Acid Dissociation Constants (K_a) and Their Temperature Dependencies (ΔH_a, ΔS_a) for a Series of Carbon- and Nitrogen-Substituted Hydroxamic Acids in Aqueous Solution

Bruce Monzyk and Alvin L. Crumbliss*

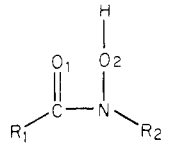
Department of Chemistry, P. M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received January 25, 1980

The acid dissociation constants (K_a) of a series of six C- and N-substituted hydroxamic acids, $R_1C(O)N(OH)R_2$ (R_1 = CH_3, C_6H_5; R_2 = H, CH_3, C_6H_5), have been determined in aqueous solution (I = 2.0) for a range of temperatures. In contrast to many other organic acids, large variations in ΔH_a and ΔS_a were found to exist for these hydroxamic acids. The pK_a data at 25 °C exhibit random variations with changes in the R_1 and R_2 substituents, while regular variations are seen in ΔH_a and ΔS_a. A plot of ΔH_a vs. ΔS_a is linear and suggests that the ionization processes for all six hydroxamic acids are the same. This requires that $CH_3C(O)N(OH)H$ and $C_6H_5C(O)N(OH)H$ ionize in aqueous solution by the loss of the O–H proton rather than the N–H proton. This is the first instance in which this differentiation has been possible and is a direct result of the temperature-dependence study. A model is presented which qualitatively rationalizes the variations in the ΔH_a and ΔS_a values. This model is based upon the changes in solvation with changes in molecular dipole which accompany ionization. It is concluded that the greater the increase in the molecular dipole upon ionization the larger the increase in solvation. This lowers ΔH_a and ΔS_a through anion–solvent interaction. Data obtained in less polar nonaqueous solvents indicate that the *N*-methyl acids [$CH_3C(O)N(OH)CH_3$ and $C_6H_5C(O)N(OH)CH_3$] exist in equilibrium with a dimer formed through H bonding.

Hydroxamic acids are weak organic acids[1] with a wide variety of applications including use as commercial flotation reagents in extractive metallurgy, as inhibitors for copper corrosion, as antifungal agents, in pharmaceuticals, as food additives, and in nuclear fuel processing. One of the characteristics of hydroxamic acids is their ability to form stable transition-metal complexes,[2] which forms the basis for their usefulness as analytical reagents.[3] The hydroxamic acid functional group has been noted to exhibit a high affinity for iron(III) relative to other biologically important metal ions. Presumably for this reason several naturally occurring siderophores have been found to possess hydroxamic acid structures.[4] This feature has also prompted the testing of synthetic and naturally occurring hydroxamic acids as therapeutic agents to remove iron from iron-overloaded mice and humans.[5-9]

The acidity of the hydroxamic acid functional group is often related to the useful application of these compounds as noted above. It is, therefore, of interest to determine the factors which influence proton dissociation, and it is to this end that we have investigated the temperature dependence of this process in aqueous solution for a series of related C- and N-substituted hydroxamic acids (I).



I, R_1 = CH_3, C_6H_5; R_2 = H, CH_3, C_6H_5

Several reports of pK_a values for hydroxamic acids are available in the literature, including single-temperature data for some of the hydroxamic acids reported here.[10] However, these data were collected at variable conditions which makes quantitative comparisons difficult. Furthermore, to the best of our knowledge, ΔH_a and ΔS_a data for acid dissociation in aqueous solution are not available in the literature for any series of related monohydroxamic acids.[11]

Experimental Section

Materials. Sodium nitrate (Fisher, ACS Certified) was recrystallized from water prior to use. Aqueous solutions were prepared by using water distilled once from acidic $K_2Cr_2O_7$ and then slowly from basic $KMnO_4$ in an all-glass apparatus with Teflon sleeves and stopcocks. The following are starting materials for synthesizing hydroxamic acids and were used without further purification: $C_6H_5C(O)Cl$ (Eastman, ACS Reagent), $CH_3C(O)Cl$ (Aldrich), $CH_3NHOH{\cdot}HCl$ (Aldrich). C_6H_5NHOH was syn-

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(2) For a recent review, see: Chatterjee, B. *Coord. Chem. Rev.* **1978**, *26*, 281.

(3) See, for example: (a) Brandt, W. W. *Rec. Chem. Prog.* **1960**, *21*, 159; (b) Mojumdar, A. K. *Int. Ser. Monogr. Anal. Chem.* **1972**, *50*.

(4) (a) Emergy, T. In "Metal Ions in Biological Systems"; Sigel, H., Ed.; Marcel Dekker: New York, 1978; Chapter 3. (b) Neilands, J. B. *Adv. Chem. Ser.* **1977**, *No. 162*, 3. (c) Neilands, J. B., Ed. "Microbial Iron Metabolism"; Academic Press: New York, 1974. (d) Neilands, J. B. In "Inorganic Biochemistry"; Eichhorn, G., Ed.; American Elsevier: New York, 1973; Chapter 5.

(5) Anderson, W. F.; Hiller, M. C., Eds. "Development of Iron Chelators for Clinical Use"; U. S. Govt. Printing Office: Washington, DC, 1977; No. (NIH) 76-994.

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(9) Grady, R. W.; Graziano, J. H.; White, G. P.; Jacobs, A.; Cerami, A. *J. Pharmacol. Exp. Ther.* **1978**, *205*, 757.

(10) For compilations of proton dissociation data, see: (a) Serjeant, E. P.; Dempsey, B. *IUPAC Chem. Data Ser.* Pergamon Press: New York, **1979**, *No. 23*; (b) Martell, A. E.; Smith, R. M. "Critical Stability Constants"; Plenum Press: New York, 1977, Vol. 3; (c) Sillen, L. G.; Martell, A. E. *Spec. Publ.-Chem. Soc.* **1964**, *No. 17*; *Spec. Publ.-Chem. Soc., Suppl. 1*, **1971**, *No. 25*.

(11) Reference 12 contains pK_a data obtained at various temperatures in an ethanol/water solvent mixture for a different series of hydroxamic acids from that reported here; the authors did not use these data to calculate ΔH or ΔS values. Reference 13 contains ΔH and ΔS values for another series of hydroxamic acids which were calculated from data obtained in dioxane/water solvent mixtures at two temperatures. Results for $C_6H_5C(O)N(OH)H$ from ref 12 and 13 are in qualitative agreement with those presented here, once correction is made for differing conditions.

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(13) Maru, P. C.; Khadikar, P. V. *Thermochim. Acta* **1978**, *27*, 373.

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thesized from $C_6H_5NO_2$ by reduction with zinc.[14]

Instrumentation. Molecular weights were determined by vapor-phase osmometry using a Hewlett-Packard Mechrolab Model 301A osmometer. ^1H NMR spectra were obtained by using a JEOL Model JNM-MH-100 100-MHz nuclear magnetic resonance instrument. IR spectra were obtained by using a Perkin-Elmer Model 297 spectrophotometer. Hydroxamatoiron(III) complexes were studied by using a Beckman Model Acta III UV/vis spectrophotometer. Gas chromatography and mass spectral data were collected by using a Hewlett-Packard 5992A GC/MS system. pH measurements were made by using a Beckman Model 4500 pH meter capable of ±0.001 pH unit precision and a Markson Polymark combination electrode.

Hydroxamic Acids. $CH_3C(O)N(OH)H$, $C_6H_5C(O)N(OH)H$, and $C_6H_5C(O)N(OH)C_6H_5$ were purchased from Eastman Chemical Co., recrystallized twice from ethyl acetate, and dried in vacuo. The purity of these compounds was checked by elemental (C, H, N) analysis (MHW Laboratories; see Table II), melting points, ^1H NMR and IR spectra, and equivalent weights obtained from pH titrations. $C_6H_5C(O)N(OH)CH_3$, $CH_3C(O)N(OH)CH_3$, and $CH_3C(O)N(OH)C_6H_5$ were prepared by reacting the appropriate acid chloride and N-substituted hydroxylamine in $(C_2H_5)_2O$ according to published procedures for similar compounds.[15] Reaction temperatures were 0, −78, and −10 °C, respectively. The product mixtures were distilled at reduced pressure (2 torr) two to four times; in the last two distillations the first 10% and last 50% of the distillate were discarded. The last portion contained much hydroxamic acid but was discarded to avoid contamination from a byproduct (most probably $R_1C(O)ONHR_2$) which distilled over with the hydroxamic acid during the latter stages of the distillation. (The carbonyl region of the IR spectrum is useful for monitoring distillate purity with respect to this byproduct.) Equivalent weights obtained from pH titrations, IR and ^1H NMR spectra, boiling points, and elemental (C, H, N) analyses (MHW Laboratories; see Table II) were used as criteria of purity. These hydroxamic acids were stored refrigerated in a desiccator containing $CaSO_4$ until use. All experiments were carried out on freshly prepared solutions of hydroxamic acids. Aqueous solutions of these hydroxamic acids (10^{-4}–10^{-3} M, pH ~5) are stable for long periods (at least 1 week) when refrigerated.

pH Titrations. Buffers for calibration were used at the temperature for which the pH values are known in conjunction with pH meter temperature-adjustment controls. Calibration values obtained before and after each pH titration were reproducible to within 0.002 pH units. All measurements were made by using a water-jacketed cell connected to a constant-temperature bath capable of maintaining temperature control to within 0.05 °C. For the determinations employing just 5 mL of sample solution, the temperature of the circulating liquid was read immediately after it exited from the titration cell. The temperature of the solution itself was read for those cases where 50-mL sample solutions were analyzed. At least 15 min was allowed for temperature equilibration for both buffers and samples. Reagents were prepared by using CO_2-free water and recrystallized $NaNO_3$. Sodium nitrate was used to maintain the ionic strength at 2.0.[16]

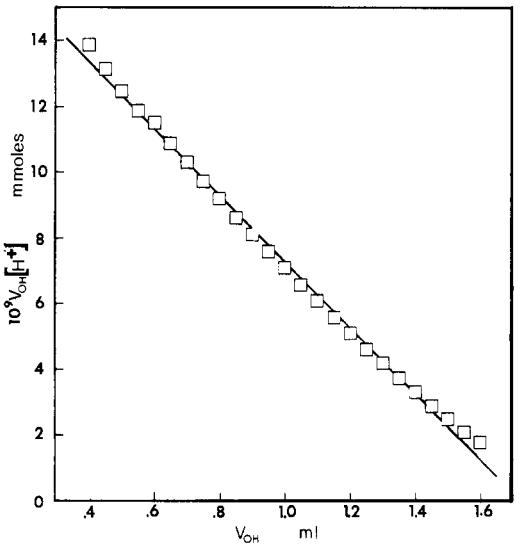

Figure 1. Analysis of potentiometric data for $C_6H_5C(O)N(OH)C_6H_5$ according to eq 1. Equal weighting of data is illustrated. The corresponding K_a value is given in Table I.

Table I. Comparison of Acid Dissociation Constant (K_a) Computational Methods for $C_6H_5C(O)N(OH)C_6H_5$[a]

method	% rxn	10^3K_a[b]
direct from pH vs. V_{OH} plot		1.11 (0.02)
eq 1, Figure 1	100	1.09 (0.05)
	75	1.01 (0.01)
eq 3, Figure 2	100	1.11 (0.05)
	75	1.01 (0.01)

[a] T = 25.0 °C; I = 2.0 ($NaNO_3$). [b] Number in parentheses represents one standard deviation determined by using ca. 25 pH and V_{OH} values.

Aqueous solutions of CO_2-free NaOH were prepared by using standard techniques[19] and standardized with dried KHP (Fisher, ACS Certified acidimetric standard). Wet CO_2-free air was passed over the capped solutions during titration. A typical experiment (except for $C_6H_5C(O)N(OH)C_6H_5$) consisted of the titration of 5.00 ± 0.01 mL of hydroxamic acid (ca. 6.4×10^{-3} M) with NaOH (2.021×10^{-2} M) using a 2-mL buret graduated in units of 0.01 mL. The addition of NaOH was made in 0.05-mL increments or less. Both solutions were 2.00 M in $NaNO_3$. Due to the lower solubility of $C_6H_5C(O)N(OH)C_6H_5$, 50 mL of a ca. 6.4×10^{-4} M solution was used. Each acidity constant (pK_a) determination was performed in triplicate at each of four temperatures, with the exception of $CH_3C(O)N(OH)CH_3$ on which two sets of triplicate determinations were made on different sample preparations at 25 °C. The pK_a value was determined from the slope of a plot of $[H^+]V_{OH}$ vs. V_{OH}, where V_{OH} is the volume of base added. For optimum precision, 20–25 data points representing the region corresponding to 20–80% of complete neutralization were used in the data analysis. Justification for this method of data analysis is presented below. Computations were performed by using a DEC Model PDP8/f minicomputer.

pK_a Determinations. Equation 1 can be derived by assuming that during any increment of the titration all of the OH^- added reacts completely with the hydroxamic acid (HA). In eq 1, $[H^+]$

$$[H^+]V_{OH} = (-K_a)V_{OH} + K_aC_iV_i/N_{OH} \quad (1)$$

$= 10^{-pH}$, V_{OH} = volume base added in liters, K_a = acid dissociation constant, C_i = initial concentration of HA, V_i = initial volume

(14) (a) Coleman, G. H.; McCloskey, C. M.; Stuart, F. A. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol III, p 668. (b) Berndt, D. C.; Fuller, R. L. *J. Org. Chem.* **1966**, *31*, 3312. (c) Berndt, D. C.; Sharp, J. K. *Ibid.* **1973**, *38*, 396.

(15) Gupta, V. K.; Tandon, S. G. *J. Indian Chem. Soc.* **1969**, *46*, 831.

(16) Measurements were made at high ionic strength (2 M $NaNO_3$) so that the resultant pK_a values could be used directly in our iron(III)–hydroxamic acid complexation studies,[17] which required acidities up to 2 M $HClO_4$. High ionic strength was maintained to ensure constant activity coefficients. Although the use of 2 M $NaNO_3$ to maintain constant ionic strength may reduce the resultant accuracy of the pK_a values (due to uncertainty in the activity coefficients) determined in this work, their magnitudes are very reasonable when compared to results found in the literature at lower ionic strength.[10] For those hydroxamic acids where literature data are available, the close agreement of the pK_a values reported here at 25°C with those previously reported at lower ionic strengths suggests that the sensitivity of the pK_a values to ionic strength is not large. Furthermore, the *relative* acidities of the hydroxamic acids should remain the same at these higher (and constant) ionic strengths since the charges involved in the ionization reaction are the same for all of the acids. Sodium ion effects are negligible over the pH and temperature range used in this study.[18]

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(18) Bates, R. G. "Determination of pH", 2nd ed.; Wiley: New York, 1973; Chapter 11.

(19) Kolthoff, I. M.; Sandell, E. B.; Meehan, E. J.; Bruckenstein, S. "Quantitative Chemical Analysis", 4th ed.; MacMillan: London, 1969; p 781.

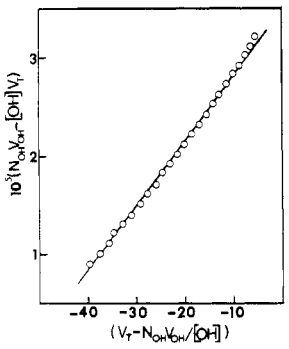


Figure 2. Analysis of potentiometric data for $C_6H_5C(O)N(OH)C_6H_5$ according to eq 3. The data represented are the same as those shown in Figure 1. Equal weighting of data is illustrated. The corresponding K_a value is given in Table I.

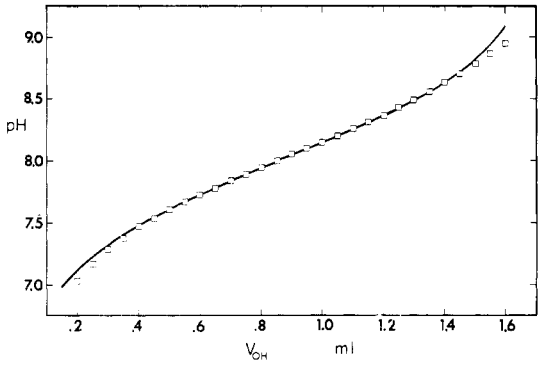


Figure 3. Correlation between experimental titration curve (□) for $C_6H_5C(O)N(OH)C_6H_5$ and that computed by using least square K_a values determined by using eq 1 (solid line). The data represented are the same as those shown in Figure 1.

of HA solution, and N_{OH} = molarity of standard NaOH. Figure 1 represents an example of the fit of eq 1 to the data for $C_6H_5C(O)N(OH)C_6H_5$. This figure demonstrates the sizable $[H^+]$ and V_{OH} changes which occur during the titration and the relatively equal weighting of the experimental data points that data reduction by eq 1 provides. The K_a values corresponding to Figure 1 and eq 1 are given in Table I.

An additional check was made on the validity of the assumption made in deriving eq 1. If complete reaction of OH^- with HA throughout the titration is not stipulated, then the equilibrium shown in eq 2 must be considered, where $K_{eq} = K_a/K_w$. This

$$HA(aq) + OH^- \overset{K_{eq}}{\rightleftharpoons} A_{aq}^- + H_2O \quad (2)$$

approach yields eq 3 (where V_t = total solution volume = V_{OH}

$$N_{OH}V_{OH} - [OH^-]V_t = C_iV_i + \left(V_t - \frac{N_{OH}V_{OH}}{[OH^-]}\right)\frac{1}{K_{eq}} \quad (3)$$

+ V_i and $[OH^-] = K_w/10^{-pH}$), which is independent of the previous assumption that the reaction of OH^- with HA is complete. Figure 2 is a plot of eq 3 for the same data used in Figure 1. Again the data points have the desirable pattern of being fairly equally spaced. Although two subtractions appear in eq 3, it is clear from Figure 2 that a high level of precision is still maintained. This arises as a result of the fact that the $[OH^-]V_t$ and V_t terms are negligibly small as compared to the $N_{OH}V_{OH}$ and $N_{OH}V_{OH}/[OH^-]$ terms, respectively. The K_a value for $C_6H_5C(O)N(OH)C_6H_5$ determined by using eq 3 is also given in Table I. (K_w was computed from the corresponding ΔH_w and ΔS_w values reported at I = 3.[10b]). From Table I it is clear that fits of the data to eq 1 or 3 yield the same K_a value and, most desirably, that the fits are not sensitive to which points at low and high V_{OH} are discarded. This feature removes the amibiguity associated with data reduction. Both data reduction methods are also useful for the middle 75% of the titration data. Figure 3 illustrates the agreement between the pH values predicted by using K_a values

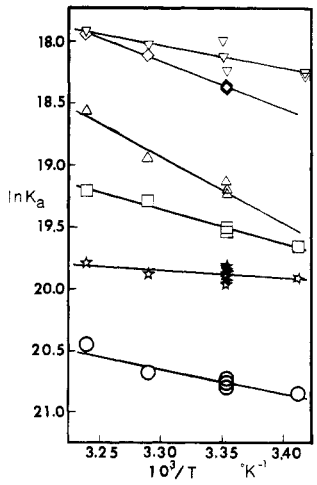


Figure 4. Plots of the logarithm of the acidity constant (K_a) vs. $1/T$ (K^{-1}) at I = 2.0 ($NaNO_3$). The symbols represent the six hydroxamic acids investigated ($R_1C(O)N(OH)R_2$): ○, $R_1 = CH_3$, R_2 = H; □, $R_1 = C_6H_5$, R_2 = H; △ $R_1 = CH_3$, $R_2 = C_6H_5$; diamond, $R_1 = C_6H_5$, $R_2 = C_6H_5$; star, $R_1 = CH_3$, $R_2 = CH_3$; inverted triangle, $R_1 = C_6H_5$, $R_2 = CH_3$.

determined from eq 1 and those determined experimentally. The fit is good in the region where both $[A^-]$ and [HA] are known accurately. Good agreement with the approximate K_a value read directly from Figure 3 (at $[A^-] = [HA]$) verifies the accuracy of the final K_a value. Since equivalent results may be obtained by using eq 1 or 3 for data reduction and since the K_a is determined directly K_a a plot of eq 1, eq 1 was used to compute the K_a values reported here.

Results

Acid dissociation constants (K_a) obtained for reaction 4 in aqueous solution [I = 2.0 ($NaNO_3$)] over a temperature

$$R_1C(O)N(OH)R_2 \overset{H_2O}{\rightleftharpoons} [R_1C(O)N(O)R_2]^- + H^+(aq) \quad (4)$$

range are listed in Table II for six related C- and N-substituted hydroxamic acids. Temperature dependencies for K_a are shown in Figure 4 and the calculated ΔH_a and ΔS_a values are listed in Table III.

In chloroform solution at ambient temperature, the N-methyl derivatives ($CH_3C(O)N(OH)CH_3$ and $C_6H_5C(O)N(OH)CH_3$) each exhibited two signals in the N-methyl region of the ^1H NMR spectrum. These occurred at δ 2.87 and 3.32 (both sharp) for $C_6H_5C(O)N(OH)CH_3$ and δ 3.22 (s) and 3.42 (br) for $CH_3C(O)N(OH)CH_3$. The positions and shapes of these signals remained unchanged regardless of method of synthesis or purification. The IR spectrum (Nujol) is consistent with extensive hydrogen bonding (very strong broad band at 2500–3810 cm^{-1} with the carbonyl absorption part of a strong plateau extending from 1400 to 1600 cm^{-1}). The use of gas chromatography coupled with mass spectral detection of $C_6H_5C(O)N(OH)CH_3$ in Et_2O showed two solutes with identical fragmentation patterns (no parent peak). Vapor-phase osmometry (toluene, 25 °C) indicated a molecular weight of 230 amu, while the theoretical value for $C_6H_5C(O)N(OH)CH_3$ is 151.2 amu. $C_6H_5C(O)N(OH)CH_3$ and $CH_3C(O)N(OH)CH_3$ react completely (assuming monomer molecular weights of 151.2 and 89.1 amu, respectively) with standardized acidic aqueous iron(III) to form intensely colored 1:1 complexes, $[Fe(R_1C(O)N(O)R_2)(H_2O)_4]^{2+}$.[17] This verifies the presence of one hydroxamate group per 151.2 amu for $C_6H_5C(O)N(OH)CH_3$ and per 89.1 amu for $CH_3C(O)N(OH)CH_3$. Finally, elemental analyses for both N-methyl derivatives (Table II) are consistent with these formula-

Table II. Analytical Data and Acid Dissociation Constants, K_a, in Aqueous Solution (I = 2.0) for the Hydroxamic Acids $R_1C(O)N(OH)R_2$

hydroxamic acid	analytical data,[a] % C	H	N	O	mp or bp, °C	dissoc const temp, °C	10^9K_a[b]
$CH_3C(O)N(OH)H$[c]	31.85 (32.00)	6.83 (6.67)	18.41 (18.67)	42.46 (42.67)	87.5-90.0[g]	19.8	0.87 (0.01)
						25.0	0.92 (0.01)
							0.95 (0.01)
							0.99 (0.01)
						30.7	1.04 (0.01)
						35.0	1.30 (0.01)
$C_6H_5C(O)N(OH)H$[c]	61.28 (61.31)	5.18 (5.11)	10.04 (10.22)	23.49 (23.36)	129.0-132.5[g]	19.9	2.87 (0.01)
						25.0	3.27 (0.02)
							3.33 (0.02)
						30.8	4.15 (0.02)
						35.5	4.52 (0.02)
$CH_3C(O)N(OH)C_6H_5$[d]	63.67 (63.57)	5.59 (6.00)	9.44 (9.27)	21.30 (21.17)	112[h]	25.0	4.44 (0.02)
							4.48 (0.02)
							4.86 (0.02)
						30.7	5.9 (0.3)
						35.0	8.6 (0.5)
$C_6H_5C(O)N(OH)C_6H_5$[e]	72.15 (73.21)	5.16 (5.21)	6.37 (6.56)	15.06 (15.01)	121.5-124.5[g]	25.0	10.4 (0.02)
							10.3 (0.02)
							10.6 (0.01)
						30.7	13.5 (0.04)
						35.0	15.9 (0.05)
$CH_3C(O)N(OH)CH_3$[c,f]	40.35 (40.44)	7.60 (7.92)	15.57 (15.72)	36.48 (35.91)	65.8[h]	19.8	2.19 (0.02)
						25.0	2.35 (0.02)
							2.42 (0.02)
							2.33 (0.02)
							2.12 (0.01)
							2.14 (0.01)
							2.18 (0.01)
						30.7	2.30 (0.02)
						35.0	2.51 (0.01)
$C_6H_5C(O)N(OH)CH_3$[c]	63.88 (63.57)	5.59 (6.00)	8.76 (9.27)	21.77 (21.17)	95[h]	19.2	11.4 (0.9)
							11.7 (0.9)
						24.9	11.9 (0.9)
						25.2	15.1 (0.9)
							13.4 (0.9)
						30.7	14.6 (1.3)
						35.1	16.4 (1.5)

[a] Theoretical values in parentheses; experimental % O found by difference. [b] Data reduction according to eq 1; number in parentheses represents one standard deviation determined by using approximately 25 pH and V_{OH} values in the region of the titration corresponding to 20-80% of complete neutralization. [c] Data for K_a calculations were obtained by using an initial acid concentration of ca. 7.7×10^{-3} M. [d] Data for K_a calculations were obtained by using an initial acid concentration of ca. 7.7×10^{-3} M at 25 °C and ca. 7.7×10^{-4} M at 30.7 and 35.0 °C. [e] Data for K_a calculations were obtained by using an initial acid concentration of ca. 7.7×10^{-4} M. [f] Multiple acid dissociation data obtained at 25 °C with two independently prepared solutions to ascertain absolute reproducibility. [g] Melting point. [h] Boiling point at 2 mmHg pressure.

Table III. Computed ΔH_a, ΔS_a, and pK_a Values for Hydroxamic Acid Dissociation in Aqueous Solution (I = 2.0)[a]

hydroxamic acid	pK_a[b]	ΔH_a, kcal	ΔS_a, cal/(K mol)
$CH_3C(O)N(OH)CH_3$	8.63 (0.01)	1.2 (0.5)	−36 (2)
$C_6H_5C(O)N(OH)CH_3$	7.87 (0.05)	3.9 (0.9)	−23 (3)
$CH_3C(O)N(OH)H$	9.02 (0.02)	4.4 (0.8)	−27 (3)
$C_6H_5C(O)N(OH)H$	8.50 (0.03)	5.5 (0.4)	−20 (1)
$C_6H_5C(O)N(OH)C_6H_5$	8.00 (0.01)	7.5 (0.2)	−11 (1)
$CH_3C(O)N(OH)C_6H_5$	8.34 (0.02)	10.5 (1.1)	−3 (4)

[a] Computed from data given in Table II. Errors are given in parentheses. [b] At 25 °C.

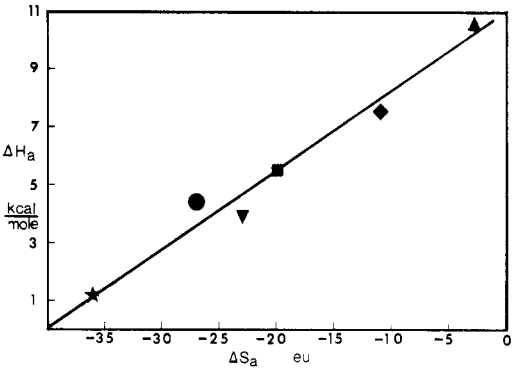


Figure 5. Isothermal plot for the six hydroxamic acids investigated; T_{iso} = 276 (22) K (R = 0.994). The symbols represent the six hydroxamic acids investigated and are defined in the caption for Figure 4.

tions. Similar effects to those observed for the N-methyl derivatives were not observed for the N-phenyl and NH hydroxamic acids.

Discussion

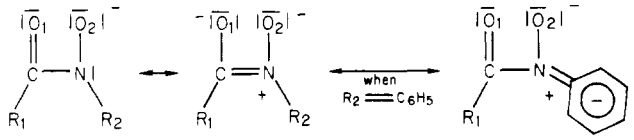
While the pK_a values at room temperature in aqueous solution show a random variation with the substituents R_1 and R_2, Figure 5 shows that there is a regular variation in ΔH_a with ΔS_a which is very sensitive to changes in the R_1 and R_2 substituents. The wide range of ΔH_a and ΔS_a variations observed in this work are such that the linear correlation shown in Figure 5 may be demonstrated to be statistically significant.[20] This isothermal plot shows that

the regular variations in ΔH_a and ΔS_a are in opposition, which accounts for the small variation in pK_a values. The isothermal temperature for these proton dissociation reactions is 276 (20) K. Therefore, at temperatures near ambient temperature, variations in pK_a with R_1 and R_2 are caused by variations in both ΔH_a and ΔS_a. This observation suggests that caution should be exercised in drawing conclusions concerning structure/acidity relationships based on variations in pK_a data alone. It is noteworthy that ΔH_a and ΔS_a parameters calculated from data obtained from ref 12 and 13 for other hydroxamic acids in mixed solvents are in qualitative agreement with the ΔH_a and ΔS_a trends shown in Figure 5.[11-13] Similar observations of isothermal relationships have been made for the proton-dissociation data of carboxylic acids and phenols, although the range of ΔH_a and ΔS_a values is not as great as that reported here.[23-25]

The linear relationship between ΔH_a and ΔS_a suggests that proton dissociation occurs by similar processes for all six hydroxamic acids investigated. Since four of the compounds are N-substituted hydroxamic acids, proton dissociation must occur at the OH site in those cases. A similar process for all of the hydroxamic acids investigated would then require that *$CH_3C(O)N(OH)H$ and $C_6H_5C(O)N(OH)H$ ionize with loss of the OH proton also (as opposed to the NH proton) in aqueous solution.* There is some abiguity in the current literature for the non-N-substituted hydroxamic acids concerning whether they act as N or O acids. Comparisons of room-temperature pK_a values for $R_1C(O)N(OH)H$ with corresponding data for $R_1C(O)N(OR_2)H$ and $R_1C(O)N(OH)R_2$ have been used to argue that it is the NH proton that is ionized in $R_1C(O)N(OH)H$.[1a,26,27] Most of these data have been obtained in mixed solvents by using R_1 and R_2 substituents other than those reported here. In interpreting the data, these authors,[1a,26,27] assume that the influence of the R_2 group on proton dissociation is small and that pK_a values at room temperature are a measure of proton-dissociation enthalpies. However, our data suggest that the influence of R_2 is not small. Moreover, if at room temperature both ΔH_a and ΔS_a play a role in determining the variations in pK_a with changes in substituents in these mixed solvent systems as it does in the aqueous system reported here, then a comparison of pK_a values obtained at a single temperature may not be a valid way to distinguish between N–H and O–H bond dissociation. Our data suggest that in aqueous solution under our conditions $CH_3C(O)N(O-H)H$ and $C_6H_5C(O)N(OH)H$ act as O acids. However, since the solvent may play an important role in the proton-dissociation process (see below) this result may not necessarily be applicable to mixed-solvent systems.

In examining the effect of the R_1 substituent on the pK_a, one finds that a comparison of hydroxamic acids where R_2 = H with the corresponding carboxylic acid is useful. The ratio of K_a values for $C_6H_5C(O)N(OH)H$ relative to those for $CH_3C(O)N(OH)$ is the same (3.5; see Table III) as the corresponding ratio for the carboxylic acids $C_6H_5C(O)OH$ and $CH_3C(O)OH$. Hence (for R_2 = H) the primary effect causing the variation in pK_a's at 25 °C with R_1 is probably due to the same factors which control the strength of carboxylic acids.[26a,28,29] A close look at the data reported here, however, shows that this relationship does not hold when $R_2 \neq H$ and that, in fact, R_2 plays a dominant role over R_1 in influencing hydroxamic acid strength at 25 °C.

In discussing the influence of R_2 on acid strength, it is instructive to consider the possible resonance forms for the conjugate base anion (II–IV). The electron density do-



II III IV

nating ability of R_2 helps to stabilize resonance form III relative to II. This allows positive charge density to build up on N and thereby stabilizes the conjugate base anion by induction. When $R_2 = C_6H_5$ additional resonance delocalization of the lone pair on N via resonance form IV is possible, which also enhances the stability of the anion by providing a buildup of positive charge density on N. Stabilization of the negative charge on O_2 in the hydroxamate ion is possible only through induction. Therefore, this analysis indicates that *the delocalization of the lone pair of electrons on N in any way to provide a formal positive charge adjacent to the negative charge on O_2 is of importance in determining acid strength.* This delocalization is influenced by the inductive and/or resonance effects of the carbonyl function, R_1, and R_2.

To a first approximation the ΔH_a values represent a difference between the enthalpy involved in breaking the hydroxamic acid O–H bond and the enthalpy of solvation of the H^+(aq) and hydroxamate ions. The negative ΔS_a values suggest solvent ordering on proton dissociation to form the highly solvated H^+(aq) and hydroxamate ions. This interpretation is consistent with the isothermal plot shown in Figure 5. For example, $CH_3C(O)N(OH)CH_3$ has the most negative ΔS_a value which indicates the strongest interaction with the solvent. Correspondingly, the ΔH_a value for $CH_3C(O)N(OH)CH_3$ is the least endothermic of the series, consistent with a large exothermic contribution from solvation effects. It may be that O–H bond enthalpy exhibits only a very small variation for the hydroxamic acids investigated and that the variations in ΔH_a that we observe are primarily due to hydroxamate anion interactions with the solvent. Evidence for the importance of the identity of R_1 and R_2 in determining the values of ΔH_a and ΔS_a, regardless of their molecular origin, may be obtained by considering the geometric isomers $CH_3C(O)N(OH)C_6H_5$ and $C_6H_5C(O)N(OH)CH_3$. The ΔH_a and ΔS_a values for these two compounds are significally different, which suggests that if solvation effects are important, then they must be primarily due to solvation of the hydroxamate moiety and not due to localized solvation of the organic substituents R_1 and R_2 attached to the C and N atoms.

Some observations may be made in terms of the relationship of resonance forms II–IV to possible solvation

(20) We have applied the method of error analysis described by Petersen et al.[21] and Wiberg[22] to our ΔH_a and ΔS_a data. According to this analysis, in order for an isothermal plot such as shown in Figure 5 to be significant, the range of observed ΔH_a values ($\Delta\Delta H_a$) must exceed twice the maximum possible error (δ) in ΔH_a, i.e., $\Delta\Delta H_a > 2\delta$. The calculated maximum possible error (δ) for our data is 2.1 kcal/mol. For our system the range of observed ΔH_a values ($\Delta\Delta H_a$ = 9.3 kcal/mol) is sufficiently large that the above condition is exceeded to the extent that $\Delta\Delta H_a > 4\delta$. Therefore this error analysis is additional evidence that the ΔH_a vs. ΔS_a correlation shown in Figure 5 is significant.

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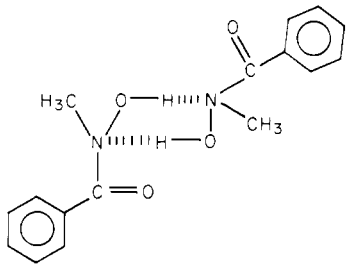
effects. When R_2 = H or CH_3, resonance forms II and III apply, with III taking on increased importance for R_2 = CH_3. When R_2 = C_6H_5, then resonance forms II–IV apply. These resonance forms may be used to consider the net *enhancement* of the molecular dipole on ionization and thus to rationalize the observed trends of ΔH_a and ΔS_a in terms of solvation effects. Although it is generally agreed that little C–N double bond character exists in the neutral hydroxamic acids,[1a] resonance form III for the hydroxamate anion has C–N double bond character which can lock the anion into the rotamer shown for maximum molecular dipole moment. Resonance form III is expected to have the maximum relative importance when R_2 = CH_3. We note that the *N*-methyl-substituted hydroxamic acids are those with the most negative ΔS_a and least positive ΔH_a values, suggesting a stronger interaction with the solvent. When R_2 = C_6H_5 resonance form IV must be considered as a resonance contributor. Contributions from resonance form II–IV may then represent a conjugate base anion with a lower molecular dipole (relative to consideration of only form II and III) and hence a lesser interaction with the solvent. This is consistent with an interpretation of ΔS_a and ΔH_a being strongly influenced by solvation effects since when R_2 = C_6H_5, the ΔS_a values are the least negative and ΔH_a the most positive of the series reported here.

In considering the physical characterization data for the *N*-methyl-substituted hydroxamic acids in nonaqueous solvents, we conclude that dimerization takes place in nonpolar media where the intermolecular forces are due to hydrogen bonding. This is consistent with the observation of multiple ^1H NMR signals in the *N*-methyl region for $CH_3C(O)N(OH)CH_3$ and $C_6H_5C(O)N(OH)CH_3$ in $CDCl_3$ solvent. Molecular weight data in toluene and gas chromatography–mass spectra results in Et_2O for $C_6H_5C(O)N(OH)CH_3$ further substantiate the existence of a monomer $\rightleftharpoons$ dimer equilibrium. The molecular weight data may be used to calculate an approximate dimerization equilibrium quotient of 20 M^{-1} for $C_6H_5C(O)N(OH)CH_3$ in toluene at 25 °C. A tentative structural assignment for the hydrogen bonded dimer for the $C_6H_5C(O)N(OH)CH_3$ system is as shown in V. Apparently a good electron donor



V

R_2 substituent is necessary for a significant amount of dimer to form. Furthermore, H-bonded association is not expected to occur in polar solvents such as H_2O.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. $CH_3C(O)N(OH)H$, 1113-25-3; $C_6H_5C(O)N(OH)H$, 495-18-1; $CH_3C(O)N(OH)C_6H_5$, 1795-83-1; $C_6H_5C(O)N(OH)C_6H_5$, 304-88-1; $CH_3C(O)N(OH)CH_3$, 13115-24-7; $C_6H_5C(O)N(OH)CH_3$, 2446-50-6.

Proton Inventory of the Water-Catalyzed Hydrolysis of 1-Acetyl-1,2,4-triazole. Examination of Ionic Strength Effects[1,2]

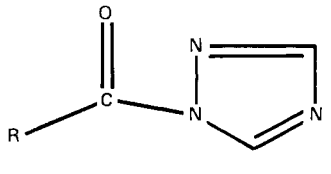
Jacob F. Patterson,[3a] William P. Huskey,[3b] and John L. Hogg*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received May 23, 1980

Proton inventories of the water-catalyzed hydrolysis of 1-acetyl-1,2,4-triazole have been completed under a variety of conditions. The solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, determined at pH 4.7 or the equivalent point on the pD rate profile at 25 °C by using acetic acid–acetate buffers at 1 M ionic strength was 3.18. The solvent deuterium isotope effects determined at ionic strengths of 1 and 0.5 M by using 10^{-3} M HCl (DCl) to control the pH(D) were 3.13 and 3.07, respectively. In all cases the proton inventories exhibit significant downward curvature and are, within experimental error, consistent with a cyclic transition state structure involving four water molecules. The equation $k_n = k_0(1 - n + 0.75n)^4$ describes the proton inventories where the value of the isotope fractionation factor for the four "in-flight" protons is 0.75. These inventories are compared to an earlier study done with no ionic strength control,[4] and several alternative transition states are considered in detail.

The mechanism of the neutral hydrolysis of 1-acyl-1,2,4-triazoles (1) has recently been probed by Karzijn and Engberts using the proton inventory technique.[4] A study of the "water reaction" of 1-acetyl-1,2,4-triazole (1, R = CH_3) completed by us at about the same time[1] and recently expanded upon lends itself to a slightly different interpretation. We report our results and point out the differences in the two studies. These differences and similarities should be of particular interest to anyone contemplating a proton inventory investigation.



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(1) Taken in part from the M.S. Thesis of Jacob F. Patterson, Texas A&M University, 1978.

(2) This research was supported by the Robert A. Welch Foundation and the National Institutes of Health (Grant No. 1 R01 GM 2543301).

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