2. The relative rate of successive stages of bromination of amino and phenolic compounds is in harmony with the idea that in such cases there is intermediate substitution of bromine in the side chain.
3. The directive influences of several substituents in the same ring are usually cumulative.
4. Chlorine and bromine seem to have exactly the same directive influence.
5. A method has been devised for estimating numerical values for directive influences. Another effect, called "general influence," has been found, by which a substituent may accelerate or retard the rate of substitution regardless of its position. This seems to be related to its effect upon the acidity of compounds, or the so-called "negative nature of atomic groups," and is not parallel with directive influence.
6. By application of the electron conception of valence, a structure has been devised for the benzene ring, sufficiently complex to account for the phenomena of substitution.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE BASE STRENGTH OF ALPHA-ALKOXYL AMINES. THE EFFECT OF OXYGEN ON THE BASICITY OF AMINES

BY T. D. STEWART AND J. G. ASTON

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A number of amino ethers of the type ($R_2N—CH_2$)OR′ have been prepared by McLeod and Robinson[1] using the reaction $H_2CO + R_2NH + R'OH \longrightarrow R_2N—CH_2—OR' + H_2O$. These compounds are simply tertiary amines containing no unsaturated (ethylenic or carbonyl) groups, and are unusual only in having an oxygen and a nitrogen atom attached to the same carbon atom. Compounds of a similar nature are found among the heterocyclic ring compounds. The aldehyde ammonias, if not polymerized, would have a similar structure. Robinson and Robinson[2] term the compounds pseudo bases and represent them by the structure $R_2N{=}CH_2\ldots OR$, where the dotted line "symbolizes a partial intramolecular electrovalency connecting the nitrogen and oxygen atoms." This is done to account for the rapid reaction toward the Grignard reagent in which the alkoxyl group (OR) is replaced by an alkyl group (R), and the rapid hydrolysis in acid which results in formaldehyde and a diethylamine salt. They discard the possibility that any appreciable amount of the base can exist in the quaternary form $[R_2N{=}CH_2]^+ OR^-$ because it may be distilled without decomposition. Such a compound would be analogous to an alkyl pyridinium base and, therefore, a very strong base.

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[1] McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

[2] Robinson and Robinson, *ibid.*, **123**, 523 (1923).

It is apparent that these amino ethers could possibly form salts by two paths: $R_2N—CH_2—O—R + H^+ \longrightarrow R_2\overset{+}{N}H—CH_2—OR$; $R_2N—CH_2—OR + H^+ \longrightarrow R_2\overset{+}{N}{=}CH_2 + ROH$. It was thought that since the salts are very unstable a study of the base strength might shed some light on the nature of the process. In addition we have here the possibility of determining in part the effect of an oxygen attached to the same carbon on the basicity of nitrogen. The only types known which meet this condition are the acid amides ($R—C{:}O—NH_2$), the aldehyde ammonias and the α-hydroxypyridines and related derivatives. The weak basicity of the first may be due to "conjugation" of the electron systems of the nitrogen with the unsaturated carbonyl group. The aldehyde ammonias are polymerized substances of salt-like characteristics. It is probable that they are intramolecularly neutralized by the hydroxyl of one molecule acting as an acid to the nitrogen of another molecule. The heterocyclic ring derivatives if unsaturated are very weak bases. In these cases we have the possibility of internal conjugation or neutralization.

Formally, at least, the amino ethers of McLeod and Robinson are simple tertiary amines, containing no unsaturated groups or ionizable hydrogen. As such, the basic dissociation constant should be between $K_B = 10^{-3}$ and $K_B = 10^{-5}$. It is indeed remarkable that of all nitrogenous bases whose strengths are known, very few fall in the range $K_B = 10^{-6}$ to $K_B = 10^{-8}$ and these are all of the heterocyclic unsaturated type, such as quinine ($K_B = 10^{-7}$) and α-picoline ($K_B = 10^{-8}$).

Various degrees of solvation of different bases are of no consequence in this connection, since we shall represent the fundamental reaction of neutralization by the equation, R_3N (solvated) + H^+ (solvated) $\longrightarrow$ $R_3\overset{+}{N}H$ (solvated), and assume that for dilute solutions the activity of the base R_3N and of the ion $R_3\overset{+}{N}H$ will be affected in the same proportion as we change solvents and concentrations as is the case for any other base and corresponding ion, in other words, that the order of magnitude of comparative base strengths will be unaffected by change of solvent, and this is found to be true experimentally for alcohol and water solutions where either no known type of tautomerism exists or where tautomeric changes do not involve any bond to the nitrogen atom.

Discussion of Results

The formation of a salt of an amine may be considered as simply the addition of a hydrogen ion to the unoccupied pair of electrons on the nitrogen atom: $R_3N{:} + H^+ \quad R_3\overset{+}{N}{:}H$. If an amine is a strong base, the equilibrium greatly favors the ammonium ion formation. There is nothing in our structural formulas to suggest the great differences observed in the tendency of different compounds to undergo this reaction. The substitution of an alkoxyl (OR) group for a hydrogen on a carbon adjacent (alpha) to the nitrogen causes a marked decrease in the tendency of the nitrogen to attach a hydrogen ion. Expressed in terms of the basic dissociation constant the tendency of most aliphatic tertiary amines is given by the value $K_B = 10^{-3}$ to $K_B = 10^{-5}$, whereas the substitution of a methoxy group reduces this to $K_B = 3.6 \times 10^{-9}$, of an ethoxy group to $K_B = 1.8 \times 10^{-8}$, and of an *iso*butoxy group to $K_B = 4 \times 10^{-7}$. The explanation of this effect may be expressed loosely in terms of the negativity of the oxygen. If we assume that in the oxygen-carbon-nitrogen chain, $R_2N—CH_2—O—R$, the electrons are pulled toward the oxygen, the result will be a relative increase in the positivity of the nitrogen and a corresponding decrease in its tendency to attract a hydrogen ion. Correspondingly, when the nitrogen is converted to a quaternary derivative of the type $[R_3N^+—CH_2—OR]I^-$, the electron pull is in the opposite direction and the reactivity of the $(—CH_2—OR)$ group, as measured by ease of hydrolysis, is greatly decreased. However, the tertiary base is extremely unstable in aqueous acid, hydrolyzing to dialkyl amine, formaldehyde and alcohol. This cannot be attributed to the formation of the ion R_2N^+H-CH_2OR, because the latter should share the stability of the quaternary derivative. Solutions of it in absolute alcohol are, in fact, quite stable but traces of water rapidly destroy the compound.

It was pointed out in the introduction to this article that very few compounds corresponded closely in base strength to these α-alkoxyl amines. Both quinine and α-picoline in water solution fall in the desired range, but in alcoholic solution compared with benzylamine and methylaniline as reference substances they were found to deviate widely from their expected positions. The latter was too weakly basic in alcohol to be useful and in the case of quinine it was found necessary to determine its base strength in alcohol as compared to benzylamine and then use the corrected value as a reference. This procedure is open to question. If picoline and quinine are changed in their respective base strengths as compared to benzylamine in alcohol and water, there is no assurance that the alkoxyl amines being studied do not also change in comparative base strength in the two solvents. It is planned to study this question further. An explanation of the anomalous base strength which involves the assumption that the alkoxyl amines are mixtures of tautomers is not satisfactory. The most reasonable tautomerism is expressed by the equation

$$\underset{\text{I}}{R_2N—CH_2—OR} \rightleftharpoons \underset{\text{II}}{[R_2\overset{+}{N}=CH_2] + \overset{-}{OR}}$$

The major portion of the substance must be represented by Formula I for reasons developed below. If then the apparently weak basicity is due to traces of the strong base II, then I must be practically neutral, which is inconceivable. Moreover, when dry hydrogen chloride forms a salt, it does so for the most part at least by adding to the alkoxyl amine and not simply by the formation of alcohol from alcoholate ion. The formation of the quaternary derivatives points in the same direction as to the mechanism of salt formation. Two other attempts were made to get positive evidence as to any other conceivable tautomerism between strong and weak bases. The first involved the assumption that tautomerism was slow compared to neutralization of the stronger base, in which case we should observe a change on standing in the partially neutralized base as more of the strong base was formed by the tautomeric change. No observations of this sort were made that could not be explained by hydrolysis of the salt to the salt of the stronger base diethylamine. The second attempt involved the rate of addition of methyl iodide to the alkoxyl amine. If only one of two possible tautomers, and the one present in small amount, reacted with methyl iodide, and the rate of the tautomerism was slow compared to the addition reaction, then the rate of addition would be proportional to the concentration of the amine alone. The rate was found to be proportional to the concentrations of both the amine and methyl iodide.

Another type of explanation of the results is based on the idea of conjugation. It is well known that the carbon-oxygen and carbon-nitrogen bonds are much more reactive than in ordinary ethers and amines. The polarity involved in this reactivity could be considered as binding in some way the unsaturation of the nitrogen atom. The physical properties of the substances do not suggest an undue polarity. They are not associated in benzene solution, they are soluble in benzene and ether, and the boiling points are not abnormally high. This, of course, does not preclude an intramolecular neutralization of stray fields of force, but does suggest the absence of anything approaching a measurable degree of ionization. In this connection it is interesting to note that the diamino derivative $R_2N—CH_2—NR_2$ is also readily hydrolyzed in acidified water and has the normal base strength of an aliphatic amine. The details of these experiments are not given here, but it may suffice to state that no difference could be noted between the diamine and diethylamine in base strength in alcoholic solution. The second base strength was of the order of $K_B = 10^{-8}$. It is also interesting that no solid quaternary compounds of the diamine could be obtained, as was true also of the butoxy derivative. This suggests that the reduction in base strength is not due to direct conjugation of the fields of force about the oxygen and nitrogen.

Attention is called to the unusual properties of the quaternary salts of the methoxy and ethoxy derivatives. These are highly ionized in water, are not easily hydrolyzed and, instead of decomposing on melting as do most quaternary iodides, melt clearly at a comparatively low temperature

(80°). The stronger bases, the butoxy derivative and the diamine R_2N—CH_2—NR_2 did not yield crystalline salts.

Experimental Part

Preparation of Materials

Diethylaminomethyl-ethyl ether was prepared by the method of McLeod and Robinson.[1] A 50% yield was obtained of a product distilling at 130–136°. and from this a middle portion was collected on distillation boiling at 133–134°, and of equivalent weight on titration of 132 to 133. The calculated equivalent weight is 131.1. Portions used for base-strength determination were freshly distilled in a thoroughly dried apparatus.

Diethylaminomethyl-*iso*butyl ether[3] was prepared by the method of McLeod and Robinson. A fraction distilling at 165–170° and of equivalent weight 164 was used. The calculated molecular weight is 160.2.

Diethylaminomethyl-methyl ether was stated by McLeod and Robinson to be hydrolyzed very rapidly and, therefore, was not obtained from the methyl alcohol present in commercial formaldehyde. The compound was prepared using the general method of McLeod and Robinson from 55 g. of diethylamine, 85 g. of 40% formaldehyde and 32 g. of methyl alcohol. The mixture was saturated with sodium carbonate and shaken for two to three hours. The non-aqueous layer was removed, anhydrous potassium carbonate added, and after three days the filtered liquid was fractionally distilled. A yield of 35 g. of product distilled from 114–120°, of which 25 g. distilled at 116.5° to 117.0° (corr.) (763.3 mm.). The equivalent weight by titration in water, using methyl orange as indicator, was 117–118; calcd., 117.1.

Pure samples of **benzylamine** and **methylaniline** were obtained by fractional distillation.

A sample of U. S. P. **quinine** was dried in a desiccator and gave in water an equivalent weight of 326, using bromo cresol purple as indicator. The molecular weight of quinine is 324.

Alcohol was purified by distillation from about 7 cc. of concd. sulfuric acid per liter, addition of 700 g. of freshly broken lime per liter and gentle agitation for two weeks. Fresh lime (300 g. per liter) was then added and after the mixture had been shaken for a week the alcohol was distilled from a water-bath into a tightly closed container for storage.

Standard alcoholic hydrogen chloride solution was prepared by passing into the absolute alcohol dry hydrogen chloride until the solution was 3–4 *N*, and then the solution was diluted to approximately 0.1 *N* with anhydrous alcohol. The hydrogen chloride was generated from pure, concd. sulfuric and hydrochloric acids. The gas was passed over a long tower of calcium chloride and finally over phosphorus pentoxide on glass wool.

Indicator solutions in absolute alcohol were prepared in the following concentrations: bromocresol purple 0.10%; methyl red 0.05%; bromophenol blue 0.10%.

The colorimeter was of the ordinary type consisting of two tubes through which light from a daylight lamp was passed; they were mounted for simultaneous observation, looking through the length of the tubes.

Experimental Results

Molecular Weight of Diethylaminomethyl-methyl Ether.—The relationship of these amino ethers to aldehyde ammonias, and the fact that

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[3] We are indebted to Mr. V. A. Green for the preparation and study of the *iso*butoxy derivative. Only a few of his measurements are included.

the latter are polymerized components made it necessary to determine the molecular weight. The determination was made by the freezing-point method, using benzene as solvent.

Sample, g.	Benzene, g.	F. p. reading		Mol. wt.
		Pure benzene	Solution	
0.2043	19.109	2.770	2.315	115.2
.3429	19.109	2.770	2.008	115.4

Preparation of Quaternary Methyl Iodides.—Since this work was done, Robinson and Robinson[4] have reported the preparation and decomposition of the compounds obtained by the addition of alkyl halides to the amino-butoxy ether. Our results differ only to the extent that we were able to obtain the methyl iodide addition products of the ethoxy and methoxy derivatives in a form suitable for the determination of melting points; 50% ethereal solutions of the two bases and 10% excess methyl iodide were allowed to stand for several days. The oily precipitate first formed crystallized on scratching the flasks. When the reaction was complete the solid product was dissolved in the least possible quantity of *n*-butyl alcohol at 60° (15 cc. per 20 g.) and the clear solution, when cooled slowly in ice, deposited crystals. Successive crystallizations gave a product that melted sharply *without decomposition.* To make sure that no decomposition accompanied melting, a thermometer was immersed in several grams of the molten material and a cooling curve plotted. The same freezing point was obtained several times from the same sample.

Ethoxy-methyl-diethyl-methylammonium Iodide.—$[C_2H_5OCH_2—N—(C_2H_5)_2CH_3]I$; m. p., 83°.

Anal. Subs., 0.2628, 0.1461: 17.42, 9.67 cc. of 0.05510 N $AgNO_3$ soln. Calcd.: I, 46.5. Found: 46.4, 46.4.

Methoxy-methyl-diethyl-methylammonium Iodide.—$[CH_3OCH_2—N(C_2H_5)_2-CH_3]I$; m. p., 116.5–117°.

Anal. Subs. 0.3676: 25.69 cc. of 0.05510 N $AgNO_3$ soln. Calcd.: I, 49.1. Found: 48.95.

The attempt to obtain the butoxy derivative crystalline did not succeed.

Rate of Addition of Methyl Iodide to the Amino Ethers.—Solutions in dry ether of diethylaminomethyl-ethyl ether and methyl iodide were placed in a thermostat at 25.5° and allowed to react. The solutions were made up by weight and the concentrations of the reactants calculated as their mole fractions, respectively. Various mixtures were allowed to stand for various periods of time. The amount of the reaction which had taken place at a given time was determined by adding acidified water and titrating the iodide ion with standard silver solution. Blank experiments showed that it was unnecessary to remove the ethereal layer containing unchanged methyl iodide before the titration. Table I gives the results of the determinations.

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[4] Ref. 2, p. 532.

Table I

The Rate of Addition of Methyl Iodide to Diethylaminomethyl-ethyl Ether in Dry Ether at 25.5 ± 0.1°

Expt.	Ethoxy deriv. mole fraction		Methyl iodide mole fraction		Time	
	Initial	Final	Initial	Final	Min.	K''
1	0.0527	0.0371	0.0527	0.0371	3715	0.00215
2	.0527	.0295	.0527	.0295	6926	.00214
3	.0261	.0208	.0261	.0208	4363	.00221
4	.0302	.0249	.0151	.00958	7073	.00226
5	.0316	.0272	.00965	.00504	10017	.00213
6	.0260	.0158	.0260	.0158	11299	.00221
					Av.	.00218

In calculating the specific reaction rate a bimolecular reaction was assumed:

$$R_3N + RI \longrightarrow R_4NI \text{ (solid)}$$

If the concentrations of the reactants were expressed as grams or moles per liter of solution, variations as high as 20% were found in the values of the specific reaction rate constants for the different experiments. This was due to the fact that fairly high concentrations were involved, and that the product of the reaction was practically insoluble in the solution. Hence as the reaction proceeded, the total number of moles of substance in solution was not constant, and the actual volume of the reacting solution decreased.[5]

The usual integrations of the equations

$$dx = K'' (C_A - x)(C_B - x)\,dt \text{ and } dx = K'' (C_A - x)^2\,dt$$

assume constant volume during the reaction. Since in the present instance the volume changed as much as 5 to 10%, the usual expression for the bimolecular rate constants could not be used.

The use of mole fractions of reactants and solvent instead of concentrations was resorted to and an equation derived for the calculation of the specific reaction rate constant. This appears to be simpler than correcting for changes of volume, and has the added advantage inherent in the use of mole fraction as a measure of chemical activity.

Let A and B be the reacting substances in a solvent S, and n_A, n_B, n_S and N_A, N_B, N_S be, respectively the number of moles, and the mole fraction of A, B and S. If the reaction rate is proportional to the mole fractions of A and B, then

$$-dN_A/dt = K(N_A)(N_B) \qquad (1)$$

If N_A and N_B are equal and remain equal throughout the reaction, we may write

$$-(dN_A/N_A^2) = K\,dt \qquad (2)$$

Integrating between the limits N_A and N_A' where N_A is the initial mole fraction of A and N_A' the mole fraction of A at time t,

$$(N_A - N_A')/N_A N_A' = Kt \qquad (3)$$

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[5] Scatchard, This Journal, **45**, 1580 (1923).

Equation 3 was used to calculate the result of Expts. 1, 2, 3 and 6. It is valid under the conditions outlined, regardless of the precipitation of part or all of the products of the reaction. In Expts. 4 and 5 N_A and N_B were not equal and, since all of the reaction product precipitated,[6] we may write

$$-\frac{d\left(\frac{n_A}{n_A + n_B + n_S}\right)}{dt} = K\frac{n_A\, n_B}{(n_A + n_B + n_S)^2} \qquad (4)$$

Since the difference between n_A and n_B is constant, $n_B = n_A - c$, where c is a constant; let $l = n_S - c$, then

$$-\frac{d\left(\frac{n_A}{2n_A + l}\right)}{dt} = K\frac{(n_A)^2 - cn_A}{(2n_A + l)^2} \qquad (5)$$

Solving for Kdt and simplifying,

$$-\frac{l\, dn_A}{n_A^2 - cn_A} = Kdt \qquad (6)$$

Integrating between the limits n_A and n_A', where n_A is the number of moles of A at zero time, and n_A' the number of moles of A at time t,

$$\left[\frac{l}{c}\ln\frac{n_A}{n_A - c}\right]_{n_A}^{n_A'} = Kt \qquad (7)$$

whence

$$\frac{n_S - c}{c}\ln\frac{n_A'(n_A - c)}{n_A(n_A' - c)} = Kt \qquad (8)$$

and

$$\frac{N_S - N_A + N_B}{N_A - N_B}\ln\frac{(N_A')(N_B)}{(N_A)(N_B')} = Kt \qquad (9)$$

where N_S, N_A, N_B and N_S' N_A' N_B' are the initial mole fractions and the mole fractions at time t of the solvents, A and B, respectively. Equation 8 in practice is the more convenient form. Table I gives the experimental data in a form for use in Equations 3 and 9 and the value of K obtained when t is in minutes; and conversion to ordinary logarithms has been made. For dilute solutions Equation 8 reduces to the usual equation involving concentrations.[7]

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[6] This is a distinct advantage in such a rate measurement, since there is no accumulation of a strong electrolyte in the solution, and the properties of the reacting solution thereby remain more nearly constant throughout the reaction.

[7] If the products of the reaction do not precipitate, two cases may be considered. First assume the reaction A + B ⟶ C + D where C and D remain in solution. The total number of moles remains constant. Proceeding as above, and using the same notation as in Equation 9, it may be shown that

$$\frac{1}{N_A - N_B}\ln\frac{N_A'\, N_B}{N_A\, N_B'} = Kt$$

Second, assume the reaction A + B ⟶ C, where C remains in the solution. The total number of moles is not constant. Using the same notation, and assuming that the

Corresponding measurements of the rate of addition of methyl iodide to diethylaminomethyl-methyl ether in ether solution gave a preliminary result for K'' for the reaction between 1.5 and 1.7×10^{-3}.

Strength of the Quaternary Hydroxides as Bases.—The aqueous solutions of the above quaternary iodides were neutral and used up neither acid nor base on titration to the methyl orange or phenolphthalein end-points. Conductivities of the salt solutions, of sodium hydroxide solutions and of mixtures of the two, were taken in a single cell, following the method used by Stewart and Maeser[8] to detect association of hydroxyl ions and quaternary ammonium ions. The conductivity of a mixture was found to be the sum of the conductivities of the salt and of sodium hydroxide at the same concentration.

Formation of the Hydrochloride of the Amino-ether Bases.—To an ethereal solution of diethylaminomethyl-ethyl ether cooled in salt and ice, was added an ethereal solution of hydrogen chloride in slight excess. The white precipitate formed was filtered off rapidly under anhydrous conditions, washed with ether and dried in a vacuum over phosphorus pentoxide. The salt melted at 75–78°.

Anal. Subs., 0.1916: 23.72 cc. of 0.0551 N $AgNO_3$. Calcd. for $C_7H_{17}ONHCl$: Cl, 21.2; for $C_5H_{12}NCl$, 29.1. Found: 24.23.

The hydrolysis of the salt in moist air is very rapid. The most probable impurity is diethylamine hydrochloride.

Decomposition of the Quaternary Methyl Iodide Derivative.—McLeod and Robinson found that when heated with alkali, their impure quaternary compounds decomposed with extreme slowness to give a tertiary amine. Before their work appeared we had arrived at the same result. Dilute acids and alkalies have no effect on the ether linkage. By heating a sample of $[(C_2H_5)_2N(CH_3)\text{-}CH_2\text{-}OCl_2H_5]I$ with 33% potassium hydroxide for three hours a 60% yield of methyl-diethylamine was obtained as the hydrochloride. The salt melted at 168–173° and gave the correct analysis for chlorine and a platinum salt of correct content of platinum.

The Strength of Diethylaminomethyl-ethyl Ether as a Base.—The rate of hydrolysis of these amino ethers in water is too rapid to allow the use of water as a solvent. Experiment showed that it was possible in absolute alcohol solution at 0° to add one equivalent of alcoholic hydrogen

number of moles of A present is greater than the number of moles of B, it may be shown for this case that

$$\frac{1 - N_A}{N_A - N_B}\, ln\, \frac{N_A'\, N_B}{N_A\, N_B'} = Kt$$

Equation 9, derived for the reaction A + B $\longrightarrow$ C + D, where neither C nor D remains in solution, may be written in the form

$$\frac{1 - 2N_A}{N_A - N_B}\, ln\, \frac{N_A'\, N_B}{N_A\, N_B'} = Kt$$

[8] Stewart and Maeser, This Journal, **46**, 2583 (1924).

chloride for each equivalent of base present, and then to titrate back all of the acid added with sodium ethylate, regenerating the unchanged base. The original base titrates at the bromocresol purple end-point only 1–2%, whereas the hydrolysis product, diethylamine, is titrated completely at that end-point. Hence if the salt of the amino-ether base changed rapidly in alcohol to the salt of diethylamine, it would not be possible to neutralize the amino-ether base with acid and then find, using the bromocresol purple end-point, that all of the acid added was available for the neutralization of sodium ethylate. Salts of these bases, in dilute alcoholic solution kept free from water, are stable for hours.

The method of comparing the base strength of the unknown bases with bases of known strength was as follows. Samples of the known and unknown bases were weighed into two colorimeter tubes of about 100 cc. capacity. The tubes were fitted with stoppers containing ground-glass plates and with a glass tube through which alcohol or alcoholic hydrogen chloride could be introduced. The concentrations of the two bases were kept the same in any one experiment, and varied from 0.02 to 0.4 *M*. Alcohol to effect the desired concentration was added to the bases in the colorimeter tubes, care being taken that the air did not come in contact with it during the transfer. A measured quantity of indicator was added to each tube and acid added to the more basic one to equalize the color of the indicator. Acid was then added in turn to one and then to the other, and color matches were obtained whenever convenient and possible.

The results are given in Tables II, III and IV. Cols. 3 and 6 give the percentages of the two bases neutralized at points where the colors matched. These values were obtained from the amounts of acid added and from the equivalent weights of the samples used. The equivalent weight in turn was obtained by titration of a sample in water using an indicator suitable for diethylamine. From the percentage of the base neutralized is calculated the ratio of salt to base in the solution, assuming that the salt concentration is equal to the concentration of the total acid added. These ratios are given in Cols. 4 and 7 for the known and unknown, respectively, together with an estimate of the probable error in the ratio (Cols. 5 and 8). A large error in the ratio may be involved in the estimation of the salt concentration, and by inability to match colors accurately, due to the buffer action of the solution. The former error is serious when the base is either very slightly or almost completely neutralized. The latter is serious at from 30 to 70% titration, since in that range the rate of hydrogen-ion concentration change is low and the indicator changes color very little. The observer is, therefore, uncertain whether the best match is at one extreme or the other. The ratio of salt to base also becomes meaningless at very low percentage neutralization because of the possibility of the presence of small amounts of basic impurities (diethylamine). These data are used to obtain the basic dissociation constant K_B on the assumption that the basic dissociation constants for two different bases are proportional to the salt-base ratios, respectively, when the solutions are at the same hydrogen concentration, If BOH and B′OH are two bases, then

$$K_B = \frac{(B^+)\,(OH^-)}{(BOH)} = \frac{(\text{salt})}{(\text{base})}\,(OH^-),\ \text{and}\ K_B{}' = \frac{(B'^+)\,(OH^-)}{(B'OH)} = \frac{(\text{salt}')}{(\text{base}')} \times (OH^-)$$

where both BOH and B′OH are weak bases. If K_B is known,

$$K_B{}' = K_B\,\frac{\text{salt}'}{\text{base}'}\Big/\frac{\text{salt}}{\text{base}}$$

when the hydroxyl-ion concentrations of the two solutions are equal. The numerical value of K_B is also based on the assumption that the relative base strengths are the same in alcohol and water. Apparently this is not true for quinine and α-picoline and perhaps many other bases, as compared to benzylamine and methylaniline. Taking the last two bases as standard points of reference, and assuming the values of K_B for each as determined in water, quinine and α-picoline should fall about halfway between. In alcoholic solution, however, the value for α-picoline proved to be shifted so much as to be useless, and that for quinine is shifted markedly toward benzylamine. The cause of this apparent shift in base strength is probably a shift in equilibrium between tautomeric forms of quinine and α-picoline produced by the change of solvent. Since no similar change is to be expected in our points of reference and in our unknown bases, it is believed that the method of comparison here used is valid. The values of K_B arrived at for the amino ethers have been tested qualitatively in water by rapid titration. The hydrolysis is slow enough to permit detection of the fact that the unhydrolyzed base is much weaker than the base produced by hydrolysis.

TABLE II

COMPARISON OF THE BASE STRENGTHS OF DIETHYLAMINOMETHYL-METHYL ETHER AND KNOWN BASES

Temperature 0°

			Titrn. of known base			Titrn. of methoxy deriv.			
Indicator	Known base	K_B in water	% Titrn.	Salt/Base	Error, % salt/base	% Titrn.	Salt/Base	Error, % salt/base	$K_B \times 10^9$
Bromocresol purple	Benzylamine	1.52×10^{-5}	94.8	18.03	10	0.42	0.00425	40	3.58
	Quinine	1.3×10^{-6}	81.1	4.27	5	.36	.00361	40	1.10
			85.7	5.96	10	.54	.00543	30	1.18
Methyl red	Quinine	1.3×10^{-5}	68.0	2.12	20	.38	.00379	30	2.32
			84.7	5.61	40	.57	.00569	30	1.32
			96.8	29.9	100	.85	.00855	15	0.372
Methyl red	Quinine K_B second	3.3×10^{-10}	9.5	0.106	30	65.00	1.86	15	5.16
			28.8	.405	5	71.1	2.47	20	1.23
Methyl red	Methyl aniline	2.55×10^{-10}	0.91	.00919	20	14	1.71	50	4.75
			2.58	.0265	20	29	0.414	30	3.98
			2.96	.0305	10	31	.455	20	3.80
			4.39	.0460	10	35	.550	15	3.05
			19.70	.246	20	88	7.86	20	8.23
			26.5	.360	15	93	13.5	50	9.56
									Av. 3.6

TABLE III

COMPARISON OF THE BASE STRENGTHS OF DIETHYLAMINOMETHYL-ETHYL ETHER AND KNOWN BASES

Temperature 0°

			Titrn. of known base			Titrn. of ethoxy deriv.			
Indicator	Known base	K_B in water	% Titrn.	Salt/Base	Error, % salt/base	% Titrn.	Salt/Base	Error, % salt/base	$K_B \times 10^8$
Bromocresol purple	Quinine	1.3×10^{-6}	58.3	1.39	7	1.28	0.0129	10	1.2
			77.9	3.52	10	1.92	.0195	10	0.72
			88.0	7.37	−40	2.46	.0252	10	.44
			92.0	11.35	−50	3.10	.0319	10	.37
Methyl red	Quinine	1.3×10^{-6}	92.5	12.7	−40	2.56	.0263	13	.27
			94.5	17.2	30	2.87	.0296	40	.22
			96.5	26.7	30	3.67	.0382	40	.19
			97.7	41.2	100	4.63	.0486	40	.15
Methyl red	Methyl aniline	2.55×10^{-10}	4.46	0.0468	10	45.1	.820	25	.45
			5.49	.0581	10	68.2	2.14	20	.94
			6.41	.0686	10	86.5	6.36	10	2.4
			7.54	.0816	20	97.3	23.3	200	10.4
Bromocresol purple	Benzylamine	1.52×10^{-5}	90.0	8.88	10	1.15	0.01165	20	2.0
			92.1	11.5	20	1.38	.0140	20	1.8
Bromocresol purple	Quinine		25.3	0.339	20	1.32	.0134	10	5.2
			34.6	.528	2000	1.53	.0155	10	3.80
								Av.	1.8

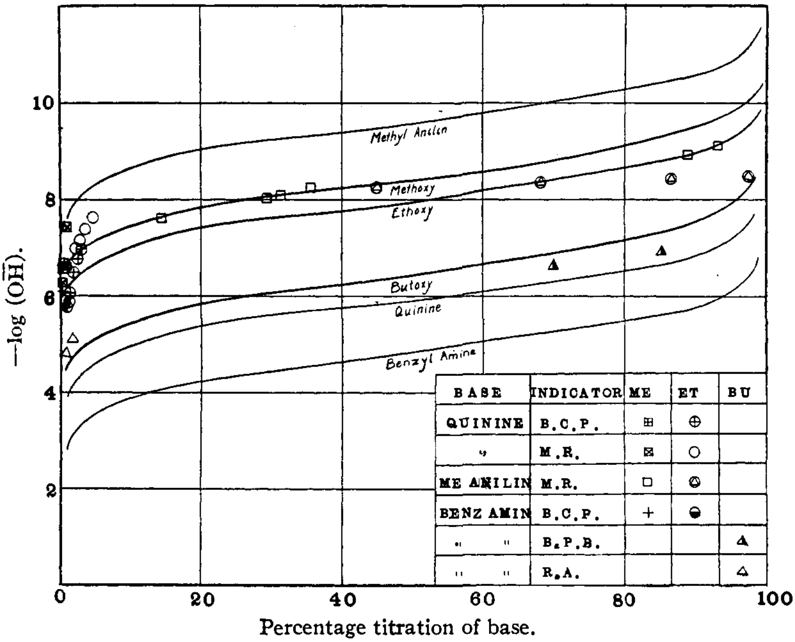
TABLE IV

COMPARISON OF THE BASE STRENGTHS OF DIETHYLAMINOMETHYL-*iso*BUTYL ETHER AND BENZYLAMINE

Known base = Benzylamine $K_B = 1.52 \times 10^{-5}$

	Titrn. of known base			Titrn. of butoxy deriv.			
Indicator	% Titrn.	Salt/base	Error, % salt/base	% Titrn.	Salt/base	Error, % salt/base	$K_B \times 10^7$
Rosolic acid	50	1	15	0.9	0.0090	20	1.4
Rosolic acid	62	1.63	15	1.8	.0183	10	1.5
Bromophenol blue	98.5	65	30	70	2.33	40	5.4
Bromophenol blue	99	99	50	85	5.6	10	8.5
							Av. 4×10^{-7}

Fig. 1 was prepared as follows. The percentage titrations of the known bases methylaniline, benzylamine and quinine were plotted against the values of —log (OH^-) for the corresponding solutions, the points being calculated from assumed values of the ratio salt/base and from the values of K_B as obtained in aqueous solution. K_B for quinine was taken as 1.3×10^{-6} for the reasons given above. This value was determined by comparing benzylamine and quinine in alcohol. With these curves as reference, the points given in Col. 3 of Tables II and III and Col. 2 of Table IV were plotted at the same ordinate as the corresponding percentage titration of the reference base. Assuming the curves to be parallel, smooth curves were drawn to represent the methoxy, ethoxy and *iso*-butoxy derivatives. At 50% titration K_B equals (OH^-). The values of K_B taken from the plots are, respectively: for diethylaminomethyl-methyl ether, 4.0 × 10^{-9}; for diethylaminomethyl-ethyl ether, 1.1 × 10^{-8}; and for diethylaminomethyl-*iso*butoxy ether, 3.7 × 10^{-7}. These values were arrived at independently of the numerical averages given in the tables and are in good agreement with them.



BASE	INDICATOR	ME	ET	BU
QUININE	B.C.P.	⊞	⊕	
"	M.R.	⊠	○	
ME ANILIN	M.R.	□	⊚	
BENZ AMIN	B.C.P.	+	◒	
" "	B.P.B.			▲
" "	R.A.			△

Fig. 1.—Titration curves of some alkoxyl amines in alcohol with reference to bases of known strength.

Summary

The basic dissociation constants of three amino ethers have been determined by comparing the fraction of the bases neutralized in alcohol solution at a given indicator end-point with the fraction of benzylamine and methylaniline neutralized at the same end-point. The values obtained are as follows: diethylaminomethyl-methyl ether, K_B = 3.6 × 10^{-9}; diethylaminomethyl-ethyl ether, K_B = 1.8 × 10^{-8}; diethylaminomethyl-*iso*butoxy ether, K_B = 4 × 10^{-7}.

Tetra-ethyldiaminomethane is as strong a mono-acid base as is diethylamine. It is suggested that since all other amine bases having basic dissociation constants in this range are either amphoteric or tautomeric substances, it is possible that these substances are also mixtures of tautomers.

The quaternary methyl iodides have been prepared. Their rates of formation in ether have been determined in two cases, and an equation developed for the calculation of a bimolecular reaction rate constant for the case where the total number of moles of substance present during a

reaction is not constant and where the rate of the reaction is taken as proportional to the mole fractions of the reacting substances. The quaternary salts melt at low temperatures without decomposition.

Diethylaminomethyl-methyl ether has been prepared for the first time.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE HARRIMAN RESEARCH LABORATORY, THE ROOSEVELT HOSPITAL]

STUDIES OF ENZYME ACTION. XXXVI
ESTER-HYDROLYZING ACTIONS OF THE CASTOR BEAN[1]

BY I. LORBERBLATT AND K. GEORGE FALK

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Introduction

The experiments described in this paper form a development of the work on castor beans published some years ago. They also parallel the study of the ester-hydrolyzing or lipase actions of animal tissues and tumors which is in progress. The topics treated here include the use of various substrates, the actions at different hydrogen-ion concentrations, some studies of the kinetics of the actions, and the solubility of the active enzyme materials in water and in sodium chloride solution. The work of others will be taken up in connection with the new experimental work.

Experimental Methods and Results

Enzyme Material.—Several preparations of castor beans[2] were used. The method of obtaining the material hull- and fat-free was described elsewhere.[3]

Substrates.—Soluble esters only were used. This may appear to limit the usefulness and applicability of the results because such esters are found only to small extents in natural sources. If comparable results could be obtained with fats and similar bodies, it would be desirable to use them as well. The enzyme material used, frequently is insoluble or in colloidal solution. The use of an insoluble substrate may introduce added complications in the way of obtaining uniform and reproducible mixtures and therefore comparable estimations of the enzyme actions. It was decided to study only esters soluble under the conditions of the experiments and in this way attempt to eliminate one of the most troublesome of the experimental factors.

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[1] Taken in part from the thesis presented by I. Lorberblatt in partial fulfilment of the requirements for the degree of Bachelor of Science at the Brooklyn Polytechnic Institute, June, 1925. Thanks are due to Professor B. P. Caldwell for his advice and suggestions in the various phases of the work and for permission to include the results in this paper.

[2] Supplied by the Baker Castor Oil Company, New York.

[3] Noyes, Lorberblatt and Falk, *J. Biol. Chem.*, **68**, 135 (1926).