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Nature of the Ortho Effect. Reactivity Correlations of the Acidic and Alkaline Hydrolyses of Ortho-Substituted *N*-Methylbenzohydroxamic Acids[1]

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Received May 31, 1977

Rates of acidic and alkaline hydrolyses of a series of ortho-substituted *N*-methylbenzohydroxamic acids have been determined at moderate acidity and very high basicity. The data are correlated by Taft's ortho polar and steric substituent constants. The results provide support for this method of correlation of quantitative data as well as support for the qualitative picture of ortho-substituent effects as described by McCoy and Riecke.

Introduction

The nature and quantitative treatment of the "ortho effect" has long interested chemists and is still unresolved.[2-4] The ratio of rate constants or equilibrium constants for similarly substituted *o*- and *p*-benzene systems[2] has been taken as a measure of ortho effects. Taft's separation of polar and steric ortho substituent effects is the best known treatment of ortho effects and has had some success in the correlation of data.[2,4] Equation 1 (Pavelich–Taft) quantitatively relates the log of the rate or equilibrium constants, k (k_0 is the constant for reaction of the compound with the reference substituent, methyl), to the polar (σ_0^*) and steric (E_s) substituent parameters for ortho-substituted benzene systems. ρ^* and δ are the respective reaction system susceptibility constants.

$$\log k = \rho^*\sigma_0^* + \delta E_s + \log k_0 \quad (1)$$

Charton has analyzed a large amount of data by linear regression and come to rather unconventional conclusions regarding the ortho effect,[2,5,6] e.g., that steric effects of ortho groups are minor. Charton represents Taft's steric effect substituent constant as

$$E_s = \alpha\sigma_I + \beta\sigma_R + \psi r_v + h \quad (2)$$

in which σ_I and σ_R are inductive and resonance substituent constants, respectively; r_v is related to the size of the substituent and is evaluated from van der Waals radii; h is an intercept term; α, β, and ψ are susceptibility constants. Charton considers the ψr_v term to be insignificant for ortho E_s values. The development and use of eq 2 and related equations has been criticized.[2,7]

McCoy and Riecke[8] have presented a qualitative picture of the ortho effect which reconciles the more conventional interpretations of proximity effects with those of Charton; in particular they have given a further interpretation to the h term of eq 2 and related equations. These authors consider and qualitatively analyze in some detail the effects of increasing the size of the ortho substituents. In the absence of specific interactions such as hydrogen bonding, the steric effect[8] will be composed of at least three effects: hindrance to solvation and to attack by a reagent, and steric hindrance to resonance. The first two effects will be rate reducing in typical ester reactions, e.g., those used by Taft to define σ^* and E_s, while the last will be a rate enhancing factor—the conjugation of the carbonyl group with the aromatic ring will be reduced in the reactant state compared to a nonhindered substrate, and in either case, the conjugation should be stronger in the

0022-3263/78/1943-0013$01.00/0

Table I. Observed and Calculated Results for Acidic Hydrolysis of Ortho-Substituted *N*-Methylbenzohydroxamic Acids at 90 °C in 0.764 M Hydrochloric Acid

Substituent	Registry no.	σ^* [a]	E_s [a]	$-\log k_{obsd}$ [b]	$-\log k_{calcd}$ [c]
CH_3	24962-87-6	0	0	4.359	4.403
OCH_3	63977-15-1	−0.22	0.99	3.964	3.977
Cl	59686-63-4	0.37	0.18	4.585	4.608
Br	63977-16-2	0.38	0	4.713	4.665
I	63977-17-3	0.38	−0.20	4.793	4.720
NO_2	63977-18-4	0.97	−0.75	5.237	5.279

[a] Ortho substituent parameters, ref 4. [b] Average first-order rate constant, s^{-1}. [c] From eq 1, $\rho^* = -0.688$, $\delta = 0.278$.

Table II. Observed and Calculated Results for Alkaline Hydrolysis of Ortho-Substitued *N*-Methylbenzohydroxamic Acids at 90 °C in 7.31 M Sodium Hydroxide

Substituent	$-\log k_{obsd}$ [a]	$-\log k_{calcd}$ [b]
CH_3	6.130	6.178
OCH_3	5.498	5.466
Cl	5.585	5.695
Br	5.915	5.850
I	6.092	6.032
NO_2	5.166[c]	

[a] Average first-order rate constant, s^{-1}. [b] From eq 1, $\rho^* = 0.863$, $\delta = 0.911$. [c] Not included in the correlation by eq 1, see text.

reactant state than in the tetrahedral-like transition state for ester hydrolysis. Depending upon the particular substrate system and reaction chosen, steric effects in an ortho-substituted system could thus be *relatively* large or small.

Results and Discussion

Our present results for the acidic and alkaline hydrolysis of ortho-substituted *N*-methylbenzohydroxamic acids combined with our earlier results for the similar reaction of ortho-substituted benzohydroxamic acids[9] support both McCoy and Riecke's interpretation of ortho effects and the usefulness of eq 1 as a first approximation to a quantitative description of the ortho effect. Data are listed in Tables I and II. The calculated data are from eq 1 with ρ^*, δ, and $\log k_0$ determined by least-squares multiple regression. The mechanisms of the hydrolysis reactions have been reported.[10]

Statistical measures[11] of the validity of the correlations in Tables I and II are the correlation coefficient, the F test, which allows for the number of degrees of freedom in the correlation, and the residuals or the differences between observed and calculated values. For the correlation by eq 1 for the acid-catalyzed hydrolysis, the correlation coefficient is 0.989 with the F test indicating the correlation to be significant within the 1% level (a highly significant correlation). Correlation with σ^* alone (eq 1 with $\delta = 0$) is poorer than with σ^* and E_s together, even though the F test is within the 1% level, since the average residual for correlation with σ^* alone is almost twice the average residual for the correlation with σ^* and E_s together. Correlation with E_s alone (eq 1 with $\rho^* = 0$) is also poorer (correlation coefficient 0.934; F test, 1% level), since not only is the average residual more than twice the average residual for correlation with σ^* and E_s together, but particularly because the calculated value for k_0 (the value for the reference compound) is significantly in error, by a factor of 1.89.

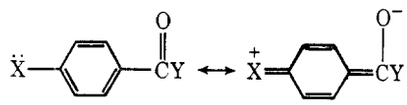
Correlation of the alkaline hydrolysis data by eq 1 is fairly good provided the datum for the nitro compound is omitted. The correlation coefficient is 0.928, the F test indicating significance not quite within the 5% level. Omission of the nitro compound is justified, since the reaction of the nitro compound appears to be abnormal because *o*-nitrobenzoic acid could not be isolated from the reaction mixture. In this connection it is worth noting that the ionic strength and base concentration were very high in the alkaline hydrolyses. Correlation of the data (nitro compound excluded) with σ^* or E_s parameters *alone* is very poor or nonexistent; the correlation coefficients are 0.448 and 0.743, respectively. Although the confidence level for the correlation of the alkaline hydrolysis rate data by eq 1 is a little lower than that for the correlation of the acid hydrolysis rate data, the correlation is evidently real. A graph of $\log k_{obsd} - \rho^*\sigma^*$ vs. E_s is acceptable, reproducing the trend of the data, and shows no curvature.

The results given above show the usefulness of eq 1 for the correlation of ortho effects in rather crowded systems. In addition it is worth noting that the correlation of the alkaline hydrolysis rate data involves a system with *very high* base concentration and ionic strength well above those usually employed in most studies. Furthermore, the observed rate constants in the alkaline hydrolysis are a sum of two contributing terms,[10] one for attack by water and the other for attack by hydroxide ion on the *N*-methylarylhydroxamate ion. The substituent effects on these two pathways must be similar or porportional, as is reasonable, in order for the observed correlation to occur.

Support for McCoy and Riecke's[8] qualitative picture of the ortho effect arises from the comparison of the correlation obtained with eq 1 for the present study (acid-catalyzed hydrolysis of ortho-substituted *N*-methylbenzohydroxamic acids) with the similar correlation for our earlier study[9] on the acid-catalyzed hydrolysis of the less hindered ortho-substituted benzohydroxamic acids. Both studies were carried out under comparable conditions and the results are well correlated by eq 1. A comparison of the ratios of the susceptibility constants, δ and ρ^*, indicates the *relative* importance of steric and polar substituent effects. Thus in the more hindered *N*-methyl series (space-filling models confirm the greater hindrance and conformational restrictions in this series) δ/ρ^* is 0.404 and in the less hindered series δ/ρ^* is 0.874. That is, steric effects appear to be *relatively less important in the more hindered system.* This result is quite consistent with McCoy and Riecke's qualitative description of the ortho effect (briefly summarized in the Introduction) in which the contributions of the *various components* of the steric ortho effect vary as a function of the reaction and the skeletal makeup of the substrate.

The above interpretations depend upon the concept that E_s represents steric or bulk effects of substituents which are reaction independent. This question has been discussed in some detail.[2,4] Two pieces of evidence indicate that E_s is a good measure of the steric effect for the substituents in Table I. First, E_s values for symmetrical ortho substituents parallel their van der Waals radii.[2] Secondly, the resonance contribution to E_s values for the substituents, except methoxy, in Table I can be shown to be negligible as follows: substituents which are electron releasing by resonance can exhibit a direct resonance interaction with the carbonyl group of the esters used to define E_s. A similar resonance interaction is included

in Hammett substituent constants, eq 3. An "insulated" para substituent constant[3,12] has been defined which eliminates



(3)

the resonance contribution shown in eq 3. Comparison of the Hammett para substituent constants[3] with these "insulated" constants[12] shows essentially no difference between the two scales for the substituents in Table I except for methoxy. Thus the resonance contribution to E_s values analogous to eq 3 is negligible except for methoxy. The resonance contribution to the E_s value for methoxy may, in reality, be smaller than anticipated by the above comparison. Taft[4] has shown for the saponification of ethyl *p*-dimethylaminobenzoate that only part of the resonance interaction of the *p*-dimethylamino group with the carbonyl group is lost in going from the ester to the saponification transition state. It is only this fraction of the resonance interaction lost which contributes to the E_s value.

The ρ^* values for the catalyzed hydrolysis of ortho-substituted benzamides,[4] benzohydroxamic acids,[9] and *N*-methylbenzohydroxamic acids are 0, −0.868, and −0.688, respectively, for similar but not identical reaction conditions. A negative ρ^* value for the hydrolysis of the benzohydroxamic acids compared to the zero value for benzamides is consistent with the greater electronegativity of *N*-hydroxyl compared to NH in changing from amides to hydroxamic acids,[9] provided that the polar effect upon the protonation step in the mechanism is greater than the polar effect on nucleophilic attack by water on the protonated intermediate. Substitution of a methyl group for the *N*-hydrogen on the hydroxamic acids should offset somewhat the effect of the substitution of hydroxyl for the *N*-hydrogen of the amide and thus reverse the *trend* in the ρ^* values.

Experimental Section

The 2-substituted *N*-methylbenzohydroxamic acids were synthesized by adaptations of the method used previously for the preparation of the 2-chloro and 2-methyl derivatives.[10] ^{1}H NMR and IR spectra are consistent with the structures listed. Satisfactory analyses (C, H, N; maximum difference between calculated and observed analysis (%): C, 0.21; H, 0.20; N, 0.16) were obtained for all new compounds and were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 2-Substituent and melting point: methoxy, 138.5–139.2 °C; bromo, 135.0–135.8 °C; iodo, 145.1–145.8 °C; nitro, 170.8–171.6 °C dec.

Kinetic measurements were accomplished using the methods and procedures described previously.[10]

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Kinetics of the Reactions of Hydrazine and Acethydrazide with Acetic Acid

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Received June 2, 1977

A kinetic study of the reactions of monoacetylhydrazine (MAH) and hydrazine (H) with acetic acid at 61 °C has been made using HPLC separation of salicylaldehyde derivatives. Both reactions involve pseudo-first-order reaction with acetic acid to produce an acetylated base and a rapid disproportionation of MAH to yield diacetylhydrazine (DAH) and hydrazine. The hydrazine acetylation is faster than the MAH acetylation. Mechanisms have been proposed for both series of reactions using approximations, and the predictions are in good agreement with experimental findings.

The reaction of hydrazine (H) with acetic acid was described by Harris and Stone.[2] This kind of reaction, a loss of basicity with time, was also reported by Medwick[3] in a study of various hydrazides. In related work, Posgay[4] found that the basicity of some amino compounds was lost owing to acetylation by acetic acid, and Kadin[5] reported that more than 10% of procainamide was acetylated in acetic acid in a few minutes at room temperature. Both authors attribute the acetylation to unavoidable small traces of acetic anhydride in glacial acetic acid. No careful kinetic study of the H or acethydrazide (MAH) reaction with acetic acid has been reported; Harris and Stone[2] used a spectrophotometric procedure that was inadequate due to the interference of MAH in the H assay.

In the present study, the reactions of H and MAH with acetic acid at 61 °C have been thoroughly investigated using specific analytical procedures. Salicylaldehyde derivatives of H and MAH [and of symmetrical diacetylhydrazine (DAH), after hydrolysis] are formed and can be separated using high-pressure liquid chromatography (HPLC). These compounds offer high molar absorptivities and make measurement of very small quantities possible. These analyses permit measurement of each hydrazine reaction participant and yield data that is used to propose a complex kinetic mechanism. Rate constants are calculated by approximation methods based on the experimental data. The findings of this study have been applied to some hydrazine derivatives that are useful analytically and medicinally.

Results and Discussion

The analytical procedure used in this study effectively separated the salicylaldehyde derivatives of MAH (retention time r_t 5.0 min) and H (r_t 16.3 min) and salicylaldehyde (r_t

0022-3263/78/1943-0015$01.00/0