A Novel Electrostatic Approach to Substituent Constants: Doubly Substituted Benzenes

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Received September 3, 1997. Revised Manuscript Received February 11, 1998

Abstract: The most negative-valued molecular electrostatic potential (MESP) minimum (V_{min}) observed over the benzene ring is proposed as a sensitive quantity for the analysis of the electronic perturbations due to the substituents attached to it. MESP topography of 45 doubly substituted benzenes is mapped at HF/6-31G** level for an appraisal of this proposition. The V_{min} values are seen to clearly reflect the changes due to the different orientations (para, meta, and ortho) and conformations of the substituents and different mechanisms of electron donation or withdrawal. Good linear correlations are obtained with V_{min} and the experimentally determined σ values of the ortho- and meta-disubstituted benzenes. New quantities, D_{p}, D_{m}, and D_{o}, introduced in this work as the substituent pair-constants respectively for the para, meta, and ortho arrangements, provide a quantitative measure of the simultaneous effect of two substituents over the aromatic nucleus. The predictive power of these quantities is checked in the case of some triply substituted benzenes using an equation $V_{\mathrm{min}} = V_{\mathrm{ben}} + \sum\Delta V_{\mathrm{min}}(\mathrm{mono}) - \sum D_{\mathrm{p}} - \sum D_{\mathrm{m}} - \sum D_{\mathrm{o}}$ where V_{ben} is the MESP minimum of benzene and $\Delta V_{\mathrm{min}}(\mathrm{mono})$ is the difference between the monosubstituted benzene V_{min} and V_{ben}. These predicted values are in fairly good agreement with the MESP values obtained at HF/6-31G** level.

Introduction

The substituent constant, first introduced by Hammett[1] in 1935, is still considered as one of the most important quantities used in physical organic chemistry.[2] This and its extended forms are widely used in the field of quantitative structure−activity relationship (QSAR).[3a] In general, it is considered as a measure of a substituent's ability to perturb the electron distribution at a reaction site. According to Hammett, it can be defined by the equation

$$\log (k/k_{\mathrm{o}}) = \rho\sigma \tag{1}$$

where k and k_{o} are rate (or equilibrium) constants for the reactions of the substituted and unsubstituted compounds, σ is the substituent constant, and ρ is called the reaction constant. The applicability of this equation or its varients[4] has been tested for numerous reactions, and in many of these cases, the logarithms of the rate or the equilibrium constants involving the members of a series of compounds are generally found to be linearly related to the σ constants.[5,6] There also appear exceptions where the deviations from linearity are observed, and these deviations are usually attributed to a variety of causes such as experimental errors, presence of reactive or catalytic impurities in the medium of reaction, change in the reaction mechanism, and failure to identify a single reaction in a multistep reaction.[3,7] Toward a positive end, however, the success of the empirical Hammett equation in treating thousands of reactions has led to the world-wide acceptance of it. Attempts have been made by many workers to furnish a theoretical basis for these concepts by finding correlations of computed quantum chemical properties such as total energy, atomic charges, electrostatic potentials, electrostatic field, average local ionization energy, etc. with the constants.[8] For example, Sotomatsu et al.[8f] have estimated the σ constants by the atomic charges calculated by the AM1 methodology on the two oxygen atoms and the proton of the carboxyl group of 27 meta- and para-substituted benzoic acids. Similarly, Kim and Martin[8g] have examined the ability of the comparative molecular field analysis method to reproduce Hammett σ constants in 49 substituted benzoic acids. From a study of 17 para-substituted anilines, Heberlein et al.[8i] have found an excellent linear relationship between 3-21G//STO-3G* amine nitrogen electrostatic potential minimum and local surface ionization energy minimum with the σ^0 Hammett constant (obtained from the ionization of phenylacetic acids) of the substituent.

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S0002-7863(97)03105-3 CCC: $15.00

In recent years, among the above mentioned properties, the molecular electrostatic potential (MESP) has attracted much attention as a meaningful descriptor in the QSAR parlance.[9-13] Politzer and co-workers[14] have been prolific in applying MESP as a tool to a large variety of chemically interesting problems, e.g., they have studied the correlations of MESP minima with the Taft parameters σ_I and σ_R. More recently, Haeberlein and Brinck[15] have analyzed the substituent effects in para-substituted phenoxide ions and found a close, linear relation between the minima of the electrostatic potential, V_{min}, observed near the phenoxide oxygen and the gas-phase acidities. The three dimensional characterization of MESP has been utilized in our laboratory[16,17] for exploring the molecular reactivities, weak intermolecular interactions, and a variety of chemical phenomena. Very recently, it was found that the critical points (CPs) of MESP of a singly substituted benzene observed near para and meta carbons have a linear relation with the corresponding σ_p and σ_m Hammett constants.[18] In addition to this, it has been shown that MESP topography can directly bring out the orientation as well as the activation−deactivation effect of a substituent on the benzene ring. An activating group shows V_{min} near the ortho and para carbons with more negative values than the benzene V_{min} and a deactivating group shows those near the meta carbons are less negative than the benzene V_{min}. For example, the V_{min} values of benzene, aniline, and nitrobenzene in au are −0.0323, −0.0405, and −0.0035, respectively. It is well-known that with every substituted benzenes the electrophilic aromatic substitution generally gives one of the isomers in good yield. For all of these reactions, a generalized reaction mechanism[19] suggests the initial formation of a π-complex followed by a σ-complex leading to the product. Since the MESP critical points over the benzene nucleus can vividly bring out the electronic effect of a particular substituent, it is logical to conclude that the position and value of the most negative MESP CP has a direct relevance with the reaction mechanism, at least at the π-complex formation stage.

In the present work, we consider doubly substituted benzenes toward an MESP topographical investigation and its relations with the Hammett constants. Although the topic of orientation and reactivity is treated in almost all the of standard organic textbooks in great detail, the discussion is often limited to the singly substituted benzenes and very little attention is given to the orientation in a benzene ring with more than one substituent.[3b,19] To a limited extent, multiply substituted benzenes can be treated by the additivity rule of Hammett σ constants. Hansch and Leo[3a] have described in some detail the problems arising due to the additivity of the σ constants. For the case of multiply substituted benzenes, the σ values are generally derived by a simple summation of the individual substituents on the benzene ring. For example, for the 3,4-diaminobenzoic acid, the σ_p and σ_m values of an amino group would be added to obtain $\sum\sigma = -0.82$. Similarly, for the case of 3,4,5-trichlorobenzoic acid,[3a] the value of σ_p for Cl (0.23) would be added to twice the value for σ_m (0.37) to obtain $\sum\sigma = 0.97$. The additivity rule naturally works well only when the groups are not interacting significantly.[20,21] Since the σ_m and σ_p values are obtained from the ionization constants of substituted benzoic acids, the additivity rule has serious drawbacks when applied to the multiply substituted benzene derivatives. For instance, in the above examples, the electronic effects due to the ortho arrangement of two amino groups or one meta and two ortho combinations resulting from the 3,4,5 arrangements of chlorines are completely neglected in the $\sum\sigma$ values. To estimate these effects, one has to find a way to monitor the subtle changes occurring in the electron distribution due to the para, meta, and ortho arrangements of two substituents attached to the benzene ring. The present work utilizes the MESP topography over the aromatic nucleus as a sensitive tool for this purpose since it is felt that the combined effect of several substituents will be more vividly seen over the aromatic nucleus rather than at any of the substituents. It is indeed this effect that will govern the initial attack in aromatic electrophilic substitution. Five different substituents with widely differing electronic effects have been considered in the present study, and the simultaneous effect of any two substituents, arranged in para, meta, and ortho orientations over the aromatic π-electron distribution as well as its relationship with the Hammett constants, is explored.

Methodology

Five substituents related to the present work are NH_2, NO_2, CH_3, Cl, and OCH_3, based on their mechanistic differences in the electron donating/accepting ability, which includes the major effects of structure on reactivity, viz., the inductive, resonance, hyperconjugative, and steric effects.[3b] NH_2 belongs to the strong electron donating (+R) group, and NO_2 is a very strong (−R) electron withdrawing group. For the methyl group, the electron donation is mainly through the inductive (+I) as well as the hyperconjugative effect. A member of the halogen group, Cl, is conventionally attributed to an unusual ability in these effects, due to the interplay of the resonance (+R) and the inductive effect (−I). The OCH_3 group is mainly electron donating due to a resonance mechanism (+R), but its CH_3 group may engender some steric problems for the corresponding doubly substituted benzenes. These five substituents constituting 45 different possibilities of doubly substituted benzenes (the para, meta, and ortho combinations) cover a wide spectrum of organic compounds in these respect. These compounds are studied at the HF/6-31G** level for the MESP topographical analysis. This level of theory has been chosen because our earlier work has revealed that HF/6-31G** MESP topography is normally adequate for a faithful representation of the π-electron distribu-

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tions in these systems.[22] Further, the effect of correlation does not change the overall topography of the MESP[23] at 6-31G** level. At this level of theory, the geometry optimization of these systems is done using the *Gaussian 94* package.[24] The optimized geometries were confirmed as local minima via a frequency calculation. In other words, only those geometries that exhibit no imaginary frequencies are employed for the MESP topographical analysis.

The MESP, $V(\mathbf{r})$, at a point $\mathbf{r}$ due to a molecular system with nuclear charges $\{Z_A\}$ located at $\{\mathbf{R_A}\}$ and electron density $\rho(\mathbf{r})$ is expressed as

$$V(\mathbf{r}) = \sum_{A}^{N} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')d^3r'}{|\mathbf{r} - \mathbf{r}'|} \qquad (2)$$

where N is the total number of nuclei in the molecule. Topological analysis[25] of $V(\mathbf{r})$ is based on locating and characterizing the critical points (CPs), viz., the points at which $\nabla V(\mathbf{r}) = 0$ and their characterization is done by calculating the number of nonzero eigenvalues of the Hessian matrix A, the elements of which are defined by

$$A_{ij} = \frac{\partial^2 V(\mathbf{r})}{\partial x_i \partial x_j}\Big|_{\mathbf{r} = \mathbf{r}_c} \qquad (3)$$

where $\mathbf{r}_c$ is a critical point. A nondegenerate minimum is always characterized by three positive eigenvalues of the Hessian.[26] The MESP topography of all the current systems has been investigated by employing the package UNIPROP.[27]

Results and Discussion

Geometry and SCF Energies. Figure 1 schematically illustrates the orientations of the substituents as brought out by the HF/6-31G** level calculations of the doubly substituted benzenes.[27] The true minimum nature of these has been verified via a frequency calculation. In most of the cases, the NH_2 group has a pyramidal structure around the N atom. In *o*-diaminobenzene, two of the amino hydrogens are almost in the plane of the benzene ring and the other two are seen above and below it. The amino group in *o*-nitroaniline assumes a planar structure with the aromatic ring. In some cases, the NO_2 group is found to be twisted out of the ring plane. This includes *o*-dinitrobenzene, *o*-chloronitrobenzene , and *o*-nitroanisole. Except for *o*-methoxyaniline, in all the other cases the C−O bond of the OCH_3 group lies in the benzene ring plane. The methyl group, whether attached to the benzene ring directly or through the oxygen, in general, possesses an orientation in which one of the C−H bonds lies in the benzene plane and the other two respectively above and below it. The exceptions are *p*-methylaniline, *o*-methoxyaniline, *p*-nitroaniline, *p*-chlorotoluene, and *m*-chlorotoluene.

The SCF energies of all these systems are examined (given as Supporting Information), and it is found that when two electron donating groups are attached to the benzene ring, the meta combination is always the most stable structure. Similarly, when electron donating and withdrawing groups are simultaneously present on the ring, the para combination is the most stable structure. Since the focus of this work is not on the energetic aspect (for a better judgment of it, higher level calculations may be required), the details of it will be described elsewhere.

MESP Minimum and the Substituent Constants. The most negative-valued MESP minima ($V_{\min}$) and the respective σ constants observed in the case of monosubstituted benzenes are shown in Table 1. The $\Delta V_{\min}$(mono) values reported in the table are obtained by subtracting the MESP value of benzene from that of the substituted benzenes. These values can be considered as a primary measure of how much the aromatic ring is activated (electron rich) or deactivated (electron deficient) toward an electrophilic attack with reference to benzene. In this regard, the $\Delta V_{\min}$(mono) values behave like the Hammett constants.[18]

Additivity of the $V_{\min}$ as well as the σ constants can be studied by monitoring the most negative valued MESP minimum in the case of doubly substituted benzenes. The carbon atom nearest to the $V_{\min}$ is depicted in Table 2 to get an idea about the position of it. Here the numbering is based on Figure 1 where C_1 is always assigned as the one at the extreme top corner of the hexagon and the other carbons are numbered clockwise. More than one center in Table 2 indicates the presence of similar or same valued CPs. Some regularities can be observed from the positions of the $V_{\min}$ which are in fact complimenting the observations made by March[3b] about the orientation in benzene ring with more than one substituent. When two activating groups are competing, the position of $V_{\min}$ is close to ortho or para to the stronger group (e.g., NH_2, CH_3 combination). Similarly, with an activating and deactivating group (e.g., NH_2, NO_2 combination), $V_{\min}$ is observed near ortho or para carbons with respect to the activating group. Also none of the 15 meta combinations shows an MESP minimum at the region between the two groups. In Table 3, $V_{\min}$ values are tabulated with V_p, V_m, and V_o representing the most negative valued MESP minimum observed over the benzene ring in the case of para, meta, and ortho combinations, respectively. The expected values are obtained by adding the respective $\Delta V_{\min}$(mono) values of each substituent to the benzene value. For example, the value of nitroaniline disregarding the relative position of NH_2 and NO_2 groups is $V = -0.0323 - 0.0082 + 0.0288 = -0.0117$ au. The difference between the expected and the observed value may be attributed to the mutual interactions of two groups attached to the benzene ring. These values are designated here as the substituent-pair constants, D_p, D_m, and D_o, respectively,

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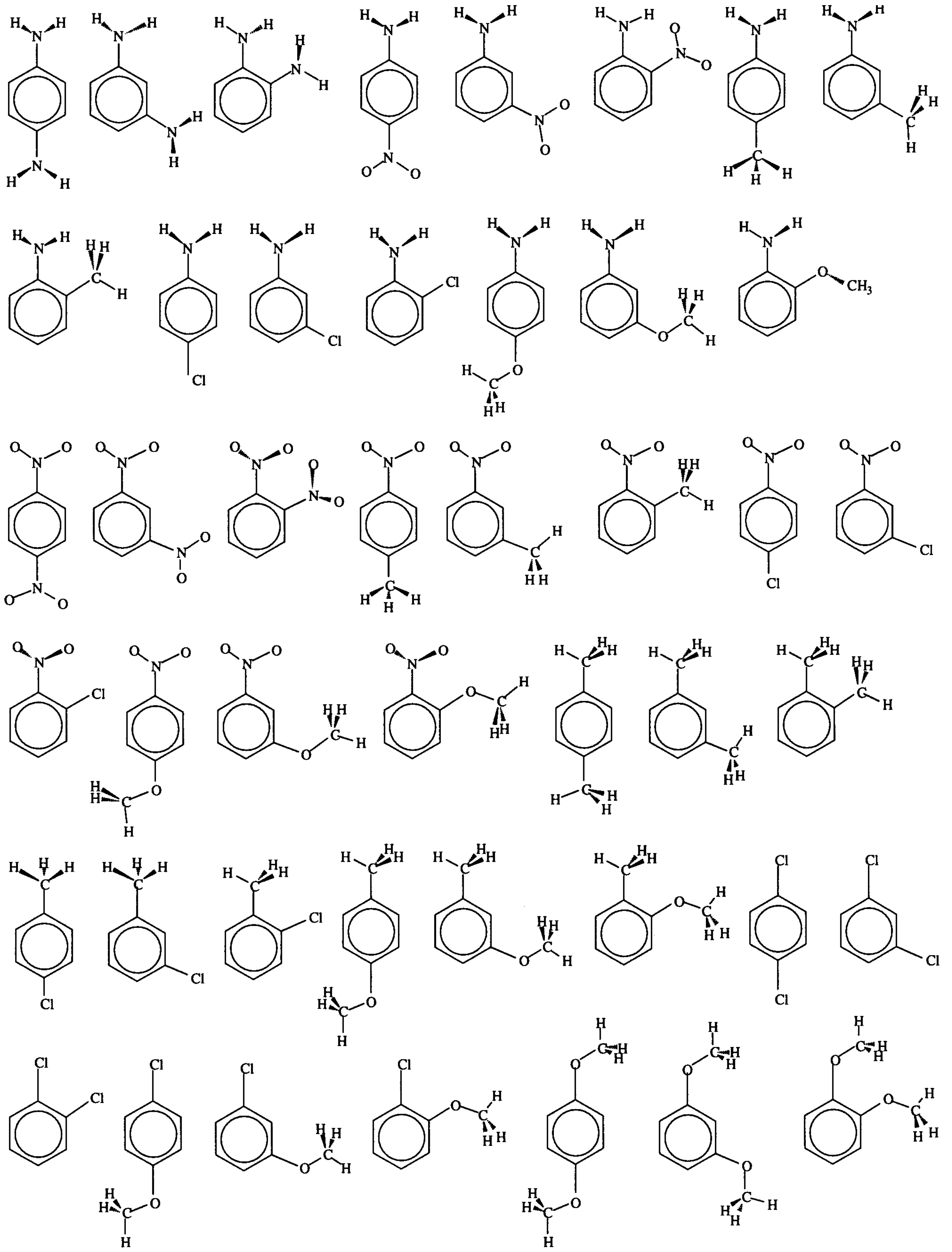

Figure 1. Schematic geometrical orientations of the substituents at HF/6-31G** level calculations of the doubly substituted benzenes.

for the para, meta, and ortho pair. A detailed analysis of Table 3 reveals the following facts.

In general, the value of the most negative MESP minimum follows additivity to a good degree. Table 3 shows that the deviations from the expected value of V_{min} are quite small in most of the cases (especially with combinations involving CH_3 or Cl), and only in eight cases out of the 45 cases studied (which are shown by bold characters in the table) are the deviations more than 0.0022 au (this value is chosen from the trends observed in Table 3). The cases showing deviations are (NH_2,

Table 1. The Most Negative MESP Minimum Value (V_{min}) in au Observed Over the Aromatic Ring in the Case of Monosubstituted Benzenes[a]

substituent	V_{min}	ΔV_{min}(mono)	σ_m	σ_p
benzene	−0.0323	0.0000	0.00	0.00
aniline	−0.0405	−0.0082	−0.16	−0.66
nitrobenzene	−0.0035	0.0288	0.71	0.78
toluene	−0.0346	−0.0023	−0.07	−0.17
chlorobenzene	−0.0196	0.0127	0.37	0.23
anisole	−0.0344	−0.0021	0.12	−0.27

[a] See text for details. The σ_m and σ_p values are from ref 6.

Table 2. The Nearest Ring Carbon Atom/s from the Most Negative MESP Minimum over the Benzene Ring[a,b]

	ring carbon atoms nearest to the V_{min}		
substituents	para	meta	ortho
$-NH_2$, $-NH_2$	$C_2/C_3/C_5/C_6$	C_4/C_6	between C_4&C_5
$-NH_2$, $-NO_2$	C_2/C_6	C_6	C_4
$-NH_2$, $-CH_3$	C_2/C_6	C_6	C_4
$-NH_2$, $-Cl$	C_2/C_6	C_6	C_6
$-NH_2$, $-OCH_3$	C_2	C_6	C_4
$-NO_2$, $-NO_2$	no negative CP	no negative CP	no negative CP
$-NO_2$, $-CH_3$	C_3/C_5	C_5	C_5
$-NO_2$, $-Cl$	no negative CP	no negative CP	no negative CP
$-NO_2$, $-OCH_3$	C_3	between C_4&C_5	C_5
$-CH_3$, $-CH_3$	between C_2&C_3/ between C_4&C_5	C_4/C_6	between C_4&C_5
$-CH_3$, $-Cl$	C_2/C_6	C_4	C_4
$-CH_3$, $-OCH_3$	between C_2/C_3	C_4/C_6	C_5
$-Cl$, $-Cl$	between C_2&C_3/ between C4&C5	C_4/C_6	between C_4&C_5
$-Cl$, $-OCH_3$	C_4	C_4	C_4
$-OCH_3$,$-OCH_3$	between C_2&C_3/ between C_4&C_5	C_6	C_5

[a] More than one point indicates same valued MESP minimum. See text and Figure 1 for details. [b] C_1 is designated as the carbon situated at the top corner of the hexagon in Figure 1. Other ring carbons are numbered clockwise.

NH_2) para and ortho, (NH_2, NO_2) ortho, and (NH_2, OCH_3) para and ortho, (NO_2, OCH_3) ortho, (Cl, Cl) ortho and (OCH_3, OCH_3) para. It may be seen that when the electron donation by a substituent is mainly through a resonance mechanism, the ortho and para positions become more electron rich compared to the meta position. Hence a second group having the same mechanistic electron donation does not prefer the para and ortho position. This could be the reason why (NH_2, NH_2), (NH_2, OCH_3), and (OCH_3, OCH_3) show high deviations at the para and ortho combinations (except the ortho OCH_3, OCH_3 combination). For the ortho OCH_3, OCH_3 combination, the steric factor may be significant. In the case of ortho (NH_2, NO_2), unlike the para and meta combinations, the NH_2 group is planar due to the weak intramolecular hydrogen bonding and thus leads to an enhancement in the overlap of its lone pair electrons with the benzene π-electrons. The twisting of the NO_2 from the benzene plane in the ortho (NO_2, OCH_3) combination will decrease the electron withdrawing capacity of it and will result in substantially more negative character compared to the para and meta combinations. Giving a simple explanation for the deviation seen in the case of ortho (Cl, Cl) is somewhat difficult. In the Cl, Cl combinations, a steady increase in the negative character is observed in the sequence para, meta, and ortho. It may be attributed to the delicate balance between the inductive and the resonance effects.

Steric Enhancement of the Negative MESP. A steady increase in the negative character of the MESP is observed when one goes from para to ortho through the meta combination in the following compounds where the substituents are (NO_2, CH_3), (NO_2, OCH_3), (CH_3, Cl), (CH_3, OCH_3), (Cl, Cl), and (Cl, OCH_3). It can be argued that the hydrogens of the CH_3 group lying close to the oxygen of the nitro group, OCH_3 group, or the Cl atom when they are placed ortho to each other may interact through a field effect. This may increase the hyperconjugative way of electron donation by the methyl group because the hyperconjugative structures will be more stabilized resulting in an enhancement in the negative value of MESP. The explanation for the (NO_2, OCH_3) and (Cl, Cl) cases has already been discussed. A mechanism similar to that given for the (Cl, Cl) case may be operating in the (Cl, OCH_3) case also. The (CH_3, OCH_3) case is already known in the literature as steric enhancement of resonance.[17d,29]

Correlation between the MESP Minimum and the Observed σ Constants. Hansch and Leo[3a] in their classic monograph have compared the experimentally determined σ values (observed σ values) with the calculated σ values ($\sum\sigma$) for some 3,4-, 3,5-, and 3,4,5-substituted benzoic acids or related systems. In general, they not only observe good agreement between the two quantities but also mention many examples where the two are not in good agreement. The observed values reported by them for the 3,4- and 3,5-systems (mostly 3,4-systems) are plotted against the MESP minimum value of the ortho (V_o) and meta (V_m) disubstituted benzenes. A reasonably good linear fit expressed by $V_{min} = -0.0300 + 0.0314\sigma$ with correlation coefficient 0.948 is obtained (cf. Figure 2). Also, it may be seen that the point (V_{min}, σ) = (−0.0323, 0) corresponding to benzene naturally lies in the vicinity of the fitted straight line. Furthermore, four additional systems containing OH group, viz., *o*-methoxyphenol, *o*-chlorophenol, *o*-dihydroxybenzene, and *m*-dihydroxybenzene, are studied, and the V_{min} corresponding to these systems are separately shown on the graph by different symbols (the OH group is a difficult case in the study of substituent constants due to the formation of phenoxide ion in the reaction medium[7a]). These points are also seen to lie close to the mean straight line interpolating those lying near the extremities. It is expected that the study of more substituents will further improve the quality of the graph. Notice that the purpose of the linear plot is to bring out the general correlation between V_{min} and σ constants and not to use it as a read-off device. In fact, separate graphs for ortho and meta combinations give better correlations (0.970 for ortho and 0.967 for meta). Inclusion of V_p (the V_{min} value of the para compounds) in the correlation graph is not possible because of the nonavailability of a σ constant corresponding to the para-disubstituted benzenes. In these cases, the reference group will be always ortho to one of the substituents, and so the experimental determination of it or even its calculation by the simple additivity method is difficult. This can be considered as one of the limitations of the applicability of Hammett constants to the multiply substituted benzenes. Furthermore, it may be noticed that even in the case of ortho combinations, there are difficulties due to the 2,3-, 3,2-, 3,4-, and 4,3-arrangements of the groups with respect to a reference group. None of this will represent the pure behavior of an ortho-disubstituted benzene. But the overall agreement of the V_{min} versus the σ constants implies that the former does behave in a manner similar to the latter. This is intuitively expected since both entities presumably reflect the electronic effects on the aromatic nucleus. In fact, the V_{min} quantity is more advantageous since it gives a direct measure of the electronic effects of two groups attached to the benzene ring without taking cognizance of a third reference group (usually a COOH group). Does it mean that one has to do complete ab initio calculations for the case of multiply substituted benzenes? It is shown below

Table 3. The Most Negative Valued MESP Minimum in au Observed over the Aromatic Ring in the Case of Different Doubly Substituted Benzenes[a]

substituents	para V_p	meta V_m	ortho V_o	expected (V_{min})	$D_p = V_{min} - V_p$	$D_m = V_{min} - V_m$	$D_o = V_{min} - V_o$
$-NH_2$, $-NH_2$	−0.0405	−0.0465	−0.0415	−0.0487	−0.0082	−0.0022	−0.0072
$-NH_2$, $-NO_2$	−0.0122	−0.0120	−0.0158	−0.0117	0.0005	0.0003	0.0041
$-NH_2$, $-CH_3$	−0.0411	−0.0424	−0.0418	−0.0428	−0.0017	−0.0004	−0.0010
$-NH_2$, $-Cl$	−0.0271	−0.0282	−0.0283	−0.0278	−0.0007	0.0004	0.0005
$-NH_2$, $-OCH_3$	−0.0391	−0.0431	−0.0369	−0.0426	−0.0035	0.0005	−0.0057
$-NO_2$, $-NO_2$				+0.0253			
$-NO_2$, $-CH_3$	−0.0056	−0.0057	−0.0078	−0.0058	−0.0002	−0.0001	0.0020
$-NO_2$, $-Cl$				+0.0092			
$-NO_2$, $-OCH_3$	−0.0067	−0.0060	−0.0101	−0.0056	0.0011	0.0004	0.0049
$-CH_3$, $-CH_3$	−0.0359	−0.0363	−0.0365	−0.0369	−0.0010	−0.0006	−0.0004
$-CH_3$, $-Cl$	−0.0212	−0.0217	−0.0223	−0.0219	−0.0007	−0.0002	0.0004
$-CH_3$, $-OCH_3$	−0.0345	−0.0359	−0.0366	−0.0367	−0.0022	−0.0008	−0.0001
$-Cl$, $-Cl$	−0.0078	−0.0083	−0.0100	−0.0069	0.0009	0.0014	0.0031
$-Cl$, $-OCH_3$	−0.0199	−0.0217	−0.0231	−0.0217	−0.0018	−0.0000	−0.0014
$-OCH_3$, $-OCH_3$	−0.0320	−0.0365	−0.0359	−0.0365	−0.0045	0.0000	−0.0006

[a] See text and Figure 1 for details.

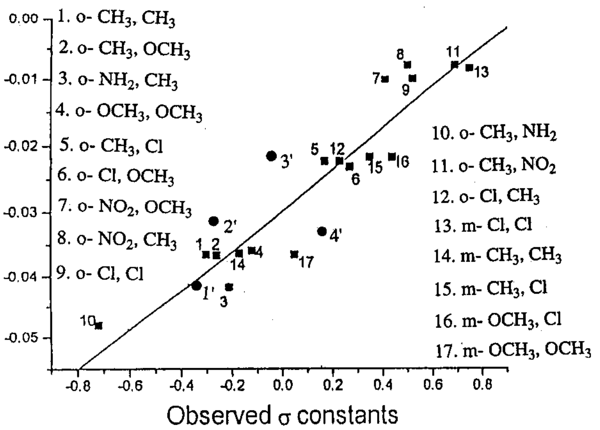

Figure 2. Correlation between V_{min} and observed values of 3,4- (ortho) and 3,5- (meta) substituted benzoic acids. The additional systems 1′, 2′, 3′, and 4′ represent *o*-OH, OCH$_3$; *o*-OH, OH; *o*-OH, Cl, and *m*-OH, OH.

that once the V_{min} values of all the doubly substituted benzenes are known, a reasonably good prediction of the V_{min} values for the multiply substituted benzenes is possible. Only exceptions arise in some cases involving strong electron withdrawing groups where the calculation of V_{min} is not possible due to the absence of a negative valued minimum (e.g., NO_2, NO_2; NO_2, Cl).

Significance of the Substituent-Pair Constants: D_p, D_m, and D_o. It is to be noted from Table 3 that when two electron donating groups are present on the ring, the observed value of V_{min}, even though more negative than the corresponding singly substituted benzene, has in general less negative character than the expected value (i.e., D_p, D_m, and D_o become negative). On the other hand, when electron donating and withdrawing groups are present, the observed value of V_{min} does not change much from the expected value, and in some cases shows more negative character (i.e., D_p, D_m, and D_o become positive). In other words, the simultaneous presence of more than one electron donating group decreases the overall electron donating capacity of the individual groups and an electron donor−acceptor combination increases it (a push−pull mechanism). As a result, a linear dependency in the value of the negative MESP minimum with the number of substituents attached to the benzene ring is quite unlikely, i.e., the additivity rule for σ constants may not work well in the case of multiply substituted benzenes. For example, with NH_2, CH_3, and NO_2 as the substituents, one can make seven different trisubstituted benzenes. It is obvious that just by adding the ΔV_{min}(mono) of each substituent to the benzene V_{min} does not distinguish the different combinations. But a further improvement can be made by subtracting from this the effect due to all para, meta, and ortho combination/s arising from the different arrangements of the substituents. Considering the substituent-pair constants D_p, D_m, and D_o introduced in the work as a good approximation to this substituent-pair effect, a general formula for the minimum MESP values of multiply substituted benzenes can be written. The formula is the following where V_{ben} is V_{min} value of benzene.

$$V_{min} = V_{ben} + \sum \Delta V_{min}(\text{mono}) - \sum D_p - \sum D_m - \sum D_o \tag{4}$$

For instance, in the case of 1-amino-, 2-methyl-, and 4-nitrobenzene the above formula will give V_{min} as −0.0134 au (i.e., $V_{min} = V_{ben} + \Delta V_{min}(NH_2) + \Delta V_{min}(CH_3) + \Delta V_{min}(NO_2) - D_o(NH_2, CH_3) - D_m(CH_3, NO_2) - D_p(NH_2, NO_2) = -0.0323 - 0.0082 - 0.0023 + 0.0288 + 0.0010 + 0.0001 - 0.0005$). The validity of this approach is checked by actually calculating the V_{min} for this molecule using the HF/6-31G** minimum geometry. The actual value turned out to be −0.0137 au (cf. Table 4). Further support is obtained from the HF/6-31G** calculations on the three different 1,2,3-arrangements of the NH_2, CH_3, and NO_2 substituents. They all show good agreement with the predicted value as reported in Table 4. Notice that only the 1,2,3-arrangements can be compared with the Hammett substituent constants. In the corresponding Hammett molecule, the reference group will be para to the group at 2. It is interesting that the Hammett σ values obtained from the additivity rule ($\sum\sigma$) reported in Table 4 are unable to match with the deactivation seen in these molecules in terms of the V_{min} values. The discrepancy must have appeared due to the neglect of the substituent-pair effects in the $\sum\sigma$ constants. The 1,2,4- and 1,3,5-trichlorobenzenes are also listed in Table 4. In the case of 1,2,4- trichlorobenzene, the deviation of V_{min} from the expected value is 0.0005 au and the other does not show a negative V_{min} over the benzene ring (eq 4 predicts the most positive MESP character to this trichloro combination).

In order to check the applicability of eq 4 in a more difficult case, the triaminobenzenes are studied at the HF/6-31G** level. Here the complication arises due to the pyramidalization of the amino group. For the cases of the observed values reported in Table 4, agreement with the predicted values is not so good. However, the prediction that the 1,3,5-triamino will show the

Table 4. Predicted and Actual Values of $V_{\min}$ in au for Triply Substituted Benzenes

substituents	$V_{\min}$ (predicted)	$V_{\min}$ (actual)	Hammett $\Sigma\sigma$
1,2,3-NH_2, NO_2, CH_3	−0.0197	−0.0178	0.55
1,2,3-NH_2, CH_3, NO_2	−0.0153	−0.0159	0.38
1,2,3-NO_2, NH_2, CH_3	−0.0170	−0.0169	−0.02
1,2,4-NH_2, CH_3, NO_2	−0.0134	−0.0137	NA[a]
1,2,3-NH_2, NH_2, NH_2	−0.0403[b]	−0.0438	−0.98
1,2,4-NH_2, NH_2, NH_2	−0.0393[b]	−0.0472	NA[a]
1,3,5-NH_2, NH_2, NH_2	−0.0503[b]	−0.0556	NA[a]

[a] Hammett constant values not available for these cases. [b] See text for an explanation.

most negative $V_{\min}$ has come true. An attempt based on the conformations of these molecules is made here to explain the discrepancies. The orientations of the amino groups at the minimum energy configurations show that in all three triaminobenzenes two of the pyramidal amino groups are more or less on one side of the benzene ring and the third one is on the other side. Representing this situation by the notation u−u−d, where u denotes a pyramid pointing upward and d another pointing downward, one needs a u−u and two u−d diamino arrangements for a proper description of the situation. Since we have used only the u−d type arrangements of the diaminobenzenes, a search for local minima geometries of the u−u type combinations at HF/6-31G** level is done. Both the para and meta u−u arrangements of the diaminobenzenes turned out to be minima with 0.00020 and 0.00024 higher in energy than the respective u−d counterparts, but the *o*-diaminobenzene does not have such a local minimum geometry. The corresponding $V_{\min}$ values are −0.0451 and −0.0491 au and the D_p and D_m values turned out to be −0.0036 au and value 0.0004 au, respectively, for the para and meta combinations. Thus, the modified $V_{\min}$ values can be predicted for 1,2,3-, 1,2,4-, and 1,3,5-triaminobenzenes by subtracting the proper D values of a u−u arrangement instead of a u−d arrangement in eq 4. The new values are −0.0429, −0.0439, and −0.0581 au, respectively, for 1,2,3-, 1,2,4-, and 1,3,5-triaminobenzenes which are in good agreement with the predicted values.

Thus, assignment of substituent-pair constants D_p, D_m, and D_o does seem to pave a way for predicting the activation or deactivation in terms of the calculated $V_{\min}$ values in the case of multiply substituted benzenes and for endeavoring to distinguish their many different combinations. Also this method has a clear advantage compared to the treatment of multiply substituted benzenes using the Hammett constants because the latter employs only the σ_p and σ_m constants (an ortho constant (σ_o) is not clearly defined), and always one position is blocked by the reference group (such as COOH). Thus the applicability of the Hammett constants is limited to only one type of combination in the case of triply substituted benzenes and not at all possible when more than three substituents are attached to the benzene ring.

Conclusions

MESP minimum over an aromatic nucleus is seen to provide a direct measure for the electronic perturbations due to a particular substituent and bears strong similarity with the classical Hammett constants. The expected value of $V_{\min}$ based on an additive model and its deviations from the observed value for the disubstituted benzenes suggest that most of them follow additivity to a good degree. Clear-cut explanations, based on the differences in the mechanism of the classical electron donation or withdrawal effects, arising due to the different arrangements of the substituents can be given for the cases where one sees large deviations. The observed σ values (the experimental values) plotted against the observed $V_{\min}$ values show a good linear correlation. Further, substituent-pair constants introduced in this work, viz., D_p, D_m, and D_o, represent the electronic effect due to the placement of two substituents in the para, meta, and ortho arrangement with the benzene ring. The introduction of such quantities is indeed needed for estimating, in a simple way, the combined effect of three or more substituents simultaneously acting over the benzene ring. In fact, it is exactly these pair-wise interactions that are excluded in the determination of Hammett constants when applied to multiply substituted benzenes that are mainly responsible for the deviations from the additivity of σ constants. The applicability of this approach is tested for predicting the $V_{\min}$ values of triply substituted benzenes, and the results are fairly encouraging. It is hoped that the procedure given in this work provides a simple and practical approach toward a better treatment of multiply substituted benzenes in the area of QSAR.

Acknowledgment. We thank Drs. L. J. Bartolotti, A. C. Limaye, A. P. Rendell, and N. Koga for making available the computer resources. S.R.G. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for sponsoring a research project [80(0022)/96/EMR-II]. C.H.S. thanks CSIR, New Delhi for the award of a senior research fellowship.

Supporting Information Available: Table of HF/6-31G** energies of the para, meta, and ortho combinations of disubstituted benzenes in au (1 page, print/PDF). See any current masthead page for ordering and Web access information.

JA973105J