

DISSOCIATION OF HYDROXAMIC ACIDS: SOLVENT EFFECTS

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Received April 17, 1992

Accepted October 5, 1992

Dedicated to the memory of the Czechoslovak Academy of Sciences (1952 – 1992).

The dissociation constants of benzohydroxamic, 4-chlorobenzohydroxamic, and 4-nitrobenzohydroxamic acids, and their N-methyl and O-methyl derivatives, were measured spectrophotometrically or potentiometrically in mixtures of 2-propanol and water. The results were extrapolated to zero ionic strength. The ratio of dissociation constants of the O-methyl and N-methyl derivatives can be taken to represent – with some approximation – the ratio of NH and OH acidities of the parent acid. This ratio increases with substitution by electron-attracting substituents, and decreases with solvent permittivity: some irregularities might be attributable to the effects of mixed solvents. It follows that 4-nitrobenzohydroxamic acid behaves essentially as N-acid in all solvents, 4-chlorobenzohydroxamic acid only in 90% 2-propanol or 80% methyl cellosolve. In benzohydroxamic acid the NH and OH acidities are comparable, the latter prevails slightly in water, the former in less polar solvents. Some apparent discrepancies in the literature can be explained in the same terms, only a few results have not yet been explained.

The dissociation of hydroxamic acids (Scheme 1) has been the object of a long-standing controversy^{1,2}. While the structure of the acid may be considered as established^{1,3,4} in favour of the carbonyl tautomer *I*, the structure of the anion is still under investigation. In terms usual in organic chemistry the problem can be formulated as follows: is the bearer of the acidic properties of hydroxamic acids the OH hydrogen (structure of the anion *III*) or NH hydrogen (structure *IV*). In more exact terms of physical chemistry, the task is to determine all equilibrium constants of the reactions $I \rightleftharpoons III$, $I \rightleftharpoons IV$, $II \rightleftharpoons IV$, and $II \rightleftharpoons V$. The older literature and even recent reviews⁵ assume the structure *III*, often without proof, simply in the belief that a hydroxyl group must be more acidic than an imino group. The first experimental support for the structure *III* was claimed by Mathis⁶ (in the crystalline state). On the other hand, the traditional view was challenged by Plapinger⁷ and one of the present authors^{8–11} who claimed an equilibrium mixture $III \rightleftharpoons IV$ or the prevailing form *IV*, respectively.

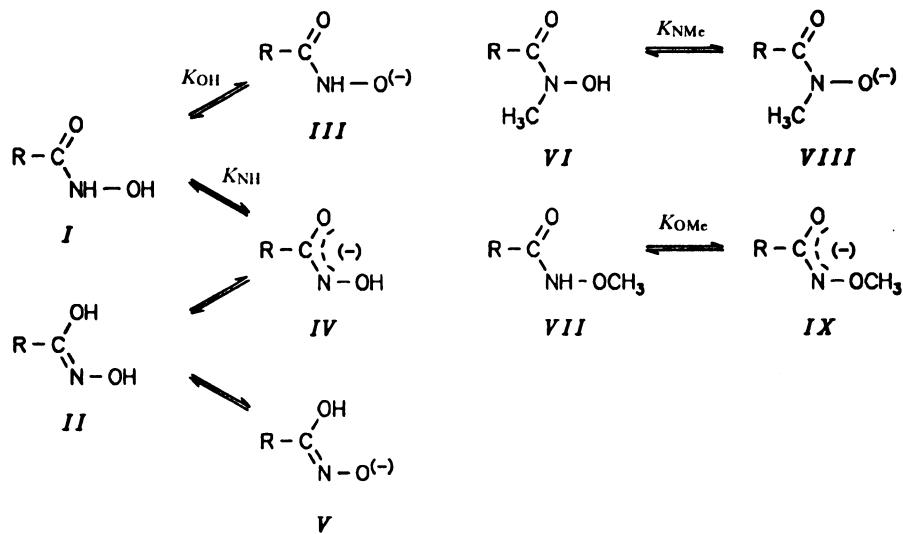
More recent experimental and theoretical findings are collected in Table I. The following remarks explain the apparent contradictions.

1. Strictly speaking, the three forms *III* – *V* are always in equilibrium, but some experimental methods cannot detect amounts less than 5 – 10%.

2. The equilibrium depends both on conditions and on the substituent. Substituents have a greater effect on the close NH hydrogen and favour¹¹ structure *IV*. No conclusions can be extended from one structure to another, nor from one set of conditions to the next.

3. Some results were reached with unwarranted assumptions and are less dependable, see the footnotes to Table I.

With these precautions in mind we may attempt to rationalize the results of Table I as follows. The anion *IV* is the more stable form of the isolated molecule^{12 – 14} and was also observed in the gas phase¹⁵. It prevails even in less polar solvents^{11, 12, 16}, particularly with stronger acids (4-nitrobenzohydroxamic^{10, 11}). In the crystalline phase the stability depends mainly on intermolecular hydrogen bonds. Structure *III* was found most often^{6, 17 – 19}, although some dependence on the specific substitution²⁰ or on the counterion⁹ is possible. The existence of *III* in solution was proven in a less convincing



In formulae *I* – *IX* : a, R = C₆H₅; b, R = 4-ClC₆H₄; c, R = 4-NO₂C₆H₄

SCHEME 1

TABLE I
Structure of the hydroxamic acid anions as inferred from various physical methods

R in RCONHOH	Solvent (state)	Cation	Method	Result ^a	Ref.
H	isol. molecule	—	3-21G	N [—] > O [—]	12
H	isol. molecule	—	MP2/6-31+G**	N [—] + O [—]	14
C ₆ H ₅	isol. molecule	—	AM1	N [—] > O [—]	13
CH ₃	gas	—	FT-ICR	N [—]	15
C ₆ H ₅	dioxan	Li ⁺ , Na ⁺	IR	N [—]	8, 9
CH ₃ , C ₆ H ₅	DMSO	Na ⁺ , K ⁺	pK, E _{ox}	N [—]	16
XC ₆ H ₄	aq. MCS	NMe ₄ ⁺	pK	N [—]	11
C ₆ H ₅	aq. MCS	NMe ₄ ⁺	pK	N [—] (O [—])	11
C ₆ H ₅	EtOH	Na ⁺	UV ^b	O [—]	27
CH ₃ , C ₆ H ₅	MeOH	Na ⁺ , K ⁺	E _{ox}	O [—]	16
C ₆ H ₅	MeOH	Na ⁺	¹⁷ O NMR	N [—]	12
XC ₆ H ₄	aq. EtOH	Na ⁺ , K ⁺	pK ^c	O [—]	23
XC ₆ H ₄	aq. EtOH	Na ⁺ , K ⁺	pK, rates	?	25, 26
C ₆ H ₅	aq. EtOH	Na ⁺	UV	N [—]	8
XC ₆ H ₄	aq. MeOH	Na ⁺	UV	N [—]	10
CH ₃ C ₆ H ₄	aq. MeOH	Na ⁺	UV	N [—] ?	10
C ₆ H ₅	H ₂ O	Na ⁺	pK, rates ^c	O [—] + N [—]	21
XC ₆ H ₄	H ₂ O	Na ⁺ , K ⁺	pK, ΔJ, ΔS ^d	O [—]	22, 23
CH ₃	H ₂ O	Na ⁺ , K ⁺	pK, ΔJ, ΔS ^d	O [—]	22, 23
2-XC ₆ H ₄	H ₂ O	Na ⁺	pK ^c	O [—] > N [—]	2
CH ₃	H ₂ O	?	pK ^{c, f}	O [—]	24
XC ₆ H ₄	H ₂ O	Na ⁺	UV ^g	O [—] + N [—]	7
HONHCO [—]	solid	NH ₃ ⁺	X-ray	O [—]	17
C ₆ H ₅	solid	K ⁺	IR ^h	O [—]	6
C ₆ H ₅	solid	Li ⁺	IR ^h	N [—]	9
XC ₆ H ₄	solid	Li ⁺ , Na ⁺ , K ⁺	IR ^h	O [—]	18
HONHCO [—]	solid	Na ⁺	IR ^h	O [—]	19
4NO ₂ C ₆ H ₄	solid	Na ⁺	ESCA	N [—]	20
C ₆ H ₅	solid	K ⁺	ESCA	O [—] ?	20

^a The results are given in a simplified form as prevalence of the O[—]-anion (III) or N[—]-anion (IV); some doubts indicated here originate in the primary references, our additional criticism is offered in the following notes. ^b The reasons for this decision are not clear, no model compounds were investigated. ^c Based essentially on comparison with N-alkyl and O-alkyl derivatives, the effect of the alkyl group being neglected. ^d Based on a statistically incorrect (see ref.²⁸) plot of ΔJ vs ΔS; the pK's were determined at very high ionic strength. ^e Based on the small steric effect of some ortho substituents. ^f The O-derivative was not available, some values were not confirmed later²². ^g Two absorption bands need not belong to two species. ^h The problem is in the assignment of O-II and N-II stretching frequencies.

way. One can observe it most likely (at least in an equilibrium $III \rightleftharpoons IV$) with unsubstituted hydroxamic acids in water^{2,7,21-24} or in mixed aqueous solvents^{23,25,26}, maybe even in pure alcohols^{16,27}. However, some of these results are to be doubted, see footnotes to Table I.

An important proof was always comparison with N-methylhydroxamic acids *VI* and O-methylhydroxamic acids *VII* as model compounds, since these yield anions of unambiguous structure, *VIII* and *IX*, respectively. (The tautomeric structure of *VII* itself is known¹.) However, the inductive and steric effects of the methyl groups were mostly neglected. At one point we attempted to account for these effects by investigating several substituents in place of the methyl group and interpolating to hydrogen¹¹, but this was accomplished only in one solvent system. Another approach is to make measurements in various solvent mixtures, with the intention of separating the solvent effect on the NH and OH acidities from the inductive effect of the substituent which is less dependent on the solvent. In this paper we report the dissociation constants of three hydroxamic acids, *Ia* - *Ic*, their N-methyl derivatives, *VIa* - *VIc*, and their O-methyl derivatives, *VIIa* - *VIIc*. In mixtures of 2-propanol with water, good solubility is assured and the relative permittivity²⁹ may be varied from 20 to 78. On the other hand, some irregularities must be anticipated, as described recently in mixed solvents³⁰. We further attempted to separate the solvent effects on the anions from those on the neutral acid molecules on the basis of measured solubilities³¹: this was possible only in the case of nitro derivatives.

EXPERIMENTAL AND RESULTS

The compounds *Ia* - *Ic*, *VIa* - *VIc*, *VIIa*, and *VIIc* were characterized previously¹¹, *VIIb* was prepared according to the literature³².

Dissociation constants were measured in mixtures of water and 2-propanol. Both distilled water and 2-propanol (p.a., Lachema) were still twice redistilled, their mixtures were prepared by weighing.

In 20%, 50% and 70% (w/w) 2-propanol and in water, the dissociation constants were measured spectrophotometrically with a Pye-Unicam SP8-100 instrument at (25 \pm 1) °C. The wavelengths used are given in Table II. The apparent values, pK' , were calculated using the equation

$$pK' = \text{pH} - \log [(A_a - A)/(A - A_b)], \quad (1)$$

where A_a , A_b and A are absorbances of the acid, anion and their mixture, respectively. Relatively high sensitivity to ionic strength was reported with several hydroxamic acids^{33,34}. For this reason our measurements were carried out at ionic strengths between $2 \cdot 10^{-3}$ and $5 \cdot 10^{-2}$ mol dm⁻³ and extrapolated to zero ionic strength according to the equation

$$pK = pK' + \sqrt{I}/(1 + \sqrt{I}). \quad (2)$$

The ionic strength was controlled by the addition of NaCl (p.a., Lachema) or - in 70% 2-propanol solutions - $(\text{CH}_3)_4\text{NCl}$ (p.a., Fluka). Further experimental details have been given in a previous paper³⁵. The pK values are given in Table II.

In 90% (w/w) 2-propanol the dissociation constants were measured potentiometrically with a pH-meter Radelkis OP-205, a glass electrode, and an Ag/AgCl electrode filled with LiCl solution in the same solvent system. The electrodes were immersed in the solvent for 20 h, and were calibrated with a set of buffer solutions. For further details see ref.³⁶. The results, extrapolated to zero ionic strength according to Eq. (2), are given in Table II, last column.

The solubilities of compounds *Ia*–*Ic* and of 4-nitrobenzoic acid were determined at 25 °C in water and in 20% and 50% 2-propanol. The temperature was maintained with an accuracy ± 0.1 °C for three weeks, then the solutions were filtered, and the concentration determined, both spectrophotometrically and polarographically. Mean values from the two methods are given in Table III.

DISCUSSION

N-Acidity versus *O*-Acidity

An inspection of Table I reveals that the existence of the anion *V* has not yet been detected in any state. Considering also claims^{1,3,4} that the hydroximic acid *II* practically does not exist, the whole scheme can be restricted to the equilibrium of *I*, *III*, and *IV*. The task is to determine, in each individual case, to what extent a hydroxamic acid behaves as an *N*-acid and to what extent as an *O*-acid. The answer can be given in

TABLE II
The p*K* values of hydroxamic acids in aqueous 2-propanol at 25 °C

Acid	Wavelength nm	p <i>K</i> in aqueous 2-propanol, % (w/w)				
		0	20	50	70	90 ^a
<i>Ia</i>	280	8.81 ^b	8.98	9.90	10.61	11.37
<i>VIa</i>	300	8.58 ^c	8.64	9.87	11.21	12.34
<i>VIIa</i>	265	8.77 ^d	9.28	10.38	10.99	12.09
<i>Ib</i>	285	8.49 ^e	8.55	9.54	10.24	10.74
<i>VIb</i>	300	8.14	9.05	9.84	10.90	12.14
<i>VIIb</i>	277	8.49	9.26	9.65	10.90	11.30
<i>Ic</i>	360	7.87 ^f	7.90	8.51	8.99	9.92
<i>VIc</i>	230	7.84 ^g	8.29	9.46	10.27	11.33
<i>VIIc</i>	370	7.34	7.67	8.54	9.59	10.46
4-Nitrobenzoic	–	3.43 ^h	4.14	5.00	5.48	6.03

^a Determined potentiometrically. ^b In reasonable agreement with most of the literature data^{21,37,38,39}: 8.80, 8.75, 8.79 and 8.91, respectively (*I* = 0.1); further measurements were carried out at high ionic strengths^{22,40,41}: 8.42, 8.88, 8.805, respectively, or at 30 °C: 8.43, ref.³³. ^c The literature²¹ gives 8.59 at *I* = 0.1, or 7.90 and 8.28 at high ionic strength^{22,42}. ^d The literature^{11,21} gives 8.89 and 8.88, respectively. ^e The literature³⁹ gives 8.70, further 8.58 and 8.62, respectively, at a high ionic strength^{40,41}. ^f The literature^{11,39,43} gives 8.02, 8.12, and 8.01, respectively, in addition 8.35 at a high ionic strength⁴¹. ^g The literature⁴² gives 7.94. ^h From ref.⁴⁴.

terms of the tautomeric equilibrium constant K_T that gives the relative population of the anions *III* and *IV*

$$K_T = K_{\text{NH}}/K_{\text{OH}}. \quad (3)$$

The relation to the experimental dissociation constant reads

$$K_{\text{exp}} = K_{\text{NH}} + K_{\text{OH}}. \quad (4)$$

Equations (3) and (4) are valid for each of the structures *a*, *b*, *c* and for each of the five solvent systems. Their approximate solution is possible by referring to the dissociation constants K_{NMe} and K_{OMe} of the methyl derivatives instead of to the unknown values K_{OH} and K_{NH} . Several methods of approximation are possible.

The first type of approximation, common in the literature²¹⁻²⁴, neglects completely any substituent effect of the methyl group, by assuming $K_{\text{OH}} = K_{\text{NMe}}$ and $K_{\text{NH}} = K_{\text{OMe}}$. Equations (5) and (6) then follow from Eqs (3) and (4).

TABLE III
Solubilities and Gibbs energies of transition of 4-nitrobenzohydroxamic acid and derivatives (25 °C)

Acid	2-Propanol % (w/w)	$c_{\text{sat}} \cdot 10^3$ mol dm ⁻³	$\Delta G_{\text{tr}}^0(\text{diss})^a$ kJ mol ⁻¹	$-\Delta G_{\text{tr}}^0(\text{IIA})^b$ kJ mol ⁻¹	$\Delta G_{\text{tr}}^0(\text{A}^-)^c$ kJ mol ⁻¹
<i>Ic</i>	0	11.5	0	0	0 (0)
	20	19.8	0.2	1.3	6.6 (5.9)
	50	86.4	3.6	5.0	20.4 (22.0)
<i>VIc</i>	0	1.35	0	0	0 (0)
	20	2.78	2.6	1.8	8.4 (5.9)
	50	38.9	9.2	8.3	22.6 (22.0)
<i>VIIc</i>	0	5.21	0	0	0 (0)
	20	11.9	1.9	2.1	7.4 (4.9)
	50	41.9	6.8	5.2	23.4 (18.1)
4-Nitro- benzoic	0	2.05	0	0	0 (0)
	20	4.38	4.0	1.9	9.8 (7.2)
	50	37.5	9.0	7.2	23.5 (26.9)
<i>VIc-VIIc</i>	20	—	0.7	-0.3	1.0 (1.0)
	50	—	2.4	3.2	-0.8 (3.9)

^a Calculated from the dissociation constants, estimated accuracy ± 0.2 . ^b Calculated from the solubilities, estimated accuracy ± 0.3 . ^c Calculated from the two preceding columns by means of Eq. (13), estimated accuracy ± 0.4 ; in parentheses – calculated by the electrostatic theory, Eq. (14).

$$K_T \approx K_{\text{OMe}} / K_{\text{NMe}} \quad (5)$$

$$K_{\text{exp}} \approx K_{\text{OMe}} + K_{\text{NMe}} \quad (6)$$

Using this approximate approach K_T can be determined from Eq. (5) while Eq. (6) serves as a test of accuracy. In our case the accuracy was very low, the deviations having been systematic: in 70% and 90% 2-propanol the alkyl derivatives are weaker acids, and in the remaining solvents stronger acids, than required by Eq. (6). The differences are as great as 0.5 pK units. The former case can be explained in terms of steric and/or electron-releasing effects of the methyl group, the latter is less clearly understandable. In any event, the method is insufficiently accurate.

In the second approximation¹¹ we may assume that the substituent effect of the methyl group is given (in terms of any "linear free energy relationship") as the product $\rho\sigma$, where the substituent constant σ need not be specified (steric, inductive etc.).

In the two equations

$$\log K_{\text{NMe}} = \log K_{\text{OH}} + \rho_O \sigma \quad (7)$$

$$\log K_{\text{OMe}} = \log K_{\text{NH}} + \rho_N \sigma \quad (8)$$

the substituent constant σ is the same and the two reaction constants ρ need not be very different in a given solvent since the distances from methyl to the ionizable proton are equal. Assuming $\rho_O = \rho_N$ we obtain instead of Eq. (4)

$$K_{\text{exp}} = (K_{\text{NMe}} + K_{\text{OMe}}) \cdot 10^{-\rho\sigma}. \quad (9)$$

Equation (5) remains without change as in the first approximation. Equation (9) can be tested for every solvent system whether $\rho\sigma$ is constant, or not. The values shown in Table IV (last line) show that the accuracy is not so bad, considering both the experimental error and discontinuities described generally in mixed solvents³⁰. Only in 20% 2-propanol the agreement is bad: the results in this solvent system should be disregarded or at least viewed as less dependable. (The described anomalies³⁰ were greatest in 25% tert-butanol: there was a jump in the dependence on solvent composition.) We considered the result of this test to be satisfactory justification for using this method, and we calculated K_T according to Eq. (5).

The results collected in Table IV are very crude due to the afore mentioned sources of inaccuracy, both experimental and theoretical. Nevertheless, their general trend is evident. Strong hydroxamic acids in less polar solvents behave exclusively as N-acids, the O-acidity makes itself felt with weaker acids and in polar solvents, particularly in water. It follows that I_c can be considered essentially an N-acid in all solvents^{10,11}, and

Ia may behave predominantly as an O-acid or as an N-acid depending on the solvent¹⁶, but the literature²¹ was not very far off in stating that in water the ratio of the two anions is approximately 1 : 1. Table IV includes several items of data concerning additional acids and solvents, some of which have already been discussed in the literature^{11,15,16,25}. A recent discussion of these data did not account for the dependence on structure and solvent (see Table IV, footnote *h*) and thus unjustly rejected the whole approach²³. In our opinion the data of Table IV might be inexact, loaded with several approximations, and in some points questionable (for instance for acetohydroxamic derivatives in water⁴⁵). Nevertheless, there is unquestionably a general trend. Note further that the solvent dependence is probably not well described in terms of the relative permittivity. Perhaps the constant E_T would work somewhat better but the values are not known for all solvent systems.

In the approach described above, it was assumed that $\rho_O = \rho_N$. This constraint might cause a systematic error in the data of Table IV when K_{OMe}/K_{NMe} is interpreted as K_{NII}/K_{OH} . Without this constraint, one gets instead of Eqs (5) and (9) the following expressions

$$K_T = \frac{K_{NMe}}{K_{OMe}} \cdot 10^{(\rho_O - \rho_N) \sigma} \quad (10)$$

TABLE IV
Tautomeric equilibrium constants ($\log K_T$) for the deprotonation of hydroxamic acids^a

Solvent	Gas ^h	DMSO ^c	80% (w/w) MCS ^d	90 ^e	70 ^e	50 ^e	20 ^e	12% (v/v) MeOH ^f	H ₂ O ^g
<i>ε_r</i>	1	46.5	33	20.6	28.8	42.6	64.2	73.1	78.3
<i>Ic</i>	—	—	1.2 ^h	0.9	0.7	0.9	(0.5)	0.3 ^h	0.5
<i>Ib</i>	—	—	—	0.8	0	0.2	(-0.2)	—	-0.3
<i>Ia</i>	—	—	~ 0.2	0.3	0.2	-0.5	(-0.6)	—	-0.2
CH ₃ CONHOH	2.5	2.5	—	—	—	—	—	—	-1.1 ⁱ
4-CH ₃ OC ₆ H ₄ . CONHOH	—	—	—	—	—	—	—	-0.6 ^h	—
ρ_O^d	—	—	—	-0.5	-0.4	0.1	?	—	0.5
				± 0.02	± 0.1	± 0.05			± 0.1

^a Estimated approximately according to Eq. (5), see Discussion. ^b Ref.¹⁵. ^c Ref.¹⁶. ^d Aqueous 2-methoxyethanol, ref.¹¹. ^e Weight percent of aqueous 2-propanol, this work. ^f Aqueous methanol, ref.²⁶. ^g This work, except acetohydroxamic acid. ^h These three values were considered²³ to show the unreliability of the method. ⁱ Calculated from the values for N-methylacetohydroxamic acid and O-methylacetohydroxamic acid⁴⁵, the latter is very different from the value for *VIIa* and does not seem quite reliable. ^j Calculated according to Eq. (9) separately for the compounds *Ia* – *Ic*, the variance is a measure of model fitting.

$$K_{\text{exp}} = [K_{\text{NMe}} + K_{\text{OMe}} \cdot 10^{(\rho_0 - \rho_N)\sigma}] \cdot 10^{-\rho_0\sigma}. \quad (11)$$

The two parameters in Eq. (11) could in principle be fitted to experimental K_{exp} ; subsequently the parameter $(\rho_0 - \rho_N)$ could be introduced into Eq. (10). However, the noise in our data was too great and reasonable estimates of the parameters were not obtainable, either with $(\rho_0 - \rho_N)$ constant in the whole series or different in each solvent system. In our opinion we must be satisfied with the method denoted as the second approximation which results in Eqs (5) and (9).

More Detailed Analysis of Solvent Effects

We have also attempted to proceed one step further by dividing the relative Gibbs energy of ionization (i.e. the solvent effects on pK) into the effects in the anion and in the undissociated acid. This would be of importance in testing the suitability of our methyl derivatives *VI* and *VII* as model compounds. Addition of 2-propanol to water increases the relative stability of the anion *IV* versus *III*. Compounds *VI* and *VII* would be better model compounds if their solvent effects were mainly due to the anions *VIII* and *IX* since the energy of the neutral species *VI* and *VII* has less relevance to the processes $I \rightleftharpoons III$ or $I \rightleftharpoons IV$. We used the experimental approach based on the determination of solubility^{31,46}. Unfortunately, this was possible only in the case of slightly soluble nitro derivatives *Ic*, *VIc*, and *VIIc*; for comparison we also measured 4-nitrobenzoic acid. The reason is that only at a low solubility can the activity coefficients be taken as equal to unity. However, nitro derivatives are not the best object of study since the change of equilibrium with solvent is relatively small. From the solubilities in a given solvent and in water, c_s and c_w , respectively, we get the Gibbs energy of transition of the neutral molecule HA

$$\Delta G_{\text{tr}}^0(\text{HA}) = RT \ln(c_w/c_s). \quad (12)$$

The transition energy of the anion follows from the thermodynamic cycle

$$\Delta G_{\text{tr}}^0(\text{diss}) = \Delta G_{\text{tr}}^0(\text{H}^+) + \Delta G_{\text{tr}}^0(\text{A}^-) - \Delta G_{\text{tr}}^0(\text{HA}), \quad (13)$$

where ΔG_{tr}^0 of the dissociation is defined from the ratio of dissociation constants in the two solvents. In Table III are listed the experimental values of $\Delta G_{\text{tr}}^0(\text{diss})$, $\Delta G_{\text{tr}}^0(\text{HA})$, and the values of $\Delta G_{\text{tr}}^0(\text{A}^-)$ calculated from them. The latter are also compared with the theoretical values calculated according to the Born equation⁴⁷

$$\Delta G_{\text{tr}}^0(\text{A}^-)_{\text{clst}} = \frac{N_A e^2 z^2}{2 r \epsilon_0} (1/\epsilon_s + 1/\epsilon_w), \quad (14)$$

where the relative permittivities ϵ_s and ϵ_w are experimental values²⁹. Comparison with theoretical values (Table III, the last two columns) gives a reasonable agreement, particularly with respect to the uncertainty in the estimated ionic radius r . It follows that $\Delta G_{tr}^0(A^-)$ is mainly due to the electrostatic contribution. Its values are positive and relative great, hence the dissociation must be suppressed by 2-propanol. Remarkably, the values of $\Delta G_{tr}^0(A^-)$ are very similar for different compounds. The comparison of N-methyl and O-methyl derivatives is carried out at the bottom of Table III. The difference values are not very significant in 20% 2-propanol, given that the experimental uncertainty is especially great in this solvent. In 50% 2-propanol $\Delta G_{tr}^0(HA)$ is more important than $\Delta G_{tr}^0(A^-)$. Therefore, we cannot justify the methyl derivatives as reliable model compounds for the ionization of the parent acid: there is no apparent reason why the energy changes in the neutral molecules *Vlc* and *VIIc* should be paralleled in the anions *IIIc* and *IVc*. More important would be the results on unsubstituted compounds *Ia*, *Vla*, and *VIIa*, which, however, cannot be investigated by the same method. We note that this reasoning concerns only the relative values with reference to water, i.e. the solvent effect. The significance of methyl derivatives as model compounds in general is not totally invalidated.

Hammett Correlations

Our data set, Table II, may be viewed as a three-dimensional matrix of which two dimensions have thus far been treated: dependence on methyl substitution and dependence on solvent. There remains the third dimension, dependence on ring substitution, which will be discussed now in terms of the Hammett equation. The Hammett correlations have been quite important in previous papers^{11,25,39,41,48}. In particular, the value of the reaction constant ($\rho = 1$ in water) was considered evidence for the dissociation on nitrogen^{11,49} (ionization on the second atom from the benzene ring as in benzoic acids). This reasoning was supported by the ρ constant of O-benzylbenzohydroxamic acids¹¹, which was of similar magnitude as the value for benzohydroxamic acids in the same solvent, while ρ for N-methylbenzohydroxamic acids was approximately one-half the magnitude. We feel that our data, restricted to three compounds, can hardly add relevant information in this respect. Nevertheless, we have collected available data on Hammett reaction constants, which are given in Table V. Neglecting the inherent inaccuracy and some unexplained irregularities (see the footnotes to Table V), it is evident that the ρ constant for N-alkyl derivatives is approximately one-half of the value for O-derivatives in the same solvent. The unsubstituted hydroxamic acids show the ρ constant more or less similar to those of the O-derivatives; this is compatible with their dissociation as N-acids¹¹. We have already mentioned¹¹ that conclusions based on the Hammett plot are not necessarily valid for all the compounds included. When a tautomeric equilibrium is involved, the two acidic hydrogen atoms are unevenly

influenced by substitution and the Hammett plot should be curved⁴⁹. The dependence of the equilibrium constant on the Hammett constants is expressed by the equation⁴⁹

$$\log K = \log (10^{\rho_N \sigma} K_N^0 + 10^{\rho_O \sigma} K_O^0), \quad (15)$$

where ρ_N and K_N^0 belong to the dissociation on nitrogen, and ρ_O and K_O^0 to the dissociation on oxygen. In fact, it would not be possible to obtain the four parameters of Eq. (15) by any nonlinear regression using the experimental data sets available in the literature. However, information resulting from the foregoing analysis enables us to fit the remaining parameters at least in some cases. Much data in the literature^{37,40,41,48} disagree with each other, particularly due to the use of different ionic strengths. We

TABLE V

Reaction constants of the Hammett equation for the dissociation of hydroxamic acids, their N-alkyl and O-alkyl derivatives

Solvent	Hydroxamic acids	N-methylhydroxamic acids	O-methylhydroxamic acids	Ref.
H ₂ O (30 °C, <i>I</i> = 0.1)	0.98	—	—	48
H ₂ O (20 °C, <i>I</i> = 1.0)	0.58	—	—	41
H ₂ O (25 °C, <i>I</i> = 0)	1.00	—	—	39
H ₂ O (25 °C, <i>I</i> = 0)	~ 1.1	~ 0.9	~ 1.8	^c
Ethanol, 12% (v/v)	0.96 ^a	0.65	1.45	26
Methoxyethanol, 80% (w/w)	1.70	0.95	1.81 ^b	11
2-Propanol, 50% (w/w)	1.7	~ 0.5	~ 2.1	^c
2-Propanol, 70 or 90% (w/w)	~ 1.9	1.2	~ 1.9	^c

^a Hammett plot yields two straight lines with equal slopes. ^b O-benzyl derivatives. ^c This work.

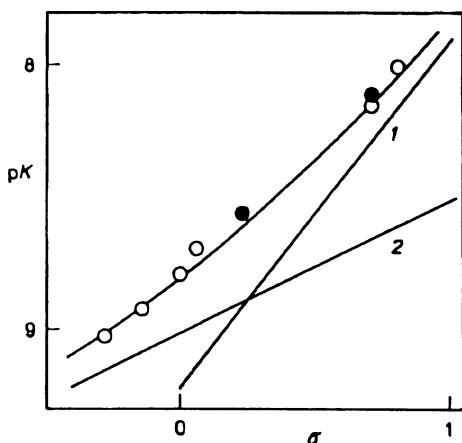


FIG. 1

Correlation of the dissociation of substituted benzohydroxamic acids with the modified Hammett equation. The curve calculated according to Eq. (15), the asymptotes correspond to the contributions of the NH acidity (1) and OH acidity (2), respectively; ○ experimental points ref.⁴⁸, ● refs^{37,41}

have chosen the longest available series of pK in water⁴⁸ and correlated it with Eq. (15). The ρ values were estimated from the data of Table V as follows: $\rho_N = 1.3$ (somewhat more than for unsubstituted acids), $\rho_O = 0.6$ (less than one-half of the latter). We got $\log K_N^0 = -9.22$ and $\log K_O^0 = -9.02$; the fit is shown in Fig. 1. The two asymptotes of the curve correspond to the NH acidity and the OH acidity, respectively. The former is the controlling factor at higher σ values, the latter at lower values. At approximately $\sigma = 0.25$, the two protons are of equal acidity, the distance from the point of intersection of the asymptotes to the curve equals $\log 2$. The fit is quite good, so the assumptions are probably realistic. Essentially the same result was obtained with another data set³⁹, but the pK values are mainly shifted by about 0.1 pK units. However, without knowing the detailed mechanism, one would draw a simple straight line in Fig. 1 with good accuracy. It is probable that several Hammett plots published in the literature should be replaced by such curves, but this is mostly impossible without additional information. The purpose of Fig. 1 and of the accompanying analysis was just to show that the effect of ring substitution agrees with the results reached in previous sections.

CONCLUSIONS

The results of this study are in general accordance with most of the data in Table I, though they are expressed more quantitatively. Hydroxamic acids usually behave as N-acids. The tautomeric equilibrium constant K_T ranges from almost 10^3 (acetohydroxamic acids in the gas phase¹⁵ or in dimethyl sulfoxide¹⁶) to approximately 0.5 (benzohydroxamic acid in water). In solution, K_T depends strongly on the solvent polarity. There are few claims in the literature which appear to disagree with this generalization. The most important discrepancy seems to be between the results of ^{17}O NMR spectroscopy¹² and those of cyclic voltammetry¹⁶ in the case of benzohydroxamic acid in methanol (Table I). In our opinion both anions should be present with the N-anion prevailing. The two methods seem to be ineffective in detecting minor components; this also applies to UV spectroscopy^{8,10,27}. Disregarding these exceptions, most of which have been insufficiently investigated, we believe that the long-standing controversy has been essentially solved. Hydroxamic acid anions represent further example where the tautomeric equilibrium depends on the solvent very strongly.

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Translated by the author (O. E.).