

These bonds are weak, being of the order of 5 kcal. per mole.¹⁶ Thermal agitation, *i.e.*, increased temperature, disrupts them leading to the disappearance of metachromasy. Conversely, lowering the temperature to near 0° induces metachromasy in solutions which are orthochromatic at room temperature.

In order for the dye "non-polar" residues to polymerize, it is necessary to secure the correct ratio of dye to substrate concentration. In the presence of a large excess of substrate, a small number of dye molecules may form the usual polar link at random, but, being widely separated, the aromatic rings of the dye cannot polymerize to yield metachromasy. In view of the findings of Rabinowitch and Sheppard^{15,14} with regard to the spacing requirement for aggregation of thiazine dyes, it should be noted that nucleic acids have been reported to have a spatial unit of 3.5 Å.¹⁷

(16) L. Pauling in K. Landsteiner, "The Specificity of Serological Reactions," Harvard University Press, Cambridge, Mass., 1945, p. 275.

(17) W. T. Astbury, "Symposia of the Society for Experimental Biology," Vol. I, Cambridge, 1947, p. 66.

The effect of solvents on the van der Waals binding also has been shown. Alcohol abolished metachromasy of toluidine blue induced by gum arabic.⁵ We have found that alcohol also abolishes metachromasy induced by nucleic acids.⁹ These findings supplement the observations of Sheppard that aggregation of thiazine dyes may involve the bonding of a molecule of water between neighboring resonating dye ions¹⁸ and those of Rabinowitch and Epstein¹⁵ that alcohol prevents the dimerization of the thiazine dyes methylene blue and thionine.

Acknowledgment.—This work was aided by a grant from the American Cancer Society to the Department of Preventive Medicine, the Johns Hopkins University School of Medicine, recommended by the Committee on Growth of the National Research Council.

(18) S. E. Sheppard and A. L. Geddes, *THIS JOURNAL*, **66**, 2003 (1944).

BALTIMORE, MARYLAND

RECEIVED MAY 26, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Acidity of Trifluorinated Alcohols and Saponification Rates of their Acetates

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Measured by an electrometric procedure, the ionization constants for CF₃CH₂OH, CF₃CH(CH₃)OH and CF₃C(CH₃)₂OH were found to be not more than 10⁻¹². In 50% aqueous acetone 0.1 N in NaOH at 25°, the saponification of CF₃CH₂OAc and CF₃CH(CH₃)OAc showed second order kinetics with *K* 0.6 and 0.15 l. mole⁻¹ sec.⁻¹. The rate constants for 0.1 N acid-catalyzed reactions expressed as *K* × 10⁶ sec.⁻¹ were found to be: CHF₂CH₂OAc 2.0, CF₃CH₂OAc 1.4, CF₃CH(CH₃)OAc 1.2, CF₃CH₂CH₂OAc 2.6 and C₆H₅OAc 4.0. These values are discussed.

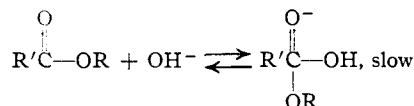
Fluorinated alcohols are known to be acidic. They are reported to form alcoholates on standing with alkali carbonates, alkaline-earth carbonates, but not bicarbonates,² not to form complexes with calcium chloride,³ tenaciously to resist dehydration,⁴ and one of them, CF₃CHOHCH₃, is reported to have an ionization constant of *K* = 10⁻⁷, intermediate between phenol and acetic acid.⁵

The following alcohols were synthesized: CF₃CH₂OH,⁶ CHF₂CH₂OH by reduction of difluoroacetic acid obtained in much improved yield, CF₃CHOHCH₃ by reduction of CF₃COCH₃ obtained in improved yield, CF₃C(CH₃)₂OH⁷ and CF₃CH₂CH₂OH.⁸

Ionization constants were determined by measuring the *pH* at the half-equivalence point, which is equal to the *pK* between the limits of 10 and 4⁹ and, for acids with *K*_a in the range of 10⁻³ to 10⁻⁵, a good approximation of it slightly beyond these limits.¹⁰ The observed results at 25° were: CF₃CH₂OH 4.0, CF₃CH(CH₃)OH 6.3 and CF₃C-

(CH₃)₂OH 2.5 × 10⁻¹². The order of magnitude contradicts that given by Swarts,⁵ 10⁻⁷, but agrees with those obtained by Richter¹¹ for HOCH₂CF₂CF₂CH₂OH, 10⁻¹¹ and 10⁻¹² and by McBee¹² for HOCH₂CF₂CF₂CH₂OH and HOCH₂(CF₂)₄CH₂OH, 10⁻¹². To test the results, U.S.P. phenol was measured in like fashion, and found to have *K* = 1 × 10⁻⁹, while the accepted value¹⁸ for specially repurified phenol is 1 × 10⁻¹⁰. Since glass electrode measurements tend to give values which are too low in solutions of *pH* > 10, and since the actual difference of *pH* before and after adding the alcohols to the sodium hydroxide was very small, it may be said that the ionization constants of these alcohols has been shown to be not more than 10⁻¹², and that a plausible value might be taken as 4 × 10⁻¹². This shows that the fluorinated alcohols are at least 10⁴ times more acid than ethanol.¹⁴

The hydrolysis of esters by hydroxide ions in aqueous solvents is known to show second order kinetics. The accepted explanation is



(1) Socony Vacuum Fellow, 1949-1950.

(2) F. Swarts, *Bull. Classe sci., Acad. Roy. Belg.*, 731-760 (1902).

(3) F. Swarts, *Bull. soc. chim. Belg.*, **43**, 471 (1934).

(4) F. Swarts, *ibid.*, **36**, 191 (1927), and J. V. Schmitz, Ph.D. dissertation, The Ohio State University, 1949.

(5) F. Swarts, *ibid.*, **38**, 99 (1929).

(6) A. L. Henne, R. M. Alm and M. A. Smook, *THIS JOURNAL*, **70**, 1968 (1948).

(7) E. Gryszkiewicz-Trochimowski, *Rec. trav. chim.*, **66**, 427 (1947).

(8) E. T. McBee and A. Truchan, *THIS JOURNAL*, **70**, 2910 (1948).

(9) G. M. Bennett, G. L. Brooks and S. Glasstone, *J. Chem. Soc.*, 1821 (1935).

(10) A. L. Henne and C. J. Fox, *THIS JOURNAL*, **73**, 2323 (1951).

(11) S. B. Richter, Ph.D. dissertation, The Ohio State University, 1951.

(12) E. T. McBee, W. F. Marzluff and O. R. Pierce, Verbal, 118th A.C.S. Meeting, Chicago, Ill., September, 1950.

(13) M. Mizutani, *Z. phys. Chem.*, **118**, 318 (1925).

(14) J. H. Hildebrand and P. S. Denner, *THIS JOURNAL*, **44**, 2824 (1922).

The reaction product could be steamed out, but it was found simpler to saw the vessel open and to scrape the bright red crystalline mixture of ammonium fluoride and fluorinated triazine (100 g. or 100% yield): $3C_2F_4 + 9NH_3 \rightarrow$

$6NH_4F + \overline{N=C(CHF_2)-N=C(CHF_2)-N=C(CHF_2)}$. This mixture was refluxed with aqueous sodium hydroxide until the ammonia evolution ceased to be perceptible (about six hours), acidified and continuously extracted with ether. Rectification of the extract gave 61 g. of wet CHF_2CO_2H which was dried by distilling from P_2O_5 to yield 49.7 g. (0.52 mole or 80% over-all) of good acid, b.p. 134° , n_D^{20} 1.3428.

CHF_2CO_2H (alternate).—In a 500-ml. steel vessel, absolute ethanol (46 g. or 1 mole) was treated with sodium (2 g.); after cooling in Dry Ice, tetrafluoroethylene (67 g. or 0.67 mole) was added. The vessel was sealed and shaken at 55° for four hours. The pressure rose to 350 p.s.i. then fell to zero. Working up gave 78 g. (77%) of CHF_2CH_2OEt , b.p. 54° . Fuming nitric acid (42 ml.) was added dropwise to this fluorinated ether (42 g. or 0.3 mole) and refluxed for 8 hours. Much etching occurred. Pouring into water permitted decantation of 23 g. (0.16 mole) of recovered fluorinated ether. Continuous extraction of the aqueous layer with ether, desiccation of P_2O_5 and distillation gave 15 g. (0.15 mole) of ethyl difluoroacetate, b.p. 100° . This is 50% conversion and almost quantitative net yield.

CHF_2CH_2OH .—Difluoroacetic acid (85.5 g. or 0.89 mole) was slowly dropped into stirred benzoyl chloride (140 ml. or 1.2 moles); progressive heating to 170° caused the distillation of CHF_2COCl (75 g., 0.65 mole or 74%) and CHF_2CO_2H (10 g., 0.1 mole or 11%). The acyl chloride was dripped into a solution of $LiAlH_4$ (15 g. or 0.4 mole) in anhydrous ether (700 ml.) at the rate permitted by the capacity of the reflux condenser. Rapid stirring was required to keep the heavy slurry formed from setting. After refluxing for one hour, water (75 ml.) was cautiously added, the ether was decanted and the residue poured over a mixture of 500 ml. of 6 N H_2SO_4 and ice. This was continuously extracted with the decanted ether. The extract gave 34 g. of wet CHF_2CH_2OH (about 69% yield); it is estimated that about 10% of product was accidentally lost during extraction.

CF_3COCH_3 (improved).—The condensation of CF_3CO_2Et (780 g. or 5.5 moles) with CH_3CO_2Et (526 g. or 6 moles) was performed as usual.²⁶ After 6 hours of reflux instead of the 60 hours used before, ether and ethanol were removed by heating on a steam-bath. Complete removal of ethanol was then insured by heating under reduced pressure until a solid cake was formed. Sulfuric acid of 25% concentration (1500 ml.) was added and allowed to stand until the cake was dissolved. Concentrated sulfuric acid (400 g.) was then added to bring the solution back to 25% acid concentration. The mixture was heated under reflux with continued stirring until the organic layer had completely disappeared. The vapors passing through the reflux condenser were directed to a Dry Ice trap which collected 511 g. (83%) of CF_3COCH_3 , b.p. $20-21^\circ$.

$CF_3CHOHCH_3$.—Trifluoroacetone (40 g. or 0.36 mole) was bubbled into a solution of $LiAlH_4$ (4 g. or 0.1 mole) in dry ether (200 ml.) under a Dry-Ice reflux condenser. After two hours of refluxing, water (50 ml.) was added with stirring, and additional ether was supplied when the mixture became too viscous. Working up as before gave 34 g. of $CF_3CHOHCH_3$, b.p. 77° , an 85% yield.

Acetylation.—All alcohols were conventionally acetylated with acetyl chloride: CF_3CH_2OAc , b.p. 78° , n_D^{20} 1.3202; CHF_2CH_2OAc , b.p. $106-106.5^\circ$; $CF_3CH_2CH_2OAc$, b.p. $112.8-113^\circ$, n_D^{20} 1.3410, d_4^{20} 1.219, AR_F 1.09; F_7O 34.5, calcd. 36.5; $CF_3CH(CH_3)OAc$, b.p. 85.6° ; $CF_3C(CH_3)_2OAc$, b.p. $94-95^\circ$, n_D^{25} 1.3424, d_4^{25} 1.14, AR 1.05.

(26) A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, THIS JOURNAL, 69, 1819 (1947).

Ionization Constants.—Ten ml. of 0.0446 N CF_3CH_2OH mixed with 7.40 ml. of 0.0303 N NaOH (half neutralization point) showed pH 11.4; hence $K = 4 \times 10^{-12}$. Ten ml. of 0.039 N $CF_3CH(CH_3)OH$ mixed with 6.40 ml. of 0.0303 N NaOH showed pH 11.2; hence $K = 6 \times 10^{-12}$. Ten ml. of 0.440 N $CF_3C(CH_3)_2OH$ mixed with 7.30 ml. of 0.0303 N NaOH showed pH 11.60; hence $K = 2.5 \times 10^{-12}$. Ten ml. of 0.064 N phenol (U.S.P.) and 10.50 ml. of 0.0303 N NaOH showed pH 8.90; hence $K = 1 \times 10^{-9}$. The precision of the pH reading was ± 0.05 unit.

Base-catalyzed Hydrolysis.—Known amounts of ester were sealed in thin wall bulbs placed in 50% aqueous acetone by weight, 0.01 N in NaOH. After holding 20 minutes in a thermostat held at $25.00 \pm 0.05^\circ$, the bulb was crushed at time zero; at time t , 1 ml. of 0.1 N HCl was added, and the excess of acid was back-titrated with 0.01 N NaOH to a phenolphthalein end-point. Separate bulbs were used for t_1, t_2, t_3 , etc. The rate constant $K = [2.303/t(a-x)] \log [b(b-x)/a(a-x)]$, where a and b are the concentration of base and ester, and x the hydrolyzed ester, is reduced to $K = [1/t] \{x/a(a-x)\}$ when a and b are approximately equal.

Hydrolysis of $CF_3CH(CH_3)OAc$ at 25.0° .— $a = 0.00907$; $b = 0.00875$; stopped with 1 ml. 0.1013 N HCl and back titrated with 0.00907 N NaOH. Time in sec.: 0, 30, 60, 120, 180, 240, 360, 480; corresponding x : 0, 0.00045, 0.00089, 0.00187, 0.00205, 0.00245, 0.00301 and 0.00350; $K = 0.155$ l. mole $^{-1}$ read from the $1/(a-x)$ vs. t slope.

CF_3CH_2OAc measured under comparable conditions gave, for two sets of measurements, $K = 0.6$ l. mole $^{-1}$ sec. $^{-1}$.

Acid-catalyzed Hydrolysis.—Aqueous acetone 50% by weight and 0.1 N in HCl was brought to $25.00 \pm 0.05^\circ$. A weighed amount of ester was diluted in this solvent to give 25.0 ml. of solution about 0.1 N in ester. A 2-ml. aliquot was withdrawn at noted intervals and titrated with 0.03 N NaOH to phenolphthalein end-point. Notations are: t , time in minutes; $[H]^+$, acid concentration at t min.; x , amount of acetic acid formed and a the ester concentration at time zero. The rate constant was determined by taking 2.303 times the slope of $\log(a-x)$ versus t plot, a procedure which is regarded¹⁹ as more accurate than the averaging of constants determined from the equation $K = [1/t] 2.303 \log [a/(a-x)]$; however, when the rates were calculated from this equation (Table II, last column) the results were practically identical.

TABLE II

ACID-CATALYZED HYDROLYSES AT $25.00 \pm 0.05^\circ$						
CHF_2CH_2OAc t , min.	$[H]^+$	x	$(a-x)$	$\log(a-x)$	$\log a/(a-x)$	10^4K min. $^{-1}$
0	0.0960	0.1263	0.1014
245	.0998	0.0037	.1226	.0885	0.0129	1.21
725	.1070	.0110	.1153	.0618	.0396	1.25
1295	.1144	.0184	.1079	.0331	.0683	1.22
1700	.1277	.0317	.0976	.0099	.0915	1.24
					Mean	1.23
0	0.09815	0.03241	0.5106
176	.09897	0.00082	.03158	.4994	0.0112	1.46
365	.09959	.00144	.03097	.4910	.0196	1.23
620	.10049	.00234	.03007	.4771	.0324	1.21
					Mean	1.30

CF_3CH_2OAc , $CF_3CH(CH_3)OAc$ and $CF_3CH_2CH_2OAc$ were subjected to similar measurements and computations.

Expressed in $K \times 10^4$ sec. $^{-1}$ the experimental values, from slope reading and from averaging, respectively, were found to be: CHF_2CH_2OAc , 2.05 and 2.10; CF_3CH_2OAc , 1.45 and 1.56; $CF_3CH(CH_3)OAc$, 1.25 and 1.36, and $CF_3CH_2CH_2OAc$, 2.6 and 3.3.

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RECEIVED SEPTEMBER 14, 1951