TABLE III

HEATS OF REACTION OF KETENE WITH DIFFERENT ALCOHOLS

1.0 cm. of capillary, 2.641 Cal.: *M*, moles of ketene added; *D*, expansion of mercury in capillary.

Alcohol	*M*	*D*, cm.	*H*
Methyl	0.001240	17.57	36.8
Methyl	.001347	19.07	36.78
Methyl	.001213	17.39	37.23
		Mean	36.93
Ethyl	.001772	24.75	36.28
Ethyl	.001734	24.30	36.40
Ethyl	.001907	26.91	36.65
		Mean	36.44
n-Propyl	.001479	20.26	35.59
n-Propyl	.001629	21.93	34.98
n-Propyl	.00281	31.09	35.41
		Mean	35.32
Isopropyl	.001371	18.79	35.61
Isopropyl	.001929	26.87	36.19
Isopropyl	.001565	21.62	35.93
		Mean	35.91
n-Butyl	.001179	16.06	35.39
n-Butyl	.001863	25.03	34.90
n-Butyl	.001543	20.86	35.05
		Mean	35.11
s-Butyl	.002420	32.36	34.72
s-Butyl	.002546	33.89	34.57
s-Butyl	.002413	31.87	34.31
		Mean	34.53
Isobutyl	.001390	18.36	34.30
Isobutyl	.002248	29.87	34.51
Isobutyl	.002166	28.60	34.30
		Mean	34.37
t-Butyl	0.002960	27.05	23.74
t-Butyl	.002625	23.75	23.50
t-Butyl	.002542	22.75	23.25
		Mean	23.49

difference is not much greater than our experimental error. On the other hand, the heat of reaction of tertiary butyl alcohol is about 11 Cal. lower than that of the others. There was no perceptible odor of the polymer from the solution in the calorimeter after the experiment with tertiary butyl alcohol.

Summary

The heat of the reaction between ketene and dilute aqueous sodium hydroxide was measured; from this measurement we have calculated the heat of formation of ketene as: 2 C(graphite) + H_2(gas) + $^1/_2O_2$ (gas) = CH_2CO (gas) + 14.78 Cal.

The heat of reaction between ketene and different aliphatic alcohols was measured. The normal alcohols methyl, ethyl, propyl, butyl and isobutyl gave the values 36.93, 36.44, 35.32, 35.11 and 34.37 Cal. per mole, respectively. The secondary alcohols isopropyl and *s*-butyl gave the values 35.91 and 34.53 Cal. per mole, respectively. *t*-Butyl alcohol gave the much lower value of 23.49 Cal. per mole.

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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. II. The Solubility of α-Amino Acids in Water and in Alcohol–Water Mixtures

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I. **Introduction.**—Amino acids and proteins although not electrolytes, bear positive and negative charges, separated by a considerable distance, even when the molecule as a whole is electrically neutral. The powerful electric fields surrounding the charged groups give rise to important interactions with neighboring molecules and ions. Hence their behavior is in many respects strikingly similar to that of strong electrolytes. Besides these charged groups, however, the proteins and amino acids contain hydrocarbon chains and various ring structures found in other organic compounds. The volumes and the specific chemical characters of these groups also profoundly affect their behavior. In attempting to characterize amino acids and proteins in terms of their composition and structure, we can neglect neither the nature of the chemical groups that they contain, nor the electrical fields of force to which their neutral molecules give rise. In so far as the molecules are small in comparison with the charge that they bear, these substances will resemble electrolytes rather than non-electrolytes in their general behavior. In so far as the molecules are large and bear but a small number of electrical charges, their behavior will depend largely upon atomic configurations. At the one extreme, we have the smallest of the amino acids,

glycine, like such salts as sodium and potassium chloride or sulfate, very soluble in water, but insoluble in alcohol; at the other, such molecules as formyl leucine or the prolamines, which are more soluble in alcohol or alcohol–water mixtures than in water.

In this and in subsequent communications we shall describe a systematic investigation of the behavior of the amino acids and certain amino acid compounds in water, in alcohol–water mixtures and in alcohol–water mixtures containing neutral salts. The solvents have been chosen to range from alcohol to strong electrolyte solutions, so as to disclose those properties of the amino acids which depend respectively upon their charged condition and upon their chemical composition.

II. Methods and Materials.—Solubility was determined by the procedures that we have generally employed. A large excess of the saturating body was equilibrated with the solvent in a shaking machine at 25° for periods of from twelve to forty-eight hours. The shorter time was found adequate for equilibrium to be obtained and no subsequent change in solubility was detected. Generally equilibration lasted from eighteen to twenty-four hours. At the end of that time the solutions were filtered and the precipitates again equilibrated with fresh solvent for another twenty-four hours. The filtrates were weighed, dried in the oven and again weighed, so that solubility was determined as weight per cent. Estimates of the solubility of amino acids based upon nitrogen analysis are generally somewhat smaller[1] and have been employed only for solubility in 90% and in absolute alcohol. Only when the analyses upon successive days demonstrated constant solubility were the measurements considered satisfactory. In the few cases in which the solubility of an amino acid in successive portions of the same solvent was not found to be constant, it was assumed that the amino acid had not been sufficiently purified. Upon adequate recrystallization, sometimes under different conditions than those originally employed, preparations were obtained in which solubility was found to be independent of the time of equilibration or of the amount of saturating body, and was constant in the repeated filtrates until the saturating body had been exhausted.

Since the analyses were generally made in duplicate on two or three successive days, the results reported are the averages of at least four analyses. The measurements made upon glycine by the gravimetric method are reported in Table I as an example of the procedure followed and of the results obtained.

TABLE I

SOLUBILITY OF GLYCINE IN ALCOHOL–WATER MIXTURES AT 25°

Vol. fr. alc. in solvent, v_2	0.00	0.05	0.10	0.15	0.20	0.40	0.60	0.80
Density of solvent	.9971	.9901	.9935	.9774	.9717	.9447	.9051	.8550
Density of solution	1.0831	1.0646	1.0464	1.0307	1.0140	.9611	.9107	.8598
Soly., g. per 1000 g. soln.								
2d soln. satd.	200.2	172.8	146.6	121.8	99.62	39.75	12.91	2.41
3d soln. satd.	199.8	173.4	146.6	121.5	99.58	39.50	13.01	2.44
4th soln. satd.	199.9	173.2	146.1	121.4	99.13			2.44
Average:	200.0	173.1	146.4	121.6	99.44	39.62	12.96	2.43
Soly., g. per liter	216.6	184.3	153.2	125.3	100.8	38.08	11.80	2.09

The method of determining solubility is described before the method of purifying the amino acids since we have found solubility to be the most sensitive criterion of purity.

Purification has varied depending upon the solubility in water and in other solvents. The amino acids have been either Eastman Kodak or Hoffmann–LaRoche products. Generally both have been studied. Three crystallizations have been considered necessary for purification, generally one from 50% alcohol and two from water. The most soluble and insoluble fractions have been discarded. Our criteria of purity have been the composition of the substance and the solubility of preparations or fractions.

Glycine, α-alanine, the two aminobutyric acids and *dl* valine and leucine yielded homogeneous products when so purified, whose ash never exceeded 0.01%. The ash of our norleucine (α-amino-*n*-caproic acid) was 0.04%. The optically active amino acids obtained were less satisfactory. *d*-Valine crystallized once from water and twice from 60% methyl alcohol had an optical rotation of $(\alpha)_D^{25°}$ +27.7° when dissolved in 20% hydrochloric acid. Its solubility dimin-

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

ished in successive portions of solvent, however, yielding in water (2) 83.56, (3) 82.85 and (4) 81.50 g. per liter. Difficulty was also encountered in obtaining *l*-leucine preparations which would give the same, or constant, solubility.

(a) *l*-Leucine obtained from Eastman Kodak Co. was twice crystallized from water and dried. Its solubility in water was approximately 24.28 g. per liter for the first three days. The optical rotation of this preparation was $[\alpha]_D^{25}$ +15.7° in 20% hydrochloric acid. No observable ash was obtained from 0.9468 g.

(b) Exhaustive extraction of an Eastman Kodak Co. preparation comparable to the above revealed a pronounced decrease in solubility. Saturation of successive portions of solvent yielded (2) 24.19. (3) 24.15. (4) 23.04. (5) 22.56 g. per liter.

(c) *l*-Leucine obtained from Hoffmann–LaRoche Co. was crystallized once from 50% alcohol and twice from water. This leucine gave a solubility in water of (1) 22.52. (2) 22.40 and (3) 22.14 g. per liter. When the first day was discarded without analysis and the experiment was carried one day longer, the solubility in water was (2) 22.6. (3) 22.2. (4) 21.4 g. per liter. The optical rotation of this preparation was $[\alpha]_D^{25}$ +16.6° at 25° in 20% hydrochloric acid.

(d) *l*-Leucine from Hoffmann–LaRoche Co., crystallized once from 50% alcohol and twice from water, yielded a constant solubility in water of 22.46 g. per liter provided a large amount of saturating body was present. This preparation gave a rotation of $[\alpha]_D^{25}$ +15.8° in 20% hydrochloric acid.

Sano[2] found the solubility of *l*-leucine to be 24.24 g. per liter at 25°. His preparation had an optical rotation of $[\alpha]_D^{15}$ +17.75° in 20% hydrochloric acid. Schmidt[3] found the solubility to be 24.4 g. per 1000 g. of water at 25°, with a preparation having a rotation of $[\alpha]_D^{20}$ +15.7°. The optical rotation of *l*-leucine was reported by Ehrlich[4] to be $[\alpha]_D^{20}$ +15.7° in 20% hydrochloric acid. He found that leucine is commonly contaminated with iso-leucine, which has a higher optical rotation. Fischer[5] obtained the value of $[\alpha]_D^{20}$ +15.59° in 20% hydrochloric acid for *l*-leucine prepared from its benzoyl derivative.

The solubilities and densities of the amino acids studied are compared with values reported in the literature in Table II.

The densities of solutions were always determined after solubility measurements indicated that equilibrium had been established. Generally densities were determined on two different solutions. They are reported only to four decimal places, whereas the measurements upon which the molal volumes are based were made to five decimal places. The apparent volume occupied by solvent and solute may be calculated either from the densities or from the product of

(2) Sano, *Biochem. Z.*, **168**, 14 (1926).
(3) Dalton and Schmidt, *J. Biol. Chem.*, **103**, 549 (1933).
(4) Ehrlich, *Biochem. Z.*, **1**, 8 (1906).
(5) Fischer, *Ber.*, **33**, 2370 (1900).

TABLE II

SOLUBILITY OF AMINO ACIDS IN WATER

Where no reference is given, the results are from this Laboratory. An asterisk denotes that results of other laboratories have been recalculated on the basis of our densities.

Ref.	Temp., °C.	Density of satd. soln.	Solubility: G. per 1000 g. water	Solubility: G. per liter of soln.	Solubility: Moles per liter of soln.
		Glycine			
(6)	20			196.1	2.613
(7)	21			196.4	2.617
(3)	25	1.0828	249.9	216.5	2.885
(8)	25		253.1	218.8*	2.915
	25	1.0831		216.6	2.886
		dl-α-Alanine			
(7)	21			138.7	1.557
(3)	25	1.0434	167.2	149.5	1.679
(8)	25		165.8	148.4*	1.666
(9)	25	1.0421		147.5	1.656
	25	1.0432		147.8	1.660
		dl-α-Amino-*n*-butyric acid			
	25	1.0456		185.6	1.800
		dl-α-Aminoisobutyric acid			
	25	1.0312		137.12	1.330
		d-Valine			
	25	1.0148		82.63	0.706
		dl-Valine			
(3)	25	1.0121	70.9	67.0	0.572
(8)	25		74.41	70.1*	.599
	25	1.0120		66.9	.571
		l-Leucine			
(7)	23			22.2	0.169
(3)	25	1.00146	24.26	23.72[a]	.181
			24.26	23.71*	.181
(2)	25			24.24	.185
	25	1.0012		24.28	.185
	25	1.0012		22.46	.171
		α-Amino-*n*-caproic acid (*dl*-Norleucine)			
(10)	23			11.5	0.0877
(3)	25		11.49	11.35*	.0865
(8)	25		11.82	11.67*	.0890
	25	0.9991		11.36	.0866
		dl-Leucine			
(6)	20			9.72	0.0741
(6)	20			9.84	.0750
(3)	25		9.91	9.80*	.0748
(8)	25		11.81	11.67*	.0890
	25	0.9988		9.75	.0744

[a] This density of Schmidt does not refer to his saturated solution, but to a solution containing 23.97 g. of *l*-leucine.

(6) Pfeiffer and Würgler, *Z. physiol. Chem.*, **97**, 128 (1916).
(7) Pfeiffer and Angern, *ibid.*, **188**, 180 (1924).
(8) Dunn, Ross and Read, *J. Biol. Chem.*, **103**, 579 (1933).
(9) Holleman and Antusch, *Rec. trav. chim.*, **13**, 276 (1894).
(10) Kudielka, *Monatsh.*, **29**, 351 (1908).

the concentration and the apparent molal volumes.[11] Although the latter increases with increase in concentration and decreases in alcohol–water mixtures, the two procedures give almost identical results.

Neither density determinations, apparent molal volumes, nor partial molal volumes yield adequate estimates of the volume occupied, respectively, by the solvent and the solute, for the positive and negative charges of amino acids result in electrostriction of the solvent, estimated in a previous communication to be 13.3 cc. per mole for α-amino acids at 25°.[12] The volume occupied by the amino acid may be considered equal to the apparent molal volume in dilute solution increased by this amount, since the apparent molal volume, Φ, varies with the concentration only in α-amino acids of short hydrocarbon chains. For glycine $\Phi = 42.8 + 1.52\sqrt{C}$, and for α-alanine $60.4 + 0.84\sqrt{C}$.

III. Density in the Solid State.—The solubility in water of an uncombined substance is an important constant, characterizing and quantitatively defining certain of its inherent properties. It depends, however, not only upon properties of the liquid phase, but also upon those of the substances in the solid state. The forces binding molecules in the crystal lattice influence solubility as well as the attractive and repulsive forces between solvent and solute. When the energy of separating the molecules of an amino acid from each other in the solid state differs widely from that of separating the molecules of other amino acids, this will also be reflected by solubility measurements. The higher solubility of α-amino-*n*-butyric acid than alanine[1] may be due to the lower crystal lattice energy of the larger amino acids. Of the two aminobutyric acids the normal amino acid is the more soluble and has a smaller density and larger molal volume in the solid state.

	α-Aminoisobutyric acid	α-Amino-*n*-butyric acid
Density in solid state	1.278	1.231
Φ in solid state	80.7	83.8
Φ in dilute soln.[12]	78.1	76.5
Solubility: moles per liter	1.330	1.800

The smaller apparent molal volume of most amino acids in solution than in the solid state has been ascribed to electrostriction of the solvent due to the charged $-NH_3^+$ and $-COO^-$ groups. The high densities of the solid are also related to close packing of the charged molecules in the crystal lattice.

Comparison is facilitated by subtracting from the apparent molal volume a constant amount for each CH_2 group. For convenience the same amounts in the solid and liquid state have tentatively been adopted. The remainder cannot be considered to yield the volume of the terminal groups, but rather to measure packing effects in the crystal. These appear to be closely similar for many amino acids, among them glycine and norleucine, which have, respectively, the shortest and longest hydrocarbon chains.

	Glycine	*dl*-α-Alanine	*d*-Valine	*dl*-Norleucine
Density in solid state	1.607	1.424	1.230	1.174
Φ in solid state	46.7	62.5	95.2	111.7
Φ—16.3 $(CH_2)_n$ in solid state	30.4	29.9	30.0	30.2
Soly.. moles per liter	2.886	1.660	0.706	0.0866

Since these amino acids appear to be packed equally closely, and since their solubilities in alcohol are not very different, it is presumably the length of the hydrocarbon chain that diminishes solubility in water. Solubility appears to diminish at the least with the second power of the molal volume.

Among isomeric α-amino acids the greater the volume in the solid state, the greater the solubility in water. Thus *l*-leucine is less dense and more soluble and *dl*-leucine denser and less soluble than norleucine. *dl*-Valine is also less soluble and much denser than its optically active isomers. Indeed alone among the amino acids, this substance appears to occupy less space in the solid state than in solution.

	dl-Valine	*dl*-Leucine	*l*-Leucine
Density in solid state	1.316	1.191	1.165
Φ in solid state	89.0	110.1	112.6
Φ—16.3 $(CH_2)_n$ in solid state	23.8	28.6	31.1
Soly.. moles per liter	0.571	0.0744	0.185

The solubilities of amino acids of high dipole moments are far greater than those of α-amino acids, even when they are packed with equal density in the solid state. The density of β-alanine is 1.404, as compared with 1.401 for *d*-α-alanine[3] and 1.424 for *dl*-α-alanine. None the less, the solubility of β-alanine in water is more than three times that of the less polar molecule. This effect is particularly striking in the larger amino acids, where the influence of the hydro-

(11) Cohn, *Science*, **79**, 83 (1934).

(12) Cohn, McMeekin, Edsall and Blanchard, THIS JOURNAL, **56**, 784 (1934).

carbon chain in diminishing solubility is entirely overcome. The densities of α- and ϵ-aminocaproic acids in the solid state are identical, namely, 1.174, but the solubility in water of the more polar molecule is 3.84 moles per liter, or over forty times that of the corresponding α-amino acid. The crystal lattice energy thus depends upon two factors; the closeness of packing, and the magnitude of the dipole moment.

IV. Dielectric Constant of Solutions.—The polarity of molecules and their dielectric behavior are important for solubility studies in two respects. First, polar molecules are in general most soluble in polar solvents, and non-polar molecules in non-polar solvents. Second, the electrical forces which so profoundly affect the solubility of ions and zwitterions are inversely proportional to the dielectric constant of the medium, which is in turn a function of the polarity of the molecules in the solution. Amino acids because of their zwitterionic nature are probably the most highly polar molecules known. Their dipole moments cannot be estimated exactly at present, but are of the order of magnitude of 15×10^{-18} e. s. u. for the α-amino acids[13,14] as compared with 6×10^{-18} for *o*-dinitrobenzene, the most polar molecule recorded in Smyth's tables.[15] In consequence of their high dipole moment they greatly increase the very high dielectric constant of water, a property possessed by only a few other molecules such as urea and formamide.

The investigations of Hedestrand,[16] Devoto,[17] and Wyman and McMeekin[18] have not only established this fact, but have demonstrated that a simple linear relation exists between the dielectric constant, D, of the solution and the concentration, C, of the amino acid.

$$D = D' + \delta C \qquad (1)$$

where δ is the increment in dielectric constant per mole of solute and D' is the dielectric constant of the pure solvent as reported by Wyman.[19] There are minor discrepancies in the values of δ reported, due perhaps to differences in purity of material and methods of measurement. For our purpose it will suffice to use the intermediate value of 22.7 for α-amino acids, which is so chosen that increased by 13.3 for each additional carbon atom separating the positive from the negative charge, the results reported by these investigators for amino acids of higher dipole moments are also described.

The rule defined by equation (1) has been extended by Wyman and McMeekin[18] to the influence of amino acids upon the dielectric constant of alcohol–water mixtures. The increment, δ, proves to be much the same for the influence of glycine upon water, alcohol–water mixtures and other solvents. Since the solubility of the amino acids greatly decreases in alcohol–water mixtures, the dielectric constant in such solutions approaches that of the solvent, and no serious error will be introduced if we employ the same value of δ for all α-amino acids in all the solvents studied until such time as the secondary discrepancies between the results reported have been reinvestigated.

V. Electrostatic Forces.—The solubility of a zwitterion, like that of an electrolyte, cannot be measured directly in the absence of electrical fields of force. If the activity be taken equal to the mole fraction in an infinitely dilute solution of the amino acid in water, then in general a will not equal N in a saturated solution. The deviation may be characterized by an activity coefficient

$$f = \frac{a}{N} = \frac{N_\infty}{N} \qquad (2)$$

in which N is the measured solubility expressed as mole fraction, and N_∞ the hypothetical solubility in the absence of any disturbing forces.

Born and Fajans in 1920 considered the change in free energy involved in the transfer of ions from an infinitely dilute gas to an infinitely dilute aqueous solution, and formulated an equation which may be written

$$\bar{F}^0 - \bar{F}^{\text{gas}} = \frac{N\epsilon^2 z^2}{2b}\left(\frac{1}{D^{0\prime}} - 1\right) \qquad (3)$$

in which ϵ is the elementary charge of the electron, z the valence of the ion, b its radius, and N Avogadro's number. If the transfer is from water to some medium other than a vacuum which has the dielectric constant, D, this equation becomes

$$\bar{F} - \bar{F}^0 = \frac{N\epsilon^2 z^2}{2b}\left(\frac{1}{D'} - \frac{1}{D^{0\prime}}\right) \qquad (4)$$

Debye and McAulay[20] employed this equation in their study of mixed solvents. They followed

(13) Wyman, THIS JOURNAL, **56**, 536 (1934).
(14) Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934).
(15) Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Company, New York, 1931.
(16) Hedestrand, *Z. physik. Chem.*, **135**, 36 (1928).
(17) Devoto, *Gazz. chim. ital.*, **60**, 520 (1930); **61**, 897 (1932); **63**, 50 (1933).
(18) Wyman and McMeekin, THIS JOURNAL, **55**, 915 (1933).
(19) Wyman, *ibid.*, **53**, 3292 (1931).
(20) Debye and McAulay, *Physik. Z.*, **26**, 22 (1925).

Born in regarding the ions as electrical spheres of radius b. The solution outside this radius b was treated as continuous and of uniform dielectric constant.

Scatchard and Kirkwood[21] have extended Debye's treatment of ions to the case of zwitterions, in part as the result of discussions in the seminar of this department. They treat the zwitterion as a molecule made up of two spheres of radius b, whose centers are separated by a distance R ($R \geqq 2b$). Both R and b are independent of the medium. In one sphere is a charge ϵz, and in the other a charge $-\epsilon z$, both with spherical symmetry. The solutions are so dilute that the mutual interaction of two zwitterions may be neglected. If the charges be removed and the molecule torn apart so that the two spheres are an infinite distance apart, the work of recharging the two spheres is given by the Debye theory. The additional electrical work is that necessary to bring the two spheres from an infinite distance to the distance R. On these assumptions they have developed an equation for zwitterions comparable to equation (4) for ions.

$$F_{es} - F^0_{es} = N\epsilon^2 z^2 \left(\frac{1}{b} - \frac{1}{R}\right)\left(\frac{1}{D'} - \frac{1}{D^{0'}}\right) \qquad (5)$$

The change in partial free energy of an ion with change of dielectric constant is determined only by the valence of the ion and its radius. The change for a zwitterion is determined not only by these, but also by the distance separating the positive and negative charges. The greater this distance, that is to say, the larger the electric moment of the dipole, the larger the change in activity coefficient for a given change in dielectric constant.

Kirkwood[14] has recently developed a treatment for a model probably resembling actual zwitterions more closely. The molecule is represented by a single sphere, whose radius we shall again call b. R again is the distance between the two charges, and ϵz and $-\epsilon z$ their magnitudes. If the two charges are equidistant from the center, $(1/b - 1/R)$ of the preceding equation is replaced by

$$\frac{3R^2}{4b^3}\left\{1 + \frac{10}{3}\left(\frac{l}{b}\right)^2 + 7\left[\left(\frac{l}{b}\right)^4 - \frac{1}{8}\left(\frac{l}{b}\right)^2\left(\frac{R}{b}\right)^2 + \frac{1}{96}\left(\frac{R}{b}\right)^4\right]\right\} \qquad (6)$$

where l is the perpendicular distance from the center of the sphere to the line connecting the two charges, that is, the distance from the center of the sphere to the center of the dipole. The characteristic dimensions of the zwitterion appear in quite different manners in the two equations, but the results are not very different if the dipole is at the center of the sphere ($l = 0$), as it must be in the first model. Under these conditions the first, but not the second, expression is independent of the molal volume.

Solutions of amino acids generally come very far from satisfying the conditions necessary for the validity of these equations. The less soluble α-amino acids are those containing longer hydrocarbon chains and cannot be considered spherical, whereas the smaller amino acids such as glycine and alanine, which might be considered spherical, are so soluble in water that the interaction between zwitterions cannot be neglected. As a rough approximation we may substitute the dielectric constant of the solution, D, for that of the solvent, D', in equation (5) in order to take into account the influence of zwitterions on each other.

An extension of the Born theory, in which the dielectric constant is considered uniform, may well prove inadequate if the zwitterions cause a redistribution of the mixed solvent in their immediate neighborhood. As a result the local dielectric constant may differ from the measured dielectric constant. Moreover, the characterization of the solvent in terms of its dielectric constant is a less satisfactory approximation than in the case of ions, since the electrostatic forces around a zwitterion are of shorter range.

Finally non-electrostatic deviations from ideal solution laws appear to play so large a role that they can never be neglected, and in certain substances appear nearly as important as the electrostatic forces.

VI. Solubility in Alcohol–Water Mixtures.—Both theoretical and practical considerations demand the accurate, quantitative formulation of the solubility relations of the amino acids in alcohol–water mixtures. From a practical point of view the crystallization of the amino acids and their separation from each other is often accomplished by means of the addition of alcohol to mother liquors which may contain one or more other components. The solubility of the amino acids in the mother liquor from which they are separated must be taken into account if the yield is to be considered quantitative. However, the

(21) Scatchard and Kirkwood, *Physik. Z.*, **33**, 297 (1932).

solvent action of amino acids due to their effect upon each other, and their effect in increasing the dielectric constants of solutions, renders this correction complicated, and more complicated the more concentrated the amino acid solutions. Decrease in the dielectric constant, such as is produced by the addition of alcohol or acetone, is accompanied by a decrease in solubility of zwitterions as of ions.

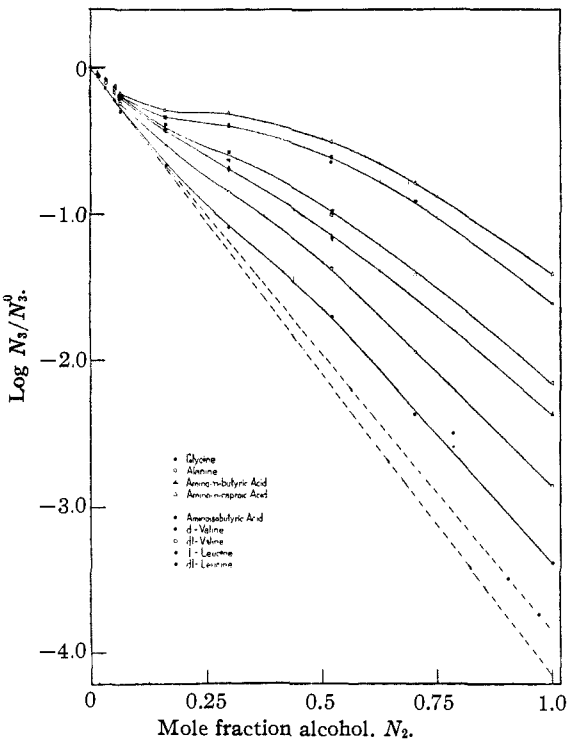

Fig. 1.—Solubility of α-amino acids in alcohol–water mixtures at 25°.

Measurements, such as are here reported, were made incidentally upon alanine by Holleman and Antusch[9] in the course of a study upon various uncharged organic molecules, which were more soluble in alcohol than in water. Their results upon alanine are confirmed by our measurements. Glycine has been studied previously in alcohol–water mixtures at 35° by Sano.[2]

The solubilities of α-amino acids in alcohol–water mixtures are recorded in Tables III and IV. The volume fraction of alcohol in the solvent varies in the first table from 0.0 to 0.15. In Table IV are the results obtained in solutions of higher alcohol content. The results are reported both as moles per liter, C, and as mole fraction, N_3. The former will be found more useful for many practical purposes, the latter is the more significant quantity for theoretical treatment, since it is independent of temperature, and since the composition of the solvent changes so largely in these experiments.

There would be certain advantages in employing a solvent of low dielectric constant in the definition of the standard state. On the other hand, the presence in alcohol of significant concentrations of both charged and uncharged molecules[22,23] renders the interpretation of behavior in this solvent more complicated. Our interests in the amino acids are largely concerned, from a chemical point of view, with their polar nature, and from a physiological point of view, with their behavior in aqueous solutions. We have, therefore, tentatively referred the measurements in this paper to the solubility in water at 25°. The logarithm of the solubility ratio, log N_3/N_3^0, is plotted against the mole fraction of alcohol in the solvent, N_2, in Fig. 1.

The logarithm of the solubility of glycine and alanine diminishes in alcohol–water mixtures nearly in direct proportion to the mole fraction of alcohol in the system. The behavior of the larger amino acids appears to be far more complicated, especially in systems containing large fractions of alcohol. Certain relations are, however, apparent. Thus the solubility ratio changes less the larger the molecular volume. This follows since these amino acids have closely similar solubilities in alcohol, whereas those of the shorter hydrocarbon chains are far more soluble in water.

In the second place comparison of *d*- and *dl*-valine and of *l*- and *dl*-leucine indicates that the solubility ratio is independent of the optical activity of the one isomer. The solubility of optically active leucine—related to its density in the solid state—is more than twice as great as that of the inactive compound, but the solubility ratio is essentially identical. Both are sufficiently insoluble to suggest that the change in the activity coefficients of these isomers with change in dielectric constant is also identical.

Comparison of leucine with its straight chain isomer, norleucine, indicates that the latter changes in activity coefficient to a far smaller extent than the more spherical branched chain compound. Similarly the solubility ratios of valine resemble those of α-amino-*n*-butyric acid

(22) Ebert, *Z. physik. Chem.*, **21**, 385 (1926).
(23) Edsall and Blanchard, THIS JOURNAL, **55**, 2337 (1933).

as nearly as they do the isomeric straight chain compound.[24] The recent studies of Webb and Lindsley[25] on the freezing points of aliphatic alcohols in water also show strikingly the resemblance of branch chain compounds to those with straight chains containing fewer carbon atoms. Further confirmation of this view is given by the studies on hydroxyproline, which despite its large molal volume behaves much like alanine. It is probable, therefore, either that the effective volume must be calculated not from density determinations, but from the length of the molecule, or that some term for the shape of the molecule will have to be introduced. The solubility ratios of butyric and of isobutyric α-amino acids are, however, essentially identical.

Influence of the Dielectric Constant.—The mole fraction of alcohol in an alcohol–water mixture is nearly proportional to the reciprocal of the dielectric constant.[19] More exactly it is proportional to the molal polarization. Therefore, very similar curves would be obtained if $\log N_3/N_3^0$ were plotted against the reciprocal of the dielectric constant of the pure solvent, $1/D'$, or more conveniently against $(1/D' - 1/D^{0\prime})$.

To express these relations in this manner would, however, obscure one of the important factors in the systems studied. The dielectric constant of a saturated amino acid solution is, as we have seen, greater than that of the pure solvent. It is very much greater if the solubility of the amino acid is high. We have, therefore, also considered solubility as a function of the dielectric constant of the saturated solution $(D' + \delta C)$.

The logarithm of the solubility ratio divided by the change of the reciprocal of the dielectric constant of the solvent and of the solution, has been calculated and recorded in the last columns of Table III. When the logarithm of the solubility ratio is divided by the expression relating the dielectric constants of the pure solvent, the ratio is very different for the different amino acids. This difference largely vanishes when the relation between solubility and the dielectric constant of the solution is considered. Instead of varying between 95 and 175, the Born–Fajans coefficient is on the average not far from 100 at sufficiently low volume fractions of alcohol.

(24) The comparison of leucine with α-aminovaleric acid, and the difference in behavior of the latter to valine, is striking.[1] Although α-aminovaleric acid has been studied, the results are not reported in this paper since no product has been obtained thus far which is a pure chemical individual.

(25) Webb and Lindsley, THIS JOURNAL, **56**, 874 (1934).

Influence of the Volume Fraction of Alcohol.—It is apparent that at high volume fractions of alcohol, and perhaps at all volume fractions, non-electrical forces largely determine the activity coefficients and solubility ratios of the amino acids. Moreover, the activity coefficients of the larger amino acids deviate far more than those of glycine from any relation proportional to change in the mole fraction of alcohol or the dielectric constant of the solution.

A theory of equilibria in systems, in terms of the molal volumes, V, and volume fractions, v, of the components, has been developed by Scatchard.[26] The theory is applicable primarily to non-polar substances, and the equations derived from it are inadequate to describe the activity coefficients even in systems as simple as alcohol–water mixtures.

The activity coefficient of water in alcohol–water mixtures has repeatedly been measured by means of vapor pressure. Although the above theory for non-polar substances might be expected to lead for a binary mixture to an equation of the type

$$\log f = Kv_2^2V \qquad (7)$$

the behavior of water in alcohol–water mixtures is far more complicated.[27] In the case of three-component systems the expression becomes still more complicated, including terms proportional to the first power of v_2 or N_2.

In point of fact the measurements on all the α-amino acids studied fall on a straight line provided a term comparable to the right-hand side of equation 7 be subtracted from the logarithm of the activity coefficient and this expression plotted against $1/D - 1/D^0$ (Fig. 2). That is to say, our results can be described by an expression of the form

$$\log N_3/N_3^0 - K_1v_2^2V = K_2(1/D - 1/D^0) \qquad (8)$$

In this expression K_2 is the Born–Fajans constant which for a zwitterion might be expected to have the dimensions of equation (5) or (6). If K_1 is put equal to 0.012, K_2 is equal to 106. If K_1 is put equal to 0.014, K_2 becomes 110. The results in Fig. 2 have been calculated on the latter basis and suggest that as a first approximation an equation of this type may be employed in characterizing amino acids of quite different molal volumes.

(26) Scatchard, *Chem. Rev.*, **8**, 321 (1931).

(27) The empirical equation $\log f = (0.004\ v_2^2 + 0.020\ v_2^2N_2)V$ does describe the existing data with a fair degree of accuracy, as does an expression of Scatchard [THIS JOURNAL, **49**, 217 (1927)], $\log f = (0.05\ N_2^2 - 0.028\ N_2^3)V$.

TABLE III

THE SOLUBILITY OF α-AMINO ACIDS IN ALCOHOL–WATER MIXTURES AT 25°

Vol. fr. alc. in solvent. v_2	Density of soln., ρ	Soly. of amino acid: Moles per liter, C	Soly. of amino acid: Mole fraction, N_3	Logarithm of soly. ratio, $\log N_3/N_3^0$	Change of soly. ratio: With dielectric constant of solvent, $\log N_3/N_3^0 \div 1/D - 1/D^0$	Change of soly. ratio: With dielectric constant of soln., $\log N_3/N_3^0 \div 1/D - 1/D^0$
			Glycine			
0.00	1.0831	2.886	0.0566	0.000	...	...
.05	1.0646	2.456	.0490	− .063	−175	−100
.10	1.0464	2.041	.0414	− .136	−170	− 99
.15	1.0307	1.670	.0346	− .214	−175	− 98
			dl-α-Alanine			
0.00	1.0432	1.660	0.0323	0.000	...	...
.05	1.0320	1.460	.0290	− .047	−131	− 90
.10	1.0211	1.250	.0254	− .104	−130	− 89
			Determinations made by Holleman and Antusch[9]			
0.00	1.0421	1.656	0.0323	0.000	...	...
.05	1.0311	1.454	.0289	− .051	−133	− 91
.10	1.0208	1.273	.0259	− .100	−120	− 86
.15	1.0101	1.077	.0224	− .165	−130	− 88
			dl-α-Amino-*n*-butyric acid			
0.00	1.0456	1.800	0.0363	0.000	...	...
.05	1.0370	1.634	.0336	− .034	− 94	− 79
.10	1.0264	1.464	.0307	− .073	− 91	− 76
.15	1.0166	1.287	.0275	− .121	− 99	− 79
			dl-α-Aminoisovaleric acid (valine)			
0.00	1.0120	0.571	0.0108	0.000	...	...
.05	1.0040	.506	.00980	− .042	−117	− 93
.10	0.9968	.444	.00882	− .087	−109	− 90
.15	.9893	.382	.00781	− .140	−115	− 93
			dl-α-Aminoisocaproic acid (leucine)			
0.00	0.9988	0.0744	0.00135	0.000	...	...
.05	.9917	.0661	.00124	− .037	−103	−100
.10	.9854	.0575	.00111	− .085	−106	−102
.15	.9793	.0494	.00099	− .134	−111	−106
			dl-α-Amino-*n*-caproic acid (norleucine)			
0.00	0.9991	0.0866	0.00158	0.000	...	...
.05	.9920	.0781	.00147	− .032	− 89	− 86
.10	.9855	.0688	.00133	− .075	− 94	− 90
.15	.9795	.0598	.00119	− .122	−100	− 95

Moreover, the lowest points are those of valine, which behaves more nearly like an α-amino acid of smaller molal volume.

Equation (8) holds most accurately in systems low in alcohol. At high volume fractions of alcohol the sums of the terms for different amino acids on the left side of the equation are brought still closer together by a still greater value for K_1. So calculated a single curve results if the left-hand expression is plotted against V_2, N_2 or $1/D$. The right-hand term in equation (8) refers change in dielectric constant to that of the concentrated aqueous amino acid solution. Although this method of correcting for the influence of zwitterions on each other appears a satisfactory approximation in such systems as are considered in Table III, substitution of alcohol for water as standard state would appear more satisfactory in comparing behavior in strongly alcoholic solutions, where the amino acid concentration may be considered negligible.

In a study, subsequently to be reported, of the change in $\log N_3/N_3^0$ of uncharged compounds closely related to the amino acids, we have noted that this quantity increases in absolute alcohol by a constant amount for each CH_2 group in the molecule. Although this law does not hold for extremely long hydrocarbon chains,

it holds accurately for the hydantoins, hydantoic acids and formyl compounds of the amino acids. It may be exemplified by comparing the hydantoic acids of glycine and alanine, which differ by one CH_2 group.

	V	$\frac{\log N_3^A}{\log N_3^0}$	$\frac{\log N_3^A}{\log N_3^0} - 0.03V_{CH_2}$
Hydantoic acid	77.6	−0.630	−1.119
Methyl hydantoic acid	94.2	−0.137	−1.115
Difference due to CH_2 group	16.6	0.493	...

The difference in log N_3 in alcohol and water is not only identical for the uncharged amino acid compounds thus far investigated, but also for the amino acids themselves and may be written 0.03 V_{CH_2}. Subtracting this quantity from the values of log N_3/N_3^0 for the various amino acids yields the results for absolute alcohol recorded in the last column of Table IV. This expression reduces to a single constant, 3.85, for the various straight chain compounds and a somewhat larger constant for amino acids of branched chains. Difference in behavior of the various amino acids is thus largely eliminated by this treatment.

The results for other volume fractions of alcohol recorded in the last column of Table IV have been obtained by subtracting the quantity $0.03v_2^2V_{CH_2}$ from log N_3/N_3^0. At each volume fraction this expression for different amino acids yields concordant values, though somewhat greater for the branched than for the straight chain compounds. The average values are graphically represented in Fig. 1 by broken lines, respectively, for the branched and straight chain compounds. So calculated an approximately linear relation results. The activity coefficients of amino acids may therefore roughly be estimated by an equation of the type

$$\log N_3/N_3^0 - 0.03\, v_2^2 V_{CH_2} = K_2 N_2 \qquad (9)$$

This relation, though more satisfactory in solutions containing large amounts of alcohol than equation (8), is less satisfactory in systems containing large amounts of water, where the effect of the high dielectric constants of the solutions must be considered. This effect as well as others is neglected by such an equation. Thus although the left-hand side of equation (9) changes with the reciprocal of the dielectric constant of mixtures containing more than 0.7 volume fractions of alcohol, there is a deviation from proportionality in systems containing approximately equal volume fractions of water and alcohol. This deviation is, however, equally great for all the amino acids and must, therefore, be ascribed to properties which they have in common, such as their amino and carboxyl groups.

The change in solubility, not due to the hydrocarbon chain, may be estimated by means of equation (9). For the hydantoic acids the quantity log $N_3/N_3^0 - 0.03V_{CH_2} = K_2 = -1.12$. Comparable calculations for the hydantoins yield −1.0, for formyl amino acids −0.84, for urea −0.75 and for water −0.42.[28]

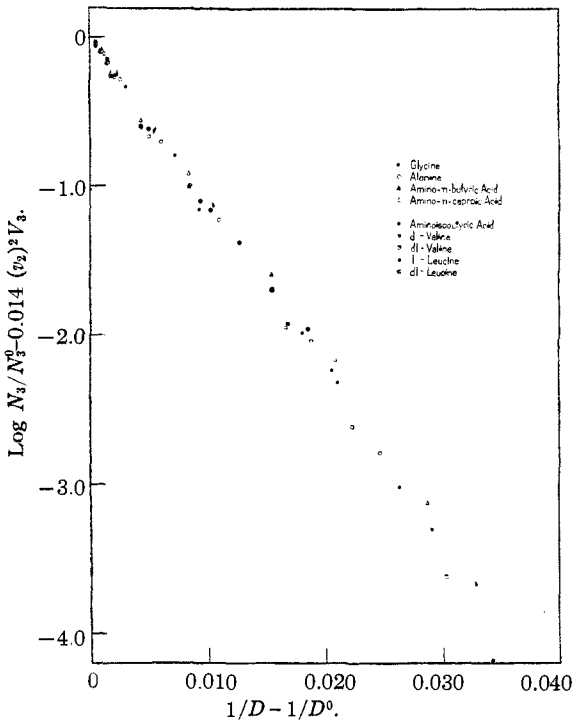

Fig. 2.—Solubility of α-amino acids in alcohol–water mixtures at 25°.

The terminal groups in all of these substances must be considered strongly polar and all, with the exception of water, contain the amide group. The negative values of this expression for terminal groups also increase roughly with their apparent volumes. These estimates of non-electrical effects[29] due to the groups which are common to amino acids, peptides and proteins, will be further considered in another communication.

In so far as we may ascribe a value for the

(28) This value for water is, of course, not a solubility ratio, but the logarithm of the activity coefficient ratio (for vapor pressures) for water in water as compared to water in alcohol.

(29) For convenience we shall consider as non-electrical forces even those due to the inherent moments of polar groups, in order to distinguish them from moments due to zwitterionic structure.

TABLE IV

THE SOLUBILITY OF α-AMINO ACIDS IN ALCOHOL–WATER MIXTURES AT 25°

Vol. fr. alc. in solvent. v_1'	α-Amino acid	Density of soln., ρ	Soly. of amino acids: Moles per liter, C	Soly. of amino acids: Mole fr., N_2	Logarithm of soly., log N_2	Logarithm of soly. ratio, log N_2/N_2^0	Log N_2/N_2^0 − 0.03$v_1^2V_{CH_2}$
0.00	Glycine	1.0831	2.886	0.0566	−1.247	0.000	0.000
	Alanine[9]	1.0421	1.656	.0323	−1.491	.000	.000
	Amino-*n*-butyric acid	1.0456	1.800	.0363	−1.440	.000	.000
	Amino-*n*-caproic acid	0.9991	0.0866	.00158	−2.801	.000	.000
	Aminoisobutyric acid	1.0312	1.330	.0261	−1.583	.000	.000
	d-Valine	1.0148	0.706	.0135	−1.870	.000	.000
	dl-Valine	1.0120	.571	.0108	−1.967	.000	.000
	l-Leucine	1.0012	.171	.00314	−2.503	.000	.000
	dl-Leucine	0.9988	.0744	.00135	−2.870	.000	.000
.20	Glycine	1.0140	1.343	.0285	−1.545	− .298	− .318
	Alanine[9]	0.9984	0.877	.0187	−1.728	− .237	− .276
	Amino-*n*-butyric acid	1.0043	1.082	.0236	−1.627	− .187	− .246
	Amino-*n*-caproic acid	0.9726	0.0516	.00107	−2.971	− .170	− .268
	Aminoisobutyric acid	.9947	.775	.0166	−1.780	− .197	− .256
	d-Valine	.9853	.409	.00864	−2.063	− .193	− .271
	dl-Valine	.9814	.318	.00669	−2.175	− .208	− .286
	l-Leucine	.9748	.0977	.00202	−2.695	− .192	− .290
	dl-Leucine	.9735	.0423	.000872	−3.059	− .189	− .287
.40	Glycine	.9611	.507	.0123	−1.910	− .663	− .741
	Alanine[9]	.9577	.402	.0103	−1.987	− .496	− .652
	Amino-*n*-butyric acid	.9629	.570	.0140	−1.854	− .414	− .649
	Amino-*n*-caproic acid	.9460	.0346	.000829	−3.083	− .282	− .673
	Aminoisobutyric acid	.9577	.401	.00979	−2.009	− .426	− .661
	d-Valine	.9528	.231	.00560	−2.252	− .382	− .695
	dl-Valine	.9512	.167	.00403	−2.395	− .428	− .741
	l-Leucine	.9469	.0620	.00149	−2.827	− .324	− .715
	dl-Leucine	.9467	.0264	.000632	−3.199	− .329	− .720
.60	Glycine	.9107	.157	.00458	−2.339	−1.092	−1.268
	Alanine[9]	.9102	.158	.00463	−2.334	−0.843	−1.195
	Amino-*n*-butyric acid	.9147	.260	.00766	−2.116	− .676	−1.204
	Amino-*n*-caproic acid	.9060	.0271	.000791	−3.102	− .301	−1.181
	Aminoisobutyric acid	.9111	.177	.00520	−2.284	− .701	−1.229
	d-Valine	.9100	.123	.00361	−2.442	− .572	−1.276
	dl-Valine	.9092	.0860	.00252	−2.599	− .632	−1.336
	l-Leucine	.9071	.0441	.00129	−2.889	− .386	−1.266
	dl-Leucine	.9067	.0186	.000542	−3.266	− .396	−1.276
.80	Glycine	.8598	.0278	.00106	−2.975	−1.728	−2.041
	Alanine[9]	.8556	.0359	.00137	−2.863	−1.372	−1.998
	Amino-*n*-butyric acid	.8586	.0668	.00255	−2.594	−1.154	−2.093
	Amino-*n*-caproic acid	.8550	.0130	.000496	−3.304	−0.503	−2.068
	Aminoisobutyric acid	.8578	.0467	.00178	−2.750	−1.167	−2.106
	d-Valine	.8565	.0373	.00142	−2.848	−0.978	−2.230
	dl-Valine	.8575	.0280	.00107	−2.971	−1.004	−2.256
	l-Leucine	.8569	.0204	.000778	−3.109	−0.606	−2.171
	dl-Leucine	.8560	.00848	.000323	−3.491	− .621	−2.186
.90	Glycine	.8254	.00556	.000254	−3.595	−2.348	−2.744
	Alanine	.8255	.00794	.000362	−3.441	−1.950	−2.742
	Amino-*n*-caproic acid	.8254	.00585	.000267	−3.573	−0.772	−2.752
	dl-Valine	.8256	.00922	.000421	−3.376	−1.409	−2.993
	l-Leucine	.8254	.00770	.000351	−3.455	−0.952	−2.932
1.00	Glycine	.7851*	.00039	.000023	−4.638	−3.391	−3.880
	Alanine	.7851*	.00076	.000045	−4.347	−2.856	−3.834
	Amino-*n*-butyric acid	.7851*	.00260	.000153	−3.818	−2.375	−3.842
	Amino-*n*-caproic acid	.7851*	.00104	.000061	−4.215	−1.414	−3.859
	dl-Valine	.7851*	.00128	.000075	−4.125	−2.158	−4.114
	l-Leucine	.7851*	.00128	.0000762	−4.125	−1.622	−4.067

* Because of the small concentration of the solute the density of the solvent has been employed.

non-electrical effect due to the terminal groups of the amino acids, we could estimate the electrical contribution due to the charged $-NH_3^+$ and $-COO^-$ groups. As a maximum this may be taken as $3.85/0.0284 = 136$. If we tentatively neglect the influence of the amide linkage and also the movement of the proton, which results in the zwitterionic condition of the amino acids and peptides, and employ the non-electrical term characteristic of hydantoic acids, we obtain as an estimate for the electrical term $(3.85 - 1.12)/0.0284 = 96$. The non-electrical effect would be still greater, were the solubility coefficient the same for the CONH as for the CH_2 group. This calculation yields a minimal estimate of the electric effect of $(3.85 - 1.72)/0.0284 = 75$.

The intermediate estimate of 96, though probably high, is very close to the ratios in systems containing very small volume fractions of alcohol (Table III) and also to that obtained by substituting in the equation of Kirkwood given above[14] constants derived from the study of the influence of neutral salts upon glycine in alcohol–water mixtures.[14] Under these circumstances the electrical forces are greatly magnified because of the low dielectric constant, and no large change in the composition of the solvent is involved.[1] Electrostatic forces can unquestionably be determined most accurately from the study either of the influence of salts upon amino acids or of amino acids upon salts in environments of low dielectric constant. Any calculation from such measurements for the influence of the composition of the solvent would, however, involve the validity of some theory regarding the behavior of zwitterions. The studies reported indicate that the change in free energy due to electrostatic forces is nearly the same for all α-amino acids. This conclusion is independent of the partition between non-electrical and electrostatic forces and of any theory regarding the latter. It is consistent with the form of equation (5) but not of equation (6), if the dipoles are at the center of the molecules. It is more probable, however, that the dipoles are situated at an equal distance from the edge of amino acid molecules.

Although the partition between electrical and non-electrical forces that can at present be made is still somewhat arbitrary, it need not remain so. The non-electrical forces characteristic of the hydantoic acids may be further analyzed in terms of those due to the amide groups and to the amino and carboxyl groups characteristic also of amino acids. In so far as one can determine the non-electrical coefficient of solubility, one can derive an equation for the activity coefficient of all aliphatic α-amino acids in alcohol–water mixtures. Although more complicated than equation (8) or (9) the constants would be susceptible of independent determination. We shall attempt, therefore, to evaluate them from the study of uncharged molecules containing the same chemical groups as the amino acids.

Summary

1. The solubilities of aliphatic α-amino acids have been studied in alcohol–water mixtures and the factors influencing solubility and change in solubility considered.

2. The solubilities of all α-amino acids in alcohol are extremely small and of the same order. Solubilities in water are far greater, and greater the shorter the hydrocarbon chain. The insolubility of amino acids in alcohol resembles that of many strong electrolytes and reflects the charged condition of the amino acid molecule.

3. The high densities of amino acids in the solid state are also characteristic of the close packing of charged molecules. The density in the solid state is greater the smaller the hydrocarbon chain. Among isomers, however, the less dense amino acid is the more soluble.

4. In systems containing small volume fractions of alcohol, the logarithm of the solubility of all amino acids (expressed as mole fraction) appears to diminish inversely as the dielectric constant. In systems containing large volume fractions of alcohol, behavior reflects the length of the hydrocarbon chain.

5. The difference between the logarithm of the solubility in water and absolute alcohol is smaller by the same amount for each CH_2 group and may be considered 0.03 times the volume of the CH_2 group.

6. Subtracting $0.03v_2^2V_{CH_2}$ from the logarithm of the solubility ratio eliminates differences between the different amino acids. All the results on straight chain compounds fall together, as do those upon amino acids with branched chains, and vary as a first approximation proportionately with the mole fraction alcohol.

7. The description of all aliphatic α-amino acids as differing by a constant amount for each CH_2 group, renders possible analysis of the ac-

tivity coefficients of all in terms of electrical and non-electrical forces due to the $-NH_3^+$ and $-COO^-$ groups.

8. On the basis of studies upon comparable uncharged molecules, tentative estimates have been made of the non-electrical, and therefore also of the electrostatic forces due to α-amino acids.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Reactions Involving Free Alkyl Groups. I. The Photo-reaction of Methane, Chlorine and Oxygen[1]

BY LOREN T. JONES AND JOHN R. BATES

Studies of the thermal[2] and photochemical[3] chlorination of methane have shown that in both cases the reaction proceeds by a chain mechanism. Coehn and Cordes found a quantum yield of 10^4 while the work of Pease and Walz indicated a much greater chain length for higher temperatures. Both reactions are strongly inhibited by traces of oxygen. The analogy between these data and the facts of the hydrogen–chlorine reaction immediately suggests that the reaction occurs through the same intermediates which characterize the hydrogen–chlorine reaction, with methyl groups taking the place of one of the hydrogen atoms of the hydrogen molecules. If this be true, the rate should obey the expression derived by Thon[4] with substitutions

$$\frac{d[CH_3Cl]}{dt} = \frac{d[HCl]}{dt} = \frac{K\,[CH_4][Cl_2]^2}{[O_2]\,(k\,[CH_4] + [Cl_2])}$$

This would be equally true were the mechanism to follow either of the two alternative schemes

I

$$Cl_2 + h\nu \longrightarrow Cl + Cl'$$
$$Cl + CH_4 \longrightarrow HCl + CH_3$$
$$CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl$$
$$CH_3 + O_2 \longrightarrow$$
$$Cl + O_2 \longrightarrow$$

II

(1) $Cl_2 + h\nu \longrightarrow Cl + Cl'$
(2) $Cl + CH_4 \longrightarrow CH_3Cl + H$
(3) $H + Cl_2 \longrightarrow HCl + Cl$
(4) $H + O_2 \longrightarrow$
(5) $Cl + O_2 \longrightarrow$

Measurements accordingly have been made to discover if this is true, and, in addition, the verification of either I or II as the correct interpretation has been attempted.

(1) The material in this paper comprises a portion of a thesis presented by Loren T. Jones to the Graduate School of the University of Michigan in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1934.

(2) Pease and Walz, THIS JOURNAL, **53**, 3728 (1931).

(3) Coehn and Cordes, *Z. physik. Chem.*, **B9**, 1 (1930).

(4) Thon, *ibid.*, **B9**, 1 (1930).

Experimental Method

The experiments were carried out in a flow system. The rate of flow of the methane and chlorine supplied in tanks was measured by pressure flowmeters. The amount of oxygen, generated electrolytically, was regulated by the current sent through the cell. The gases were mixed and dried in a drying tower before entering the reaction unit consisting of a glass spiral illuminated by a Pyrex mercury arc. Since traces of oxygen have a very marked influence on the reaction at low oxygen concentrations, an analysis of the methane and chlorine for oxygen content was made. Approximately 3000 cc. of chlorine, when bubbled into a bulb filled with an iodide solution, gave about 30 cc. of residual gas. This was transferred to an Orsat gas analysis apparatus where the gas was first bubbled through an alkali solution to remove any traces of chlorine or other acidic gases that might be present before absorbing the oxygen in an alkaline hydrosulfite solution. There was found 0.25% oxygen in the chlorine and 0.8% in the methane. The reaction was studied by determining the amount of hydrogen chloride and unreacted chlorine in the off-gas by absorbing it in an iodide solution. The iodine liberated was titrated with a thiosulfate solution; the acid formed during the reaction was determined with alkali.

The reaction was carried out at 5, 25 and 45° at atmospheric pressure. A series of determinations was first made in which the methane–chlorine–oxygen ratio was constant, as the total rate of flow was increased from 135 cc. per minute to 370 cc. per minute.

The amount of hydrogen chloride formed after a ten-minute run remained constant within 10%, as can be seen from Table I.

Since there is a possibility of fluctuation of light intensity, a check was made at frequent intervals