metabolite (2-methyl ester) was then isolated from the extracted mixture by low-pressure silica gel chromatography (1:19 ethyl acetate–hexane) and was analyzed by NMR.[8] Essentially quantitative retention of deuterium in the metabolite was indicated by its mass spectrum (Figure 1b),[9] which exhibited both a base peak (due to decarbomethoxylation) and a molecular ion one mass unit higher than the corresponding peaks in the spectrum of a reference sample (Figure 1a). Deuterium retention and localization of the label on the methylene group of the acetic acid side chain were independently confirmed by the NMR analysis, the sharp two-proton singlet adjacent to the ester methyl in a reference sample (Figure 1a) being replaced by a broad (deuterium coupled) one-proton signal in the metabolite (Figure 1b).

The chemical oxidation of acetylenes has been the focus of considerable experimental attention.[10] However, the intrinsic instability of the strained antiaromatic oxirene moiety has foiled all attempts to directly demonstrate its existence, although indirect evidence supports its transient formation.[10] Particularly relevant is the oxidative conversion of disubstituted acetylenes to disubstituted ketenes due to substituent migration.[8a,d] Surprisingly, however, no mechanistic studies have been carried out on the chemical oxidation of terminal acetylenes. The fate of the deuterium on oxidation of [1-^{2}H]-**1** with *m*-chloroperbenzoic acid in the presence of methanol (as a ketene trap) has therefore been examined.[11] The spectroscopic data on the methyl 2-biphenylacetate thus obtained (Figure 1c), virtually indistinguishable from that of the biological product (Figure 1b), places beyond question the occurrence of an intramolecular 1,2 shift in the chemical process. The observation of a 1,2-hydride shift in both the peracid oxidation and microsomal metabolism of a triple bond[12] establishes that acetylenic moieties are in fact oxidatively metabolized and lucidly demonstrates that this oxidative process involves reaction of the activated oxygen with the π bonds rather than with the terminal C–H bond of the acetylene.

This laboratory has recently demonstrated that the prosthetic heme moiety of cytochrome P-450 is alkylated during catalytic turnover of terminal acetylenes.[7,14] A mechanism involving an electron-deficient transient species generated by oxygen transfer to the acetylenic π bonds has been proposed for this suicidal interaction.[7] Both phenylacetylene[7a] and biphenylacetylene[14] mediate such cytochrome P-450 destruction, even though neither is a particularly effective agent. The present evidence for π-bond involvement in oxidative metabolism of acetylenes confirms a key aspect of the proposed destructive mechanism and suggests that enzyme destruction and metabolite formation are competitive outcomes of enzymatic triple bond oxidation.

Acknowledgment. Biphenylacetylene was kindly provided by Dr. R. E. McMahon (Eli Lily Co.). Support for the mass spectrometer facility is provided by NIH Grant RR 00719. This research was funded by NIH Grant GM 25515.

(9) The intensity of the peak at *m/e* 157 in Figure 1b suggests the presence of a trace of undeuterated **2**. This most likely reflects slow chemical exchange of the methylene protons in **2** subsequent to the metabolic reaction.

(10) (a) Stille, J. K.; Whitehurst, D. D. *J. Am. Chem. Soc.* **1964**, *86*, 4871. (b) McDonald, R. N.; Schwab, P. A. *Ibid.* **1964**, *86*, 4866. (c) Concannon, P. W.; Ciabattoni, J. *Ibid.* **1973**, *95*, 3284. (d) Ciabattoni, J.; Campbell, R. A.; Renner, C. A.; Concannon, P. W. *Ibid.* **1970**, *92*, 3826. (e) Timm, U.; Zeller, K. P.; Meier, H. *Chem. Ber.* **1978**, *111*, 1549.

(11) A mixture of deuterated biphenylacetylene (10 mg) and 12 mg of *m*-chloroperbenzoic acid was stirred for 24 h in CH_2Cl_2 containing 1% MeOH. The resulting reaction mixture was washed ($NaHCO_3$) and concentrated.

(12) By analogy with the oxidative NIH shift of aromatic hydrogens,[13] the present class of rearrangements could properly be termed the UC shift.

(13) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science* **1967**, *158*, 1524.

(14) Under conditions similar to those already published,[7a] a 10 mM concentration of biphenylacetylene brings about a 10% loss of cytochrome P-450 in 30 min.

(15) Fellow of the Alfred P. Sloan Foundation.

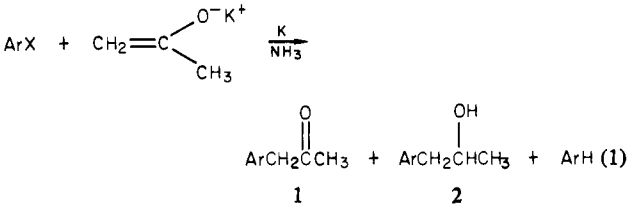
Paul R. Ortiz de Montellano,*[15] Kent L. Kunze
Department of Pharmaceutical Chemistry
School of Pharmacy, University of California
San Francisco, California 94143
Received July 28, 1980

Product Ratios Dependent on and Independent of the Left Group in a Single Series: Potassium Metal Provoked Reactions of Aryl Halides with Amide and Acetone Enolate Ions That Occur during Mixing[1]

Sir:

The term "leaving group" has been variously used by physical organic chemists, for example, sometimes for a nucleofugal group in a molecule eligible to react with a nucleophile, sometimes for the nucleofuge detached as a consequence of reaction, often nonspecifically for both these meanings as well as for the group as it exists in the transition state. We use in the title the unusual term, "left group", because we refer to a system in which selection between alternative products is strongly influenced by leaving groups which have become detached from the substrate at the point of selection.

The system to which we refer is that of aryl halides (ArX) reacting with potassium acetone enolate and potassium metal in liquid ammonia.[2,3] Products are an arylacetone (**1**), the corresponding 1-aryl-2-propanol (**2**), and the dehalogenation product (ArH) (eq 1). Observed product distributions are strongly de-



pendent on the halogen. For example, with fluorobenzene the amount of benzene is high (~30%) and the ketone/alcohol (**1**/**2**) ratio is low (<0.3), while with iodobenzene the amount of benzene is low (~5%) and the **1**/**2** ratio is high (>5). Although these product distributions vary somewhat from experiment to experiment, the dominant factor in their determination is the identity of the halogen. Minor changes in the aromatic moiety do not have much effect on the product distribution.[3]

These reactions are understood in terms of the elaborated $S_{RN}1$ mechanism[4] sketched in Scheme I.[3] This is a radical chain mechanism, although the chain is sometimes forestalled by the incursion of termination steps. Step 1 is the initiation component, steps 2, 3, and 4 are the propagation cycle, and steps 6 and 8 effect termination. Steps 5, 7, and 9 are proton-transfer reactions, and step 10 involves electron transfer. According to this mechanism, product selection between substitution (**1** plus **2**) and dehalogenation (ArH) involves competition between steps 3 and 6 while selection between ketone (**1**) and alcohol (**2**) concerns whether step 4 or 8 is utilized.

A noteworthy feature of this mechanistic representation is that, despite the observed strong leaving group effects on product composition, *the leaving group is not present in the reacting species at the points where product selection occurs.* Actually this is not quite completely the case inasmuch as ArX is involved in step 4 which is competitive with step 8, but we have shown that the identity of the halogen at this point is not the dominant factor.[3] Insight into the origin of these effects is provided, within the $S_{RN}1$ framework, by the postulate that reaction occurs *during the mixing process* with the rate of fragmentation of $[ArX]^{-}\cdot$ (in step 2) being identified as the major factor that determines product distribution.

The general idea of this mechanistic model is that reaction occurs during mixing of a solvated electron-containing zone of solution (in ammonia) with a solvated electron-free zone that contains aryl halide molecules as well as enolate ions. When a small portion of solvated electron-containing solution swirls into the solvated electron-free zone, reaction with aryl halide molecules

(1) Research supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(2) R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **94**, 683 (1972).

(3) R. R. Bard, J. F. Bunnett, X. Creary, and M. J. Tremelling, *J. Am. Chem. Soc.*, **102**, 2852 (1980).

(4) J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978).

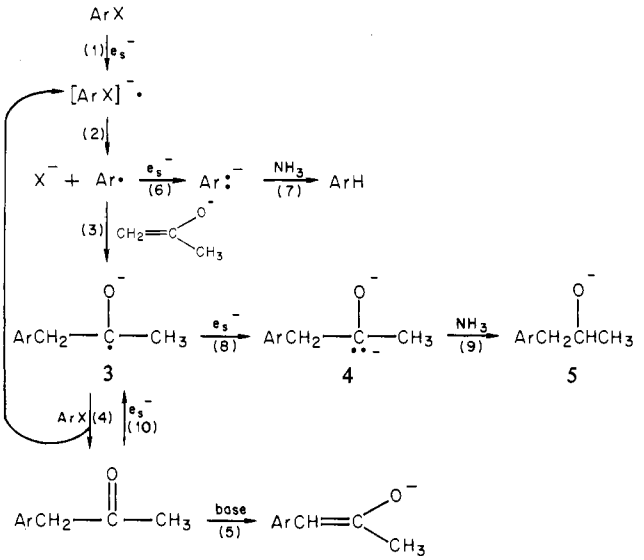
0002-7863/80/1502-7375$01.00/0

Table I. Potassium-Stimulated Competitive Reactions of Halomesitylenes with Potassium Amide and Potassium Acetone Enolate in Liquid Ammonia[a]

expt no.	ArX (M)[b]	[enolate],[c] M	$[KNH_2]$, M	product yields,[d] % 7	8	9	10	ArX recovered,[d] %	k_{en}/k_{NH_2}[e]	7/8[f]
1	6f (0.3)	0.341	0.232	2.8	5.6	11.7	80	0	0.49	0.50
2	6f (0.6)	0.215	0.371	1.8	3.1	18.2	77	0	0.46	0.58
3	6c (0.7)	0.333	0.252	10.2	7.6	26.4	45[g]	0.4	0.51	1.34
4	6c (0.8)	0.226	0.361	5.3	4.0	30.3	41[g]	3.7	0.49	1.33
5	6b (0.4)	0.345	0.274	15.5	3.4	26.1	43[g]	2.9	0.57	4.6
6	6b (0.6)[h]	0.243	0.304	7.2	1.3	22.5	30[g]	16	0.47	5.5
7	6i (0.6)[h]	0.245	0.382	13.5	0.4	43.5	21[g]	17	0.50	34
8	6i (0.3)	0.252	0.364	9.5	<0.2	29.0	25[g]	33	0.47	>40
9	6i (0.3)	0.320	0.236	24.8	2.0	42.2	17[g]	10	0.47	12

[a] All reactions were run in 100 mL of ammonia at −33 °C and were effected by the addition of small bits of potassium. [b] The initial concentration (moles/liter) of the halomesitylene is shown in parentheses. [c] Potassium acetone enolate. [d] As determined by GLC analysis using a 1/8 in × 6 ft 20% Carbowax, 20M Chromosorb P AW 20–100 column with *m*-xylene and naphthalene as internal standards. [e] The ratio of rates for substitution involving enolate and amide as inferred from the initial nucleophile concentrations and the product ratios, on the assumption of first-order involvement of each nucleophile. [f] Ratio of ketone to alcohol in the enolate substitution product. [g] 2–8% of mesitylene dimer, recognized by GC/MS, was also observed. [h] Some of the halomesitylene was initially insoluble.

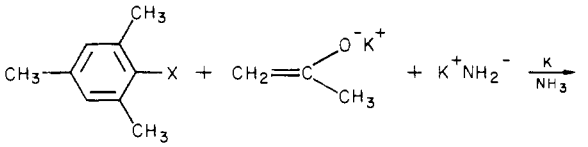
Scheme I



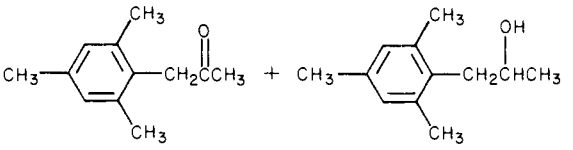
(step 1) brings about mutual annihilation to form $[ArX]^{-}\cdot$. What happens then depends on how fast these radical anions fragment[5] in step 2. If they fragment rapidly (e.g., when X = I), steps 2, 3, 4, and 5 may be largely completed before massive mixing with further solvated electrons occurs, and the arylacetone enolate ion so formed is obtained as arylacetone upon acidification and workup. If they fragment somewhat slowly (e.g., when X = Cl), the system may only have progressed to the stage of ketyl radical anion **3** or to arylacetone by the time of massive mixing with solvated electrons. Once the electrons arrive in force, steps 10, 8, and 9 predominate and 1-aryl-2-propoxide ion is formed. If the $[ArX]^{-}\cdot$ fragment very slowly (e.g., when X = Ph_2As[6,7]), the system may not have got beyond Ar· or even $[ArX]^{-}\cdot$ when the main body of electrons arrives, and ArH is formed via steps 6 and 7.

Our present interest is in probing this model, which to date has successfully accommodated a number of unusual and otherwise very perplexing observations, especially in search of experimental manifestations that may reveal some inadequacy of it. One challenging test is to place acetone enolate ion in competition with a second nucleophile of different character.[8] If the halogen has left at the point of interaction of the aryl moiety with the nucleophile, as postulated in Scheme I, the relative reactivity of two competing nucleophiles should be insensitive to the identity of the halogen, despite the major dependence of other product ratios on this factor.

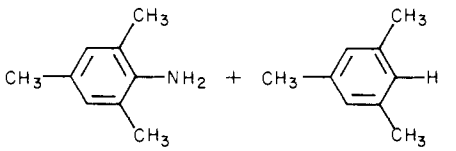
A suitable system for application of this test must meet two requirements: (1) the substitution products must be resistant to secondary cleavage induced by solvated electrons and (2) the nucleophiles must be unreactive with the aryl halides under reaction conditions except as provoked by the addition of solvated electrons. Diethyl phosphite ion[8] is an unsuitable nucleophile for this purpose because diethyl phosphonate esters are cleaved by KNH_2[9] or by solvated electrons in ammonia.[10] Amide ion satisfies the first criterion but would generally fail the second because most aryl halides can react with KNH_2 by the aryne mechanism.[11] We therefore chose to use the four 2-halomesitylenes as substrates in potassium-stimulated reactions with mixtures of acetone enolate and amide ions. The overall reaction is that of eq 2.



6f, X = F
6c, X = Cl
6b, X = Br
6i, X = I



7 **8**



9 **10** (2)

Our experiments are summarized in Table I. They show that, in a single system, two kinds of product ratio depend strongly on the leaving group while one kind of product ratio is independent of the leaving group.

(5) See C. P. Andrieux, C. Blocman, J.-M. Dumas-Bouchiat, and J.-M. Saveant, *J. Am. Chem. Soc.*, **101**, 3431 (1979).
(6) Recent work by R. A. Rossi, R. A. Alonso, and S. M. Palacios (privately communicated) indicates that $[Ar_3As]^{-}\cdot$ fragment to form Ar· and Ar_2As^{-}. However, Ph_3As and acetone enolate in ammonia, when treated with potassium,[7] form benzene in high yield but no **1** or **2**.
(7) R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **96**, 112 (1974).
(8) C. Galli and J. F. Bunnett, *J. Am. Chem. Soc.*, **101**, 6137 (1979).
(9) H. Feuer, W. D. Van Buren II, and J. B. Grutzner, *J. Org. Chem.*, **43**, 4676 (1978).
(10) R. A. Jackson and J. F. Bunnett, unpublished work.
(11) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

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.

Michael J. Tremelling,[15] J. F. Bunnett*
University of California
Santa Cruz, California 95064
Received June 30, 1980

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 ^2H 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.

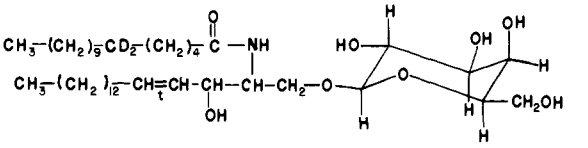


Figure 1. Structure of *N*-palmitoylgalactosylceramide.

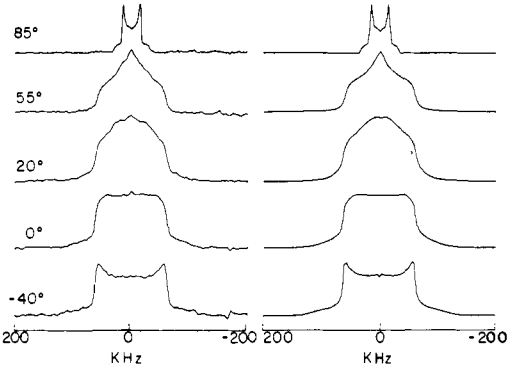


Figure 2. (Left) Experimental 45.2-MHz ^2H NMR spectra of aqueous dispersions of 6,6-d_2PGAC–50 wt % H_2O, obtained as a function of temperature. (Right) Theoretical simulations of the experimental spectra. The following parameters were used: −40 °C, P_1:P_2 = 0.98:0.02, k_{12} = 3 (±2) × 10^3 s^{-1}; 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 ^2H 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 ^1H 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 ^2H 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 ^2H spectra may be easily interpreted.

We show on the left of Figure 2 typical ^2H 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) ^2H 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 ^2H-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.

0002-7863/80/1502-7377$01.00/0