THE ACIDITY OF SOME AROMATIC FLUORO ALCOHOLS AND KETONES[1]

ROSS STEWART AND R. VAN DER LINDEN[2]

ABSTRACT

A series of five trifluoroacetophenones and five phenyl trifluoromethyl carbinols have been synthesized and their ionization constants in water measured. They are the unsubstituted, *p*-methoxy, *p*-methyl, *m*-bromo, and *m*-nitro compounds. The ketones exist as hydrates in aqueous solution and each is about two pK units stronger than the corresponding alcohol. The acidities of both series are correlated by the Hammett relation with ρ values of 1.11 and 1.01 for the ketone hydrates and alcohols respectively. The acid strengths vary from a pK_a of 9.18 for *m*-nitro-α,α,α-trifluoroacetophenone to 12.24 for *p*-methoxyphenyl trifluoromethyl carbinol.

In connection with an investigation of the mechanism of the permanganate oxidation of alcohols (1) we have examined a series of trifluoromethyl carbinols (2). These were chosen because their enhanced acidity permitted measurements to be made of the concentration of the alkoxide ion believed to be the intermediate in the oxidation mechanism. The trifluoromethyl carbinols and the ketones from which they are prepared are interesting compounds in their own right because of their acidities, the hydrates of the latter being of similar strength to phenols. We would like to report herein the synthesis of a series of substituted phenyl trifluoromethyl alcohols and ketones and the determination of their acidities.

EXPERIMENTAL

Reagents

α,α,α-Trifluoroacetophenone was obtained from Columbia Organic Chemicals and was fractionally distilled before use. All other reagents used were of reagent grade.

p-Methyl-α,α,α-trifluoroacetophenone

p-Tolylmagnesium bromide was prepared in the usual way from *p*-bromotoluene (34.7 g, 0.203 mole) and an equivalent amount of magnesium. Trifluoroacetic acid (7.5 g, 0.066 mole) dissolved in ether was added dropwise with vigorous stirring over a period of 2 hours at room temperature. After refluxing for 1 hour the reaction mixture was poured onto a 10% sulphuric acid – ice mixture and extracted several times with ether. The ether extracts were dried and distilled and a clear fraction boiling at 69° at 13 mm was obtained; yield, 30–50%, $n_D^{25} = 1.4710$ (lit., $n_D^{20} = 1.4693$ (3)); 2,4-dinitrophenylhydrazone, m.p. 133–136°. Calc. for $C_9H_7OF_3$: C, 57.4; H, 3.7; F, 30.3. Found: C, 57.8; H, 3.9; F, 26.8. This compound has been synthesized previously using a different procedure (3).

m-Bromo-α,α,α-trifluoroacetophenone

To a Carius tube of approximately 100 ml volume was added α,α,α-trifluoroacetophenone (20 g, 0.115 mole), anhydrous ferric chloride (0.1 g), and bromine (9 ml, 0.168 mole). The mixture was cooled in liquid nitrogen, the tube was sealed and then heated in a furnace for 6 days at 130°.

After reaction the liquid was extracted with aqueous sodium bromide and then fractionally distilled giving a small amount of unreacted ketone, a solid residue, and a clear liquid, b.p. 83.5° at 12 mm, $n_D^{24} = 1.5030$; yield, 50%. Calc. for $C_8H_4OF_3Br$: C, 38.0; H, 1.5; F, 22.5. Found: C, 38.2; H, 1.6; F, 20.6. 2,4-Dinitrophenylhydrazone, m.p.

---

[1] *Manuscript received November 18, 1959.*
Contribution from the Department of Chemistry, University of British Columbia, Vancouver, B.C.
[2] *Present address: Imperial Oil Limited, Sarnia, Ontario.*

121.5–123°. Calc. for $C_{14}H_8O_4N_4F_3Br$: C, 38.6; H, 1.9; N, 12.9; F, 13.2. Found: C, 38.8; H, 2.5; N, 12.0; F, 12.0.

As a check on the identity of this compound a sample was hydrolyzed with aqueous base and gave *m*-bromobenzoic acid, identical with an authentic sample.

m-Nitro-α,α,α-trifluoroacetophenone

Sixty milliliters of concentrated sulphuric acid was added slowly with stirring to trifluoroacetophenone (27.2 ml, 0.2 mole) with the temperature kept at 0° or below. A nitrating mixture (made up from 12 ml concentrated nitric acid, 4 ml fuming nitric acid, and 24 ml concentrated sulphuric acid) was added dropwise with cooling to keep the temperature from rising above 0°. A yellow solid began to precipitate after part of the nitrating mixture had been added. The mixture was poured onto crushed ice and extracted with ether. The latter was dried and on removal of the ether gave a yellow oil which on fractional distillation gave a pale yellow, low melting solid, b.p. 113° at 12 mm; yield, 75%. Calc. for $C_8H_4O_3F_3N$: C, 43.8; H, 1.8; F, 26.0; N, 6.4. Found: C, 43.4; H, 1.9; F, 24.3; N, 6.6. 2,4-Dinitrophenylhydrazone, m.p. 128–132°. Calc. for $C_{14}H_8O_5N_5F_3$: C, 42.2; H, 2.0; N, 17.6; F, 14.3. Found: C, 43.1; H, 2.8; N, 17.0; F, 13.4.

Alkaline hydrolysis of the ketone gave *m*-nitrobenzoic acid, identical with an authentic sample.

p-Methoxy-α,α,α-trifluoroacetophenone

This compound was prepared by the Grignard procedure essentially as described for *p*-methyl-α,α,α-trifluoroacetophenone. B.p. 64° at 0.5 mm; $n_D^{23} = 1.5051$. Calc. for $C_9H_7F_3O_2$: C, 52.9; H, 3.5. Found: C, 51.9; H, 3.6. 2,4-Dinitrophenylhydrazone, m.p. 104–105° (decomp.).

Phenyl Trifluoromethyl Carbinols

The unsubstituted, *m*-bromo, and *p*-methyl compounds were prepared by a lithium aluminum hydride reduction of the corresponding ketones by a standard method. Data are listed in Table I. The yields of crude product before purification were of the order of 80–90%.

TABLE I

Physical properties and analytical data for the fluoro alcohols

YC_6H_4-$CHOHCF_3$	B.p.	Refractive index	Phenyl-urethan m.p.	Analysis*	
				Calculated	Found
H	82° (13 mm)	$1.4590^{25°}$			
			103–104°	C, 61.0; H, 4.1; F, 19.3	C, 61.2; H, 4.2; F, 19.0
p-CH_3O	80° (0.5 mm)	$1.4780^{23°}$		C, 52.4; H, 4.4	C, 52.2; H, 4.6
p-CH_3	94.5° (12 mm)	$1.4650^{24°}$		C, 56.9; H, 4.7; F, 30.0	C, 57.1; H, 5.0; F, 26.6
			104–105°	C, 62.1; H, 4.5; F, 18.4; N, 4.5	C, 62.1; H, 4.5; F, 16.7; N, 5.1
m-Br	115° (12 mm)	$1.5005^{27°}$		C, 37.1; H, 2.4; F, 22.4; Br, 31.4	C, 38.0; H, 2.5; F, 20.0; Br, 31.6
m-NO_2	106° (2 mm) (m.p. = 47–48°)			C, 43.5; H, 2.7; F, 25.8; N, 6.3	C, 43.7; H, 3.1; F, 23.7; N, 6.4
			102–103°	C, 53.0; H, 3.2; F, 16.8; N, 8.2	C, 53.1; H, 3.6; F, 16.3; N, 8.3

*Analysis by A. Bernhardt, Mulheim, West Germany.

m-Nitrophenyl Trifluoromethyl Carbinol

m-Nitro-α,α,α-trifluoroacetophenone (10 g, 0.045 mole) and aluminum isopropoxide

(8.2 g, 0.04 mole) dissolved in 40 ml of dry isopropyl alcohol were distilled slowly for 2 hours with the alcohol being replaced as it distilled. The mixture was poured onto a 3 *M* HCl–ice mixture and extracted with ether. Distillation yielded a viscous oil, b.p. 106° at 2 mm, which crystallized on standing. Recrystallization from benzene – petroleum ether gave pale yellow needles, m.p. 47–48°.

p-Methoxyphenyl Trifluoromethyl Carbinol

This compound was prepared by essentially the method described for *m*-nitrophenyl trifluoromethyl carbinol. See Table I for physical constants.

pK_a *Measurements*

Stock solutions of the alcohols and ketones of appropriate concentration were prepared by weighing out the pure liquids (purified in most cases by gas chromatography), and dissolving them with shaking in distilled water. Usually 10 ml of these solutions and 10 ml of phosphate buffer were added to a 25-ml volumetric flask which was then made up to volume with distilled water. The buffer consisted of 0.02 *M* Na_2HPO_4 solution to which 1 *N* NaOH or 1 *N* H_2SO_4 was added to produce approximately the desired pH. Solutions more basic than pH 13 were obtained by using NaOH directly rather than the buffer. The pH of these solutions was obtained directly from the concentration of NaOH present. The optical density of a few milliliters of the buffered ketone or alcohol solution was then measured using a Beckman DU spectrophotometer at a suitable wavelength. The latter was located by measuring the entire spectrum of the ketone or alcohol in neutral and basic solution (usually pH 4.0 and 13.6) using a Cary model 14 recording spectrophotometer. The absorption maxima are listed in Tables I and II. The cell compartment of the DU spectrophotometer was kept at 25° by means of thermospacers.

TABLE II

Ultraviolet spectral data for trifluoroacetophenone and derivatives

Trifluoro-acetophenone	Neutral aqueous solution		Basic aqueous solution		Cyclohexane solution	
	λ_{max}	ϵ	λ_{max}	ϵ	λ_{max}	ϵ
Unsubstituted	267	350	266	144	253	13,300
	260	474	260	237	288	1000
	255	427	256	278		
	250	345	250	247		
m-Br	274.5	342	273.5	213	254	10,500
	267.5	451	267	306	302	1520
	261.5	358	261	258		
	255 (sh)	250	255 (sh)	200		
m-NO_2	263	14,000	269	13,600	233	20,800
					302	900
					292	1050
p-CH_3	265	590	294	73	264	15,700
	259	607	260	356		
			253	390		
			243	410		
p-CH_3O	300	1360	276	980	289	15,900
	277	1530	270	1080	231	9300
	270	1390			225	11,000

After the optical density readings were made the pH of the remainder of the solution was measured using a Beckman model G pH meter which was standardized against buffer at pH 7.00 and 10.00. It has been reported (4) that trifluoroacetophenones are decomposed by alkali to CHF_3 and the corresponding benzoic acid. The alkaline solutions we used were stable during the time of the measurements but it was noted that decomposition was occurring in some cases after a few hours.

Calculations

For all the compounds studied a plot of optical density against pH gave a typical titration curve. The ionization constants were calculated using the equation,

$$pK_a = \mathrm{pH} \pm \log\,[(D - D_{A^-})/(D_{HA} - D)]$$

where D is the optical density of the solution at the selected wavelength, D_{A^-} that at complete ionization obtained by measuring the optical density of a 0.6 N NaOH solution of the compound (corrected in the case of the alcohols for incomplete ionization), and D_{HA} that of the completely unionized form obtained by a measurement at pH 4. A minimum of three values in the vicinity of half ionization was obtained for each compound and these values averaged to obtain the values listed in Table III. The probable error varies from compound to compound because of the differences in spectra but is generally of the order of ± 0.06 pK units.

The wavelengths in millimicrons used for the pK measurements were as follows, with the alcohol listed first and the ketone second: H (260, 260); *p*-CH_3O (280, 276); *p*-CH_3 (269, 260); *m*-Br (274, 274.5 and 267.5); *m*-NO_2 (330, 320).

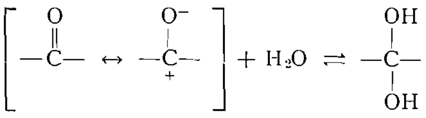
TABLE III

Ultraviolet spectral data for phenyl trifluoromethyl carbinol and derivatives

Phenyl trifluoromethyl carbinol	Neutral aqueous solution		Basic aqueous solution	
	λ_{max}	ϵ	λ_{max}	ϵ
Unsubstituted	266	140	262	149
	260	210	257	200
	256	224	251	165
	250	163	247	130
m-Br	274	254	274	162
	267	340	267	244
	261	286		
m-NO_2	264	7600	270	7000
p-CH_3	265	156	271	192
	260	225	262	275
	254	194	256	230
p-CH_3O	278	1130	277	1080
	272	1320	271	1240

RESULTS

Polyfluorinated ketones exist in the hydrated form in aqueous solution (5, 6) presumably because of the strongly electron-withdrawing group which raises the energy of the dipolar canonical structure and shifts the following equilibrium to the right.



$$\left[\;-\overset{\displaystyle O}{\overset{\|}{C}}- \;\leftrightarrow\; -\overset{\displaystyle O^-}{\overset{|}{\underset{+}{C}}}-\;\right] + H_2O \rightleftharpoons -\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle OH}{|}}{C}}}-$$

The trifluoroacetophenones reported herein are all hydrated in aqueous solution as can be seen from an examination of their ultraviolet spectra. Table II which lists the absorption maxima of the ketones in cyclohexane and in water and Fig. 1 which shows the spectrum of *m*-bromo-α,α,α-trifluoroacetophenone in water reveal the absence of the usual phenyl ketone absorption in aqueous solution. The latter spectrum appears when these compounds are dissolved in cyclohexane. (The absorption of the *p*-methoxy ketone at 300 mμ is probably due to the presence of some unhydrated ketone since this ketone is the one expected to be least hydrated in water.) When trifluoroacetophenone is dissolved in ethanol the characteristic phenyl ketone absorption at 253 mμ rapidly decays until the spectrum resembles that in aqueous solution.

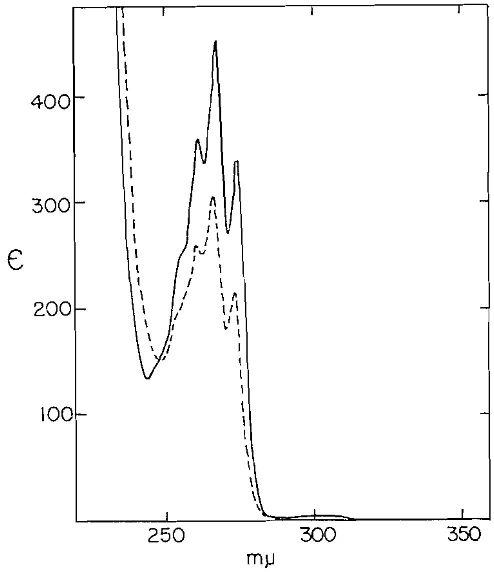


FIG. 1. The ultraviolet spectrum of *m*-bromo-α,α,α-trifluoroacetophenone in water: solid line, pH 4; broken line, pH 13.

The ultraviolet spectrum of the hydrate of trifluoroacetophenone is essentially a benzene spectrum modified by the side chain. When one of the hydroxyls in the side chain is ionized in basic solution the spectrum is sufficiently altered to enable measurements of the concentrations of the two forms to be made (Fig. 1).

The same applies to the alcohols, and in fact the spectra of the ketone hydrates and their anions were found to be very similar to those of the corresponding alcohols and their anions. Tables II and III reveal the close similarity in the wavelength maxima in the two series. The extinction coefficients are, however, somewhat larger for the ketone hydrates than for the alcohols.

Comparison of Acidities in the Two Series

The ionization constants of the alcohols and ketone hydrates are listed in Table IV; Fig. 2 shows the pK values plotted against σ, the Hammett substituent constant (7, 8). A satisfactory linear relation is obtained for both series. It can be seen that the ketone hydrates are about 2 pK units more acidic than the alcohols. This 100-fold increase in

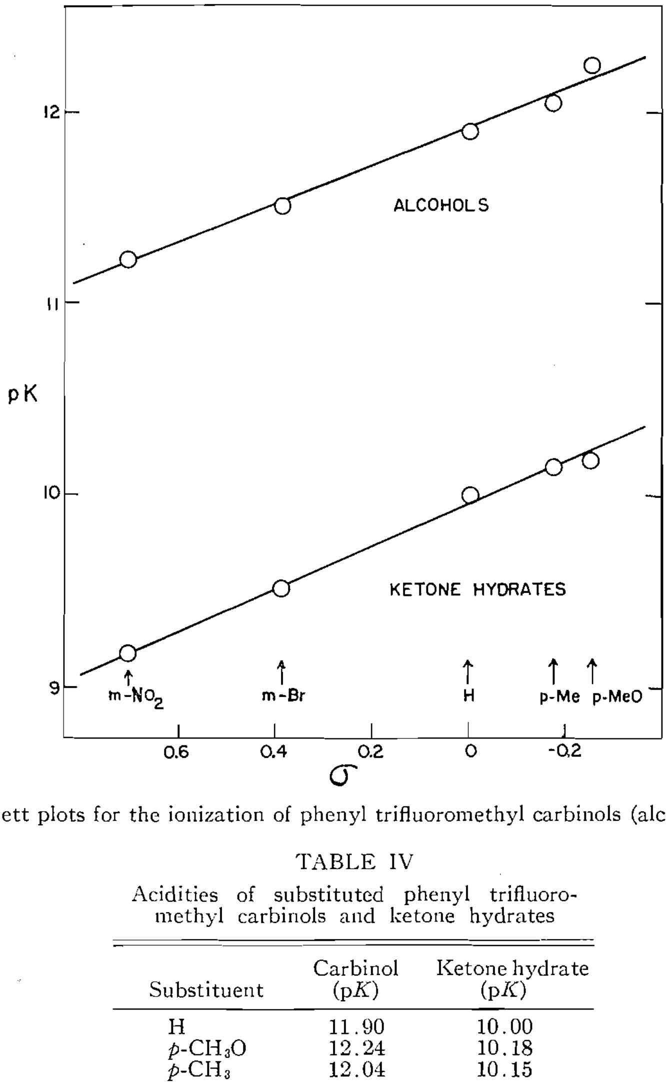


FIG. 2. Hammett plots for the ionization of phenyl trifluoromethyl carbinols (alcohols) and ketones.

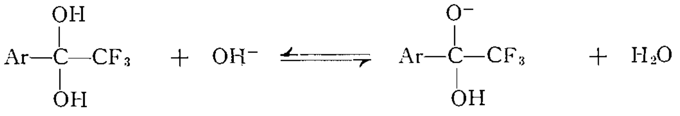
TABLE IV

Acidities of substituted phenyl trifluoromethyl carbinols and ketone hydrates

Substituent	Carbinol (pK)	Ketone hydrate (pK)
H	11.90	10.00
p-CH$_3$O	12.24	10.18
p-CH$_3$	12.04	10.15
m-Br	11.50	9.51
m-NO$_2$	11.23	9.18

ionization constant (50-fold if a statistical correction is made for the extra ionizable proton in the ketone hydrate) is due entirely to the electronegative nature of the additional oxygen atom in the former.

$$\mathrm{Ar{-}\underset{H}{\overset{OH}{C}}{-}CF_3} + \mathrm{OH^-} \rightleftharpoons \mathrm{Ar{-}\underset{H}{\overset{O^-}{C}}{-}CF_3} + \mathrm{H_2O}$$

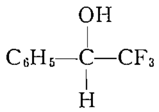
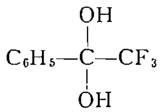
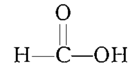
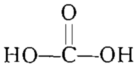
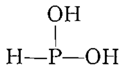
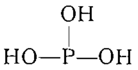
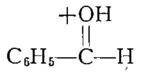
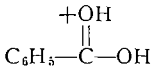


$$\mathrm{Ar{-}\underset{OH}{\overset{OH}{C}}{-}CF_3} + \mathrm{OH^-} \rightleftharpoons \mathrm{Ar{-}\underset{OH}{\overset{O^-}{C}}{-}CF_3} + \mathrm{H_2O}$$

In these two systems resonance effects on the ionization are completely absent and it is worth comparing the effect of the additional oxygen atom on the acidity of the hydroxyl group with that in analogous cases. Table V shows that the addition of an oxygen atom to formic acid, hypophosphorous acid, and benzaldehyde conjugate acid produces much smaller charges in acidity than the addition of an oxygen atom to phenyl trifluoromethyl carbinol. In the former cases the electron-withdrawing inductive effect of oxygen is largely cancelled by its electron-donating resonance effect, assuming in the case of phosphorous acid that resonance occurs with the expanded valence shell of phosphorus. Resonance involving the oxygen atoms is not possible in the case of the ketone hydrates.

TABLE V

Effect of oxidation on acidities

Acid	K_{I}	Acid	K_{II}	$K_{\text{II}}/K_{\text{I}}$	Reference
 $C_6H_5-\overset{\overset{\displaystyle OH}{\vert}}{\underset{\underset{\displaystyle H}{\vert}}{C}}-CF_3$	1.2×10^{-12}	 $C_6H_5-\overset{\overset{\displaystyle OH}{\vert}}{\underset{\underset{\displaystyle OH}{\vert}}{C}}-CF_3$	1.0×10^{-10}	80	Herein
 $H-\overset{\overset{\displaystyle O}{\Vert}}{C}-OH$	1.8×10^{-4}	 $HO-\overset{\overset{\displaystyle O}{\Vert}}{C}-OH$	2×10^{-4}*	~1	(9)
 $H-\overset{\overset{\displaystyle OH}{\vert}}{P}-OH$	1×10^{-2}	 $HO-\overset{\overset{\displaystyle OH}{\vert}}{P}-OH$	1.6×10^{-2}	1.6	(10)
 $C_6H_5-\overset{\overset{\displaystyle ^{+}OH}{\Vert}}{C}-H$	1.2×10^{7}	 $C_6H_5-\overset{\overset{\displaystyle ^{+}OH}{\Vert}}{C}-OH$	1.8×10^{7}	1.5†	(11, 12)

*Corrected for incomplete hydration of CO_2.

†This ratio varies with the substituent in the ring. The *p*-CH_3O substituent reduces the importance of resonance *within* the carbonyl group and raises this ratio to a value of 13.

The Reaction Constant

The values of the reaction constant, ρ (the slopes in Fig. 2) (7, 8), are 1.01 for the alcohols and 1.11 for the ketone hydrates. Values close to 1.0 are expected for ionizations in which the proton is removed from the second atom of the side chain (13) as in both the present cases.*

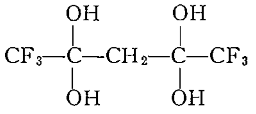
Rate of Ionization of the Fluoroketones

When the fluoroketones reported herein are dissolved in water they react rapidly to form the hydrates since the spectrum taken immediately after solution is effected is identical with that taken after long standing. The ionization of these weak acids is essentially instantaneous as expected for hydroxylic compounds. This rather obvious point is referred to here because certain fluorinated ketone hydrates have been shown to ionize only slowly with base. Thus hexafluoroacetylacetone which exists in solution as

---

*NOTE ADDED IN PROOF: *Since there is no conjugation between the sidechain and the substituents in these series one should obtain a better correlation with the recently derived σ^0 values (R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. Glick. J. Am. Chem. Soc.* **81**, *5352 (1959)) than with the standard sigma values. Even though σ and σ^0 are not greatly different for the substituents studied in this work it does appear that the correlation is slightly better for σ^0 than for σ.*

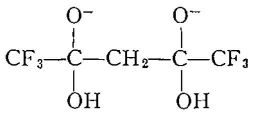
the dihydrate, I,



$CF_3-\underset{OH}{\overset{OH}{C}}-CH_2-\underset{OH}{\overset{OH}{C}}-CF_3$

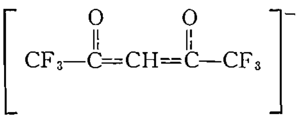
I

although a much stronger acid (pK = 4.35) than trifluoroacetophenone hydrate (pK = 10.0) ionizes at a relatively slow rate requiring over 3 hours for neutralization with 1 M NaOH (14, 15). A similar situation exists with thenoyltrifluoroacetone (14). The reason for the apparent discrepancy is the following. The stable anion of I is undoubtedly not ion II, but ion III.



$CF_3-\underset{OH}{\overset{O^-}{C}}-CH_2-\underset{OH}{\overset{O^-}{C}}-CF_3$

II



$\left[CF_3-\overset{O}{\overset{\|}{C}}=CH=\overset{O}{\overset{\|}{C}}-CF_3\right]^-$

III

The slow neutralization by base is due to ion II, which is almost certainly formed immediately by the action of strong base, having to revert to the unhydrated form and then eliminate a proton from the central carbon to form the more stable ion III. Such an enolate anion is, of course, not possible with aromatic ketones so that the further, slow, ionization does not take place.

ACKNOWLEDGMENT

The financial support of the National Research Council is gratefully acknowledged.

REFERENCES

1. R. STEWART. J. Am. Chem. Soc. **79**, 3057 (1957).
2. R. STEWART and R. VAN DER LINDEN. To be published.
3. J. D. PARK, H. A. BROWN, and J. R. LACKER. J. Am. Chem. Soc. **73**, 709 (1951).
4. J. H. SIMONS and E. O. RAMLER. J. Am. Chem. Soc. **65**, 389 (1943).
5. A. L. HERNE, J. W. SHEPHARD, and E. J. YOUNG. J. Am. Chem. Soc. **72**, 3577 (1950).
6. E. H. COOK and R. W. TAFT, JR. J. Am. Chem. Soc. **74**, 6103 (1952).
7. L. P. HAMMETT. Physical organic chemistry. McGraw-Hill Book Co., Inc., New York. 1940. Chap. VII.
8. H. H. JAFFÉ. Chem. Revs. **53**, 191 (1953).
9. W. W. LATIMER and J. H. HILDEBRAND. Reference book of inorganic chemistry. Macmillan Co., New York. 1951. p. 282, 285.
10. W. W. LATIMER and J. H. HILDEBRAND. Reference book of inorganic chemistry. Macmillan Co., New York. 1951. p. 229.
11. K. YATES and R. STEWART. Can. J. Chem. **37**, 664 (1959).
12. K. YATES. Ph.D. Thesis, The University of British Columbia, Vancouver, B.C.
13. R. W. TAFT, JR. and I. C. LEWIS. J. Am. Chem. Soc. **80**, 2436 (1958).
14. R. W. TAFT, JR. and E. H. COOK. J. Am. Chem. Soc. **81**, 46 (1959).
15. L. G. VAN UITART. M.Sc. Thesis. The Pennsylvania State College. 1951. Referred to in ref. 14.