2. A new technique is developed and described.

3. The diffusion coefficients of crystal violet in alcohol–water mixtures are determined.

4. A possible explanation for an observed break in the regularity of the experimental curve is suggested.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

Studies in the Physical Chemistry of Amino Acids, Peptides and Related Substances. V. Influence of Amino Acids, Urea and Alcohol upon the Velocity Constants of Chemical Reactions[1]

BY DANELLA STRAUP AND EDWIN J. COHN

The velocity constants of most chemical reactions are not independent of changes in the medium but vary with the ionic strength and the dielectric constant. The variation with change in salt concentration appears to be explained adequately by Brönsted's[2] theory of reaction rates, which considers the rate proportional to the activity coefficients of the reactants and inversely proportional to the activity coefficient of the critical complex. In the present communication we are concerned with the influence of alcohol, urea and amino acids upon reaction rates. All of these substances profoundly influence the dielectric constant of the medium and their activity coefficients vary in a very different manner from those of electrolytes.

In dilute electrolyte solution activity coefficients, and therefore changes in reaction rate, may be estimated by means of the Debye limiting law. The effect of more concentrated electrolytes or of non-electrolytes may be calculated by the method of Christiansen.[3] This method has been recently discussed by Harned and Samaras,[4] La Mer[5] and Scatchard.[6] The Brönsted–Christiansen and Debye–Hückel theories yield[6]

$$\log \frac{k}{k_0} = \frac{\epsilon^2 Z_A Z_B}{2.303\, DKT}\,\frac{\kappa}{1 + \kappa a} \qquad (1)$$

in which k is the velocity constant in the salt solution, k_0 that in the absence of salt, K is the Boltzmann constant, κ the reciprocal distance proportional to the square root of the ionic strength, and a the distance of closest approach of the ions. The velocity constant should vary, according to equation (1), not only with the valence, Z, and ionic strength, μ, of the electrolytes, but with any change in the dielectric constant[7] of the solution, D, from its value in the standard state, D_0. Signifying by k' the velocity constant at zero ionic strength in a medium having a dielectric constant other than that of the standard state, equation (1) may be written

$$\log \frac{k}{k'} = \frac{Z_A Z_B\, (D_0/D)\, \sqrt{(D_0/D)\mu}}{1 + (a/3)\, \sqrt{(D_0/D)\mu}} \qquad (2)$$

When D is equal to D_0, k' is equal to k_0.

The effect of changing dielectric constant on reactions between ions at zero ionic strength has been calculated[6] as

$$\log \frac{k'}{k_0} = \frac{\epsilon^2 Z_A Z_B}{2.303\ KTa}\left(\frac{1}{D} - \frac{1}{D_0}\right) = \frac{242.3\ Z_A Z_B}{a}\left(\frac{1}{D} - \frac{1}{D_0}\right) \qquad (3)$$

This equation is analogous to the Born–Fajans equation for equilibrium relations.

Amino acids, due to their zwitterionic structure, exert electrostatic forces in solution. Since they do not contribute to the ionic strength, Debye's equation does not apply even in dilute solution. Solutions of amino acids have high dielectric constants and attempts have been made to describe the effect of amino acids on activity coefficients[8] in terms of the Born–Fajans equation. Another treatment of the effect of amino acids is described later on in this paper.

Two types of reactions have been studied: (1) a reaction between a non-electrolyte and an ion, and (2) a reaction between two ions. The thio-

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[1] A preliminary account of this investigation was read to the Society of Biological Chemists [*J. Biol. Chem.*, **105**, Proc. 87 (1934)].

[2] Brönsted, *Z. physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925); Brönsted and Livingston, THIS JOURNAL, **49**, 435 (1927).

[3] Christiansen, *Z. physik. Chem.*, **113**, 35 (1924).

[4] Harned and Samaras, THIS JOURNAL, **54**, 9 (1932).

[5] La Mer, *Chem. Rev.*, **10**, 179 (1932).

[6] Scatchard, *ibid.*, **10**, 229 (1932).

[7] The dielectric constants of the solvents employed have been determined by Wyman [THIS JOURNAL, **53**, 3292 (1931); *ibid* , **55**, 4116 (1933)]. In dilute solution they have been estimated by the equation: $D = D_0 + \delta C$, where D_0 is 78.54 at 25°, δ is 2.8 for urea, 22.7 for α-, and 36 for β-amino acids [Wyman and McMeekin, *ibid.*, p. 908].

[8] Failey, *ibid.*, **54**, 576 (1932).

sulfate ion was employed in both reactions; in the one type in the reaction with uncharged alkyl iodide molecules, in the other with bromoacetate ions, for which there is a positive salt catalysis. Both types of reactions have previously been shown to be bimolecular.

Materials and Methods.—All solutions were made up immediately before starting each experimental run.

Thiosulfate solutions were made from a stock solution of 0.1 *N* sodium thiosulfate which was standardized with weighed samples of resublimed iodine, dried over calcium chloride. A tenth dilution of this solution was titrated against standard iodine. These two standardizations agreed within 0.1%. 0.01 *N* iodine solutions were standardized with arsenic trioxide obtained from the U. S. Bureau of Standards, according to the method of Washburn.[9]

The glycine used was three times recrystallized from water. The urea obtained from the Eastman Kodak Co. was once recrystallized. Methyl iodide of Eastman Kodak and also of Kahlbaum, and ethyl iodide of Kahlbaum were used without further purification. Both preparations of methyl iodide gave the same results.

Reactions were carried out at 25 ± 0.03°. In the reaction with alkyl iodide and thiosulfate, the methyl iodide or ethyl iodide was added to the thiosulfate solutions containing the additional component at 25° from a weight buret. The reaction was carried out in special flasks to allow of pipetting without loss of alkyl halide by volatilization. Some of the experiments with these reactions were repeated using a separate flask for each determination. In these cases a saturated solution of ethyl iodide or a half saturated solution of methyl iodide was added to the thiosulfate solution, taking precaution to avoid loss by volatilization during the transfer of the solutions.

Bromoacetate solutions were made from weighed samples of bromoacetic acid, obtained from Eastman Kodak Co., and dried over sulfuric acid, and titrated with standard sodium hydroxide using phenolphthalein as indicator. The concentration of the sodium bromoacetate was checked by allowing it to react with a three-fold excess of thiosulfate and determining the concentration of thiosulfate remaining when the reaction was completed. The concentration of the sodium bromoacetate solution as determined by weighing, titration with sodium hydroxide and reaction with thiosulfate agreed within 0.5%.

Reaction between Thiosulfate and Alkyl Iodides.—Both salts and amino acids increase the rate of reaction between the bromoacetate and thiosulfate ions, and diminish that between the latter and uncharged alkyl iodides. The experimental error in determining the velocity constant of the latter reaction is greater, due to the tendency toward volatilization of the nonelectrolyte.[10] The values of *k* for this reaction, given in Table I, are the averages of at least three determinations during the run. They are accurate only to two significant figures.

TABLE I

INFLUENCE OF ADDITIONAL COMPONENTS UPON THE VELOCITY CONSTANT OF THE REACTION

$$RI + S_2O_3^{=} \longrightarrow RS_2O_6^{-} + I^{-}$$

	Concn. of additional component, moles per liter	*k*	Log *k*/*k*₀
	Ethyl alcohol		
CH_3I	0.00	1.98	0.000
	1.72	2.52	.104
	3.44	3.45	.241
	5.11	4.92	.395
C_2H_5I	0.00	0.11	.000
	3.44	.18	.214
	5.11	.21	.281
	Urea		
CH_3I	0.00	1.95	0.000
	1.00	2.06	.024
	5.00	2.05	.022
	Glycine		
CH_3I	0.00	1.98	0.000
	.40	1.75	− .054
	.62	1.67	− .074
	1.00	1.50	− .121
C_2H_5I	0.00	0.11	.000
	.40	.10	− .041
	.62	.09	− .087
	Sodium chloride		
CH_3I	1.00	1.32	−0.176
	Potassium chloride		
C_2H_5I	0.00	0.11	0.000
	.10	.10	− .041
	.40	.09	− .087
	1.00	.08	− .138

The addition of glycine to the solution brings about a decrease in the velocity constant for both the reaction of methyl iodide and of ethyl iodide with thiosulfate ion (Fig. 1). The effect of amino acids is less than that of electrolytes, but is of the same order of magnitude, whereas urea has only a slight effect on these reactions. Ethyl alcohol on the other hand brings about a large increase in the velocity constant for both reactions.

In order to test the influence of the dielectric constant upon reaction rates, solutions have been prepared, having the same dielectric constant as water, but different compositions. The values of the velocity constant for the alkyl iodide–thiosulfate reaction in solutions isodielectric with water are given in Table II. The addition of glycine or urea to alcoholic solutions yields lower

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[9] Washburn, THIS JOURNAL, **30**, 31 (1908).

[10] The initial concentration of thiosulfate in these experiments was 0.01 *N*, the initial concentration of alkyl iodide varied from 0.005 to 0.010 *N*.

velocity constants than in the alcohol solutions alone, but the decrease is far smaller than that expected on the basis of proportionality between change in velocity constant and change in dielectric constant.

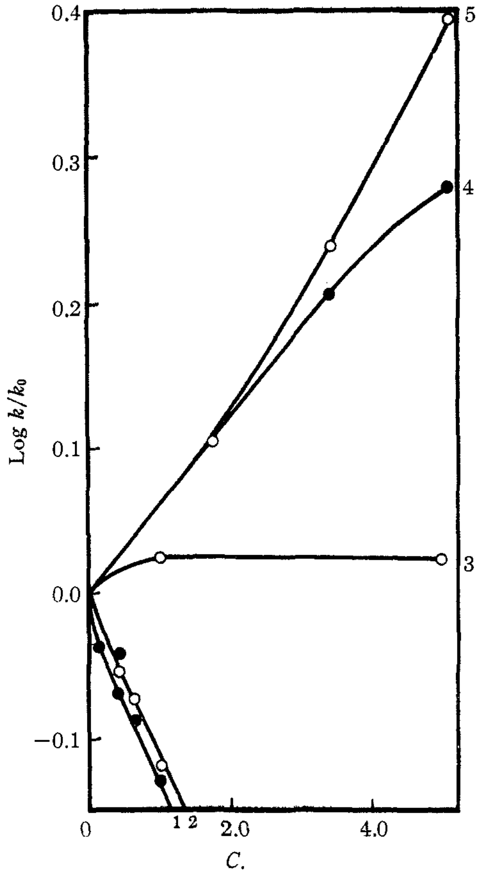

Fig. 1.—Hollow circles represent methyl iodide, solid circles ethyl iodide, in media containing (1) potassium chloride; (2) glycine; (3) urea; (4) and (5) ethanol.

Indeed the effect of glycine or of urea in diminishing the velocity constant is not very different in 20 or 30% alcohol from that in water. The rate of reaction in mixtures of glycine or urea and alcohol appears to depend rather upon specific properties of solute molecules than upon the dielectric constant of the solution.

TABLE II

VELOCITY CONSTANT OF THE REACTION

$RI + S_2O_3^{=} \longrightarrow RS_2O_3^- + I^-$

IN MIXTURES OF KNOWN DIELECTRIC CONSTANT

Medium	D	$1/D-1/D_0$	Log k/k_0
	CH_3I		
20% Alcohol	69.47	+0.0017	+0.241
0.40*m* glycine in 20% alcohol	78.55	.0000	+ .204
0.40*m* glycine in water	87.62	− .0013	− .054
30% Alcohol	64.45	+ .0028	+ .395
0.62*m* glycine in 30% alcohol	78.52	.0000	+ .241
0.62*m* glycine in water	92.61	− .0019	− .074
5.00*m* urea in 30% alcohol	78.55[a]	.0000	+ .353
5.00*m* urea in water	91.07[a]	− .0018	+ .022
	C_2H_5I		
20% Alcohol	69.47	+0.0017	+0.214
0.40*m* glycine in 20% alcohol	78.55	.0000	+ .113
0.40*m* glycine in water	87.62	− .0013	− .041
30% alcohol	64.45	+ .0028	+ .281
0.62*m* glycine in 30% alcohol	78.52	.0000	+ .154
0.62*m* glycine in water	92.61	− .0019	− .087

[a] The urea concentrations were calculated on the basis of $\delta = 2.82$.

Reaction between Thiosulfate and Bromoacetate Ions.—The reaction between bromoacetate and thiosulfate ions has repeatedly been studied. Recently La Mer,[11] La Mer and Fessenden,[12] and Kappanna[13] have shown that the velocity constant of this reaction is influenced by the ionic strength according to the expectation from the theory of Debye and Hückel. On the basis of linear extrapolation in the presence of monovalent cations, La Mer and Fessenden[12] estimate log k_0 to be $\bar{1}.396$. Kilpatrick[14] has employed equation (1) to describe several reaction rates, putting a, for convenience, equal to 3 Å. Accepting La Mer and Fessenden's value for k_0 for the bromoacetate reaction, our measurements yield values of a of 5.30, 5.19, 5.89, 5.67. The intermediate value of 5.6 Å. is employed in subsequent calculations.[15]

Effect of Alcohol.—In striking contrast to its effect upon the reaction between the alkyl iodides and thiosulfate, ethyl alcohol has very little influence on the reaction between thiosulfate and bromoacetate ions. Alcohol produces a very marked change in the dielectric constant of the solution, however, and one might therefore anticipate a large change in velocity constant of the basis of equation (3). The change in the logarithm of the velocity constant of these solu-

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(11) La Mer, THIS JOURNAL, **51,** 3341 (1929).

(12) La Mer and Fessenden, *ibid.*, **54,** 2351 (1932).

(13) Kappanna, *J. Ind. Chem. Soc.*, **6,** 419 (1929).

(14) Kilpatrick, THIS JOURNAL, **56,** 2326 (1934).

(15) La Mer and Fessenden's measurements as well as ours are better described by a still higher value of a, 6.2 Å., and of log k_0, $\bar{1}.398$. On the other hand, Kappanna's measurements in dilute solutions yield $\bar{1}.376$ for log k_0. It is probable that an equation more complicated than (1) should be employed in concentrated salt solutions.

tions with change in the dielectric constant is calculated in Table III, where k^* is the velocity constant of a solution of the same ionic strength, but with no additional component. So considered, the result bears no relation to the expectation.

TABLE III

INFLUENCE OF ADDITIONAL COMPONENTS UPON THE VELOCITY CONSTANT OF THE REACTION

$BrCH_2COO^- + S_2O_3^= \longrightarrow S_2O_3CH_2COO^= + Br^-$

Concn. of additional component[a] C	Velocity constant k	$\frac{\text{Log } k/k^*}{\left(\frac{1}{D} - \frac{1}{D_0}\right)}$	$\frac{\text{Log } k'/k_0}{\left(\frac{1}{D} - \frac{1}{D_0}\right)}$	$\frac{\text{Log } k/k^*}{C}$
Ethyl alcohol, $\sqrt{\mu} = 0.204$				
0.00	0.485			
1.70	.468	−19	− 53	−0.0088
3.41	.473	− 7	− 39	− .0032
5.11	.483	− 1	− 34	− .00039
6.81	.475	− 2	− 35	− .00132
8.52	.476	− 1	− 35	− .00094
Urea, $\sqrt{\mu} = 0.204$				
0.00	0.485			
1.00	.517	−65	− 95	0.028
2.00	.551	−68	− 96	.028
3.22	.596	−72	−102	.028
4.00	.630	−77	−106	.028
5.00	.660	−77	−109	.028
Glycine, $\sqrt{\mu} = 0.204$				
0.00	0.486			
.10	.516	−74	−100	0.26
.20	.539	−65	− 93	.23
.26	.553	−63	− 91	.22
.30	.565	−65	− 92	.22
.40	.588	−63	− 92	.21
.62	.640	−62	− 91	.19
1.00	.744	−65	− 94	.19
Glycine, $\sqrt{\mu} = 0.228$				
0.00	0.516			
.11	.548	−65	− 98	0.24
.21	.580	−70	−101	.24
.42	.635	−65	− 99	.21
Glycine, $\sqrt{\mu} = 0.270$				
0.00	0.548			
.10	.577	−64	−103	0.23
.20	.608	−65	−101	.23
.40	.662	−62	− 99	.21
Glycine, $\sqrt{\mu} = 0.289$				
0.00	0.576			
.10	.599	−47	− 86	0.17
.20	.632	−59	− 97	.21
.40	.685	−58	− 96	.19
α-Alanine, $\sqrt{\mu} = 0.204$				
0.00	0.483			
.11	.513	−65	− 97	0.25
.22	.538	−62	− 93	.21
.44	.600	−66	− 97	.22
α-Alanine, $\sqrt{\mu} = 0.228$				
0.00	0.513			
.22	.570	−61	− 93	0.21
.44	.627	−61	− 93	.20
α-Alanine, $\sqrt{\mu} = 0.289$				
0.00	0.570			
.22	.627	−54	− 87	0.19
.44	.683	−55	− 88	.18
β-Alanine, $\sqrt{\mu} = 0.228$				
0.00	0.517			
.10	.555	−56	− 89	0.31
.20	.586	−51	− 85	.27
.40	.660	−54	− 87	.27

[a] Equal concentrations of the materials were employed in the experiments of $\sqrt{\mu} = 0.204$ and 0.289. In those of $\sqrt{\mu} = 0.228$ the concentration of thiosulfate was double and that of $\sqrt{\mu} = 0.270$ half that of the bromoacetate.

Both our measurements and conclusions regarding the influence of alcohol in this reaction are consistent with those of Kappanna,[13] whose measurements extend up to 80% alcohol and over a wide range of ionic strengths. We have attempted to correct both his measurements and ours for the increased electrostatic forces in media of low dielectric constant by means of equation (2). The estimated values of k' substituted in equation (3) yield values which vary from 53 to approximately 35 in our measurements and to 22 in Kappanna's measurements in 80% alcohol.[16] The expectation, according to equation (3), is 86.6 if a is equal to 5.6 Å. It is perhaps not surprising that the agreement is no better, for other effects than those due to electrostatic forces should unquestionably be considered.

Effect of Urea.—Whereas urea has no appreciable effect upon the velocity constant of the reaction between thiosulfate and an uncharged molecule, it greatly increases the rate of reaction with the bromoacetate ions.[17] Values of log k/k^* for the bromoacetate reaction are negative

(16) Kappanna's measurements are most satisfactorily studied by plotting D/D_0 log k against $\sqrt{(D_0/D)\mu}$. The curve for 80% alcohol is superimposable throughout its length with that for water, but the other curves, especially that for 20% alcohol, are very different.

(17) The dissertation of Mildred Elsie Kamner, Columbia University 1934, has been received since this was written. Miss Kamner has also studied urea, as well as sucrose, glycerol and dioxane. She reports that all of these increase the rate of this reaction, and concludes that "there is no simple relation between the dielectric constant of the solvent and the velocity constant." The ratio log k/k^* calculated from her result with urea at approximately the ionic strengths studied by us, is in excellent agreement with those in Table III. The velocity constant in the presence of dioxane, 0.567, is very close to that reported by Kappanna for the same ionic strength in 80% alcohol, 0.589, and the solutions are approximately isodielectric. The influence of the other substances studied is far smaller even than that of urea, and of a different order than that of the amino acids.

in ethyl alcohol and positive in urea. Since $(1/D - 1/D_0)$ is positive in alcohol, but negative in urea, the ratios have the same sign (Table III). Moreover, the ratios in the case of urea are approximately those predicted by equation (3). Substituting values of k/k^* in this equation yields estimates of a from 6.3 to 7.5 Å., whereas correcting for diminished electrostatic forces at higher dielectric constants by means of equation (2) (k'/k_0) yields values of a from 4.4 to 5.1 Å. The influence of urea upon this reaction is in the direction and of the order to be expected from its effect on the dielectric constant.

Effect of Amino Acids.—The effects of glycine and α-alanine upon the dielectric constant of solutions, and upon the velocity constant of the bromoacetate–thiosulfate reaction are almost identical. Where they have been studied at the same concentration and ionic strength, the influence of α-alanine appears to be slightly smaller than that of glycine, but the effect of β-alanine with its higher dipole moment is very much greater. The changes in velocity constant with changes in dielectric constant are, moreover, of the same order for urea and the amino acids (Table III), though there is a tendency for them to increase with concentration in the presence of urea and generally to decrease in the presence of glycine. The greater influence of β-alanine on the dielectric constant is reflected in a somewhat smaller value of the ratio in the calculations in the third, though not those in the fourth column, which are corrected for the diminished electrostatic forces at higher dielectric constants. The influence of amino acids and urea upon the velocity constant of this ionic reaction thus appears, as a first approximation, to depend upon their influence on the dielectric constant of the solution.

Isodielectric Solutions.—If the rate of the thiosulfate bromoacetate reaction depended only upon change in ionic strength and dielectric constant, k should be the same in mixtures however constituted, having the same dielectric constant as water. The experiments reported in Table IV demonstrate that this is too simple a postulate in reactions between ions, as well as in reactions between ions and uncharged molecules (Table II).

A slight difference in the effect of urea and glycine on the bromoacetate reactions may be mentioned. The velocity constants are smaller in alcoholic than in aqueous solutions containing the same concentration of urea, but are greater for glycine in alcohol than in water, an effect interpretable in terms of increased electrostatic forces in alcoholic solutions.

TABLE IV

VELOCITY CONSTANT OF THE REACTION $BrCH_2COO^- + S_2O_3^= \longrightarrow S_2O_3CH_2COO^- + Br^-$ IN MIXTURES OF KNOWN DIELECTRIC CONSTANT

Medium	k	D	Log k/k^*	Log k'/k_0
0.4m Glycine at $\sqrt{\mu} = 0.289$				
Water	0.685	87.62	0.076	0.126
20% Alcohol	.724	78.55	.100	.100
0.4m Glycine at $\sqrt{\mu} = 0.204$				
Water	0.588	87.62	0.083	0.121
20% Alcohol	.604	78.55	.095	.092
0.62m Glycine at $\sqrt{\mu} = 0.204$				
Water	0.640	92.61	0.120	0.176
30% Alcohol	.702	78.52	.160	.157
3.22m Urea at $\sqrt{\mu} = 0.204$				
Water	0.596	87.62	0.089	0.128
20% Alcohol	.574	78.55[a]	.073	.073
5.00m Urea at $\sqrt{\mu} = 0.204$				
Water	0.666	92.64	0.138	0.191
30% Alcohol	.588	78.55[a]	.083	.083

[a] These solutions may have had slightly lower dielectric constants. Urea concentrations were calculated on the basis of $\delta = 2.82$.

The effect of amino acids on the velocity constant of this reaction is less than that of electrolytes, but is of the same order of magnitude. In order to facilitate comparison the values of k in the presence of electrolytes estimated by La Mer and Fessenden[12] and by Kiss[18] have been plotted in Fig. 2 against the concentration beyond $\sqrt{\mu}$ equal to 0.2, at which k^* equals 0.486.[19] Although the influence of amino acids and of salts is of the same order of magnitude, the influence of electrolytes varies as the square root of the ionic strength, whereas that of urea and of amino acids varies as the first power of the concentration. The influence of amino acids is therefore described by the ratio $(\log k/k^*)/C$. All our measurements are so calculated in Table III and show that the change in velocity constant with change in amino acid concentration increases (1) with decreasing values of C, (2) of μ, and (3) with increasing values of the dipole moment of the amino acid.

The Kirkwood Equation.—The lack of agreement between change in velocity constant and

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(18) Kiss, *Z. anorg. allgem. Chem.*, **209**, 236 (1932).

(19) The data of Kiss (18) on the effect of electrolytes of high concentrations do not give the actual concentration of the reactants, and the ionic strength due to the reactants is not taken into account here.

change in dielectric constant is not limited to rates of reactions but occurs in any consideration of activity coefficients. Kirkwood has recently developed a theoretical equation for the activity coefficients of amino acids[20] in terms of the distance, R, separating the positive and negative charges of the zwitterion, the mean distance of closest approach of zwitterion and ion, a, the concentration of the former, C, and the ionic strength of the latter, μ. Assuming that the relative distributions of the ions of valence Z_A and Z_B is determined by electrostatic forces, both in the presence and absence of zwitterions, Kirkwood has developed equations[21] relating change in velocity constant to amino acid concentration. Ignoring multipole moments of higher order than the dipole, his equation valid only at low zwitterion concentration becomes

$$\frac{\log k/k^*}{C} = \frac{3\pi N\epsilon^4 Z_A Z_B}{2303\,(DKT)^2}\,\frac{R^2}{a}\,\frac{1+\kappa a/2}{(1+\kappa a+\kappa^2 a^2/3)^2} \tag{4}$$

Substituting numerical values at 25° yields

$$\frac{D/D_0 \log k/k^*}{(D_0/D)\;C} = 0.125 Z_A Z_B \frac{R^2}{a} \times \frac{1+0.165a\sqrt{(D_0/D)\mu}}{(1+0.329a\sqrt{(D_0/D)\mu}+0.036a^2\,(D_0/D)\mu)^2} \tag{5}$$

Glycine.—The value of R for glycine has been estimated to be 3.17 Å. by Kirkwood[20] on the basis of our measurements upon the solvent action of lithium chloride on glycine in alcohol–water mixtures[22] and to be 3.1 Å. by Scatchard and Prentiss[23] on the basis of freezing point measurements. The distance of closest approach, a, may be taken as the sum of the radius of the glycine, 2.82, estimated from its molal volume[24] and one-half the value of a for the ions estimated by equation (1). The valence of the reacting ions being two and one, the expression $0.125\,Z_A Z_B R^2/a$ becomes 0.44 if a for the ions be taken as 5.6 Å. and the influence of amino acids on the rate of reaction at the ionic strengths becomes

$\sqrt{\mu}$	$\left(\frac{\text{Log } k/k^*}{C}\right)$ Obs.	$\left(\frac{0.44\,(1+0.93\sqrt{\mu})}{(1+1.85\sqrt{\mu}+1.14\,\mu)^2}\right)$ Calcd.
0.204	0.26	0.26
.228	.24	.24
.270	.23	.22
.289	.21	.21

The agreement with the highest results recorded in Table III is considerably greater than is warranted by the simplifying assumptions on which the theory and calculations are based. A larger value for a, or a smaller value of R, would render the agreement less satisfactory.

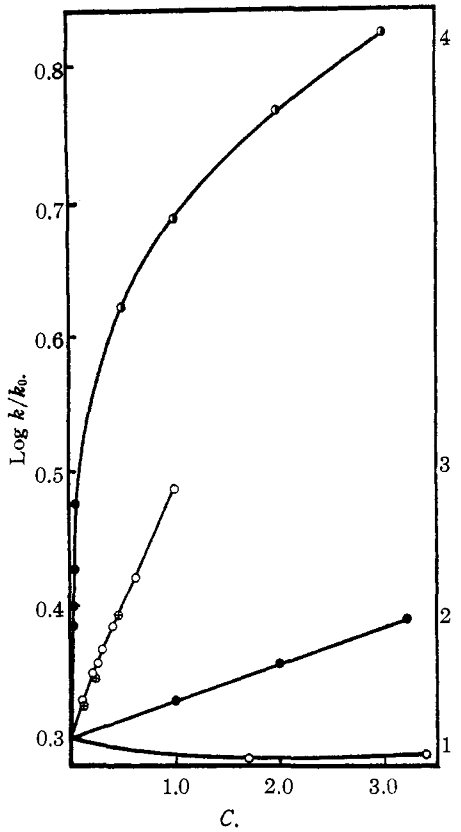

Fig. 2.—Concentration of reactants, $a = b$ = 0.010: (1) ethanol, ○; (2) urea, ●; (3) glycine, ○ and α-alanine, ⊕; (4) sodium salts, La Mer and Fessenden, ●; and Kiss, ◑.

Alanine.—The radius of both α- and β-alanine is somewhat greater than that of glycine, 3.08 Å.[24] and so is the dipole moment of the β-alanine. Assuming the amino acids to be rods leads to a value of R of 4.4 Å., whereas the assumption that the increment in dielectric constant, δ, increases as the square of R[25] leads to 3.9 Å. for this constant when the amino group is in the β-position.

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(20) Kirkwood, *J. Chem. Physics*, **2**, 351 (1934).

(21) We are indebted to Dr. Kirkwood for developing this very interesting consequence of his theory. On the basis of the Brönsted–Christiansen theory (with the assumption that the distance of closest approach of the ions in the so-called critical complex is the same as the mean distance of closest approach of the zwitterion to the ions) he obtains for low amino acid concentrations

$$\log_{10}\frac{k}{k^*} = \frac{2\pi N Z_A Z_B \epsilon^2}{2303\,(DKT)^2}\,C\sum_{n=1}^{\infty}\frac{(2n+1)\,Q_n}{(2n-1)(n+1)^2\,a^{2n-1}}\,\frac{(2n+1)K_{n-1}K_{n+1}-(2n-1)K_n^2}{K_{n+1}^2}$$

the symbols having the same significance as in his paper (20).

(22) Cohn, *Naturwissenschaften*, **20**, 663 (1932).

(23) Scatchard and Prentiss, THIS JOURNAL, **54**, 2696 (1932).

(24) Cohn, McMeekin, Edsall and Blanchard, *ibid.*, **56**, 784 (1934).

(25) Wyman, *ibid.*, **56**, 536 (1934).

	$\left(\frac{0.0425\ R^2\ (1 + 0.97\ \sqrt{\mu})}{(1 + 1.93\ \sqrt{\mu} + 1.25\ \mu)^2}\right)$		
	α-Alanine	β-Alanine	
$\sqrt{\mu}$	$R = 3.1$	$R = 3.9$	$R = 4.4$
0.228	0.22	0.35	0.44

The observed values for α-alanine (Table III) are 0.21 and for β-alanine 0.31 at this ionic strength and the lowest amino acid concentration.

Kirkwood's equation should hold only for very dilute solutions, whereas the concentrations of the glycine studied in alcohol–water mixtures were appreciable (Table IV). None the less the following comparison can be made with aqueous solution containing the same glycine concentration, and having the same ionic strength (Table III).

Volume fraction alcohol, v_2	$\sqrt{\mu}$	Amino acid concn., C	$\left(\frac{\text{Log } k/k^*}{C}\right)$	$\left(\frac{D/D_0 \log k/k^*}{(D_0/D)C}\right)$
0.0	0.204	0.40	0.21	0.26
.2	.204	.40	.24	.24
.0	.289	.40	.19	.24
.2	.289	.40	.25	.25
.0	.204	.62	.19	.27
.3	.204	.62	.26	.26

The right-hand expression of equation (2) changes very little with change in dielectric constant. Thus the calculated value at infinite dilution of glycine at $\sqrt{\mu} = 0.204$ is 0.25 for 20% alcohol as compared with 0.26 for water.

Urea.—Whether or not urea is a zwitterion remains a controversial question and is considered elsewhere.[26] On the assumption[25] that the increment in dielectric constant, δ, increases as the square of the dipole distance, and that the radius of urea is 2.6 Å.[24] a becomes 5.4 Å. and the right-hand side of equation (5) yields 0.033 at the ionic strength at which urea has been studied. The observed ratio was 0.028 (Table III). The calculated effect of urea in 20 and 30% alcohol is 0.031. The observed values are 0.023 and 0.015.

Kirkwood's equation was developed on the assumption that the dipole moment is large relative to that of a solvent molecule, and this condition does not obtain for urea. In the cases for which it was intended the Kirkwood equation appears to describe the effect of zwitterions as satisfactorily as does the Debye equation that of ions.

Summary

1. The rates of reaction of thiosulfate with uncharged alkyl iodide molecules and with bromoacetate ions have been studied.

2. The rates of reaction with the uncharged molecule are increased with alcohol and to a small extent by urea, and decreased by ions and by amino acids.

3. The rate of reaction with ions is increased by salts, amino acids and urea and but slightly influenced by alcohol.

4. Whereas salts increase the logarithms of the velocity constant proportionately with the square root of the concentration, the effect of amino acids and urea varies with the concentration.

5. Both urea and the amino acids increase the dielectric constant of water proportionately with the concentration. That the influence upon the rate of reaction is not due merely to change in dielectric constant is indicated by the effect of alcohol, and of urea and glycine in alcoholic solutions isodielectric with water.

6. Kirkwood's equation for the activity coefficients of the amino acids extended to apply to rates of reaction satisfactorily describes the observed results in terms of the valence of the reactants, the dimensions of ions and amino acids and the dipole moments of the amino acids.

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[26] Cohn, "Annual Review of Biochemistry," 1935, Vol. IV, p. 93.