Asian Journal of Chemistry Vol. 19, No. 1 (2007), 55–66

Modular Modelling Analysis of the *o*-, *m*- and *p*-Directing Influences of Substituents in Electrophilic Attack on Aromatic Compounds

FAZLUL HUQ
School of Biomedical Sciences, Faculty of Health Sciences, C42, The University of Sydney
P.O. Box 170, Lidcombe, NSW 1825, Australia
Fax: (61)(2)93519520; Tel: (61)(2)93519522; E-mail: f.huq@fhs.usvd.edu.au

Molecular modelling analyses using molecular mechanics, semi-empirical, DFT and *ab initio* calculations were carried out to investigate the effect of substituents in electrophilic substitution in benzene derivatives. The results of calculations show that the *ortho-*, *meta- and para*-directing influences of substituents in electrophilic attack are governed by the net atomic charges rather than relative stability of the resulting isomers.

Key Words: *ortho-*, *meta-*, *para*-Directors, Electrophilic, Molecular modelling.

INTRODUCTION

When substituted benzenes undergo electrophilic attack, groups already present on the ring affect both the rate of the reaction and the site of attack[1, 2]. The groups that cause the ring to be more reactive than benzene itself are called activating groups and the ones that cause the ring to be less reactive are called deactivating groups. Substituent groups can also influence the orientation of the attack by the incoming electrophile. Groups in one category tend to bring about electrophilic substitution primarily at *ortho* and *para* positions and hence are called *ortho-para* directors. Groups in the other category tend to direct the incoming electrophile towards substitution at the *meta* positions. These groups are called *meta* directors. For example, toluene is more reactive towards electrophilic substitution than benzene and the methyl group in toluene is an *ortho-para* director whereas nitro group (NO_2) is a strong deactivating group (nitrobenzene undergoes nitration 104 times slower than benzene) and is a *meta* director. Table-1 lists some of the *ortho-para* and *meta* directors. Table-2 gives product percentages in electrophilic substitution in monosubstituted benzenes.

The reactivity and orientation in electrophilic aromatic substitutions are controlled by an interplay of inductive and resonance effects. An inductive effect may be defined as the withdrawal or donation of electrons through σ bond due to polarity of bonds in functional groups. A resonance effect may be defined as the withdrawal or donation of electrons through a π bond due to the overlap of *p*-orbital on the substituent with that on the aromatic ring. For example, halogens *p*-orbital on the substituent with that on the aromatic ring. For example, halogens and nitro groups inductively withdraw electrons through the σ bond linking the substituent to a benzene ring whereas alkyl groups donate electrons through the same effect. Carbonyl, cyano, and nitro substituents withdraw electrons from the aromatic ring by resonance –π electrons flow from the rings to the substituents, leaving a positive charge in the ring. All activating groups donate electrons to the ring whereas all deactivating groups withdraw electrons away from the ring.

TABLE-1

EFFECT OF SUBSTITUENTS ON ELECTROPHILIC AROMATIC SUBSTITUTION[1]

ortho-para Directors				*meta* Directors	
Strongly activating	Moderately activating	Weakly activating	Weakly deactivating	Strongly activating	Moderately activating
$—NH_2$	$—NHCOCH_2$	$—CH_3$	—F	$—NO_2$	$—C{\equiv}N$
—NHR	—NHCOR	$—C_2H_5$	—Cl	$—NR_3^+$	$—SO_3H$
$—NR_2$	$—OCH_3$	—R	—Br	$—CF_3$	—COOH
—OH	—OR	$—C_6H_5$	—I	$—CCl_3$	—COOR

TABLE-2

PERCENTAGES OF PRODUCTS IN ELECTROPHILIC SUBSTITUTION[2]

Group	Product percentages		
	ortho	*meta*	*para*
—F	13	1	86
—Cl	35	1	64
—Br	43	1	56
—I	45	1	54
$—CH_3$	63	3	34
—OH	50	0	50
$—NHCOCH_3$	19	2	79

Attempts have been made to correlate the influence of the substituents with the power of the attacking group. An empirical equation that is widely applicable in this regard is the Hammet equation[3, 4] that may be described as follows. For a reaction performed on a substrate molecule that can be represented as XGY, where Y is the site of reaction, X a variable substituent and G is a skeleton group to which X and Y are attached, the Hammet equation can be written as:

$$\log (k/k_0) = \rho\sigma$$

where k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions and σ is a constant characteristic of the group X. In a way, the ρ values sum up the inductive and resonance effects of substituents.

The Hammet equation has been applied to many reactions and many functional equation has also been shown to many physical measurements, IR frequencies and NMR chemical shifts[7].

Attempts have been made to deduce the linear form of the Hammet equation from low level quantum mechanical calculations[6]. Most efforts have been directed towards obtaining possible values of the substituent constant σ. The reaction mechanisms of the H-exchange and methylation of benzene catalyzed by various Lewis acid catalysts were investigated by Vos *et al.*[8] through DFT calculations.

In this study molecular modelling analyses using molecular mechanics, semi-empirical, DFT and *ab initio* calculations were carried out using the programs HyperChem 7.0[5] and Spartan'02[6] to investigate the effect of substituents in electrophilic substitution in benzene derivatives.

EXPERIMENTAL

The structures of mono- and disubstituted derivatives of benzene listed in Tables 1 and 2 were optimized based on molecular mechanics, semi-empirical, DFT and *ab initio* calculations. The RMS gradient was set at 0.001 as a termination condition. The heat of formation, enthalpy, entropy and Gibb's free energy were calculated based on single point calculations as per the routine PM3 using the program HyperChem 7.0. Spartan'02 was used to carry out B3LYP density functional calculations using the basis set 6-31G*. HyperChem 7.0 was also used to carry out *ab initio* calculations. For optimized structures, net atomic charges were calculated and 2D contours for electrostatic potential around atoms were plotted. The charges on *ortho*, *meta* and *para* carbon atoms of the parent compound were noted to provide information on the preferred position(s) for electrophilic attack. The greater the negative charge, the greater would be the likelihood of electrophilic attack at the position. Total energies and heats of formation of the compounds resulting from *ortho*, *meta* and *para* substitution in the parent compounds also provided information on the relative stabilities of isomers and hence likely position(s) of electrophilic attack. It will be seen later that atomic charges, rather total energies and heats of formation, provide informations that are in line with experimental observations as applied to preferred position(s) of electrophilic attack.

RESULTS AND DISCUSSION

Table-3 gives the total energies and heats of formation of a number of compounds obtained from benzene by replacement of one or more hydrogens by substituents. The heats of formation of 2-hydroxytoluene, 3-hydroxytoluene and 4-hydroxytoluene are respectively –29.62, –31.00 and –30.91 kcal mol^{-1}, indicating that the three isomers are almost equally stable with 2-hydroxytoluene being the least stable one and 3-hydroxytoluene being the most stable isomer among the three. The results suggest that the methyl group would be a weakly activating *meta*-directing group. In actual fact, the methyl group is a weakly activating *ortho-para* directing group. A similar observation was made when the total enthalpies and free energies of the isomers (obtained from DFT calculations) were

TABLE-3
HEATS OF FORMATION OF COMPOUNDS BASED ON PM3 SINGLE POINT CALCULATIONS USING HyperChem 7.0

Isomers and their heats of formation (kcal mol^{-1})						Comments
-Hydroxytoluene	–29.62	3-Hydroxytoluene	–31.00	4-Hydroxytoluene	–30.91	*Meta*-substitution of toluene preferred over *ortho*- and *para*-substitution
Trichloromethyl)-4-ydroxybenzene	–41.70	(Trichloromethyl)-2-hydroxybenzene	–40.06	(Trichloromethyl)-3-hydroxybenzene	–40.84	*Para*-substitution of (trichloromethyl)benzene most preferred and *ortho*-substitution least preferred
Trifluoromethyl)-4-ydroxybenzene	–180.59	(Trifluoromethyl)-2-hydroxybenzene	–180.82	(Trifluoromethyl)-3-hydroxybenzene	–179.50	*Para*-substitution of (trichloromethyl)benzene most preferred and *meta*-substitution least preferred
-Hydroxychlorobenzene	–26.99	3-Hydroxychlorobenzene	–28.35	4-Hydroxychlorobenzene	–28.39	*Ortho*-substitution of chlorobenzene least preferred
-Chloromethoxybenzene	–21.31	3-Chloromethoxybenzene	–21.38	2-Chloromethoxybenzene	–17.41	*Ortho*-substitution least preferred and *meta*-substitution most preferred
-Hydroxybenzoic acid	–111.94	2-Hydroxybenzoic acid	–112.85	3-Hydroxybenzoic acid	–110.66	*Meta*-substitution most preferred
-Chloro-4-hydroxybenz-dehyde	–61.58	3-Chloro-4-hydroxybenzaldehyde	–62.37	—	—	3-Chloro-4-hydroxybenzaldehyde is more stable
,2-Diaminobenzene	32.78	1,3-Diaminobenzene	27.78	1,4-Diaminobenzene	29.89	*Meta*-substitution is preferred over *ortho*- and *para*- substitutions
-Bromoanisole	–3.19	3-Bromoanisole	–7.07	4-Bromoanisole	–7.03	*Meta*- substitution preferred over *ortho*- and *para*-substitutions
-Bromo-2-chlorobenzene	25.78	1-Bromo-3-chlorobenzene	24.67	1-Bromo-4-chlorobenzene	24.56	*Ortho*-substitution is least preferred
,2-Diaminobenzene	32.78	1,3-Diaminobenzene	27.78	1,4-Diaminobenzene	29.89	*Meta*-substitution preferred over *ortho*- and *para*-substitutions
-Hydroxybenzoic acid	–112.85	3-Hydroxybenzoic acid	–110.66	4-Hydroxybenzoic acid	–111.94	*Meta -substitution least preferred*

considered (results of calculations not given in the paper). Thus, it can be said that the relative stabilities of the three isomers fail to explain why *ortho-para* substitution of toluene is preferred over *meta* substitution. To take another example, trichloromethyl group (Table-1) is known to be a strongly activating *meta*-director. However, if the heats of formation are considered, one would conclude that *para* substitution would be most preferred in trichloromethylbenzene. Similarly it can be seen that for most of the parent compounds corresponding to compounds listed in Table-3, the calculated heats of formation fail to explain either partly or fully the known directions in *ortho*, *para* and *meta* substitution. Next we shall consider the net charges on atoms to see whether these are better able to provide an explanation of the directing influences of substituents.

Figs. 1–19 give the net charges on atoms of toluene, phenol, trifluormethylbenzene, flurobenzene, chlorobenzene, bromobenzene, iodobenzene, methoxybenzene, benzoic acid, 4-hydroxybenzaldehyde, nitrobenzene, aniline, phenyl methyl amine, acetanilide, 1,4-dihydroxybenzene, 1,2,4-trihydroxybenzene, 1,2,4,5-tetrahydroxybenzene, 1,2,3,4,5-pentahydroxybenzene and phenylbenzene respectively. It can be seen that in the case of toluene, the carbon atoms at *ortho* and *para* positions have slightly more negative charges than the carbon atoms at the *meta* positions, indicating that *ortho* and *para* substitution in toluene would be preferred over *meta* substitution. In the case of phenol, it can be seen that the negative charges at *ortho* and *para* carbon atoms are much greater than those at the *meta* positions, indicating that the hydroxyl group is a strongly activating *ortho-para* director. In the case of trifluormethylbenzene it is found that the carbon atoms at the *meta* positions have a much greater net negative charge than those at the *ortho* and *para* positions, indicating that trifluoromethyl group is a strongly activating *meta* director. In the case of fluorobenzene, the carbon atoms at the *ortho* and *para* positions are found to have greater negative charges than those at the *meta* positions, indicating that F is an *ortho-para* director. Similarly it can be seen that Cl, Br and I are also *ortho-para* directors in deceasing order of strength. To take still another example, let us consider charges on carbon atoms of 1,2,4-trihydroxybenzene. It can be seen that the third ring carbon (which is *ortho t*o carbon atoms at the second and fourth positions) has a much greater negative charge than the other two carbons each of which is *ortho* to one OH-bonded carbon but *meta* to another. Again the conclusion drawn from net charges on atoms agrees with the results expected. In the case of 1,2,4,5-tetrahydroxybenzene, third and sixth carbon atoms are each *ortho* to one OH-bonded carbon and *meta* to another whereas in the case of 1,2,3,4,5-pentahydroxybenzene, the only position available to electrophilic attack (*i.e.*, the sixth position) is *ortho* to two OH-bonded carbon atoms, *meta* to two others and *para* to one and hence the carbon at the sixth position of 1,2,3,4,5-pentahydroxybenzene has a greater negative charge than the carbons at the third and sixth positions of 1,2,4,5-tetrahydroxybenzene. Similar considerations will show that net charges on carbon atoms invariably provide an explanation for the *ortho, para* and *meta* directing influences of existing groups in electrophilic aromatic substitution.

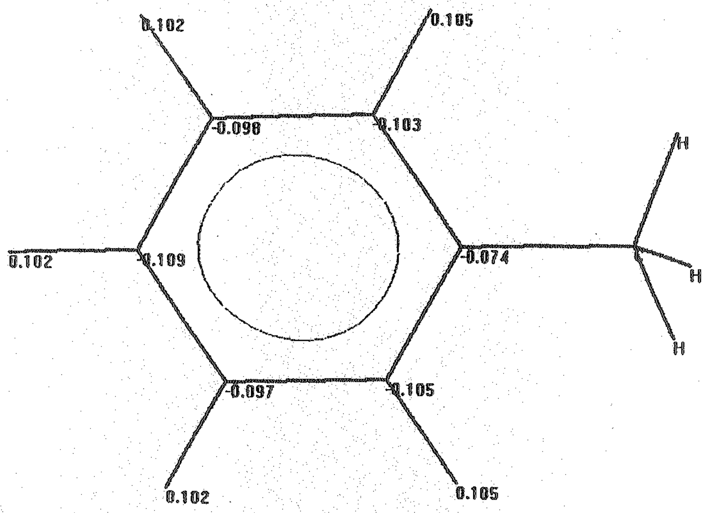

Fig. 1. Net charges on atoms of toluene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

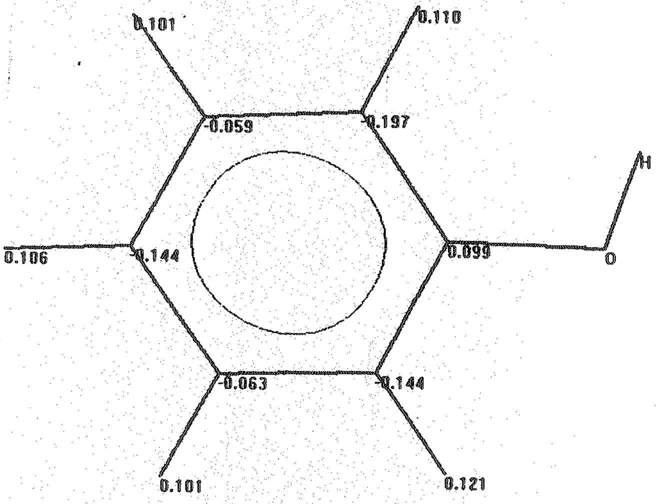

Fig. 2. Net charges on atoms of phenol-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

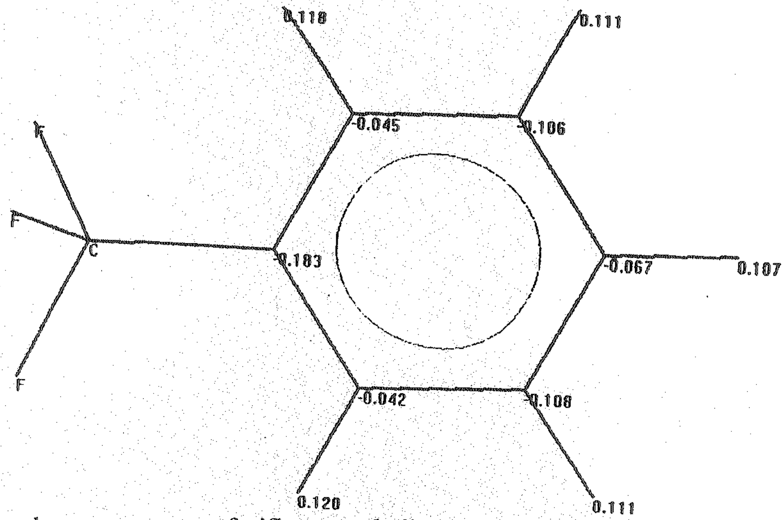

Fig. 3. Net charges on atoms of trifluoromethylbenzene-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

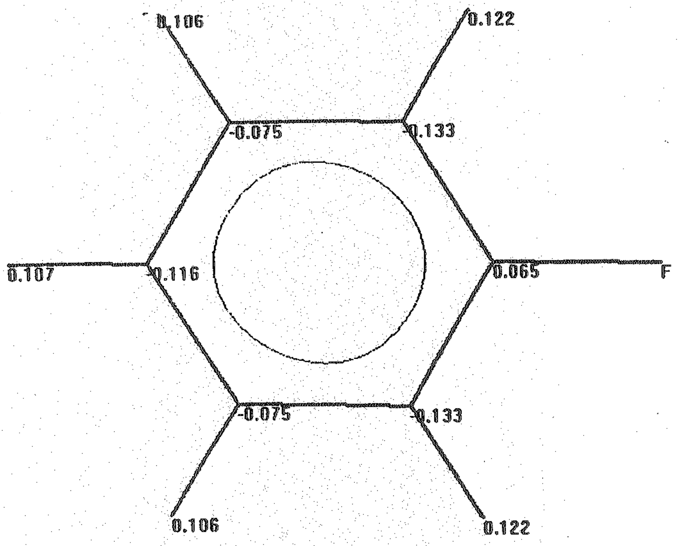

Fig. 4. Net charges on atoms of fluorobenzene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

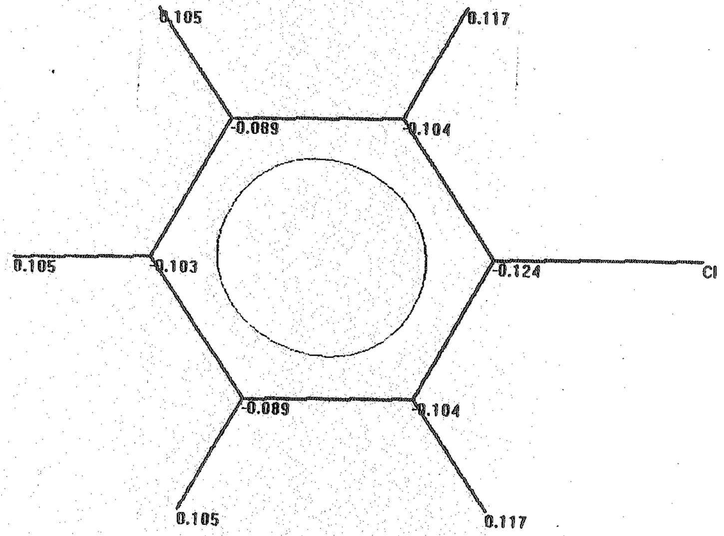

Fig. 5. Net charges on atoms of chlorobenzene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

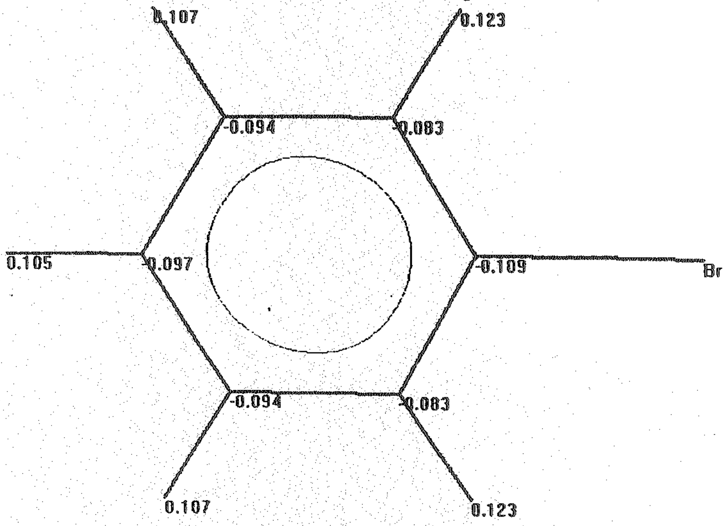

Fig. 6. Net charges on atoms of bromobenzene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

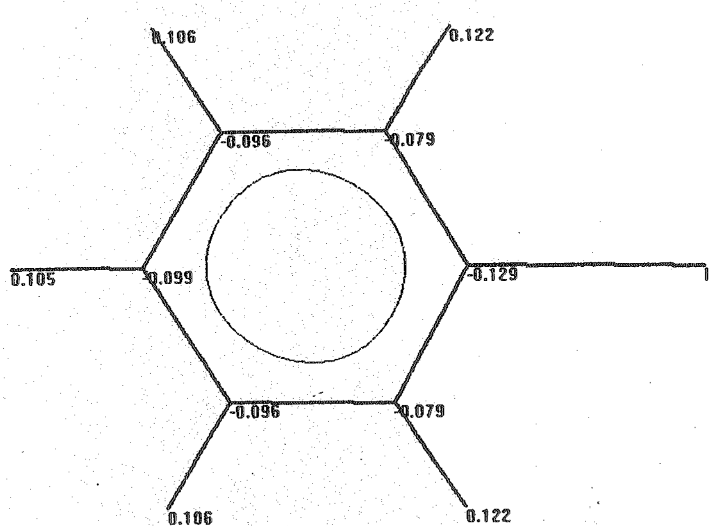

Fig. 7. Net charges on atoms of iodobenzene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

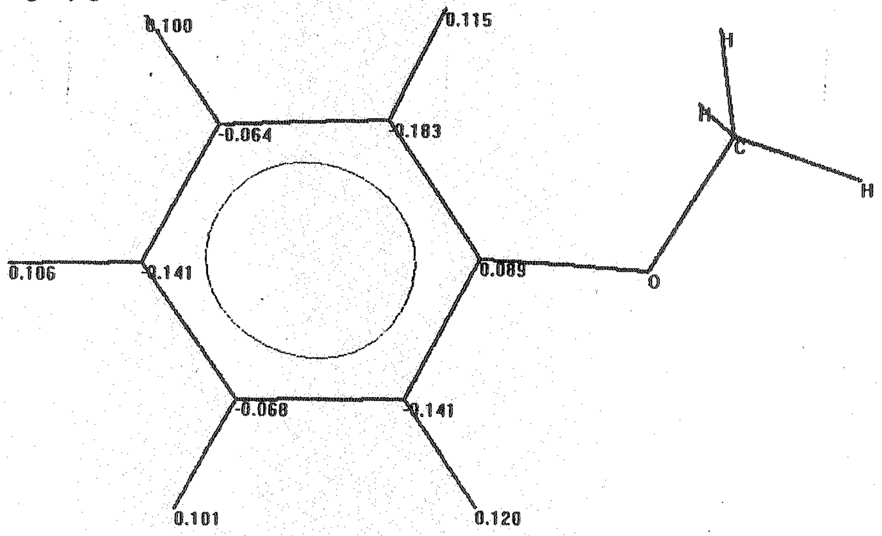

Fig. 8. Net charges on atoms of methoxybenzene-carbon atoms at the *ortho* and *para* positions have slightly greater charges than those at the *meta* positions

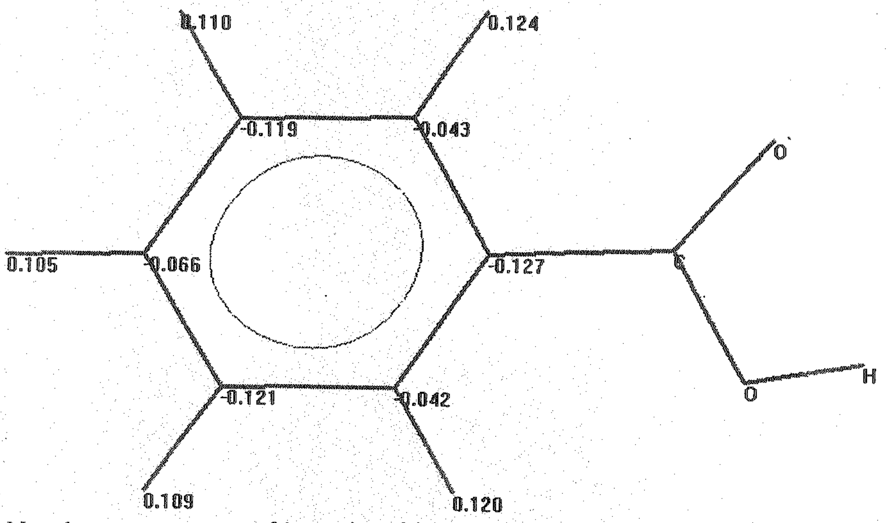

Fig. 9. Net charges on atoms of benzoic acid-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

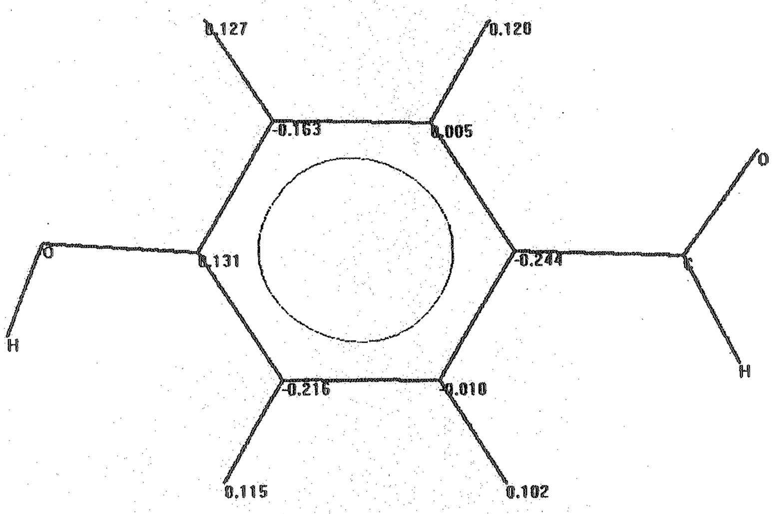

Fig. 10. Net charges on atoms of 4-hydroxybenzaldehyde-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

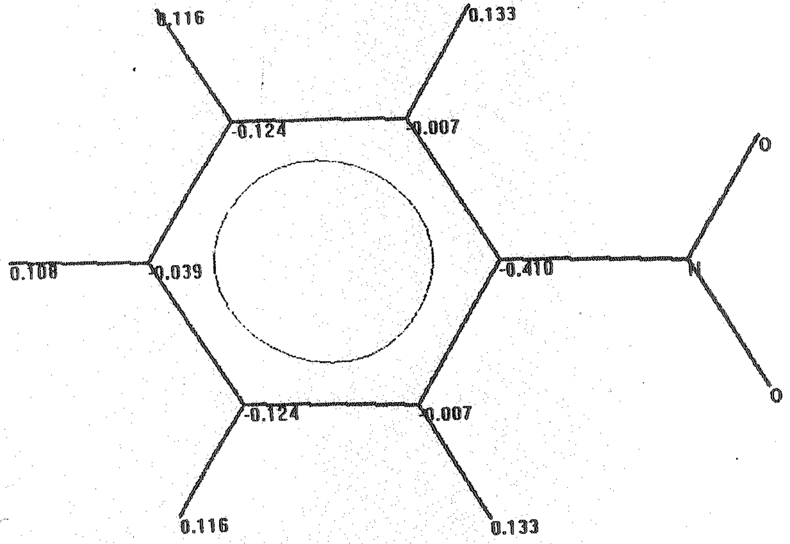

Fig. 11. Net charges on atoms of nitrobenzene-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

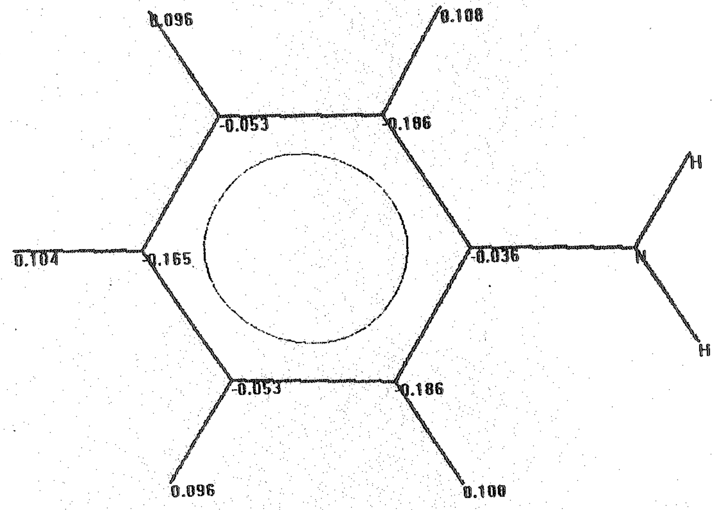

Fig. 12. Net charges on atoms of aniline-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

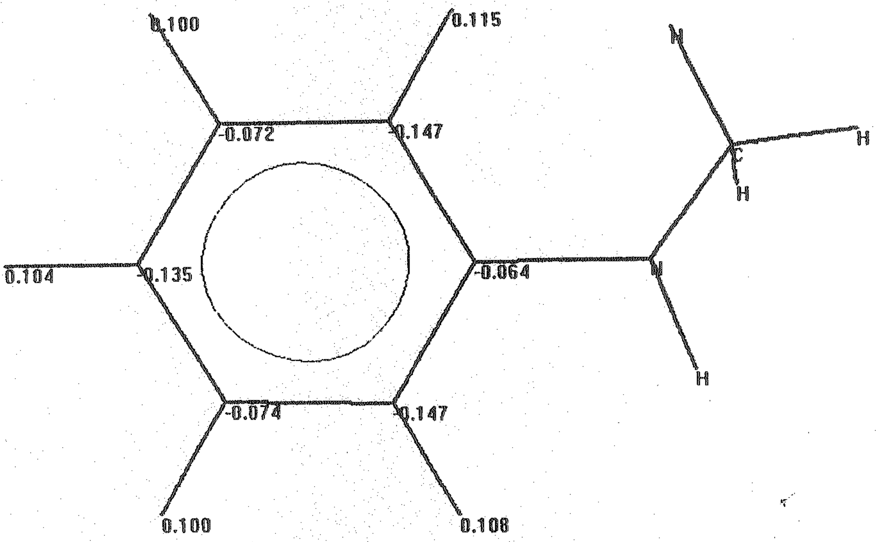

Fig. 13. Net charges on atoms of phenyl methyl amine-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

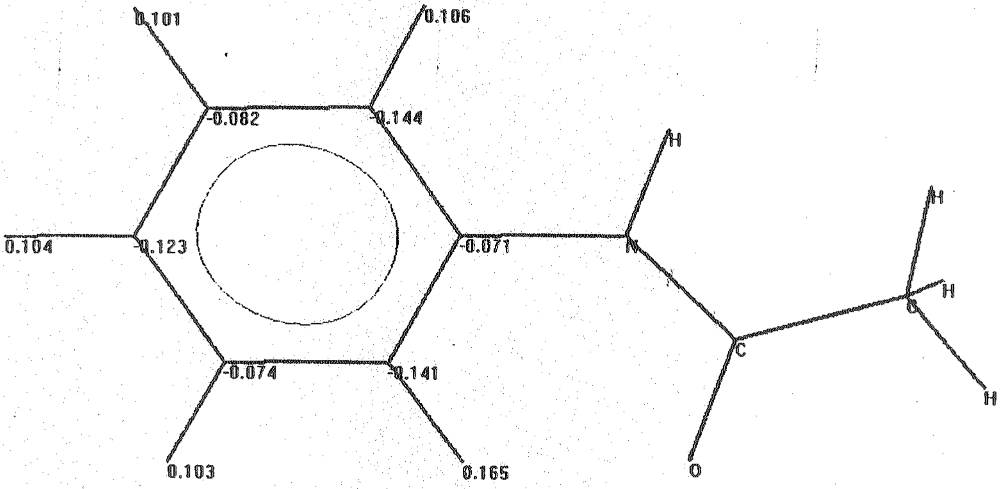

Fig. 14. Net charges on atoms of acetanilide-carbon atoms at the *meta* positions have slightly greater charges than those at the *ortho* and *para* positions

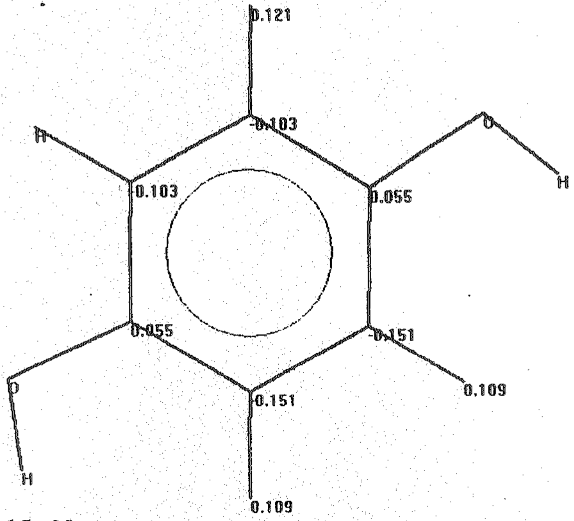

Fig. 15. Net charges on atoms in 1,4-dihydroxy benzene

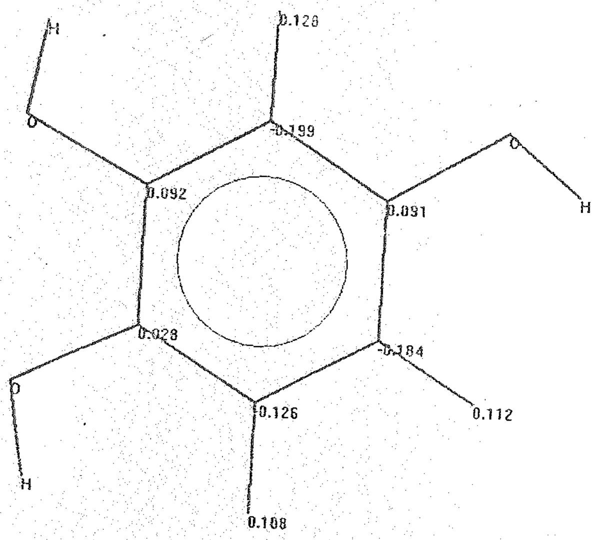

Fig. 16. Net charges on atoms of 1,2,4-trihydroxy benzene

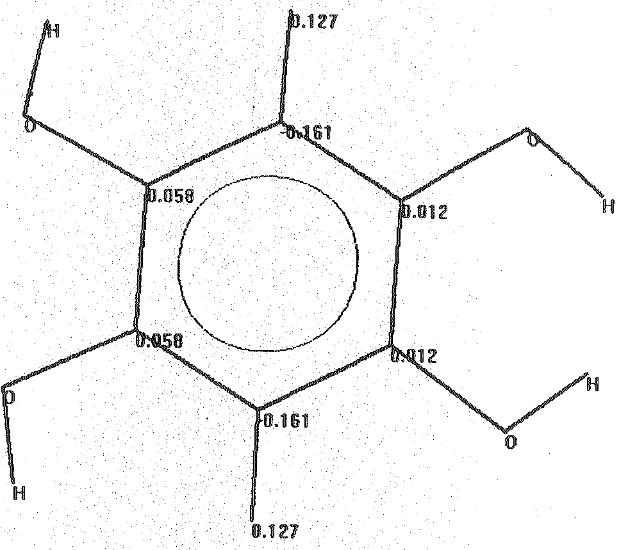

Fig. 17. Net charges on atoms in 1,2,4,5-tetrahydroxy benzene

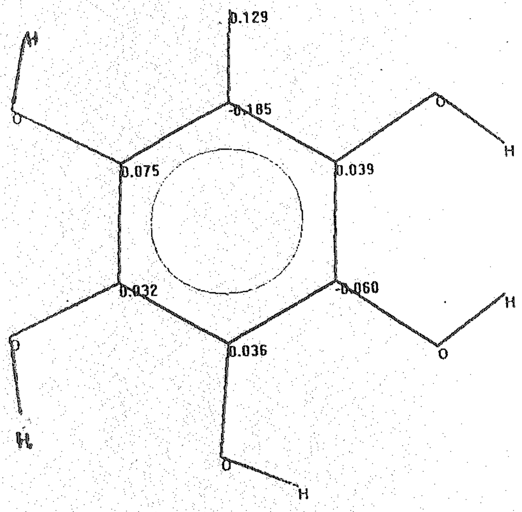

Fig. 18. Net charges on atoms of 1,2,3,4,5-pentahydroxy benzene

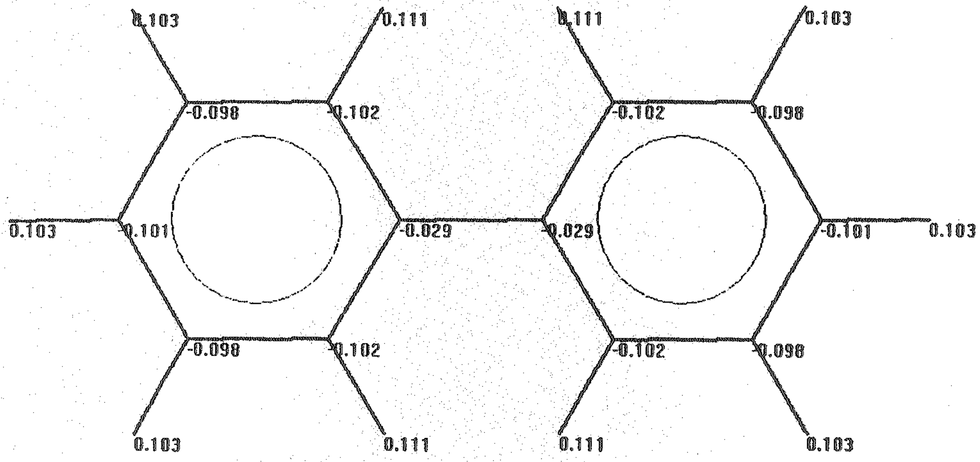

Fig. 19. Charges on atoms of phenyl benzene-carbon atoms at the *ortho-para* positions have greater net negative charges than those at the *meta* positions

and *meta* directing influences of existing groups in electrophilic aromatic substitution.

Conclusion

Molecular mechanics, semi-empirical, DFT and *ab initio* calculations show that *ortho-para*, and *meta*-directing influences of substituents and activation or deactivation of the ring towards substitution can be better explained in terms of net charges on atoms rather than on the basis of thermodynamic properties such as heat of formation, total enthalpy, entropy and free energy.

REFERENCES

1. T.W.G. Solomon, John Wiley & Sons, New York-London-Sydney-Toronto (1976).
2. J. McMurray, Organic Chemistry, 5th Edn., Brooks/Cole (2000).
3. H.H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
4. M.B. Smith and J. March, March's Advanced Organic Chemistry, 5th Edn., Wiley & Sons, New York-Chester-Weiheim-Brisbane-Singapore-Toronto, p. 693 (2001).
5. A.M. Vos, R.A. Schoonheydt, F. De Proft and P. Geerlings, *J. Catal.*, **220**, 333 (2003).
6. Ö. Exner and S. Bohm, *J. Org. Chem.*, **67**, 6321 (2002).
7. N.B. Chapman and J. Shorter, Correlation Analysis in Chemistry: Recent Advances, Plenum, NY, p. 357 (1978).
8. A.M. Vos, K.H. L. Nulens, F. De Proft, R.A. Schoonheydt and J.C.P. Geerlings, *J. Phys. Chem.*, **106**, 2026 (2002).
9. HyperCube HyperChem, Release 7 for Windows, 7.0 Edn.; HyperCube, Ed. (2002).
10. Spartan'02 Windows, Wavefunctio, Inc. Irvine, CA 92612 USA (2001).

(*Received*: 30 December 2004; *Accepted*: 9 May 2006) AJC-4907