



An electrostatic scale of substituent resonance effect

Fareed Bhasha Sayyed, Cherumuttathu H. Suresh*

Computational Modelling and Simulation Section, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum 695 019, India

ARTICLE INFO

Article history:

Received 7 September 2009

Revised 10 October 2009

Accepted 14 October 2009

Available online 17 October 2009

Keywords:

Resonance effect

Molecular electrostatic potential

Isodesmic reactions

Density functional theory

Substituent effects

ABSTRACT

Substituent resonance constant, σ_R^v is calculated from substituted benzenes using molecular electrostatic potential (MESP). The reliability of σ_R^v is rigorously verified using isodesmic reactions and found that the energy component of substituent resonance effect is proportional to σ_R^v . Thus the MESP approach enabled the definition to an electrostatic scale of substituent resonance effect.

© 2009 Elsevier Ltd. All rights reserved.

Resonance effect is one of the most widely used qualitative concepts in chemistry.¹ Though it is not considered as an observable property, its use is wide spread to interpret molecular stability, reactivities of conjugated molecules,² rationalizing hydrogen bonding^{3,4} and in understanding the co-ordination of ligands to metals.⁵ Substituents (X) exhibit profound influence on the molecular properties of attached molecular units and the resonance contribution of 'X' is quantified as resonance constant (σ_R).^{6,7} Taft et al. introduced the dual substituent parametric (DSP) equation ($\sigma_p = \sigma_1 + \sigma_R$) to derive the σ_R .^{6,8,9} However, Exner and Böhm¹⁰ found that the validity of DSP equation is limited as the acceptor substituents are properly not expressed by σ_R and suggested two different resonance scales for both acceptors and donors. Several scales have been proposed as alternative to resonance constants; based on infrared intensities (IR),^{11–14} NMR chemical shifts^{9,15,16} and isodesmic reaction energies.^{1,17,18} The energies of resonance substituent effects turned out to be an unsatisfactory scale,^{1,6} IR scale requires detailed spectral analysis.¹⁹ Thus, to evaluate the substituent resonance effect, an easy, reliable and efficient method through an observable molecular property is yet to be established. Since the substituent resonance effect depends on the extent of interaction between 'X' and reaction centre,²⁰ a resonance scale must also interpret accurately the electron-donating as well as electron-withdrawing ability of the 'X'. In this Letter, we outline a simple and meaningful approach to estimate σ_R from mono-substituted benzenes using molecular electrostatic potential (MESP). Previous work has shown that MESP is an excellent descriptor to interpret the substituent effects.^{21–26} Since MESP is

an experimentally observable property²⁷ and intimately related to the electron distribution, the use of MESP will definitely change the status of resonance effect from a qualitative concept to a quantitative concept.

The MESP can be computed using Eq. 1, where $\{Z_A\}$ is the nuclear charge

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(r') d^3 \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|} \quad (1)$$

and $\rho(\mathbf{r})$ is the electron density.^{28–30} The MESP is calculated at B3LYP/6-31G(d,p) level³¹ using geometries optimized at the same level. For all calculations, GAUSSIAN03³² suite of programs have been used. In Figure 1, the MESP isosurfaces of four systems are shown to illustrate the effect of substituent over the π -region of various carbon atoms of the phenyl ring. In benzene, the D_{6h} symmetry guarantees equal distribution of MESP in all the carbon atoms. In fluorobenzene and aniline, the most negative-valued MESP or the MESP minimum (V_{\min}) is observed near the *para* carbon whereas in benzonitrile V_{\min} is observed near the *meta* carbon. V_{\min} also indicate the electron-rich character over the respective carbon atoms. In general, when an electron-donating substituent (EDS) is attached to the phenyl ring, the region close to *ortho* and *para* carbons is more electron rich³³ than the vicinity near *meta* carbon whereas in the case of electron-withdrawing substituents (EWS) the *meta* carbons are the most electron rich (Scheme S1). Similarly, the features observed over the π -region are also reflected at the nuclei of carbon atoms of the phenyl ring. The MESP at the *meta* carbon atom (V_m) is more negative than the MESP at the *para* carbon atom (V_p) for EWS and V_p is more negative than V_m for EDS. For instance, NH_2 shows a V_m value of -9253.95 kcal/mol and a V_p value of -9259.47 kcal/mol whereas CN shows V_m value

* Corresponding author. Tel.: +91 0471 2515264.

E-mail address: sureshch@gmail.com (C.H. Suresh).

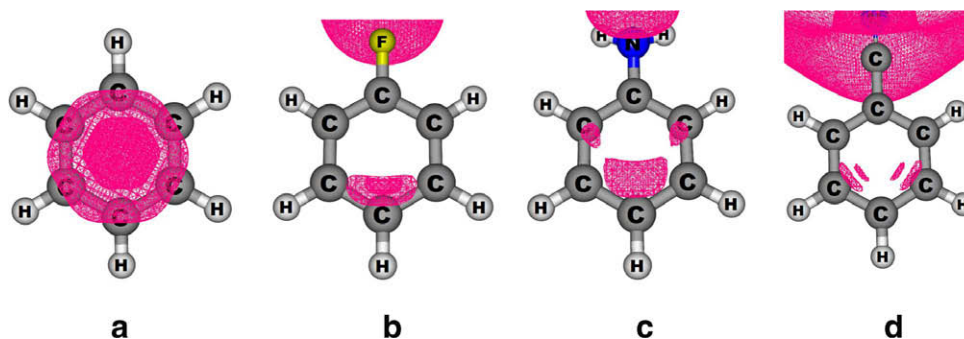


Figure 1. MESP isosurfaces of mono-substituted benzenes. (a) H, (b) F, (c) NH₂ (d) CN. The isosurface values in kcal/mol are -16.32, -12.24, -23.03 and -2.95, respectively, for H-, F-, NH₂- and CN-substituted benzenes.

Table 1
Molecular electrostatic potential (MESP) at the *meta* (V_m) and *para* (V_p) carbons of mono-substituted benzenes and MESP-derived resonance constants (σ_R^v)

Substituent	V_m	V_p	σ_R^o ^a	σ_R^v
H	-14.7409	-14.7409	0.00	0.00
CH ₃	-14.7440	-14.7454	-0.10	-0.88
C ₂ H ₅	-14.7448	-14.7466	-0.10	-1.13
CH(CH ₃) ₂	-14.7442	-14.7451	-0.12	-0.56
C(CH ₃) ₃	-14.7447	-14.7460	-0.13	-0.82
CH=CH ₂	-14.7392	-14.7390	-0.05	0.13
C ₆ H ₅	-14.7395	-14.7400	-0.10	-0.31
CH ₂ OH	-14.7440	-14.7459	-0.06	-1.19
CH ₂ SH	-14.7366	-14.7368	—	-0.13
CH ₂ Cl	-14.7306	-14.7300	-0.03	0.38
NH ₂	-14.7471	-14.7559	-0.47	-5.52
NHCH ₃	-14.7496	-14.7584	-0.52	-5.52
N(CH ₃) ₂	-14.7515	-14.7602	-0.53	-5.46
N=NH	-14.7171	-14.7177	—	-0.38
NHCOCH ₃	-14.7368	-14.7438	-0.42	-4.39
OH	-14.7395	-14.7466	-0.40	-4.46
OCH ₃	-14.7420	-14.7487	-0.43	-4.20
OCH ₂ CH ₃	-14.7430	-14.7498	-0.44	-4.27
OCH(CH ₃) ₂	-14.7435	-14.7518	-0.43	-5.21
OC ₆ H ₅	-14.7391	-14.7464	-0.36	-4.58
OCOCH ₃	-14.7333	-14.7374	-0.24	-2.57
SH	-14.7328	-14.7371	-0.19	-2.70
SCH ₃	-14.7376	-14.7419	-0.25	-2.70
F	-14.7284	-14.7346	-0.34	-3.89
Cl	-14.7248	-14.7281	-0.22	-2.07
Br	-14.7251	-14.7279	-0.23	-1.76
CHO	-14.7237	-14.7191	0.24	2.89
COCH ₃	-14.7301	-14.7254	0.22	2.95
CONH ₂	-14.7319	-14.7284	0.13	2.20
CSNH ₂	-14.7279	-14.7244	—	2.20
COOH	-14.7283	-14.7241	0.29	2.64
COOCH ₃	-14.7307	-14.7274	0.16	2.07
CN	-14.7133	-14.7115	0.09 ^b	1.13
NO ₂	-14.7094	-14.7071	0.17	1.44
CF ₃	-14.7226	-14.7217	0.10	0.56
COCl	-14.7139	-14.7091	0.21	3.01
Li	-14.7804	-14.7776	0.14	1.76
SiCl ₃	-14.7175	-14.7145	0.09	1.88
Si(CH ₃) ₃	-14.7437	-14.7416	0.03	1.32
PH ₂	-14.7354	-14.7369	-0.05	-0.94
P(CH ₃) ₂	-14.7401	-14.7413	-0.08	-0.75
NHNH ₂	-14.7506	-14.7598	-0.49	-5.77
SO ₂ Cl	-14.7131	-14.7113	0.11	1.13
SOCH ₃	-14.7259	-14.7258	-0.07	0.06
BCl ₂	-14.7237	-14.7168	0.30	4.33
NO	-14.7152	-14.7105	0.25	2.95
CH ₂ CHO	-14.7317	-14.7324	-0.11	-0.44
CH ₂ CH ₂ CH ₃	-14.7440	-14.7451	-0.11	-0.69
CH ₂ Br	-14.7307	-14.7302	-0.02	0.31
CH ₂ OCH ₃	-14.7449	-14.7450	-0.04	-0.06

V_m and V_p value are in au and σ_R^v in kcal/mol.

^a Values are taken from Ref. 14.

^b Value is taken from Ref. 7.

of -9232.74 kcal/mol and V_p value of -9231.61 kcal/mol. It may be noted that the interaction of 'X' on the *meta* carbon is primarily due to inductive effect ($\rho_1\sigma_1 = 0.86\rho\sigma_m$)³⁴ while the effect of 'X' on the *para* carbon comprises both resonance and inductive effects.³⁵ Thus, the difference between V_p and V_m is primarily due to the resonance contribution of 'X'. However, the substituent inductive effect is nearly the same on all the carbons of aromatic ring as reported by Moreland.³³ Following this argument, we define the MESP-based resonance constant (σ_R^v) as $V_p - V_m$. The V_p and V_m values are evaluated for a set of fifty substituted benzenes (Table 1). Interestingly, substituents classified as '*ortho-para* directing' in electrophilic substitution reactions showed a negative sign for σ_R^v and the rest (*meta* directing) showed a positive sign. The linear correlation between σ_R^v and σ_R^o (resonance constants derived from IR) shown in Figure 2 clearly suggests that MESP is a vital tool for the estimation of the resonance effect of substituents and serves as an alternate measure of the resonance constants.

The efficacy of the σ_R^v is rigorously tested in substituted phenols by considering 26 substituents using three sets of isodesmic reactions³⁶ (Scheme 1). The reaction energies of the isodesmic reactions, (1), (2) and (3) are designated as ΔE_1 , ΔE_2 and ΔE_3 , respectively. The reaction (1) quantifies energy component of the resonance contribution of 'X' with the OH. The correlation between ΔE_1 and σ_R^v ($r = 0.988$) illustrates the use of σ_R^v as a measure of substituent effect where the 'through conjugation effect' occurs between the reaction centre and the substituent (Fig. 3a). Regarding isodesmic reaction (2), the *meta* substituent can interact with 'OH' mainly through inductive effect whereas the *para* substituent interacts with 'OH' through both inductive and resonance effects.³⁴ Therefore, ΔE_2 will serve as a good measure of resonance effect of 'X'. The linear correlation between ΔE_2 and σ_R^v ($r = 0.987$) strongly supports this argument and validates the use of the MESP approach to estimate resonance

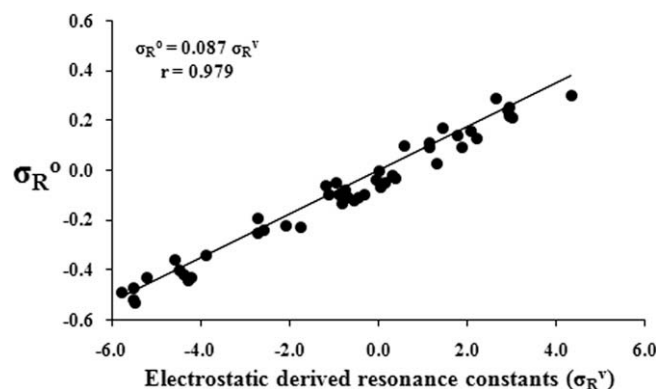
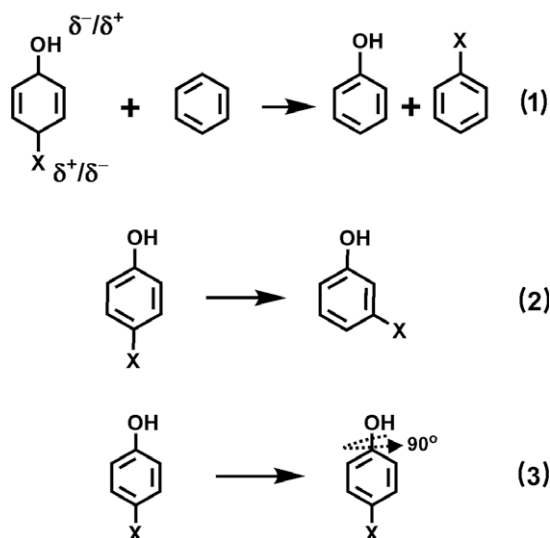


Figure 2. Correlation between the σ_R^o and MESP-derived σ_R^v values.



Scheme 1. Isodesmic reactions studied to validate the electrostatic scale of resonance effect. X = substituent.

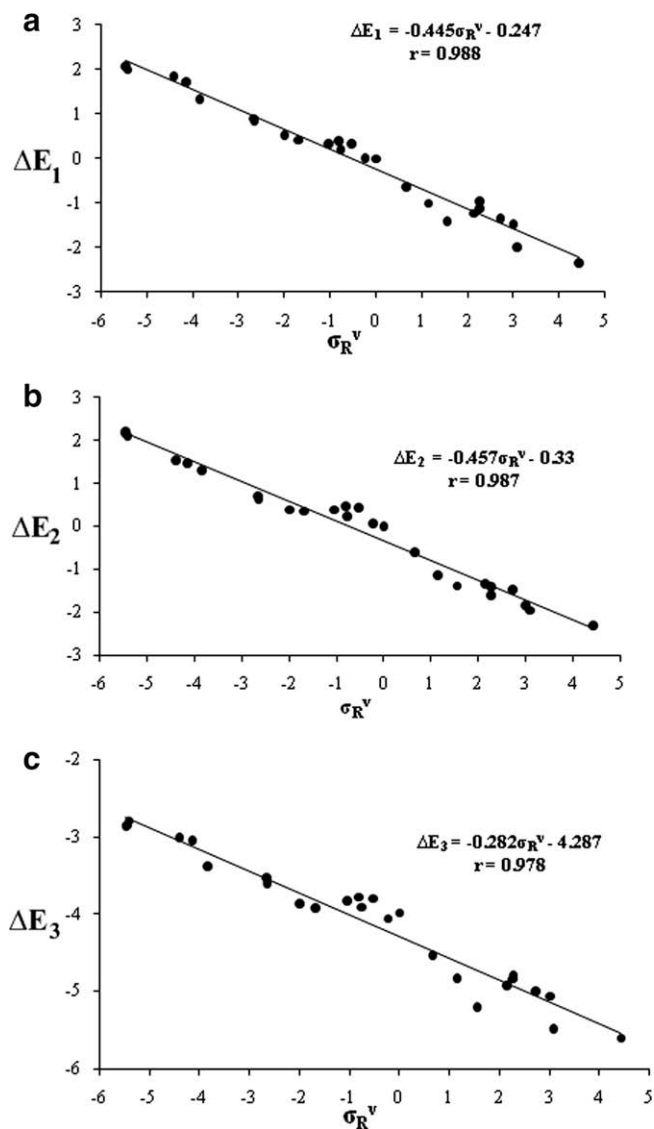


Figure 3. Dependence of isodesmic reaction energies (in kcal/mol) and the MESP-derived resonance constants (σ_R^v).

effects (Fig. 3b). The isodesmic reaction (3) corresponds to the rotation of OH group wherein the OH group is rotated by 90° with respect to the phenyl ring, the X...OH resonance interaction will be effectively removed and no significant change will occur to the inductive effect.² The correlation of ΔE_3 with σ_R^v is linear with $r = 0.978$ (Fig. 3c). Thus the three linear correlations of isodesmic reaction energies with σ_R^v , suggest that σ_R^v is a reliable measure of substituent resonance effect. The proposed electrostatic scale of substituent resonance effect is easy to compute and is expected to be useful in QSAR and QSPR studies of organic molecules.

Acknowledgements

Authors are thankful to CSIR-India for providing research facilities and F.B.S is thankful to CSIR for providing Junior Research Fellowship. The research grant from the Department of Science and Technology (DST), Government of India (Project No. SR/S1/OC-41/2006) is gratefully acknowledged.

Supplementary data

Canonical structures of mono-substituted benzenes, SCF energies, isodesmic reaction energies of substituted phenols and optimized geometries of 50 mono-substituted benzenes. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.064.

References and notes

- Exner, O.; Bohm, S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1994.
- Silva, P. J. *J. Org. Chem.* **2009**, *74*, 914.
- Krygowski, T. M.; Zachara-Horeglad, J. E. *Tetrahedron* **2009**, *65*, 2010.
- Liu, T.; Li, H.; Huang, M.-B.; Duan, Y.; Wang, Z.-X. *J. Phys. Chem. A* **2008**, *112*, 5436.
- Ott, H.; Pieper, U.; Leusser, D.; Flierler, U.; Henn, J.; Stalke, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 2978.
- Krygowski, T. M.; Stepien, B. T. *Chem. Rev.* **2005**, *105*, 3482.
- Krygowski, T. M.; Ejsmont, K.; Stepien, B. T.; Cyranski, M. K.; Poater, J.; Sola, M. *J. Org. Chem.* **2004**, *69*, 6634.
- Taft, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4231.
- Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
- Exner, O.; Böhm, S. *J. Phys. Org. Chem.* **2007**, *20*, 454.
- Angelelli, J. M.; Brownlee, R. T. C.; Katritzky, A. R.; Topsom, R. D.; Yakhontov, L. *J. Am. Chem. Soc.* **1969**, *91*, 4500.
- Angelelli, J.-M.; Katritzky, A. R.; Pinzelli, R. F.; Sinnott, M. V.; Topsom, R. D. *J. Am. Chem. Soc.* **1969**, *91*, 4013.
- Brownlee, R. T. C.; Cameron, D. G.; Topsom, R. D.; Katritzky, A. R.; Pozharsky, A. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, *3*, 282.
- Katritzky, A. R.; Topsom, R. D. *Chem. Rev.* **1977**, *77*, 639.
- Taft, R. W.; Lewis, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 5343.
- Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Anderson, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, *85*, 3146.
- Exner, O.; Bohm, S. *J. Mol. Struct.: THEOCHEM* **2002**, 103.
- Exner, O.; Bohm, S. *J. Mol. Struct.: THEOCHEM* **2005**, 125.
- Palat, K., Jr.; Waissner, K.; Exner, O. *J. Phys. Org. Chem.* **2001**, *14*, 677.
- Niwa, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 226.
- Gadre, S. R.; Suresh, C. H. *J. Org. Chem.* **1997**, *62*, 2625.
- Galabov, B.; Ilieva, S.; Schaefer, H. F., III. *J. Org. Chem.* **2006**, *71*, 6382.
- Suresh, C. H.; Gadre, S. R. *J. Am. Chem. Soc.* **1998**, *120*, 7049.
- Suresh, C. H.; Gadre, S. R. *J. Phys. Chem. A* **2007**, *111*, 710.
- Suresh, C. H.; Alexander, P.; Vijayalakshmi, K. P.; Sajith, P. K.; Gadre, S. R. *Phys. Chem. Phys.* **2008**, *10*, 6492.
- Gross, K. C.; Seybold, P. G.; Peralta-Inga, Z.; Murray, J. S.; Politzer, P. *J. Org. Chem.* **2001**, *66*, 6919.
- Naray-Szabo, G.; Ferenczy, G. G. *Chem. Rev.* **1995**, *95*, 829.
- Gadre, S. R.; Shirsat, R. N. *Electrostatics of Atoms and Molecules*; Universities Press: Hyderabad, 2000.
- Bonnaccorsi, R.; Scrocco, E.; Tomasi, J.; Pullman, A. *Theor. Chim. Acta* **1975**, *36*, 339.
- Politzer, P.; Murray, J. S. *Theor. Chem. Acc.* **2002**, *108*, 134.
- Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
- Frisch, M. J. T.; G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Yangar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.

- Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D.J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; GAUSSIAN 03, Revision C.02; Gaussian: Wallingford, CT, 2004.
33. Roberts, J. D.; Moreland, W. T. *J. Am. Chem. Soc.* **1953**, 75, 2167.
 34. Holtz, H. D.; Stock, L. M. *J. Am. Chem. Soc.* **1964**, 86, 5188.
 35. Brownlee, R. T. C.; Katritzky, A. R.; Topsom, R. D. *J. Am. Chem. Soc.* **1965**, 87, 3260.
 36. Krygowski, T. M.; Stepień, B. T.; Cyrański, M. K.; Ejsmont, K. *J. Phys. Org. Chem.* **2005**, 18, 886.