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Charged Substituents in Correlations of Electronic Substituent Effects[1]

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It is shown from electrostatic equations that charged substituents cannot be included with dipolar groups in one general scale of electronic substituent effects. This is illustrated by both theoretical calculations and examples from the literature.

Correlations involving Hammett substituent constants have become an important part of organic chemistry. Such σ values provide a numerical scale of the electronic substituent effect on various properties and reactivities measured at some center (Y) elsewhere in the molecule. The basic eq 1 describes the effect of a substituent (X) on

$$P_X - P_H = \sigma\rho \qquad (1)$$

some property P in a series of molecules XGY where P_H is the value where X = H. The ρ value is an indication of the transmission ability within the molecular framework G. The substituent constants σ are supposed to be invariable from one framework to another. A more recent development[2] was eq 2, where allowance is made for the

$$P_X - P_H = \sigma_F\rho_F + \bar{\sigma}_R\rho_R \qquad (2)$$

separate transmission of two separate electronic effects σ_F,[3] the through-space electrostatic effect of the substituent on the property, and $\bar{\sigma}_R$, the resonance effect of the substituent, which can be represented by various scales depending on electron demand. Again, it is supposed that σ_F or any particular scale of $\bar{\sigma}_R$ values is independent of the particular system or property considered.

It has not been appreciated,[4] however, that it is impossible to meet this consideration of a general scale of σ_F values for both polar and dipolar substituents at the same time. This follows from the basic electrostatic equations. Thus, eq 3 represents the energetic effect of a monopolar

$$\Delta E = \frac{1}{Dr} \qquad (3)$$

substituent (considered as being of unit charge) on a probe which is also a monopole (as, for example, in the anion of a carboxylic acid or in protonated amine in measurement of acidity), where D is the effective dielectric constant. Equation 4 shows the effect of a dipole substituent of local

$$\Delta E = \frac{\mu \cos \theta}{Dr^2} \qquad (4)$$

dipole μ subtending an angle θ to a monopolar probe. Even if the dipole is at 0° to the probe, as, for example, for a symmetrical substituent in the para position of a benzene ring, the equations still differ by a power of r, the distance from the substituent to the probe. Thus, if we define ρ_F in terms of some well-defined σ_F values for dipolar substituents, as is usual, then the σ_F values obtained for polar substituents will only be appropriate for that particular value of r. If we go to a second system of different r', then the values will not be constant but will differ by the factor r'/r. Wepster[5] has shown that inclusion of data for NMe_3^+ and SO_3^- in Hammett plots of aromatic acidities gave σ "constants" for the two charged substituents which increased dramatically in magnitude with increasing distance. The results for NMe_3^+, in particular, can be nearly quantitatively rationalized in terms of the different distance dependencies of monopoles and dipoles.

A similar situation exists for properties which respond to the polarization of a probe bond. For a polar substituent, for the simple case where the pole is coaxial with the probe, eq 5 applies for the polarization energy, while for

$$\Delta\epsilon = \frac{1}{Dr^2} \qquad (5)$$

$$\Delta\epsilon = \frac{2\mu}{Dr^3} \qquad (6)$$

the same condition for a dipolar substituent, eq 6 applies.[7] Once again, there is a difference in the power of r involved. There is an additional problem here if one compares the ratio of eq 4 to eq 3, with $\theta = 0°$, to the ratio of eq 6 to eq 5, since they differ by a factor of 2. The result of this is that even for a fixed system (r is constant), the values of σ_F obtained for polar substituents, based on a standard set for dipolar groups, differ by a factor of 2 depending on the property measured. The situation is even further complicated if the geometry is not as simple as that in the examples here.

In their original work in obtaining σ_F values, Taft and his collaborators[8] did not list values for charged substituents. However, many subsequent authors[9] have done so using values obtained mainly by equilibria or physical properties such as infrared on NMR absorption. One particular approach[10] to substituent constants has even proposed to divide field and resonance effects by using the charged NMe_3^+ substituent as a standard. The validity of basing a treatment of mainly neutral dipolar substituents upon the behavior of monopolar groups has been questioned,[11,12] and the difference of distance dependence

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(1) Part 5 of the series Theoretical Studies of the Inductive Effect. For Part 4, see ref 13.

(2) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Progr. Phys. Org. Chem.* **1973**, *10*, 1.

(3) Such σ_F values were earlier designated σ_I.

(4) See, however, ref 6, 12, and 13.

(5) Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720.

(6) Reynolds, W. F. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 985.

(7) Can be derived simply from equations in Smith, J. W. "Electric Dipole Moments"; Butterworths: London, 1955.

(8) See, for example, ref 2 and Taft, R. W. *J. Phys. Chem.* **1960**, *64*, 1805.

(9) See references in Exner, O. In "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978. For examples of more recent references, see: Binev, I. G.; Kuzmanova, R. B.; Kaneti, J.; Juchnovski, I. N. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1533. Vassileva, P. J.; Binev, I. G.; Juchnovski, I. N. *Spectrochim. Acta* **1983**, *39A*, 709.

(10) Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 492.

(11) Holz, D. *Chem. Rev.* **1971**, *71*, 139. Shorter, J. In "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978. Shorter, J. "Correlation Analysis of Organic Reactivity"; Research Studies Press: New York, 1982; p 59, 60, 65.

(12) Reynolds, W. F.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 1989. Hoefnagel, A. J.; Oosterbeek, W.; Wepster, B. M. *J. Org. Chem.* **1984**, *49*, 1993. Charton, M. *J. Org. Chem.* **1984**, *49*, 1997.

Table I. ΔE Values[a] for Method A and Δq_α[b] for Method B (See Text) as Calculated at the ab Initio Molecular Orbital 4-31G Level

	method A, r =			
	4.45 Å	7 Å	10 Å	15 Å
NH_2	2.04	0.88	0.44	0.20
OH	3.71	1.8	0.92	0.37
F	6.22	2.70	1.39	0.64
CH_3	−0.27	−0.07	−0.03	−0.01
CF_3	5.64	2.32	1.21	0.56
CHO	3.34	1.44	0.79	0.38
CN	6.39	3.11	1.70	0.82
NO_2	8.92	3.21	1.66	0.78
NH_3^+	59.30	40.63	29.70	20.52
O^-	−57.30	−39.59	−29.18	−20.28
CO_2^-	−48.85	−35.99	−27.19	−19.33
β^a	0.0744	0.1789	0.3345	0.6949
C^b	−0.0145	−0.0116	−0.0053	0.0076
cc[c]	0.991	0.968	0.956	0.945
	method B, r =			
	4 Å	5 Å	7 Å	10 Å
NH_2	41	12	10	1
OH	85	48	20	8
F	133	76	31	12
CH_3	−3	−1	0	0
CF_3	117	69	30	12
CHO	62	38	17	7
cN	126	76	34	14
NO_2	184	108	47	18
NH_3^+	564	396	228	123
O^-	−503	−363	−215	−118
CO_2^-	−355	−282	−177	−102
β^b	0.0036	0.0058	0.0141	0.0329
C^b	0.0002	0.0246	0.0011	0.0366
cc[c]	0.9999	0.992	0.995	0.975

[a] ΔE values (kcal mol^{-1}) for process A. [b] See eq 9. [c] Correlation coefficient. [d] Δq_α[e] values in 10^4 electrons, positive sign taken as increase in electron population over 1.0000. [e] Corrected for small disturbances in HH/HH.

Table II. Effective σ_F Values for Monopoles

	method A, r =			
	4.45 Å	7 Å	10 Å	15 Å
X				
NH_3^+	4.39	7.26	9.93	14.27
O^-	−4.28	−7.09	−9.77	−14.09
CO_2^-	−3.65	−6.45	−9.10	−13.42
	method B, r =			
	4 Å	5 Å	7 Å	10 Å
X				
NH_3^+	2.03	2.32	3.21	4.08
O^-	−1.81	−2.08	−3.03	−3.85
CO_2	−1.28	−1.61	−2.50	−3.32

Table III. Comparison of Apparent Field Constants, σ_F, for NR_3^+ and for Representative Dipolar Substituents Based on Acidities for (a) Aliphatic Systems and (b) XCH_2 Pyridinium Ions

	aliphatic system			
	XCH_2CO_2H[b]	1[c]	2[d]	3[e]
Cl[a]	0.45	0.45	0.45	
CN	0.45	0.46	0.45	0.45
NH_3^+	0.54	0.53	0.58	0.59
$N(CH_3)_3^+$		0.73	0.91	

	pyridinium ions		
	o[f]	*m*[g]	*p*[h]
Cl	0.45	0.45	0.45
Br	0.43	0.46	0.46
CN	0.59	0.55	0.58
NH_3^+	0.76	0.79	0.81
$NH_2CH_3^+$	0.79	0.86	0.89
$NH(CH_3)_2^+$	0.88	0.94	1.01

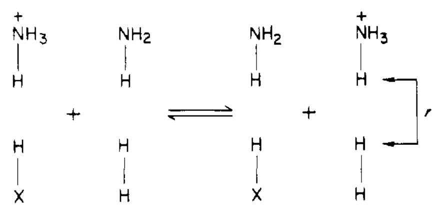
[a] F constants estimated from experimental pK_a values by scaling so that $\sigma_F = 0.45$ for Cl (or Br). [b] Reference 16. [c] Reference 17, see text for structure. [d] Reference 10, see text for structure. [e] Reference 18, see text for structure. [f] Reference 19, *o*-(XCH_2)-pyridinium ion. [g] Reference 20, *m*-(XCH_2)pyridinium ion. [h] Reference 21, *p*-(XCH_2)pyridinium ion.

of the electronic effect of dipoles and poles pointed out.[6,13]

We illustrate below the problems of considering both polar and dipolar substituents in the one scale, both from theoretical calculations and using values for the literature.

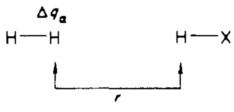
Calculations and Results

We have recently obtained[13] a theoretical scale of substituent field parameters for dipolar substituents using either of two methods. In the first, method A, the energy was calculated for the hypothetical proton transfer process (eq 7). As an alternative, method B, we calculated the



(7)

relative polarization of the electron population in hydrogen molecules as in eq 8.



(8)

The first process is described by eq 4 and the second by eq 6. In both cases, we found an excellent correlation of the results (ΔE or Δq_α) vs. literature σ_F values. We were thus able to obtain[13] a scale of theoretically derived σ_F values for a wide variety of dipolar substituents.

We report here results including the typical monopolar substituents NH_3^+, O^-, and CO_2^- at various values of r. In each case, we use the calculated values of ΔE or Δq_α for a range of dipolar substituents (NH_2, OH, F, Me, CF_3, CHO, CN, NO_2) to define β in eq 9 using our earlier reported σ_F values for these groups.

$$\sigma_F = \beta \Delta E \text{ (or } \Delta q_\alpha) + C \qquad (9)$$

Thus, we can use β and the calculated value of ΔE or Δq_α to obtain effective σ_F values for the monopoles under the various conditions. The calculated values of ΔE and Δq_α, together with β and C values, are given in Table I, and the σ_F values for monopoles in are given Table II.

All calculations were made at the ab initio molecular orbital 4-31G level by using the GAUSSIAN80 program.[14] The calculations were performed by using standard geometries[15] for NH_3, NH_4^+, and HX.

Discussion

The theoretical calculations reported in Table I and II fully confirm the expectations discussed above. First, for dipolar substituents interacting with a molecule, as in

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(13) Marriott, S.; Topsom, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 7.

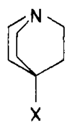
(14) Binkley, J. S.; Whiteside, R. A.; Khrishnan, R.; Seeger, R.; DeFrees, D. J.; Schleger, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. "Gaussian 80–An Ab-Initio Molecular Orbital Program", Department of Chemistry, Charnegie-Mellon University, Pittsburg, 1980.

(15) Pople, J. A.; Beveridge, D. L. "Approximate Molecular Orbital Theory"; McGraw-Hill; New York, 1970.

method A, the ΔE values fall off with distance approximately as $1/r^2$ $(1/r^{1.87})$, as anticipated from eq 4. With dipolar substituents polarizing a bond, as in method B, the effect falls off with distance approximately as $1/r^3$ $(1/r^{2.8})$, as expected from eq 6. The ΔE and Δq_α values for the dipolar substituents are used to obtain the β and C values for eq 9 for each series, and the correlation coefficients are also reported in Table I.

The values of σ_F derived for the monopoles (Table II) are seen to alter with distance as anticipated in the introduction. As expected, the values increase approximately linearly with distance. Further, the values obtained by method A are approximately twice the magnitude of those by method B, as anticipated above from a comparison of eq 2–6. It would thus seem well proven that general σ_F values cannot be derived for monopolar substituents by using data scaled to dipolar substituents.

This is further illustrated by pK_a values for seven series of compounds (see Table III). All are chosen as examples of systems where only field effects should be present. They are data for 2-substituted acetic acids,[16] 4-substituted quinuclidines **1**,[17] 4-substituted bicyclooctanecarboxylic acids **2**,[10] 4-substituted cyclohexanecarboxylic acids **3**,[18] and ortho,[19] meta,[20] and para,[21] XCH_2-substituted pyridines. The Cl, Br, and CN substituents are chosen as typical dipolar substituents with all pK_a values scaled to give $\sigma_F = 0.45$ for Cl. While σ_F values for the other two dipolar substituents remain essentially constant, the values for NR_3^+ change dramatically in the direction one would predict from the geometrical considerations; that is, they increase with increasing distance. The actual values here cannot be compared with those calculated above, since the electronic effect of a charged substituent is particularly sensitive to changes in solvent and counterion.[22] Experimental data do not appear to be available to check the second problem discussed above, relating to the factor of 2 between equation 5 and 6. The data required would be, for example, both NMR and pK_a results for systems of corresponding geometry under identical solvent conditions.



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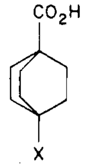

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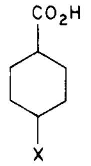

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Conclusion

Overall then it is clearly not reasonable to quote σ_F values for polar substituents. Such values would only be valid for the particular geometry and method of measurement employed. It is also clearly unreasonable to base a scale of substituent values for mainly dipolar substituents on the value for the charged NMe_3^+ groups as has been done for the $\mathcal{F}$ values of Swain.[10]

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(16) Kortum, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* **1960**, *1*, 189.

(17) Grob, C. A.; Schaub, B.; Schlageter, M. G. *Helv. Chim. Acta* **1980**, *63*, 57.

(18) Data for Br and CN from Siegel, S.; Komarny, K. *J. Am. Chem. Soc.* **1960**, *82*, 2549. Data for NH_3^+ from Kirderova, J.; Farrell, P. G.; Edward, J. T.; Halle, J.-C.; Schaal, R. *Can. J. Chem.* **1978**, *56*, 1130.

(19) Fischer, A.; King, M. J.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3059.

(20) Fischer, A.; King, M. J.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3068.

(21) Fischer, A.; King, M. J.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3072.

(22) See ref 5 and 12, and, for example: Hartshorn, S. R.; Ridd, J. H. *J. Chem. Soc. B.* **1968**, 1063. Rees, J. H.; Ridd, J. H.; Ricci, A. *J. Chem. Soc., Perkin Tran. 2* **1976**, 294 and references therein.

Synthesis and Oxidative Coupling of (±)-3-Oxoreticuline

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The synthesis and oxidative coupling of 3-oxoreticuline (**8**) are described. Reaction of **8** with iodosobenzene diacetate in the presence of trifluoroacetic acid gave 16-oxosalutaridine (**12**), 16-oxopallidine (**13**), 5-oxoisoboldine (**14**), and 13-oxothalidine (**15**) in yields of 27%, 8%, 6%, and 10%, respectively. Oxidation of **8** with vanadium oxytrichloride gave **13**, **14**, and **15** in yields of 26%, 11%, and 9%, respectively.

The key step in the biosynthetic pathway to codeine (**1**) and morphine (**2**) is the intramolecular oxidative coupling of a 1-benzyltetrahydroisoquinoline, reticuline (**3**), to give salutaridine (**4**).[1] Efforts to carry out the in vitro oxidative coupling of reticuline or *N*-acyl-*N*-norreticuline derivatives using a range of oxidants have given a variety of yields of the four possible products of a direct coupling between the two phenol rings, namely, salutaridine (**4**),[2] pallidine (**5**),[3] corytuberine (**6**),[4] and isoboldine (**7**),[5] or their respective *N*-acyl-*N*-nor derivatives. A major problem in synthetic application of this method has been the inability to direct the regiochemical outcome of the coupling step. McDo-

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(1) Barton, D. H. R.; Kirby, G. H.; Wiechers, A. *J. Chem. Soc. C* **1966**, 2313.

(2) (a) Schwartz, M. A.; Mami, I. *J. Am. Chem. Soc.* **1975**, *97*, 1239. (b) Szantay, C.; Blasko, G.; Barczai-Beke, M.; Pechy, P.; Dornyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509.

(3) (a) Kametani, T.; Kozuka, A.; Fukumoto, K. *J. Chem. Soc. C* **1971**, 1021. (b) Blasko, G.; Dornyei, G.; Barczai-Beke, M.; Pechy, P.; Szantay, C. *J. Org. Chem.* **1984**, *49*, 1439.

(4) Kametani, T.; Ihara, M. *Heterocycles* **1979**, *12*, 893.

(5) Schwartz, M. A. *Synth. Commun.* **1973**, *3*, 33.

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