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# Ionization of Hydroxamic Acids in Aqueous Solutions

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**Synopsis.** Thermodynamic ionization constants of sixteen hydroxamic acids at 25 °C and 35 °C in aqueous solution and the corresponding $\Delta H°$ (standard enthalpy change) are presented.

Hydroxamic acids have extensive application in analytical[1] and medicinal chemistry.[2] The ionization of a hydroxamic acid has been found to have a strong bearing on its effectiveness as an analytical[1] or biological[3] reagent. This led to several studies on the determination of ionization constants of hydroxamic acids.[3-5] Most of these studies, however, were performed in media of high, constant ionic strength and at a single temperature (usually 25 °C) and the results are valid for only these conditions. The determination was carried out without taking necessary precaution to avoid carbon dioxide from the titration-solutions. The presence of dissolved atmospheric gases such as $CO_2$ in the hydroxamic acid solutions during pH titrations are liable to effect the ionization. In the present communication, thermodynamic ionization constants of a number of hydroxamic acids, determined under rigorously controlled conditions at 25 °C and 35 °C are reported.

## Experimental

*Hydroxamic Acids.* The hydroxamic acids were prepared by following the general method of Blatt.[6] They were recrystallized repeatedly until they showed a sharp melting point. The purity was checked by microanalysis, gas-liquid chromatography and IR spectroscopy. Conductivity water was used throughout. All other reagents were of analytical grade.

*Determination of Thermodynamic Ionization Constants.* A weighed quantity of hydroxamic acid was placed in a thermostated titration vessel containing 50 ml of aqueous $HClO_4$ solution ($1.00\times10^{-3}$ M). Nitrogen, after being passed in succession through a train of guard tubes containing, pyrogallic acid, 3 M KOH solution and distilled water, was bubbled into the titration vessel. The rest of the experimental set-up for pH titration and the method of calculation of ionization constants was essentially the same as that described by Goldberg.[7] The expressions involved are:

$$K_a = \frac{[H^+][A^-]\gamma_{H^+}\cdot\gamma_{A^-}}{[HA]\gamma_{HA}} \quad (1)$$

where HA represents hydroxamic acid. It follows that

$$pK_a = -\log[H^+] + \log\frac{[HA]}{[A^-]} + 2\log\frac{1}{\gamma_\pm} \quad (2)$$

the activity coefficient of uncharged species being taken as unity.

The log $[H^+]$ values are read from the pH meter and $\gamma_\pm$, the mean activity coefficient, is obtained by interpolation of the data from Harned and Owen.[8] The titration was repeated until two sets of values differing within $\pm0.01$ pH units were obtained.

## Results and Discussion

The results for one representative titration, namely for salicylohydroxamic acid at 25 °C, are given in Table 1. The thermodynamic ionization constants of fourteen

TABLE 1. DETERMINATION OF THERMODYNAMIC IONIZATION CONSTANT OF SALICYLO HYDROXAMIC ACID AT 25 $\pm$0.1 °C
(Salicylohydroxamic acid)=0.01 M, (KOH)=0.1000 M.

| I Titrant (0.1000 M KOH) ml | II pH | III Stoichiometric concentration HA | III Stoichiometric concentration $A^-$ | IV $HA/A^-$ | V log of column IV | VI $\log 1/\gamma_\pm$ | VII $pK_a$ |
|---|---|---|---|---|---|---|---|
| 0.50 | 6.45 | 0.009 | 0.001 | 9/1 | 0.954 | 0.015 | 7.42 |
| 1.00 | 6.80 | 0.008 | 0.002 | 8/2 | 0.602 | 0.021 | 7.42 |
| 1.50 | 7.02 | 0.007 | 0.003 | 7/3 | 0.368 | 0.025 | 7.41 |
| 2.00 | 7.23 | 0.006 | 0.004 | 6/4 | 0.176 | 0.028 | 7.41 |
| 2.50 | 7.32 | 0.005 | 0.005 | 5/5 | 0.000 | 0.032 | 7.42 |
| 3.00 | 7.54 | 0.004 | 0.006 | 4/6 | −0.176 | 0.035 | 7.40 |
| 3.50 | 7.75 | 0.003 | 0.007 | 3/7 | −0.368 | 0.037 | 7.42 |
| 4.00 | 7.97 | 0.002 | 0.008 | 2/8 | −0.602 | 0.040 | 7.41 |
| 4.50 | 8.33 | 0.001 | 0.009 | 1/9 | −0.954 | 0.042 | 7.42 |
| Result: Av. $pK_a = 7.41\pm0.01$ | | | | | | | |

pH values are accurate to $\pm0.01$ units.

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Table 2. Thermodynamic ionization constants and standard enthalpy changes

| No. | Hydroxamic acid | $pK_a$ at 25 ±0.1 °C | $pK_a$ at 35±0.1 °C | $\Delta H°$ |
|---|---|---|---|---|
| 1 | Benzo- | 8.89±0.01 | 8.79±0.02 | 4.21 |
| 2 | *N*-Phenylbenzo- | 8.41±0.01 | 8.30±0.01 | 4.62 |
| 3 | Formo- | 8.78±0.02 | 8.67±0.01 | 4.62 |
| 4 | Glycine- | 7.80±0.02 | 7.71±0.01 | 3.79 |
| 5 | D-Tyrosine- | 9.35±0.02 | 9.21±0.02 | 5.89 |
| 6 | L-Tyrosine- | 9.35±0.02 | 9.21±0.02 | 5.89 |
| 7 | D-Lysine- | 8.11±0.01 | 7.98±0.02 | 5.47 |
| 8 | L-Lysine- | 8.11±0.02 | 7.98±0.02 | 5.47 |
| 9 | L-Lacto- | 9.45±0.01 | 9.37±0.01 | 3.37 |
| 10 | Chloroaceto- | 8.53±0.01 | 8.42±0.01 | 4.62 |
| 11 | *o*-Aminobenzo- | 9.29±0.02 | 9.17±0.02 | 5.05 |
| 12 | *p*-Hydroxybenzo- | 9.06±0.01 | 8.95±0.02 | 4.62 |
| 13 | Salicylo- | 7.41±0.01 | 7.33±0.01 | 3.37 |
| 14 | 5-Nitrosalicylo- | 6.89±0.01 | 9.01±0.01 | 3.37 |
| 15 | *N*-Phenylcinnamo- | 9.11±0.01 | 9.01±0.01 | 4.21 |
| 16 | *N*-Furoylbenzo- | 8.14±0.02 | 8.02±0.01 | 5.05 |

hydroxamic acids along with those of reference substance benzo- and *N*-phenylbenzohydroxamic acids are given in Table 2, together with the values of standard enthalpy change, $\Delta H°$, obtained by integrating van't Hoff's equation[9] at two temperatures, $T_1$ (298 K) and $T_2$ (308 K):

$$\log \frac{K_{a_2}}{K_{a_1}} = \frac{\Delta H°(T_2 - T_1)}{4.567 T_1 T_2}$$

where $\log K_a = -pK_a$.

Since the hydroxamic acids differ widely in structure and basicity ($pK_a$ between 6.89 to 9.45 at 25 °C), it can be assumed that $\Delta H°$ is in general positive for the ionization of hydroxamic acids. There is, however, no definite trend in the magnitudes of change in values of $\Delta H°$ with change in the groups attached to the functional –C=O and –N–OH groups. It can be seen that while increase in the conjugation at the –C=O site (compound XV) increases the basicity of the compound relative to benzohydroxamic acid, introduction of $\pi$ systems at the –N–OH fragment reduces the basicity (compounds II, XVI). With hydroxamic acids derived from amino acids, the $pK_a$ values are in line with the basicity of the corresponding amino acids.[10]

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