Quantification of substituent effects using molecular electrostatic potentials: additive nature and proximity effects†

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Several *ortho*, *meta*, and *para* substituted benzoic acids have been studied to quantify the substituent effects by analysing subtle variations in the molecular electrostatic potential minimum (V_{min}) at the response site of the carboxylic acid moiety using density functional theory. For the first time, the *ortho* substituent effect is separated into contributions from electronic and proximity effects. A molecular fragment approach in conjunction with a rotation experiment on the COOH moiety of benzoic acid was used to quantify the proximity effects. The quantified proximity effect is in accord with previously proposed steric parameters. The proximity effect-corrected V_{min} of *ortho* systems showed excellent linear correlations to both V_{min} of *para* and *meta* systems which enabled the computation of the *meta* : *para*, *ortho* : *para* and *meta* : *ortho* electronic effect ratios yielding respective values of 1 : 1.108, 1 : 1.042 and 1 : 1.047. The additive nature of the substituent effects was also tested using the V_{min} computation on multiply-substituted benzoic acids. It is found that the total substituent effect is approximately 86.3% of the sum of the individual contributions which was in contrast to a value of 98.5% observed in aliphatic systems (*Phys. Chem. Chem. Phys.*, 2008, **10**, 6492–6499).

Introduction

Understanding the correlation between the structure of molecules and their chemical reactivity is one of the fundamental objectives in modern chemistry.[1] When the 'X' derivative of a molecule 'M–H' is made, the 'X' will have a direct and significant effect on the chemical properties of 'M', and this effect in comparison with 'H' is considered as the substituent effect.[2,3] To quantify substituent effects, Hammett introduced substituent constants which are primarily derived from the ionization of substituted benzoic acids.[4] These substituent constants[5–8] successfully explained the reactivities of a variety of aromatic molecules, when the substituent is at the *meta* or *para* position with respect to the reaction centre.[9–15] On the other hand, the Hammett substituent constants for *ortho* substitution have been rarely used to explain the chemical reactivity as they failed in many cases due to interplay with proximity effects at the reaction centre.[16] In a recent review,[17] Exner and Böhm have pointed out that applying the Hammett equation to *ortho* systems is difficult due to the existence of intramolecular hydrogen bonds, steric inhibition of resonance, steric hindrance and short-range polar effects. These effects are collectively termed an '*ortho* effect' or 'proximity effect'.[17] In *ortho* substitution, the steric inhibition of resonance relates to any structural modification that leads to distortion of the coplanarity between reaction centre and phenyl group and thereby reduces the electron delocalization between them.[18] Exner and co-workers have investigated steric inhibition of resonance in the case of *ortho* alkyl substituted benzoic acids and methyl substituted acetophenones, and concluded that the substituents that exhibit strong steric hindrance at the reaction centre bring about a significant torsion angle (Fig. 1), whilst substituents that exhibit weak steric hindrance leave the reaction centre planar with the phenyl ring.[19–22] For instance, in the case of *o*-t-butyl benzoic acid, the bulky *ortho* substitution inhibits the coplanarity of COOH and phenyl ring and this in turn enhances its acidity to a value 0.74 higher than benzoic acid (the pK_a (H) = 4.20, pK_a (*o*-t-butyl) = 3.46, pK_a (*m*-t-butyl) = 4.28, and pK_a (*p*-t-butyl) = 4.40).[17]

Several experimental studies have been employed to understand the nature of the *ortho* electronic substitution effect.[23–26] All these experimental results have limitations, such as the elimination of the bulky *ortho* substituent effect to correlate

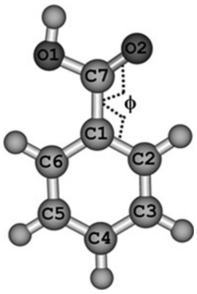

Fig. 1 Definition of torsion angle ϕ ($O_2C_7C_1C_2$).

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† Electronic supplementary information (ESI) available: Plots of V_ϕ *vs.* ϕ, V_{PE} *vs.* $E_S[\rho(r)]$, V_o *vs.* polar effect parameters, and linear plots among *ortho*, *meta* and *para* substituent effects along with the co-ordinates of the optimized structures of the *ortho*, *meta* and *para* substituted benzoic acids. See DOI: 10.1039/b9nj00333a

with *para* substituent effect and approximating the *ortho* and *para* electronic effects to be the same.[27,28] However, a method which can accurately quantify the electronic as well as the proximity effects of *ortho* substituents is yet to be established. Attempts have been made by many research groups to establish a theoretical basis for substituent effects using computed chemical descriptors such as, total core-electron binding energy shifts,[29] atomic charges,[30–32] electrophilicity index,[33] QSAR studies[34–36] and energy of protonation.[37] Molecular electrostatic potential (MESP) is a well established descriptor to study non-covalent interactions, electrophilic substitution reactions and a variety of chemical phenomenon.[38–45] From a number of studies based on topological properties of MESP, it has been recognized that MESP is one of the most promising molecular properties that can accurately interpret the electron donating as well as electron withdrawing power of the substituents.[46–51] The main focus of this article is to develop a method based on MESP to quantify the proximity effects and also to establish the inter-relationships among *ortho*, *meta* and *para* substituent effects. Moreover, MESP approach is extended to multiply-substituted systems to study the additive nature of substituent effects.

Computational details

Computational calculations involved in this study have been performed with density functional theory (DFT) incorporating Becke's three parameter exchange functional with Lee, Yang and Parr's (B3LYP)[52,53] method as implemented in the Gaussian03 suite of programmes.[54] The split valance basis set with polarization functions 6-31G(d,p) is employed in all the calculations. Previous work has shown that the B3LYP/6-31G(d,p) level wave function is adequate for studying the MESP features of organic systems.[48,49,55] The MESP, $V(\mathbf{r})$ at a point $\mathbf{r}$ due to a molecular system with nuclear charges located at $\mathbf{R}_A$ and electron density $\rho(\mathbf{r})$ is expressed in eqn (1) where N is the total number of nuclei in the molecule.[39,56]

$$V(\mathbf{r}) = \sum_{A}^{N} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')d^3\mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|} \qquad (1)$$

MESP can be an experimentally derived quantity[57] and it interprets the reactivities of organic molecules.[58–60] In the present study, benzoic acid and its 23 substituted derivatives for each of *ortho*, *meta* and *para* positions were considered. Substituents which will exhibit inductive, steric, resonance and hyper conjugative effects were included in this study. Various possible conformers of all substituents for *meta* and *para* positions are studied and the most stable conformers are considered. In the case of *ortho* systems, the proximity effect operates and therefore the substituent can either orient towards the carbonyl of the COOH or the hydroxyl of the COOH. Therefore, to describe the relative values of proximity effects using the same type of reference structures, the orientation of the substituent towards the carbonyl of the COOH moiety is selected for all *ortho* systems.

Results and discussion

MESP and Hammett substituent constants

The aromatic ring, the OH oxygen and the carbonyl oxygen are the electron rich sites of benzoic acid and at these sites one can locate negative valued MESP minima (V_{min}) (*cf.* Fig. 2). In benzoic acid, the V_{min} on the aromatic ring (−9.89 kcal/mol) is located near the *meta* carbon. At the OH of the COOH, the V_{min} is −24.07 kcal/mol whereas the CO of the COOH shows a V_{min} value of −44.59 kcal/mol. The carbonyl oxygen is clearly more electron rich than the OH due to the sp^2 hybridization of the former. All the systems except the CN, NO_2, $CONH_2$, and $COCH_3$ substituted benzoic acids showed V_{min} on the aromatic ring. The lack of a negative potential on the aromatic ring is due the strong electron withdrawing effect of these substituents. In all the *ortho* systems, the CO of the COOH experiences more interaction with the substituent compared to the OH of the COOH. Therefore, among the three V_{min} sites, the V_{min} at the OH was considered for assessing the substituent effects. Hereafter, the notation of 'V_{min}' will correspond to the V_{min} observed at the OH of the COOH moiety.

The relative V_{min} obtained with respect to the V_{min} of unsubstituted benzoic acid (−24.07 kcal/mol) is designated as V_o for *ortho*, V_m for *meta* and V_p for *para* substituted systems and the values are presented in Table 1. Based on the relative V_{min} values, the electron activating or deactivating ability of the substituent can be predicted. For instance, in *para* substituted benzoic acids, the electron activating ability of the substituent is $N(CH_3)_2$ > $NHCH_3$ > NH_2 > $OCH(CH_3)_2$ > OCH_2CH_3 > OCH_3 > NHOH ~ OH > $C(CH_3)_3$ > $CH(CH_3)_2$ > CH_3 > CH_2CH_3 > C_6H_5 > H > CH_2F > F > $CONH_2$ > $COCH_3$ > Br > Cl > CHO >

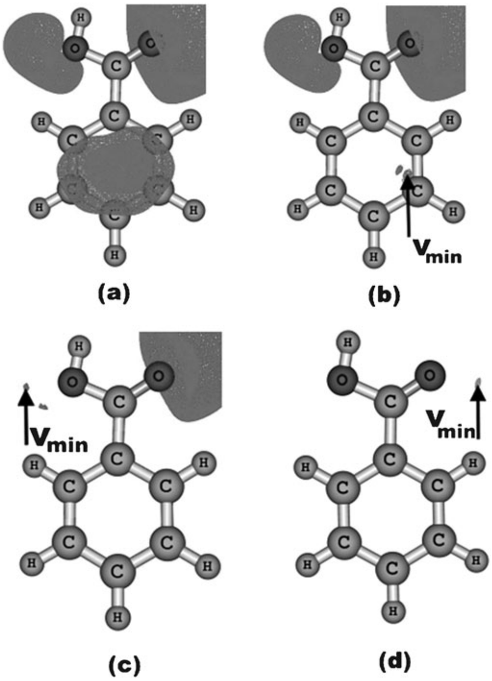

Fig. 2 In (a), (b), (c) and (d), different values (−8.70, −9.89, −24.07, −44.59 kcal/mol, respectively) of the MESP isosurface of benzoic acid are shown. In (b), (c), and (d), the location of V_{min} is depicted.

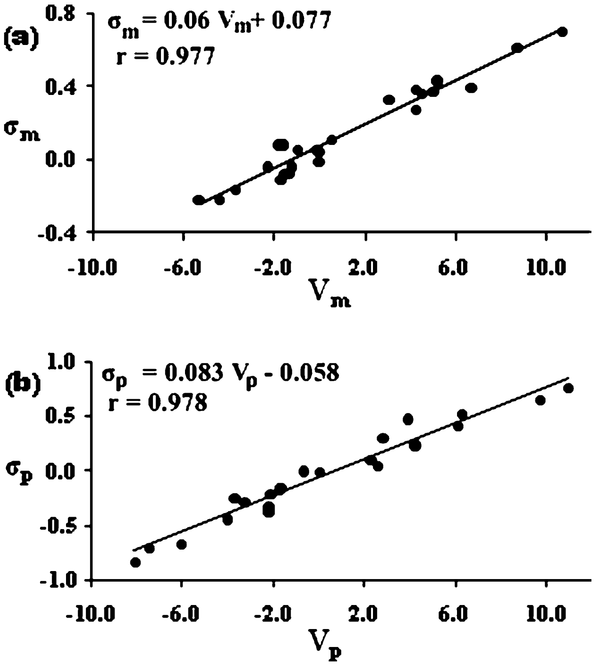

Fig. 3 Relative V_{min} at the OH of COOH in *meta* and *para* substituted benzoic acids plotted with Hammett constants. (a) V_m *vs.* σ_m (b) V_p *vs.* σ_p.

$CF_3 > CN > NO_2$. The halogens (F, Cl, Br) are the only *ortho*, *para* directing substituents placed below the 'H'. V_m and V_p showed good linear relationships to the Hammett constants σ_m and σ_p, respectively (Fig. 3), which suggests that the true nature of the substituent effect is associated with these electronic descriptors and they may be used as an alternate measure of substituent effects. However, V_o showed only a poor linear correlation (correlation coefficient (c.c.) is 0.583) with the Hammett σ_o constant. It may be noted that in the case of *ortho* systems, the σ_o values differ considerably for various set of reactions,[27] unlike σ_m and σ_p, σ_o cannot be universally applied to various types of reaction series. The poor correlation between V_o and σ_o can be mainly attributed to the proximity effects.

Quantification of proximity effects

Two major proximity effects exist in *ortho* substituted systems, *viz*. (i) the through space COOH···X interactions and (ii) the steric effects of X. In order to quantify the first effect, a molecular fragment approach is developed. In this approach, at first a fragment showing the proximity effect is identified and separated from the remaining portion of the molecule (Fig. 4a and 4b). In the next step, the unused valences of the carbon atoms (C_1 and C_2 in Fig. 4b) of the fragment are filled by adding hydrogen atoms at an optimum distance through a constrained optimization (only the new C–H distances are optimized) to generate a new structure and this will resemble the *cis*-(COOH, X) form of ethylene (Fig. 4c). The corresponding *trans* form is then generated by rotating the C_1–C_2 bond by 180° (Fig. 4d). The relative V_{min} with respect to 'X = H' is calculated for both the *cis* and the *trans* forms and designated as V_c for the *cis* and V_t for the *trans*. In the *cis* form, the proximity effect is preserved nearly to the same extent as that of the parent molecule while the C_1–C_2 rotation leading to the *trans* form will remove this effect. Therefore, we can expect the difference between V_c and V_t to be a measure of the proximity effect.

Table 1 The relative V_{min} values of *ortho* (V_o), *meta* (V_m) and *para* (V_p) substituted benzoic acids and Hammett substituent constants

No.	Substituents[a]	V_o	V_m	V_p	σ_m[b]	σ_p[b]
1	$N(CH_3)_2$	−7.72	−5.30	−8.13	−0.21[c]	−0.83
2	$NHCH_3$	−3.19	−4.46	−7.50	−0.21	−0.70
3	NH_2	−3.16	−3.76	−6.12	−0.16	−0.66
4	$OCH(CH_3)_2$	−6.04	−1.74	−4.08	0.08[d]	−0.45
5	OCH_2CH_3	−4.79	−1.62	−3.67	0.08[d]	−0.24
6	OCH_3	−4.40	−1.02	−3.21	0.06[e]	−0.27
7	NHOH	−0.22	−2.31	−2.18	−0.04	−0.34
8	OH	5.03	0.02	−2.17	0.05[e]	−0.37
9	$C(CH_3)_3$	−4.94	−1.68	−2.07	−0.10	−0.20
10	$CH(CH_3)_2$	−3.04	−1.24	−1.79	−0.04	−0.15
11	CH_3	−0.72	−1.30	−1.76	−0.07	−0.17
12	CH_2CH_3	−1.52	−1.49	−1.68	−0.07	−0.15
13	C_6H_5	−3.95	−0.06	−0.70	0.06	−0.01
14	H	0.00	0.00	0.00	0.00	0.00
15	CH_2F	3.56	0.52	2.35	0.12	0.11
16	F	1.89	3.11	2.54	0.34	0.06
17	$CONH_2$	3.85	4.21	2.87	0.28	0.31[f]
18	$COCH_3$	4.81	5.06	3.89	0.38	0.47[f]
19	Br	3.85	4.21	4.12	0.39	0.23
20	Cl	1.49	4.47	4.25	0.37	0.23
21	CHO	3.41	6.75	6.12	0.40[g]	0.42
22	CF_3	2.15	5.23	6.24	0.43	0.54
23	CN	8.88	8.79	9.71	0.62[g]	0.66
24	NO_2	1.53	10.67	10.98	0.71	0.78

[a] The substituents are arranged in increasing order of the V_p values. [b] Hammett substituent constants are taken from ref. 14. [c] Taken from ref. 4. [d] Taken from ref. 12. [e] Taken from ref. 6. [f] Taken from ref. 36. [g] Taken from ref. 5.

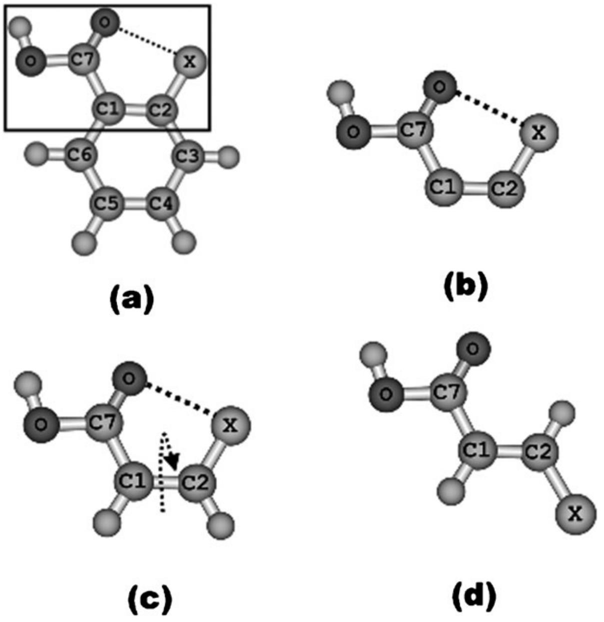

Fig. 4 Model systems constructed for quantification of proximity effects. The dotted lines represent the proximity interaction between X and COOH.

It may be noted that when bulky substituents like $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_5 are substituted at the *ortho* position, a large ϕ value is obtained due to steric hindrance. In the molecular fragment procedure, since the *cis* and *trans* form of the fragments retain the same ϕ value of the parent molecule, the steric-induced proximity effect which leads to the twisting of the COOH is not accounted for in the (V_c–V_t) values. In order to assess the effect of ϕ on the V_{min}, a free model experiment is carried out with unsubstituted benzoic acid. In this procedure, benzoic acid is modelled for ϕ values in the range 0–90° at an interval of 4.5°. This experiment was done by fixing the C_1–C_7 distance and the $\angle C_2$–C_1–C_7 angle (*cf.* Fig. 1) to those of the planar benzoic acid. The V_{min} for the OH moiety of the COOH is determined at each interval of ϕ. The V_{min} value for $\phi = 0$ is set as zero and the relative V_{min} of other ϕ values are designated as V_ϕ. The ϕ values are plotted against V_ϕ to fit to a 2nd order polynomial which indicates that V_ϕ is highly sensitive to the twisting of the COOH group (c.c. = 0.999, *cf.* Fig. S1 in ESI†). As the ϕ value increases, the negative character of the V_ϕ is increased (Table S1 in ESI†), suggesting that a bulky group capable of producing considerable twist at the COOH group can significantly affect the overall electron distribution in the system through a strong steric-induced proximity effect.

Thus the total proximity effect, V_{PE} in the *ortho* substituted system can be represented as the sum of (V_c–V_t) and V_ϕ (eqn (2)).

$$V_{PE} = (V_c–V_t) + V_\phi \qquad (2)$$

Both V_m and V_p represent purely electronic effects (transmitted through the σ and π bonds) of substituents as they are nearly unaffected by proximity effects, while the V_o represents the total of electronic and proximity effects. Therefore, the through-bond electronic effect of the *ortho* substituent (designated as V_o^{PE}) can be obtained by correcting the V_o value with the corresponding V_{PE} values as defined in eqn (3).

$$V_o^{PE} = V_o–V_{PE} \qquad (3)$$

In Table 2, the values of V_c, V_t, V_ϕ, V_{PE}, and V_o^{PE} are presented along with the ϕ values. In the case of alkyl groups, the proximity effect V_{PE} is mainly due to steric hindrance and accordingly the steric hindrance follows the order C_6H_5 > $C(CH_3)_3$ > $CH(CH_3)_2$ > CH_2CH_3 > CH_3. This order is in accord with the steric constants proposed by Taft (E_s),[61,62] Charton (υ),[63] and the B-value proposed by Schlosser *et al.*[64] Further, the V_{PE} is also validated by finding a linear correlation (c.c is 0.910) with the electron density based steric constants ($E_s[\rho(\mathbf{r})]$).[65] This correlation suggests that the V_{PE} can be used as a measure of steric effect (Fig. S2a in ESI†).

In Fig. 5, the values of V_o, V_o^{PE}, V_m, and V_p for all the substituents are compared to show the ability of the molecular fragment approach coupled with a free model experiment. The V_m and V_p values show a similar substituent effect pattern as they are not affected by the proximity effect whereas V_o deviates significantly from the corresponding V_m and V_p values. On the other hand, the proximity effect-corrected V_o^{PE} shows nearly the same substituent effect trend as those of V_m and V_p. Thus, it is clear that V_o^{PE} represents a through-bond electronic effect that is similar to V_m and V_p. Further, validation of V_o^{PE} is done by finding a linear correlation of it with the Exner's[28] polar effect parameters (polar effects transmitted through the bonds derived by approximating *ortho* and *para* effects are same) where a c.c. of 0.957 is obtained (Fig. S2b in ESI†). In summary, the combination of a molecular fragment approach and free model experiment can exclusively quantify the proximity effects, and V_o^{PE} can be considered as a proximity effect-free *ortho* substituent constant.

Table 2 V_{min} based parameters for the quantification of proximity effect[a]

Substituent	ϕ	V_ϕ[b]	V_c	V_t	V_c–V_t	V_{PE}	V_o^{PE}
$N(CH_3)_2$	16.28	−2.27	−12.39	−12.89	0.50	−1.78	−5.95
$NHCH_3$	0.01	0.00	−10.98	−13.15	2.17	2.17	−5.36
NH_2	0.93	−0.14	−10.04	−11.80	1.76	1.62	−4.77
$OCH(CH_3)_2$	4.22	−0.64	−11.04	−9.71	−1.33	−1.97	−4.07
OCH_2CH_3	−0.04	0.01	−10.13	−8.79	−1.35	−1.34	−3.45
OCH_3	0.16	−0.03	−9.72	−8.26	−1.46	−1.49	−2.91
NHOH	2.09	−0.32	−5.06	−7.01	1.95	1.63	−1.85
OH	0.01	0.00	1.00	−2.70	3.71	3.71	1.33
$C(CH_3)_3$	38.82	−4.55	−2.15	−4.06	1.91	−2.64	−2.30
$CH(CH_3)_2$	17.15	−2.38	−2.98	−4.03	1.05	−1.33	−1.71
CH_3	−0.03	0.00	−3.40	−3.70	0.29	0.30	−1.02
CH_2CH_3	8.12	−1.20	−2.92	−3.75	0.83	−0.37	−1.15
C_6H_5	21.78	−2.92	−2.85	−3.01	0.16	−2.76	−1.19
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CH_2F	0.00	0.00	2.29	1.24	1.05	1.05	2.50
F	−0.03	0.00	−0.11	1.20	−1.31	−1.31	3.20
$CONH_2$	31.79	−3.95	8.21	5.29	2.92	−1.03	4.88
$COCH_3$	4.99	−0.75	5.20	3.75	1.44	0.69	4.12
Br	−0.03	0.00	1.71	2.97	−1.26	−1.26	5.10
Cl	0.00	0.00	1.81	3.25	−1.44	−1.44	2.93
CHO	0.14	−0.02	2.97	5.50	−2.53	−2.55	5.96
CF_3	18.84	−2.58	5.90	7.02	−1.12	−3.70	5.85
CN	−0.01	0.00	9.29	10.69	−1.40	−1.40	10.28
NO_2	42.65	−4.83	8.96	12.63	−3.67	−8.51	10.04

[a] The ϕ values are in degrees and all other values are in kcal/mol. [b] Calculated by the equation shown in Fig. S1 (in ESI†).

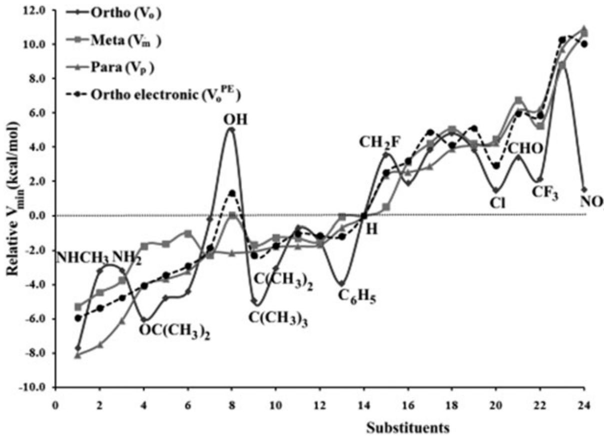

Fig. 5 A comparative diagram showing the relative V_{min} of *ortho* (V_o), *meta* (V_m), and *para* (V_p) substituted benzoic acids, and the proximity effect-corrected parameter (V_o^{PE}). The dotted horizontal line differentiates the electron activating and electron deactivating nature of substituents. For the numbering of substituents, see Table 1.

Ortho, ***meta*** and ***para*** relationships

A variety of methods have previously been developed to understand the interrelationships among *ortho*, *para*, and *meta* substituent effects. To address *ortho–para* relationships, Charton mentioned that "*only in an exceptional case is the* ortho-*electrical effect likely to have the same composition as the* para-*electrical effect*".[27] On the other hand, some authors approximated that the *ortho* and *para* electronic effects are similar in magnitude.[66–68] More than a decade ago Pytela[69,70] described the ratio of *para*/*meta* substituent effects on the basis of a classification of substituents into three groups *viz*. donors, acceptors, and neutral ones. Recently, Exner and Böhm[9] studied these relationships by classifying the substituents into two categories *viz*. (i) those having a lone pair of electrons at the α-position, and (ii) those having no lone pair at the α-position, and estimated that the *para*/*meta* ratio[9] is 1.20 for the second category. Using an isodesmic reaction approach Exner *et al.*[28] also derived the *ortho*/*para* ratio to a value of 0.81 for substituted benzoic acids. Very recently Segurado *et al.*[71] applied an electrostatic modelling approach to benzoate anions and reported a value of 0.985 for the *para*/*meta* ratio and a substantially smaller value of 0.397 for the *ortho*/*para* ratio. All these treatments on substituent effects were based on the classification of substituents into different categories and a single line of correlation leading to *para*/*meta*, *para*/*ortho*, and *ortho*/*meta* ratio was elusive. The single line correlation approach is more useful for comparing the general trend of substituent effects than the sophisticated approaches involving classification of substituents into different categories. The plots in Fig. 5 strongly suggest that the proximity effect-corrected V_o^{PE} and the proximity effect-free V_m and V_p follow a near parallel trend and therefore these parameters may be used in a single line correlation approach to compare the substituent effects. We find that $V_p = 1.108\ V_m$ (c.c. is 0.958), $V_p = 1.042\ V_o^{PE}$ (c.c. is 0.972), and $V_o^{PE} = 1.047\ V_m$ (c.c. is 0.969), where the *y*-intercept is set as zero (Fig. S3 in ESI†). Therefore, the ratios *para* : *meta*, *para* : *ortho* and *ortho* : *meta* electronic substituent effect are 1.108 : 1, 1.042 : 1 and 1.047 : 1, respectively and the electronic substituent effects follow the order *para* > *ortho* > *meta*.

Additive nature of substituent effects

The additive nature of substituent effects arises when the total substituent effect observed in a multiply-substituted compound is equal to the sum of the effect produced by the individual substituents. For example, in the case of saturated hydrocarbons, the total inductive effect observed for multiple substituents is the sum of the inductive effect of individual substituents,[49] and in several reaction series the activation energies of multiply-substituted compounds are expressed in terms of individual contribution of substituents.[72–74] In the present work, the additive nature of substituent effects is analyzed by using the V_{min} approach through a representative set of substituents *viz*. Cl, CH_3, OH, NH_2 and CN. The selected systems and the notation of the structures are shown in Fig. 6.

In the case of multiply-substituted systems, the calculated relative V_{min} with respect to 'H' is designated as V_{cal} and the predicted relative V_{min} is designated as V_{pred}. The V_{cal} and V_{pred} values observed on the OH moiety of the COOH for all the structures are presented in Table 3. For example, the V_{pred} of 2,3,5-trimethyl benzoic acid can be calculated as $V_{pred}(2,3,5\text{-}CH_3) = V_{cal}(2\text{-}CH_3) + V_{cal}(3\text{-}CH_3) + V_{cal}(5\text{-}CH_3) = -0.72 - 1.30 - 1.30 = -3.32$ kcal/mol and the actual V_{cal} is −3.41 kcal/mol. The V_{pred} and the V_{cal} show an excellent linear correlation (Fig. 7) indicating that the substituent effects largely follow an additive rule. This additive rule is not perfect as the V_{cal} is 0.863 times the V_{pred}, however the majority of the systems showed that the difference between V_{pred} and V_{cal} was less than 2 kcal/mol. In general, for electron withdrawing groups, the actual electron deactivation is less than the expected value. Similarly, for electron donating groups, the actual electron activation is less than the expected value. It may be noted that a perfect additive rule cannot be expected because in multiple substitution when two groups occupy adjacent positions (*e.g*. 2,3,4-X and 3,4,5-X) significant proximity effects may operate as was pointed out earlier by Jaffe.[1]

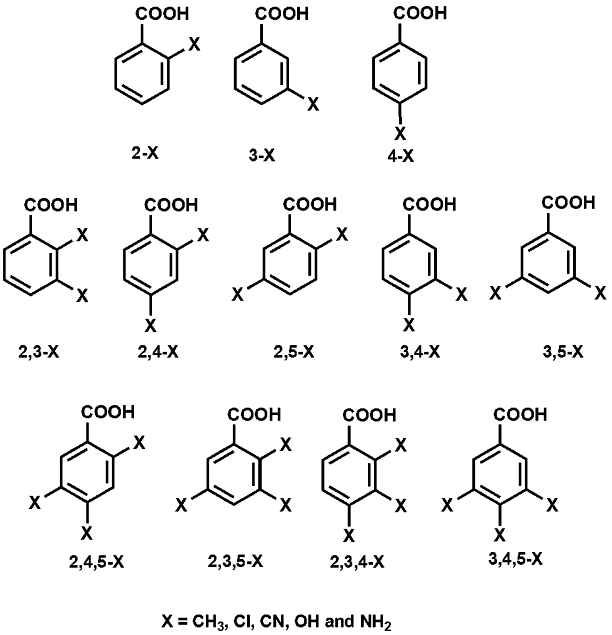

Fig. 6 Substituted systems considered for testing the additive nature of substituent effects.

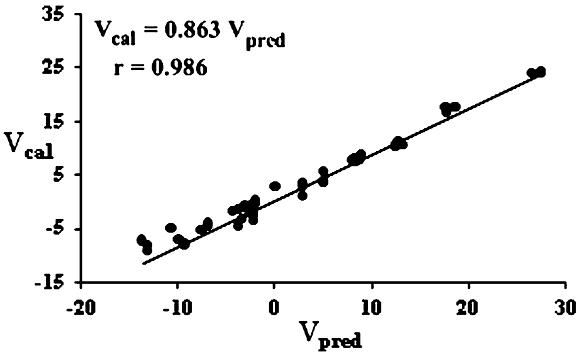

Fig. 7 Correlation between actual V_{min} and predicted V_{min}.

Table 3 V_{cal} and V_{pred} values (in kcal/mol) are presented for mono and multiply-substituted benzoic acids

System	V_{cal}	$V_{pred}{}^{a}$	System	V_{cal}	$V_{pred}{}^{a}$
2-Cl	1.49	—	2,3,5-CH_3	−3.41	−3.32
3-Cl	4.47	—	2,4,5-CH_3	−1.59	−3.78
4-Cl	4.25	—	3,4,5-CH_3	−1.84	−4.36
2-CH_3	−0.72	—	2,3-OH	5.49	5.05
3-CH_3	−1.30	—	2,4-OH	2.94	2.86
4-CH_3	−1.76	—	2,5-OH	3.40	5.05
2-OH	5.03	—	3,4-OH	−2.45	−2.15
3-OH	0.02	—	3,5-OH	2.81	0.04
4-OH	−2.17	—	2,3,4-OH	3.45	2.88
2-NH_2	−3.16	—	2,3,5-OH	3.78	5.07
3-NH_2	−3.76	—	2,4,5-OH	1.05	2.88
4-NH_2	−6.12	—	3,4,5-OH	−3.58	−2.13
2-CN	8.88	—	2,3-NH_2	−4.22	−6.92
3-CN	8.79	—	2,4-NH_2	−8.11	−9.28
4-CN	9.71	—	2,5-NH_2	−4.57	−6.92
2,3-Cl	7.34	5.96	3,4-NH_2	−7.25	−9.88
2,4-Cl	7.72	5.74	3,5-NH_2	−5.41	−7.52
2,5-Cl	7.81	5.96	2,3,4-NH_2	−9.24	−13.04
3,4-Cl	7.64	8.72	2,3,5-NH_2	−5.14	−10.68
3,5-Cl	8.74	8.94	2,4,5-NH_2	−8.21	−13.04
2,3,4-Cl	10.08	10.21	3,4,5-NH_2	−7.40	−13.64
2,3,5-Cl	11.06	10.43	2,3-CN	17.10	17.67
2,4,5-Cl	10.46	10.21	2,4-CN	17.55	18.59
3,4,5-Cl	10.56	13.19	2,5-CN	16.72	17.67
2,3-CH_3	−0.54	−2.02	3,4-CN	17.68	18.50
2,4-CH_3	−0.74	−2.48	3,5-CN	17.53	17.58
2,5-CH_3	0.06	−2.02	2,3,4-CN	24.23	27.38
3,4-CH_3	−0.96	−3.06	2,3,5-CN	24.05	26.46
3,5-CH_3	−2.28	−2.60	2,4,5-CN	23.92	27.38
2,3,4-CH_3	−4.79	−3.78	3,4,5-CN	23.98	27.29

[a] V_{cal} and V_{pred} of mono substituted systems are the same and were not included in the correlation shown in Fig. 7.

Conclusions

We have shown that in the case of substituted benzoic acids, the MESP minimum (V_{min}) at the lone pair region of OH on the functional group COOH serves as an excellent descriptor of the substituent effects. It is also shown that V_{min} can be used as an alternate measure for Hammett substituent constants. The V_{min} approach provided *a* unified way to study substituent effects without categorising the substituents into different classes[9,69,70] and also offered the mutual relationships among the *ortho*, *meta*, and *para* systems where the order of substitutent effect is *para* > *ortho* > *meta*. Multiply-substituted systems can also be studied using the V_{min} approach and it was found that substituent effects largely follow (86.3%) an additive rule. However, this additivity rule was not as perfect as observed in the case of aliphatic systems (98.5%).[49]

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