cooled and examined for the extents of polymerization and the molecular weights of the products in the usual way.

Summary

The polymerization of 3.46 molar styrene in benzene has been examined in vacuum at 64.0 and 74.0° in the presence of 0.0208 to 0.0714 molar benzoyl peroxide and 0.00444 to 0.00463 benzoquinone. Small concentrations of quinones appeared to increase the rates of decomposition of the peroxide. The presence of benzoquinone led to induction periods, followed by polymerizations which attained their maximum rates fairly rapidly.

During the induction periods, approximately equimolar quantities of quinone and peroxide were consumed.

The rates of polymerization after the induction periods appeared to be 83–91% of the rates which would be calculated for similar conditions in the absence of prior induction periods; the molecular weights of the polymers appeared to be 89–95% of the calculated molecular weights.

Substituted benzoquinones and hydroquinone derivatives possessing free hydroxyl groups led to more retardation than was observed after the induction periods. In all retardations the rates decreased more than the molecular weights.

The nature of retardation and inhibition reactions and the relation between the structure of hydroquinones and their efficiency as retarders are discussed. In the inhibition reaction, quinone appears to react with two radicals and be converted partly to diethers of hydroquinone and partly to hydroquinone derivatives retaining free hydroxyl groups.

CAMBRIDGE 39, MASSACHUSETTS
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[CONTRIBUTION FROM THE NUTRITIONAL RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

The Effect of Nicotinamide on the Solubility of Riboflavin in Water

BY DOUGLAS V. FROST

Nicotinamide is now widely used in pharmacy to increase the solubility of riboflavin in water. The present study deals with this behavior of nicotinamide, particularly in solutions of varying acidity.

Experimental

The magnitude of the solubilizing effect of various concentrations of nicotinamide was first determined at room temperature. Supersaturated solutions of riboflavin in nicotinamide solutions adjusted to *p*H 5.0 with hydrochloric acid were made by heating. On cooling at room temperature the excess riboflavin crystallized and was separated by filtration. The concentration of riboflavin remaining in solution was determined fluorometrically. The results are shown in Table I. Certain lots of riboflavin appeared to be 5–10% less soluble than other lots, even though the physical and chemical characteristics appeared similar. Such differences are thought to be greater than the experimental error involved in the over-all solubility determination. No satisfactory explanation for this observed difference between lots is apparent.

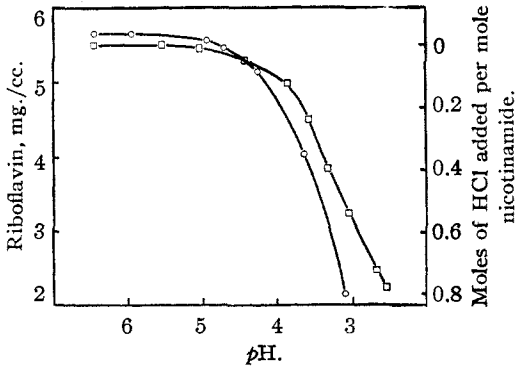

Fig. 1.—The relation of riboflavin–nicotinamide solubility to *p*H. Comparison with the potentiometric titration curve of a 1% solution of nicotinamide against 0.1 normal hydrochloric acid: —O—O—, riboflavin concentration in 20% nicotinamide; —□—□—, potentiometric titration of nicotinamide with hydrochloric acid.

TABLE I

EFFECT OF INCREASING CONCENTRATIONS OF NICOTINAMIDE ON THE SOLUBILITY OF RIBOFLAVIN AT *p*H 5.0

Nicotinamide, % in soln.	0	5	10	20	30	40	50
Riboflavin, % in soln.	0.011	0.1	0.24	0.56	1.0	1.6	2.5
Ratio of nicotinamide to riboflavin in soln.	0	50	42	36	30	25	20

It can be seen from these results that the solubility of riboflavin in a 5% solution of nicotinamide is increased some nine times over that in pure water, and that this effect increases somewhat more than proportionately with the concentration of the nicotinamide. Thus the solubility of the riboflavin in a 50% solution of nicotinamide is twenty-five times that in a 5% solution.

We next determined the solubility of riboflavin in 20% solutions of nicotinamide acidified with varying amounts of hydrochloric acid, and made accompanying measurements of the *p*H of each saturated solution. The results are shown in Fig. 1, where the concentration of riboflavin is plotted against the *p*H. It can be seen from this figure that acidity has little effect on the solubility (*ca.* 0.56% in a neutral 20% solution of nicotinamide) until the *p*H has been lowered to about 5.0. Thereafter, the solubility decreases rapidly until at *p*H 3 it is only about 0.2%.

This behavior can be correlated with the titration curve of nicotinamide, also shown in Fig. 1. It can be seen that nicotinamide has almost no buffering capacity for hydrochloric acid until a *p*H of about 5.0 is reached, after which further additions of hydrochloric acid produce a slow decrease in *p*H.

A 20%, but not a 10%, solution of nicotinamide hydrochloride held riboflavin in solution to the extent of 0.1%.

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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[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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(4) Brookfield and McKendrick, British Report, 1944.