Independent of the nucleofuge is the relative reactivity of the enolate ion with respect to the amide ion, as reckoned from the relative amount of **7** and **8** formed vis-à-vis **9**, taking into account the concentrations of the two nucleophiles.[12] The rate constant ratio, $k_{enolate}/k_{NH_2^-}$, is identical within experimental error for all four 2-halomesitylenes, with value 0.5. Amide ion is twice as reactive as acetone enolate ion with the indicated mesityl radical intermediate.[13] The constancy of this rate ratio supports the hypothesis that the halogen has departed before the aryl moiety interacts with the nucleophile or nucleophiles.

Strongly dependent on the nucleofugal group is the ratio of mesitylene (**10**) to combined substitution products, which varies from as high as 4/1 with **6f** to as low as 1/4 with **6i**. Also strongly dependent is the ketone/alcohol (**7**/**8**) ratio, which changes from about 0.5 with **6f** to as high as 40 with **6i**. These dependencies are consistent with the model of $S_{RN}1$ reaction during mixing, as outlined above.[14]

Thus far, our efforts to find some inadequacy in the model of $S_{RN}1$ reaction during mixing are not very successful. These efforts have, however, demonstrated a very unusual juxtaposition of constancy and sharp variability of product ratios within a single reaction series.

(12) J. F. Bunnett in "Investigation of Rates and Mechanisms of Reactions", 3rd ed., E. S. Lewis, Ed., Wiley, New York, 1974, Part I, p 159.
(13) Toward phenyl radical, as determined in a similar experiment with diphenyl sulfide as substrate, amide ion was found to be 1.9 times as reactive as acetone enolate ion (at −78 °C): J. F. Bunnett and B. F. Gloor, unpublished experiment.
(14) A secondary factor affecting the **7**/**8** ratio is the amide ion concentration. From **6f**, **6b**, and **6i**, the **7**/**8** ratio is higher at higher amide ion concentrations. This effect is plausibly attributed to acceleration of proton transfer step 5 with consequent reduction of the steady-state concentration of arylacetone and therefore of the backsliding conversion of it to 1-aryl-2-propoxide ion via steps 10, 8, and 9 when the solvated electrons arrive en masse. We have observed similar behavior in reactions of PhCl and PhI with acetone enolate ion (eq 1); the **1**/**2** ratio is higher at higher potassium *tert*-butoxide concentrations.
(15) On sabbatical leave from Vassar College, 1979–1980.

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Restricted Rotational Isomerization in Polymethylene Chains

Sir:

Although gauche–trans isomerization is a commonly accepted mechanism for reorientation of polymethylene chains, there is a dearth of direct experimental evidence for the existence of gauche isomers. Presumably this is because of the short lifetimes involved, and, correspondingly, spectroscopic techniques operating in the frequency range above 10^{10} Hz provide the most convenient means of detecting such species.[1] In addition, in discussions of gauche–trans isomerization of small molecules in the gaseous phase, it is generally assumed that all gauche isomers which do not violate the pentane rule ($g^{\pm}g^{\mp}$) are available as possible chain configurations. We present here results of ^{2}H NMR studies which strongly suggest the existence of long-lived gauche isomers ($\tau \sim 10^{-5}$–10^{-6} s) in polymethylene chains of glycolipid bilayers. Moreover, the spectra suggest some novel features of gauche–trans isomerization in condensed media; in particular, the results can only be interpreted in terms of a model involving restricted isomerization. By restricted, we mean that of the four possible diamond lattice orientations available for a CD vector at a particular carbon segment, only two are appreciably populated.

(1) Flory, P. J., "Statistical Mechanics of Chain Molecules"; Interscience: New York, 1969; p 49.

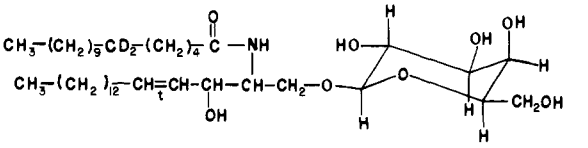

Figure 1. Structure of *N*-palmitoylgalactosylceramide.

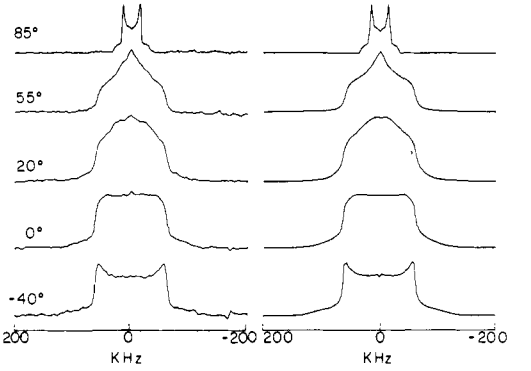

Figure 2. (Left) Experimental 45.2-MHz ^{2}H NMR spectra of aqueous dispersions of 6,6-d_2PGAC–50 wt % H_2O, obtained as a function of temperature. (Right) Theoretical simulations of the experimental spectra. The following parameters were used: −40 °C, P_1:P_2 = 0.98:0.02, k_{12} = 3 (±2) × 10^3 s^{-1}; 0 °C, P_1:P_2 = 0.8:0.2, k_{12} = 2.5 (±0.5) × 10^5 s^{-1}; 20 °C, P_1:P_2 = 0.7:0.3, k_{12} = 9 (±2) × 10^5 s^{-1}; 55 °C, P_1:P_2 = 0.5:0.5, $k_{12} \geq 3 \times 10^6$ s^{-1}; 85 °C, axially symmetric spectrum with $\Delta\nu_{Q\perp}$ = 28.2 kHz. Uncertainties in P_1 and P_2 are 5–10%.

Figure 1 shows the structure of the glycolipid studied, *N*-palmitoylgalactosylceramide (PGAC), which has been ^{2}H labeled at the 6 position of the *N*-acyl chain by chemical synthesis.[2] Cerebrosides, like other lipids, undergo first-order thermotropic phase transitions from a relatively ordered lamellar crystalline or gel phase to a disordered lamellar liquid crystalline phase.[3] However, in contrast to most naturally occurring lipid molecules, the transition temperatures (T_c) of cerebrosides are relatively high,[4] 82 °C for the *N*-palmitoyl derivative studied here.[2,3] In addition, in cerebroside bilayers, rotation of the molecules about their long axis for all $T < T_c$ is slow on our NMR time scale. Evidence for this is available from a number of different experiments. For example, [^{13}C]carboxamido-labeled cerebrosides dispersed in excess water show axially asymmetric ^{13}C NMR powder patterns (under conditions of ^{1}H dipolar decoupling) which are essentially identical with those obtained from a dry powder for all $T < T_c$.[5] These two features of cerebrosides permit observation of restricted rotational isomerization. In particular, since axial diffusion is effectively absent, any narrowing of ^{2}H NMR spectra of chain-labeled species must be due to internal modes of chain reorientation. Furthermore, the high glycolipid T_c allows us to drive thermally activated modes of chain isomerization to the fast exchange limit, where ^{2}H spectra may be easily interpreted.

We show on the left of Figure 2 typical ^{2}H NMR spectra of *N*-palmitoylgalactosylcerebroside labeled with $^2H_2$ at the 6 position of the acyl chain (6,6-d_2PGAC) as a function of temperature in the range −40–85 °C.[6] At sufficiently low temperatures (−40

(2) Skarjune, R.; Oldfield, E. *Biochim. Biophys. Acta* **1979**, *556*, 208.
(3) Skarjune, R.; Oldfield, E.; Shipley, G. G., unpublished results.
(4) Oldfield, E.; Chapman, D. *FEBS Lett.* **1972**, *21*, 303.
(5) Huang, T. H.; Wittebort, R. J.; Skarjune, R.; Griffin, R. G.; Oldfield, E., to be published.
(6) ^{2}H spectra were obtained using the quadrupole echo technique (Davis, J. H.; Jeffrey, K. R.; Bloom, M.; Valic, M. I.; Higgs, T. P., *Chem. Phys. Lett.* **1976**, *42*, 390) with a 2–2.5-μs $\pi/2$ pulse, a τ delay of 30–50 μs, and quadrature phase detection. Samples consisted of ~50–70 mg of lipid dispersed in an equivalent weight of ^{2}H-depleted H_2O. Temperature control was achieved with a gas flow system. Simulations were corrected for rolloff due to finite pulse width (Bloom, M.; Davis, J. H.; Valic, M. I. *Can. J. Phys.*, in press) and distortions arising from the echo τ value being comparable to the motional correlation times (Spiess, H. W.; Silescue, H. *J. Magn. Reson.*, in press). We thank Drs. Bloom and Spiess for preprints describing these calculations.

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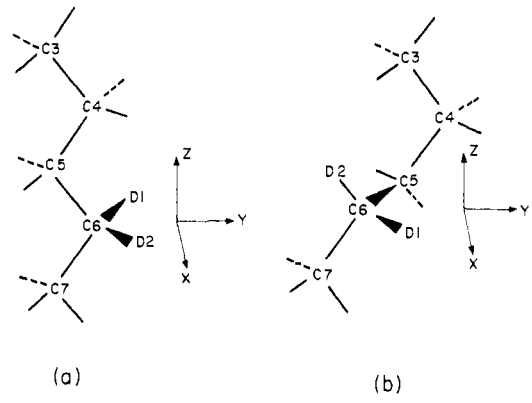

Figure 3. Twofold jump isomerization in a polymethylene chain segment: (a) trans configuration; (b) gauche configuration. Note that in the gauche configuration D1 assumes the orientation originally occupied by D2.

°C) the expected axially symmetric ($\eta = 0$) ^{2}H NMR spectrum is observed, characteristic of an immobile or nearly immobile acyl chain. As the temperature is raised, this spectrum is motionally averaged, first collapsing to a flat-topped spectrum (0 °C), then the center becomes rounded (20 °C), and finally for $T \gtrsim 40$ °C, a totally axially asymmetric spectrum is observed—the asymmetry parameter is unity—and the total spectral breadth is ~120 kHz. For $T > T_c = 82$ °C (liquid-crystal phase) the spectrum is essentially the same as that found for other lipids, being axially symmetric with a quadrupole splitting ($\Delta\nu_{Q\perp}$) of ~30 kHz.[2,7,8] Observation of axially asymmetric spectra suggests that the motional process responsible for the collapse has twofold or lower symmetry. In addition, the nature of the motion must be such that it results in an $\eta = 1$ spectrum, and the total breadth of this spectrum must be ~120 kHz. One motional process which satisfies these requirements is two-site gauche–trans isomerization.

Figure 3a shows an all-trans chain deuterated at the C6 segment, together with a Cartesian XYZ coordinate system, with Z parallel to the chain axis and Y bisecting the DCD angle. When a gauche bond appears in the chain, a structure such as that shown in Figure 3b forms, and it can be seen that D1 assumes the orientation originally occupied by D2. In the limit of fast exchange and assuming equal populations of the two isomers shown in Figure 3, the expected spectrum is easily calculated. The component along Z is unaffected by the motion and is $\omega_\perp$, while the component along Y is zero, since the two C–D vectors are, by virtue of the tetrahedral bonding, at the "magic angle" with respect to this direction. Since the tensor must be traceless, the third (X) component is $-\omega_\perp$. Thus, with this type of twofold motion between equally populated sites and with $(e^2qQ/h) \sim 167$ kHz, the spectrum is totally axially asymmetric and its breadth $\Delta = 2\omega_\perp \sim 120$ kHz. The motionally averaged tensor for D2 is congruent to that for D1; it has the same principal values but a different orientation. Similar line shapes have been observed in ^{2}H spectra of crystalline hydrates.[9]

Shown on the right of Figure 2 are theoretical simulations of the experimental spectra. It is assumed that the C–D bond is jumping between two diamond lattice sites having an angular separation of 109.5°, occupation probabilities P_1^{eq} and P_2^{eq}, and a rate constant k_{12} satisfying microscopic reversibility ($P_1^{eq}k_{12} = P_2^{eq}k_{21}$). The spectrum obtained at 55 °C is in the fast motion limit, $k_{12} = 3.1 \times 10^6$ s^{-1}, and its shape is determined predominantly by P_1^{eq} and P_2^{eq}. Conversely, the low-temperature spectrum obtained at −40 °C approaches the slow limit, $k_{12} = 3.1 \times 10^3$ s^{-1}. At temperatures between these limits, spectra are in the intermediate exchange region, and consequently the line shapes

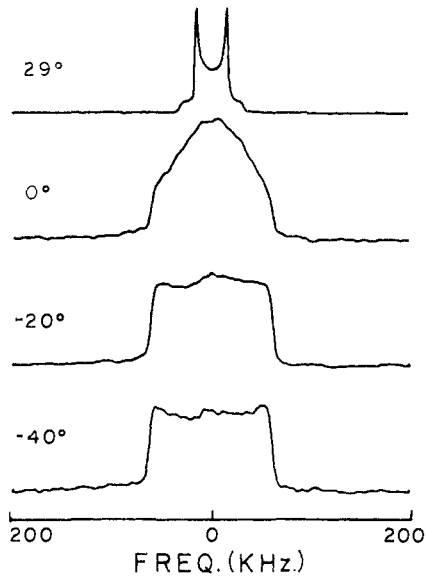

Figure 4. Experimental ^{2}H NMR spectra of 6,6-d_2DMPC–50 wt % H_2O dispersions as a function of temperature. The intermediate exchange spectra for this lipid are very similar to those for PGAC, which suggests that restricted gauche–trans isomerization also occurs in lecithins.

are sensitive to both the populations and exchange rates. However, satisfactory theoretical line shapes can only be obtained for a limited range of populations and k_{12}. For example, the flat-topped spectrum observed at 0 °C cannot be simulated if the populations depart from those given by more than 5–10%; uncertainties in the k_{12}'s are given in the figure caption.[10] Note that a typical lifetime for a conformational isomer at these temperatures is 10^{-5}–10^{-6} s.

In principle there are of course other gauche isomers which could be involved in the motional process. For isntance, isomerization about C4–C5 could occur in the other direction. Also, if isomerization occurs about C5–C6, then other CD tensor orientations are obtained. In general this leads to a four-site chemical exchange problem where the CD vectors are oriented along the principal directions of a tetrahedron, one corresponding to the trans state and three corresponding to gauche states. It can be shown that this type of reorientation will yield an $\eta = 1$ spectrum if the occupation probabilities generate twofold symmetry about the "average" tensor orientation. However, if greater than two-site exchange is allowed, then the breadth of the spectrum is less than the observed 120 kHz. In particular, for three-site exchange with occupation probabilities of $^1/_2$, $^1/_4$, and $^1/_4$, Δ = 88 kHz and for four-site exchange with probabilities of $^1/_3$, $^1/_3$, $^1/_6$, and $^1/_6$, Δ = 42 kHz.[5] Thus, the only way to obtain an $\eta = 1$ spectrum with the required 120-kHz breadth, as is shown in Figure 2, is to have primarily two-site isomerization such as that shown in Figure 3.[11]

At first thought it might appear unreasonable that only one of the three possible gauche CD vector orientations at a given carbon is populated. However, we are not dealing with an isolated gas-phase chain. Instead, the N-acyl chain is connected to a sphingosine moiety, and thus modes of isomerization which take the N-acyl chain into the neighborhood of the sphingosine chain will be sterically unfavorable. In addition, the chains are embedded in a lattice (albeit a soft one) which should also constrain the

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(8) Oldfield, E.; Meadows, M.; Rice, D.; Jacobs, R. *Biochemistry* **1978**, *17*, 2727.
(9) Mehring, M. "NMR Basic Principles and Progress"; Springer-Verlag: New York, 1976; Vol. 11. Soda, G.; Chiba, T. *J. Chem. Phys.* **1969**, *50*, 439.

(10) The angular minimum for trans–gauche isomerization is generally assumed to be 112° for gas-phase molecules. Since this quantity is uncertain for condensed media we have assumed tetrahedral geometry (120°) for the calculations of Figure 2. Using 112° produces an ~5% difference in the P_i which is within our experimental error.
(11) For 6,6-d_2PGAC two-site isomerization is sufficient to explain the spectra. However, recent results for other chain positions indicate that at least a third and perhaps a fourth site are involved in the isomerization, though not with equal populations.

modes of isomerization. One motional model which has been discussed in connection with conformational reorientation in situations like this (e.g., polymers) is the Boyer crankshaft motion[12] which may be represented by TTTGTG'TTT ⇄ TTTTTGTG'T. This motion, which is equivalent to the diffusion of a GTG' sequence by two units along the chain, leaves the ends of the chain in place during the isomerization. However, at specific carbon segments, G ⇄ T and T ⇄ G' conformational jumps occur, and these are "two-site" jumps which would produce the effects observed in the ^2H NMR line shapes.

It should also be mentioned that torsional oscilltions could contribute to averaging of the ^2H NMR spectra. In fact, if these oscillations are sufficiently large (±70°), they will result in an $\eta = 1$ spectrum of 120-kHz breadth. Since the maximum in the trans–gauche energy barrier occurs at ±60°, it appears that this mechanism would reduce to discrete isomerization if the bonds were rigidly coupled and the oscillations were constrained to a single carbon segment. However, this seems physically implausible; a more reasonable mechanism might involve smaller angular excursions at individual segments which would accumulate to ±70° excursions at the carbon of interest. Alternatively, torsional oscillations within discrete rotational isomers may be contributing to the averaging process. Thus, while the diamond lattice jumping model provides a convenient physical and mathematical framework to understand our results, it may represent an oversimplification of the motional processes which are actually present.

Finally, it is reasonable to inquire if this type of phenomenon is a general property of polymethylene chains in lipid bilayers, and there is some evidence that this is indeed the case. For example, we have shown in Figure 4 spectra of 1-myristoyl-2-[6,6-$^2H_2$]myristoyl-*sn*-glycero-3-phosphocholine (DMPC) and note that the spectra observed for this lipid at −20 and 0 °C are remarkably similar to the cerebroside spectra at 0 and 20 °C, respectively. Since lecithins undergo phase transitions at much lower temperature (23.5 °C in the case of DMPC), it is not possible to obtain a fast-limit $\eta = 1$ spectrum. Nonetheless, the similarities in the low-temperature line shapes, where axial diffusion is absent, suggest that the motional processes in both types of lipid bilayers are similar. Thus, we tentatively conclude that lecithins are also undergoing the type of restricted rotational isomerization discussed for glycolipids.[13]

In summary, we have observed for the first time axially asymmetric deuterium spectra from a specifically ^2H-labeled polymethylene chain. This special line shape suggests that the motional process responsible for it is discrete reorientation, and its breadth is only consistent with a two-site exchange process between trans and gauche isomers. At temperatures just below T_c, the jump rate is in the fast exchange limit and the two allowed diamond lattice sites are equally probable. As the temperature is lowered, both the jump rate and one of the site probabilities decrease. The similarity between line shapes in glycolipids and lecithins suggests that this mechanism may be common to polymethylene chains in lipid bilayers.

Acknowledgment. Thanks are accorded to M. G. Munowitz for his assistance in the early stages of the line-shape calculations and J. Schaefer for helpful comments regarding reorientation mechanisms in polymers. This work was supported in part by the National Institutes of Health (Grants CA-00245, GM-23289, GM-25505, and RR-00995), the National Science Foundation (Grant PCM 78-23021, Contract C-670), and the Alfred P. Sloan Foundation.

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(13) DMPC spectra in the temperature range 10–23 °C are complicated by the presence of a pretransition (Ladbrooke, B. D.; Chapman, D. *Chem. Phys. Lipids* **1969**, *3*, 304). As a consequence, we believe they consist of a superposition of spectra from molecules which are undergoing slow axial diffusion and molecules which are not. These spectra will be discussed in a future publication.

(14) USPHS National Research Service Postdoctoral Fellow, 1978–1980.
(15) Alfred P. Sloan Research Fellow, 1978–1980; USPHS Research Career Development Awardee, 1979–1984.
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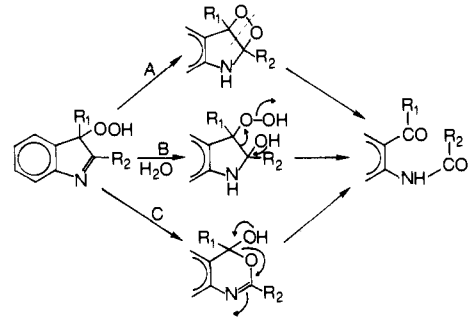
Received June 16, 1980

Differentiation between Criegee Rearrangement and Dioxetane Rearrangement Mechanisms for the Decomposition of α,β-Unsaturated Hydroperoxides

Sir:

There are three known mechanisms for the decomposition of α,β-unsaturated hydroperoxides which result in C—C bond scission and the formation of C=O bonds (for example, eq 1). Rearrangements by mechanism C received consideration in the 1940s and 1950s, but little since.[1,2] The involvement of pathway A in the decomposition of 3-(hydroperoxy)indolenines is supported by the chemiluminescence which accompanies this process.[3] However, Witkop[2] presented arguments for C rearrangement of the structurally related 11-(hydroperoxy)tetrahydrocarbazolenine, and Hamilton[4] has pointed out that path C should be favored over A due to the ring strain which accompanies dioxetane formation. It has been possible in several systems to determine the extent of competition between paths A and B.[5,6] Under the anhydrous and anerobic conditions of this study, path **B** cannot be operative. We report herein a means for determining the extent of competition between reaction A and another intramolecular rearrangement which we can only assume to be a Criegee-type reaction (path C).[7] This procedure depends upon the reductive trapping



(1)

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