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Dissociation Constants of Glycine, Alanine, Proline, Valine, Glutamine & γ-Aminobutyric Acid in Methanol & Ethanol-Water Mixtures

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The ionisation constants of glycine, alanine, proline, valine, glutamine and γ-aminobutyric acid have been determined *p*H-metrically in ethanol-water and methanol-water mixtures at very low ionic strengths and at 25°.

THE effect of non-aqueous solvents on the dissociation constants of acids and bases is not well understood, even though the advantages and utility of non-aqueous and mixed solvents for improving analytical methods involving complexation have been well-emphasized[1]. The literature[2] provides numerous studies on the dissociation constants of carboxylic acids. However, comparatively little is known regarding the effect of solvents on the dissociation of amino acids.

In view of these facts, we have undertaken studies on the protonation equilibria of a number of amino acids like glycine, alanine, proline, valine, glutamine and γ-aminobutyric acids in methanol and ethanol water mixtures *p*H-metrically. The choice of the present solvent systems was dictated by the nature of the protolytic behaviour of the amino acids closely resembling water yet differing much in physical properties.

The amino acids (except GR E. Merck variety) were purified by crystallization from water-ethanol mixtures. Methanol and ethanol were purified and the weight percentages of the organic solvent were determined in the same way as described before[3,4]. The slight traces of water present, if any, in the organic solvents were neglected.

Perchloric acid and caustic soda were of E. Merck reagent grade and were standardized in the usual way. Other chemicals were of reagent grade. All the solutions were made in doubly distilled water.
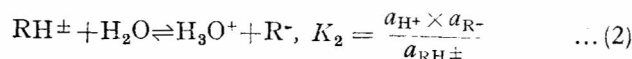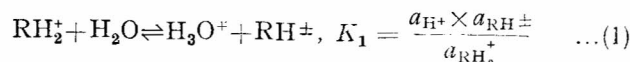
For the determination of the acid dissociation of dipolar ions, a known concentration of the amino acid was neutralized to different extents with perchloric acid and the hydrogen ion concentration measured. The process was repeated with different concentrations of the different dipolar ions in various methanol-water and ethanol-water mixtures.

For the determination of the second dissociation of the amino acids, the process was the same; only $HClO_4$ was replaced by caustic soda.

The *p*H-meter readings were taken at 25° using a Cambridge bench type battery operated *p*H-meter.

Since the amino acids are present predominantly as dipolar ions (i.e. $^+NH_3RCO_2^-$), these are represented as $RH^\pm$ and the dissociation equilibria in acid (if dissociation of carboxylic group is considered) and alkali (if dissociation ammonium ion is considered) can be represented by Eqs. (1) and (2).

$$RH_2^+ + H_2O \rightleftharpoons H_3O^+ + RH^\pm, \quad K_1 = \frac{a_{H^+} \times a_{RH^\pm}}{a_{RH_2^+}} \quad ...(1)$$

$$RH^\pm + H_2O \rightleftharpoons H_3O^+ + R^-, \quad K_2 = \frac{a_{H^+} \times a_{R^-}}{a_{RH^\pm}} \quad ...(2)$$

or

$$pK_1 = pH - \log\frac{C_{RH^\pm}}{C_{RH_2^+}} - \log\frac{f_{RH^\pm}}{f_{RH_2^+}}$$

$$= pH - \log\left(\frac{C}{a - C_{H^+}} - 1\right) - \log\frac{f_{RH^\pm}}{f_{RH_2^+}}$$

and

$$pK_2 = pH + \log\left(\frac{C}{b - C_{OH^-}} - 1\right) - \log\frac{f_{R^-}}{f_{RH^\pm}}$$

where C = concentration of neutral amino acid, a or b = concentration of acid or base respectively, and C_H^+ or C_{OH^-} = concentration of H^+ ion or OH^- ion in the experimental solution (determined *p*H-metrically). The appropriate corrections were made for the mixed solvents using the well known method described earlier[5-7]. Though the 'correction factors' for the mixed solvents were known[7], we considered it desirable to find out the 'correction factor' with each set of measurement to avoid any error resulting from (i) change in the asymmetry potential of the glass electrode and (ii) liquid-junction potential of uncertain magnitude.

Since the ionic strengths of the solutions were very low $(3-6 \times 10^{-3}M)$ activity coefficients were approximated to unity.

The method is almost similar to that of Edsall and Blanchard[8].

The pK_1 and pK_2 values at 25° determined in different percentages of methanol-water and ethanol-water mixtures are presented in Table 1. The results are in very good agreement with the reported values for glycine and alanine in ethanol-water mixture determined potentiometrically by Edsall and Blanchard[8].

As expected, pK_1 values of all the amino acids increase with increase in the alcohol content of the mixtures but the magnitude of increase is smaller than that of corresponding carboxylic acid due to 'dipolar character' of the acids.

The pK_1 values were found to be linear function of $1/\epsilon$ and mole-fraction of alcohol at low percentages of alcohol. Slight improvement was observed when water activity was taken into consideration[9]. It is to be noted that the proportion of the neutral form of acid increases[8] with increase in alcohol content resulting in deviations.

TABLE 1 — DISSOCIATION CONSTANTS OF AMINO ACIDS IN METHANOL-WATER AND ETHANOL-WATER MIXTURES

Alcohol (%, v/v)	Glycine		Alanine		Proline		Valine		Glutamine		γ-Aminobutyic acid	
	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2
METHANOL-WATER												
10	2·57	—	2·55	—	2·12	—	2·45	—	2·47	—	4·14	—
20	2·63	9·63	2·66	9·80	2·20	10·61	2·60	9·76	2·55	—	4·19	—
30	2·66	—	2·70	—	2·25	—	2·65	—	2·62	—	4·34	—
40	2·90	—	2·97	—	2·52	—	2·95	—	2·84	—	4·56	—
50	3·18	—	3·20	—	2·67	—	3·16	—	3·14	—	4·73	—
60	3·36	9·78	3·46	9·9	2·88	10·55	3·42	9·83	3·40	—	5·00	10·60
70	3·5	—	3·60	—	3·02	—	3·58	—	3·52	—	5·18	—
80	3·64	9·74	3·76	9·82	3·28	10·50	3·76	9·85	3·68	9·20	5·32	10·65
ETHANOL-WATER												
10	2·55	—	2·53	—	2·12	—	2·52	—	2·50	—	4·12	—
20	2·66	9·68	2·70	9·85	2·20	10·63	2·68	9·80	2·60	—	4·19	—
30	2·70	—	2·79	—	2·27	—	2·78	—	2·70	—	4·40	—
40	2·88	—	2·97	—	2·48	—	2·96	—	2·90	—	4·54	—
50	3·05	—	3·13	—	2·73	—	3·15	—	3·15	—	4·80	—
60	3·38	9·83	3·49	9·98	2·97	10·58	3·38	9·90	3·35	—	5·05	10·62
70	3·53	—	3·61	—	3·16	—	3·65	—	3·55	—	5·28	—
80	3·73	9·73	3·91	9·88	3·49	10·51	3·92	9·85	3·85	9·22	5·48	10·68

It is well known that the role of solvents on the ionization constants of weak acids and bases is not clearly understood in terms of Born equation[10] or modified equations[11,17]. The problem is extremely complicated in the case of 'zwitterions' presumably with different and changing solvational properties with change in alcohol content. The change in ΔpK values, though it should be accounted in terms of "electrostatic" and "non-electrostatic" parts, is of little value in view of limited accuracy of the equations and in the absence of accurate values of radii of ions of amino acids. The significance of solute-solvent interactions and 'medium effect' thus remains unexplained.

The changes in pK_2 with increase in alcohol content are rather small and it is not possible to draw definite conclusions with the limited data available.

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Ionization Constants of Some N-Arylform-amido-N'-arylthiocarbamides at Different Temperatures

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Acid dissociation constants of N-s-diphenylform-amido-N'-phenylthiocarbamide, N-s-diphenylform-amido-N'-p-tolylthiocarbamide, N-s-diphenylform-amido-N'-o-tolylthiocarbamide, N-s-diphenyl-formamido-N-benzylthiocarbamide, N-benzoylform-amido-N'-phenylthiocarbamide, N-benzoylformamido-N'-p-tolylthiocarbamide, N-benzoylformamido-N'-o-tolylthiocarbamide and N-benzoylformamido-N'-benzylthiocarbamide have been determined potentiometrically in 75% aq. acetonitrile (v/v) and at fixed ionic strength (0·1) over the temperature range 15-45°. The values of free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) have been calculated for the ionization process. The values of pK_m (minimum pK_a values at temp. 0°C) have also been calculated.

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