Hydrogen Chemical Shifts of Aliphatic Compounds in Carbon Tetrachloride, Trifluoroacetic Acid, and Trifluoroacetic Acid–Sulfuric Acid[1]

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Hydrogen n.m.r. spectra of solutions of aliphatic halides, trifluoroacetates, nitriles, acetates, ketones, alcohols, and ethers were determined in carbon tetrachloride, trifluoroacetic acid, and trifluoroacetic acid–sulfuric acid. In the acidic solvents, downfield shifts are observed for hydrogens in the vicinity of hydrogen-bonded oxygen- and nitrogen-containing groups.

In connection with studies of enhanced inductive effects in trifluoroacetic acid, attributable to hydrogen bonding between trifluoroacetic acid and oxygen- or nitrogen-containing substituent groups,[2] we were prompted to examine the effect of such hydrogen bonding upon the hydrogen n.m.r. spectra of representative aliphatic compounds. The effect of the more acidic mixed solvent, trifluoroacetic acid–sulfuric acid, was also examined. Large solvent shifts were found which, in appropriate instances, may be employed to advantage in analysis of n.m.r. spectra.

Experimental Section

Pipets long enough for convenient filling of n.m.r. tubes were prepared from 8-mm. glass tubing and calibrated to deliver 40, 350, 10, and 100 μl., respectively. In the usual experiment, 40 μl. of sample, 350 μl. of solvent (carbon tetrachloride or trifluoroacetic acid), and 10 μl. of 30% tetramethylsilane (TMS) in carbon tetrachloride (more easily pipetted than pure TMS) were mixed in an n.m.r. tube to give 400 μl. of 10% solution. The spectra were determined at 60 Mc. on a Varian A-60 spectrometer, and then 100 μl. of 96–98% sulfuric acid was added to the tube containing the trifluoroacetic acid solution. The contents of the latter tube were thoroughly mixed, and the spectrum was again determined. Interestingly, tetramethylsilane was stable in the strongly acidic trifluoroacetic acid–sulfuric acid mixture except on long standing, after which peaks downfield from TMS appeared. Tetramethylsilane is reported to be both insoluble and unstable in sulfuric acid.[3]

Results

Attention was focused on the chemical shifts of the hydrogen atoms attached to the carbon atom carrying an electron-attracting substituent, since such chemical shifts would be expected to be affected to the greatest extent by an enhancement of the inductive effect of the substituent owing to hydrogen bonding to the solvent or to actual protonation of the substituent.

In Table I, methyl, ethyl, and isopropyl compounds are compared. The chemical shifts in parts per million from tetramethylsilane are given for the carbon tetrachloride spectra, followed by the downfield shift in parts per million on changing to the solvents trifluoroacetic acid and trifluoroacetic acid–sulfuric acid, respectively. The smaller solvent shifts of the CH_3 protons of the ethyl groups are tabulated in Table II. In Table III solvent shifts are compared for several compounds which possess the same functional group. The methyl ketones were chosen because of interest in long-range coupling, which may occur in protonated ketones, as mentioned in the Discussion section.

Discussion

The expectation that downfield n.m.r. shifts would occur for hydrogens in the proximity of hydrogen-bonded or protonated aliphatic functional groups is confirmed by the results reported in Tables I–III. Although the present study constitutes only a survey of empirical (but useful) solvent shift effects, it seems helpful, as a working hypothesis, to picture the solvent shift observed on changing from carbon tetrachloride to trifluoroacetic acid as a phenomenon associated with hydrogen bonding, and to associate the additional shifts observed upon adding sulfuric acid to the trifluoroacetic acid with the protonation of the more basic substituents (alternatively, the latter shift could reflect increased hydrogen bonding). Within this conceptual framework it is further helpful to recognize four types of functional groups. (1) The halides show minimal "hydrogen-bonding" shifts and exhibit no tendency to undergo protonation. (2) The trifluoroacetates and nitriles show moderate "hydrogen-bonding" shifts, but exhibit little tendency to interact further (presumably by protonation) upon addition of sulfuric acid. (3) Acetates and ketones show large "hydrogen-bonding" shifts in trifluoroacetic acid and an even larger shift upon adding sulfuric acid. (4) Alcohols and ethers show very large "hydrogen-bonding" shifts; the latter show additional still larger shifts upon adding sulfuric acid, whereas the former are esterified slowly (half-life of 10–30 min.) in trifluoroacetic acid and immediately in trifluoroacetic acid–sulfuric acid.

The postulated behavior of the different aliphatic compounds is in accord with the known properties of the solvents and functional groups involved. Thus, trifluoroacetic acid has an H_0 value of -4.4[4a] or -3.46[4b] as measured by two indicators, and would probably not protonate any of the functional groups studied, especially since the acidity of the trifluoroacetic acid solvent is probably further decreased in the 10% solutions of aliphatic compound in trifluoroacetic acid.[5] Trifluoroacetic acid–sulfuric acid, on the other hand, has a much higher acidity (H_0 = -7.59 for 0.763 moles of sulfuric acid/1000 g. of trifluoroacetic acid[6]),

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[2] (a) P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, **85**, 3608 (1963); (b) P. E. Peterson and C. Casey, *Tetrahedron Letters*, 1569 (1963).

[3] N. C. Deno, H. G. Richey, N. Friedman, J. Hodge, J. Houser, and C. Pittman, Jr., *J. Am. Chem. Soc.*, **85**, 2991 (1963).

[4] (a) F. A. Bovey and G. V. D. Tiers, *ibid.*, **81**, 2870 (1959); (b) H. H. Hyman and R. A. Garber, *ibid.*, **81**, 1847 (1959).

[5] For pK_a values of protonated aliphatic functional groups, see E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

[6] G. Dallinga and G. Ter Maten, *Rec. Trav. Chim.* **79**, 737 (1960).

TABLE I

SOLVENT EFFECTS ON THE CHEMICAL SHIFT IN METHYL, ETHYL, AND ISOPROPYL DERIVATIVES

	Methyl			Ethyl			Isopropyl		
RX	δ_{CH_3} (CCl_4), p.p.m.	Shift, p.p.m., CCl_4 to CF_3CO_2H	Shift, p.p.m., CF_3CO_2H to CF_3CO_2H–H_2SO_4	δ_{CH_2} (CCl_4), p.p.m.	Shift, p.p.m., CCl_4 to CF_3CO_2H	Shift, p.p.m., CF_3CO_2H to CF_3CO_2H–H_2SO_4	δ_{CH} (CCl_4), p.p.m.,	Shift, p.p.m., CCl_4 to CF_3CO_2H	Shift, p.p.m., CF_3CO_2H to CF_3CO_2H–H_2SO_4
RCl							4.12	0.12	0.05
RBr				3.35	0.07	0.05	4.20	0.12	0.05
$ROCOCF_3$			0.05[a]	4.40	0.12	0.07			0.03[b]
RCN	1.95	0.13	0.10	2.32	0.15	0.08			
$R{-}\overset{\overset{O}{\|}}{C}{-}OH$	2.03	0.18	0.40						
$R{-}O{-}\overset{\overset{O}{\|}}{C}CH_3$	3.60	0.25	0.38	4.03	0.27	0.45	4.90	0.25	0.45
$R_1R_2C{=}O$	2.05[c]	0.30	0.45	2.33[d]	0.30	0.47	2.52[e]	0.30	0.43
ROR	3.32	0.33		3.58	0.38		3.90	0.43	
ROH				3.35	0.45	0.63			

[a] For ester formed *in situ* from the alcohol. In trifluoroacetic acid δ_{CH_3} was 4.05. [b] For ester formed *in situ* from the alcohol. In trifluoroacetic acid δ_{CH} was 4.33. [c] Acetone. [d] Diethyl ketone. [e] Methyl isopropyl ketone.

TABLE II

METHYL GROUP CHEMICAL SHIFTS IN ETHYL DERIVATIVES, XCH_2CH_3

X	δ (CCl_4), p.p.m.	$\Delta\delta$, p.p.m., CCl_4 to CF_3CO_2H	$\Delta\delta$, p.p.m., CF_3CO_2H to CF_3CO_2H–H_2SO_4
I	1.87	−0.03	0.0
Br	1.67	−0.02	0.0
$OCOCF_2CF_3$	1.42	0.05	0.03
$OCOCF_3$	1.42	0.03	0.02
$C{\equiv}N$	1.28	0.07	0.03
$OCOCH_3$	1.23	0.12	0.20
$\overset{\overset{O}{\|}}{C}CH_2CH_3$	1.02	0.15	0.20
OH	1.18	0.20	
OCH_2CH_3	1.13	0.18	0.27

TABLE III

SOLVENT EFFECTS ON THE METHYL GROUP CHEMICAL SHIFT IN METHYL KETONES

Ketone	δ_{CH_3} (CCl_4), p.p.m.	$\Delta\delta$, p.p.m., CCl_4 to CF_3CO_2H	$\Delta\delta$, p.p.m., CF_3CO_2H to CF_3CO_2H–H_2SO_4
CH_3COCH_3	2.05	0.30	0.45
$CH_3COCH_2CH_3$	2.03	0.32	0.52
$CH_3CO(CH_2)_2CH_3$	2.03	0.32	0.52
$CH_3COCH(CH_3)_2$	2.05	0.28	0.50

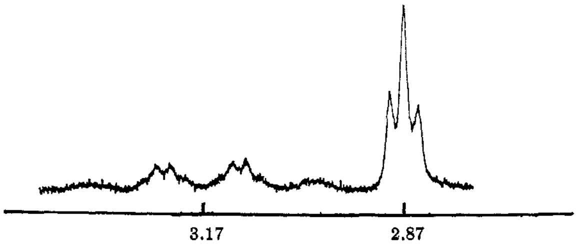

Figure 1.—Long-range coupling in the n.m.r. spectrum of $CH_3COCH_2CH_3$ (methyl ethyl ketone) in trifluoroacetic acid–sulfuric acid. The CH_3CO group appears as a triplet at δ 2.87 (J = 1 c.p.s.) owing to coupling to the CH_2 group. The CH_2 quartet at δ 3.17 likewise shows additional splitting (J = 1 c.p.s.), which may be discerned in the two larger peaks of the quartet.

and predominant protonation of some of our compounds in this mixed solvent seems plausible. In this connection it is notable that some of the trifluoroacetates formed by addition of sulfuric acid to the corresponding alcohol were insoluble in trifluoroacetic acid–sulfuric acid. The trifluoroacetate esters accordingly resemble halogen compounds in their lack of basicity. A comparison may be made with the substituent groups, CF_3O, CF_3S and F_5S.[7] The low basicity of nitriles is reflected in the small effect of added sulfuric acid upon chemical shifts found in the present study. Finally, it may be mentioned that independent evidence for strong hydrogen bonding of the type postulated above is available from Raman and infrared spectral measurements carried out by Professor Bernard Rice and co-workers.[8] In photographic Raman studies, it was found that the nonhydrogen-bonded form of acetonitrile was not observable in 2:1 molar ratios of trifluoroacetic acid–acetonitrile, although the hydrogen-bonded and nonhydrogen-bonded forms were clearly differentiated when appropriate molar ratios of the components were employed.[8b] In contrast, no comparable evidence for hydrogen bonding of ethyl bromide could be obtained. In a complementary infrared study,[8c] trifluoroacetic acid was found to be much more strongly hydrogen bonded to ethyl acetate in carbon tetrachloride solvent than were phenols (for which information was available from the literature). If the above-mentioned unpublished evidence were not available, use of the term "hydrogen-bonding shift" to describe the observed solvent shifts of hydrogen n.m.r. chemical shifts would perhaps not be justified.

It should be noted at this point that the hydrogen-bonding properties of trifluoroacetic acid appear also to be reflected in the large downfield chemical shifts of $(CH_3)_2C^{13}{=}O$, compared with the C^{13} n.m.r. frequencies in nonhydrogen-bonding solvents.[9] Taft and coworkers have attributed solvent-modified fluorine chem-

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[7] (a) W. A. Sheppard, *J. Am. Chem. Soc.*, **83**, 4860 (1961); (b) W. A. Sheppard, *ibid.*, **84**, 3072 (1962); *cf.* ref. 8.

[8] (a) We are grateful to Professor Rice for permission to mention these results prior to publication. (b) B. Hohman, S.C.N., Ph.D. Dissertation, St. Louis University, 1964; available from University Microfilms, Ann Arbor, Mich. (c) C. L. Kong, M.S. Thesis, St. Louis University, 1965.

[9] (a) G. E. Maciel and G. C. Ruben, *J. Am. Chem. Soc.*, **85**, 3903 (1963). The dielectric constant listed by these authors for trifluoroacetic acid (39.5) is an older value. A revised value (8.42, 20°) appears to be the preferred one: (b) W. Dannhauser and R. H. Cole, *ibid.*, **74**, 6105 (1952).

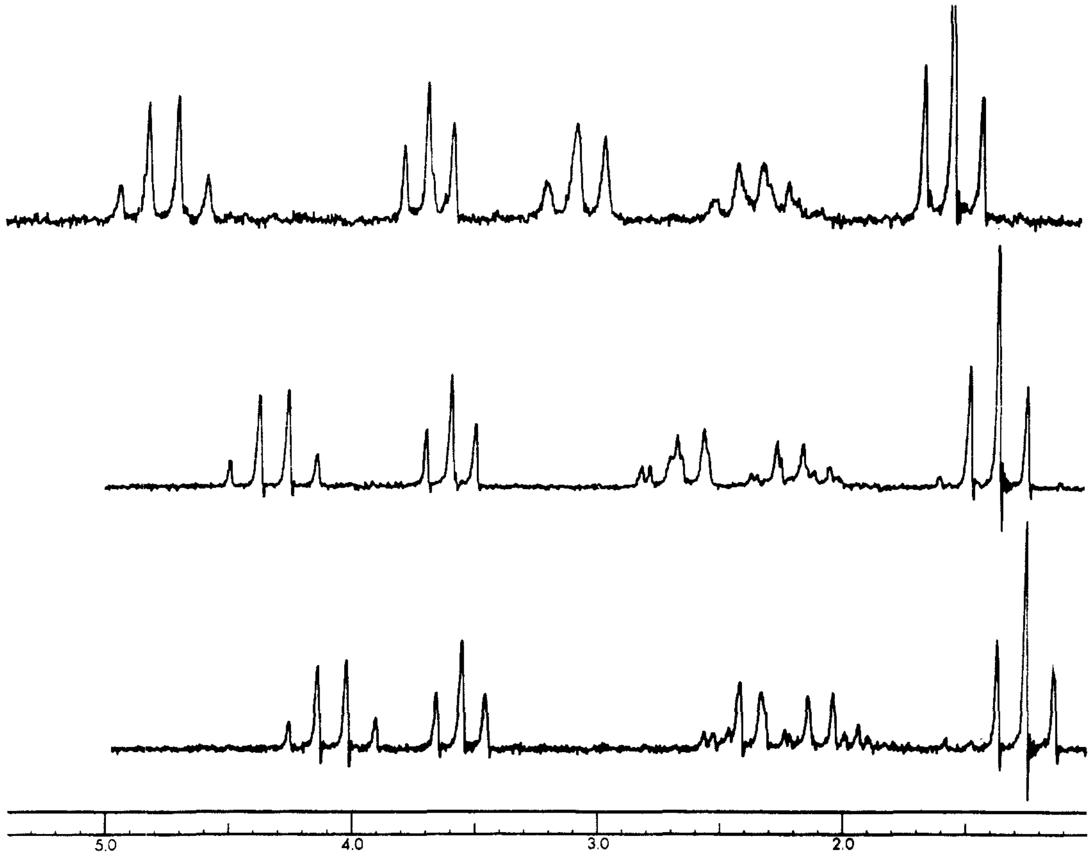

Figure 2.—N.m.r. spectra of $CH_2ClCH_2CH_2CO_2CH_2CH_3$ (ethyl γ-chlorobutyrate) in carbon tetrachloride (lower), trifluoroacetic acid (middle), and trifluoroacetic acid–sulfuric acid (upper). The chemical shifts of the two types of hydrogens in the $RCH_2CH_2CO_2$ group are similar in carbon tetrachloride, resulting in a complex spectrum in the region δ 1.8 to 2.6. The CH_2CO_2 hydrogens are shifted downfield in the acidic solvents, to δ 3.08 (in the top spectrum), permitting observation of the expected triplet and quintet.

ical shifts in *meta*-substituted fluorobenzene to hydrogen bonding, particularly in trifluoroacetic acid.[10] Although aromatic compounds were used, a possible correlation with aliphatic inductive effects seems to be implied in this instance,[10] justifying comparison of Taft's results with ours.

Long-Range Coupling in Protonated Ketones.—Olah and co-workers have recently shown that coupling (J = 7 c.p.s.) between nonvicininal protons is shown in the n.m.r. spectrum of the isoamyl cation in antimony pentafluoride.[11] Interestingly, the methyl group of methyl isopropyl ketone in trifluoroacetic acid–sulfuric acid is a doublet, J = 1.0 c.p.s., while methyl n-alkyl ketones show methyl triplets, J = 1.0 c.p.s., attributable to coupling induced by the vacant p orbital in protonated ketones, *e.g.*, $CH_3C(OH)CH_2R$. In Figure 1 solvent effects on long-range coupling are illustrated for the n.m.r. spectrum of methyl ethyl ketone. As expected, incompletely resolved splitting was evident also in each peak of the CH_2 or CH multiplet of the appropriate ketones. Acetone showed no splitting of peaks, as predicted for compounds having the coupled hydrogens equivalent.

Application.—Use of trifluoroacetic acid as an n.m.r. solvent may permit separation of peaks which overlap in other solvents, if both shifting and nonshifting hydrogens are involved. Compounds containing both halogen and oxygen are in this category. An example of such spectrum simplification *via* solvent shift is shown in Figure 2. Alcohols are particularly amenable to study. Their solvent shifted spectrum may be obtained in trifluoroacetic acid solutions immediately after the components are mixed. The solvent-insensitive spectrum of the trifluoroacetate ester then develops with a half-life of 10 (methanol) to 30 min. (secondary alcohols), and is the only spectrum observed after a few hours. The unusually large chemical shift differences between the CH peaks in R_2CHOH and $R_2CHO_2CCF_3$ permits easy observation of both compounds simultaneously. Thus, 2-propanol having its C-H septet at δ 3.90 in trifluoroacetic acid is converted, on standing or on adding sulfuric acid, to the trifluoroacetate whose septet is at δ 5.33.[12] Finally, it may be noted that the marked similarity in the behavior of methyl, ethyl, and isopropyl compounds (Table II) and of a series of compounds having the same functional group (Table III) indicates that solvent shifts are reasonably invarient to structural changes in the compounds studied.

Solvent shifts arising from magnetic anisotropy of solvent molecules have often been employed in the simplification of n.m.r. spectra, particularly those shifts arising from ring-current effects of aromatic solvents, including benzene, dimethylaniline, nitro-

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(10) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).

(11) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastien, *ibid.*, **86**, 1360 (1964).

(12) Large solvent shifts reported for the n.m.r. spectra of norbornanol in trifluoroacetic acid–sulfuric acid by G. Fraenkel, P. D. Ralph and J. P. Kim [*Can. J. Chem.*, **43**, 674 (1965)] are, in view of our results, attributable to esterification. The reported recovery of norbornanol from the solutions could be due to hydrolysis of the trifluoroacetate ester during isolation of the product.

benzene, and pyridine.[13] Solvent shifts reported in this paper are perhaps not so widely applicable to spectrum simplification as those owing to solvent magnetic anisotropy, but do have the important advantages of being relatively large and more predictable in direction and magnitude. A solvent-shift study similar to that reported here has recently been reported.[14] Deuteriochloroform, acetic acid, and trifluoroacetic acid solvents were used in a study of N-methyl group chemical shifts. Several oxygen-containing functional groups were included, however. Relatively small Δδ values were observed (*e.g.*, Δδ for acetone, on changing from deuteriochloroform to trifluoroacetic acid, was 0.17), possibly as a result of the hydrogen-bonding properties of chloroform.

(13) (a) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1965); (b) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

(14) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1848 (1965).

The Formation of Radical Intermediates in Formazan–Tetrazolium Salt Systems[1]

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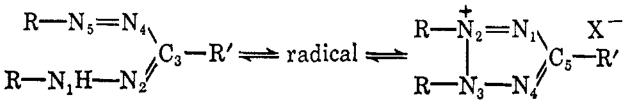
Oxidation of formazans or reduction of tetrazolium salts gives rise to a paramagnetic product stable to oxygen at 25°. Particularly high yields of the radical are formed by the reduction of tetrazolium salts by the propiophenone enolate anion. Possible structures of the radical are considered.

There are distinct resemblances between the formazan–tetrazolium salt oxidation–reduction system and the following thermodynamically reversible systems: hydroquinones–quinones,[2] benzoin–benzil,[3] and hydrazo compounds–azo compounds.[4] These processes, which involve the over-all transfer of two electrons per molecule, can proceed by the stepwise addition of individual electrons.[4] We have conducted electron spin resonance studies on several formazan–tetrazolium salt systems which indicate a facile, one-electron oxidation of the formazan anion or reduction of the tetrazolium salt.



formazan tetrazolium salt

formazan

1, R = R' = C_6H_5
3, R = C_6H_5; R' = *p*-$CH_3OC_6H_4$
5, R = C_6H_5; R' = *p*-$NO_2C_6H_4$
7, R = C_6H_5,' R' = $CO_2C_2H_5$
9, R = C_6H_5; R' = CH_3

tetrozolium salt

2, R = R' = C_6H_5; X^- = Br^-
4, R = C_6H_5; R' = *p*-$CH_3OC_6H_4$; X^- = NO_3^-
6, R = C_6H_5; R' = *p*-$NO_2C_6H_4$; X^- = Br^-
8, R = C_6H_5; R' = $CO_2C_2H_5$; X^- = Br^-
10, R = C_6H_5; R' = CH_3; X^- = Br^-

The quinone–hydroquinone disproportionation is one of many that fit the generalized sequence[5]

$$\pi + \pi H_2 \xrightleftharpoons{B^-} 2\pi^-$$

Other examples are known, particularly in the area of dihydropyridines, that illustrate the analogous disproportionation[6]

$$\pi^{+2} + \pi \rightleftharpoons 2\pi^+$$

The formazan–tetrazolium salt disproportionation is an interesting variation fitting the generalized scheme

$$\pi^+ + \pi H \xrightleftharpoons{B^-} 2\pi$$

Results

Formazans in the presence of potassium *t*-butoxide and a trace of oxygen, generate free radicals in a variety of solvents. In the absence of oxygen, crimson solutions of the anion are formed, but no e.s.r. signal is detected. The corresponding tetrazolium salts in the presence of potassium *t*-butoxide, in the absence or presence of oxygen, produce the same radical species. Propiophenone, base, and tetrazolium salts, in the absence of oxygen, produced higher free-radical concentrations (Table I) than was observed for tetrazolium salts in the absence of a reducing agent or from mixtures of formazans and tetrazolium salts. This suggests considerable electron transfer in the propiophenone experiments and designates tetrazolium salts as good electron acceptors.[7] Formazan anions are only fair donors, judging by the extent of electron transfer observed for formazan–tetrazolium salt mixtures.

Figure 1 shows the 15-line e.s.r. spectrum observed either by oxidation of **1** or reduction of **2**. This spectrum, with only minor modification of hyperfine splitting constants (h.f.s.c.), was also observed from **1** and **2** in *t*-butyl alcohol solutions containing potassium *t*-butoxide as well as in a solvent composed of 80% *t*-butyl alcohol and 20% water. The same spectrum was observed in dimethyl sulfoxide with sodium hydride

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(1) Electron Transfer Processes. III. For part II, see E. T. Strom and G. A. Russell, *J. Am. Chem. Soc.*, **87**, 3326 (1965). This work was supported by a grant from the National Science Foundation.

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(3) A. Weissberger, H. Mainz, and E. Strasser, *Ber.*, **62**, 1942 (1929); A. Weissberger, *ibid.*, **65**, 1815 (1932); L. Michaelis and E. S. Fletcher, *J. Am. Chem. Soc.*, **59**, 1246 (1937); J. L. Ihrig and R. G. Caldwell, *ibid.*, **78**, 2097 (1956).

(4) L. Michaelis and M. P. Schubert, *Chem. Rev.*, **22**, 437 (1938).

(5) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **84**, 4155 (1962).

(6) R. M. Elafson, D. H. Anderson, H. S. Gutowsky, R. B. Sandin, and K. F. Schulz, *ibid.*, **85**, 2622 (1963); H. Hart, J. S. Fleming, and J. L. Dye, *ibid.*, **86**, 2079 (1964); A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964).

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