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Note

Heterocyclic hydroxamic acids: Effect of temperature on the protonation equilibria

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INTRODUCTION

Hydroxamic acids have been extensively employed in analytical[1] and medicinal[2] chemistry. The ionisation of a hydroxamic acid has been found to have a strong bearing on its effectiveness as an analytical[1] or biological[3] reagent. Several ionisation constants of hydroxamic acids have been reported[4–6] but there is no systematic study on heterocyclic hydroxamic acids. Further, most of the reported constants are "concentration" constants, obtained in media of high, constant, ionic strength and at a single temperature (usually 25°C). These constants are valid for only those conditions in which they have been determined. In the present communication, thermodynamic protonation constants of a number of heterocyclic hydroxamic acids are reported at 25 and 35°C. In a recent communication[7] we have reported formation constants of binary proton–ligand, metal–ligand, and ternary metal–mixed ligand complexes involving nicotino- and isonicotino-hydroxamic acids. These studies have been initiated considering the paucity of information on heterocyclic systems in comparison to the corresponding benzenoid systems. The studies are part of the extensive studies on the relationship of structure to the sensitivity and selectivity of hydroxamic acids.

EXPERIMENTAL

Hydroxamic acids

The hydroxamic acids were prepared by following the general method of Blatt[8]. They were repeatedly recrystallised to a constant, sharp melting point and their purity was checked by microanalysis, gas–liquid chromatography and IR spectroscopy.

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Determination of thermodynamic protonation constants

A weighed quantity of hydroxamic acid was placed in a thermostated titration vessel containing 50 ml of water. Nitrogen, after being passed through a train of guard tubes containing, in succession, pyrogallic acid, 3 M KOH solution and distilled water, was bubbled into the titration vessel. The remaining experimental set-up for pH titration and the method of calculation of ionisation constants was esentially the same as detailed by Goldberg[9]. The expressions involved are

$$K_a = \frac{[H^+]\,[A^-]\,\nu_{H^+}\,\nu_{A^-}}{[HA]\,\nu_{HA}} \tag{1}$$

where HA represents hydroxamic acid. It follows

$$pK_a = -\log [H^+] + \log \frac{[HA]}{[A^-]} + 2 \log \frac{1}{\nu_\pm} \tag{2}$$

$-\log [H^+]$ values were read from the pH meter and $\nu_\pm$, the mean activity coefficient, was obtained by interpolation of data from Harned and Owen[10]. Titrations were performed repeatedly until two sets of values differing within $\pm$ 0.01 pH units were obtained.

RESULTS AND DISCUSSION

Experimental observations for one representative titration, namely for iso-nicotinohydroxamic acid at 25 °C, are recorded in Table 1. Thermodynamic ionisation

TABLE 1

DETERMINATION OF THERMODYNAMIC IONISATION CONSTANT OF ISO-NICOTINOHYDROXAMIC ACID AT 25 $\pm$ 0.1 °C

[Iso-nicotinohydroxamic acid] = 0.01 M, [KOH] = 0.1000 M

I *Titrant (0.1000 M KOH) ml*	*II* *pH*[a]	*III* *Stoichiometric concentration*		*IV* *HA/A⁻*	*V* *Log of column IV*	*VI* *log 1/$\nu_\pm$*	*VII* *pK_a*
		HA	*A⁻*				
0.50	6.99	0.009	0.001	9/1	0.954	0.015	7.96
1.00	7.36	0.008	0.002	8/2	0.602	0.021	7.98
1.50	7.56	0.007	0.003	7/3	0.368	0.025	7.97
2.00	7.77	0.006	0.004	6/4	0.176	0.028	7.97
2.50	7.93	0.005	0.005	5/5	0.000	0.032	7.96
3.00	8.09	0.004	0.006	4/6	−0.176	0.035	7.95
3.50	8.30	0.003	0.007	3/7	−0.368	0.037	7.97
4.00	8.54	0.002	0.008	2/8	−0.602	0.040	7.98
4.50	8.88	0.001	0.009	1/9	−0.954	0.042	7.97

Result: Av. pK_a = 7.97 $\pm$ 0.02

[a] pH values are accurate to $\pm$ 0.01 units.

TABLE 2

THERMODYNAMIC IONISATION CONSTANTS OF HETEROCYCLIC HYDROXAMIC ACIDS AT 25 AND 35°C

No.	*Hydroxamic acid*	pK_a *at 25 ± 0.1°C*	pK_a *at 35 ± 0.1°C*	ΔH° *kcal*
I	Benzo-	8.89[a] ± 0.01	8.79 ± 0.02	4.20
II	Nicotino-	8.54 ± 0.01	8.54 ± 0.01	3.78
III	N-phenylbenzo-	8.41[b] ± 0.01	8.30 ± 0.01	4.62
IV	N-phenylnicotino-	8.14 ± 0.02	8.05 ± 0.02	3.78
V	Isonicotino-	7.97 ± 0.02	7.90 ± 0.02	2.95
VI	2-furo-	8.28 ± 0.01	8.18 ± 0.02	4.20
VII	2-theno-	8.57 ± 0.02	8.46 ± 0.02	4.62
VIII	Quinaldino-	8.23 ± 0.01	8.14 ± 0.02	3.78
IX	N-phenylquinaldino-	7.95 ± 0.02	7.84 ± 0.01	4.62
X	Pyrazine-	8.26 ± 0.01	8.18 ± 0.01	2.95
XI	Pyrimidine-2-carbox-	8.01 ± 0.01	7.90 ± 0.02	4.62
XII	Indole-3-aceto-	8.70 ± 0.02	8.59 ± 0.01	4.62
XIII	N-*p*-tolylnicotino-	8.69 ± 0.01	8.60 ± 0.01	3.78
XIV	N-*p*-tolylquinaldino-	8.32 ± 0.01	8.24 ± 0.02	3.36

[a] Reported 8.91 (ref. 12).
[b] Reported 8.41 (ref. 1).

constants of twelve heterocyclic hydroxamic acids along with those of reference substances benzo- and N-phenylbenzohydroxamic acids are presented in Table 2. Table 2 also includes values of standard enthalpy change, ΔH^0, which were obtained by integration of vant Hoff's equation[11] at two temperatures T_1 (298 K) and T_2 (308 K)

$$\log \frac{K_2}{K_1} = \frac{\Delta H^0 (T_2 - T_1)}{4.567\, T_1 T_2} \qquad (3)$$

where $\log K = -pK_a$.

It is seen that although ΔH^0 is positive for all acids studied, indicating the endothermic nature of protonation in all cases, there is no definite trend in the magnitudes of change in value of ΔH^0 with change in the groups attached to the functional –C=O and –N–OH groups. In all cases, presence of heterocyclic rings has resulted in an acid-strengthening effect on compounds relative to corresponding non-heteroaromatic acids. This may be due to inductive electron-withdrawing tendencies of heterocyclic N, O or S atoms. Introduction of phenyl groups (compounds I and III, II and IV, VIII and IX) causes resonance stabilisation of acid anions relative to the protonated acids, while methyl groups (compounds II and XIII, VIII and XIV) enhance the basicity of the acids through inductive electron-donation.

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