An Independent, Kinetic Method for Determining Acid Dissociation Constants in Methanol[1]

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The reaction of thiophenoxide ion with 2,4-dinitrofluorobenzene (ArF) is a suitable basis for a kinetic method for determining pK's of weak acids in methanol. In a thiophenol solution buffered by the weak acid, the concentration of thiophenoxide ion and therefore the pseudo-first-order rate coefficient are governed by the pK and composition of the buffer. This method is wholly independent of other pK determinations, but gives results (for thiophenol, acetic acid, chloroacetic acid, pyridine, and N-methylpiperidine) in good agreement with the better determinations by other methods. This method is easily employed in a laboratory well equipped for spectrophotometric kinetics. It should also be applicable in other waterlike solvents and solvent mixtures.

Ionic equilibria in methanol, ethanol, and many partially aqueous solvent mixtures are similar in character to those in water. Although ion association effects are more serious in these solvents, pK_a's of weak acids can nevertheless be determined in them by methods which are familiar in aqueous chemistry.[2,3] Determinations by means of conductance measurements,[3a] or potentiometric measurements using the hydrogen electrode,[3b] or differential titrations using the glass electrode[3c,4] are all sound in principle, but chemical factors limit the scope of each method. Also, their instrumentation requirements make some of them difficult to apply in particular laboratories.

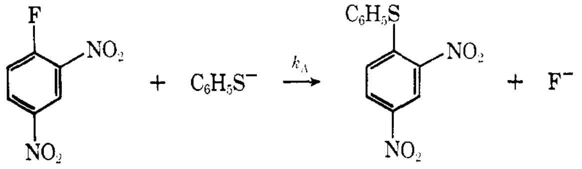
pK_a determinations by indicator methods[3d,5] are both sound in principle and convenient in practice, if a good spectrophotometer is available. However, they require knowledge of the pK_a of an indicator whose acid dissociation constant is within one or two powers of ten of the acid under study, and in a new solvent or solvent mixture some other type of measurement is generally required to establish the indicator pK_a's.

Despite the availability of these good methods, the situation is not entirely satisfactory even in the familiar solvent, methanol. For example, pK_a's reported for thiophenol within the last 15 years differ by more than 3pK_a units,[6-10] and each extreme is "confirmed" by independent measurements in another laboratory!

Kinetic methods for the determination of pK_a's are not generally held in high regard.[11a] For the most part they have concerned acid-catalyzed hydrolysis reactions, and it is possible that their low repute stems from the unawareness of early workers of the distinction between specific lyonium ion catalysis and general acid catalysis or of the significance of salt and medium effects on reaction rates.

We now describe a kinetic method for determination of acid dissociation constants which is independent of other methods, involves few assumptions, and is convenient to apply in a laboratory well equipped for rate measurements in solution.

The Reaction of Thiophenoxide Ion with 2,4-Dinitrofluorobenzene.—Thiophenoxide ion reacts rapidly with 2,4-dinitrofluorobenzene (symbolized ArF), according to eq 1. In methanol at 25.0°, the second-order rate coefficient (k_A) is 780 l. mole^{-1} sec^{-1}. This value stems from determinations reported in Table I of an accompanying paper.[12] The rate coefficient is unaffected by the presence of excess thiophenol, and the reaction is not catalyzed by the general acids or bases of carboxylate or tertiary amine buffers, or by the solvated proton.[12]



(1)

pK_c of Thiophenol.—The reactivity of thiophenoxide ion is so great that reaction 1 occurs at a measurable rate even in a methanolic solution of thiophenol containing p-toluenesulfonic acid (PTS) at the level of 10^{-4} to 10^{-3} M. Data are reported in Table IX of the accompanying paper.[12] In this system, dissociation of thiophenol (eq 2) is strongly repressed by the solvated

$$C_6H_5SH \rightleftarrows C_6H_5S^- + H^+ \qquad (2)$$

protons furnished by the virtually complete dissociation of p-toluenesulfonic acid. The data cited show, as discussed elsewhere,[12] that the reaction observed is entirely that of eq 1.

The pseudo-first-order rate coefficient, k_ψ, is governed by the rate coefficient for reaction 1 and the dissociation constant of thiophenol (K_{PhSH}), according to the relationship now presented as eq 3. Knowing k_ψ and the

$$k_\psi = k_A K_{PhSH}[C_6H_5SH]/[H^+] \qquad (3)$$

two concentration terms from experiment, and k_A as described above, we can calculate K_{PhSH}. From the data in the second set of three experiments in the cited Table IX, pK_{PhSH} is reckoned as 10.92 at μ 0.01, and from the first set of three pK_{PhSH} is 10.57 at μ 0.1.[13]

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[1] This investigation was supported by Public Health Service Research Grant No. GM 14647 from the National Institute of General Medical Sciences.

[2] I. M. Kolthoff and S. Bruckenstein in "Treatise on Analytical Chemistry," Part I, Vol. 1, I. M. Kolthoff and P. J. Elving, Ed., The Interscience Encyclopedia, Inc., New York, N. Y., 1959, Chapter 13.

[3] E. J. King, "Acid-Base Equilibria," The Macmillan Co., New York, N. Y., 1965: (a) Chapter 2; (b) Chapter 3; (c) Chapter 4; (d) Chapter 5.

[4] E. Grunwald, *J. Amer. Chem. Soc.*, **73**, 4934 (1951).

[5] I. M. Kolthoff and L. S. Guss, *ibid.*, **60**, 2516 (1938).

[6] pK_a's reported recently for C_6H_5SH in CH_3OH are 8.65,[7] 8.3,[8] 11.63,[9] and 10.9.[10]

[7] R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1062 (1962).

[8] J. G. David and H. E. Hallam, *Trans. Faraday Soc.*, **60**, 2013 (1964).

[9] J. Hine and W. H. Brader, Jr., *J. Amer. Chem. Soc.*, **75**, 3964 (1953).

[10] B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *ibid.*, **88**, 1911 (1966).

[11] *Cf.* A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., Ltd., London, 1962: (a) p 12; (b) p 135.

[12] J. F. Bunnett and N. S. Nudelman, *J. Org. Chem.*, **34**, 2038 (1969).

[13] μ represents the total concentration of 1:1 electrolytes. We hesitate to call it "ionic strength" because of the demonstrated inequality of salt effects in this system.

The former value is in excellent agreement with $pK_{PhSH} = 10.9$ at μ 0.01 or less, determined by Clare, *et al.*,[10] by an indicator method. It is close to one other determination in the recent literature, but quite far from two others.[6]

As a check on these determinations, similar experiments were performed utilizing sulfuric acid instead of PTS. Results are presented in Table I. In reckoning pK_{PhSH}, sulfuric acid was treated as a monoprotic acid. The averate pK_{PhSH} at μ 0.1 is 10.56, in superb agreement with that obtained (10.57) with PTS as the proton source. At μ 0.01, the average pK_{PhSH} in Table I is 10.84; this compares with 10.92 when PTS was the strong acid.

Table I

Reaction of 2,4-Dinitrofluorobenzene with Thiophenoxide Ion in Methanol at 25.0° in the Presence of Sulfuric Acid[a]

$10^4[H_2SO_4]$, M	[LiCl], M	$10^6 k_\psi$, sec^{-1}	$10^9 k_\psi \cdot [H_2SO_4]$, $M\ sec^{-1}$	$10^{11} K_{PhSH}$, M	$pK_{c,PhSH}$[d]
0.242[b]	0.100	9.98	2.42	2.67	10.57
0.970[b]	0.100	2.54	2.46	2.72	10.57
2.42[b]	0.100	1.09	2.63	2.92	10.54
13.70[c]	0.100	0.200	2.62	2.90	10.54
1.31[c]	0.0100	1.03	1.35	1.49	10.83
3.27[c]	0.0097	0.441	1.44	1.60	10.80
9.70[b]	0.0090	0.132	1.29	1.42	10.86
13.10[c]	0.0760	0.0951	1.25	1.38	10.86

[a] $[C_6H_5SH]$, 0.116 M. [b] [ArF] = 1.13×10^{-3} M. [c] [ArF] = 5.65×10^{-4} M. [d] Average pK_{PhSH} are 10.55 at μ 0.1, and 10.84 at μ 0.01.

The fact that these measurements agree so well with those in which PTS was the strong acid is of special significance because it shows that bisulfate ion is only slightly dissociated in methanol. We were unable to find any data in the literature concerning the second dissociation of sulfuric acid in methanol.

pK_c of Acetic Acid.—In an acetate-buffered solution, the solvated proton concentration is governed by the composition of the buffer and the dissociation constant, K_{HOAc}, of acetic acid. If thiophenol in known amount is also present, the solvated proton concentration governs the thiophenoxide ion concentration, which in turn governs k_ψ for reaction with ArF. As thiophenoxide ion is consumed by ArF, the equilibria quickly shift to restore its original concentration. The applicable mathematical expression is that of eq 4. From

$$k_\psi = \frac{k_A K_{PhSH}[C_6H_5SH][CH_3COO^-]}{K_{HOAc}[CH_3COOH]} \qquad (4)$$

knowledge of k_A, K_{PhSH}, and the experimental k_ψ under various concentration conditions, one can reckon K_{HOAc}.

Appropriate data are set forth in Table III of an accompanying paper.[12] The average pK_{HOAc} is 9.58 at μ 0.1. Some other pK's reported for acetic acid are 9.65,[14a] 9.34,[14b] 9.65,[5] 9.6,[10] 9.62,[14c] 9.68,[14d] and 9.72.[14e]

pK_c of Chloroacetic Acid.—By the same principles, and from the data of Table II of an accompanying paper,[12] pK_c for chloroacetic acid at μ 0.01 is reckoned as 7.33. This is the average value from the five runs; the individual values ranged from 7.31 to 7.34. This compares with $pK_c = 7.7$ from indicator measurements reported by Clare, *et al.*,[10] and 7.4 as reported by Ogston and Brown.[15]

pK_c of Pyridine.—Relevant experimental data are set forth in Table II of this paper. The principles discussed above again apply, but a new factor is superimposed, namely, the variation of K_{PhSH} and k_A as LiCl is replaced as an electrolyte by an amine hydrochloride. This factor is discussed in an accompanying paper.[12] Because of it, the K_c values reckoned from the four experiments of Table II are not constant, even though the "ionic strength" is constant. A plot of K_c *vs.* the square root of buffer concentration[16] is presented as Figure 1; it is approximately linear, and the intercept of the line drawn gives a K_c of 5.6×10^{-6} M at zero buffer concentration and a LiCl concentration of 0.10 M. pK_c is then 5.25. Rochester[17] has reported pK_a for pyridine, determined by an indicator method, as 5.37 and pK_c in 0.1 M NaCl as 5.7.

Table II

Reaction of 2,4-Dinitrofluorobenzene with Thiophenoxide Ion in Methanol at 25.0° in the Presence of Pyridine–Pyridinium Chloride Buffers[a]

[Pyridine],[b] M	[LiCl], M	$[C_6H_5SH]$, M	$10^4 k_\psi$, sec^{-1}	$10^6 K_c$,[c] M
0.0080	0.0920	0.118	4.95	4.95
0.0200	0.0800	0.123	5.10	5.01
0.0400	0.0600	0.119	5.98	4.14
0.100	Nil	0.118	7.30	3.36

[a] [ArF], 5.72×10^{-4} M. [b] $[C_5H_5N \cdot HCl] = [C_5H_5N]$ in all experiments. [c] Extrapolation to zero buffer concentration (and [LiCl] 0.10 M) gives K_c for pyridinium ion 5.6×10^{-6} M.

pK_c of N-Methylpiperidine.—We now consider the data of Table IV of an accompanying paper.[12] Again because of the dependence of K_{PhSH} and k_A on whether the electrolyte is LiCl or amine hydrochloride, K_c is not constant as the electrolyte composition is varied, even though the total concentration of 1:1 electrolyte is held constant. A plot of K_c *vs.* the square root of buffer concentration[16] is approximately linear (Figure 2), and the intercept gives a K_c value of 2.8×10^{-10} M at zero buffer concentration and 0.10 M LiCl. pK_c is then 9.56. To our knowledge, the pK of N-methylpiperidine in methanol has not previously been determined. However, we note that the pK_c difference between N-methylpiperidine and pyridine in methanol is 4.3 according to our measurements, while the difference in water is 4.9.[18] An actual equality of differences would not be expected because of differential solvation effects.

On the Dissociation of HF in CH_3OH.—In several runs, the rate of reaction of 2,4-dinitrofluorobenzene (initial concentration 5.6×10^{-4} M) with thiophenol in N_2-flushed, unbuffered methanol was measured. Representative runs are presented in Table III of this paper.

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[14] (a) N. Bjerrum, A. Unmack, and L. Zechmeister, *Kgl. Danske Videnskab. Selskab, Mat. Fys. Medd.*, **6** (11), 34 (1925); *Chem. Abstr.*, **19**, 3196 (1925); (b) L. D. Goodhue and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1329 (1934); (c) M. Kilpatrick and R. D. Eanes, *ibid.*, **75**, 586 (1953); (d) I. D. Tabagua, *Tr. Sukhumsk. Gos. Ped. Inst.*, **15**, 119 (1962); *Chem. Abstr.*, **60**, 14373 (1964); (e) R. Gaboriaud, *Compt. Rend., C*, **263**, 911 (1966).

[15] A. G. Ogston and J. F. Brown, *Trans. Faraday Soc.*, **31**, 574 (1935).

[16] This extrapolation procedure has been utilized because it is empirically useful. The intercepts in plots of k_ψ *vs.* the first power of buffer concentration led to nearly the same K_c values.

[17] C. H. Rochester, *J. Chem. Soc.*, *B*, 33 (1967).

[18] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. Ltd., London, 1965, pp 139, 141.

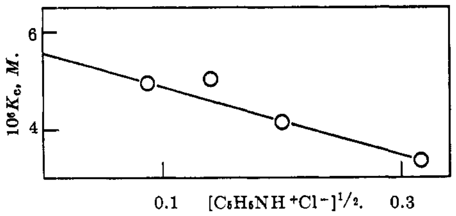

Figure 1.—Dissociation of pyridinium ion; plot of K_c *vs.* $[C_5H_5NH^+Cl^-]^{1/2}$.

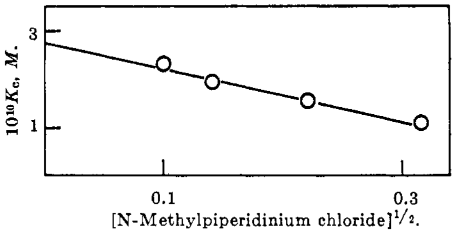

Figure 2.—Dissociation of *N*-methylpiperidinium ion; plot of K_c *vs.* square root of N-methylpiperidinium chloride concentration.

TABLE III

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOL IN UNBUFFERED METHANOL AT 25.0°[a]

$[C_6H_5SH]$, M	Obsd 10^3k_ψ, sec^{-1}	10^3k_ψ, sec^{-1}, expected if no HF dissocn[b]
0.044	0.28	0.56
0.050	0.19	0.61
0.092	0.94	0.83
0.220	1.7	1.3
0.350	2.15[c]	1.6
0.540	7.6	2.0

[a] All solutions were bubbled with N_2, and cuvettes were flushed with N_2. [b] Based on K_{PhSH} 1.2×10^{-11} M. [c] Average of two runs.

In these runs, two solute acids were present: thiophenol and HF, the latter a by-product of the formation of 2,4-dinitrophenyl phenyl sulfide. If the HF were extensively dissociated, the solvated protons generated by the reaction would soon be present in concentration (*ca.* 10^{-4} M) about two orders of magnitude greater than from dissociation of the thiophenol. The increased solvated proton concentration would repress dissociation of the thiol and cause a pronounced decrease in slope of plots of log $(A_\infty - A_t)$ *vs.* time. However, these first-order kinetic plots were for the most part good straight lines. An example is presented as Figure 3. In this example, only a modest decrease in slope occurs, and then only commencing in the second half-life. Moreover, if $[H^+]$ is assumed to be *ca.* 10^{-4} M, the observed k_ψ values are about two orders of magnitude greater than they ought to be with respect to the known values of k_A and K_{PhSH}. Thus HF, even at the concentration level of 10^{-4} M, is but slightly dissociated in methanol.

If HF is assumed not to dissociate at all, the k_ψ values predicted from knowledge of $[C_6H_5SH]$, K_{PhSH}, and k_A are close to those observed; see Table III. The discrepancies between predicted and observed values are perhaps due to adventitious acidic or basic impurities, to which this unbuffered system should be quite sensitive.

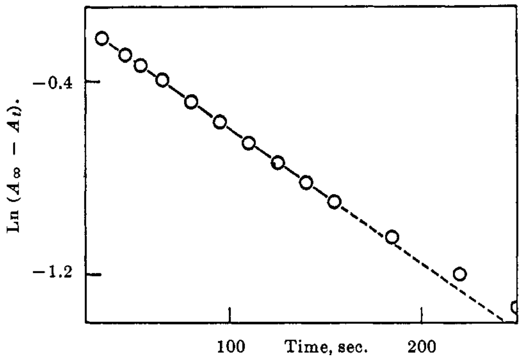

Figure 3.—Reaction of ArF with thiophenol in unbuffered methanol. First-order kinetic plot for a typical run; initial concentrations: ArF, 5.6×10^{-4} M; C_6H_5SH, 4.30×10^{-1} M. The first-order rate coefficient is 5.57×10^{-3} sec^{-1}.

To our knowledge, the pK_a of HF in methanol has not been measured. However, Chapman, *et al.*,[19] obtained kinetic evidence showing that aniline hydrofluoride is largely dissociated to free aniline in ethanol, whereas piperidine hydrofluoride is not appreciably dissociated in that solvent.

Discussion

In this study, this new method for determining pK's in methanol has been applied to four acids or bases in addition to the key acid, thiophenol. In one case no comparison pK is available, but in all of the other four cases the pK's determined in this work are in good agreement with the better determinations in the literature. On the basis of its performance, this method appears to be at least as accurate as any of the others.

Remarkably few assumptions are involved in this method. The chief one, as we have applied it, has been neglect of activity coefficient effects. The values we have determined are therefore concentration dissociation constants, designated K_c. Thermodynamic dissociation constants, K_a, referred to infinite dilution in methanol, could no doubt be determined by this method if measurements were made at a series of electrolyte concentrations so as to allow extrapolation to infinite dilution.

Limitations.—Qualitatively, this method would be difficult if not impossible to apply if the acid under study or its conjugate base were reactive enough with either 2,4-dinitrofluorobenzene (ArF) or thiophenoxide ion to compete substantially with the reaction of eq 1. For example, we would anticipate complications in applying this method to certain primary and secondary amines which are quite reactive with ArF. Piperidine, for instance, is about $^1/_{120}$ as reactive as thiophenoxide ion with ArF in methanol.[20] On the other hand, it was applied easily and successfully to determination of pK_c for chloroacetic acid; although the latter undoubtedly reacts with thiophenoxide ion, the reaction rate is evidently too low to interfere.

Quantitatively, this method is limited to acids stronger than thiophenol and, at the other extreme, by the very low rate of reaction of thiophenol with ArF when the solvated proton concentration is as high as

(19) N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301 (1951); N. B. Chapman, R. E. Parker, and P. W. Soanes, *ibid.*, 2109 (1954).

(20) J. F. Bunnett, T. Kato, and N. S. Nudelman, *J. Org. Chem.*, **34**, 785 (1969); N. S. Nudelman, unpublished observations.

10^{-3} *M; cf.* Table I. It is thus useful for determination of p*K*'s approximately in the range of 3–10. No doubt its range could be extended at the weak acid limit by using an aliphatic mercaptan instead of thiophenol. In water, alkanethiols have pK_a's about four units greater than thiophenol.[11b] However, in that case it might be necessary to determine the p*K* of the thiol in methanol by reaction with ArF in a buffered solution (*e.g.*, acetate buffer) rather than in a solution of PTS or sulfuric acid.

The odor of thiophenol or another thiol might be thought a severe disadvantage. In our experience, odor problems can virtually be eliminated if most transfers are made in the fume hood, if transfers are made neatly, and particularly if all thiol-containing residues and rinsings are first poured into a jar containing water and an oxidizing agent (*e.g.*, $KMnO_4$) rather than directly into the laboratory sink.

Other Solvents.—Although our determinations were all made in methanol, this method should be applicable with equal ease and rigor to other waterlike solvents including especially mixtures of water with organic cosolvents. The indicator method, which is perhaps the chief rival of this kinetic method in regard to convenience of application, suffers from the disadvantage in a new solvent that first the pK_a of the indicators be used must be determined. Conventionally, that would imply conductimetric or potentiometric measurements preceding the actual photometric work with the indicator. With this kinetic method, the same general type of technique, photometric kinetics, is used throughout.

Experimental Section

For the most part, materials and methods were as described in an accompanying paper.[12] Pyridine (Aldrich reagent) was refluxed over sodium for 2 hr and distilled over sodium; bp 115°. Pyridine–pyridinium chloride buffer was prepared by mixing a standard solution of hydrogen chloride in methanol (titrated after László[21]) with twice its molar amount of a standard solution of pyridine in methanol. The ampoule technique was used for the runs of Table I and direct observation of reacting solutions in a Gilford spectrophotometer for those of Tables II and III.

Registry No.—Methanol, 67-56-1; 2,4-dinitrofluorobenzene, 70-34-8; thiophenoxide ion, 13133-62-5; thiophenol, 108-98-5.

[21] N. László, *Gyógyszerészet*, 215 (1966).

Reactions of Chloro Olefins with Difluoramine[1]

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The reaction of 2-chloro-2-penten-4-one with difluoramine and fuming sulfuric acid gave 2,2,4,4-tetrakis-(difluoramino)pentane, 2-chloro-2,4,4-tris(difluoramino)pentane, and 2-chloro-3,4,4-tris(difluoramino)pentane. *cis*-3-Chlorocrotonic acid gave 3-chloro-3-(difluoramino)butyric acid but ethyl 3-chlorocrotonate did not react. 1,1-Dichloro-1-buten-3-one gave 1,1-dichloro-3,3-bis(difluoramino)-1-butene when a very large excess of difluoramine was used and N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]acetamide with less difluoramine. A possible mechanism for the formation of the latter compound is presented. The reaction of 1,1-dichloroethylene with difluoramine and fuming sulfuric acid gave 1,1-dichloro-1-(difluoramino)ethane and 1-chloro-1,1-bis(difluoramino)ethane.

In a previous paper[2] it was demonstrated that *gem*-bis(difluoramino)alkanes can be prepared in a reversible reaction of ketones and aldehydes with difluoramine in the presence of sulfuric acid. Acrylic acid and its esters underwent Michael addition of difluoramine under these conditions, whereas methyl vinyl ketone underwent Michael addition and subsequent replacement of the carbonyl group. This investigation has been extended to chlorinated substrates with the prospect of exploring chemical similarities between chlorine and difluoramino groups. Halogenlike electronic effects of difluoramino groups have been discussed previously.[3] The reversibility of the *gem*-bis(difluoramino)alkane formation shows that difluoramino groups as well as halogens can act as leaving groups in sulfuric acid. Graham, Freeman, and Johnson[4] have also obtained a low yield of 2,2-bis(difluoramino)propane from 2-chloro-2-(difluoramino)propane and difluoramine in sulfuric acid.

2-Chloro-2-penten-4-one was found to react with difluoramine and fuming sulfuric acid to give three products which could not be separated by distillation (Scheme I). The components, comprising 90, 5, and 5% of the sample (15, 0.9, and 0.9% yields), were separated by gas chromatography and were identified by elemental analysis and ir and nmr spectra as 2,2,4,-4-tetrakis(difluoramino)pentane, 2-chloro-2,4,4-tris(difluoramino)pentane, and 2-chloro-3,4,4-tris(difluoramino)pentane, respectively. The expected product of Michael addition of difluoramine to 2-chloro-2-penten-4-one is 2-chloro-2-difluoramino-4-pentanone, and replacement of the carbonyl group with two difluoramino groups would give 2-chloro-2,4,4-tris(difluoramino)-pentane. Ionization of chloride ion from this product and alkylation of difluoramine by the resulting carbonium ion would give 2,2,4,4-tetrakis(difluoramino)-pentane. The formation of 2-chloro-3,4,4-tris(difluoramino)pentane can be rationalized on the basis of a 1,2-hydride shift in a chlorocarbonium ion followed by alkylation of difluoramine by the resulting secondary carbonium ion.

The reaction of *cis*-3-chlorocrotonic acid with refluxing difluoramine (bp −23°) in the presence of fuming sulfuric acid gave the Michael adduct, 3-chloro-3-

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[1] This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

[2] K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

[3] K. Baum, *J. Org. Chem.*, **32**, 3648 (1967).

[4] W. H. Graham, J. P. Freeman, and K. E. Johnson, private communication.