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Computational Study of the Reactivity of *N*-Phenylacetamides in the Alkaline Hydrolysis Reaction

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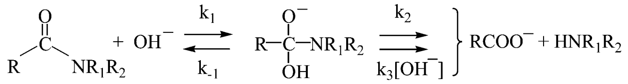
A number of molecular quantities were tested as reactivity indexes for the alkaline hydrolysis reaction of a series of 15 *N*-phenylacetamides para substituted in the aromatic ring. The Hammett σ constants and the shifts of carbonyl stretching mode frequencies correlate satisfactorily with the predicted Hartree−Frock (HF)/6-31+G(d) and density functional theory B3LYP/6-31+G(d,p) energy changes for the rate-determining stage of the reaction, namely, the addition of a hydroxide ion and formation of a tetrahedral intermediate. Natural bond orbital atomic charges at the carbonyl carbon atom, the site of the nucleophilic attack, also offer a satisfactory basis for discussing the reactivity of the carbonyl compounds studied. The electrophilicity index ω describes well the overall tendency of the changing reactivity of the studied compounds. A quantitative description of the reactivity of the studied amides in the reaction considered is provided by the theoretically estimated electrostatic potential at the carbonyl carbon atom. The linear regression correlation coefficients for the connection between the energy changes for the rate-determining stage of the amide hydrolysis and the electrostatic potential at the carbonyl carbon atom are over 0.99 with both levels of theory employed. The electrostatic potential at the nuclei is recommended as an accurate local reactivity index.

1. Introduction

The present computational study aims at describing quantitatively the reactivity of a series of *N*-arylacetamides, $R-C_6H_4-NHCOCH_3$, with respect the alkaline hydrolysis reaction. The hydrolysis of different types of amides has been the subject of numerous experimental[1−12] and, in more recent times, computational studies.[13−20] This interest is motivated by the importance of this reaction for organic chemistry, as well as the fact that it is regarded as a model process for the cleavage of peptide bonds.[13] In their 1991 paper, Brown et al.[12a] summarized key data regarding the H_3O^+ and OH^- promoted amide hydrolysis. In the case of alkaline hydrolysis the reaction is described by the general scheme



$$RC(=O)NR_1R_2 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R-C(O^-)(OH)-NR_1R_2 \underset{k_3[OH^-]}{\overset{k_2}{\longrightarrow}} RCOO^- + HNR_1R_2$$

Experimental studies on the alkaline hydrolysis of *N*-arylacetamides (acetanilides) have produced conflicting reports regarding the rate-determining stage of the reaction as well as the kinetic order with respect to the hydroxide ion.[1,2,6,8,11] Most theoretical studies[14c,14m,19,20] on amide hydrolysis reveal that there is no energy barrier for the formation of the tetrahedral intermediate (TD) in the case of the gas-phase process. The ab initio HF/6-31+G(d) results of O'Brien and Pranata[15] showed, however, that there is a barrier for the formation of the TD if the energy of a pre-reactive complex is taken into account.

In a recent study of some of the present authors[21] the alkaline hydrolysis of *N*-phenylacetamide was reinvestigated by applying quantum mechanical computations at the RHF/6-31+G(d), B3LYP/6-31++(d,p), and QCISD/6-31++G(d,p) levels of theory. The results showed that in both the gas phase and the water solution the first stage of the reaction is rate-determining, namely, the nucleophilic addition of the hydroxide ion and formation of a TD. The rate of the reaction depends, therefore, on the interaction of a typical nucleophile (OH^-) and the positively charged carbonyl carbon atom of the amides, which is an electrophilic center. It was considered that for such reactions the electrostatic attraction forces between the local reaction centers of the reactants will be an important driving force behind the process. It is expected, therefore, that molecular parameters linked to the electron density distribution may be employed in characterizing the reactivity of amides in the alkaline hydrolysis reaction. The hydrolysis of a series of 15 para-substituted *N*-phenylacetamides was studied by applying Hartree−Fock (HF) and density functional theory (DFT) computations.

We tested a number of different molecular parameters as reactivity indexes for the alkaline hydrolysis reaction of *N*-phenylacetamides. Classical reactivity descriptors such as the Hammett σ constants[22−24] were explored. Atomic charges at the reaction center obtained according to several different density partitioning schemes were also determined and used. The applicability of the electrostatic potential at the nuclei (EPN)[25,26] as a reactivity index for this type of chemical reaction was also analyzed. EPN has been demonstrated to be an excellent reactivity index for the process of hydrogen bonding.[27−30] Li and Evans[31] emphasized that terms describing the Coulombic interaction between reactants can be employed as appropriate selectivity indexes for chemical reactions. Politzer et al.[32,33] showed that minima and maxima in the molecular surface electrostatic potential (MEP) can be successfully used in quantifying the reactivity of molecules in both nucleophilic and electrophilic reactions. It should be underlined that both MEP and EPN are accurately defined quantum mechanical quantities, fully independent of particular electron density partitioning schemes. Finally, the electrophilicity indexes of Parr et al.[34] were evaluated and tested.

The amide reactants characterized in the present study are shown in Chart 1. Para-substituted derivatives were selected

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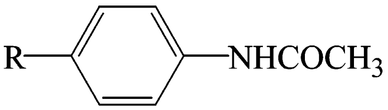
CHART 1. [a]



[a] R = H, CH_3, CH_3O, C_2H_5O, NH_2, CH_2F, Cl, COOH, NO_2, SO_2NH_2, $COCH_3$, CHO, CHF_2, CF_3, NO.

to avoid the possible influence of steric effects on the reaction. On the experimental side rate constants for the alkaline hydrolysis of seven para-substituted *N*-phenylacetamides were reported by Sorci and Macaladi.[11]

In a recent work Compodonico et al.[35] proposed theoretical electrophilicity and nucleophilicity scales derived from electronic indexes to characterize the reactivity of carbonyl compounds. The use of the MEP in describing the reactivity of some carbonyl compounds was considered by Murray et al.[32]

2. Computational Methods

2.1. Electronic Structure Computations. Ab initio and DFT computations were carried out with the Gaussian 94 and 98 program packages.[36] The theoretical research was performed at the HF/6-31+G(d)[37] and B3LYP/6-31+G(d,p)[38] levels of theory. The basis sets include diffuse functions, which are necessary for the proper description of anionic transition states (TSs).[14m] The TSs were fully optimized using HF and DFT methods by traditional TS optimization via the Berny algorithm.[39] The TS structures were also characterized by analytic computations of harmonic vibrational frequencies at the same level/basis sets. Zero-point vibrational energies were taken into account in evaluating the energies of reactants and TSs. In the cases of substituents where more than one conformer is possible for the respective para-substituted acetanilides, the computations were restricted to the lowest energy conformers. These conformers were determined from preliminary HF/3-21G calculations. The trans structure for the −CO−NH− moiety was used throughout the present study on the basis of earlier theoretical conformational analysis of acetanilides.[40]

2.2. Atomic Charges. Atomic charges are expected to serve as an appropriate reactivity index describing the reactivity of the studied molecules with respect to the nucleophilic attack by the hydroxide ion. Atomic charges according to four different partitioning methods were obtained: Mulliken charges,[41] electrostatic potential derived charges following the ChelpG[42] and MK[43] schemes, and natural bond orbital (NBO) charges.[44] It is seen that alternative schemes in evaluating atomic charges lead to quite divergent results. The performance of the different methods has been discussed recently.[45]

2.3. EPN. The molecular electrostatic potential values at the site of atoms were also evaluated. The electrostatic potential at a particular nucleus (A) is defined by eq 1 at $r = R_Y$ (radius vector of the respective nucleus) as the term at $R_Y = R_A$ is dropped out[26]

$$V_Y \equiv V(R_Y) = \sum_{A \neq Y} \frac{Z_A}{|R_Y - R_A|} - \int \frac{\rho(r')}{|R_Y - r'|} \, dr' \qquad (1)$$

In this equation, Z_A is the charge on nucleus A with radius vector R_A, $\rho(r)$ is the electronic density function of the respective molecule, and r' is a dummy integration variable. Equation 1 is written in atomic units and contains a summation over all atomic nuclei, treated as positive point charges as well as integration over the continuous distribution of the electronic charge. The molecular electrostatic potential values at each atom of the isolated monomer molecules were obtained using the Gaussian 98 set of programs.[36]

TABLE 1: Energy Change for the Rate-Determining Stage of the Alkaline Hydrolysis of *N*-Phenylacetanilides from HF/6-31+G(d) Computations and Reactivity Descriptors

substituent R	ΔE [kcal/mol]	Hammett σ constant[a]	calcd ν(C=O)[b] [cm^{-1}]	electrophilicity index ω[c] [eV]
H	−13.63	0.000	1740	1.17
CH3	−12.88	−0.170	1736	1.10
OCH2CH3	−13.62	−0.240	1735	1.13
OCH3	−13.76	−0.268	1735	1.14
NH2	−11.66	−0.660	1728	0.96
CH2F	−16.55	0.110	1745	1.25
CHO	−20.32	0.220	1754	1.37
Cl	−17.79	0.227	1744	1.25
CHF2	−18.47	0.320	1748	1.34
COOH	−19.52	0.450	1755	1.34
COCH3	−18.69	0.502	1752	1.32
CF3	−20.26	0.540	1753	1.42
SO2NH2	−22.67	0.620	1757	1.47
NO2	−24.55	0.778	1762	1.57
NO	−22.65	0.910	1759	1.41
correlation coefficient		0.941	0.975	0.974

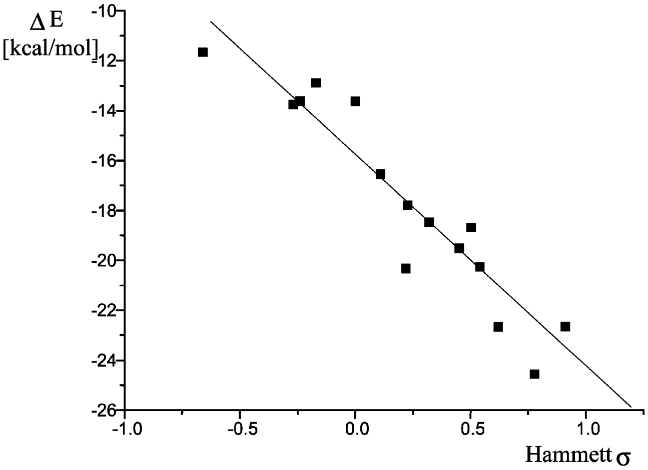
[a] From ref 24. [b] Scaling factor 0.8929 from ref 52. [c] Calculated using data for highest occupied molecular orbital and lowest unoccupied molecular orbital energies.

In previous studies from this laboratory[27−29] it was shown that the EPN can be applied as a highly accurate descriptor of the ability of molecules belonging to several different classes to form hydrogen bond complexes either as proton donors or as proton acceptors. Excellent linear relationships between theoretically estimated electrostatic potential values at nuclei, V_Y, and binding energies were found. These studies are summarized in a review.[30]

2.4. Electrophilicity Index. The global electrophilicity index was defined by Parr et al.[34] by the relationship $\omega = \mu^2/\eta$. It has been shown[46] that the electronic chemical potential μ and the global hardness η do not change significantly upon solvation. Thus, the intrinsic gas-phase values for the electrophilicity index derived from eq 1 can be used to characterize the properties of electrophilic ligands. Therefore, gas-phase values for μ and η were used to derive the electrophilicity indexes of the studied substituted arylamides. Contreras and co-workers[47−50] explored the application of the ω index approach in describing substituent effects and solvent influence on the electrophilicity of various types of compounds. A comprehensive review on electronic reactivity indexes derived within the DFT formalism was recently published by Geerling et al.[51]

3. Results and Discussion

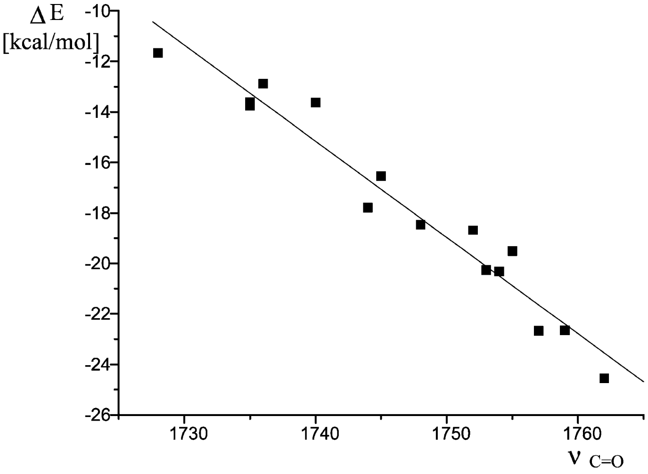
The selected series of 15 aryl amides offers a possibility to systematically follow the effect of changing the electronic structure on the energetics of the alkaline hydrolysis reaction. The influence of distant substituents in the para position in the aromatic ring was evaluated by the ab initio HF/6-31+G(d) method and by DFT computations at the B3LYP/6-31+G(d,p) level. As mentioned, in a previous study[21] it was established that the rate-determining stage of the reaction is the addition of the nucleophilic agent OH^- to the reaction center of the amide with an attack at the carbonyl carbon atom. The substituted *N*-phenylacetamides act in the conditions of this reaction as electrophiles. Because the initial attack is the rate-determining stage, it can be expected that the properties of the monomer amides in their ground state will influence significantly the



$$\Delta E = -8.69\sigma - 15.87$$

$$n = 15;\ r = 0.941;\ sd = 1.41$$

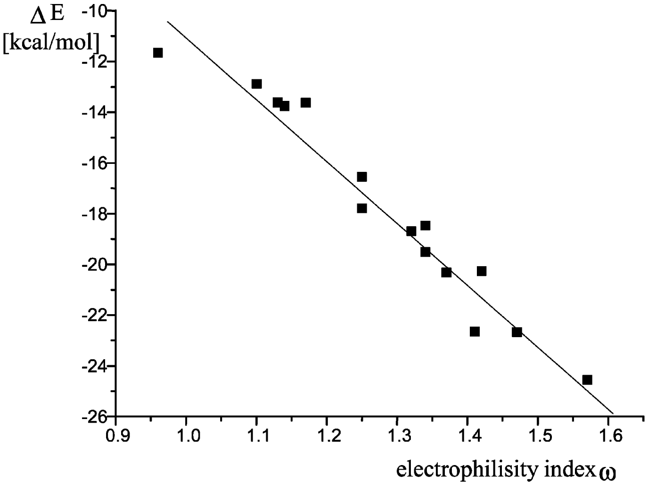
Figure 1. Plot between Δ*E* and the Hammett *σ* constants for para-substituted acetanilides.



$$\Delta E = -0.38\ \nu_{C=O} + 645.76$$

$$n = 15;\ r = 0.975;\ sd = 0.92$$

Figure 2. Plot between Δ*E* and the calculated carbonyl stretching frequencies computed at the HF/6-31+G(d) level of theory for para-substituted acetanilides.



$$\Delta E = -24.16\omega + 13.19$$

$$n = 15;\ r = 0.974;\ sd = 0.93$$

Figure 3. Plot between Δ*E* and the global electrophilicity index computed at the HF/6-31+G(d) level of theory for the para-substituted acetanilides.

TABLE 2: Atomic Charges and Electrostatic Potential at the Carbonyl Carbon Atom of Substituted *N*-Phenylacetanilides from HF/6-31+G(d) Computations

substituent	Δ*E*	q_C [e]				
R	[kcal/mol]	MPA	ChelpG	MK	NBO	V_C [au]
H	−13.63	0.8380	1.0302	1.0269	0.831 17	−14.5951
CH3	−12.88	0.8224	1.0147	1.0007	0.830 55	−14.5978
OCH2CH3	−13.62	0.8377	1.0088	1.0030	0.830 58	−14.5965
OCH3	−13.76	0.8319	0.9897	0.9996	0.830 62	−14.5959
NH2	−11.66	0.6736	1.0358	1.0027	0.829 97	−14.6041
CH2F	−16.55	0.8595	1.0175	1.0257	0.832 20	−14.5903
CHO	−20.32	0.8848	0.9973	0.9895	0.833 44	−14.5821
Cl	−17.79	0.8102	1.0097	1.0065	0.832 12	−14.5877
CHF2	−18.47	0.8681	1.0081	1.0167	0.832 95	−14.5860
COOH	−19.52	0.8399	1.0083	1.0037	0.833 28	−14.5841
COCH3	−18.69	0.8706	1.0106	1.0023	0.833 20	−14.5852
CF3	−20.26	0.8810	1.0089	1.0144	0.833 33	−14.5827
SO2NH2	−22.67	0.8909	1.0014	1.0129	0.833 81	−14.5769
NO2	−24.55	0.8801	0.9631	0.9817	0.834 48	−14.5737
NO	−22.65	0.8425	0.9213	0.8873	0.833 61	−14.5791
correlation coefficient		0.652	0.651	0.408	0.976	0.992

energetics of the interaction with the hydroxide ion. A number of different reactivity indexes were evaluated following the procedures outlined in the preceding section.

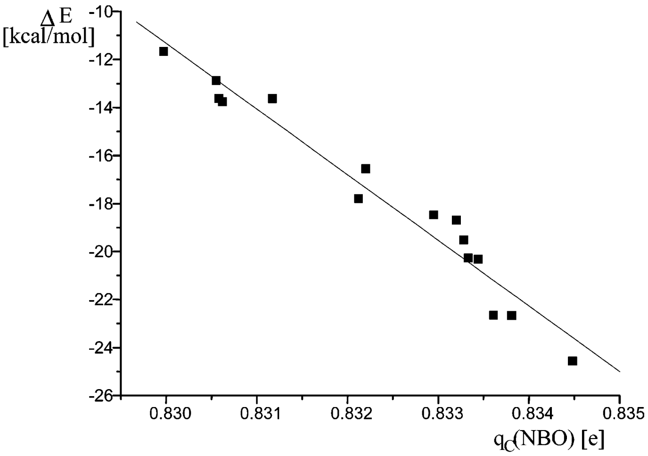
The energies of all 15 reactants and TS structures for the rate-determining stage of the reaction were fully optimized and characterized by computations of vibrational frequencies at the same level/basis sets. The respective energy changes evaluated from HF computations are presented in Table 1 together with a number of quantities that characterize the changing electronic structure of the amides under the influence of polar substituents in the aromatic ring. The quantities include the Hammet *σ* constants,[24] the computed carbonyl stretching mode frequencies, and the electrophilicity index *ω*. The linear regression correlation coefficients given in the last row of Table 1 characterize the dependencies between the theoretically estimated energy changes for the rate-determining stage of the reaction and the different reactivity parameters. In Figure 1 the plot between Δ*E* and the usual Hammett *σ* constants for para substituents is illustrated. A better linear dependence is found when Δ*E* is correlated with the carbonyl stretching frequencies (Figure 2). The dependence illustrates the usefulness of spectroscopic parameters in characterizing the changes in electronic structure and the reactivity of a given series of structurally related molecules. Figure 3 illustrates the dependence between the global electrophilicity index *ω* and the energy change for the rate-determining stage of the reaction. It is seen that quite satisfactory dependence is obtained at this level of theory ($r = 0.974$). As we will see later, however, lower correlation coefficient for the same dependency is obtained from B3LYP/6-31G+(d,p) computations.

Alternative local parameters that are expected to characterize the reactivity of the studied electrophiles were evaluated. Four types of atomic charges as well as the electrostatic potential at the carbonyl carbon atoms were theoretically determined. The Mulliken, ChelpG, MK, and NBO charges as well as the EPN values as obtained from the HF computations are presented in Table 2. The correlation coefficients for the dependencies of Δ*E* with these parameters are given in the last row of the table. It is seen that the Mulliken, ChelpG, and MK charges do not correlate well with Δ*E*. The dependence between Δ*E* and the NBO charges at the carbonyl carbon is linear (Figure 4). Finally,

TABLE 3: Energy Change for the Rate-Determining Stage of the Alkaline Hydrolysis of *N*-Phenylacetanilides from B3LYP/6-31+G(d,p) Computations and Reactivity Descriptors

substituent R	ΔE [kcal/mol]	Hammett σ constant[a]	calcd ν(C═O)[b] [cm^{-1}]	electrophilicity index ω[c] [eV]	q_C[d] [e]	V_C [au]
H	−20.31	0.000	1690	1.11	0.6782	−14.6199
CH3	−19.47	−0.170	1687	1.04	0.6767	−14.6228
OCH2CH3	−17.96	−0.240	1682	0.92	0.6744	−14.6253
OCH3	−18.16	−0.268	1682	0.94	0.6747	−14.6243
NH2	−17.29	−0.660	1680	0.87	0.6725	−14.6283
CH2F	−24.64	0.110	1693	1.35	0.6802	−14.6139
CHO	−30.01	0.220	1700	2.10	0.6829	−14.6051
Cl	−24.18	0.227	1691	1.26	0.6793	−14.6128
CHF2	−26.62	0.320	1695	1.46	0.6815	−14.6096
COOH	−28.40	0.450	1698	1.83	0.6823	−14.6085
COCH3	−27.87	0.502	1696	1.91	0.6818	−14.6089
CF3	−28.37	0.540	1697	1.56	0.6825	−14.6066
SO2NH2	−29.90	0.620	1698	1.65	0.6829	−14.6057
NO2	−34.38	0.778	1703	2.86	0.6847	−14.5978
NO	−34.73	0.910	1703	3.25	0.6845	−14.5991
correlation coefficient		0.946	0.977	0.923	0.967	0.993

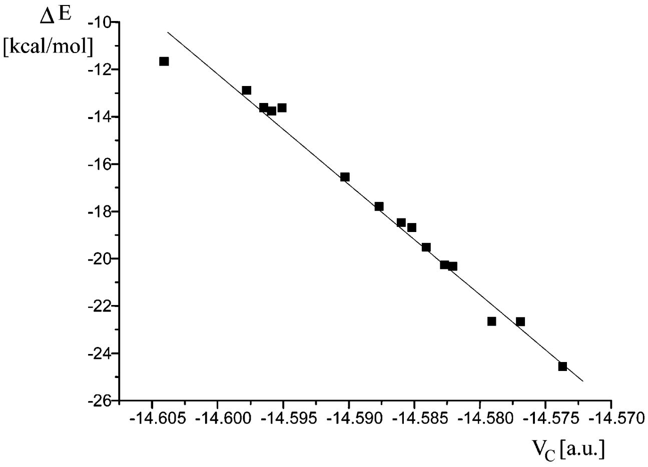
[a] From ref 24. [b] Scaling factor 0.9613 from ref 52. [c] Calculated using data for highest occupied molecular orbital and lowest unoccupied molecular orbital energies. [d] NBO atomic charge at the carbonyl carbon atom.



$$\Delta E = -2720.36\ q_C\,(\mathrm{NBO}) + 2246.50$$

$$n = 15;\ r = 0.976;\ sd = 0.90$$

Figure 4. Plot between ΔE and the NBO charges at the carbonyl carbon atom computed at the HF/6-31+G(d) level of theory for para-substituted acetanilides.



$$\Delta E = -459.85\ V_C - 6726.05$$

$$n = 15;\ r = 0.992;\ sd = 0.53$$

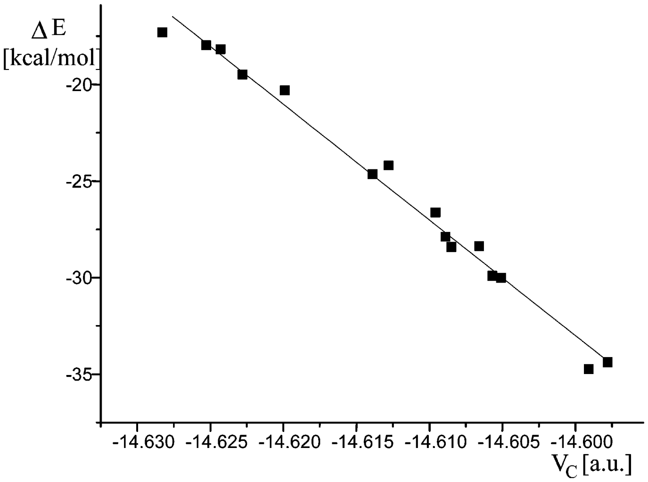
Figure 5. Plot between ΔE and the electrostatic potential at the carbonyl carbon atom computed at the HF/6-31+G(d) level of theory for para-substituted acetanilides.

it is seen (Table 2) that the electrostatic potentials at the carbonyl carbon atom (V_C) correlate excellently with the energy changes accompanying the rate-determining stage of the reaction. The dependence is shown in Figure 5. It is gratifying to find that an easily accessible electronic parameter describes in quantitative terms the reactivity of the studied aryl amides in the alkaline hydrolysis reaction. As already mentioned, EPN are rigorously defined quantities obtained from the electron density function (eq 1). These parameters reflect accurately the effect of the variations in electron density from molecule to molecule on the properties of the reaction center. Thus, EPN values do not bear the deficiencies of the different partitioning schemes in deriving atomic charges.

Analogous computations on the energetics of the alkaline hydrolysis reaction of *N*-phenylacetamides were performed by applying density functional computations at the B3LYP/6-31+G(d,p) level. The results obtained are presented in Table 3. It comprises all reactivity indexes that have shown satisfactory results from the HF computations. The computed energy changes from reactants to the fully optimized first TS of the hydrolysis reaction are given together with the Hammet σ constants, the computed C═O stretching mode frequencies, the electrophilicity index ω, the NBO atomic charge, and the EPN values at the carbonyl carbon atom.

The dependence with the σ constants is not quite satisfactory. It should be remembered, however, that the Hammet constants are experimental quantity solutions. Thus, the relatively low correlation coefficients with the theoretical ΔE values are not unexpected. The correlation with the computed ν(C═O) frequencies is quite good, in accord with the HF results already discussed. The global electrophilicity index ω provides a satisfactory qualitative description of the reactivity of the *N*-phenylacetamides in the alkaline hydrolysis reaction (Table 1). The respective correlation coefficient is 0.923. The evaluated NBO charges at the carbon atom offer again a sensible basis for discussing the reactivity of the studied compounds with respect the nucleophilic attack of the hydroxide ion. The respective correlation coefficient is 0.967.

The best description of the reactivity of the studied compounds comes again from the EPN value for the carbon atom of the C═O group in the substituted *N*-phenylacetamides. The relationship is shown in Figure 6. To our knowledge EPN values



$$\Delta E = -601.67\ V_C - 8817.43$$

$$n = 15;\ r = 0.993;\ sd = 0.69$$

Figure 6. Plot between Δ*E* and the electrostatic potential at the carbonyl carbon atom computed at the B3LYP/6-31+G(d,p) level of theory for para-substituted acetanilides.

have not been employed in the literature as reactivity indexes for chemical reactions. The present results show that, for reactions, the rate of which is strongly dependent on the initial attraction between the reactants, the EPN values may serve as an excellent reactivity index. The great benefit of using this quantity is that it can be easily evaluated, describes local properties of the reaction center involved, and, finally, no approximations in its evaluation are involved, aside from the general physical and mathematical assumptions inherent in for the respective quantum mechanical methods employed.

4. Conclusions

A number of reactivity indexes were explored in describing the reactivity of a series of 15 *N*-phenylacetamides para-substituted in the aromatic ring in the alkaline hydrolysis reaction. The Hammett *σ* constants and the shifts of carbonyl stretching mode frequency correlate satisfactorily with the theoretically estimated at HF/6-31+G(d) and DFT B3LYP/6-31+G(d,p) levels of theory energy changes for the rate-determining stage of the reaction: the addition of a hydroxide ion and formation of a TD. NBO atomic charges at the carbonyl carbon atom, the site of the nucleophilic attack, provide also a satisfactory basis for discussing the reactivity of the studied carbonyl compounds. The global softness *S* and the global electrophilicity *ω* indexes describe satisfactorily the overall tendencies of the changing reactivity of the studied compounds. The best reactivity index for the studied reaction appeared to be the theoretically estimated electrostatic potential at the carbonyl carbon atom. The evaluated linear regression correlation coefficients for the dependencies between the energy changes for the rate-determining stage of the amide hydrolysis and the electrostatic potential at the carbonyl carbon atom are over 0.99 at both levels of theory employed. The EPN values are recommended as an accurate local reactivity index.

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