The *p*H was about 1.3 in each instance. This indicates that part of the solvent effect of nicotinamide for riboflavin is independent of the pyridine grouping. Since formamide and acetamide have both been found to have solvent action for riboflavin in aqueous solution, it is thought that this residual solvent effect of nicotinamide hydrochloride lies in the amide grouping.

In pharmacologic studies, a solution of 20% nicotinamide and 0.5% riboflavin was well tolerated by injection. In chronic toxicity studies, however, near toxic levels were noted to produce fatty livers in rats on a stock diet. In further nutritional studies, in which we used a highly synthetic diet containing 18% casein, a level of 1 mg. of nicotinamide per gram body weight per day was found to produce fatty livers in rats. The most likely explanation of the pathological effect of excessive intake of nicotinamide is found in the increased requirement for active methyl compounds to form excretory products, such as trigonelline and N'-methylnicotinamide.[1,2] An artificial deficiency of methionine, or other active methyl donors, created in this way apparently leads to changes in fat metabolism in the liver.

Discussion

Compounds which have been described for the preparation of riboflavin solutions are: urea and urethan,[3] sodium desoxycholate and N-methylacetamide,[4] nicotinamide and water soluble salts of nicotinic acid,[5,6] alkali metal borates,[7] boric acid,[8] acetamidine salts,[9] water soluble salts of 2,4-dihydroxybenzoic acid and its mono-alkyl ethers[10] and water soluble salts of benzoic acid and various mono-substituted benzoic acids.[11] Certain riboflavin esters, notably the succinates,[12] have been prepared. The latter show increasing solubility but decreasing biologic activity with an increase in the number of ester substitutions in the ribityl grouping. The boric acid esters,[7,8] are fully active biologically but are unstable at *p*H more acid than 6.0. Because riboflavin becomes increasingly unstable with increasing alkalinity, the usefulness of the boric acid complexes in solution is limited. The basis for the solvent effect of the other compounds named has not been described.

It is interesting to note that the presence of nicotinamide appears to change the course of reduction of riboflavin by sodium hydrosulfite. Also addition of alkali to a riboflavin–nicotinamide solution produces a change of color from brown to dark blue and then to brown again. In the absence of nicotinamide, no blue color appears.

Acknowledgment.—The riboflavin analyses were made by Mr. Elmer O. Krueger, and the pharmacologic studies by Dr. R. K. Richards. Dr. D. Mark Hegsted provided valuable counsel throughout the study.

Summary

The solubility of riboflavin in nicotinamide solutions was found to decrease progressively at *p*H values more acid than 5. At *p*H 5 riboflavin solubility increased from about 0.1% to about 2.5% with an increase of nicotinamide concentration from 5 to 50%.

The observed strong solvent effect of nicotinamide on riboflavin appears to be related to its chemical constitution; both the pyridine and amide groups are involved. An acid which forms an addition salt reduces the solvent action of nicotinamide but does not eliminate it.

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(2) P. Handler and W. J. Dann, *ibid.*, **146**, 357 (1942).
(3) S. A. Schou and B. Fretheim, *Dansk. Tidskr. Farm*, **14**, 97 (1940).
(4) R. Kuhn, *Klin. Woch.*, **17**, 222 (1938).
(5) E. L. Auhagen, U. S. Patent 2,256,604.
(6) D. V. Frost, U. S. Patent 2,407,412.
(7) M. S. Auerbach, U. S. Patent 2,332,548.
(8) D. V. Frost, *J. Biol. Chem.*, **145**, 693 (1942); U. S. Patent 2,388,261.
(9) A. E. Jurist, U. S. Patent 2,358,331.
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NORTH CHICAGO, ILLINOIS RECEIVED AUGUST 30, 1946

[CONTRIBUTION FROM NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Some Properties of Methyl Fluoroacetate and Fluoroethanol[1]

BY CHARLES C. PRICE[2] AND WILLIAM G. JACKSON[3]

The discovery of the unusual toxic and rodenticidal properties of the fluoroacetates has prompted an investigation designed to extend the knowledge of the properties and chemical behavior of these interesting compounds.

The rate of hydrolysis of methyl fluoroacetate in distilled water was followed by measurement of the *p*H. The hydrolysis was slow, only about 2.5% having hydrolyzed within sixty hours at 22–24°. From the data, the values for the constants in the following rate expression were estimated.

$$dx/dt = k'[\text{ester}]$$
$$k' = (k_a[OH^+] + K_b[OH^-] + k_w)$$

The values for the over-all rate (Table I) were most satisfactorily accounted for by the following values: $k_a = 0.3$, $k_b = 10^7$ liters mole^{-1} hr.$^{-1}$, and k_w negligible. Brookfield and McKendrick[4] have reported a value of 0.33 for k_a from meas-

(1) The work described in this paper was done under a contract, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the University of Illinois.
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(3) Present address: The Upjohn Company, Kalamazoo, Michigan.
(4) Brookfield and McKendrick, British Report, 1944.

urements of hydrolysis in 0.1 N hydrochloric acid. They also reported complete hydrolysis within thirty-five seconds in 9.85 mM sodium hydroxide. Our estimated value for k_b would predict a half-life of 2×10^{-3} second under these conditions. The values chosen for the constants also predict a minimum rate of hydrolysis in the pH range 2.0 to 3.5 and a half-life for hydrolysis at pH 7 of less than one hour.

The alkylation of sodium thiosulfate by haloacetates (excluding fluorides) has been extensively investigated.[5-9] The bimolecular velocity constants at 25° using 0.1 M concentrations of each reactant are 1.32, 0.888, and 0.0086, for iodo-, bromo- and chloroacetates, respectively.[5] The reaction of methyl or sodium fluoroacetate with sodium thiosulfate failed to proceed to a measurable extent in twenty-four hours at 25°.

At 88°, the reaction of sodium fluoroacetate (1.0 N) and sodium thiosulfate (1.9 N) proceeded with measurable velocity (k_2 = 0.00164 liters mole^{-1} min.$^{-1}$, Fig. 2), being 50% complete in three and sixth-tenths hours. Methyl fluoroacetate reacted more rapidly but the blank decomposed so rapidly as to make accurate kinetic analysis impossible. At high dilutions, sodium fluoroacetate (5.6 mM) showed no reaction in eight hours while methyl fluoroacetate (6.3 mM) reacted to the extent of 30% in eight hours. These phenomena bear out the conclusions of Backer and Van Mels[5] and others that the undissociated haloacetate molecule rather than the haloacetate ion is the reactive species. The Bunté salt could not be isolated from the reaction mixture above but was prepared by reaction between methyl chloroacetate and sodium thiosulfate.

The failure of Bunté salt formation by sodium fluoroacetate in dilute solution and at room temperature instigated a search for other sulfhydryl compounds which might alkylate faster than thiosulfate. The work of Smythe[10] indicated that thioglucose, thiosalicylic acid, cysteine, glutathione, thioglycol and thiosulfate reacted with iodoacetate with decreasing velocity in the order given. Since the rate constant of thiosalicylic acid was about thirty times that of thiosulfate for alkylation by iodoacetate, it was chosen for evaluation as a reagent for cleaving fluoroacetates.

The reaction of thiosalicylic acid with methyl chloroacetate was carried out and observed to be much faster than the corresponding reaction with thiosulfate, in agreement with the previous data on the iodoacetates. The product, S-carbomethoxymethylthiosalicylic acid was identified by melting point[11] and by the melting point of its hydrolysis product, S-carboxymethylthiosalicylic acid.[12] This product could not be isolated from a reaction of thiosalicyclic acid with methyl fluoroacetate.

In the course of the work, the p-bromophenacyl ester (m. p. 96.5–97°) and the p-toluide (m. p. 129–130°) derivatives of fluoroacetic acid were prepared and characterized.

A few experiments with fluoroethanol demonstrated it to be more stable toward oxidation with permanganate or hypochlorite than ethanol. Perhaps the resistance to oxidation was responsible for its failure to respond to the haloform test. Fluoroethanol was also unreactive toward thiosulfate.

Experimental[13]

Methyl fluoroacetate[14] was redistilled before use; b. p. 102°, m. p. −40°, $n^{15}D$ 1.3704. Its solubility in water at 0° was found to be approximately 15 g. per 100 ml. **Sodium fluoroacetate** was prepared by saponification in 50% alkali followed by addition of ethanol to precipitate the salt as white plates.

The **Duclaux constants**[15,16,17] for dilute solutions of fluoroacetic acid were estimated by the standard procedure

21.8 mM	A, 1.16;	B, 1.10;	C, 1.07
10.9 mM	0.86	1.16	1.22

Hydrolysis of Methyl Fluoroacetate in Water.—A fourth neck was added to a 3-necked, 1-liter flask to allow accommodation of a condenser, thermometer and two electrodes of a Beckman pH meter. The pH of the distilled water used had been raised from 5.5 to 7.6 by boiling and allowing to cool under an ascarite tube. This treatment probably removed much carbonate as carbon dioxide and possibly some ammonia, leaving sodium (from glass) and some ammonium and carbonate ions as non-removable impurities. Ten ml. (126 millimoles) of methyl fluoro-

TABLE I

RATE OF HYDROLYSIS OF METHYL FLUOROACETATE IN WATER AT 23°

Time, hr.	$10^5 \times$ (mole/l. hydrolyzed)	$10^6k'$	$3 \times 10^5[H^+]$	$10^{13}[OH^-]$
10	34	523	98	331
11	44	518	121	269
12	52	426	142	229
13	58	310	156	209
14	63	315	167	195
15	69	320	183	182
17	81	325	205	158
20	97	325	236	148
25	128	360	291	110
35	204	490	411	79
45	291	500	540	60
55	388	550	652	50
65	491	600	760	43

(5) Backer and van Mels, *Rec. trav. chim.*, **49**, 363 (1930).
(6) Krapivine, *J. chim. phys.*, **10**, 289 (1912).
(7) Price and Twiss, *J. Chem. Soc.*, **95**, 1489 (1909).
(8) Stutz and Shriner, THIS JOURNAL, **55**, 1242 (1933).
(9) Slator, *J. Chem. Soc.*, **85**, 1287 (1904).
(10) Smythe, *J. Biol. Chem.*, **114**, 601 (1936).
(11) Weselsky and Joachimowitz, *Monatsh.*, **35**, 1089 (1914).
(12) Kalle and Co., German Patent 177,346 (*Chem. Zentr.*, **49**, II, 1888 (1906)).
(13) All melting points are corrected.
(14) Obtained from the Monsanto Chemical Company. The fluoroacetates and fluoroethanol are toxic compounds and were handled only with due precaution against direct contact or inhalation of the vapors.
(15) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1940, (a) p. 132, (b) p. 120, (c) p. 38, (d) p. 53.
(16) Duclaux, *Ann. chim. phys.*, [5] **2**, 233, 289 (1874).
(17) Richmond, *Analyst*, **33**, 305 (1908).

acetate was added to 700 ml. of water in the reaction vessel which was maintained at approximately 23°. The subsequent hydrolysis was followed by observing over a seventy-four period the fall in *p*H due to the ionization of the fluoroacetic acid formed in the reaction. The meter was standardized against a phthalate buffer.

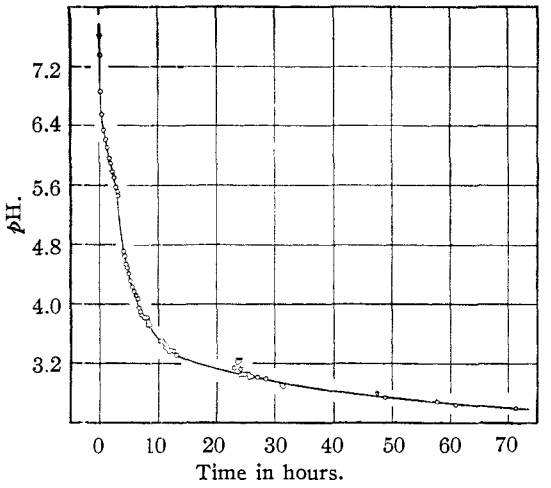

Fig. 1.—The hydrolysis of 0.178 *M* methyl fluoroacetate in water at 23°.

From the smooth curve through the data (Fig. 1) and the temperature corrections for the observed *p*H, the concentrations of the various species were estimated readily using the value for the dissociation constant for fluoroacetic acid (2.17×10^{-3}) from the conductivity measurements of Swarts.[18] The rate of disappearance of ester was then estimated graphically to give the instantaneous pseudo-first order reaction rate, k'. The results are summarized in Table I.

Reaction of Fluoroacetates with Thiosulfate.—Sodium thiosulfate pentahydrate (14 g., 56.4 millimoles) was placed in each of two flasks equipped with reflux condensers and side-arms for insertion of sampling pipets. To one flask was added 50 ml. of water and 4 ml. (50.4 millimoles) of methyl fluoroacetate; to the second was added 50 ml. of water and 4 ml. of methyl acetate. A blank omitting the methyl acetate gave results the same as that containing this ester. The sample and blank were refluxed gently in an oil-bath and, at intervals, portions were withdrawn, cooled to room temperature and measured volumes run into standard iodine solution in an acetate buffer. The excess iodine was back-titrated with standard thiosulfate solution with addition of starch near the end-point. An approximate half-life of one to two hours was obtained,

TABLE II

REACTION OF METHYL FLUOROACETATE WITH SODIUM THIOSULFATE

Hr.	Sample, *N*	Blank, *N*
1.00	...	0.915
1.25	0.748	...
1.50	...	.928
3.75	...	.935
4.00	.370	...
5.85	...	.945
6.00	.312	...
11.50	...	.970
11.75	.275	...
23.45	...	.970
23.50	.220	...

(18) Swarts, *Bull. acad. roy. Belg.*, [3] **31**, 675 (1896).

but the change in the blank was enough to interfere with accurate kinetic analysis of the data (Table II). The plot of log $(a(b - x)/b(a - x))$ *vs.* time could be caused to deviate in either direction from linearity by neglecting or considering the change in the blank.

Sodium thiosulfate (12.40 g., 50 millimoles) and sodium fluoroacetate (9.5 g., 95 millimoles) were dissolved in water, diluted to 50 ml., and heated in a bath at 88° while 9 g. of sodium acetate and 12.40 g. of thiosulfate were likewise dissolved and diluted as a blank. The blank remained sufficiently constant to allow calculation of a bimolecular velocity constant k_2 for the sample of 0.00164 ± 0.00003 liter/mole minute. The bimolecular plot of the data (Fig. 2) is linear past 50% completion (3.6 hours). The gradual deviation from linearity after this point is undoubtedly due to the established decomposition of Bunté salts at this temperature to form disulfides with the liberation of sulfur dioxide.[7,8]

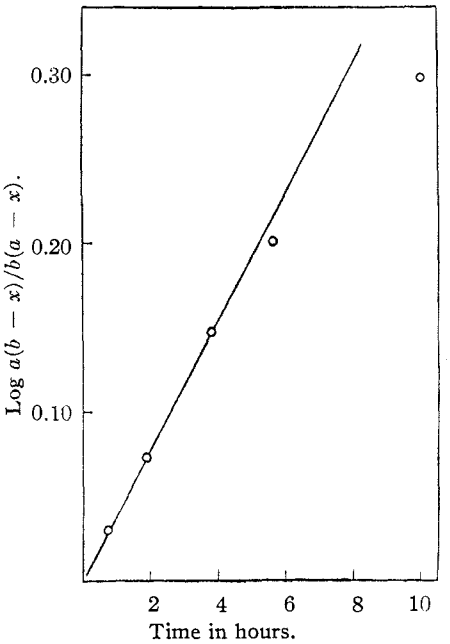

Fig. 2.—The reaction of 1.90 *M* sodium fluoroacetate (b) with 1.00 *M* sodium thiosulfate (a) in aqueous solution at 85–90°.

A dilute solution of sodium fluoroacetate (5.6 mM) and sodium thiosulfate (four-fold excess) was maintained at 100° and showed only slight reaction after five hours. Methyl fluoroacetate (6.3 mM) with four-fold excess of thiosulfate showed about 30% reaction in eight hours. The blank decomposed too rapidly to justify further treatment of the data.

Sodium S-Carbomethoxymethylthiosulfate.—To 12.40 g. (50 millimoles) of sodium thiosulfate dissolved in 10 ml. of water was added 4.40 ml. (50 millimoles) of methyl chloroacetate prepared by methanolysis of chloroacetyl chloride. The inhomogeneous mixture was shaken mechanically overnight at room temperature after which titration with standard iodine solution indicated 94% reaction. The mixture was evaporated to dryness at a temperature not exceeding 45°, the residue boiled briefly with 200 ml. of absolute ethanol and filtered hot. From the cooled filtrate was obtained 3.44 g. (39%) of a snow-white solid. A wide melting range was observed beginning at 150°. The compound was purified for analysis by two recrystallizations from methanol.

Anal. Calcd. for $C_3H_5O_5S_2Na$: C, 17.31; H, 2.42. Found: C, 17.58; H, 2.68.

An analysis delayed six weeks showed sulfur, 21.47%

(calcd. S, 30.84). The low value is an indication of the instability of the salt.

S-Carbomethoxymethylthiosalicylic Acid.—Thiosalicylic acid (3.85 g., 25 millimoles) was treated with dilute alkali until a *p*H corresponding to the monosodium salt was obtained. Upon addition of 2.20 ml. (25 millimoles) of methyl chloroacetate, homogeneity was obtained almost instantly. Within twenty minutes (room temperature) a considerable amount of precipitate had formed which was filtered after forty minutes, dried and found to melt at 113–122°. Recrystallization from ethanol raised the melting point to 126–127°, in agreement with the established value.[11] The compound could be hydrolyzed with alkali to S-carboxymethylthiosalicylic acid, which, after one recrystallization from glacial acetic acid, melted at 208–213°.[12]

An analogous trial utilizing methyl fluoroacetate and thiosalicylic acid produced no precipitate after several hours standing at room temperature. The solution was boiled for one and one-half hours, cooled and filtered to yield a small amount of yellow solid, which, after three recrystallizations, melted at 281–284° and was thought to be the disulfide (dithiodisalicylic acid, m. p. 289°).[19]

Acidification of the original filtrate allowed nearly quantitative recovery of thiosalicylic acid.

***p*-Bromophenacyl Fluoroacetate.**—A water solution of sodium fluoroacetate and *p*-bromophenacyl bromide was refluxed according to the usual procedure[15a] resulting in the isolation of *p*-bromophenacyl fluoroacetate. Recrystallization from aqueous ethanol afforded white crystals, m. p. 96.5–97.0°.

Anal. Calcd. for $C_{10}H_8O_3BrF$: C, 43.67; H, 2.92. Found: C, 43.94; H, 3.05.

Reaction Products of Fluoroacetic Acid and *p*-Toluidine.—To 2 g. (20 millimoles) of sodium fluoroacetate was added 4.28 g. (40 millimoles) of recrystallized *p*-toluidine. Approximately 2 ml. (24 millimoles) of concentrated hydrochloric acid was added and the mixture was refluxed in a 20-cm. test-tube supported in an oil-bath at 140°. After two hours one ml. of benzene was added and heating continued for a few minutes until refluxing stopped and the reaction appeared complete.

The mixture was boiled briefly with 15 ml. of ethanol and then poured into 150 ml. of hot water. A brown oil separated immediately and turned granular upon agitation. The mixture (still hot) was filtered and the precipitate dried to yield 1.66 g. (6.5 millimoles) of impure *p*-toluinoacetyl-*p*-toluide. The filtrate was cooled in ice to yield white crystals which, after filtration and drying, yielded 1.15 g. (6.9 millimoles) of fluoroacetyl-*p*-toluide.

Both compounds had suitable solubility coefficients in aqueous ethanol or ligroin, but the latter seemed to purify them more effectively. Recrystallized repeatedly from ligroin (b. p. 87–95°), the mono- and disubstituted compounds melted at 129–130° and 136–137°, respectively. The mixed melting point was depressed some 20°.

Anal. Calcd. for $C_9H_{10}ONF$: C, 64.68; H, 6.03. Found: C, 64.81; H, 6.10. Calcd. for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13. Found: C, 75.81; H, 7.12.

Reaction of Fluoroethanol with Thiosulfate.—A rate measurement was attempted using methods described above for the analogous reaction with fluoroacetate. At 85°, an aqueous solution of fluoroethanol (1 ml., 17.3 millimoles) and thiosulfate (4.29 g., 17.3 millimoles) showed only 1% reaction after four and one-half hours, and 3.4% after twenty-one hours. The concentration of reactants was 346 mM and the total volume was 50 ml.

Reaction of Fluoroethanol with Hypoiodite.—Use of the standard techniques[15d] employed for the haloform test gave indication of a negative reaction. Addition of 1 ml. (17.3 millimoles) of fluoroethanol to 50 ml. of 0.876 *N* iodoform reagent (42.8 milli-equivalents) and 2 ml. of 10% sodium hydroxide caused a decrease in iodine titer of only 7% after five hours at 50–70°.

(19) Gattermann, *Ber.*, **32**, 1150 (1899).

Summary

Methyl fluoroacetate is soluble to the extent of about 15% in cold water. It hydrolyses very slowly, only about 2.5% in sixty hours in distilled water. The hydrolysis is catalyzed by alkali to a much more marked degree than by acid.

The fluorine in fluoroacetates is remarkably inert, but was slowly displaced by thiosulfate to the extent of 50% in several hours at 88°.

The *p*-bromophenacyl ester and the *p*-toluide of fluoroacetic acid have been characterized.

Neither fluoroacetate nor fluoroethanol is attacked by dilute aqueous hypochlorite.

NOTRE DAME, INDIANA RECEIVED SEPTEMBER 12, 1946

[CONTRIBUTION NO. 215 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION OF E. I. DU PONT DE NEMOURS & COMPANY, INC.]

Diffusion of Vapors in Films

BY PRINCE E. ROUSE, JR.

The permeation of vapors through films of organic polymers has considerable theoretical interest and is of great practical importance if the film is to be used as a protective wrapping. The interactions of vapors with organic materials have been investigated by measurements of permeation and of sorption, but there have been few studies of the diffusion coefficient of a vapor in a film. Since knowledge of the behavior of the diffusion coefficient should provide useful information concerning the nature of the association of the vapor with the film a method of investigating the dependence of the diffusion coefficient upon the concentration of the vapor in the film has been developed. This paper will describe this method and will present some typical results obtained with it.

A method introduced by Daynes[1] and developed by Barrer[2] obtains the diffusion coefficient of gases through films from the time-lag in the establishment of the steady state of transfer. In this method the rate of transfer is measured at intervals until the rate becomes constant; the intercept, L, of the straight line representing the steady state upon the time axis is related to the diffusion coefficient by the equation

$$D = t^2/6L$$

where t is the thickness of the film. The deriva-

(1) H. Daynes, *Proc. Roy. Soc.* (London), **97A**, 286 (1920).

(2) R. M. Barrer, *Trans. Faraday Soc.*, **35**, 628, 644 (1939); *ibid.*, **36**, 1235 (1940); *Phil. Mag.*, **28**, 148 (1939).