# pH-Stat Measurement of Substituent Effects in Hydroxamate Nucleophile Displacements at Carbonyl Centers

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The "charge effect" previously discussed for nucleophilic displacements on isopropyl methylphosphonofluoridate by non-$\alpha$ but not by $\alpha$ nucleophiles has been investigated in analogous reactions occurring at carbonyl centers. The catalytic coefficients determined (by use of a sensitive pH-stat of improved design) for a variety of neutral and cationic *para*-substituted benzohydroxyamates in reaction with both *p*-nitrophenyl benzoate and *p*-nitrophenyl *p*-nitrobenzoate have been plotted in both Brønsted and Hammett linear free-energy relationships. The unusual similarity of the corresponding $\beta$ (Brønsted) and the $\rho$ (Hammett) values of these esters in reaction with the same series of $\alpha$ nucleophiles has received some consideration. Though limited to hydroxamate nucleophiles, these data (considered in Table IV) are consistent with the conclusion that the "charge effect" could be a reflection of the differences in the mechanism of charge dispersal in the respective transition states for $\alpha$ and non-$\alpha$ nucleophiles attacking unsaturated centers.

A "charge effect" resulting from the occurrence of a cationic site in the nucleophile and increasing its reactivity (relative to its base strength) has been identified[1,2] for phenate anions in displacement reactions of methyl phosphonofluoridates. The absence of this "charge effect" has also been demonstrated[2] for a series of hydroxamic acid anions in the same reactions. The proposal has been advanced,[2] consequently, that testing for the "charge effect" may be applied as a probe of the factors involved in nucleophilic reactivity. It is based on the suggestion that all $\alpha$ nucleophiles[3] fail to exhibit this effect compared with non-$\alpha$ nucleophiles because of differences in the origins of their nucleophilic properties.

The general objective of our current program of investigation of carbonyl reactivity toward nucleophiles is to determine the scope of these conclusions regarding the "charge effect." In this report we present the results obtained in studies of the reactivity of a series of hydroxamic acid anions with carboxylic esters, undertaken for comparison with phosphonate esters[2] to evaluate the influence of the substrate in this test of the characteristics of $\alpha$ nucleophiles.

## Experimental Section

**General Preparations of Hydroxamic Acids.**—Most of the benzohydroxamic acids employed in the basicity and kinetic measurements discussed below were prepared by methods described earlier.[4-9] However, the cationic hydroxamic acid which had been prepared only once previously[10] was of special interest to our objectives. We therefore report its synthesis and characterization by slightly different procedures.

TABLE I

| Compound | p$K_a$[a] |
|---|---|
| *p*-Methoxybenzohydroxamic acid | 10.29 |
| Benzohydroxamic acid | 10.9 |
| *p*-Chlorobenzohydroxamic acid | 9.67 |
| *p*-Nitrobenzohydroxamic acid | 8.91 |
| *p*-Trimethylammoniumbenzohydroxamic acid–iodide | 8.90 |

[a] Measured in 50% dioxane–water solution.

**Preparation of the Iodine Salt of *p*-Trimethylammoniumbenzohydroxamic Acid.**—The quaternized benzoate[10] was the raw material for this step. Two solutions were prepared in separate vessels: (1) this consisted of 6.9 g of metallic sodium in 100 ml of dry methanol; (2) this consisted of 14.1 g of hydroxylamine hydrochloride in 100 ml of dry methanol. Solutions 1 and 2 were rapidly mixed at room temperature and the sodium chloride thus precipitated was filtered with suction. To the filtrate was added 30 g of the quaternized benzoate and the resulting solution was stirred for 45 hr at room temperature under a nitrogen blanket. The reaction mixture was acidified with glacial acetic acid and the excess methanol and acetic acid were evaporated to the point of near dryness. The residual solid was recrystallized four times from hot water. The crystalline product, 11 g, had mp 193.5–195° dec and analyzed satisfactorily for $C_{10}H_{15}N_2O_2I$.

*Anal.* Calcd for $C_{10}H_{15}N_2O_2I$: C, 37.28; H, 4.69; N, 8.10; I, 39.39. Found: C, 37.25; H, 4.82; N, 8.57; I, 39.66.

**p$K_a$ Measurements.**—The p$K_a$ values (Table I) of all the hydroxamic acids considered in this report were measured on a Sargent Model D titrimeter under the following conditions: (1) the hydroxamic acid concentration was approximately 0.001 *M* in 50% dioxane–water solution which was 0.1 *M* with respect to potassium chloride as supporting electrolyte; (2) the controlled temperature was 25 ± 0.1°; (3) the titrating medium was always covered with an oxygen-free nitrogen atmosphere; (4) the titrating base used was *ca.* 0.05 *M* KOH in 50% dioxane–water solution.

**Kinetic Measurements.**—The rates of hydrolysis of *p*-nitrophenyl benzoate with the various benzohydroxamic acids listed in the accompanying tables were measured by means of an exclusive high speed recording pH-stat. This instrument was designed and constructed for the express purpose of pursuing very rapid hydrolytic rates at constant, preset hydrion concentrations in both aqueous and nonaqueous media. The equipment proved to be very adequate for the task of pursuing the relatively rapid reaction of hydroxamate-catalyzed *p*-nitrophenyl benzoate and *p*-nitrophenyl *p*-nitrobenzoate hydrolysis. A full description of this apparatus is given in a subsequent section of this report.

The procedural details established for making a reproducible rate run may be outlined as follows.

**For *p*-Nitrophenyl Benzoate.**—(1) A solution was prepared first consisting of 240 ml of 50% dioxane–water which was 0.1 *M* in KCl and either 0.005, 0.007, or 0.01 *M* in the selected hydroxamic acid. It was adjusted by addition of exactly 5 ml of water and the required amount of KOH solution to bring it to pH 11.0 at 25° under nitrogen. (2) A solution exactly 5 ml in volume and containing either 0.0005 or 0.001 *M* of *p*-nitrophenyl benzoate in pure dioxane was rapidly injected from a delivery syringe into the reaction flask. (3) The recorded data of milliliters of standard KOH solution required to maintain pH 11.0 as a function

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(1) (a) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Bellington, Jr., and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964); (b) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, R. A. Stephani, and E. Cook, *ibid.*, **86**, 4959 (1964).

(2) J. Epstein, P. L. Cannon, Jr., H. O. Michel, B. E. Hackley, Jr., and W. A. Mosher, *ibid.*, **89**, 2937 (1967).

(3) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

(4) A. L. Green, G. L. Lainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

(5) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **77**, 3651 (1955).

(6) R. Swidler and G. M. Sternberg, *ibid.*, **78**, 3594 (1956).

(7) M. A. Stolberg and W. A. Mosher, *ibid.*, **79**, 2618 (1957).

(8) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959).

(9) R. Swidler, R. E. Plapinger, and G. M. Sternberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959).

(10) G. Benoit and A. Funke, *Bull. Soc. Chim. Fr.*, 257 (1958).

of time were treated by the Guggenheim method for computing the pseudounimolecular rate constant $k_{obsd}$. (4) The catalytic coefficients $k_{A^-}$ were computed from eq 1 where $[A^-]$ is the con-

$$k_{obsd} = k_{H_2O}[H_2O] + k_{OH^-}[OH^-] + k_{A^-}[A^-] \qquad (1)$$

centration of the hydroxamic acid anion after plotting in each instance the linear elements of this equation, $k_{A^-}$ *vs.* $[A^-]$.

**For *p*-Nitrophenyl *p*-Nitrobenzoate.**—(1) A solution was prepared first consisting of 240 ml of 50% dioxane–water which was 0.1 *M* in KCl and a certain molarity of the selected hydroxamic acid. It was adjusted by exactly 5 ml of water, 3 ml of pure dioxane, and the required amount of KOH solution to bring it to pH 11.0 at 6.0° under nitrogen. (2) A solution exactly 2 ml in volume and containing 0.0001 *M* of *p*-nitrophenyl *p*-nitrobenzoate in dioxane was rapidly injected from a delivery syringe into the reaction flask. The same technique was employed for the *p*-nitrophenylbenzoate runs. The concentration of the hydroxamate anion $[A^-]$ was obtained from the following well-established relationship (eq 2), where $pK_a$ is the ionization constant

$$pH = pK_a + \log [A^-]/([HA] - [A^-]) \qquad (2)$$

of a given hydroxamic acid in 50% dioxane–water and pH is 11.0 ± 0.05 for all runs. The $k_{A^-}$ was equal to the slope of the line obtained from the plots of log $k_{obsd}$ *vs.* $[A^-]$. The $k_{OH^-}$ was computed from eq 3.

$$k_{obsd} = k_{OH^-}[OH^-] \qquad (3)$$

**The pH-Stat.**—The schematic diagram and electronic assembly of these instruments are given in the accompanying Figures 1a and 1b. The particular advantages of these com-

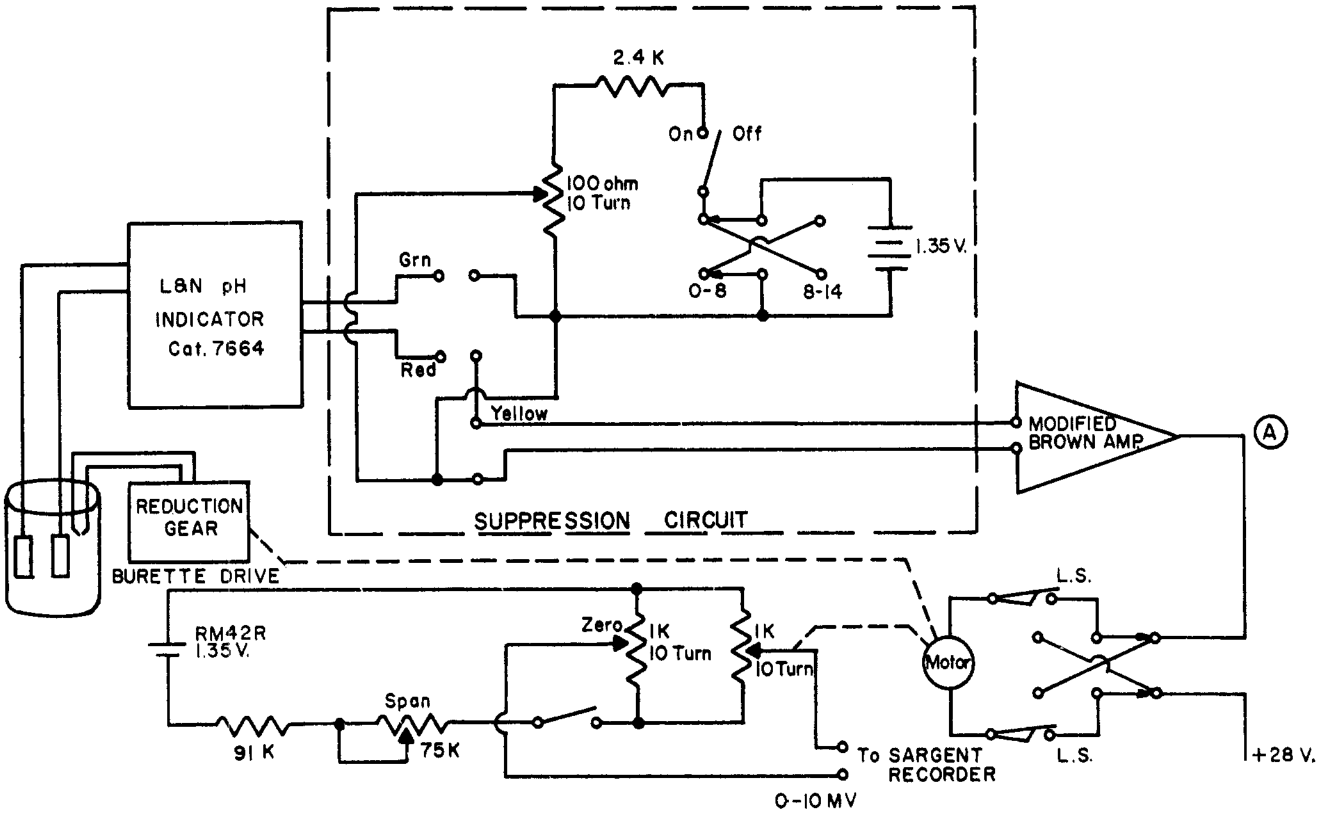
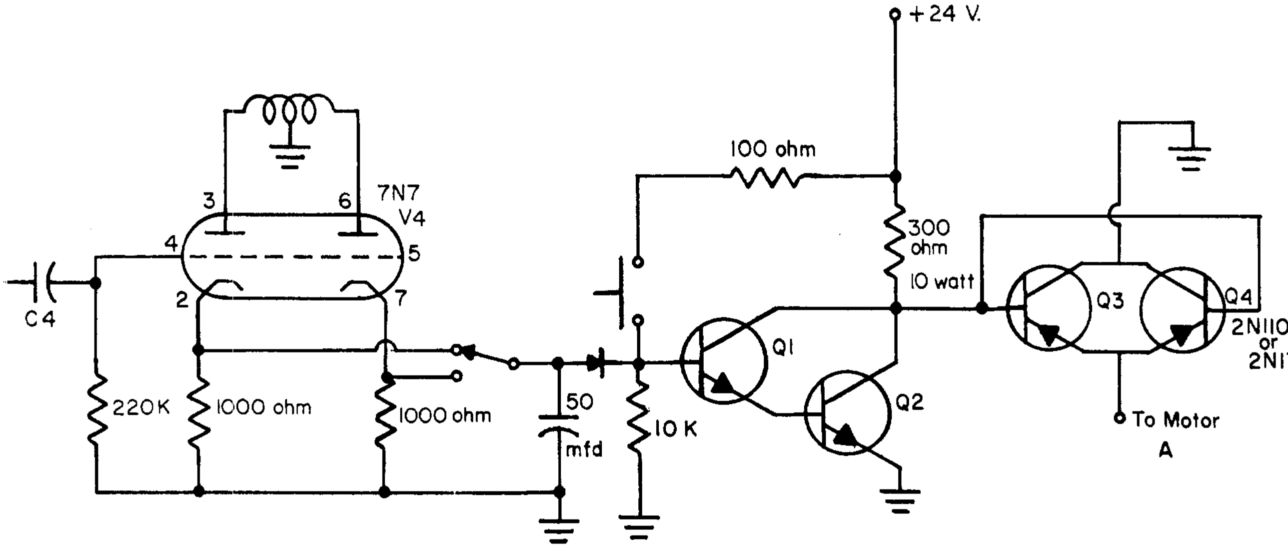


Figure 1a.—pH-Stat.



Q1, Q2 - 2N1479
Q3, Q4 - 2N1100 or 2N174
CR1 - 1N2071 or equiv.

Figure 1b.—Brown amplifier modification.

Table II

Summary of Kinetic Results for *p*-Nitrophenyl Benzoate[a]

| Catalysts $p$-X-$C_6H_5C(=O)NHOH$, X | Run 1 $[C_0]$,[b] $10^2$ *M* | Run 1 $[C]$,[b] $10^2$ *M* | Run 1 $k_{obsd}$, $min^{-1}$ | Run 2 $[C_0]$,[b] $10^2$ *M* | Run 2 $[C]$,[b] $10^2$ *M* | Run 2 $k_{obsd}$, $min^{-1}$ | Run 3 $[C_0]$,[b] $10^2$ *M* | Run 3 $[C]$,[b] $10^2$ *M* | Run 3 $k_{obsd}$, $min^{-1}$ | Summary values, $k_c \times 10^2$, l. $mol^{-1}$ $min^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3O$ | 0.50 | 0.42 | 0.53 | 0.75 | 0.63 | 0.63 | 1.0 | 0.84 | 0.82 | 1.04 |
| H | 0.50 | 0.45 | 0.42 | 0.75 | 0.68 | 0.57 | 1.0 | 0.91 | 0.74 | 0.84 |
| Cl | 0.50 | 0.48 | 0.29 | 0.75 | 0.72 | 0.39 | 1.0 | 0.96 | 0.49 | 0.54 |
| $NO_2$ | 0.50 | 0.50 | 0.07 | 0.75 | 0.74 | 0.10 | 1.0 | 0.99 | 0.13 | 0.13 |
| $N^+(CH_3)_3$ $I^-$ | 0.50 | 0.50 | 0.07 | 0.75 | 0.74 | 0.11 | 0.96 | 0.96 | 0.13 | 0.14 |

[a] Reaction conditions discussed in Experimental Section. [b] $[C_0]$: initial concentration of hydroxamic acid. $[C]$: initial concentration of hydroxamic acid anion.

Table III

Summary of Kinetic Results for *p*-Nitrophenyl *p*-Nitrobenzoate[a]

| Catalysts $p$-X-$C_6H_5C(=O)NHOH$, X | Run 1 $[C_0]$,[b] $10^3$ *M* | Run 1 $[C]$,[b] $10^3$*M* | Run 1 $k_{obsd}$, $min^{-1}$ | Run 2 $[C_0]$,[b] $10^3$ *M* | Run 2 $[C]$,[b] $10^3$ *M* | Run 2 $k_{obsd}$, $min^{-1}$ | Run 3 $[C_0]$[b], $10^3$ *M* | Run 3 $[C]$,[b] $10^3$ *M* | Run 3 $k_{obsd}$, $min^{-1}$ | Run 4 $[C_0]$,[b] $10^3$ *M* | Run 4 $[C]$,[b] $10^3$ *M* | Run 4 $k_{obsd}$, $min^{-1}$ | Run 5 $[C_0]$,[b] $10^3$ *M* | Run 5 $[C]$,[b] $10^3$ *M* | Run 5 $k_{obsd}$, $min^{-1}$ | Summary values, $k_c \times 10^3$, l. $mol^{-1}$ $min^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3O$ | 0.50 | 0.42 | 0.82 | 0.67 | 0.56 | 0.96 | 1.0 | 0.84 | 1.69 | | | | | | | 1.91 |
| H | 0.50 | 0.45 | 0.78 | 0.75 | 0.68 | 1.04 | 1.0 | 0.91 | 1.20 | 1.20 | 1.09 | 1.55 | | | | 1.47 |
| Cl | 0.50 | 0.48 | 0.50 | 0.75 | 0.72 | 0.67 | 1.0 | 0.96 | 0.78 | 1.25 | 1.19 | 1.29 | 1.50 | 1.43 | 1.42 | 1.02 |
| $NO_2$ | 1.0 | 0.99 | 0.22 | 1.88 | 1.86 | 0.52 | 2.0 | 1.98 | 0.58 | | | | | | | 0.28 |
| $N^+(CH_3)_3$ $I^-$ | 1.0 | 0.99 | 0.25 | 1.49 | 1.50 | 0.30 | 2.0 | 1.98 | 0.49 | | | | | | | 0.24 |

[a,b] See Table II.

Chart I

Brown Amplifier Modifications

1. Remove V3 from socket
2. Disconnect filmaments to V3
3. Connect pins 4 and 5 of V4 together
4. Change R8 to 220-kilohm 1-W resistor
5. Disconnect the jumper between pins 2 and 7 of V4
6. Remove R5 and R12
7. Add a 1-kilohm 1-W resistor from pin 2 of V4 to ground
8. Add a 1-kilohm 1-W resistor from pin 7 of V4 to ground

pared with the most recent[11] pH-stat equipment available for kinetic applications may be summarized as follows. (1) Proportional control: the response speed of the titrant delivery system is proportional to the degree of unbalance of the chemical system. In Malmstadt's instrument[11] incremental additions of titrant are provided. Increments are totalized on a counter and strip-chart recorder. There are some very apparent advantages for kinetics to be realized in the use of our delivery system compared with Malmstadt's. (2) Reaction *vs.* time profile: this form of data can be converted easily into its first derivative and recorded directly as reaction velocity which other modern instruments cannot accomplish. In a future article an anticipator circuit attached to this instrument to minimize overshoot due to electrode system response time lag will be described. These developments shown in Chart I were designed by Dr. Fred Fritz at this laboratory.

The rectifier section of V2 (7F7) can be removed and silicon rectifiers (IN2071 or equivalent) can be used to replace this portion of V2.

The triode state of V2 that was removed by the preceding operation can be wired and used as an extra stage of amplification if so desired.

## Results

The p$K_a$ values measured for the five *para*-substituted benzohydroxamic acids constituting the reaction series in 50% dioxane–water solution are given in Table I. The reaction rates at 25° and their dependencies on hydroxamic acid and hydroxamate anion concentrations are listed in Table II for *p*-nitrophenyl benzoate displacement reactions. Therein also are tabulated the catalytic coefficients determined from plots of these rate data, $k_{obsd}$ *vs.* $[A^-]$, assuming the linear relationship in eq 1 in which all lines of the reaction series members must pass through the origin, since the values of the uncatalyzed reaction coefficient, $k_{OH^-}$, in all cases were determined (according to eq 3) to be less than 0.01 $min^{-1}$ and $k_{H_2O}$ $[H_2O]$ products were zero. Table III contains an array of the corresponding data for *p*-nitrophenyl *p*-nitrobenzoate displacements.

In Brønsted plots (Figure 2) of the log $k_A$- *vs.* p$K_a$ for the reaction of the series of *para*-substituted hydroxamate anions with both ester substrates the cationic substituent (trimethylammonium), where the ionization constant is almost identical with that of the *p*-nitro, shows catalytic coefficient values which plot very close to the line comprising all the points of the respec-

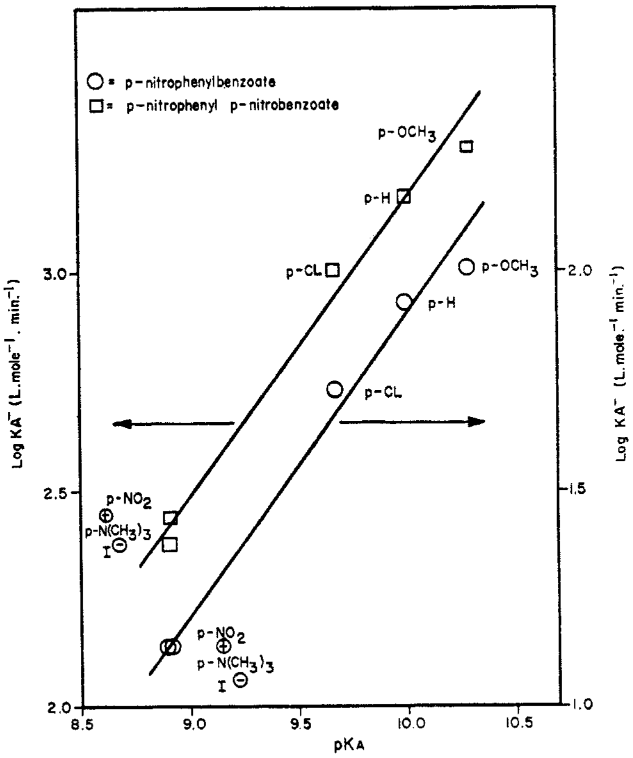


Figure 2.

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(11) H. V. Malmstadt and E. H. Prepmeier, *Anal. Chem.*, **37**, 34 (1965).

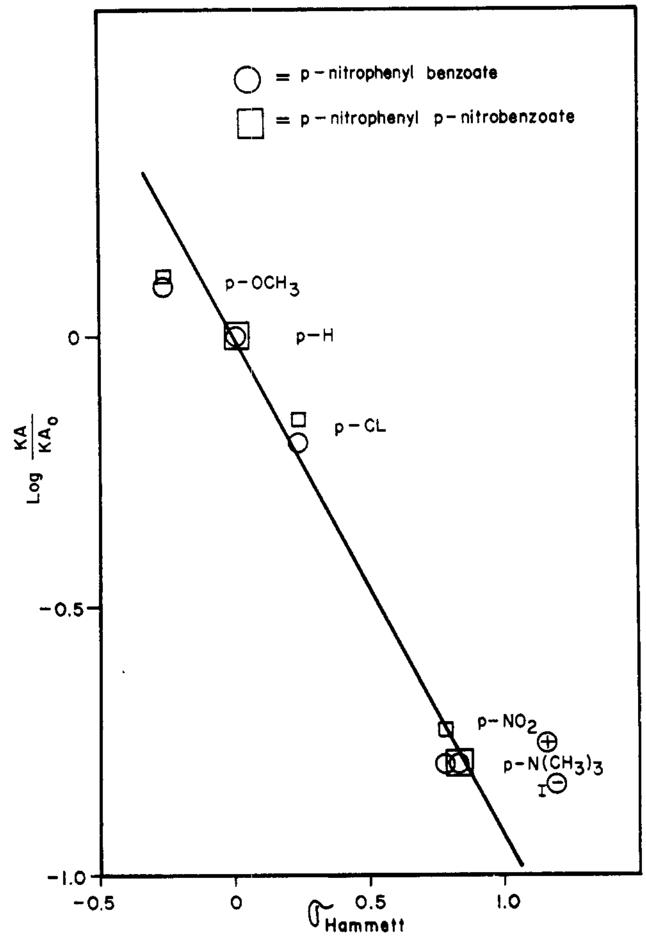


Figure 3.

tive substrate reaction series. Certainly the deviation of the cationic substituents from coincidence with the least-squares slope (the Brønsted $\beta$ value) is well within experimental error and considerably less than that predicted by the "charge effect" observed for cationic phenate anion nucleophiles. It is to be noted, furthermore, that the $\beta$ values of both substrates are nearly identical, being 0.67 for *p*-nitrophenyl benzoate and 0.70 for *p*-nitrophenyl *p*-nitrobenzoate. Apparently the considerable difference in electron deficiency of the respective carbonly reaction centers exerts no important influence on the reaction characteristic measured by $\beta$.

In Hammett plots (log $k_A/k_{A_0}$ *vs.* $\sigma_H$) the identical slope $\rho = -0.86$ is obtained for both ester substrates. The largest deviations from the line in either case (which are still not very large) are found for the *p*-methoxy-substituted nucleophile. A somewhat improved fit results, however, when $\sigma^0$ values[9] are used in place of $\sigma_H$ (Figure 3).

It will be recalled that the normal substituent constants $\sigma^0$ are applicable in cases where the *para* substituent in an aromatic side-chain reaction exerts its influence purely through its field effect and not *via* a $\pi$ inductive effect;[12] the incursion of resonance factors in the transition state furthermore seems quite unlikely.

## Discussion

The complete absence of a "charge effect" in displacements by (the nucleophiles) hydroxamate anions on esters, regardless of the degree of electron deficiency at the carbon seat of reaction, might be regarded with some surprise. The interpretations of Epstein, *et al.*, suggest that there is no electrostatic contribution through repulsion of the dissociating proton in the ionization of $\alpha$ acids as there is in non-$\alpha$ acids. This interpretation clearly predicts the positive deviations observed for cationic substituents in plots of p$K_a$ *vs.* log $k_A$- in the latter cases.

Except for this difference in behavior of $\alpha$ and non-$\alpha$ nucleophiles in displacement reactions on various ester substrates there are many elements of similarity to be noted from the results presented (above) and earlier studies in this area. There are, for instance, no dramatic differences in the Brønsted $\beta$ values (Table IV) to be associated with the nature of the substrate (phosphorous or carbonyl reaction center), its degree of electron deficiency (as related to the conjugation of electron-withdrawing substituents with the reaction center), or the nature of the nucleophile ($\alpha$ or non-$\alpha$). The same conclusion would seem to apply to the slope of the Hammett linear free-energy relations being compared in Table IV.

TABLE IV
LINEAR FREE-ENERGY PARAMETERS FOR PERTINENT DISPLACEMENT REACTIONS

| Substrate | Nucleophile (type) reaction series | $\beta$ value | $\rho_H$ | Ref |
|---|---|---|---|---|
| Methylphosphonofluoridate | Phenate (non-$\alpha$) | 0.59 | −0.80 | 1a |
| Methylphosphonofluoridate | Catecholate (non-$\alpha$) | 0.80 | | 1a |
| Methylphosphonofluoridate | Pyrogallate (non-$\alpha$) | 0.76 | | 1a |
| Methylphosphonofluoridate | Ketoximate ($\alpha$) | 0.64 | | 1a |
| Methylphosphonofluoridate | Hydroxamate ($\alpha$) | 0.80 | | 1a |
| *p*-Nitrophenyl benzoate | Hydroxamate ($\alpha$) | 0.67 | −0.86 | This work |
| *p*-Nitrophenyl *p*-nitrobenzoate | Hydroxamate ($\alpha$) | 0.70 | −0.86 | 1a |

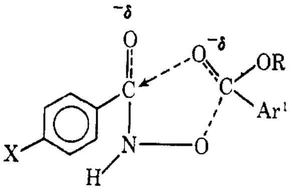
These data must be regarded as somewhat surprising in view of the earlier conclusions of Swain and Langsdorf[13] based on extensive studies of the displacement reaction. These workers demonstrated that the value of $\rho$ is dependent on the structure of the substrate and on the structure of the nucleophile in typical cases. The clear departure of the data in Table IV from these guidelines may perhaps be correlated with the relative constancy of Brønsted $\beta$ values also listed. The parameter $\beta$ is usually regarded as a measure of the extent of bonding between the reactants in the transition state. These results may then be taken to signify that all of the nucleophiles ($\alpha$ and non-$\alpha$) have achieved a comparable degree of affiliation with the reaction centers in the transition state, more or less independently of the degree of electron deficiency, or other characteristics of the reaction seat in the substrate.

An attractive explanation, in keeping with these considerations and capable of understanding the origin of the "charge effect," would suggest that the negative charge developed in the transition states of these displacement reactions is stabilized to a corresponding degree. Apparently this is true regardless of the nature of the nucleophile, so that all nucleophiles (both $\alpha$ and non-$\alpha$), which have been studied thus far in this respect, can contribute to charge dispersal at the reac-

(12) J. O. Roberts, R. A. Clement, and J. J. Drysdale, *J. Amer. Chem. Soc.*, **73**, 2181 (1951).

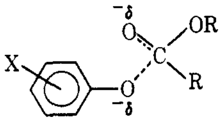
(13) C. G. Swain and W. P. Langsdorf, Jr., *ibid.*, **73**, 2813 (1951).

tion seat. In the case of α nucleophiles possessing a neighboring locus of unsaturation, a structural feature is available which is capable of coordinating the released electron pair of the carbonyl under attack. This event may be formulated in several alternative ways (for instance transition state I) in the case of the hydroxamate anion (pair) depending on where the site of electron density resides in the nucleophile.[14]



transition state I

Even though the reactivity of anions with carbonyl or phosphonyl centers may vary with structure, the position of the displacement transition state along the reaction coordinate (according to Table IV) may be relatively independent of the structure of the nucleophile. Consequently, it is of interest to compare such α anions with phenate nucleophiles which do not possess an analogous facility for accommodating the development of transition-state charge. There would, in fact, appear to be a tendency to accumulate negative charge (as represented by the transition state II) with the approach of the phenate anion to the unsaturated reaction center.



transition state II

The difference in mechanism of charge dispersal for these two types of nucleophiles may afford the explanation of the "charge effect" that is operative in the one case (non-α) and not the other. As pointed out by Epstein, *et al.*,[3] the trimethylammonio group can function as an electron sink in hydroxamic acids, and thus, as with any other electron-withdrawing group, there can be no extraordinary electrostatic contribution in the ionization of the α acid. A similar analysis can be applied to the transition state I. By contrast, the more concentrated negative charge of the phenolic transition state and the closer grouping of anion charge centers of II result in exaltation of the electrostatic effect of the cationic charge of the remote trimethylammonio group.

There is an entirely equivalent way of expressing the "charge effect" in terms of the degree of charge dispersal in I *vs.* II. Evidently the negative charge in the hydroxamate transition state is smeared out over a large number of electronegative atoms. This circumstance diminishes the magnitude of coulombic interactions with cationic centers in the attacking nucleophile. (Substituents other than those bearing a full positive charge exercise their influence through charge–dipole interactions which constitute an inverse higher power function of the distance of their separation than charge–charge interactions). By contrast the proton-anion pair developing in the phenolic transition state results in exaltation of the electrostatic effect of the cationic charge of the remote trimethylammonio group, a reflection of the closer grouping of the anionic charge centers in II.

**Registry No.**—*p*-Methoxybenzohydroxamic acid, 2593-85-3; benzohydroxamic acid, 1005-00-1; *p*-chlorobenzohydroxamic acid, 2593-22-8; *p*-nitrobenzohydroxamic acid, 3236-38-2; iodide salt of *p*-trimethylammoniumbenzohydroxamic acid, 18593-15-2; *p*-nitrophenyl *p*-nitrobenzoate, 1037-31-6; *p*-nitrophenyl benzoate, 959-22-8.

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[14] See, for instance, O. Exner and B. Kakar, *Coll. Czech. Chem. Commun.*, **28**, 1965 (1963); G. M. Sternberg and R. W. Swidler, *J. Org. Chem.*, **30**, 2362 (1965); R. E. Plapinger, *ibid.*, **24**, 802 (1959).