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Quantitative Description of Steric and Electrical Effects of Planar π-Bonded Groups. 2. Planar π-Bonded Substituents Ortho to a Nonplanar Active Site

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A method has been developed which for the first time makes possible the assignment of the proper steric and delocalized (resonance) electrical effect constants to planar π-bonded ortho substituents. The method has been shown to apply to NO_2, Ph, and COZ where Z is OMe, OEt, NH_2, Me, H, and Ph. The dihedral angle θ between an ortho planar π-bonded substituent, Xpπ, and the planar π-bonded skeletal group, Gpπ, to which it is attached is primarily a function of the size of Xpπ and of the active site, Y, bonded to the adjacent carbon atom of Gpπ. Electrical effects of Xpπ and possibly also of Y are of much less importance. The ortho substituent effect is almost always largely electrical in nature, although significant small steric effects frequently occur. The localized (field and/or inductive) electrical effect of an ortho substituent is between 1 and 2.6 times the size of that of a para substituent and is almost always larger. The delocalized electrical effect of an ortho substituent ranges from 0.3 to 1.2 times that of a para substituent and is usually smaller. The composition of the ortho electrical effect varies over a much greater range than that of the para electrical effect.

In the first paper of this series[1] we established the geometry of a system consisting of a planar π-bonded group, Xpπ, and a nonplanar group, Xnp, attached to vicinal positions in a planar bonded skeletal group, Gpπ. We now consider the problem of the calculation of delocalized electrical effect substituent constants, σ_D, which correspond to a particular value of the dihedral angle, θ, of the Xpπ group. This problem results from the fact that both the steric effect and the delocalized electrical effect of an Xpπ group bonded to Gpπ vary as a function of the steric requirements of an adjacent Xnp group. From the geometry previously determined for this type of system (Figure 1) we may define the effective van der Waals radius of the Xpπ group MZ^1Z^2 as in eq 1 when $r_{VZ^1} < r_{VZ^2}$. The line

$$r_{V,Xp\pi} \equiv d' + r_{VZ^1} \qquad (1)$$

PP″ through the group axis of Xpπ is perpendicular to the plane of Gpπ. The group axis of Xpπ is collinear with the Xpπ–Gpπ bond. The line P′V is the perpendicular through Z^1 to P″. Then, $d = P^1Z^1$.

In general, the steric parameter υ is defined as

$$\upsilon_X \equiv r_{VX} - r_{VH} = r_{VX} - 1.20 \qquad (2)$$

Then

$$\upsilon_{Xp\pi} = d' + r_{VZ^1} - 1.20 \qquad (3)$$

Clearly

$$d' = d \cos \theta \qquad (4)$$

where d is the distance between the point of intersection of the perpendicular through Z^1 to the group axis and Z^1 (Figure 2). From eq 3 and 4

$$\upsilon_{Xp\pi} = d \cos \theta + r_{VZ^1} - 1.20 \qquad (5)$$

or

$$\cos \theta = (\upsilon_{Xp\pi} - r_{VZ^1} + 1.20)/d \qquad (6)$$

Equations 5 and 6 show the dependence of the steric parameter for an Xpπ group upon the dihedral angle θ. The σ_D constant of an Xpπ group must also depend upon the dihedral angle since the extent of π delocalization is a function of θ. The dependence of the resonance effect on θ is well reviewed by Jaffé and Orchin[2] and briefly by Hall.[3] The majority of the workers who have estimated values of θ have made use of an equation of the type

$$Q_\theta = Q_0 \cos^2 \theta \qquad (7)$$

or one derived from it.[4] In this equation, Q is the quantity of interest, and the subscript θ indicates the value of Q is that for the dihedral angle θ. The subscript 0 indicates the value of Q is for $\theta = 0°$. This relationship has been applied to the determination of dihedral angles from UV spectra[5] and NMR spectra[6] and to represent the delocalized effect of an Xpπ group as a function of θ.[7] The approach has been criticized[8] in regard to its use for UV spectra, and an alternative method for use with UV spectra has been proposed by Suzuki.[9] An equation related to eq 7 has been used to calculate delocalized electrical effect constants, however.[10] Although eq 8 is said to be preferable at very small values of θ^2, this is the region of θ which

$$Q_\theta = Q_0 \cos \theta \qquad (8)$$

is of least interest as the variation in υ and σ_D will be negligible for $\theta \leq 10°$. In view of this, the fact that eq 7 has been applied previously to the calculation of σ_D, and the general preference of other workers for eq 7, we have chosen it for the calculation of $\sigma_{D\theta}$. Thus, eq 7 with $Q = \sigma_D$ results in

$$(\sigma_{D\theta}/\sigma_{D0})^{1/2} = \cos \theta \qquad (9)$$

Substitution of eq 9 in eq 6 gives

$$(\sigma_{D\theta}/\sigma_{D0})^{1/2} = (\upsilon_{Xp\pi} - r_{VZ} + 1.20)/d \qquad (10)$$

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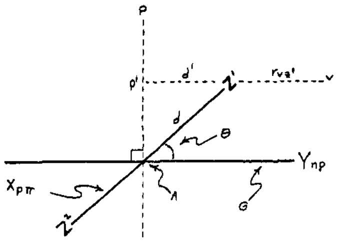

Figure 1. Geometry of 2-Xpπ–C_6H_4Ynp. Ynp is a nonplanar active site and Xpπ a planar-bonded group; $d = AZ^1$, $d^1 = P^1Z^1$.

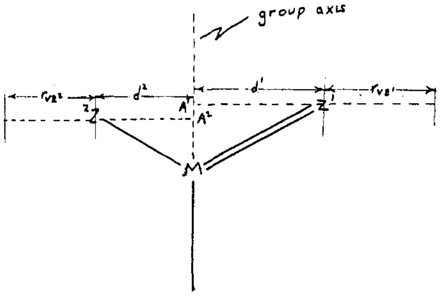

Figure 2. Type I Xpπ group. Only M and Z^1 are π bonded: $A^1Z^1 = d^1$, $A^2Z^2 = d^2$, $R^1Z^1 = r_{VZ^1}$, $R^2Z^2 = r_{VZ^2}$, $\upsilon^1_{max} = d^1 + r_{VZ^1} - 1.20$, and $\upsilon^2_{max} = d^2 + r_{VZ^2} - 1.20$. (This figure and Figure 1 of preceding paper are identical.)

As $\sigma_{D\theta}$ must lie between 0 and σ_{D0}, both it and σ_{D0} must have the same sign. Then

$$|\sigma_{D\theta}/\sigma_{D0}|^{1/2} = (\upsilon_{Xp\pi} - r_{VZ} + 1.20)/d \qquad (11)$$

Rearranging eq 11

$$|\sigma_{D\theta}|^{1/2} = |\sigma_{D0}|^{1/2}(\upsilon_{Xp\pi} - r_{VZ} + 1.20)/d \qquad (12)$$

As $|\sigma_{D0}|^{1/2}$, r_{VZ}, and d are constant, eq 12 has the form

$$|D_{D\theta}|^{1/2} = a_1\upsilon_{Xp\pi} + a_0 \qquad (13)$$

where

$$a_1 = |\sigma_{D0}|^{1/2}/d,\ a_0 = (1.20 - r_{VZ})|\sigma_{D0}|^{1/2}/d \qquad (14)$$

The minimum value of $\upsilon_{Xp\pi}$ is determined by the half-thickness of the Xpπ group, $r_{V,0.5,Xp\pi}$. Thus

$$\upsilon_{min,Xp\pi} = r_{V,0.5,Xp\pi} - 1.20 \qquad (15)$$

For this value of $\upsilon_{Xp\pi}$, $\sigma_{D\theta}$ is minimal, although not necessarily zero as θ may be less than 90° at this point.

The σ_D value which corresponds to any given value of υ may be calculated from eq 13. Unfortunately, no method is available for determining a priori the appropriate υ value. We have shown that θ is a function of $r_{V,Xnp}$ according to eq 16. Unless a_{30} and a_{11} are known, θ cannot be calculated.

$$1/\sin\theta = a_{30}/\textstyle\sum r + a_{11} \qquad (16)$$

$$\text{where } \textstyle\sum r = r_{V,Xnp} + r_{V,min,Xp\pi} \qquad (17)$$

In order to include an Xpπ group in a data set in which the substituents exhibit a steric effect, it is necessary to know θ so that the appropriate values of the delocalized electrical effect parameter σ_D and the steric parameter υ can be used. This is particularly important due to the fact that the majority of the delocalized electrical effect acceptor groups commonly encountered are Xpπ groups (NO_2, COZ). We have developed a method for the application of correlation analysis to data sets that exhibit a steric effect and contain Xpπ groups. Our procedure is as follows.

(1) A basis set, which contains only those members of the data set that show minimal dependence of their steric effect on conformation, is correlated with the LDS equation (eq 18). In eq 18, Q is the quantity to be correlated,

$$Q_X = L\sigma_{IX} + D\sigma_{DX} + S\upsilon_X + h \qquad (18)$$

and σ_I is a parameter which represents the localized electrical effect. The σ_D and υ parameters were described above.

(2) The data point for an Xpπ group is now added to the basis set. Separate correlations are carried out with eq 18 by using υ values for Xpπ and increasing them in convenient increments from υ_{min} to υ_{max} (Figure 2), and the corresponding σ_D values are calculated from eq 13. The proper values of $\upsilon_{Xp\pi}$ and $\sigma_{D,Xp\pi}$ are those which result in the best correlation of the data set with eq 18. The best correlation is that which results in maximum values of statistics such as the F test or $100R^2$ (where R is the multiple correlation coefficient) or in minimum values of such statistics as the standard error of the estimate, S_{est}, or the Exner f statistic (defined as the ratio of S_{est} to the root mean square of the data). To be meaningful, it is also necessary that the best correlation give values of the regression coefficients L, S, and S which are not significantly different from those obtained for the correlation of the basis set in step 1.

Any data set can be written in the form XGY where X is a variable substituent, Y is the active site at which some measurable chemical reactivity, physical property, or bioactivity takes place, and G is a skeletal group to which X and Y are bonded.

We may now test the validity of this method. To avoid possible complications arising from the variable steric effect of a planar π-bonded active site, Ypπ, we have considered in this paper only the simple case of a nonplanar active site, Ynp.

In order to provide a proper test of the method, it is necessary that the data sets studied should be well characterized.[11,12] A well-characterized data set must have a sufficient number of data points and must vary widely in substituent type in order to have a large enough range in σ_I, σ_D, and υ to ensure that the members of the data set will not cluster in one or two regions of the range. The most desirable data sets, designated as primary (P) sets, have ten or more data points. They include the substituents H, alkyl (Ak), alkoxy or amino, F or I, and Cl or Br and a sterically well-behaved delocalized electrical effect acceptor group such as CN or CF_3. Furthermore, they have a range in υ of not less than 0.75 Å. Finally, it is vital that (1) the electrical and steric effect parameters of the set members be independent of each other, (2) the data set gives an excellent correlation with eq 18, and (3) the data set exhibits a significant steric effect.

Only if these three conditions are met will the data set provide a meaningful test of the method. An extensive literature search resulted in 13 primary data sets. As not all of these can be expected to meet the above requirements, we have considered two supplementary types of data set. In the first type, all but one of the requirements for a primary set are met, but the set has only eight or nine points or, alternatively, only one type of halogen substituent. Such data sets are designated secondary (S) sets. Seven such data sets are available. In the second type of supplementary set, the number of data points is six or more, and of the six types of substituent which must be present in a primary set, only five are required. These sets are designated as tertiary (T). They have been studied by

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[11] Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1.

[12] Charton, M. *Chem. Technol.* **1974**, 502; **1975**, 245.

a modification of our proposed method. The first step is identical with that described previously; the basis set is correlated with the LDS equation (eq 18). This allows the calculation of the percent delocalized effect, P_D, defined as[13] in eq 19. P_D is a measure of the composition of the

$$P_D = 100D/(L + D) \quad (19)$$

electrical effect. In the second step of the modified method the data set which now consists of the basis set and an Xpπ data point is correlated with eq 20,[13] where σ_n is a com-

$$Q_X = \rho\sigma_{n,X} + S\upsilon_X + h \quad (20)$$

posite substituent constant defined by As eq 19 has only

$$\sigma_{n,X} \equiv \sigma_{IX} + [P_D/(100 - P_D)]\sigma_{DX} \quad (21)$$

two independent variables, satisfactory results can be obtained with fewer points in the set. Four tertiary data sets are available.

Results

The data sets were correlated with eq 18 by multiple linear regression analysis. The data used are presented in Table I. The σ_I values for all groups and the σ_D values for Xnp groups are from our compilation.[13] The υ values for Xnp groups are from our collection.[14] The σ_D values corresponding to a particular υ value for Xpπ groups were calculated from eq 13. These values for the Xpπ studied in this work are reported in Table I of the supplementary material (hereafter abbreviated as SM). The complete statistics for the correlations of the basis sets are given in Table II(SM). Seven of the thirteen primary data sets, five of the secondary sets, and two of the tertiary sets meet all of the requirements cited above for a valid test of the method (test sets). Of the 24 data sets which gave a satisfactory correlation, nine did not exhibit a significant steric effect.

The second step of the method was then carried out with the test sets. The complete statistics for the υ and σ_D values of Xpπ which gave the best correlation are given in Table II(SM). The Xpπ groups studied include NO_2, Ph, Vi (vinyl), and C(O)Z with Z = H, Me, Ph, OMe, OEt, NH_2. In every case the goodness of fit depended on the choice of υ (and therefore σ_D), and a best fit was observed corresponding to some particular υ value or narrow range. Furthermore, in every case there was no significant difference between the regression coefficients obtained for the basis set and those obtained for the best correlation of step 2. In Table II values of F, $100R^2$, S_{est}, and f are given for two typical sets. The values for the remaining sets are set forth in Table V(SM). It must be noted that set 306 did not give a significant value of D and therefore represents only a partial test of the method.

In determining the value of θ, $100R^2$ was used as the indicative statistic, and correlations differing in $100R^2$ by 0.03 or less were considered equivalent. The υ value reported in Table II(SM) represents the midpoint of the range of equivalent values, and the value of θ reported corresponds to that value of υ.

Discussion

There are three questions which arise from this work. (1) Is the proposed method of treating Xpπ groups valid and useful? (2) What conclusions can be drawn concerning the factors which determine the dihedral angle of Xpπ groups? (3) What do these results reveal concerning the nature of the ortho effect?

Validity of the Method. The 15 data sets which met the conditions stated above for test sets include rate and equilibrium constants, NMR chemical shifts, and IR stretching frequencies. Among the Xpπ groups studied are substituted carbonyl (COZ) groups and the vinyl, phenyl, and nitro groups. The proposed method requires that there be a maximum value of the F and $100R^2$ statistics and a minimum value of the S or f statistics for the correlations with the LDS equation (or the ρ_S equation) as υ (and σ_D) is varied. This is indeed the case in every one of the 15 test sets available for study. In all cases the goodness of fit was best for a particular value or narrow range of υ (and of course the corresponding σ_D values). We conclude that the method is indeed valid.

The utility of the method depends on whether the use of the optimal values of υ and σ_D for an Xpπ group results in a significantly better fit of the data to the correlation equation. Before the existence of the method proposed here the only way of dealing with Xpπ groups was to assume that they were either coplanar with the benzene ring ($\upsilon = \upsilon_{max}$) or perpendicular to it ($\upsilon = \upsilon_{min}$). As a convenient measure of the significance of the improved correlation we may use the quantity Δ defined as in eq 22, where $(100R^2)^*$

$$\Delta = (100R^2)^* - (100R^2) \quad (22)$$

is the maximum value of $100R^2$ observed and $(100R^2)$ is the value of $100R^2$ obtained when υ is υ_{min} or υ_{max} (Δ_{min} or Δ_{max}, respectively). Values of Δ_{min} and Δ_{max} are reported in Table V(SM).

It must be noted that best results with set 42 were obtained on exclusion of the data points for X = H and *t*-Bu. As a result, this set is classified as T.

Finally, when more than one Xpπ group was available for a given data set, all of the available data points were combined into one overall correlation by using the previously determined best υ and σ_D values for each Xpπ group. These sets are designated simply by the set number and σ_D type, thus 2M is the set which includes all members of set 2 and was correlated with the σ_R^- constants.

We have considered a value of $\Delta > 0.25$ to be significant. Of the 27 examples in Table III(SM), 12 show values of Δ_{min} and Δ_{max} which are significant. In these examples the actual value of υ and the corresponding value of σ_D are important factors in the goodness of fit of the data. Thus, in 44% of the available examples improved correlations are obtained. It follows, then, that it is frequently necessary in correlating chemical reactivities and physical properties with the LDS equation to be able to determine the proper value of υ (and the corresponding value of σ_D) for Xpπ groups.

Factors Determining θ. In data sets of the type XpπGYnp we may examine the effects of varying the Xpπ group, the Ynp active site or the skeletal group G, while holding the reaction conditions (medium, temperature, pressure) constant. Unfortunately, the data available are very limited. Combining results obtained from the rate constants for the reaction of 2-substituted pyridines with MeI in MeCN at 30 °C (set 42) and in Me_2SO at 23 °C (set 43), we have obtained values of θ for COZ groups with Z = Me, OMe, OEt, H, and Ph and also for the Ph group itself. We have correlated the values of $1/\sin\theta$ for these groups with the modified LDS equation

$$(1/\sin\theta_X) = L^*\sigma_{IX} + D^*\sigma_{RX} + S^*\textstyle\sum r + h^* \quad (23)$$

where

$$\textstyle\sum r = r_{VX} + r_{VMe} \quad (24)$$

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Table I. Data Used in the Correlations

(P1) pK_a, 2-$\mathrm{XC_6H_4OH}$, $\mathrm{H_2O}$, 25 °C[a]
H, 9.98; *t*-Bu, 11.16; Et, 10.20; *i*-Pr, 10.34; Me, 10.28; MeO, 9.98; F, 8.81; Cl,8.48; Br, 8.44; I, 8.51; CN, 7.15; $\mathrm{NO_2}$, 7.23

(P2) pK_a, 2-$\mathrm{XC_6H_4NH_3^+}$, $\mathrm{H_2O}$, 25 °C[b]
H, 4.606; Br, 2.53; *t*-Bu, 3.78; Cl, 2.65; Et, 4.37; F, 3.20; I, 2.60; *i*-Pr, 4.42; MeO, 4.52; Me, 4.44; OEt, 4.482; CN, 0.95; $\mathrm{MeSO_2}$, 0.06; $\mathrm{NO_2}$, −0.26; $\mathrm{CONH_2}$, 2.941; NHAc, 3.337

(S3) pK_a, 2-$\mathrm{XC_6H_4NH_3^+}$, 1% aqueous EtOH, 25 °C[c]
H, 4.63; Br, 2.61; Cl, 2.70; Et, 4.30; F, 3.17; I, 2.61; MeO, 4.48; Me, 4.46; CN, 0.77; $\mathrm{NO_2}$, −0.15; $\mathrm{CO_2Me}$, 2.32; $\mathrm{CO_2Et}$, 2.39

(S4) 10^4K_a, 2-$\mathrm{XC_6H_4OCH_2CO_2H}$, $\mathrm{H_2O}$, 25 °C[d]
H, 6.75; Me, 5.93; MeO, 5.88; $\mathrm{NO_2}$, 12.7; CN, 10.6; F, 8.22; Cl, 8.90; Br, 7.53; I, 6.72

(P5) pK_a, 2-$\mathrm{XC_6H_4CHO}$ + $\mathrm{OH^-}$, $\mathrm{H_2O}$, 25 °C[e]
OEt, 15.18; *i*-Pr, 14.99; OMe, 14.96; H, 14.90; Me, 14.86; I, 13.67; Cl, 13.64; Br, 13.59; F, 13.56; $\mathrm{CF_3}$, 13.41; $\mathrm{NO_2}$, 12.89

(T9) kr, 2-$\mathrm{DC_6H_4X}$ + $\mathrm{NH_2^-}$, $\mathrm{NH_3(1)}$[f]
F, 10^6; $\mathrm{CF_3}$, 10^5; PhO, 2×10^4; H, 1; Me, 0.2; OMe, 500; $\mathrm{Me_2N}$, 1.4; Ph, 4.7

(P11) log kr, 2-$\mathrm{XC_6H_4O(CO)NHMe}$ + $\mathrm{OH^-}$, 10% aqueous EtOH, 38 °C[a]
H, 2.38; *t*-Bu, 0.83; *sec*-Bu, 1.47; Pr, 1.66; Et, 1.67; *i*-Pr, 1.69; Me, 1.80; *i*-PrO, 2.36; EtO, 2.48; MeO, 2.53; F, 3.89; Cl, 3.92; Br, 4.10; I, 4.01; CN, 5.44; $\mathrm{NO_2}$, 5.79

(P12) $10^{-2}kr$, 2-$\mathrm{XC_6H_4OAc}$ + $\mathrm{OH^-}$, 3% aqueous EtOH, 25 °C[g]
H, 1.65; F, 4.63; Cl, 3.35; Br, 3.69; I, 3.30; Me, 0.74; Et, 0.67; *i*-Pr, 0.61; *t*-Bu, 0.32; OMe, 1.20; CN, 20.2; $\mathrm{NO_2}$, 13.1

(P13) 10^3kr, 2-$\mathrm{XC_6H_4O(CO)NMe_2}$ + $\mathrm{OH^-}$, 10% aqueous EtOH, 25 °C[g]
H, 2.30; F, 3.18; Cl, 2.06; Br, 1.78; I, 1.30; Me, 0.64; *sec*-Bu, 0.38; *t*-Bu, 0.33; $\mathrm{CF_3}$, 3.25; OMe, 1.15; $\mathrm{NO_2}$, 4.51

(S31) 10^2kr, 2-$\mathrm{XC_6H_4CO_2Et}$ + $\mathrm{OH^-}$, 56% aqueous MeAc, 25 °C[h]
Cl, 0.440; Br, 0.2992; I, 0.1633; CN, 12.20; OEt, 0.1156; Me, 0.03381; $\mathrm{NO_2}$, 1.690; $\mathrm{NH_2}$, 0.028 00; H, 0.2891

(S41) k_rel, 2-$\mathrm{XC_6H_4N^+Me_3}$ + $\mathrm{PPh_3}$[i]
H, 1; Me, 1.00; Et, 1.49; *i*-Pr, 2.88; PhO, 10.9; *t*-Bu, 50.2; Cl, 70.4; CN, 163; CHO, 74.2; Ph, 8.40

(T42) k_rel, 2-$\mathrm{XC_6H_4N}$ + MeI, MeCN, 30 °C[j]
H, 1.00;[k] Me, 0.50; Et, 0.19; *i*-Pr, 0.080; *t*-Bu, 0.000 20;[k] $\mathrm{PhCH_2}$, 0.089; Br, 0.0044; CN, 0.0020; OPh, 0.0094; $\mathrm{NH_2}$, 0.50; Ph, 0.010; Ac, 0.00091; COH, 0.0023; $\mathrm{CO_2Et}$, 0.0072; Bz, 0.0054

(S43) k_rel, 2-$\mathrm{XC_6H_4N}$ + MeI, $\mathrm{Me_2SO}$, 23 °C[l]
H, 1.0; Me, 0.38; Et, 0.17; $\mathrm{CH_2Ph}$, 0.081; Cl, 0.0039; Br, 0.0039; CN, 0.022; $\mathrm{NH_2}$, 1.23; NHAc, 0.0082; $\mathrm{CO_2Me}$, 0.0084

(T44) log k_rel, 2-$\mathrm{XC_6H_4N}$ + MeI, MeAC[m]
H, 0; Me, −0.42; Cl, −2.37; Br, −2.62; CN, −3.09; OMe, −1.96; OEt, −2.00; Vi, −1.55; CHO, −2.99; Ph, −1.86; NHAc, −2.46

(P51) k_rel, 2-$\mathrm{XC_6H_4I}$ + Ph·, $\mathrm{CCl_4}$, 60 °C[n]
$\mathrm{NH_2}$, 7.6; MeO, 8.3; EtO, 8.5; F, 14.5; Me, 16.9; H, 17; Et, 19.7; Cl, 25.9; Ph, 34; Br, 50; I, 77; $\mathrm{CF_3}$, 103; $\mathrm{NH_2}$, 186

(P61) $E_{1/2}$, 2-$\mathrm{XC_6H_4I}$, $\mathrm{LiClO_4}$[o]
H, 1.655; Me, 1.688; Et, 1.685; Ph, 1.570; $\mathrm{NH_2}$, 1.565; OH, 1.535; OMe, 1.567; OEt, 1.587; $\mathrm{CF_3}$, 1.343; F, 1.374; Cl, 1.375; Br, 1.322

(P62) $E_{1/2}$, 2-$\mathrm{XC_6H_4I}$, $\mathrm{Me_4NCl}$[o]
H, 1.467; Me, 1.495; Et, 1.478; Ph, 1.327; $\mathrm{NH_2}$, 1.416; OH, 1.391; OMe, 1.393; OEt, 1.405; $\mathrm{CF_3}$, 1.190; F, 1.205; Cl, 1.203; Br, 1.153

(T101) k_rel, 2-D-3-$\mathrm{XC_6H_3N^+Me}$ + $\mathrm{OH^-}$, $\mathrm{D_2O}$, 75.0 °C[p]
H, 1.0; CN, 5.3×10^4; Cl, 2.6×10^3; I, 440; OMe, 62; $\mathrm{NO_2}$, 1.4; $\mathrm{ND_2}$, 9.4×10^5

(S102) pK_a, 2-X-thiazoles, $\mathrm{H_2O}$, 25 °C[q,r]
$\mathrm{SO_2Me}$, −2.82; Cl, −0.75; Br, −0.86; OMe, 1.57; $\mathrm{NMe_2}$, 5.27; H, 2.51; Me, 3.43; Et, 3.37; *t*-Bu, 3.15; $\mathrm{NH_2}$, 5.32; $\mathrm{NO_2}$, −5.08; Ph, 2.52; NHAc, 1.68

(S210) ortho partial rate factors, PhX + $\mathrm{F_2}$, $\mathrm{CCl_3F}$, −78 °C[s]
Me, 8.46; CN, 0.0178; $\mathrm{NO_2}$, 0.00459; $\mathrm{CF_3}$, 0.0144; OMe, 123.12; Br, 0.0828; Cl, 0.192; F, 0.264; H, 1

(P301) δ (CH), ^{1}H NMR, 2-$\mathrm{XC_6H_4OH}$, $\mathrm{Cl^-}$, $\mathrm{CH_2Cl_2}$[t]
OMe, 7.76; *t*-Bu, 9.49; Me, 9.48; $\mathrm{PhCH_2}$, 9.70; OPh, 9.36; H, 9.69; F, 9.98; Cl, 10.22; Br, 10.34; I, 10.60; $\mathrm{CO_2Me}$, 10.62; Ac, 12.11; CN, 10.12; CHO, 11.00; $\mathrm{NO_2}$, 10.91; Ph, 9.69; Bz, 11.76

(P302) δ (OH), ^{1}H NMR, 2-$\mathrm{XC_6H_4OH}$, $\mathrm{Me_2SO}$, 40 °C[u]
F, 9.70; Cl, 10.00; Br, 10.07; I, 10.20; $\mathrm{NO_2}$, 10.8; CN, 10.97; $\mathrm{CF_3}$, 10.44; Me, 9.10; Et, 9.07; Pr, 9.06; *i*-Pr, 9.07; *sec*-Bu, 9.03; *t*-Bu, 9.17; $\mathrm{ViCH_2}$, 9.19; $\mathrm{PhCH_2}$, 9.29; $\mathrm{CH_2OH}$, 9.18; Ph, 9.46; CHO, 10.75; Ac, 11.97; Bz, 10.61; $\mathrm{CO_2Me}$, 10.55; OH, 8.70; OMe, 8.76; OEt, 8.66

(P303) ν(CO), $\mathrm{cm^{-1}}$, 2-$\mathrm{XC_6H_4O(CO)Et}$, $\mathrm{CCl_4}$[v]
t-Bu, 1760.6; Me, 1760.7; H, 1762.8; OMe, 1765.6; I, 1770.3; F, 1772.2; Br, 1771.1; Cl, 1771.1; $\mathrm{CF_3}$, 1774.2; CN, 1776.8; $\mathrm{NO_2}$, 1778.7

(P304) $J(^{13}\mathrm{C{-}H})$, Hz, ^{1}H NMR 2-$\mathrm{XC_6H_4Me}$[w]
$\mathrm{NO_2}$, 129.4; CHO, 127.8; $\mathrm{CO_2H}$, 128.0; CN, 127.9; F, 127.9; Cl, 127.9; Br, 127.8; I, 128.2; OH, 126.9; OMe, 126.9; H, 125.8; Me, 125.7; Et, 125.6; $\mathrm{NH_2}$, 125.6; $\mathrm{NMe_2}$, 126.4

(S306) ν(OH), $\mathrm{cm^{-1}}$ 2-$\mathrm{XC_6H_4N}$ + MeOH[x]
H, 3364; Et, 3333.7; Me, 3335.6; OMe, 3416.2; OPh, 3451.3; Cl, 3452; F, 3477; CN, 3481.2; Vi, 3360.3; Ac, ~3443; Bz, ~3455; Br, 3451.3

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Table II. Values of F, $100R^2$, S_{est}, and f for Two Typical Examples[a]

υ	F	$100R^2$	S_{est}	f	υ	F	$100R^2$	S_{est}	f
0.50	25.59	93.89	0.280	0.332	0.57	28.08	94.40	0.251	0.318
0.55	28.78	94.53	0.265	0.314	0.67	25.46	93.86	0.263	0.333
0.60	31.23	94.93	0.255	0.302	0.77	20.96	92.63	0.288	0.364
0.65	32.47	95.12	0.250	0.296	0.87	17.04	91.09	0.316	0.400
0.70	32.34	95.10	0.251	0.297	0.97	13.56	89.05	0.351	0.444
0.75	31.02	94.90	0.256	0.303	1.07	11.22	87.07	0.381	0.482
0.80	28.52	94.48	0.285	0.315	1.17	9.490	85.06	0.410	0.519
0.85	26.02	93.98	0.278	0.329	1.27	8.205	83.12	0.435	0.551
0.90	23.51	93.38	0.291	0.345	1.37	7.241	81.29	0.458	0.580
0.95	20.86	92.60	0.308	0.365	1.47	6.508	79.61	0.479	0.606
					1.57	5.941	78.09	0.496	0.628
					1.67	5.497	76.73	0.511	0.647
					1.77	5.208	75.76	0.522	0.661
					1.87	4.916	74.68	0.533	0.675
					1.97	4.689	73.73	0.543	0.688
					2.07	4.533	73.12	0.549	0.696
					2.15	4.407	72.56	0.555	0.703

[a] For F, $100R^2$, S_{est}, f; for other sets, see Table V in the supplementary materisl.

Values of r_{VX} were as follows: Ph, 1.77 (half-thickness); Ac, CO_2Et, CO_2Me, Bz, 1.52 ($r_{V\theta}$); HCO, 1.20 (r_{VH}). All r_V values were chosen to represent the minimum thickness of the X$p\pi$ group. We invoke the principle of minimal steric interaction and assume that the group will choose a conformation such that steric repulsion is minimized and will therefore be directed such that its smallest dimension is directed toward Ynp.

The results are reported in Table II(SM) (set 1011). They indicate that θ is a function of both electrical and steric effects of X$p\pi$. Further support for this argument comes from a correlation of $1/\sin\theta$ for only the COZ groups with eq 25. The results (set 1012, Table III(SM)) again

$$(1/\sin\theta_Z) = L^*\sigma_{IZ} + D^*\sigma_{RZ}^{+} + S^*\sum r + h^* \qquad (25)$$

suggest a dependence of upon both electrical and steric effects. They are not conclusive as σ_I is highly linear in σ_R, and the dependence on the localized electrical effect is therefore uncertain.

We now consider the variation of θ with Ynp as X$p\pi$ and G are held constant. Unfortunately, data are unavailable for a range of Ynp under common reaction conditions. We have examined the correlation of $1/\sin\theta$ values obtained for NO_2 groups in seven sets of 2-$O_2NC_6H_4$Ynp with the LDS equation in the form of eq 26. The Ynp's included

$$(1/\sin\theta_Y) = L^*\sigma_{IY} + D^*\sigma_{RY} + S^*\sum r + h^* \qquad (26)$$

in the correlation are OH (set 1), NH_2 (set 2), O(CO)NHMe (set 11), OAc (set 12), O(CO)NMe_2 (set 13), CO_2Et (set 31), and I (set 51). The data sets included both rate and equilibrium constants. In eq 26

$$\sum r = r_{VY} + r_{V,\min,NO_2} \qquad (27)$$

For the basic hydrolyses of CO_2Et, O(CO)NHMe, O(CO)NMe_2, and OAc the steric effect was assumed to be represented by the υ value for the tetrahedral intermediate, 2-XC_6H_4–W–C(OH)(O^-)CZ. W is O or is nonexistent, and Z = OEt, Me, NHMe, or NMe_2. For the groups for which W is O, υ values of 1.11, 1.18, and 1.28 for Z = Me, NHMe, and NMe_2, respectively, were calculated from the extended branching equation.[15] The υ value for no W and Z = OEt was assumed to be equal to υ for CO_3. Values of σ_I and σ_R were estimated where necessary from out work.[13] Both L^* and D^* were not significant; therefore, the correlation was repeated with the S equation (eq 28). The results

$$(1/\sin\theta_Y) = S^*\sum r + h \qquad (28)$$

(Table III(SM), set 1013) are very good. Again, in this set σ_I is linear in $\sum r$, and therefore a dependence on σ_I cannot be excluded.

Overall, θ seems to certainly depend on steric effects of both Ynp and X$p\pi$ and very likely depends on electrical effects of X$p\pi$. It may possibly depend on the localized electrical effect of Ynp as well.

Our results show that the steric effect is the predominant factor in determining θ. When sufficient data are available for a given X$p\pi$ group, its dependence on υ_Y in any new data set can be calculated from the correlation equation obtained by fitting the available data to eq 28. This θ value may then be used to select appropriate values of $\upsilon_{Xp\pi}$ and $\sigma_{D,Xp\pi}$ from those given in Table I(SM).

It must be emphasized that the method described here is not suitable for the accurate determination of dihedral angles, as for most X$p\pi$ it is not sufficiently sensitive. The sensitivity can, of course, be increased by choosing X$p\pi$ with very large σ_D and small υ. A large υ value would require that θ be the maximum for almost all Y. The (CO)CN group might be suitable for this purpose.

Nature of the Electrical Effect in Ortho-Substituted Systems. Ehrenson, Brownlee, and Taft[11] have shown that four different types of σ_D constants (σ_R, $\sigma_R{}^{\circ}$, $\sigma_R{}^{+}$, $\sigma_R{}^{-}$) are required to account for the delocalized effect in 4-substituted benzene systems (4-XC_6H_4Y). Our own results are in complete agreement with their conclusion.[13]

Let us then compare the type of σ_D constant required for best fit in the 2- and 4-substituted benzenes and pyridines. The results show that although 4-substituted phenols and anilinium ions always require the use of $\sigma_R{}^{-}$ and 4-substituted pyridines the use of $\sigma_R{}^{+}$, their 2-substituted analogues frequently give the best correlation with σ_R. This suggests that sensitivity to the electronic requirements of the active site are greater at the para than at the ortho position.

Further evidence is provided by values of ϕ_L and ϕ_D, and these quantities are defined by eq 29. Values of ϕ_L, ϕ_D,

$$\phi_L = L_2/L_4 \qquad (29a)$$

$$\phi_D = D_2/D_4 \qquad (29b)$$

and their standard errors are reported in Table VI(SM). The ϕ_L values range from 0.9 to 2.7 and in 11 of the 12 values available, ϕ_L is significantly greater than 1. As is expected from the shorter distance between an ortho substituent and the active site, the localized effect is almost always greater from the 2- than from the 4-position. The ϕ_D values range from 0.3 to 1.2 with five values significantly

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[15] Charton, M. "Abstracts, EUCHEM Conference on Correlation Analysis in Organic Chemistyr" Assisi, Italy, 1979; p P-3.

smaller than 1 and only a single value significantly larger than 1. It seems likely that, in general, the delocalized effect in the 2-position is smaller than that in the 4-position. In sets 1, 4, 11, and 42, a best fit required the use of σ_R for the 2-substituted and σ_R^- or σ_R^+ for the 4-substituted derivatives. This will not affect the ϕ_L values at all as we find that L is not significantly affected by the choice of ϕ_D. The ϕ_D values will be affected, since although the σ_R, σ_R^-, and σ_R^+ values used in this work are all on the same scale, D values obtained with σ_R^- and σ_R^+ will be somewhat smaller than those obtained for the same data set with σ_R. Thus, ϕ_D for sets 1, 4, 11, and 42 has been calculated with D_4 values that are too small. As an increase in D_4 results in a decrease in ϕ_D, the true ϕ_D values for these sets should be somewhat less than those in Table V(SM).

Finally, the values of P_D, the percent delocalized contribution to the overall electrical effect as defined in eq 22, are useful in comparing electrical effects at the ortho and para positions. Values of P_D are reported in Table II(SM) together with their standard errors. They vary over a very considerable range, from 0 to 60. We have previously remarked that this wide range of P_D is characteristic of ortho-substituted systems. By contrast, para-substituted systems exhibit a much narrower range of P_D (generally 35–65) while meta-substituted systems have P_D values in a very narrow range, generally between 25 and 35.

Significance of the Steric Effect in Ortho-Substituted Systems. The steric effect is usually a minor component of the overall ortho substituent effect. This is evidenced by the values of P_S, the percent of the steric component in the overall substituent effect given by eq 30.

$$P_S = |S|100/(|L| + |D| + |S|) \qquad (30)$$

Values of P_S are reported in Table II(SM). Of the 24 sets that gave significant correlation with the LDS equation, for nine sets P_S was 0 (S was not significant), for four sets P_S was 0.1–10.0, for four sets it was 10.2–20.0, for six sets it was 20.1–30.0, and for 1 set it was greater than 30. This conclusion is in accord with the results obtained from extensive studies of rates of reaction of 2-substituted benzoic acids with diazodiphenylmethane in a wide range of protic[16] and aprotic[17] solvents. Although a significant steric effect was found in every data set, all of which were well characterized, in only one set was $P_S > 20$. Overall, the results obtained for well-characterized data sets are in agreement with our conclusion some years ago that the effect of ortho substitutes is predominantly electrical in nature.[18] It must be pointed out, however, that although electrical effects are predominant, small but significant steric effects were observed in 15 of the 24 sets which give meaningful results. Thus, detectable steric effects will frequently occur in data sets for ortho-substituted systems.

LDS Equation as a Model of the Ortho Effect. The 25 data sets studied here, together with the 17 extensive data sets involving the rate constants for the reaction of 2-substituted benzoic acids with diazodiphenylmethane in various solvents, represent almost all of the best data sets available for ortho-substituted systems. They encompass a fairly wide range of chemical reactivity, physical properties, and reaction conditions. Taking $100R^2$ as a convenient measure of the goodness of fit of the model, we find that of these 42 data sets, six had values of $100R^2 >$ 99.00, ten had values from 98.01 to 99.00, sixteen had values from 96.01 to 98.00, six had values from 94.01 to 96.00, three had values from 90.01 to 94.00, and one had a value less than 90.00. Thus, 32 of the 42 data sets had values of $100R^2$ greater than 96.00. Obviously, the LDS equation is a very good model for chemical reactivity and physical properties of ortho-substituted systems. A comparison of $100R^2$ values for 2- and 4-substituted benzene and pyridine data sets (Table VI(SM)) shows, however, that the LD equation is usually somewhat more effective at modeling 4-substituted systems than the LDS equation is at modeling 2-substituted systems. Nevertheless, the LDS equation is an effective, and probably the best, model of the ortho substituent effect now available.

Conclusions

The method described above permits *for the first time* the assignment of proper steric and delocalized electrical effect constants to planar π-bonded substituents. This resulted in significant improvement in the correlation for more than 40% of the examples studied.

The dihedral angle θ between a planar π-bonded substituent and a planar π-bonded skeletal group depends largely on steric requirements of the substituent and the adjacent active site. It also depends to a lesser extent on electrical effects of the substituent and possibly of the active site as well.

The ortho substituent effect is primarily an electrical effect. Although significant steric effects are frequently detected, they are almost always small.

The localized electrical effect of an ortho substituent is from 1 to 2.6 times that of a para substituent and is almost always larger. The delocalized electrical effect of an ortho substituent is from 0.3 to 1.2 times that of a para substituent and is usually smaller. The composition of the ortho electrical effect has a much greater range than that of the para electrical effect.

Supplementary Material Available: Talbes of σ_D and υ values as a function of θ, of complete statistics for all of the correlations, of values of Δ and of ϕ, of values of F, $100R^2$, S_{est}, and f (17 pages). Ordering information is given on any current masthead page.

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