to support our electric field interpretation. This slope is also small enough to rule out any σ-inductive mechanism. The observed value of $\Delta\delta$ at a *cis*-9-unsaturated bond is 8% of that for a *cis*-5-unsaturated bond whereas even the Branch and Calvin treatment of inductive effects would predict a value only 1% of that for the *cis*-5 bond.[17]

Dependence of the Shifts on Solvent. The fact that the observed distance dependence is slightly greater than that predicted could have its origin in the complex solvent dielectric effects which one expects for field dependent phenomena. In the long hydrocarbon chains of fatty acids and their esters the reaction field treatment of solvent effects based on a molecular model in which the dipole is part of a spherical molecule of isotropic polarizability is clearly not applicable.[7,20,21] However, a qualitative prediction of solvent effects in the present case can be made if we assume the dipole to be a point surrounded isotropically by molecules of the solution (excluding its own hydrocarbon chain). The field at a distant double bond will then appear to be that from a dipole of magnitude $3\epsilon\mu/(2\epsilon + 1)$, where μ is the dipole moment *in vacuo* and ϵ is the dielectric constant of the solution.[22] Further, if we can consider the double bond to have a similar environment, then the electric field it experiences should depend on $(1 + 2\epsilon)^{-1}$.

In Figure 5 we present a log–log plot of $\Delta\delta$ *vs.* $(1 + 2\epsilon)$ for methyl petroselinate (methyl *cis*-6-octadecenoate) in a series of chloroform–acetone mixtures as solvents. Methyl petroselinate was chosen because it shows large values of $\Delta\delta$ which can be measured quite

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(19) C. Tanford, "Physical Chemistry of Macromolecules," Wiley, New York, N. Y., 1967, pp 150–170.

(20) J. K. Becconsall and P. Hampson, *Mol. Phys.*, 10, 21 (1966).

(21) L. Onsager, *J. Amer. Chem. Soc.*, 58, 1486 (1936).

(22) J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955, p 148.

accurately and because it is unlikely to self-associate to any great degree. The solvents were chosen to be compatible with the solubility properties of the ester and to give a wide range of dielectric constants for the solvent. Solution dielectric constants were estimated by Debye's formula from the constants for the pure substances.

Figure 5 illustrates qualitatively the predicted solvent dielectric dependence in that $\Delta\delta$ does decrease as ϵ increases. The slope of -0.7 which is close to the theoretical value of -1.0 may be somewhat fortuitous. One component of our solvent system, chloroform, has a small tendency to hydrogen bond to the ester moiety which could lead to an enhanced dipole and greater than expected shifts for low dielectric points.[23] Other solvents, such as cyclohexane and ethyl acetate, do not in fact fall on the acetone–chloroform line but on a line of somewhat less negative slope.

Slopes which are less steep than -1.0 are not inexplicable and may indicate that contributions more typical of the reaction field type should be considered for conformers which bring the double bond very close to the head group. These contributions tend to reinforce the head group dipole field and oppose contributions from the mechanism we have used to describe the solvent effects. Other types of solvent–solute interaction or even dielectric saturation may also be sources for this type of deviation. However, the reaction field contribution is appealing in that one would expect it to decrease as the double bond is moved down the chain and its contribution would help rationalize the steeper than expected decrease of $\Delta\delta$ with bond position discussed in the previous section. It also explains why, for *cis*-9-unsaturated chains, we have observed a greater change of $\Delta\delta$ with solvent than in the *cis*-6-unsaturated methyl petroselinate.

Direction of the Shifts. The most concrete support for the electric field interpretation involves the direction of the shifts. For all the compounds we have studied, the dipole is directed such that the potential increases as one moves toward the head group. For unsaturated carbons the polarizability of the double bond is very large; thus the electron density on the unsaturated carbon nearer to the head group will be increased while that on the other unsaturated carbon will be decreased. In view of the established correlation of electron density with shift,[24] the carbon nearer the head group is predicted to be shifted upfield. This interpretation agrees with the two instances in which we have been able to make positive assignments (methyl *cis*-9-hexadecenoate and methyl *cis*-7-tetradecenoate) and forms the basis for assignment of peaks in all our spectra. For compounds in which the dipole direction will be opposite with respect to the chain, such as primary amines, we would predict the assignments to be reversed.

There are other qualitative observations of the ^{13}C shifts in fatty acids and esters which can be explained on the basis of polarizabilities and shift/electron. The relevant polarizability quantity is the vectorial bond polarizability sum over every bond connected to the carbon in question. The large value of this quantity for unsaturated carbons is consistent with their high electric field shifts. The lower sensitivity of methylenes to field effects, as evidenced by their apparent equivalence beyond the C-6 carbon, is due to the similar magnitudes of C–H and C–C bond polarizabilities (see Table III). Comparison of the shifts of unsaturated carbons in palmitoleic (*cis*-9-hexadecanoic) and stearolic (9-octadecynoic) acids shows that there is approximately the same sensitivity to electric field effects for double and triple bonds. On the basis of polarizabilities one would have expected $\Delta\delta$ to be about 1.5 times greater in the sp hybridized system (stearolic acid). However, differences in sensitivity of chemical shift to electron density for various carbons must also be taken into account. Although no correlation of shifts with electron density appear to have been performed for alkynes, there is some evidence to suggest that the correlation coefficient is likely to be at least 30% smaller for the triple bonded carbons.[25] This would explain the similarity of the observed $\Delta\delta$ values in the two systems.

Magnitude of the Shifts. The simplest solvent system would be one in which the dielectric constant is unity. Such systems do not exist; however, an estimate of $\Delta\delta$ in such a system can be obtained by extrapolating the data for acetone and cyclohexane solutions to a dielectric constant of one. Using this method, $\Delta\delta$ for methyl petroselinate is found to be 1.34 ppm. With this shift difference and our calculated value of the field at the double bond in the ideal system, a value of 9.3×10^{-11} esu^{-1} is obtained for A_{zz}. The magnitude of this coefficient is very large and of some significance in light of its potential application in conformational analysis. It is about five times the size of the corresponding coefficient for saturated carbon shifts[8] and about 45 times the size of the corresponding coefficient for proton shifts in C–H bonds.[7]

The magnitude is particularly striking in terms of the difference, $\Delta\delta$, between the shifts of adjacent carbons along a chain, because adjacent unsaturated carbons shift in opposite directions. This means that $\Delta\delta$ for olefinic carbons is about 15 times that for a corresponding pair of saturated carbons.[8]

In attempts to rationalize ^{13}C shift trends it has become common practice to correlate shifts of analogous carbons in a series of closely related molecules with calculated charge densities.[26–29] Although such correlations have usually been used to rationalize response to substituent changes, simple charge density calculations can be performed in a manner which mimics the effect of a point charge; thus, the re-

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(23) In two other cases for which we have data, that of an unsaturated acid in a chloroform–acetone system and for an unsaturated methyl ester in a chloroform–methanol system, the decrease of $\Delta\delta$ with dielectric constant is respectively greater than and less than that for the ester in a chloroform–acetone system. This behavior would be predicted on the basis of hydrogen bonding considerations, for a hydrogen bond to a head group oxygen will increase the positive charge on C_1 and hence the field along the chain.

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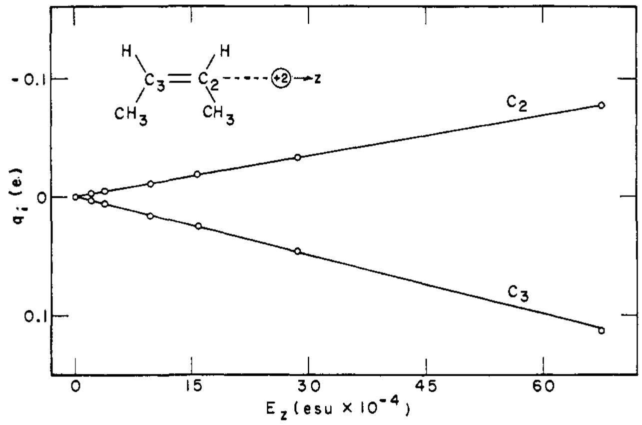

Figure 6. Changes in charge density, calculated by the CNDO method, for the olefinic carbons of *cis*-2-butene, due to a point charge placed on the double bond axis.

sponse of our system to an electric field arising from a point charge at various distances from the molecule can be predicted. Charge densities were calculated using the CNDO/2 method[30] for *cis*-2-butene in the H-eclipsed conformation (our model for the unsaturated site) with a simulated charge on the C-2–C-3 bond axis at 5, 7, 9, 15, and 20 Å from the C-3 carbon.[31] Figure 6 shows the results of these calculations; the atomic charge densities, q_i, for the two olefinic carbons are plotted as a function of field strength at the C-2–C-3 bond midpoint. The calculated values for each olefinic carbon atom were fitted by a nonlinear regression program to a power series with terms up to second order in E_z.

$$\delta q = a_0 + a_1E_z + a_2E_z^2 \qquad (6)$$

The linear coefficient of the difference between the charges on the two unsaturated carbons, a_1(C-3) − a_1(C-2), taking E_z to be the field at the center of the double bond, is 2.66 ± 0.01 × 10^{-7} e/esu. The second-order term falls off very rapidly and for positions analogous to that of the C-5 carbon in *cis*-5-tetradecenoic acid it is less than 0.01% of the linear term.

Using the shift/electron value of 182 ppm/e, derived by Nelson, *et al.*,[29] for a series of monosubstituted benzenes, and the charge/field coefficient derived above, a value of 2.5 × 10^{-11} esu^{-1} is obtained for A_{zz} of a single unsaturated carbon. This value differs from our observed value of 9.3 × 10^{-11} esu^{-1} by a factor of 3.7. However, it is still large compared to the A_{zz} values for protons[7] and for ^{13}C in methylenes.[8]

It is useful to note that the changes in charge density can also be estimated by considering them to be due to a sum of polarizations of individual bonds according to a formula simular to that proposed by Horsley and Sternlicht[5]

$$\delta q = \sum b_{zz}E_z/el \qquad (7)$$

which is a vectorial sum over each of the bonds of the atom. E_z is the field resolved parallel to each bond, l the bond length, b_{11} its empirical longitudinal polarizability as shown in Table III, and e the electronic charge. The predicted value of A_{zz} using this method, and once again ignoring A_{xx} and A_{yy}, is 5.5 × 10^{-11} esu^{-1}, a much closer estimate of our observed value.

There are several factors which may account for the difference between observed and calculated values. First, the coefficient of the shift produced at an isolated double bond per electron has not been investigated and the value of 182 ppm/e which we have used might well be in error. Secondly, the calculation of fields in flexible systems is difficult and can vary dramatically with minor errors in our model. For example, an error of one C–C bond in our description of the chain would reduce E_z by a factor of 2. Thirdly, our assumption that the complex methyl ester head group could be represented by a point dipole is suspect. In fact, we would calculate very similar values of $\Delta\delta$ for an alcohol and a methyl ester which have similar total dipole moments. However, the value of $\Delta\delta$ observed for the alcohol, which has a less complex head group, is about $^1/_2$ that for the ester and is much closer to our estimated value.

In view of these possibilities, we would prefer to quote a range for the value of A_{zz} from 2.5 to 9 × 10^{-11}. This rather large range represents the difference between our experimental and theoretical values. In either limit, however, the sensitivity of chemical shift is greater than that previously observed for other nuclei and it holds much significance for conformational studies.

Conclusion

Because of electric field effects, the ^{13}C chemical shift is a parameter which will be highly dependent on molecular geometry. It will vary with distance between a localized molecular charge distribution and an identifiable ^{13}C site, and it will depend on the orientation of the bonds containing this site relative to the local electric field. Moreover, the magnitude of its dependence on electric field, at least for unsaturated systems, is such that electric field contributions can dominate other contributions to variation in ^{13}C shift and can be easily resolved at large bond–charge separations. Since conformational studies depend on the existence of measurable parameters that are highly dependent on molecular geometry and originate with a single easily identifiable source, we feel that electric field induced ^{13}C shift studies will find wide application in the study of molecular geometry.

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(31) The effect of a point charge was simulated by an appropriately placed helium atom. The 1s electrons were "removed" by setting the one-electron energy parameter $U_{1s,1s}$ for helium to +50.0 eV and the molecular charge to +2. The resonance integral proportionality constants $\beta_{\mathrm{HeH}}{}^0$ and $\beta_{\mathrm{HeC}}{}^0$ were chosen to be −9.00 and −12.75 eV, respectively; the helium 1s exponent was taken to be 1.70, the value given by Slater's rules. Charge densities at helium (always less than 0.0028 e) and at the two olefinic carbon atoms were found to be insensitive to variation of any of the semiempirical parameters.