large error. This is the basis for the approximate rule that successive dissociation constants of a given acid of the type being discussed here fall at equal intervals along a pK scale.

In Table I are listed a few acids together with those values of their dissociation constants which have been given in the most recent compilation. From these values and equation 4, other dissociation constants have been calculated and are included in the table. Only in the cases of phosphoric and arsenic acids is it possible to compare observed and calculated values, since these are the only ones with three measured dissociation constants. This comparison is made by calculating the value of the constant α from K_2 and K_3, and from K_3 and K_4. Two recent sets of dissociation constants for phosphoric acid, not differing a great deal, have been employed. The agreement for each set is quite satisfactory, and the two sets give the same average value: $\alpha = 3.8 \times 10^4$. The calculated value of K_1 was obtained using this average value of α and $K_2 = 7.7 \times 10^{-3}$. The agreement between the two values of α for arsenic acid is better than for phosphoric acid. Evidence for the validity of equation 4 as a good approximation is not limited, however, to these two examples, for the success of the general methods of Branch and Calvin and of Kossiakoff and Harker must also be considered as evidence. As a matter of fact, equation 4 may readily be derived from the fundamental equation[14] (for water as solvent) used by Branch and Calvin.

The calculated dissociation constants of $H(HO)_3P^+$, $(HO)_3S^+$, $(HO)_3Se^+$, $(HO)_5Te^+$, $(HO)_4P^+$, $(HO)_4As^+$ and $(HO)_6I^+$ (all of the same order of magnitude) predict the expected virtually complete ionization into the uncharged molecule and hydrogen ion, in the solvent water. The acid $CH_3CHClCH_2(HO)_3As^+$ is, on the other hand, a somewhat less strong acid.

Further constants of $(HO)_6Te$ and of $(HO)_6I^+$ could have been calculated, but the "extrapolation" from two experimental constants certainly become less valid for more "distant" constants.

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Summary

A simple equation is obtained which makes it possible, when two or more dissociation constants are known, to predict other unmeasured dissociation constants of symmetrical inorganic oxygen acids. A few examples are given, including some acids which are positively charged. The relationship of this equation to other methods is pointed out. The equation is not restricted as to solvent.

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(14) Equation 7, p. 204.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE DENVER CHEMICAL MANUFACTURING CO.]

The Interaction of Amides with Amines: A General Method of Acylation[1]

BY ALEXANDER GALAT AND GERTRUDE ELION

Various authors have observed the formation of substituted amides when aromatic amines are heated with amides.[2,3,4,5,6] More recently, good yields have been reported for the preparation of disubstituted ureas by the reaction between carbamide and aromatic amines.[7a] and poorer yields with aliphatic amines.[7b] In addition, monosubstituted ureas have been prepared by the treatment of primary amines with nitrourea.[8]

The latest work on this subject, dealing with the interaction of amides and aniline,[9] indicates that yields are generally poor and that, with certain amides, *e. g.*, *i*-butyramide, the reaction does not take place at all. There is no indication in the literature of the application of this reaction to the aliphatic series, probably because the lower aliphatic amines are too volatile, while the higher ones have not been generally available until recently.

Hoffman[10] discovered that acetamide reacted satisfactorily with the hydrochloride of an amine, namely, hydroxylammonium chloride

$$CH_3CONH_2 + HONH_3Cl \longrightarrow NH_4Cl + CH_3CONHOH$$

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(1) Original manuscript received September 13, 1939.

(2) Fleischer, *Ber.*, **9**, 995 (1876).

(3) Kelbe, *ibid.*, **16**, 1199 (1883).

(4) Just, *ibid.*, **19**, 1202 (1886).

(5) Freund and Goldsmith, *ibid.*, **21**, 2461 (1888).

(6) Hirst and Cohen, *J. Chem. Soc.*, **67**, 830 (1895).

(7) (a) Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922); (b) Davis and Blanchard, *ibid.*, **45**, 1816 (1923).

(8) Davis and Blanchard, *ibid.*, **51**, 1790, 1801, 1806 (1929).

(9) Hurd, Dull and Martin, *ibid.*, **54**, 1974 (1932).

(10) Hoffman, *Ber.*, **22**, 2855 (1889).

a reaction which was further studied by Francesconi and Bastiani.[11] It has now been found that this interaction of amides with amine hydrochlorides is a general reaction. With it one may conveniently acylate either aliphatic or aromatic amines. The hydrochlorides were preferred to other salts of the amines because of their lower melting point.

The procedure consists of mixing the two reactants, the amide being slightly in excess of the theoretical quantity, and melting them. After a short time, usually several minutes, ammonium chloride separates and the reaction is complete.

$$R'NH_2HCl + NH_2COR'' \longrightarrow R'NHCOR'' + NH_4Cl$$

The reaction also takes place when the sulfate of the amine is used, ammonium sulfate being eliminated. The temperature required depends on the reactants. Amides such as formamide react at 60–70°, whereas for urea a temperature of 250° must be reached in order to complete the reaction.

Typical of this procedure are the following preparations.

N-Methylacetamide.—67.5 g. (1 mole) of methylamine hydrochloride was heated with 67.5 g. (1.15 moles) of acetamide. After a few minutes, ammonium chloride began to precipitate. The heating was continued for several minutes more, to complete the reaction. Chloroform was then added to the product of the reaction, the ammonium chloride filtered off, and the solvent removed by distillation. The N-methylacetamide was collected between 202 and 206°; yield, 55 g. (75.3%).

N-Acetyl-α-naphthylamine.—17.95 g. (0.1 mole) of α-naphthylamine hydrochloride was heated with 10 g. (0.17 mole) of acetamide until the precipitation of ammonium chloride was complete. This required only several minutes. The product of the reaction was treated with hot water, filtered and washed to remove the ammonium chloride. Upon recrystallization from hot ethyl alcohol, 14.8 g. of the product (80% of theoretical yield), of m. p. 132°, was obtained.

The following amines have been acylated by this method: methylamine, ethylamine, propylamine, glycine, aniline, aminophenols, toluidines, benzylamine, phenylethylamine, naphthylamines and benzidine. It was likewise found possible to acylate the NH_2 of the hydrazine group by this means. The guanidines, on the other hand, did not respond to this procedure.

The following amides were tried successfully: carbamide, formamide, acetamide, propionamide, *i*-butyramide and benzamide. In all cases, the yield was above 70% and was, indeed, often close to 100%.

The advantages of this method of acylation are several. First, it obviates the use of such irritating and corrosive reagents as acetic anhydride, acetyl chloride, benzoyl chloride and the like. The elimination of the corrosive effects of acids, acid anhydrides and acid chlorides is particularly advantageous in the industrial applications of acylation.

Another advantage is that the amino group is selectively acylated; other groups in the molecule, which might be affected by acylating agents such as acids, acid chlorides and acid anhydrides, are not acylated by this method. Moreover, the procedure herein described effects complete acylation in a matter of minutes. In addition, as has been mentioned above, yields are excellent.

Summary

A simple procedure for the acylation of amines has been developed. It consists of melting the salt of an amine with an amide, whereupon acylation is effected selectively on the amino group in a few minutes with very good yields.

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[11] Francesconi and Bastiani, *Gazz. chim. ital.*, **34**, I, 428 (1904).