[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Physico-Chemical Studies of the Simpler Polypeptides. II. The Kinetics of the Alcoholysis of the Polyglycine Esters[1]

BY SAMUEL GLASSTONE AND EDWARD F. HAMMEL, JR.

When mono-, di-, tri- or tetra-glycine is heated with alcoholic hydrochloric acid, it dissolves readily and simultaneous esterification occurs; this is the standard method developed by Fischer[2] for the preparation of the polyglycine ester hydrochlorides. When the procedure was applied to penta- or hexa-glycine, however, dissolution was found to be very slow, and the solution on cooling or upon concentration gave a residue of equivalent weight much lower than would be expected for the corresponding ester. It was also observed that when solutions of tetraglycine ethyl ester hydrochloride were concentrated *in vacuo*, the products had an equivalent weight of about 200, instead of 310.6. It was evident, therefore, that alcoholytic splitting of the polyglycine chain was occurring in the acid medium. Some experiments on the decomposition of simple polypeptides[3] and of some proteins[4] by alcoholic hydrochloric acid have been carried out but since information on the subject was scanty, it appeared of interest to make a more extended study. In the present paper, therefore, the kinetics of the alcoholysis of di-, tri-, tetra-, penta- and hexa-glycine esters in the presence of hydrochloric acid are described; the results are discussed and an attempt is made to elucidate the reaction mechanism.

Experimental

Preliminary experiments showed that in order to obtain measurable rates of splitting of polyglycine esters in alcohol solutions saturated with hydrogen chloride, it was necessary to work in the vicinity of the boiling point of the solution. Under these conditions, difficulties arise on account of the occurrence of the reaction

$$HCl + C_2H_5OH = C_2H_5Cl + H_2O$$

This not only results in the formation of water, which is known to affect the rate of splitting in alcoholic solution,[4b] but at the same time the amount of catalyst, hydrochloric acid or hydrogen (ethoxonium) ions, is diminished. It seemed improbable that accurate values of the specific reaction rates could be determined especially when the reactions were slow; nevertheless, reasonably satisfactory results have been obtained as will be seen below.

To the solution of dry hydrogen chloride gas in 99.9% ethyl alcohol was added sufficient pure di-, tri-, or tetraglycine ester hydrochloride, prepared and purified according to the methods described in Part I,[5] to make a 0.025 *N* solution. The suspension was then set to boil gently under reflux, the access of moisture from the air being prevented by a calcium chloride tube. Dissolution of the solid was complete within five minutes after boiling began and the clarification of the solution was taken as zero time for the reaction. Samples of the clear liquid were then withdrawn at various intervals and evaporated to dryness on a steam-bath which required about two minutes. A definite weight (*ca.* 0.03 g.) of the dry residue was dissolved in water 2 cc. of a 5% neutral formalin solution was added and the mixture was titrated potentiometrically with standard carbonate-free sodium hydroxide solution using a glass electrode.

Since penta- and hexa-glycine ethyl ester hydrochlorides could not be prepared in the usual manner, as was mentioned earlier, the free peptides were employed to determine rates of alcoholysis. This was justifiable since independent experiments had shown that esterification of the lower peptides occurred almost immediately upon going into solution. An excess of the sparingly soluble, finely powdered, peptide was boiled gently under reflux with 100 cc. of hydrochloric acid solution in ethyl alcohol. After certain time intervals the solid was removed by filtration through sintered glass and the filtrate was concentrated rapidly *in vacuo* to a volume of about 5 cc.; this was finally evaporated to dryness on a steam-bath, and the residue analyzed in the manner described above.

The experimental results obtained with 2 *M* hydrochloric acid in 99.9% ethyl alcohol are summarized in Table I. The methods of evaluating the specific reaction rates are described below.

Calculation of Rate Constants.—For the sake of brevity the following generalized notation will be adopted: G_n, concentration at any time t of the ester hydrochloride containing n glycine residues; G_n^0, initial concentration of the species G_n; E_n, equivalent weight of the ester hydrochloride containing n glycine residues; k_n, specific rate constant for the cleavage reaction of the G_n ester

(1) This work has been assisted, in part, by a grant from the Penrose Fund of the American Philosophical Society to Professor Eugene Pacsu.

(2) Fischer, "Untersuchungen über Aminosäure, Polypeptide, und Proteine," Vol. I, Verlag Julius Springer, Berlin, 1906.

(3) Abderhalden and Hanslian, *Z. physiol. Chem.*, **77**, 285 (1912).

(4) (a) Pfannl, *Monatsh.*, **31**, 81 (1910); (b) Pribram, *Z. physiol. Chem.*, **71**, 472 (1911); (c) Weizmann and Agashe, *Biochem. J.*, **7**, 437 (1913).

(5) Glasstone and Hammel, THIS JOURNAL, **63**, 243 (1941).

TABLE I

ALCOHOLYSIS OF POLYGLYCINE ESTER HYDROCHLORIDES IN 2 *M* HYDROCHLORIC ACID

Ester hydrochloride or free peptide used	Concn. at the commencement	Milli-equivalents of amino nitrogen based on 1 g. sample obsd. at: (Time in minutes) 15	30	45	60	90	120	Specific reaction rate computed at: (Time in minutes) 7.5	15	22.5	30	Av. spec. reaction rate
Diglycine ester HCl	0.025 *M*	5.60	5.86	..	6.23	6.50	6.73	0.0147	0.0138	0.0127	0.0118	0.013
Triglycine ester HCl	.025 *M*	5.19	5.66	5.96	6.16	6.53	6.80	.0547	.0540	....	....	.054
Tetraglycine ester HCl	.025 *M*	4.76	5.60	5.99	..	6.50	6.70	.0543	.0543	....	....	.054
Pentaglycine	Satd. soln.	3.73	4.46	4.96	5.30	5.83	..	.039	.041	....	....	.040
Hexaglycine	Satd. soln.	..	4.46	..	5.06	..	5.69	108	....	....	....	.11

hydrochloride; t, time, measured from the instant at which all the ester hydrochloride is in solution.

(a) **Diglycine Ester.**—The product of alcoholysis is known to consist exclusively of glycine ethyl ester hydrochloride, or some free glycine hydrochloride if an appreciable amount of water is present; the reaction $G_2 \rightarrow 2G_1$ may thus be regarded as being of the first order since the ethoxonium ion is in large excess. It follows, therefore, that

$$-\mathrm{d}G_2/\mathrm{d}t = k_2G_2$$
$$\therefore G_2 = G_2^0e^{-k_2t} \qquad (1)$$

Further, since

$$\mathrm{d}G_1/\mathrm{d}t = 2k_2G_2 \qquad (2)$$

by substituting (1) into (2), integrating, and noting that $G_1 = 0$ when $t = 0$, the result is

$$G_1 = 2G_2^0(1 - e^{-k_2t}) \qquad (3)$$

The total number of equivalents T, of G_1 and G_2 at any time t is then

$$T = G_1 + G_2 = G_2^0(2 - e^{-k_2t})$$

and the total weight of the mixture of ester hydrochlorides at any instant is

$$W = E_1G_1 + E_2G_2$$

The ratio of T to W gives the total number of equivalents of amino-nitrogen per unit weight of mixed ester hydrochlorides obtained by evaporating the reaction mixture; since this has been determined experimentally, k_2 can be evaluated for different times t.

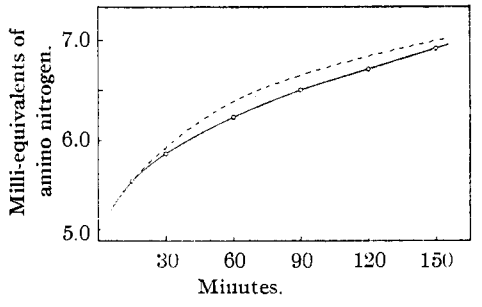

Fig. 1.—Diglycine ester hydrochloride.

In view of the changes taking place in the solution, as mentioned above, calculations were made with the data for short reaction times only; these were obtained either from direct measurement or by interpolation of the experimental data. In order to see how far later measurements were in harmony with those obtained after short time intervals, a mean value 0.013 was assumed for k_2 and T/W calculated for various times; the results are shown by the dotted curve in Fig. 1 in which the experimental data are represented by the full curve. The fact that the latter is the lower of the two is to be attributed to the decrease in concentration of the hydrochloric acid as the reaction proceeds.

(b) **Triglycine Ester.**—Since it is unlikely that both peptide linkages will be broken simultaneously in a reaction involving three molecules, it is probable that the triglycine ester is split in two consecutive first order stages; in the first diglycine- and glycine-esters are formed and in the second the diglycine ester is decomposed. In order to evaluate k_3 for the reaction $G_3 \rightarrow G_2 + G_1$, it may be supposed that in the early stages of the reaction the extent of the alcoholysis of diglycine ester hydrochloride is negligible. Then

$$\mathrm{d}G_3/\mathrm{d}t = -k_3G_3$$

from which

$$G_3 = G_3^0e^{-k_3t}$$

and as before

$$G_2 = G_1 = G_3^0(1 - e^{-k_3t})$$
$$T = G_1 + G_2 + G_3 = G_3^0(2 - e^{-k_3t})$$

and

$$W = E_1G_1 + E_2G_2 + E_3G_3$$

It is thus possible to evaluate k_3; the results are given in Table I.

By utilizing the values of k_2 and k_3 it should be possible to calculate the course of the reaction over longer periods of time. In this case the value of G_3 at any instant is equal to $G_3^0e^{-k_3t}$ as before; those of G_2 and G_1 may be obtained, with the help of a method of solution for a series of consecutive

first order reactions developed by Bateman,[6] by integration of the equations

$$dG_2/dt = k_3G_3 - k_2G_2$$
$$dG_1/dt = k_3G_3 + 2k_2G_2$$

the constants of integration being determined by the fact that both G_2 and G_1 equal zero when $t = 0$. From these equations the ratio T/W may be evaluated for various times. The results obtained in this manner taking $k_2 = 0.013$ and $k_3 = 0.054$ are shown by the dotted curve in Fig. 2. This is also above the experimental curve, as is to be expected for the reason given in connection with diglycine ester.

(c) **Tetraglycine Ester.**—The first stage of the reaction may be either the fission of one molecule of the tetra- into two molecules of diglycine ester followed by cleavage of the latter, or fission of the tetra- into glycine- and tri-glycine-esters, followed by the decomposition of the latter as described above, or both types of reaction may occur simultaneously. It is probable that the second type of splitting predominates. In a somewhat analogous case Abderhalden[7] isolated the cleavage products of tetraglycine as benzoyl derivatives after treatment of the free peptide with both N sodium hydroxide and erepsin. In each case the terminal glycine residue was found to have been split off rather than a molecule of diglycine, showing that the first point of attack is not the middle of the molecule.[8] It will be seen also that the specific rates assuming the primary cleavage reaction yields two molecules of diglycine ester hydrochloride are not constant even over short periods of time. In addition, the curve calculated on the basis of this type of splitting shows certain discrepancies which are incompatible with the results in the previous cases. In order to simplify the treatment the kinetics for the two possible mechanisms are considered separately.

Considering, therefore, that tetraglycine ester decomposes into one molecule of glycine- and one of triglycine-ester hydrochloride, equations are developed to give k_4. Owing to the fact that the triglycine ester decomposes so rapidly, it is not possible to neglect this reaction when calculating k_4; the decomposition of diglycine was, however, neglected. The basic equations employed for the

(6) Bateman, *Proc. Cambridge Phil. Soc.*, **15**, 423 (1910).

(7) Abderhalden, *Fermentforschung*, **13**, 459 (1933).

(8) This conclusion is not in agreement with that reached by Kuhn, Molster and Freudenberg, *Ber.*, **65B**, 1179 (1922), as a result of alkaline hydrolysis of the free peptide. There appears, however, to be an error in the calculations of these workers which will be discussed in another paper.

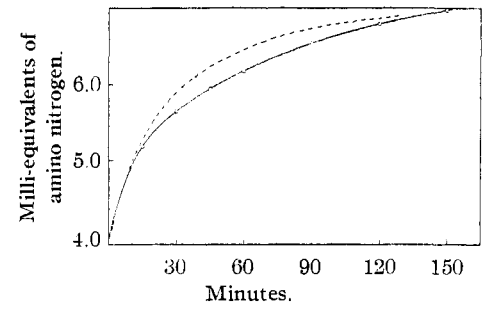

Fig. 2.—Triglycine ester hydrochloride.

reactions $G_4 \rightarrow G_3 + G_1$, and $G_3 \rightarrow G_2 + G_1$ may be derived from integration of the following relationships

$$dG_4/dt = -k_4G_4$$
$$dG_3/dt = k_4G_4 - k_3G_3$$
$$dG_2/dt = k_3G_3$$
$$dG_1/dt = k_4G_4 + k_3G_3$$

determining the constants as outlined previously. Taking $k_3 = 0.054$ and proceeding as in the previous cases, the values of k_4 recorded in Table I were obtained. The fact that k_4 obtained in this manner is almost identical with k_3 supports the view that the $G_4 \rightarrow G_3 + G_1$ type of fission is predominant.

For the purpose of obtaining a calculated reaction curve, as before, all the steps of the reaction must be taken into consideration. The rate equations employed for dG_4/dt and dG_3/dt are the same as above; the others, however, are now

$$dG_2/dt = k_3G_3 - k_2G_2$$
$$dG_1/dt = 2k_2G_2 + k_3G_3 + k_4G_4$$

From these, equations giving the values of G_1, G_2, G_3 and G_4 at any instant were derived; they are, however, too lengthy to be quoted here. The difficulty of calculating T was increased by the fact that the expression involves the term $k_3 - k_4$, which as seen from Table I is close to zero. It was necessary therefore to take limits of the various expressions as k_3 approached k_4. The results are shown by the dotted curve A in Fig. 3;

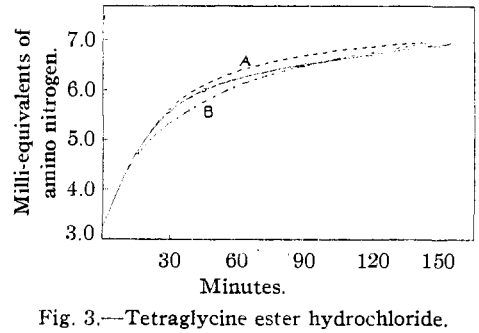

Fig. 3.—Tetraglycine ester hydrochloride.

this bears the same general relationship to the experimental curve as do the corresponding curves in Figs. 1 and 2.

If the alternative type of splitting, *viz.*, $G_4 \rightarrow 2G_2$, is now considered, it is seen that the ratio T/W may be found from integration of the following equations

$$dG_4/dt = -k_4G_4$$
$$dG_2/dt = 2k_4G_4 - k_2G_2$$
$$dG_1/dt = 2k_2G_2$$

and k_4 may be evaluated at various intervals of time. The constants so determined show a decided drift, not observed in the other cases, k_4 changing from 0.058 at seven and one-half minutes to 0.087 for thirty minutes. Assuming, however, the variation to be due to experimental error, the curve calculated taking $k_4 = 0.058$ has been plotted in Fig. 3 as the dotted curve B. It will be seen that the experimental curve in this case lies above the theoretical curve. Since every factor operating at the start of the reaction, *i. e.*, drop in catalyst concentration and, as will be seen later, the presence of small amounts of water, tends to cause the reaction to proceed more slowly, it is improbable that the primary decomposition of the tetra- to two di-glycine ester molecules occurs to any great extent.

(d) **Pentaglycine Ester.**—In this case the solution may be regarded as being always saturated with pentaglycine ester hydrochloride so that its concentration is constant throughout. Two types of cleavage of the pentaglycine chain, *viz.*, $G_5 \rightarrow G_4 + G_1$ or $G_5 \rightarrow G_3 + G_2$, can occur as the primary stage. Since G_4 and G_3 decompose at approximately the same initial rate, it does not seem possible to distinguish easily between the two types of fission; the specific reaction rate observed would be approximately the same in both cases. For the purposes of calculation it was assumed that G_1 and G_4 are formed, since this reaction probably predominates. The rate equations are

$$G_5 = a$$

where a is a constant

$$dG_4/dt = k_5a - k_4G_4$$
$$dG_3/dt = k_4G_4 - k_3G_3$$
$$dG_2/dt = k_3G_3 - k_2G_2$$
$$dG_1/dt = 2k_2G_2 + k_3G_3 + k_4G_4 + k_5G_5$$

(e) **Hexaglycine Ester.**—The treatment here is analogous to that in the previous case since the solution may be taken as being saturated with hexaglycine ester hydrochloride throughout the course of the experiment. If G_6 is split into G_5 and G_1, there will be five successive reactions of which the first four have appreciable rates. The evaluation of the rate constant for the alcoholysis of the hexaglycine ester even if the last step, *i. e.*, the decomposition of diglycine, is neglected is extremely tedious and so a modified procedure was adopted. The value of k_6 was calculated for a short time interval taking into consideration (a) the first stage only, *i. e.*, $G_6 \rightarrow G_5 + G_1$, (b) the first two stages, *i. e.*, $G_6 \rightarrow G_5 + G_1$, $G_5 \rightarrow G_4 + G_1$, (c) the first three stages, *i. e.*, $G_6 \rightarrow G_5 + G_1$, $G_5 \rightarrow G_4 + G_1$, $G_4 \rightarrow G_3 + G_1$. The rate equations for the last case are analogous to those employed in the treatment of the tetrapeptide ester and those for the other cases can be derived from this by simplification. The results obtained for the time interval 7.5 minutes assuming k_5 and k_4 to be 0.040 and 0.054, respectively, were for (a) 0.143, for (b) 0.112 and for (c) 0.109. It is apparent therefore that, provided the time interval is sufficiently short, the fourth and fifth stages of the reaction do not occur to any appreciable extent and can be neglected. It may be noted that if the assumption is made that the first stage is $G_6 \rightarrow G_4 + G_2$ or $G_6 \rightarrow 2G_3$, the resulting specific rate constant differs but little from that calculated above.

Influence of Acid Concentration.—In order to obtain some indication of the influence on the specific rate of the concentration of the hydrochloric acid catalyst, some experiments were performed with 0.025 M solutions of di-, tri- and tetraglycine ethyl ester hydrochloride in the presence of 0.17 M hydrochloric acid in 99.9% ethyl alcohol. The final results are given in Table II. The column headed "obsd." gives the experimental specific reaction rates derived by the methods already described, while the column marked "calcd." shows the value which would be obtained if the rate were proportional to the acid concentration.

TABLE II

SPECIFIC REACTION RATES OF ALCOHOLYSIS IN 0.17 M HYDROCHLORIC ACID

Peptide ester hydrochloride	Obsd.	Calcd.
Diglycine	0.0006	0.0011
Triglycine	.0042	.0046
Tetraglycine	.0044	.0046

The agreement for the tri- and tetra-glycine esters is good but the discrepancy in the case of diglycine ester is probably due to the fact that

the reaction in the dilute acid solution is so slow that the increase in amino-nitrogen is very much smaller than in the other cases. Consequently a small experimental error in the measurement of that increase would cause an appreciable variation in the rate constant. If measurements are taken over a longer time period in order to avoid the above mentioned source of error, considerable changes in the nature of the medium occur.

Influence of Water Concentration.—The view has been expressed[4a,b] that in the alcoholysis of peptides and proteins, the actual splitting is a hydrolytic reaction, brought about by small quantities of water present, and that this is followed by esterification of the free acid with the regeneration of the water. If this were so, extrapolation of the rate constant to zero water concentration should yield a rate constant of zero. It would be expected also that the addition of further small amounts of water should increase the reaction rate. Kinetic measurements, therefore, were made with 0.025 *M* solutions of di-, tri- and tetraglycine esters in ethyl alcohol containing 0.1, 0.4 and 1.4% of water in the presence of 0.5 *M* hydrochloric acid. The results are shown graphically in Fig. 4. It is evident that increasing the amount of water, within limits, actually decreases the reaction rate, the influence being most marked with the first additions. Results[9] of a similar nature have been obtained in esterification reactions in which water can play no part. Hence it appears to be established that the splitting of the polypeptide ester hydrochlorides, at least in the presence of small amounts of water, is a true alcoholysis.

Discussion

Irrespective of whether the actual cleavage is due to water or alcohol, the reactions under consideration undoubtedly involve the approach of the appropriate hydrogen ion, *i. e.*, H_3O^+ or $C_2H_5OH_2^+$, to the peptide linkage. Since the ester hydrochloride which is being split has a positive charge at one end, it is probable that the consequent repulsion of the hydrogen ion associated with a molecule of substrate will greatly increase the free energy of activation for the reaction at the nearest peptide linkage and hence decrease the reaction rate. The carbethoxy group at the other end of the molecule will tend to act, through the chain, in a similar sense, but its effect will be very small compared with the influence of the whole unit charge on the nitrogen atom. If factors such as these played no part, the rate of alcoholysis of triglycine ester hydrochloride (k_3) should be twice as great as that of the diglycine ester since the former has two peptide linkages and the breaking of either yields the same products. The fact that it is about four times as great is due to the much larger distance of one of the linkages from the positively charged end of the molecule; as a rough approximation the specific rate at the peptide linkage farthest from the positively charged nitrogen atom (see k_3, Table I) is about three times as great as that at the nearer linkage. This is very roughly what is to be expected if the difference in the free energies of activation at the two points is to be ascribed to the difference in the electrostatic repulsion suffered by the approaching positively charged ion.

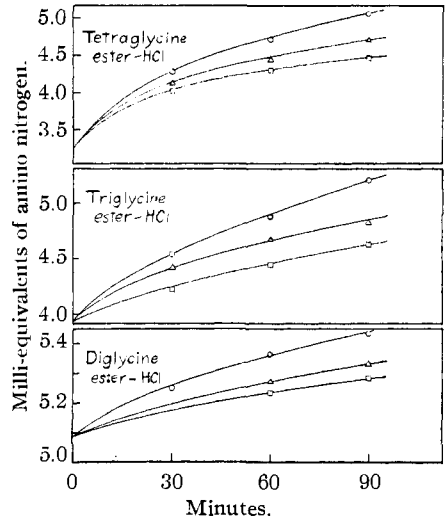

Fig. 4.—O, 99.9% alcohol; △, 99.6% alcohol; □, 98.6% alcohol.

Tetraglycine ester hydrochloride has three peptide bonds at which fission can occur. Since the specific rate of the alcoholysis is nearly the same as that of the triglycine ester it appears that the central linkage is broken with difficulty. The similarity in the specific rates of the tetra- and triglycine esters is analogous to the similarity in the dissociation constants of the free peptides; the peptide bond farthest from the positively charged end of the molecule in the triglycine ester is already so far away that the introduction of another glycine residue has no appreciable influence. As previously explained, the results of

(9) (a) Goldschmidt, *Ber.*, **29**, 2208 (1896); (b) Goldschmidt and Sunde, *ibid.*, **39**, 711 (1906); (c) Goldschmidt and Udby, *Z. physik. Chem.*, **60**, 728 (1907).

the present work are not to be regarded as very accurate, and so the low specific rate of alcoholysis of pentaglycine ester may be partly due to the change in experimental technique which had to be adopted owing to the sparing solubility of the pentaglycine. The increase in the rate of the reaction involving hexaglycine ester hydrochloride from a value of about 0.05 to more than 0.10 appears to be outside the range of experimental error.

It is of interest to recall that in passing from penta- to hexa-glycine the dissociation constant[5] also undergoes an unexpected change, and it is possible that both this and the increase in the specific rate of the alcoholysis are due to a change in the structure of the polyglycine chain when a sixth unit is added. The increased reaction rate may perhaps be due to the breaking of peptide linkages other than the extreme ones; this is, however, not certain since the results could be explained equally well by an appreciable increase of entropy due to a change of structure accompanying the formation of the activated state for the $G_6 \rightarrow G_5 + G_1$ reaction.

On the basis of the arguments presented above, a general parallelism may be expected between the rates of alcoholysis of the polyglycine esters in acid solution and the hydrolysis of the peptides themselves in the presence of either acid or alkali. Some studies[8,10] have been made of the fission of the glycine peptides in acid and alkaline solution. The results, however, do not appear to be very reliable, and so a reinvestigation of the kinetics of hydrolysis of the simpler polypeptides is being undertaken.

Summary

1. The kinetics of the alcoholysis of di-, tri-, tetra-, penta- and hexa-glycine esters have been studied in the presence of hydrochloric acid as catalyst.

2. The specific rate of the first stage of the reaction, which is believed to involve the splitting off of a single glycine residue in each case, increases fourfold from the di- to the tri-glycine ester, is almost constant for the tri-, tetra- and penta-esters, and increases again with the hexa-glycine ester.

3. The change from di- to tri-glycine ester is analogous to that observed in the dissociation constant of glycine and diglycine and is attributed to electrostatic forces; the increase in the rate of alcoholysis observed with hexaglycine ester may be due to a structural change.

4. The fission of the polyglycine esters is shown to be a true alcoholysis, and not a hydrolytic reaction followed by esterification.

(10) (a) Abderhalden and Suzuki, *Z. physiol. Chem.*, **173**, 250 (1928); (b) Levene, *J. Biol. Chem.*, **82**, 167 (1929).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Diffusion of Electrolytes and of the Ions in their Mixtures

BY JEROME R. VINOGRAD AND JAMES W. MCBAIN

Data have been lacking for the diffusion of many of the simplest electrolytes. These are now supplied.

Mixtures also have been studied both experimentally and theoretically with some very striking new results. In contrast to the fairly minor effect of concentration upon single electrolytes are the relatively enormous effects of admixtures with other electrolytes which may bring an ion to a standstill or make the hydrogen travel faster than even a completely freed hydrogen ion would do.

The present studies begin with cases in which all the diffusion is proceeding in the same direction from salt solution into water or more dilute solution. These are especially simple because several of the effects so prominent in the Debye–Hückel theory of conductivity where ions travel in opposite directions are here minimized because they travel together.

We then discuss cases where ions diffuse through buffer salts or against other electrolytes, and show that all are embraced in the principles implicit in the classical equations of Nernst,[1] Arrhenius[2] and Planck.[3] Very much later Debye[4] related diffusion phenomena to Einstein's 1906

(1) Nernst, *Z. physik. Chem.*, **2**, 613 (1888).

(2) Arrhenius, *ibid.*, **10**, 51 (1892).

(3) Planck, *Wied. Ann.*, **39**, 161 (1890); **40**, 561 (1890); *Sitzber. preuss. Akad. Wiss.*, p. 285 (1927); p. 9 (1929); p. 367 (1930); p. 113 (1931). For references to later authors who have published particular forms of these equations see McBain and Dawson, THIS JOURNAL, **56**, 53 (1934), and also T. Theorell, *Proc. Natl. Acad. Sci.*, **21**, 152 (1935).

(4) Debye, *Physik. Z.*, **18**, 144 (1917).