Polarization-Corrected Electrostatic Potentials of Aromatic Compounds

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Abstract: The electrostatic potentials (EPS) corrected for polarization (TPS) of the aromatic compounds benzene, aniline, chlorobenzene, nitrobenzene, phenol, benzamide, and *N*-phenylacetamide have been calculated at the *ab initio* SCF level within three basis sets: 6-31G**, MINI-1, and STO-3G. For chlorobenzene in its MINI-1-optimized geometry, the calculation was also performed within MINI-1**. By reference to 6-31G**, the MINI-1-computed EP is much more satisfactory than the STO-3G-computed EP, whereas the MINI-1 and STO-3G basis sets give very similar total potentials corrected for polarization (TPs). The MINI-1** basis set appears to be miscalibrated for computing EPs. It provides qualitative results that differ from those obtained with the 6-31G** basis set. The EP has a negative well above the middle of the benzene ring, while the TP exhibits a negative crown just above the benzene carbon atoms, where electrophilic attack takes place. The TP calculated for the interaction of nitrobenzene with a hydride ion instead of a proton allowed analyzation of the effects of polarization on the positive EP above the N–C bond.

Introduction

In the density functional theory framework,[1] the various forms of the Fukui function $f(r)$ can provide the regions favorable for nucleophilic, electrophilic, and radical attack.[2,3]

Independently, in the usual LCAO–MO approach, the electrostatic potential (EP) is very often considered as a powerful tool in the qualitative study of the reactivity of molecules.[4–15] In previous studies and if one excepts the use of semiempirical methods,[16] the EPs of most aromatic compounds were computed at the *ab initio* SCF level within a minimal basis set of the STO-nG series.[9–13]

Furthermore, it has already been stated that the polarization term[15,17–22] and even the charge-transfer term[22] should be added to the EP in order to obtain the correct classification of molecule reaction sites. Nevertheless, the polarization correction was rarely made[23] on aromatic compounds.

Moreover, it has already been pointed out that the minimal STO-3G basis set performed poorly[24] for the calculation of the interaction energy components compared with those of the double-ζ or even the minimal MINI-1[25] basis sets.

The aim of the present work is 2-fold: to compare, for the first time, the efficiency of the minimal basis set MINI-1 with those of STO-3G and 6-31G** in the calculation of the EP and to emphasize the importance of the polarization correction (PL) on the EP. To the authors knowledge, EP + PL has never been used to determine the nucleophilic attack sites of a molecule and the path leading to the carbon to be substituted in the electrophilic attack was not as apparent when EP was considered alone.

Informatic Tools. The calculations were performed on a FPS264 processor (38 Mflops) attached to a VAX-4200. Geometry was optimized with GAUSSIAN86-88.[26] The potential maps were determined with a FPS264 adaptation of links 100, 301, 302, and 604[27] of GAUSSIAN70 for EPs without 3d atomic orbtials and an implementation of GAUSSIAN76[28] including MEPHISTO[29] for EPs with 3d atomic orbitals and for TPs in all cases.

(1) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(2) Langenaeker, W.; De Decker, M.; Geerlings, P. *THEOCHEM* **1990**, *207*, 115.
(3) Langenaeker, W.; Demel, K.; Geerlings, P. *THEOCHEM* **1991**, *234*, 329.
(4) Bonaccorsi, R.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1970**, *52*, 5270.
(5) Goursot, A.; Fajula, F.; Daul, C.; Weber, J. *J. Phys. Chem.* **1988**, *92*, 4456.
(6) Murray, J. S.; Politzer, P. *Chem. Phys. Lett.* **1988**, *152*, 364.
(7) Truhlar, D. G. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981; p 85.
(8) Weinstein, H.; Osman, R.; Green, J. P.; Topiol, S. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981; p 309.
(9) Politzer, P.; Abrahmsen, L.; Sjoberg, P. *J. Am. Chem. Soc.* **1984**, *106*, 855.
(10) Politzer, P.; Bar-Adon, R. *J. Phys. Chem.* **1987**, *91*, 2069.
(11) Murray, J. S.; Evans, P.; Politzer, P. *Int. J. Quant. Chem.* **1990**, *37*, 271.
(12) Murray, J. S.; Lane, P.; Politzer, P.; Bolduc, P. R. *Chem. Phys. Lett.* **1990**, *168*, 135.
(13) Murray, J. S.; Ranganathan. S.; Politzer, P. *J. Org. Chem.* **1991**, *56*, 3734.
(14) Sanz, F.; Manaut, F.; Jose, J.; Segura, J.; Carbo, M.; De la Torre, R. *J. Mol. Struct. (THEOCHEM)* **1988**, *170*, 171.
(15) Tomasi, J. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981; p 257.
(16) Culberson, J. C.; Zerner, M. C. *Chem. Phys. Lett.* **1985**, *122*, 436.
(17) Bartlett, R. J.; Weinstein, H. *Chem. Phys. Lett.* **1975**, *30*, 441.
(18) Bonaccorsi, R.; Scrocco, E.; Tomasi, J. *Theor. Chim. Acta* **1976**, *43*, 63.
(19) Truhlar, D. G.; Dixon, D. A.; Eades, R. A. *J. Phys. B* **1979**, *12*, 1913.
(20) Douglass, C. H., Jr.; Weil, D. A.; Charlier, P. A.; Eades, R. A.; Truhlar, D. G.; Dixon, D. A. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981; p 173.
(21) Dehareng, D.; Dive, G.; Ghuysen, J. M. *Theor. Chim. Acta* **1991**, *79*, 141.
(22) Moriishi, H.; Kikuchi, O.; Suzuki, K.; Klopman, G. *Theor. Chim. Acta* **1984**, *64*, 319.
(23) Dive, G.; Dehareng, D. *Int. J. Quant. Chem.* **1993**, *46*, 127.
(24) Alagona, G.; Ghio, C.; Cammi, R.; Tomasi, J. *Int. J. Quant. Chem.* **1987**, *32*, 207.
(25) Tatewaki, H.; Huzinaga, S. *J. Comput. Chem.* **1980**, *1*, 205. Sakai, Y.; Tatewaki, H.; Huzinaga, S. *J. Comput. Chem.* **1981**, *2*, 100. Sakai, Y.; Tatewaki, H.; Huzinaga, S. *J. Comput. Chem.* **1981**, *2*, 108.
(26) GAUSSIAN 86: Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fluder, E. M.; Topiol, S.; Pople, J. A., Carnegie-Mellon Quantum Chemistry Publishing Unit, Carnegie-Mellon University, Pittsburgh, PA 15213.
(27) Peeters, D.; Sana, M. DENPOT, University of Louvain, Louvain-la-Neuve, Belgium, Q.C.P.E. 360, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN 47405.
(28) GAUSSIAN76, Q.C.P.E. 368, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN 47405.

0002-7863/93/1515-6877$04.00/0

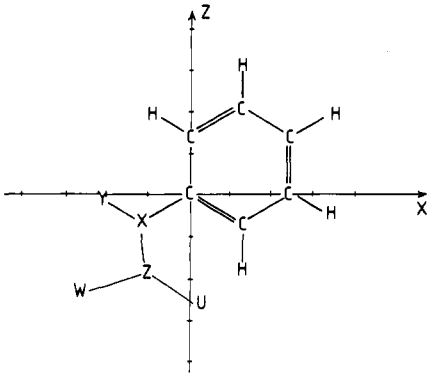

Figure 1. Schematic representation of the studied compounds in their reference frame. Aniline and nitrobenzene: X = N; Y = Z = H and O, respectively; no U or W. Chlorobenzene: no Y, Z, U, or W; X = Cl. Phenol: X = 0; Y = H; no Z, U, or W. Benzamide: X = C; Y = O; Z = N; U = W = H. *N*-Phenylacetamide: X = N; Y = H; Z = C; U = O; W = CH_3.

Theoretical Framework. A charge distribution creates an electrostatic potential $V(r)$ around itself. In the case of a molecular system, it is expressed without approximation by

$$V(r) = \sum_{A} Z_A/|\vec{R}_A - \vec{r}| - \int dr' \rho(r')/|\vec{r}' - \vec{r}| \qquad (1)$$

where Z_A is the charge of nucleus A and $\rho(r')$ is the electronic density function of the molecule.

Equation 1 expresses the electrostatic interaction energy between the charge distribution and a proton. Its quantum chemistry expression is written as

$$V(r) = \sum_{\mu}\sum_{\nu} D_{\mu\nu} \int dr' \chi_\mu(\vec{r}') \frac{1}{|\vec{r}' - \vec{r}|} \chi_\nu(\vec{r}') + \sum_{A} Z_A/|\vec{R}_A - \vec{r}| \qquad (2)$$

where $D_{\mu\nu}$ are the density matrix elements in the basis of the $\chi_\mu(r')$ atomic orbitals (AOs).

When the isolated charge distribution is perturbed by an external charge Q, polarization takes place and a correction term, V_{PL}, must be introduced. In the perturbation theory framework applied to the SCF approximation,[29,30] V_{PL} is written as

$$V_{PL}(r) = Q^2 \sum_{i}^{occ}\sum_{a}^{vir} (\epsilon_i - \epsilon_a)^{-1} \times \left[\sum_{\mu}\sum_{\nu} c_{\mu i} c_{\nu a} \int dr' \chi_\mu(\vec{r}') \frac{1}{|\vec{r}' - \vec{r}|} \chi_\nu(\vec{r}')\right]^2 \qquad (3)$$

where ϵ_i and $c_{\mu i}$ are the MO eigenvalues and eigenvectors in the basis of the $\chi_\mu(r)$ AO.

It thus follows that the total corrected potential (TP) is

$$TP = V(r) + V_{PL}(r) \qquad (4)$$

and that, in cases where the charge distribution interacts with a nucleophilic hydride,[23] the total interaction energy (TEH) is

$$TEH = -V(r) + V_{PL}(r) \qquad (5)$$

As described below, electrophilic attacks on benzene, aniline, chlorobenzene, nitrobenzene, phenol, benzamide, and *N*-phenylacetamide (Figure 1) have been studied in terms of EP and TP. The nucleophilic attack of nitrobenzene, whose positive EP has a maximum on the N–C bond, has been studied in terms of TEH.

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(30) Allen, L. C. *Phys. Rev.* **1960**, *118*, 167.

Table I. EP and TP Minimum Well Values (kcal/mol) and Positions (Å) by Reference to Figure 1, within the 6-31G** Basis Set[a]

molecule	value	X	Y	Z	location
	EP				
benzene	−19.80	0.8	±1.6	1.2	AIR
aniline	−25.80	−1.2	±1.6	−0.8	AN
	−26.83	2.0	±1.6	1.2	AIRp
	−25.62	1.6	±1.6	0.0	AIRo-m
	−25.34	0.8	±1.6	1.2	AIRo-m
chlorobenzene	−17.40	−1.6	±1.6	−1.6	ACl
	−11.71	1.6	±2.0	1.2	AIRp-m
nitrobenzene	−48.80	−2.4	0.0	−2.4	NO
	−2.14	2.0	±2.0	0.4	AIRm-p
	−2.11	1.2	±2.0	1.6	AIRm
phenol (OH in plane)	−45.15	−1.2	0.0	−2.0	NO
	−19.70	2.0	±1.6	1.2	AIRp
	−19.20	1.6	±1.6	0.0	AIRo-m
phenol (OH perpendicular)	−50.50	−2.0	−0.8	−0.4	NO
	−49.78	−1.2	−0.8	−1.6	NO
	−19.05	2.0	−1.6	0.8	AIRp
	−18.80	0.8	−2.0	1.2	AIRo–m
benzamide	−63.34	−3.6	0.0	0.4	NO
	−60.30	−2.8	0.0	1.2	NO
	−13.49	0.8	±2.0	1.6	AIRo–m
N–phenylacetamide	−60.39	−0.8	0.0	−4.0	NO
	−20.23	1.6	±1.6	0.0	AIRo–m
	−20.22	2.0	±1.6	0.8	AIRp
	TP				
benzene	−92.50	1.2	±1.2	2.0	AIR
aniline	−97.92	−1.2	±1.2	−0.8	AN
	−106.90	2.4	±1.2	1.6	P
	−105.83	0.0	±1.2	1.2	O
chlorobenzene	−53.03	−2.0	±1.2	−0.4	ACl
	−52.83	−1.2	±1.2	−1.6	ACl
	−85.02	2.4	±1.2	1.2	P
	−84.83	0.0	±1.2	1.2	O
	−84.68	1.2	±1.2	−0.8	O
	−83.80	1.2	±1.2	2.0	M
	−83.55	2.4	±1.2	0.0	M
nitrobenzene	−126.22	−2.0	0.0	−2.4	NO
	−74.06	1.2	±1.2	2.0	M
	−73.88	2.4	±1.2	0.0	M
	−70.70	2.4	±1.2	1.2	P
	−70.13	1.2	±1.2	−0.8	O
benzamide	−153.80	−2.4	±0.4	0.8	NO
	−151.62	−3.2	0.0	−0.4	NO
	−87.74	1.2	±1.2	2.0	M
	−86.13	2.4	±1.2	0.0	M
	−84.43	2.4	±1.2	1.2	P

[a] Abbreviations: AIRp = above the inside of the aromatic ring near the para carbon; AIRm = above the inside of the aromatic ring near the metal carbon; AIRo = above the inside of the aromatic ring near the ortho carbon; P = above the para carbon; O = above the ortho carbon; M = above the meta carbon; NO = near the oxygen; AN = above the nitrogen; ACl = above the chlorine.

Computations and Basis Sets. The geometries of the compounds were optimized at the *ab initio* SCF level within the 6-31G**, MINI-1, and STO-3G basis sets. All the molecules were frozen planar. The EP maps were computed within the same basis sets. The TP maps were calculated at the MINI-1 level, and some of them were compared with those calculated at the 6-31G** and STO-3G levels. With chlorobenzene in its MINI-1-optimized geometry, the calculation was also performed within the MINI-1** basis set.

In the cases of aniline, benzamide, and *N*-phenylacetamide, a "homemade" MINI-1′ basis set[31] was used in which the recalibrated 2s and 2p nitrogen scaling factors provide an optimized planar formamide.

The conformations of phenol were optimized with the OH function within and perpendicular to the benzene plane, respectively.

(31) Dive, G.; Dehareng, D.; Ghuysen, J. M. *Theor. Chim. Acta* **1993**, accepted for publication.

Table II. EP and TP Minimum Well Values (kcal/mol) and Positions (Å) by Reference to Figure 1, within the MINI-1 (or MINI-1′) Basis Set[a,b]

molecule	value	X	Y	Z	location
	EP				
benzene	−18.10	1.6	±1.6	0.8	AIR
aniline	−29.11	−1.2	±1.2	−0.8	AN
	−23.36	1.6	±1.6	1.2	AIRp
chlorobenzene	−17.60	−2.4	±1.6	−0.8	ACl
	−9.09	1.6	±1.6	0.8	AIRp-m
MINI-1**	−16.89	−1.6	±1.6	−1.6	ACl
	−16.70	−2.0	±1.6	−0.4	ACl
	−18.08	1.2	±1.6	0.8	AIR
nitrobenzene	−51.00	−2.4	0.0	−2.4	NO
	−1.41	1.2	±2.0	1.2	AIRm
phenol (OH in plane)	−51.79	−1.2	0.0	−2.0	NO
	−16.87	2.0	±1.6	0.8	AIRp
	−16.83	1.6	±1.6	0.0	AIRo-m
phenol (OH perpendicular)	−55.78	−2.0	−0.8	−0.4	NO
	−53.76	−1.2	−0.8	−1.6	NO
	−17.90	0.8	−1.6	0.8	AIRo-m
benzamide	−59.37	−3.6	0.0	0.0	NO
	−12.80	1.2	±1.6	1.2	AIRm
	−12.13	0.8	±1.6	0.4	AIR
N-phenylacetamide	−51.93	0.0	0.0	−4.0	NO
	−19.91	1.6	±1.6	0.0	AIRo-m
	TP				
benzene	−45.13	1.2	±1.2	−0.8	AIR
aniline	−63.76	−1.2	±1.2	−0.8	AN
	−56.77	2.4	±1.2	1.6	P
	−55.93	0.0	±1.2	1.6	O
chlorobenzene	−27.80	−2.0	±1.6	−1.2	ACl
	−38.48	0.0	±1.2	1.6	O
	−38.44	1.2	±1.2	−0.8	O
	−37.50	2.4	±1.2	1.6	P
	−36.57	2.4	±1.2	−0.4	M
MINI-1**	−54.70	−2.0	±1.2	−0.4	ACl
	−53.54	−1.6	±1.2	−1.6	ACl
	−73.58	0.4	±1.2	1.6	AIRo-m
	−72.64	2.0	±1.2	1.6	AIRm-p
nitrobenzene	−113.65	−1.6	±0.4	−2.8	NO
	−29.67	2.4	±1.2	−0.4	M
	−29.24	1.2	±1.2	2.4	M
	−29.20	0.0	±1.2	1.6	O
	−28.82	1.6	±1.2	−0.8	O
	−28.37	2.4	±1.2	1.6	P
phenol (OH in plane)	−91.67	−1.2	±0.4	−1.6	NO
	−48.22	2.4	±1.2	1.6	P
	−45.77	0.0	±1.2	1.6	O
phenol (OH perpendicular)	−98.58	−1.6	−0.8	−1.2	NO
	−48.25	1.2	−1.2	−0.8	O
	−47.83	0.0	−1.2	1.6	O
	−45.92	2.4	−1.2	1.6	P
	−43.79	2.4	−1.2	0.0	M
benzamide	−124.71	−3.2	±0.4	0.4	NO
	−41.16	1.2	±1.2	2.4	M
	−40.13	2.4	±1.2	0.0	M
	−40.46	2.4	±1.2	1.6	P
N-phenylacetamide	−116.32	0.0	±0.4	−3.6	NO
	−54.89	1.2	±1.2	−0.8	O
	−50.55	0.0	±1.2	1.6	O
	−51.81	2.4	±1.2	1.6	P

[a] For chlorobenzene, the MINI-1** values are also given. [b] For abbreviations, see Table I.

The 3D grid contained at least 17 680 points. The potential grid step size was 0.4 Å. It allowed computation of a big potential map, but it was too large to locate precisely the minimum wells. The minima are taken as the points where the potential is lower than at all the surrounding points. No further research, as for instance the gradient search proposed by Sanz *et al.*,[14] was made. Because of the step size, the minima above the aromatic ring varied by 0.5 kcal/mol at the most and the minima around the oxygen of the phenol (OH perpendicular) varied by about 2 kcal/mol. Tables I–III give the minima values and their positions by reference to the frame shown in Figure 1. In the subsequent figures, the potential isocontours are shown in planes parallel to the molecular plane and no particular orientation is chosen[14] to represent them.

Table III. EP and TP Minimum Well Values (kcal/mol) and Positions (Å) by Reference to Figure 1, within the STO-3G Basis Set[a]

molecule	value	X	Y	Z	location
	EP				
benzene	−10.18	0.8	±1.6	0.8	AIR
aniline	−30.94	−1.2	±1.2	−0.8	AN
	−15.33	1.6	±1.6	1.2	AIRm-p
chlorobenzene	−24.53	−2.4	±1.2	−0.4	ACl
nitrobenzene	−52.05	−2.4	0.0	−2.4	NO
phenol (OH in plane)	−51.84	−1.2	±0.4	−1.6	NO
	−9.29	2.0	±1.6	0.8	AIRp
phenol (OH perpendicular)	−57.77	−1.6	−0.8	−1.2	NO
	−9.44	1.2	−1.6	0.0	AIRo
benzamide	−58.47	−3.2	0.0	0.8	NO
	−5.91	0.8	±1.6	1.2	AIRo-m
N-phenylacetamide	−56.52	−0.4	0.0	−4.0	NO
	−12.04	1.6	±1.6	0.0	AIRo-m
	TP				
benzene	−48.17	0.0	±1.2	0.0	AIR
aniline	−70.25	−1.2	±0.8	−0.8	AN
	−59.36	2.4	±1.2	1.6	P
	−58.04	0.0	±1.2	1.6	O
	−52.45	2.4	±1.2	0.0	M
nitrobenzene	−137.01	−1.2	±0.8	−2.4	NO
	−134.25	−3.2	±0.4	0.0	NO
	−33.14	2.4	±1.2	0.0	M
	−32.90	1.2	±1.2	2.0	M
	−32.90	1.2	±1.2	−0.8	O
	−31.57	2.4	±1.2	1.2	P

[a] For abbreviations, see Table I.

Results and Discussion

Effects of the Basis Sets on EP and TP. By reference to the 6-31G** basis set, STO-3G largely underestimates the EP above the aromatic ring and even fails to find any negative potential in this environment in the case of chlorobenzene and nitrobenzene. The 6-31G** − STO-3G differences range from −7.5 to −12 kcal/mol (Tables I and III). STO-3G also overestimates the EP around the heteroatoms of all the compounds studied.

Though MINI-1 underestimates the EP above the aromatic ring and overestimates the EP around the heteroatoms, and therefore behaves as a minimal basis set, the differences by reference to 6-31G** do not exceed 3.5 kcal/mol (Tables I and II). Furthermore, chlorobenzene and nitrobenzene have a negative potential well above the aromatic ring. Hence MINI-1 is clearly a much better basis set for computing EP than STO-3G (Figure 2).

Note that the MINI-1** basis set (Table II) largely overestimates the EP above the aromatic ring, which is even larger than the EP around the chlorine atom.

Regarding the TP computations, both STO-3G and MINI-1 largely underestimate the polarization correction. However, STO-3G is somewhat better at computing the absolute values (Table III) and MINI-1 is somewhat better at distinguishing the ortho, meta, and para substitutions. MINI-1** gives a large polarization correction, but it generates wells that are located at the middle of the bonds, and not above the carbon atoms. MINI-1** seems not to be suitable for the TP calculation of chlorobenzene at the MINI-1 geometry.

Finally, a comparison of the minima found in benzene and in the other molecules X under study, expressed by $\delta EP = EP^{min}_{benzene} - EP^{min}_{X}$ or $\delta TP = TP^{min}_{benzene} - TP^{min}_{X}$ (Table IV), shows that these differences are not very basis set dependent. The variations are about 1 kcal/mol for the EP and 3 kcal/mol or less for the TP.

Polarization Effects. The polarization significantly increases the negative well by 5–7 kcal/mol from benzene to phenol, aniline,

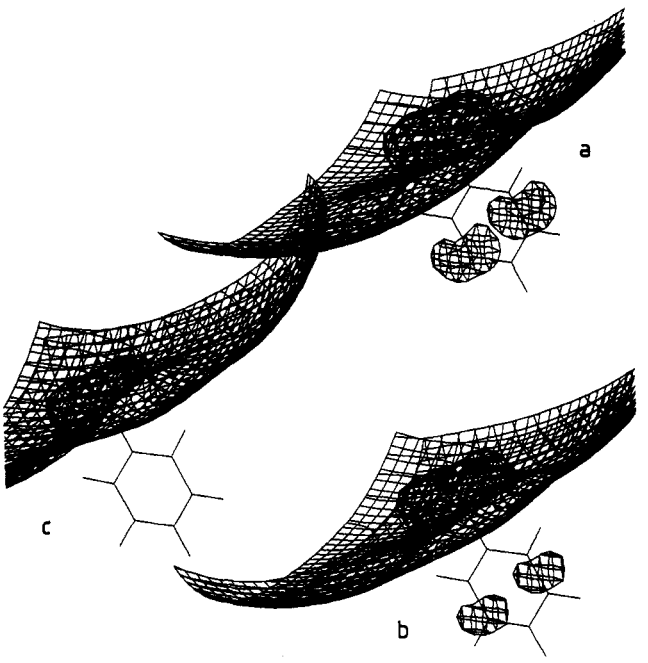

Figure 2. 3D EP maps at −1 kcal/mol for nitrobenzene within (a) 6-31G**, (b) MINI-1, and (c) STO-3G.

Table IV. Potential Differences (kcal/mol) between the Minimum Found in Benzene and the Minimums above the Aromatic Rings Found in Molecules X, as a Function of the Basis Set

X	basis set	EP difference	TP difference
aniline	6-31G**	7.03	14.40
	MINI-1	5.26	11.64
	STO-3G	5.15	11.19
chlorobenzene	6-31G**	−8.09	−7.48
	MINI-1	−9.01	−6.65
	STO-3G	>−10.18	
nitrobenzene	6-31G**	−17.66	−18.44
	MINI-1	−16.69	−15.46
	STO-3G	>−10.18	
phenol (OH in plane)	6-31G**	−0.10	
	MINI-1	−1.23	3.09
	STO-3G	−0.89	
phenol (OH perpendicular)	6-31G**	−0.75	
	MINI-1	−0.20	3.12
	STO-3G	−0.74	
benzamide	6-31G**	−6.31	−4.76
	MINI-1	−5.30	−3.97
	STO-3G	−4.27	
N-phenylacetamide	6-31G**	0.43	
	MINI-1	1.81	9.76
	STO-3G	1.86	

and *N*-phenylacetamide (in 6-31G** and MINI-1), but it varies only slightly from benzene to chlorobenzene, nitrobenzene, and benzamide (Table V). This feature is probably related to the resonance-donating effect characterized by the negative σ_R of aniline, phenol, and *N*-phenylacetamide.[6,9]

The amide–$CONH_2$ function is characterized by a slightly positive σ_R (0.08)[6,32] and a positive σ_I (0.28) that express the inductive electron attraction.[6,9] Consistently, both the EP and TP negative wells located above the aromatic ring decrease from benzene to benzamide. However, upon polarization by the electrophile, the attractive character of $-CONH_2$ is slightly decreased because of a ≈1 kcal/mol resonant electronic increase occurring over the aromatic ring [from −5.3 (EP) to −3.97 (TP) in MINI-1; Table IV]. This might explain the very low σ_R value.

Similarly, the very high attractive character of nitrobenzene is slightly enhanced in 6-31G** (−17.66 to −18.44; Table IV) and slightly decreased in MINI-1 (−16.69 to −15.45; Table IV). These small variations (≈1 kcal/mol) due to polarization can be related to the small value of σ_R (0.10) for nitrobenzene.

Given the lack of preciseness of the 3D grid, one may compare the pair (σ_R, σ_I) and the pair (δEP, δTP) for a given substitution (Table IV).

-If both δEP and δTP are positive, the σ_R is negative and $|\sigma_R| \gg \sigma_I$.

-If δEP < 0 and δTP > 0, $\sigma_I > 0$ (≈0.3), $\sigma_R < 0$, and $|\sigma_R| \approx \sigma_I$.

-If both δEP and δTP are negative, $\sigma_I \gg 0$ (≥0.45); if δTP is significantly less negative than δEP, $\sigma_R < 0$; if δTP ≈ δEP, σ_R has a low (<0.2) positive or negative value and $|\sigma_R| \ll \sigma_I$.

A statistical analysis was performed on the data from Tables IV and V. The correlation matrix between σ_I, σ_R, δEP, δTP, and δPL, calculated with either 6 points or 4 points (δTP, δPL in 6-31G**), is presented in Table VI. The linear regressions δEP (σ_I) and δTP (σ_R) calculated for the two basis sets in the same group are shown in Figure 3. Although the number of cases is limited to 6 or even to 4, the statistical analysis provides meaningful relationships. From Table VI, the polarization component δPL is better correlated to σ_R than to σ_I, whereas δEP is more closely related to σ_I than to σ_R. Nevertheless, the two inductive and resonant effects are undoubtedly related as well as are δEP and δTP or δPL.

Furthermore, it is evident from Table VI and Figure 3 that the MINI-1 results are very close to the 6-31G** ones.

The 2D EP maps above the aromatic ring and the absolute positions of the minima (Tables I–III) show a slight preference for electrophilic attack on the meta, ortho, or para position depending on the compound, but the absolute minimum always lies above the aromatic ring. Conversely, the TP negative wells appear as funnels above the carbon atom that is susceptible to meta, ortho, or para substitution (Figure 4). The polarization by the electrophile drives the reagent toward a particular carbon atom, not above the aromatic ring.

The nitroaromatics have gained much attention[9,10,12] because they bear an EP maximum which is located approximately over

Table V. Polarization Components of TP (kcal/mol) for the Seven Molecules, within 6-31G** and MINI-1, Evaluated as the Difference between TP and EP at Their Minima above the Aromatic Ring

molecule	basis set	polarization
benzene	6-31G**	−72.70
	MINI-1	−27.03
aniline	6-31G**	−80.07
	MINI-1	−33.41
chlorobenzene	6-31G**	−73.31
	MINI-1	−29.39
nitrobenzene	6-31G*	−71.92
	MINI-1	−28.26
phenol (OH in plane)	MINI-1	−31.35
phenol (OH perpendicular)	MINI-1	−30.35
benzamide	6-31G**	−74.25
	MINI-1	−28.36
N-phenylacetamide	MINI-1	−34.98

Table VI. Correlation Matrices for σ_I, σ_R[6,32], δEP, δTP, and δPL in 6-31G** and MINI-1[a,b]

	σ_I	σ_R	δEP1	δTP1	δPL1	δEP2	δTP2	δPL2
σ_I	1.0							
σ_R	0.707	1.0						
δEP1	−0.935	−0.896	1.0					
δTP1	−0.919	−0.890	0.998	1.0				
δPL1	−0.857	−0.895	0.966	0.981	1.0			
δEP2	−0.937	−0.856	0.989	0.993	0.961	1.0		
δTP2	−0.880	−0.883	0.972	0.999	0.982	0.989	1.0	
δPL2	−0.608	−0.855	0.804	0.918	0.953	0.838	0.909	1.0

[a] See Tables IV and V. [b] Abbreviations: δXP1 corresponds to δXP in 6-31G** and δXP2 corresponds to δXP in MINI-1 with XP = EP, TP, or PL.

(32) Charton, M.; In *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; Wiley: New York, 1981; Vol. 13, p 119. *Ibid.* 1987; Vol. 16, p 287.

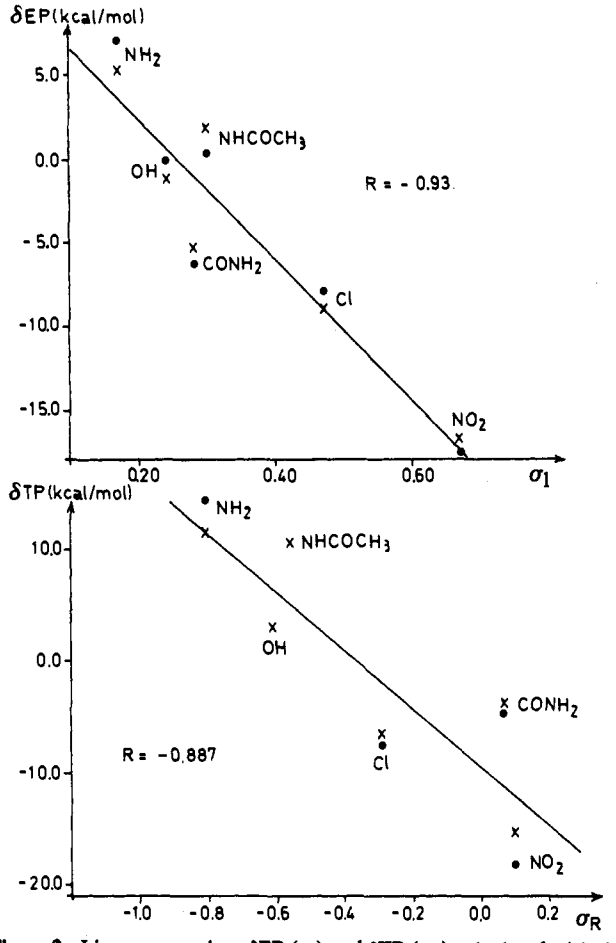

Figure 3. Linear regressions δEP (σ_I) and δTP (σ_R) calculated with the two basis sets in the group.

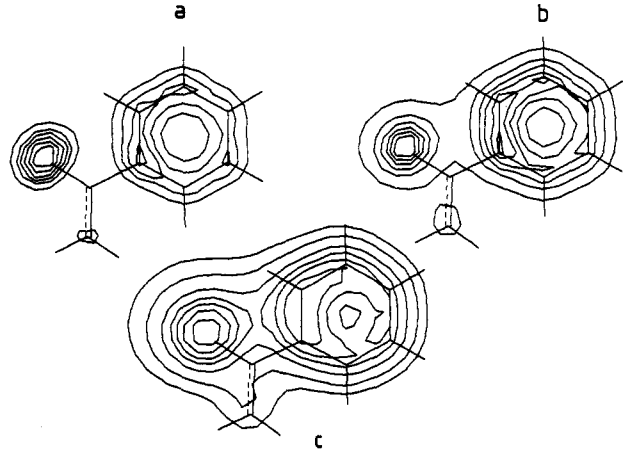

Figure 4. 2D TP maps for benzamide within the 6-31G** basis set in the plane (a) Y = 1.2 Å, with contours at −100, −95, −90, −85, −80, and −70 kcal/mol; (b) Y = 1.6 Å, with contours at −62, −60, −58, −55, −50, and −40 kcal/mol; (c) Y = 2 Å, with contours at −39, −37, −35, −33, −30, −25, and −20 kcal/mol.

the midpoint of the C–N bond. This property is peculiar because a positive EP is usually found over the position of the nuclei, not over the bonds. It indicates a possible pathway for nucleophilic attack, and the $EP_{mid,max}$ height[12] has been related to the "impact sensitivity" of these compounds. In the present work, the nucleophilic attack of nitrobenzene was studied via the negative (attractive) channels of the TEH (eq 5) (Figure 5), not via the positive EP. Clearly this EP feature is reinforced by the TEH shape, and the MINI-1 and 6-31G** potentials behave similarly at least at a qualitative level. As shown by Figure 5, the channel progressively slips from the middle of the C–N bond toward the

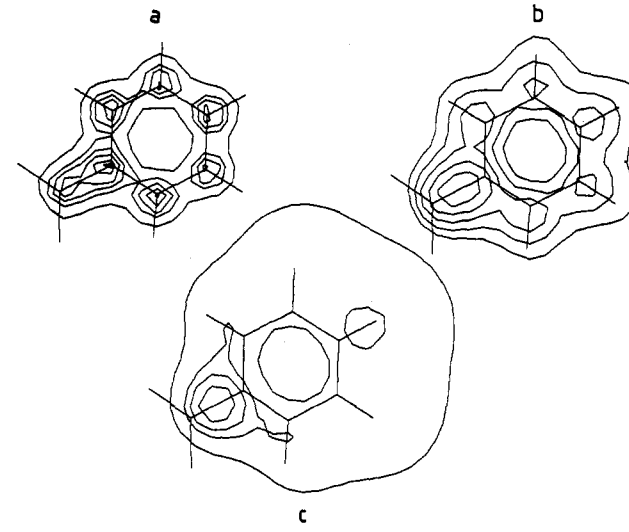

Figure 5. 2D TEH map for nitrobenzene within MINI-1 in the plane (a) Y = 1.2 Å, with contours at −115, −110, −100, −90, −80, and −60 kcal/mol; (b) Y = 1.6 Å, with contours at −40, −35, −30, −25, and −20 kcal/mol; (c) Y = 2 Å, with contours at −19, −17, −15, and −10 kcal/mol.

susceptible carbon atom. Once more, the reactive polarization opens the route to the right carbon that is to be substituted.

Donating/Attracting Character of the Benzene Substituent. Among the molecules studied, and as is derived from the δEP differences by reference to benzene (Table IV), aniline and *N*-phenylacetamide are the only ones which have strong and weak electron-donating substituents, respectively. This characteristic is enhanced by the polarization which forces the substituent to resonantly increase the electronic density above the aromatic ring, as can be estimated by comparing their respective δTP and polarization differences with the benzene values δPL (Tables IV and V) to the δEP.

Except for the two phenol conformations, the other molecules have attracting substituents, the stronger being $-NO_2$. Again, a polarization resonant electronic "feedback" is observed since, in most cases, the absolute TP difference with benzene is smaller than the EP difference. Phenol is particular. The OH function is a weak attractor on the basis of EP and a weak donor on the basis of TP.

As a result of its polarization effect, the electrophile induces a variation in the electronic density above the aromatic carbon atoms with marked preferences for the ortho, meta, or para position according to the nature of the substituent. In the cases studied, polarization always causes an increased electronic density, except in the case of nitrobenzene within the 6-31G** basis set.

Specificity of Electrophilic Attack. In terms of the TP, whose preference for ortho or para attack is basis set dependent (Table VII), the difference between these two positions is small, about 1 kcal/mol.

The attacks on the ortho or para position seem to be equivalent in the cases of aniline, chlorobenzene, and nitrobenzene. The para position is preferred for phenol (OH in plane) and the ortho position for phenol (OH perpendicular) and *N*-phenylacetamide. The resonant effect is favored for phenol (OH in plane) which is more stable than the other conformer (OH perpendicular) by ≈3–4 kcal/mol, as a result of a better disposition of the oxygen lone pairs that can interact with the aromatic ring. The resonant effect does not favor the para position relative to the ortho position, but the ortho position probably feels more strongly the attraction exerted by OH. In the case of phenol (OH perpendicular), merging of the oxygen lone pair's negative wells and the ortho wells induces a preference for the two equivalent ortho positions. This also applies to *N*-phenylacetamide. The well on the carbonyl oxygen tends to merge with the well of one of the ortho positions,

Table VII. TP Differences (kcal/mol) between the ortho, para, and meta minima as a Function of the Basis Set[a]

molecule	o-m		o-p[b]		m-p[b]	
	6-31G**	MINI-1	6-31G**	MINI-1	6-31G**	MINI-1
aniline			1.06	0.85		
chlorobenzene	−1.03	−1.91	0.19	−0.98	1.22	0.93
nitrobenzene	3.93	0.47	0.57	−0.83	−3.36	−1.30
phenol (OH in plane)				2.45		
phenol (OH perpendicular)		−4.46		−2.34		2.12
benzamide					−3.31	−0.70
N-phenylacetamide				−3.09		

[a] Abbreviations: o = ortho position; m = meta position; p = para position. [b] Position difference.

which explains the ≈4 kcal/mol difference between the two ortho positions (Table II).

The ortho/para position preference for substitution *versus* the meta position is due to the resonant effect. Though an induction effect occurs in chlorobenzene, the ortho/para positions are still preferred (Table IV).

The distinction between meta and ortho/para is the same whatever the basis set used. The difference in meta *versus* (ortho/para) ranges from ≈1 to ≈4 kcal/mol and depends on the basis set used.

The electrophilic substitution at the meta position is favored with nitrobenzene and benzamide. Clearly the inductive electron-attracting character of the substituents is responsible for the meta specificity.

Summary

The derivation of reaction sites in a molecule is usually performed by the calculation of the EP. However, this property only shows a general tendency and is obviously inadequate in some cases, as for instance the determination of nucleophilic reaction sites.

This work emphasizes the usefulness of using the TP instead of the EP to clearly point out the specific reaction sites of a molecule. While the EP alone locates electrophilic attack above the aromatic ring, inclusion of the polarization to the EP, giving rise to the TP, induces the formation of funnels which drive the reagent to the specific carbon atom. By generating the polarization, the electrophile reagent induces a resonant electronic "feedback" from the substituent to the aromatic ring. The specificity of the electrophilic attack is accounted for by the TP and can be explained by the balance between the resonance-donating and inductive-attracting character of the substituent.

The TP and EP should be calculated at the best handleable accuracy level. This work presents, for the first time, the very high quality of the minimal MINI-1 basis set, compared with the large 6-31G** one, for the derivation of EP and TP. The MINI-1** basis set, however, is miscalibrated for this type of calculation.

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