1.980 N perchloric acid, and the second syringe was filled with an acetonitrile solution of the aldal acetal. The entire system was flushed out several times by firing the accuator to force equal volumes of the two solutions into the reactor. The system was then rezeroed (scope) and the reaction started by firing the accuator. The trace of absorbance vs. time was recorded on the scope and then transferred onto a strip-chart recorder. The values of absorption and time were taken from the chart, and rate constants were calculated by least-squares methods. These k_{obsd} values were converted to $k_{H_3^+O}$ values by division with the known concentration of perchloric acid (0.99 M).

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Registry No. (R = H, R′ = Me), 628-90-0; (R = H, R′ = Et), 5648-29-3; (R = Me, R′ = Me), 3752-99-6; (R = Me, R′ = Et), 80243-06-7; (R = Me, R′ = *n*-Pr), 80243-07-8; (R = Me, R′ = *n*-Bu), 80243-08-9; (R = Et, R′ = Me), 80243-09-0; (R = Et, R′ = Et), 80243-10-3; (R = Et, R′ = *n*-Pr), 80243-11-4; (R = Et, R′ = *n*-Bu), 80243-12-5; (R = *n*-Pr,R′ = Et), 80243-13-6.

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

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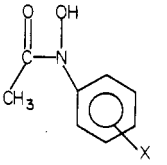
The acid dissociation constants (K_a) of a series of eight substituted *N*-phenylacetohydroxamic acids, $CH_3C(O)N(OH)C_6H_4X$ (X = H, 4-CH_3, 4-Cl, 4-I, 3-I, 3-CN, 4-CN, 4-$C(O)CH_3$), have been determined in aqueous solution (I = 2.0) for a range of temperatures. The pK_a data at 25 °C exhibit a small variation with the substituent X in the direction expected according to their Hammett substituent constants ($\rho \approx 0.1$). These small variations in pK_a values are due to compensating trends in ΔH_a and ΔS_a, which show significant variation with substituent. These results are discussed in terms of the substituent's influence on hydroxamate anion–solvent interactions and the relative influence on pK_a of a substituted phenyl group attached to the C or N end of the hydroxamate moiety.

Hydroxamic acids[1] are remarkably versatile as reagents in organic and inorganic analysis, in pharmaceuticals, in food additives, and in nuclear fuel processing. They form very stable transition-metal complexes,[2] hence their usefulness as analytical reagents.[3]

The application of these compounds often depends upon the acidity of the hydroxamic acid functional group. The factors which influence proton dissociation are therefore of interest. This report[4] describes an investigation of the electronic influence of substituents on the proton dissociation reaction in aqueous solution. Temperature-dependent acid dissociation constants have been determined for a series of substituted *N*-phenylacetohydroxamic acids (I). ΔH_a and ΔS_a values have been calculated and related



I, X = H, 4-CH_3, 4-Cl, 4-I, 3-I, 3-CN, 4-CN, 4-$C(O)CH_3$

to values determined for another series of C- and N-substituted hydroxamic acids previously reported from this laboratory.[5] Only very limited temperature-dependent pK_a data for hydroxamic acids are available in the literature.[2a,6-8]

Our results, along with those obtained previously from our laboratory[5] are compared with pK_a data in the literature for substituted benzohydroxamic acids, $YC_6H_5C(O)N(OH)H$.[7,9] This comparison allows us to comment on the origin and relative effectiveness of the influence of the C and N substituent on hydroxamic acid acidity in aqueous solution.

Experimental Section

Materials. 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 stop-

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(2) For two recent reviews see: (a) Agrawal, Y. K. *Russ. Chem. Rev. (Engl. Transl.)* **1979**, *48*, 948. (b) Chatterjee, B. *Coord. Chem. Rev.* **1978**, *26*, 281.

(3) See for example: (a) Agrawal, Y. K. *Rev. Anal. Chem.* **1980**, *5*, 3. (b) Brandt, W. W. *Rec. Chem. Prog.* **1960**, *21*, 159. (c) Mojumdar, A. K. *Int. Ser. Monogr. Anal. Chem.* **1972**, 50.

(4) A preliminary report of some of these results has been made: Monzyk, B.; Brink, C. P.; Crumbliss, A. L. "Abstract of Papers", Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Sept 1980, American Chemical Society: Washington, DC, 1980.

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(6) Dessolin, M.; Laloi-Diard, M. *Bull. Soc. Chim. Fr.* **1971**, 2946.

(7) Maru, P. C.; Khadikar, P. R. *Thermochim. Acta* **1978**, *27*, 373.

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cocks. Sodium nitrate (Fisher and Mallinckrodt, ACS certified) was recrystallized from the twice distilled water prior to use. The following starting materials for synthesizing hydroxamic acids were used without further purification: acetyl chloride (Aldrich), 4-nitrobenzonitrile (Aldrich), 3-nitrobenzonitrile (Aldrich), 4-nitroacetophenone (Aldrich), 4-nitrotoluene (Aldrich), 4-chloronitrobenzene (Eastman), and nitrobenzene (Fisher). 4-Iodonitrobenzene was prepared by a modified procedure for similar compounds.[10]

Instrumentation. ^{1}H NMR spectra were obtained by using a JEOL Model JNM-MH-100 spectrometer. ^{13}C NMR spectra were obtained by using a JEOL Model JNM-FX60 Fourier transform spectrometer. IR spectra were obtained by using a Beckman Model 4500 pH meter and a Fisher Model 620 pH meter, both capable of 0.0001-pH-unit precision, and a Markson Polymark combination electrode. Solutions were dispensed from a Gilmont ultraprecision micrometer buret capable of 0.0001-mL precision. Elemental analyses were obtained from MHW Laboratories.

Hydroxamic Acids. Although some of these substituted *N*-phenylacetohydroxamic acids have been previously prepared by a variety of techniques (X = H, 4-CH_3, 4-Cl, 4-I, 4-$C(O)CH_3$), a thorough synthetic preparation and purification method for the entire series has not been presented in the literature. The procedure presented here represents a very cost and time efficient means of synthesizing hydroxamic acids in high purity. All hydroxamic acids except $CH_3C(O)N(OH)$-4-C_6H_4I were prepared as described below by reacting $CH_3C(O)Cl$ with the appropriate substituted *N*-phenylhydroxylamine in $(C_2H_5)_2O$ according to a modified procedure for similar compounds.[11] $CH_3C(O)N(OH)$-4-C_6H_4I was prepared by a procedure analogous to that described by Chandravanshi and Gupta.[12]

The substituted *N*-phenylhydroxylamines were prepared by adding a 2:1 molar ratio of Zn dust with the appropriate substituted nitrobenzene according to reaction 1. Typically, 0.2 mol

$$2Zn + XC_6H_4NO_2 \xrightarrow{H_2O/NH_4Cl} XC_6H_4NHOH + 2ZnO \quad (1)$$

of ammonium chloride were dissolved in 400 mL of twice-distilled H_2O. The appropriate substituted nitrobenzene (0.2 mol) was added to the solution, and the mixture was heated with stirring until the temperature reached ca. 60 °C. Zn dust, 0.4 mol, was added over 20 min. As the reaction proceeded, the temperature rose to 70–80 °C. Care was taken so that the temperature never exceeded 80 °C. After the Zn addition was complete, the mixture was stirred an additional 15–20 min or until the temperature returned to 60–65 °C. While still hot, the solution was filtered with suction to remove the zinc oxide. The solid was washed with ca. 300–400 mL of hot (90 °C) water to remove as much hydroxylamine from the zinc oxide as possible. The filtrate was saturated with NaCl (ca. 300 g) and placed in an ice/salt bath. The substituted phenylhydroxylamine formed crystals within 1 h which were isolated by filtration and redissolved in ether to remove NaCl. The ether was stripped off and the substituted phenylhydroxylamine dried in a vacuum desiccator for 3–6 h. The substituted phenylhydroxylamines were used without further purification immediately after preparation. Long-term storage of the hydroxylamines is not advised since they are known to deteriorate over rather short periods of time. The substituted phenylhydroxylamines prepared in this report were typically pale yellow crystals, although occasionally a golden oil resulted.

Acetyl chloride was reacted with the substituted phenylhydroxylamine according to reaction 2 in as close to a 1:1 ratio

$$XC_6H_4NHOH + CH_3C(O)Cl \xrightarrow[-78\ °C]{(C_2H_5)_2O/NaHCO_3} CH_3C(O)N(OH)C_6H_4X + HCl \quad (2)$$

as possible, as an excess of acid chloride reduces yields and complicates purification. Typically, 0.1 mol of substituted phenylhydroxylamine were dissolved in 100 mL of $(C_2H_5)_2O$. $NaHCO_3$ (0.15 mol/0.1 mol of hydroxylamine) was added, and the solution was stirred vigorously at −78 °C. The $CH_3C(O)Cl$ in 100 mL of $(C_2H_5)_2O$ was added dropwise to the substituted phenylhydroxylamine solution over a 1-h period. Stirring continued for 8–12 h while the reaction temperature slowly reached ambient. The mixture was filtered (to eliminate solid $NaHCO_3$) and stripped to dryness. The crude product was occasionally a solid but very typically a gold-colored oil. Purification proceeded by first stirring the crude product in ca. 5 M NH_4OH for 10–15 min. The solution was filtered and the filtrate cooled below 0 °C. H_2SO_4 (6 M, cooled below 0 °C) was added dropwise to the alkaline solution until the pH was ca. 2. In all cases, a solid product formed as the solution became acidic. The mixture was cooled to −78 °C to ensure complete precipitation. (The crude product is most likely contaminated with unreacted substitution nitrobenzene, and therefore this purification technique is not recommended for those starting materials that are soluble in alkaline solution.) A white crystalline or amorphous solid was isolated by filtration for each hydroxamic acid reported here and was recrystallized from ethyl acetate. Typical overall yields for the final recrystallized product ranged from 20% to 30%. All hydroxamic acids were refrigerated until used. Although experimental measurements were made by using freshly prepared solutions of hydroxamic acids, aqueous solutions (10^{-3}–10^{-2} M, pH ~5) are stable for long periods (at least 1 week) when refrigerated.

The compounds were characterized by their ^{1}H and ^{13}C NMR and IR spectra. In chloroform solution at ambient temperature each hydroxamic acid exhibited a sharp singlet at δ 2.15 in the ^{1}H NMR spectrum corresponding to the *C*-methyl group. *N*-Phenyl peaks were sharp singlets at ~δ 7.0 to ~8.0 for the para-substituted phenylacetohydroxamic acids, and there were a series of undefinable peaks at ~δ7.0 to ~8.0 for the meta-substituted phenylacetohydroxamic acids. In all cases, the experimental ratio of peak areas were within 10% of theory. In chloroform solution at ambient temperature, each hydroxamic acid exhibited a weak broad peak between δ166 and 171 in the ^{13}C NMR spectrum corresponding to the carbonyl carbon. Several sharp peaks ranging from δ125 to 139 correspond to the *N*-phenyl group. The *C*-methyl group exhibits a sharp singlet at ~δ 20. The IR spectrum (Nujol, $CHCl_3$) for each hydroxamic acid includes a strong band between 1600 and 1700 cm^{-1} corresponding to the carbonyl stretching vibration.

Elemental analysis (C, H, N) and melting points were used as criteria of purity, and are as follows (theoretical values are in parentheses): $CH_3C(O)N(OH)C_6H_5$, 63.5–66 °C, C, 63.37 (63.57), H, 5.81 (5.96), N, 9.30 (9.27); $CH_3C(O)N(OH)$-4-C_6H_4Cl, 108–111 °C, C, 52.63 (51.75), H, 4.35 (4.31); $CH_3C(O)N(OH)$-4-C_6H_4I, 108.5–111.5 °C, C, 33.80 (34.66), H, 3.03 (2.89), N, 5.04 (5.05); $CH_3C(O)N(OH)$-3-C_6H_4I, 75–77 °C, C, 34.65 (34.66), H, 2.81 (2.89), N, 4.98 (5.05); $CH_3C(O)N(OH)$-3-C_6H_4CN, 64–64.5 °C, C, 61.18 (61.36), H, 4.42 (4.55), N, 16.03 (15.91); $CH_3C(O)N(OH)$-4-$C_6H_4C(O)CH_3$, 144.5–145.5 °C, C, 62.33 (62.18), H, 5.99 (5.70), N, 7.29 (7.25); $CH_3C(O)N(OH)$-4-C_6H_4CN, 145–148 °C, C, 61.63 (61.36), H, 4.57 (4.55), N, 15.90 (15.91); $CH_3C(O)N(OH)$-4-$C_6H_4CH_3 \cdot {}^1/_3H_2O$, 70–71 °C, C, 63.19 (63.53), H, 5.84 (6.32), N, 8.70 (8.23).

pH Titrations. The technique and data manipulation for the pH titrations are described in detail in a previous report.[5] A typical experiment consisted of the titration of 50 ± 0.05 mL of hydroxamic acid (ca. 1×10^{-3} M) with 0.01-mL increments of NaOH (ca. 1×10^{-1} M) by using an ultraprecision microburet. The ionic strength was held constant (I = 2.0) with $NaNO_3$.[13]

(10) Fieser, L. F.; Williamson, K. L. "Organic Experiments", 3rd ed.; D. C. Heath: Lexington, MA, 1975; p 157.
(11) Gupta, V. K.; Tandon, S. G. *J. Indian Chem. Soc.* **1969**, *46*, 831.
(12) Chandravanshi, B. S.; Gupta, V. K. *Indian J. Chem., Sect. B* **1978**, *16B*, 241.

(13) 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,[14,15] 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, comparison of hydroxamic acid pK_a data obtained previously in our laboratory at 2.0 M ionic strength[5] with literature data obtained at lower ionic strength[16] is good. This 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 ranges used in this study.[17]
(14) Brink, C. P.; Crumbliss, A. L., manuscript in preparation.

Table I. Acid Dissociation Constants, K_a, in Aqueous Solution (I = 2.0) for the Hydroxamic Acids $CH_3C(O)N(OH)C_6H_4X$

X	T, °C	10^9K_a [a]
4-I	19.5	3.66 (0.11)
	25.0	5.11 (0.04)
	30.0	6.46 (0.01)
	35.0	6.62 (0.26)
	41.5	7.77 (0.37)
4-Cl	20.5	3.08 (0.01)
	25.0	4.27 (0.07)
	30.3	5.38 (0.62)
	34.5	6.37 (0.06)
	40.0	5.63 (0.03)
3-I	20.0	3.44 (0.02)
	25.0	4.92 (0.10)
	30.2	5.67 (0.29)
	35.0	6.77 (0.17)
	39.6	7.35 (0.45)
4-CN	25.0	5.57 (0.06)
	30.5	7.71 (0.23)
	35.5	10.02 (0.17)
	40.3	9.55 (0.32)
	44.5	12.31 (0.47)
4-CH_3	20.0	0.972 (0.04)
	25.3	1.53 (0.06)
	30.5	1.44 (0.01)
	34.7	1.89 (0.04)
	40.5	2.49 (0.26)
4-$C(O)CH_3$	25.5	4.53 (0.05)
	30.8	5.04 (0.02)
	35.0	6.05 (0.21)
	40.5	8.01 (0.13)
	44.2	9.68 (0.01)
3-CN	25.4	5.42 (0.05)
	30.5	7.81 (0.12)
	35.0	8.84 (0.09)
	40.0	10.71 (0.20)
	44.5	14.05 (0.21)
H [b]	20.0	2.28 (0.21)
	25.0	3.75 (0.02)
	30.0	5.17 (0.04)
	35.0	6.07 (0.06)
	40.0	7.42 (0.08)

[a] Each K_a value represents an average of one to three independent determinations. The number in parentheses represents the standard deviation of the average for the independent determinations. [b] Data presented here represent an independent preparation of the hydroxamic acid and a redetermination of K_a over a slightly broader temperature range; the results are comparable with those obtained previously in our laboratory.[5]

Each acidity constant (pK_a) determination was performed at least in triplicate at each of five temperatures.

Results and Discussion

Acid dissociation constants (K_a) obtained for reaction 3 in aqueous solution (I = 2.0, $NaNO_3$) over a temperature

$$CH_3C(O)N(OH)C_6H_4X \rightleftharpoons [CH_3C(O)N(O)C_6H_4X]^- + H^+(aq) \qquad K_a \quad (3)$$

range are listed in Table I for a series of eight related substituted N-phenylacetohydroxamic acids. Calculated ΔH_a and ΔS_a values are listed in Table II. These results indicate that hydroxamic acids are weak organic acids and that the pK_a variations for these substituted N-phenylacetohydroxamic acids are small at 25 °C. We consider in detail the factors which influence these pK_a values.

It is of interest to determine whether substituents on the carbonyl or nitrogen side of the hydroxamate moiety have a greater influence on the acid dissociation reactions of hydroxamic acids. Several reports have been made in the literature of pK_a values for substituted benzohydroxamic acids $YC_6H_4C(O)N(OH)R$ (R = H, 4-C_6H_4Cl).[2a,6,9] Correlations have been made of acidity constants (log K_a)

Table II. 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] at 25 °C	ΔH_a, kcal/mol	ΔS_a, cal/K mol
$CH_3C(O)N(OH)$-4-C_6H_4I	8.29 (0.01)	5.7 (0.6)	−19 (2)
$CH_3C(O)N(OH)$-4-C_6H_4Cl	8.37 (0.01)	6.3 (1.6)	−17 (5)
$CH_3C(O)N(OH)$-3-C_6H_4I	8.31 (0.01)	6.3 (0.6)	−17 (2)
$CH_3C(O)N(OH)$-4-C_6H_4CN	8.25 (0.01)	7.0 (0.7)	−14 (2)
$CH_3C(O)N(OH)$-4-$C_6H_4CH_3$	8.81 (0.01)	7.6 (0.9)	−15 (3)
$CH_3C(O)N(OH)$-4-$C_6H_4C(O)CH_3$	8.34 (0.01)	7.8 (0.5)	−12 (2)
$CH_3C(O)N(OH)$-3-C_6H_4CN	8.26 (0.01)	8.8 (0.5)	−8 (2)
$CH_3C(O)N(OH)$-C_6H_5 [c]	8.42 (0.01)	10.9 (1.0)	−2 (3)

[a] Computed from linear least-squares analysis of replicate K_a determinations at each temperature given in Table I. The number in parentheses represents the standard deviation obtained from the linear least-squares analysis. [b] The number in parentheses represents the reproducibility of each 25 °C pK_a determination. Measurement of the variance of the linear plot of log K_a vs. $1/T$ for each acid dissociation constant[23] gives 0.046 log units. [c] This work. These results represent a redetermination of K_a over a slightly wider temperature range than used previously and are in excellent agreement with our previously reported values: ΔH_a = 10.5 (1.1) kcal/mol, ΔS_a = −3 (4) cal/K mol.[5]

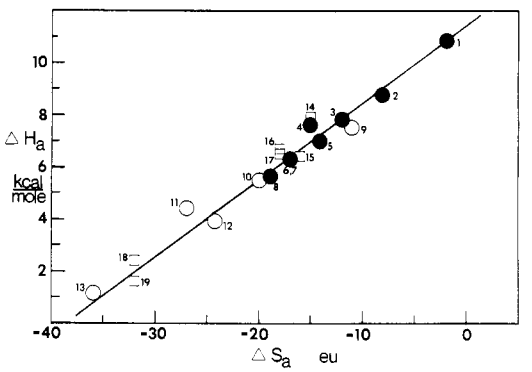


Figure 1. ΔH_a vs. ΔS_a plot for the substituted N-phenylacetohydroxamic acids described in this report (closed circles, compounds 1–8) and a series of C- and N-substituted hydroxamic acids studied previously in this laboratory[5] (open circles, compounds 9–13). The solid line represents the linear least-squares fit for the hydroxamic acids studied in this laboratory (closed and open circles, compounds 1–13).[18,21] The open squares represent ΔS_a and ΔH_a data calculated from ref 6:[35] 1, $CH_3C(O)N(OH)$-C_6H_5; 2, $CH_3C(O)N(OH)$-3-C_6H_4CN; 3, $CH_3C(O)N(OH)$-4-$C_6H_4C(O)CH_3$; 4, $CH_3C(O)N(OH)$-4-$C_6H_4CH_3$; 5, $CH_3C(O)N(OH)$-4-C_6H_4CN; 6, $CH_3C(O)N(OH)$-3-C_6H_4I; 7, $CH_3C(O)N(OH)$-4-C_6H_4Cl; 8, $CH_3C(O)N(OH)$-4-C_6H_4I; 9, $C_6H_5C(O)N(OH)C_6H_5$; 10, $C_6H_5C(O)N(OH)H$; 11, $CH_3C(O)N(OH)H$; 12, $C_6H_5C(O)N(OH)CH_3$; 13, $CH_3C(O)N(OH)CH_3$; 14, 4-$CH_3OC_6H_4C(O)N(OH)H$; 15, 4-$NO_2C_6H_4C(O)N(OH)H$; 16, $C_6H_5C(O)N(OH)H$; 17, 4-$ClC_6H_4C(O)N(OH)H$; 18, 4-$CH_3OC_6H_4C(O)N(OH)CH_3$; 19, 4-$NO_2C_6H_4C(O)N(OH)CH_3$.

(15) Monzyk, B.; Crumbliss, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 6203.
(16) Serjeant, E. P.; Dempsey, B., *IUPAC Chem. Data Ser.* **1979**, *No. 23*.
(17) Bates, R. G. "Determination of pH", 2nd ed.; Wiley: New York, 1973; Chapter 11.

at 25 °C for these substituted benzohydroxamic acids with Hammett σ parameters for the substituent Y. The observed ρ values are $\sim$1. A similar linear correlation is observed between log K_a at 25 °C and σ for the series of substituted *N*-phenylacetohydroxamic acids, $CH_3C(O)N(OH)C_6H_4X$, reported here, but with a ρ value of $\sim$0.1. These results suggest that at 25 °C in aqueous solution the hydroxamic acid pK_a values are more sensitive to variations in the substituted phenyl group when attached to the carbonyl carbon atom than when attached to the nitrogen atom of the hydroxamic acid moiety. However, a more meaningful evaluation of the substituent effect can be made through an analysis of the parameters (ΔH_a, ΔS_a) which contribute to the free-energy changes for hydroxamic acid dissociation.

ΔS_a and ΔH_a for the eight substituted *N*-phenylacetohydroxamic acids studied in this work are included in Figure 1.[18] The plot indicates that there is a regular variation in ΔH_a and ΔS_a which is very sensitive to changes in the substituent. While both ΔH_a and ΔS_a contribute significantly to ΔG_a at 298 K, it is clear that the changes in ΔH_a and ΔS_a for the series are compensating.[21] The compensation effect is based on the fact that ΔH_a and ΔS_a change in the same direction, causing the resulting variations in ΔG_a with substituent to be less than they would be when controlled by either ΔS_a or ΔH_a alone. The ρ value of 0.1 at 25 °C reflects this small variation in ΔG_a and yet does not address the possibility that the substituents affect ΔH_a and ΔS_a, both of which contribute to ΔG_a.

In an attempt to better understand an appropriate interpretation of the application of the Hammett equation to hydroxamic acids, it is useful to carefully consider the temperature-dependent data available for the standard Hammett reaction series, substituted benzoic acids. As described in the literature, $T\Delta S°$ values for substituted benzoic acids account for approximately 95% of $\Delta G°$ (at 298 K) and exactly parallel variations in $\Delta G°$.[24-26] That is, a plot of $T\Delta S°$ vs. σ yields a ρ value of 1. $\Delta H°$ values for the series are very small ($0 < \Delta H° < 0.80$ kcal/mol)[24-26] and essentially invariant.[27] This implies that the dissociation process for benzoic acids in aqueous medium is exclusively $\Delta S°$ controlled. This $\Delta S°$ dominance has been described in the literature in terms of solvation effects.[24,29,30]

Many reaction series involving substituted phenyl compounds have been successfully correlated with the substituted benzoic acid series in aqueous medium. It is now clear, however, that the interpretation of entropy and enthalpy changes is often an important part of gaining some detailed understanding of substituent effects.[24,31,32] Good correlations between σ and $\Delta G°$ may not be found for those reaction series where both $\Delta H°$ and $\Delta S°$ contribute significantly to $\Delta G°$, particularly when $\Delta H°$ and $\Delta S°$ are compensating. Consequently, comparisons of ρ values with other reaction series may not serve as an index for electronic changes in the molecule. Comparisons between $T\Delta S°$ and σ, however, may give some insight into the substituents' effect on reaction series[33] as evidenced in the benzoic acid dissociation reaction. For example, at 25 °C the ΔS_a values are significantly affected by variations in substituents for the substituted *N*-phenylacetohydroxamic acids when compared to the substituted benzoic acids. That is, over a Hammett σ range of 0.83, the variation in ΔS_a ($\Delta\Delta S_a$) is 17 eu for the substituted *N*-phenylacetohydroxamic acids, as compared to 3 eu for the benzoic acids over the same Hammett σ range.[34]

The good correlation between substituted benzohydroxamic acids and σ parameters can now be understood in terms of their similarity to the substituted benzoic acid system. Enthalpy and entropy data are available for four substituted benzohydroxamic acids. These have been included in Figure 1.[35] It is clear that the four substituted benzohydroxamic acids fall, within error, on the line shown in Figure 1. On their own, however, these four data points may not have a statistically significant ΔH_a range.[18,36]

(18) The ΔH_a and ΔS_a range obtained in this study and illustrated in Figure 1 can be demonstrated to be statistically significant. We have applied the method of error analysis described by Petersen et al.[19] and Wiberg[20] to the ΔH_a and ΔS_a data for the thirteen hydroxamic acids studied in this laboratory. The closed circles represent the substituted *N*-phenylacetohydroxamic acids described in this work, and the open circles represent the five C- and N-substituted hydroxamic acids reported in ref 5. According to this analysis, in order for the range of ΔH_a values to be taken as a significant trend, that range ($\Delta\Delta H_a$) 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 these 13 data points is 2.3 kcal/mol. The range of observed ΔH_a values ($\Delta\Delta H_a$ = 9.7 kcal/mol) is sufficiently large that the above condition is exceeded to the extent that $\Delta\Delta H_a > 4\delta$. The ΔH_a and ΔS_a data for the eight substituted *N*-phenylacetohydroxamic acids alone also define a statistically significant trend in $\Delta\Delta H_a$.

(19) Petersen, R. C.; Markgraf, J. H.; Ross, S. D. *J. Am. Chem. Soc.* **1961**, *83*, 3819.

(20) Wiberg, K. B. "Physical Organic Chemistry"; Wiley: New York, 1964; pp 376-379.

(21) Krug[22] maintains that an isokinetic relationship is a prerequisite for strict compensation between ΔH and ΔS. Several reports (e.g., ref 22 and 23) have challenged the validity of an isokinetic relationship which is based strictly on a linear relationship between ΔH and ΔS since the methods for obtaining these parameters involve mutually dependent errors. Both Krug[22] and Exner[23] have proposed different statistical means of testing a data set to ensure a true isokinetic relationship. At the most general level, if a linear enthalpy–entropy relationship due to chemical effects exists, the plots of log K_a vs. $1/T$ must show convergence to a single point, implying one temperature (the isokinetic temperature) at which all reactions in the series exhibit the same free-energy change. The statistical methods of Krug and Exner evaluate the precision of the convergence point. Plots of log K_a vs. $1/T$ for our data set can be extrapolated toward a reasonable convergence point, as required for an isokinetic relationship. However, application of the rigorous mathematical treatments of either Krug or Exner suggests that an exact isokinetic temperature is not defined for our system, and therefore our data do not fit the more strict criteria for a true isokinetic relationship. Nevertheless, since log K_a vs. $1/T$ shows a convergence and since our observed range of ΔH values is statistically significant,[18] interpretations based on the extremes of the ΔH_a range shown in Figure 1 should be valid.

(22) Krug, R. R. *Ind. Eng. Chem. Fundam.* **1980**, *19*, 50.

(23) Exner, O. *Collect Czech. Chem. Commun.* **1972**, *37*, 1425; **1975**, 40, 2762; *Progr. Phys. Org. Chem.* **1973**, *10*, 411.

(24) Larson, W. M.; Hepler, L. G. In "Solute Solvent Interactions"; Coetzee, J. F., Ritchie, C. C., Ed.; Marcel Dekker: New York, 1969; Chapter 1.

(25) Matsui, T.; Ko, H. C.; Hepler, L. *Can. J. Chem.* **1974**, *52*, 2906.

(26) Hambly, A. N. *Rev. Pure Appl. Chem.* **1965**, *15*, 87.

(27) References 23, 25, and 28 suggest that there is an isokinetic relationship between $\Delta S°$ and $\Delta H°$ for substituted benzoic acids.

(28) Bolton, P. D.; Fleming, K. A.; Hall, F. M. *J. Am. Chem. Soc.* **1972**, *94*, 1033.

(29) Calder, G. V.; Barton, T. J. *J. Chem. Educ.* **1971**, *48*, 338.

(30) McMahon, T. B.; Kebarle, P. *J. Am. Chem. Soc.* **1977**, *99*, 2222.

(31) Hansen, L. D.; Hepler, L. G. *Can. J. Chem.* **1972**, *50*, 1030. Hepler, L. G. *Ibid.* **1971**, *49*, 2803.

(32) Bolton, P. D.; Hepler, L. G. *Q. Rev., Chem. Soc.* **1971**, *25*, 521.

(33) Hepler, L. D.; Woolley, E. M. In "Water; A Comprehensive Treatise"; Franks, F., Ed.; Plenum Press: New York, 1973; Vol. 3.

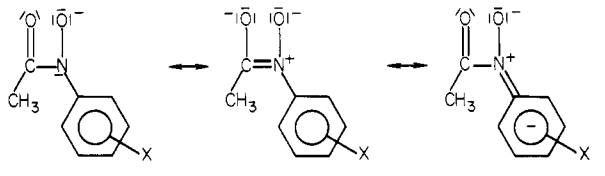
(34) This does not imply, however, that there should be a linear correlation found between ΔS_a and σ for the substituted *N*-phenylacetohydroxamic acids such as is found for the benzoic acid series, since in the former case ΔH_a makes a significant contribution to ΔG_a, while in the latter case the reaction series is essentially isoenthalpic.

(35) Reference 6 contains pK_a data obtained at various temperatures in an ethanol/water solvent mixture for a series of hydroxamic acids; the authors did not use the data to calculate ΔS_a or ΔH_a values. The 25 °C pK_a values are in excellent agreement with 25 °C pK_a values determined in 100% water in ref 9 for the same hydroxamic acids. We therefore have used the temperature-dependent data of ref 6 to calculate ΔH_a and ΔS_a. These values were used in our analysis without further correction for differing conditions, and, therefore, caution should be exercised in the comparative analysis. However, the eight data points for the substituted *N*-phenylacetohydroxamic acids reported from this laboratory[5] were all obtained by a common technique and set of conditions, and thus, comparisons can be made within this data set without question.[18,21]

(36) Error limits are not available for the pK_a data in ref 6.

Furthermore, ΔH_a values, while contributing significantly to ΔG_a, are essentially invariant. The $T\Delta S_a$ values are responsible for the variations in ΔG_a. It is interesting to note that over the Hammett σ range of 0.78, the variation in ΔS_a ($\Delta\Delta S_a$) for the substituted benzohydroxamic acids is 3 eu, which is identical with the variation in ΔS found for the benzoic acids.[37]

The influence that the substituent has on the entropies of ionization can be understood in terms of solvent–solute interactions.[24] As the anion becomes less effective in orienting the solvent (water) molecules, entropies for the acid dissociation reaction become more positive. Electron-withdrawing substituents are usually associated with a decreased effectiveness in solvent ordering. This is because electron-withdrawing substituents are capable of delocalizing the negative charge over the entire molecule. Resonance forms II–IV illustrate this point for the substituted *N*-phenylacetohydroxamic acids reported here. As X becomes more electron withdrawing, all three resonance forms are important. However, when X is electron donating, electron delocalization can be achieved only through an inductive mechanism; only resonance form II applies when X is a resonance electron donor. This results in a greater net molecular dipole moment for electron donors relative to electron acceptors, since in the latter case contributions from all three resonance forms are possible. The greater molecular dipole moment causes the increased orienting effect on the solvent molecules.



II III IV

As noted above, the substituents affect the ΔS_a range to the same extent for the substituted benzohydroxamic acids and substituted benzoic acids. The ΔS_a range for the substituted *N*-phenylacetohydroxamic acids, however, is approximately 6 times larger. This suggests that the substituent more effectively influences solvent ordering by affecting the extent of electron delocalization when it is positioned on the nitrogen side of the hydroxamate moiety than when it is positioned on the carbon side. Although the substituent effect manifests itself in terms of larger variations in pK_a values for the substituted benzohydroxamic acids, our study suggests that the substituents may influence the degree of electron delocalization considerably more for the substituted *N*-phenylacetohydroxamic acids (as shown by the variations in ΔH_a and ΔS_a). Similarly, Idoux et. al.[38] have noticed a difference in the transmission of a substituent's electronic effect when comparing C- and N-substituted amides.

Interpretation of these solute–solvent interactions can be extended one step further with data previously collected in this laboratory for a series of 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).[5] Figure 1 includes the ΔH_a and ΔS_a values for this series of hydroxamic acids. It is significant that in considering all of the hydroxamic acids shown in Figure 1 (including those for which ΔH_a and ΔS_a values were computed from ref 6[35]), those with phenyl or substituted phenyl attached to N (regardless of the C substituent) are on the upper right end of the plot (i.e., have maximum relative values of ΔH_a and ΔS_a), and those with alkyl groups attached to N are at the lower left end of the plot (i.e., have minimum relative values of ΔH_a and ΔS_a). This is consistent with the solvent–anion interactions described above and demonstrates the significant influence of the N substituents. Maximum values of ΔH_a and ΔS_a indicate minimum anion–solvent interaction. This is consistent with negative charge delocalization brought about by application of resonance forms II–IV. Minimum values of ΔH_a and ΔS_a indicate more anion–solvent interaction which would be expected for those anions with less charge delocalization. Such is the case when the N substituent is H or alkyl, thereby eliminating the possibility for resonance delocalization shown in IV. A phenyl group on the C end of the hydroxamate moiety cannot delocalize the N lone pair of electrons and, therefore, has a lesser relative influence on solvent–anion interactions.[39]

For those hydroxamic acids of structure $R_1C(O)N(OH)H$, there is some question in the current literature concerning whether ionization occurs with loss of the N–H or O–H proton.[1,40,41] Two different types of arguments have been used to suggest that it is the proton on the nitrogen atom which has the acidic properties.[40] First, comparisons are made of the dissociation constants for compounds of the general type $R_1C(O)N(OR_3)R_2$. Second, ρ values for two different hydroxamic acid series are compared, and conclusions are drawn on the basis of their relative magnitude. In view of the results presented here, these arguments should be viewed with caution.

Comparisons have been made for pK_a values obtained in 80% methylcellosolve: 4-$NO_2C_6H_4C(O)N(OH)H$, $pK_{a_{mcs}}$ = 8.99; 4-$NO_2C_6H_4C(O)N(OCH_3)H$, $pK_{a_{mcs}}$ = 9.09; 4-$NO_2C_6H_4C(O)N(OH)CH_3$, $pK_{a_{mcs}}$ = 10.29. The acidic hydrogen is argued to be that of the NH group since the N derivative is a weaker acid than the O derivative by more than 1 order of magnitude.[40] This argument does not hold when comparing the pK_a values determined in 12% $EtOH/H_2O$ for the same series of hydroxamic acids where the following values are obtained: 4-$NO_2C_6H_4C(O)N(OH)H$, $pK_a(EtOH/H_2O)$ = 8.13; 4-$NO_2C_6H_4C(O)N(OCH_3)H$, $pK_a(EtOH/H_2O)$ = 7.82; 4-$NO_2C_6H_4C(O)N(OH)CH_3$, $pK_a(EtOH/H_2O)$ = 8.11.[6] Following the previous arguments, one would conclude that the acidic proton is from the OH group since the O derivative pK_a value is now the least consistent with the other two acids. Furthermore, if one compares a second similar series of hydroxamic acid pK_a values determined in 12% $EtOH/H_2O$, it is clear that no conclusion can be made regarding which proton is acidic: $CH_3OC_6H_4C(O)N(OH)H$, $pK_a(EtOH/H_2O)$ = 9.07; $CH_3OC_6H_4C(O)N(OCH_3)H$, $pK_a(EtOH/H_2O)$ = 9.36; $CH_3OC_6H_4C(O)N(OH)CH_3$, $pK_a(EtOH/H_2O)$ = 8.79.[6] The difficulty in making comparisons of this type by using compounds of the general form $R_1C(O)N(OR_3)R_2$ is that the R_2 group is not held constant, and according to our results the N substituent can have a significant effect on the factors (ΔH_a and ΔS_a) which influence acidity.

The second argument presented involves a comparison of ρ values for N-substituted and O-substituted benzohydroxamic acids relative to substituted benzoic acids.[40]

(37) Preliminary results from experiments being conducted in our laboratory using a substituted *N*-methylbenzohydroxamic acid series with a wide range of σ values also show a very narrow ΔS_a range. Brink, C. P.; Crumbliss, A. L., unpublished results.

(38) Idoux, J.; Keifer, G. E.; Baker, G. R.; Puckett, W. E.; Spence, F. J.; Simmons, D. S.; Constant, R. B.; Watlock, D. J.; Fuhrman, S. L. *J. Org. Chem.* **1980**, *45*, 441.

(39) See also ref 5 for a thorough analysis of the C- and N-substituted hydroxamic acids.

(40) Exner, O.; Simon, W. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4078.

(41) Shenderovich, V. A.; Ryaboi, V. I.; Kriveleva, E. D.; Ionin, B. I.; Vainshenker, I. A.; Dogadina, A. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1979**, *49*, 1530.

The ρ value for the substituted benzohydroxamic acids is approximately the same as that for the substituted benzoic acids while *N*-methyl benzohydroxamic acids [$XC_6H_4C(O)N(OH)CH_3$] have a much lower ρ value. These results are explained[40] by suggesting that for both the benzoic acids and the benzohydroxamic acids, the acidic proton (if one assumes a NH acid for the hydroxamic acids) is separated from the substituent by two atoms. For the N-substituted hydroxamic acids, the acidic proton must be from the O–H group which is now three atoms removed from the substituent. The lower value of ρ is expected since the effect of the substituent must extend through three atoms as opposed to two atoms.

As described in this report, the ρ value for our substituted N-phenylacetohydroxamic acids is much less than the ρ value for substituted benzoic acids, yet the acidic proton is the same number of atoms removed from the substituent for both series. Our results suggest that there are several important factors which may have more influence on ρ values than distance between the substituent and the acidic site.

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Registry No. $CH_3C(O)N(OH)$-4-C_6H_4I, 67274-49-1; $CH_3C(O)N(OH)$-4-C_6H_4Cl, 1503-91-9; $CH_3C(O)N(OH)$-3-C_6H_4I, 80584-64-1; $CH_3C(O)N(OH)$-4-C_6H_4CN, 80584-65-2; $CH_3C(O)N(OH)$-4-$C_6H_4CH_3$, 27451-21-4; $CH_3C(O)N(OH)$-4-$C_6H_4C(O)CH_3$, 67274-51-5; $CH_3C(O)N(OH)$-3-C_6H_4CN, 80584-66-3; $CH_3C(O)N(OH)C_6H_5$, 1795-83-1; 4-ClC_6H_4NHOH, 823-86-9; 4-CNC_6H_4NHOH, 24171-84-4; 4-$CH_3C_6H_4NHOH$, 623-10-9; 4-$C(O)CH_3C_6H_4NHOH$, 10517-47-2; 3-CNC_6H_4NHOH, 24171-82-2; C_6H_5NHOH, 100-65-2; acetyl chloride, 75-36-5; 4-nitrobenzonitrile, 619-72-7; 3-nitrobenzonitrile, 619-24-9; 4-nitroacetophenone, 100-19-6; 4-nitrotoluene, 99-99-0; 4-chloronitrobenzene, 100-00-5; nitrobenzene, 98-95-3; 4-iodonitrobenzene, 636-98-6.

α-Nitro Ketones. 6.[1] Synthesis and Conformation of 2-Methyl-2-nitro-, *cis*- and *trans*-6-Methyl-2-nitro-, and *cis*- and *trans*-2,6-Dimethyl-2-nitrocyclohexanones

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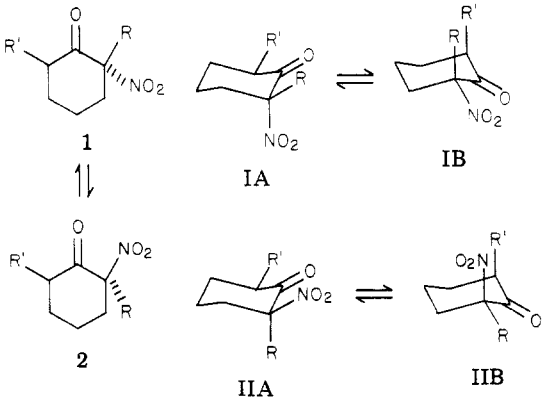
Nitration of the most substituted (thermodynamically more stable) enol acetate or trimethylsilyl ether of 2-methylcyclohexanone and the phase-transfer methylation of 2-nitrocyclohexanone serve as methods of preparation of 2-methyl-2-nitrocyclohexanone, whereas nitration of the least substituted enol acetate or trimethylsilyl ether of 2-methylcyclohexanone and methylation of the dianion of 2-nitrocyclohexanone lead to *cis*- and *trans*-6-methyl-2-nitrocyclohexanone. Nitration of the enol acetate or trimethylsilyl ether of 2,6-dimethylcyclohexanone and methylation of either 2-methyl-2-nitro- or 6-methyl-2-nitrocyclohexanone are methods of preparation of *cis*- and *trans*-2,6-dimethyl-2-nitrocyclohexanone. ^1H NMR chemical shift and coupling constant data were used to determine the preferred conformations of the cyclohexanones: 2(e)-methyl-2(a)-nitro, *cis*-6(e)-methyl-2(e)-nitro, *trans*-6(e)-methyl-2(a)-nitro, *cis*-2(e),6(e)-dimethyl-2(a)-nitro, *trans*-2(a)-methyl-6(e)-methyl-2(e)-nitro.

In our previous studies[1,3] on the synthesis of α-nitro ketones, the enol acetates that were nitrated were prepared from the ketones and acetic anhydride or isopropenyl acetate. Unsymmetrical ketones led to a mixture of enol acetates which were either separated by GLC and nitrated separately or nitrated as a mixture and the resulting isomeric nitro ketones separated by chromatography or crystallization. We had also demonstrated that the amyl nitrate nitration of potassium enolates generated from unsymmetrical ketones is also nonregioselective.[1] Furthermore, we[3] had observed that the nitration of 2-methyl-4-*tert*-butyl-1-acetoxycyclohexene gave a poor yield of the corresponding 2-nitro ketone and that the isomeric enol acetate 6-methyl-4-*tert*-butyl-1-acetoxycyclohexene could not be directly prepared regioselectively from the corresponding ketone, 2-methyl-4-*tert*-butylcyclohexanone, and isopropenyl acetate or acetic anhydride.[4] Because these preceeding results had a direct bearing on our syntheses of branched-chain sugars, it became important to determine the feasibility of synthesizing α-nitro ketones with a methyl group on the α-carbon as well. We therefore chose to study the synthesis of 2-methyl-, 6-methyl-, and 2,6-dimethyl-2-nitrocyclohexanones via the nitration of ketone derivatives and also to attempt the methylation of α-nitro ketones. In this paper we report the results of such

Scheme I. Configurational and Conformational Equilibria of 2-Nitrocyclohexanones



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