

hydroxide). As the reaction proceeded the undissolved yellow quinone went into solution and after about 1 hr the solution became nearly clear and colorless. The reaction solution was then poured into 1000 ml of ice water to give 14.8 g (0.507 mol, 75% yield) of the diepoxide **11**, mp 206–209°.

Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.98; H, 4.14. Found: C, 73.94; H, 4.15.

The ir spectrum of **11** shows characteristic absorptions at 1720, 1260, 690, and 750 cm^{-1} . The nmr spectrum (DMSO- d_6) shows two absorptions in a ratio of 10:2, at, respectively, δ 7.48 and 4.18. The mass spectrum of **11** shows a molecular ion peak at m/e 292 in accord with the formulation $C_{18}H_{12}O_4$.

2-Chloro-5-hydroxy-3,6-diphenyl-4-benzoquinone (12). A dioxane-ethanol solution (10:1) of 8 g (0.027 mol) of 2,3,5,6-diepoxy-2,5-diphenyl-1,4-benzoquinone (**11**) was treated with 10 ml of concentrated hydrochloric acid. After heating to reflux for a few minutes to accomplish complete solution, the reaction was allowed to stand at ambient temperature for 7 days. During this time several additional 10-ml portions of acid were added. Filtration of the cooled reaction solution gave a beautiful yellow-orange dioxane complex of the quinone **12**. The dioxane was readily re-

moved *in vacuo* to give 5.8 g (69% yield) of the known¹⁹ 2-chloro-5-hydroxy-3,6-diphenyl-1,4-benzoquinone, mp 212° (recrystallized from dioxane).

Vulpinic Acid (13). The butenolide (**3j**) (2.0 g, 0.007 mol) was dissolved in a minimum amount of boiling methanol. To this solution was added 0.5 ml of concentrated HCl. Cooling this solution resulted in the precipitation of 2.1 g (95% yield) of vulpinic acid (**14**). This product was identical (mixture melting point and infrared) to an authentic sample of the natural product.²⁰

Conversion of the Azidoquinones 1a, 1b, and 1g, Respectively, to the Butenolides 3a, 3b, and 3g in Sulfuric Acid- d_2 . The azidoquinones **1a**, **1b**, and **1g** were converted to the corresponding butenolides **3a**, **3b**, and **3g**, respectively, by the general method. The acid used was 98% D_2SO_4 and the products were isolated by pouring the acid solution into 98% D_2O . The butenolides obtained under these conditions were identical in *all respects* with those obtained under protic conditions, *i.e.*, no exchange was observed.

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General Acid Catalysis and the pH-Independent Hydrolysis of 2-(*p*-Nitrophenoxy)tetrahydropyran

Thomas H. Fife and Lily H. Brod

*Contribution from the Department of Biochemistry,
University of Southern California, Los Angeles, California.
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Abstract: The hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran is characterized by a pH-independent reaction at pH values greater than 4.0. This reaction has a D_2O solvent isotope effect of approximately unity; $k_{D_2O}/k_{H_2O} = 1.1$ for hydrolysis in solvent containing 50% dioxane and $k_{D_2O}/k_{H_2O} = 0.9$ for hydrolysis in H_2O or D_2O . The value of ΔS^\ddagger is +2.2 eu. The pH-independent reaction is strongly accelerated by increasing the polarity of the solvent, being 48.7 times more rapid in water than in 50% dioxane- H_2O . Thus, this reaction is most likely a unimolecular decomposition to *p*-nitrophenoxide ion and a resonance stabilized carbonium ion. Bond breaking is also relatively important in comparison to protonation in the transition state of the general acid catalyzed reaction as evidenced by the Brønsted coefficient of 0.5 and the positive value of ρ (0.9) obtained in formic acid catalyzed hydrolysis of the series of 2-(substituted phenoxy)tetrahydropyrans.

Acetals having strongly electron-withdrawing substituents in the leaving group, which reduce basicity and at the same time increase the ease of C–O bond breaking, are hydrolyzed with partially rate-determining protonation by hydronium ion and a pronounced general acid catalysis.¹ In the case of 2-(*p*-nitrophenoxy)tetrahydropyran there is a large plateau in the pH-rate constant profile at pH values greater than 4.¹ Plateau regions have also been observed in the hydrolysis of various types of glycosides,² but the mechanistic significance of the pH-independent reactions is obscured by the presence of neighboring groups, hydroxyl or acetamido, which could participate in the reaction. A further complication encountered with glycosides is that hydroxide ion catalysis is observed. A fast pH-independent reaction has also been detected with tropone diethyl ketal, a ketal whose hydrolysis is catalyzed by general acids.³ The elucidation of the mechanism of a pH-independent acetal hydrolysis reaction would be of great importance in furthering understanding of the

factors influencing the hydrolysis of these compounds. Therefore, in view of the structural simplicity of 2-(*p*-nitrophenoxy)tetrahydropyran and the lack of hydroxide ion catalysis, a detailed investigation of its pH-independent hydrolysis was carried out and is reported in this paper.

Experimental Section

Materials. 2-(*p*-Nitrophenoxy)tetrahydropyran was that previously studied.¹ Dioxane was purified by the method of Fieser⁴ and was stored frozen in brown bottles. Deuterium oxide (99.8%) was obtained from Bio-Rad Co.

Kinetic Measurements. The rates of hydrolysis were measured in H_2O , D_2O , and in solvent containing 10 and 50% dioxane (v/v). The rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the appearance of *p*-nitrophenol at 330 $m\mu$ or *p*-nitrophenoxide ion at 400 $m\mu$. The acetal, dissolved in purified dioxane, was added directly to the thermostated solution in the cuvette by means of a calibrated dropping pipet. One drop was added and the solution was then stirred vigorously. The reactions were followed to at least 75% of completion, and infinity points were taken at greater than 10 half-lives and were stable. Values of k_{obsd} were calculated with an Olivetti Underwood Pro-

(1) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).

(2) D. Piszkiwicz and T. C. Bruce, *ibid.*, **89**, 6237 (1967).

(3) E. Anderson and T. H. Fife, *ibid.*, **91**, 7163 (1969).

(4) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

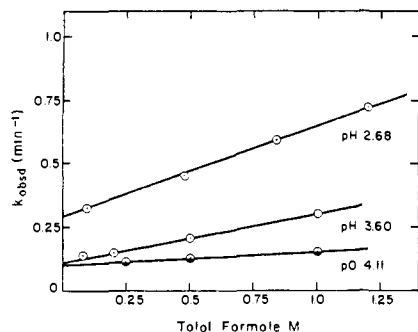


Figure 1. Plot of k_{obsd} for hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran vs. total formate buffer concentration at 50° and $\mu = 0.5$ with KCl in H₂O ○ and D₂O ●.

gramma 101 programmed to calculate the least-squares slopes of plots of $\ln((OD_{\infty} - OD_0)/(OD_{\infty} - OD_t))$ vs. time. Constant temperature ($\pm 0.1^\circ$) was maintained by circulating water from a Precision Scientific Co. Temprol Model 154 constant-temperature circulating bath through a Zeiss constant-temperature cell holder.

In the determination of the activation parameters, the rates of hydrolysis were measured at four temperatures (30.0, 39.2, 50.0, and 58.0°) $\pm 0.1^\circ$. The rates were determined in triplicate at each temperature with an average deviation in the rate constants of less than 2%.

In work utilizing D₂O as the solvent, the glass electrode correction formula of Fife and Bruce⁵ was employed in the determination of a_D .

The pH of each solution was measured with a Model 22 Radiometer pH meter standardized with aqueous buffers. The glass electrode gives the correct pH reading in concentrated dioxane-H₂O mixtures.⁶ The pK_a values in 50% dioxane-H₂O of the general acid catalysts were determined by measuring the pH of half-neutralized solutions.

Results

In Table I rate constants are given for the hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran in the solvents water, 10% dioxane-H₂O, 50% dioxane-H₂O, D₂O, and 50% dioxane-D₂O. The reaction at pH values

Table I. Rate Constants for Hydrolysis of 2-(*p*-Nitrophenoxy)tetrahydropyran at 50°

Solvent	pH or pD	k_{obsd} , min ⁻¹	k_H , l. mol ⁻¹ min ⁻¹
50% dioxane-H ₂ O	1.30	0.470 ^a	9.40
10% dioxane-H ₂ O	3.0	0.0893	89.3
H ₂ O (HCl, $\mu = 0.5$)	2.09	1.12	130
H ₂ O (HCl, $\mu = 0.5$)	3.0	0.195	132
H ₂ O	2.64	0.49 ^b	
H ₂ O	2.68	0.29 ^b	
H ₂ O	3.61	0.107 ^b	
D ₂ O	4.11	0.10 ^b	
50% dioxane-H ₂ O	4.62	0.0019 ^b	
50% dioxane-D ₂ O	5.12	0.00205 ^b	
H ₂ O	4.64	0.073 ^b	
H ₂ O	6.71	0.0705 ^b	
H ₂ O 0.001 M NaOH		0.0630 ^c	
H ₂ O 0.01 M NaOH		0.0636 ^c	
H ₂ O 0.10 M NaOH		0.0629 ^c	
D ₂ O 0.01 M NaOD		0.0542 ^c	
50% dioxane-H ₂ O 0.05 M NaOH		0.0013	
50% dioxane-D ₂ O 0.05 M NaOD		0.0014	

^a Data from ref 1. ^b Rate constant obtained by extrapolation to zero buffer concentration, $\mu = 0.5$ with KCl. ^c $\mu = 0.1$ with KCl.

(5) T. H. Fife and T. C. Bruce, *J. Phys. Chem.*, **65**, 1079 (1961).

(6) H. P. Marshall and E. Grunwald, *J. Chem. Phys.*, **21**, 2143 (1953).

greater than 4.0 is pH independent. The D₂O solvent isotope effect for that reaction is close to unity, k_{D_2O}/k_{H_2O} being 1.1 in the solvent containing 50% dioxane and 0.9 in the absence of dioxane. There is a pronounced effect of increasing the solvent polarity in the pH-independent reaction, the rate constant being 48.7 times greater in H₂O than in 50% dioxane-H₂O. The second-order rate constant for formic acid catalysis is 31.2 times greater in H₂O than in 50% dioxane-H₂O.

Rate constants for hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran in aqueous 0.01 M NaOH at temperatures ranging from 30.0 to 58° are presented in Table II. The value of ΔH^* is 24.1 ± 0.2 kcal/mol, and ΔS^*

Table II. Rate Constants for Hydrolysis of 2-(*p*-Nitrophenoxy)tetrahydropyran at Various Temperatures ($\pm 0.1^\circ$)^a

Temp, °C	k_{obsd} , min ⁻¹
30.0	0.00526
39.2	0.0193
50.0	0.0636
58.0	0.178

^a In H₂O with 0.01 M NaOH and $\mu = 0.1$.

has the value $+2.2 \pm 0.6$ eu at 50°. The reported uncertainties were calculated from the standard error of a plot of $\ln k_{\text{obsd}}$ vs. $1/T$.

Second-order rate constants for general acid catalyzed hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran are given in Table III. In Figure 1 is shown a plot of

Table III. Second-Order Rate Constants for General Acid Catalysis of the Hydrolysis of 2-(*p*-Nitrophenoxy)tetrahydropyran^a

Acid	pK_a	Solvent	k_{HA} , l. mol ⁻¹ min ⁻¹	k_{HA}/k_{DA}
Dichloroacetic	2.56	50% dioxane-H ₂ O	0.282	
Chloroacetic	3.95	50% dioxane-H ₂ O	0.023	
Chloroacetic	2.64	H ₂ O	0.818	
Formic	4.64	50% dioxane-H ₂ O	0.013 ^b	2.65
Formic	5.09	50% dioxane-D ₂ O	0.0049	
Formic	3.60	H ₂ O	0.406	3.4
Formic	4.11	D ₂ O	0.12	
Acetic	6.09	50% dioxane-H ₂ O	0.00092	
Acetic	4.62	H ₂ O	0.071	

^a At 50° and $\mu = 0.5$ with KCl. ^b Reference 1.

k_{obsd} vs. total formate buffer concentration in H₂O and D₂O. The solvent isotope effect for the formic acid catalyzed reaction, k_{HA}/k_{DA} , is 3.4 while the intercept is nearly the same in the two solvents, $k_{D_2O}/k_{H_2O} = 0.9$. A plot of $\log k_{HA}$ vs. the pK_a values of the catalyzing acids with H₂O as the solvent is shown in Figure 2. The slope of the line is -0.5 . A similar plot in the case

Table IV. Second-Order Rate Constants for Formic Acid Catalysis of the Hydrolysis of 2-(*para*-Substituted phenoxy)tetrahydropyrans^a

<i>para</i> substituent	k_{HCOOH} , l. mol ⁻¹ min ⁻¹
H	0.0028
Cl	0.0041 ^b
NO ₂	0.013 ^b

^a At 50° in 50% dioxane-H₂O (v/v). ^b Reference 1.

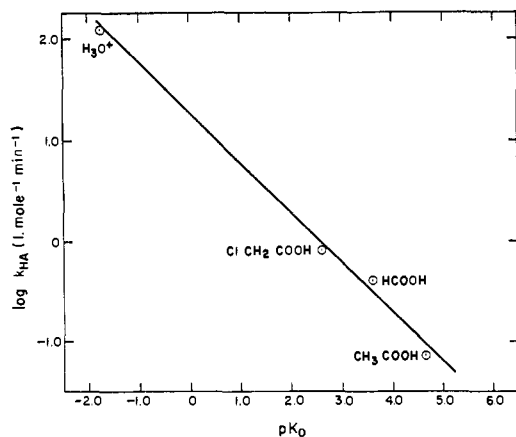


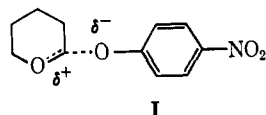
Figure 2. Plot of $\log k_{HA}$ for general acid catalyzed hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, in H_2O at 50° and $\mu = 0.5$, vs. the pK_a of the catalyzing acid.

of 50% dioxane- H_2O as the solvent had a slope of -0.69 .

In Table IV are presented second-order rate constants for formic acid catalyzed hydrolysis of 2-phenoxy, 2-(*p*-chlorophenoxy), and 2-(*p*-nitrophenoxy)tetrahydropyran. In Figure 3 is shown a plot of $\log k_{HA}$ vs. σ , the Hammett substituent constant.⁷ The value of ρ is $+0.9$.

Discussion

The experimental evidence points to a mechanism for the pH-independent hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran involving a unimolecular reaction as in I. Thus, if water catalysis was occurring it might



reasonably be expected that the reaction would be significantly slower in D_2O as the solvent than in H_2O . The observed D_2O solvent isotope effect, however, is approximately unity. The entropy of activation of $+2.2$ eu is also indicative of the unimolecular mechanism, since water catalysis should give rise to a highly negative ΔS^\ddagger . A more negative value of ΔS^\ddagger might actually have been expected since the developing charges would be solvated.

The magnitude of the rate acceleration produced by increasing the polarity of the solvent (48.7 times upon going from 50% dioxane- H_2O to H_2O) is consistent with a mechanism in which there is a high degree of ionic character in the transition state but is also, of course, in accord with water catalysis. Rate increases produced by increasing the solvent polarity are observed in the acid-catalyzed hydrolysis of acetals and ketals,⁸ but these effects are generally much smaller than in the pH-independent reaction. Hydronium ion catalyzed hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, in which partially rate determining proton transfer occurs, is accelerated by only a factor of 13.8 upon changing the solvent from 50% dioxane- H_2O to H_2O .

(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(8) T. H. Fife and L. H. Brod, *J. Org. Chem.*, **33**, 4136 (1968).

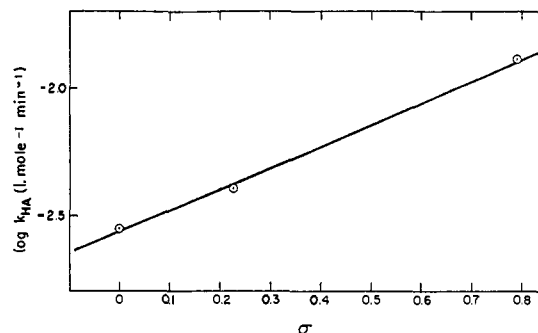
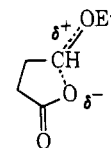


Figure 3. Plot of $\log k_{HA}$ for formic acid catalyzed hydrolysis of 2-(substituted phenoxy)tetrahydropyran, at 50° in 50% dioxane- H_2O , $\mu = 0.5$, vs. σ , the Hammett substituent constant.

An alternative formulation to I would involve water catalysis with proton transfer not having progressed to a significant extent in the transition state. In this mechanism bond breaking in the transition state would also be of great importance. It is unlikely, however, that H_2O is functioning as a general acid in view of the magnitude of the Brønsted coefficient for general acid catalysis (0.5) and the relatively large rate constant for pH-independent hydrolysis. The point for water catalysis would lie far above the line in the plot of $\log k_{HA}$ vs. pK_a .

The high sensitivity to solvent polarity and D_2O solvent isotope effect of about unity in the spontaneous hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran is similar to what is observed in pH-independent hydrolysis of γ -ethoxy- γ -butyrolactone⁹ which also most likely proceeds with unimolecular decomposition, in accord with the mechanism suggested for hydrolysis of other acylals.¹⁰ The reasons for a unimolecular mechanism are



undoubtedly the same in the two cases; the carbonium ion intermediate is resonance stabilized and the leaving group is quite good, the combination of these two effects leading to a spontaneous reaction. An additional example of a pH-independent reaction brought about by an excellent leaving group and a reasonably stable carbonium ion is that observed in the hydrolysis of benzaldehyde methyl S-(2,4-dinitrophenyl)thioacetal,¹¹ and again the ratio k_{D_2O}/k_{H_2O} is 0.9. Ortho esters form carbonium ions more stable than the tetrahydropyranyl carbonium ion but apparently do not hydrolyze by pH-independent pathways. However, ortho esters combining high carbonium ion stability with a good leaving group have not been studied. The rate of hydrolysis of tropone diethyl ketal is pH independent at pH values greater than 10.³ With that ketal the leaving group is poor, but the carbonium ion intermediate is of exceedingly great stability.

Increasing the ease of bond breaking by electron withdrawal in the leaving group would be expected to increase greatly the rate of the spontaneous reaction

(9) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965).

(10) P. Salomaa, *Suomen Kemistilehti*, **B**, **37**, 86 (1964).

(11) T. H. Fife and E. Anderson, unpublished data.

but would decrease the rate of hydronium ion catalyzed reaction by decreasing basicity,¹² thereby making the pH-independent reaction easy to detect with those compounds. Accordingly, the hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran is completely pH independent at pH values greater than 4 while that point is reached at 0.05 *M* HCl with benzaldehyde methyl S-(2,4-dinitrophenyl)thioacetal.¹¹ In contrast, the great carbonium ion stability in the case of tropone diethyl ketal facilitates both the spontaneous and the hydronium ion catalyzed reactions, although not necessarily to the same extent, resulting in a reaction that is completely pH independent only at high pH values.

The positive ρ value of 0.9 for formic acid catalyzed hydrolysis of substituted phenoxy tetrahydropyrans in contrast to the negative ρ (-0.9) when hydronium ion is the catalyst,¹ again indicates that bond breaking is very important in the transition state when a weak acid catalyst is employed. It is reasonable that this would be the case since with a weak acid catalyst proton transfer would be more difficult than with hydronium ion, therefore requiring greater bond breaking to reach the transition state. It is of considerable interest to note that the lysozyme-catalyzed hydrolysis of phenolic glycosides is also characterized by a positive ρ of 1.23.¹³ The reasons for the positive ρ in the enzymatic reaction are probably similar to those in the formic acid catalyzed reaction with the substituted phenoxytetrahydropyrans.

In the acid-catalyzed hydrolysis of simple acetals, carbon-oxygen bond breaking is normally rate determining.¹⁴ In order to obtain rate-determining protonation by hydronium ion and general acid catalysis, either basicity must be decreased and/or the facility of the bond breaking step must be increased. With 2-(*p*-nitrophenoxy)tetrahydropyran both features are present, basicity has been decreased by the presence of the nitro substituent and the ease of C-O bond breaking has been increased, but it is clear that it is the latter factor that is predominantly responsible for the observed effects. This is attested to by the fast spontaneous reaction which is certainly due to the facility of bond breaking. In the case of tropone diethyl ketal,³ the C-O bond breaking step has been made easy by the great stability

(12) The ρ value for hydronium ion catalyzed hydrolysis of 2-aryloxytetrahydropyrans is -0.9, and that for hydrolysis of benzaldehyde methyl S-(substituted phenyl)thioacetals is -1.0.

(13) G. Lowe, G. Sheppard, M. L. Sinnott, and A. Williams, *Biochem. J.*, **104**, 893 (1967).

(14) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

of the carbonium ion formed as an intermediate, resulting in general acid catalysis in spite of the poor leaving group.

The nonobservance of general acid catalysis in the hydrolysis of *p*-nitrophenyl β -D-glucopyranoside² in contrast to the analogous tetrahydropyran series, possibly is due to the reduced stability of the glucosyl carbonium ion produced by the hydroxyl group substituents in the pyranose ring. This is reflected in the much faster rates of hydrolysis of tetrahydropyran acetals than glycosides. It has been estimated that the acid-catalyzed hydrolysis of 2-methoxytetrahydropyran proceeds 3.1×10^7 times faster than that of methyl α -D-glucopyranoside.¹⁶

DeWolfe, *et al.*,¹⁶ have recently claimed that benzophenone ketals are subject to very weak general acid catalysis by chloroacetic and dichloroacetic acids, but not by formic acid.¹⁷ Although basicity considerations are undoubtedly of importance, it is probable that the small reported effects, if significant, are mainly due to the stability of the intermediate carbonium ion.

Two other examples of buffer catalyzed acetal hydrolysis have been observed, the buffer acid catalysis of the hydrolysis of benzaldehyde methyl phenyl acetal,¹⁸ an example of general acid catalysis arising from the same structural features influencing the hydrolysis of the phenoxytetrahydropyrans, and the hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane which is catalyzed by formic acid.¹⁹ Several pieces of evidence pointed consistently to an A2 mechanism for the latter compound, although not without ambiguity. In support of this mechanism it was found that substitution of a methyl group at the reaction center produces a rate decrease in the hydronium ion catalyzed reaction of 540 times in comparison with the analogous benzaldehyde derivative.⁸

Acknowledgment. This work was supported by research grants from the National Institutes of Health and the National Science Foundation.

(15) E. Dyer, C. P. J. Glaudemans, M. J. Koch, and R. H. Marchessault, *J. Chem. Soc.*, 3361 (1962).

(16) R. H. De Wolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1969).

(17) We have been unable to detect buffer catalysis with benzophenone diethyl ketal and the ethylene glycol ketal of *p,p'*-dimethoxybenzophenone even at very high concentrations of formate and chloroacetate buffers.

(18) E. Anderson and B. Capon, *Chem. Commun.*, 390 (1969).

(19) T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).