# Predicting Reactivities of Organic Molecules. Theoretical and Experimental Studies on the Aminolysis of Phenyl Acetates

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The quality of reactivity predictions coming from alternative theoretical approaches as well as experimental reactivity constants is examined in the case of the ester aminolysis process. The aminolysis of a series of para-substituted phenyl acetates is studied. The barrier heights for the rate-determining stage of the aminolysis of 16 phenyl acetate derivatives were predicted by employing density functional theory at the B3LYP/6-31+G(d,p) level. Experimental kinetic studies were carried out for the *n*-butylaminolysis of seven *p*-substituted phenyl acetates in acetonitrile. The results show that the electrostatic potential at the carbon atom of the carbonyl reaction center provides an excellent description of reactivities with regard to both theoretical barrier heights and experimental rate constants. The performance of other reactivity indices, Mulliken and NBO atomic charges, electrophilicity index, and Hammett constants, is also assessed.

## 1. Introduction

The principal aim of the present research is to assess the quality of reactivity predictions coming from alternative theoretical approaches as well as experimental reactivity constants. The selected model process for these studies is the ester aminolysis reaction of a series of para-substituted phenyl acetates. The ester aminolysis plays a crucial role in the generation of amide functional groups in proteins and peptides. The biological process has received much attention in experimental[1–7] and computational work.[8,9] The ester aminolysis is also an important reaction in organic chemistry and has been the subject of numerous kinetic[10–19] and theoretical studies.[20–32] These studies have focused on the influence of various factors on the rate and mechanism of the reaction. The detailed understanding of the chemistry of the process (mechanism, reactivity, and catalysis) is, therefore, of importance for both chemistry and biology. Advances in electronic structure theory offer new opportunities in quantifying the reactivity of organic molecules.[33–40] Alternative global and local reactivity indices and electronic parameters have been tested with varying success.[40–49] It is of special interest to assess the performance of reactivity indices by comparison not only with theoretically determined activation barriers but with appropriate experimental kinetic results as well. The derivatives and reaction studied are presented in Chart 1.

In a previous computational study[29a] on the ester aminolysis process, it was shown that under a general-base catalysis, the most favored pathway for the reaction is an addition/elimination stepwise mechanism involving two transition states. If general-base catalysis is not involved, results for the parent compound of phenylacetate[29e] predict a distinctly lower barrier for the concerted mechanism. Thus, in the present work, we explored both mechanistic pathways for the reaction. The theoretical activation energies are rationalized in terms of global and local reactivity indices derived from density functional theory (DFT). Experimental kinetic measurements for the reaction of seven substituted phenyl acetates and *n*-butyl amine in acetonitrile were carried out. Thus, the predictive power of the theoretically evaluated reactivity indices was assessed by direct comparison with experimental results.

Phenyl acetates have been used as model compounds in studies of the kinetics and mechanism of the ester aminolysis. Jencks and Carriuolo[50] investigated the reaction of phenyl acetate with several amines in aqueous solution and found that the process is general-base catalyzed. In a later work[51] from the same laboratory, the kinetics of the reaction of phenyl acetate and meta- and para-substituted derivatives with pyrazole under different types of catalysis were examined. Bruice and co-workers[10e,52,53] studied the aminolysis of phenyl acetate and five ring-substituted derivatives with various amines in aqueous solution. The authors established a complex kinetic equation that reflected the presence of non-catalyzed, general-base, and general-acid catalyzed pathways, as well as the parallel reaction of hydrolysis, assisted by the hydroxide ions formed during the process. Oleinik et al.[54] studied the kinetics of the aminolysis of *p*-nitrophenyl acetate and 2,4-dinitrophenyl acetate by a number of aliphatic amines in various solvents. The kinetic results of these authors indicated that depending on the nature of the participating ester or amine, the transition state for the rate-controlling stage can have a reactant-like or intermediate-like structure. Lee and co-workers[55] investigated the kinetics of the aminolysis of five substituted in the aromatic ring phenyl acetates by benzyl amines in dimethyl sulfoxide solution. Pseudo-first-order and second-order rate constants were evaluated as well as activation parameters for the two esters studied. Sung et al.[56] examined the stability of a zwitterionic intermediate in aqueous solution in the aminolysis of phenyl acetate with the aid of theoretical computations. Rajarathnam et al.[57,58] experimentally investigated the kinetics of the aminolysis of a series of meta- and para-ring-substituted phenyl acetates by imidazole in aqueous medium.

In designing the conditions for the present kinetic experiments, we selected acetonitrile as solvent in order to avoid the

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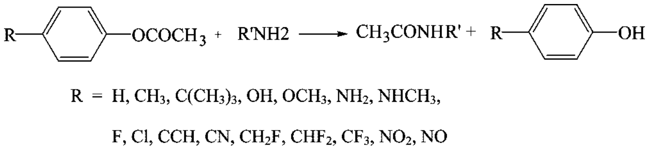
**CHART 1: R = H, $CH_3$, $C(CH_3)_3$, OH, $OCH_3$, $NH_2$, $NHCH_3$, F, Cl, CCH, CN, $CH_2F$, $CHF_2$, $CF_3$, $NO_2$, NO**



more complex process in aqueous medium, as discussed above. We studied the kinetics of the aminolysis for seven para-substituted derivatives containing both electron-withdrawing and electron-donating groups. The distant electronic effects in these compounds are expected to reflect purely electronic influences of the substituents.

## 2. Computational Methods and Kinetic Experiments

**2.1. Electronic Structure Computations.** The computations were carried out with the Gaussian 94[59] and Gaussian 03[60] program packages. The structure of reactants and transition states associated with the addition stage of the reactions studied were fully optimized by using the B3LYP DFT method[61] with the 6-31+G(d,p) basis set.[62,63] These structures were further characterized by analytic computations of harmonic vibrational frequencies at the same level of theory. The transition state structures were located by the traditional transition-state optimization by using the Berny algorithm.[64] Zero-point vibrational energies were taken into account in evaluating the energies of reactants and transition states. In the cases of substituents where more than one conformer is possible for the respective para-substituted phenyl acetates, the computations were restricted to the lowest energy conformers. These conformers were determined from preliminary HF/3-21G calculations. The Cartesian coordinates of all optimized structures of reactants and transition states are given in the Supporting Information.

**2.2. Atomic Charges.** Atomic charges are expected to serve as the appropriate reactivity indices describing the reactivity of the studied molecules with respect to the nucleophilic attack by ammonia or another amine. Atomic charges according to two different partitioning methods were obtained: Mulliken charges[65] and NBO charges.[66] The performance of the different methods for evaluating atomic charges was discussed recently.[67]

**2.3. Electrostatic Potential at nuclei (EPN).** The electrostatic potential values at the atomic sites were also evaluated. The electrostatic potential at a particular nucleus (Y) positioned at $R_Y$ is defined by eq 1, where the singular term $R_A = R_Y$ has been excluded:[68a]

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

In this equationm, $Z_A$ 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 an integration over the continuous distribution of the electronic charge. The molecular electrostatic potential values at each atom of the isolated monomer molecules were obtained by using the Gaussian set of programs.

In previous studies,[48a–c] it was shown for the first time 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 proton acceptors. EPN proved also a reliable reactivity index for chemical reactions as well.[48d,e] The EPN found recently further successful applications as reactivity descriptor.[69a–k]

**2.4. Electrophilicity Index.** The global electrophilicity index was defined by Parr, Szentpály, and Liu[40] by the relationship $\omega = \mu^2/\eta$, where $\mu$ is the electronic chemical potential and $\eta$ is the global hardness. Excellent reviews on the applications of the electrophilicity index were recently published by Chattaraj et al.[44a,b]

**2.5. Pseudo-first Order Kinetics.** Pseudo-first Order Kinetics of the reaction of seven *p*-substituted phenyl acetates at 25°C was followed by IR spectroscopy. All experiments were carried out in acetonitrile solution. The temperature was kept constant at 25 ± 0.1°C. At least 10-fold molar excess of *n*-butylamine was present in the reaction mixture. The typical concentrations of the esters were about 0.1 M, and those of *n*-butylamine were 1M. The actual concentrations used are given in Table S1 of the Supporting Information. The amine concentration was about 10 w%. Each rate constant was determined as an average of three independent experiments. The maximum deviations from the mean values were within ±5%. The reactions were followed to more than 85% transformation of the reactant phenyl acetates. Changes of concentration of the initial phenyl acetates were measured at the peak of the carbonyl stretching band. The carbonyl bands of the amide reaction products have distinctly lower frequencies. Thus, no interference from this absorption affects the absorbance of the initial reactant band used in the analytical measurements. A 0.13 mm sodium chloride IR cell was used.

Considerable difficulties were encountered in determining the pseudo-first-order kinetic constant of *p*-nitrophenyl acetate because of the exceptionally high rate of the process in the concentration range used for the other phenyl acetates. In the case of *p*-nitrophenyl acetate, we used 20-fold lower concentrations for both substrate and amine to slow down the reaction rate. Still, the total reaction time was less than three minutes. Thus, the accuracy of kinetic measurements for this particular pseudo-first-order constant was lower compared to that of the remaining esters from the series, within ±7%. For the para-nitro derivative, a cell with 0.60 mm thickness (NaCl) was used.

To normalize the pseudo-first-order rate constants obtained, we divided $k_{obs}$ to the concentration of amine. To justify this approach, we carried out further experiments with the parent compound of phenyl acetate. The reaction was followed at 1:1 molar ratio between ester and amine at 25°C. The process lasted more than three days. The plot between $1/C_{substrate}$ and time produced a straight line, indicating second-order kinetics for the overall process. The dependence is illustrated in Figure S1 of the Supporting Information. Literature data[13h,j,m] for the esters aminolysis in acetonitrile report a second-order kinetics for the process.

The para-substituted phenyl acetates studied were either commercial products (Fluka, Aldrich) or were synthesized by using known methods.[70a,b]

## 3. Results and Discussion

**3.1. Computational Results.** The computational part of the present study aims at quantifying the reactivity of a series of *p*-substituted phenyl acetates in the ester aminolysis reaction by using ammonia as a model nucleophilic agent. The para-substitution offers the possibility to assess the varying reactivity of the compounds under the influence of electronic effects without interference of steric or other entropy-related influences.

As already emphasized, the principal aim of the present study is to critically assess the accuracy of reactivity predictions

**TABLE 1: Theoretically Evaluated Barrier Heights for the Stepwise and Concerted Mechanisms of the Aminolysis of para-Substituted Phenyl Acetates and Reactivity Indices**

| substituent R | $\Delta E_{TS1}$ [kcal/mol] | $\Delta E_{CTS}$ [kcal/mol] | Hammett $\sigma$ constant[a] | electrophilicity index $\omega$[b] [eV] |
|---|---|---|---|---|
| H | 42.19 | 32.33 | 0 | 0.0284 |
| $CH_3$ | 42.58 | 32.96 | −0.170 | 0.0286 |
| $C(CH_3)_3$ | 42.58 | 32.93 | −0.200 | 0.0285 |
| OH | 42.83 | 33.04 | −0.370 | 0.0283 |
| $OCH_3$ | 42.98 | 33.35 | −0.268 | 0.0284 |
| $NH_2$ | 43.24 | 34.18 | −0.660 | 0.0247 |
| $NHCH_3$ | 43.41 | 34.44 | −0.592 | 0.0255 |
| F | 41.96 | 31.57 | 0.060 | 0.0332 |
| Cl | 41.54 | 30.80 | 0.227 | 0.0322 |
| CCH | 41.38 | 30.48 | 0.230 | 0.0351 |
| CN | 40.04 | 27.76 | 0.660 | 0.0444 |
| $CH_2F$ | 41.40 | 30.76 | 0.110 | 0.0342 |
| $CHF_2$ | 41.34 | 30.29 | 0.320 | 0.0385 |
| $CF_3$ | 40.55 | 28.97 | 0.540 | 0.0404 |
| $NO_2$ | 39.43 | 26.17 | 0.778 | 0.0620 |
| NO | 39.30 | 25.86 | 0.910 | 0.0609 |
| Correlation Coefficients | | | | |
| with $\Delta E_{TS1}$ | | | 0.982 | 0.940 |
| with $\Delta E_{CTS}$ | | | 0.976 | 0.959 |

[a] From refs 71a and b. [b] Calculated using data for the ionization potential and electron affinity of the reactants.

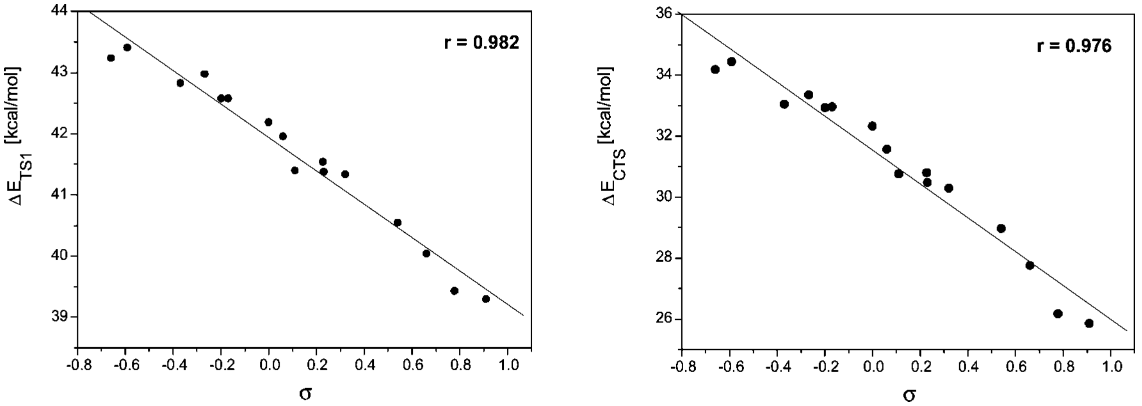


**Figure 1.** Dependences between theoretically evaluated activation energies for stepwise ($\Delta E_{TS1}$) and concerted ($\Delta E_{CTS}$) mechanism for the aminolysis of phenyl acetates and the Hammett sigma constants.

obtained by applying different theoretical or experimentally based approaches. The following quantities were evaluated from DFT computations: Mulliken[65] and NBO atomic charges,[66] electrophilicity index,[34] and EPN.[68] On the experimental side, the Hammett sigma constants were applied.

As mentioned earlier, the focus of our study was the attack of the nucleophile at the reaction center leading to neutral transition state 1 (TS1) under a general-base-catalyzed process or to neutral transition state CTS under a concerted mechanism for the uncatalyzed process.

An intriguing problem associated with the mechanism of ester aminolysis is the possible formation of zwitterionic intermediates and transition states. The possibility for formation of such an intermediate was discussed in an earlier study (ref 29a). It was emphasized that theoretical studies of Oie et al.[20] and Zipse at al.[22] did not find transition states associated with zwitterionic intermediates. MP2/6-31G(d,p) computations carried out by some of the present authors for the reaction of methyl formate and methylamine also failed to identify zwitterionic transition states and intermediates. As already mentioned, Sung et al.[56] established by theoretical computations that extended water associates can stabilize a zwitterionic intermediate in the aminolysis of phenyl acetate. A definitive answer with respect to the participation of zwitterionic structures along the reaction path needs, evidently, further studies and careful comparisons of the energetic of the reaction along alternative mechanistic pathways.

Parameters associated with the electronic structure of the reactant phenyl acetates are, therefore, expected to describe the reactivity of the compounds in the reaction studied. The computed activation energies associated with the addition stage of the reaction are presented in Table 1. These activation barriers are juxtaposed to the experimental Hammett substituent constants as well as to the theoretically evaluated electrophilicity index $\omega$ for the reactant esters. The correlation coefficients for the linear plots between the activation energies ($\Delta E_{TS1}$ and $\Delta E_{CTS}$) and these quantities are given in the last rows of Table 1. It is seen that the dependence between barrier heights and experimental sigma constants is satisfactory with a linear regression correlation coefficient $r = 0.982$ for the stepwise and 0.976 for the concerted pathways. The dependence is illustrated in Figure 1. The data obtained show also (Table 1) that the electrophilicity index $\omega$ provides qualitatively correct prediction of reactivity for the reaction studied, although the respective correlation coefficients are lower ($r = 0.940$ for the stepwise and 0.959 for the concerted pathways). The somewhat lower predictive ability of $\omega$ for the process studied may be attributed to the global nature of the index. Thus, all substituents with

**TABLE 2: Theoretically Evaluated Barrier Heights for the Stepwise and Concerted Mechanisms of the Aminolysis of para-Substituted Phenyl Acetates and Reactivity Descriptors**

| substituent R | $\Delta E_{\mathrm{TS1}}$ [kcal/mol] | $\Delta E_{\mathrm{CTS}}$ [kcal/mol] | $q_{\mathrm{C}}$ (Mulliken) [e] | $q_{\mathrm{C}}$ (NBO) [e] | $V_{\mathrm{C}}$ [au] |
|---|---|---|---|---|---|
| H | 42.19 | 32.33 | 0.472842 | 0.8140 | −14.5925 |
| $CH_3$ | 42.58 | 32.96 | 0.469286 | 0.8135 | −14.5951 |
| $C(CH_3)_3$ | 42.58 | 32.93 | 0.446169 | 0.8135 | −14.5954 |
| OH | 42.83 | 33.04 | 0.454127 | 0.8133 | −14.5948 |
| $OCH_3$ | 42.98 | 33.35 | 0.463674 | 0.8130 | −14.5967 |
| $NH_2$ | 43.24 | 34.18 | 0.453770 | 0.8131 | −14.5998 |
| $NHCH_3$ | 43.41 | 34.44 | 0.455569 | 0.8126 | −14.6017 |
| F | 41.96 | 31.57 | 0.469911 | 0.8151 | −14.5875 |
| Cl | 41.54 | 30.80 | 0.493098 | 0.8145 | −14.5855 |
| CCH | 41.38 | 30.48 | 0.485823 | 0.8143 | −14.5871 |
| CN | 40.04 | 27.76 | 0.510167 | 0.8159 | −14.5749 |
| $CH_2F$ | 41.40 | 30.76 | 0.469181 | 0.8145 | −14.5867 |
| $CHF_2$ | 41.34 | 30.29 | 0.490435 | 0.8149 | −14.5841 |
| $CF_3$ | 40.55 | 28.97 | 0.495201 | 0.8156 | −14.5795 |
| $NO_2$ | 39.43 | 26.17 | 0.525401 | 0.8179 | −14.5715 |
| NO | 39.30 | 25.86 | 0.544451 | 0.8173 | −14.5728 |
| Correlation Coefficients | | | | | |
| with $\Delta E_{\mathrm{TS1}}$ | | | 0.942 | 0.965 | 0.991 |
| with $\Delta E_{\mathrm{CTS}}$ | | | 0.953 | 0.971 | 0.989 |

electrophilic properties may influence the value of $\omega$. In such cases, $\omega$ may not be quite accurate in describing the local reactivity of the carbonyl reaction center.

Li and Evans[41] emphasized that terms describing the Coulombic interaction between reactants can be employed as appropriate selectivity indices for chemical reactions. Politzer et al.[45] and Gadre and Suresh[49] showed that minima and maxima in the molecular surface electrostatic potential can be successfully used in quantifying the reactivity of molecules in both nucleophilic and electrophilic reactions. Kollman et al.[68b] analyzed reactivity in terms of values of the molecular electrostatic potential at certain distances from the atoms of the reaction center. As mentioned, in earlier studies from our laboratories, it was established that the EPN describes perfectly the reactivity of molecules for the process of hydrogen bonding.[48a–c] EPN was first applied as reactivity index in the case of chemical reaction in a computational study on the alkaline hydrolysis of *N*-phenyl acetamides.[48d] It was also shown that sigma constants for monosubstituted benzenes can be quantitatively predicted by using atomic electrostatic potentials determined from quantum mechanical computations.[48e] The electrostatic attraction between the reactants can also be described by theoretically evaluated atomic charges at the respective atoms. In Table 2, the computed Mulliken and NBO atomic charges associated with the carbonyl carbon atom, the reaction center for the nucleophilic attack, are given. The last column contains the theoretically estimated electrostatic potential values at the carbonyl carbon ($V_{\mathrm{C}}$). The correlation coefficients for the dependences between $\Delta E$ and the atomic charges presented in the last rows of Table 2 reveal that the Mulliken and NBO charges describe qualitatively correctly the variations of the reactivity of the phenyl esters studied.

Neuvonen et al.,[72] in their study on the influence of electron-withdrawing substituents on the electronic structure and reactivity of several series of phenyl or acyl-substituted methyl acetates, discussed the interdependence between electronic structure, spectroscopic parameters, and reactivity of the compounds. These authors applied IR and NMR spectroscopies and PM3 semi-empirical MO computations to analyze the changing electronic structure of the carbonyl bond under the influence of substituents. They concluded that electron-withdrawing substituents reduce the electrophilicity of the carbonyl group, opposite to experimental kinetic results and expectations. The authors explain the unusual result with a proposed decreased ground-state resonance stabilization of the esters under the influence of these substituents. In a later study, Contreras et al.[73] brought alternative arguments in defining the electrophilic abilities of phenyl acetates. They explained the enhanced reactivity of phenyl acetates containing electron-withdrawing groups simply in terms of the varying electrophilicity index $\omega$ of the compounds. These authors pointed out that the $\omega$ index represents better the electrophilicity of the compounds than quantities derived from population analysis. In a newer study, Neuvonen et al.[74] used results from HF/6-31G* and MP2/6-31G* theoretical computations as basis for discussing the reactivity of the carbonyl group in reactions of phenyl esters. In this work, the authors discussed the varying reactivity of several phenyl acetates in terms of frontier orbitals properties.

The results from the present study, although in agreement with the interpretation of the reactivity in terms of variations of the $\omega$ index or properties of the frontier orbitals, do not support the conclusions in the above works[72,73] that the reactivity of the compounds cannot be related to the electron-density distribution in the monomer esters. Considerable increase in the net Mulliken charges at the carbonyl carbon under the influence of electron-withdrawing substituents in the aromatic ring is predicted by the present more accurate DFT computations compared to the semi-empirical PM3 data reported in ref 72. Both Mulliken and NBO charges predict qualitatively well (Table 2) the reactivity of the phenyl esters in the aminolysis reaction. The correlation of the theoretical activation energies with the $q_{\mathrm{C}}$(NBO) values is, as expected, slightly better ($r = 0.965$ for the stepwise pathway and 0.971 for the concerted mechanism). Most importantly, both of these methods show that electron-withdrawing substituents in the aromatic ring increase the partial positive charge at the carbonyl carbon, thus facilitating the attack by the nucleophile. Electron-donating substitients have the opposite effect. It should be emphasized that the atomic charges are model-dependent quantities. Definitive information regarding the electron density variations at the reaction center is provided by the EPN. The $V_{\mathrm{C}}$ values obtained (Table 2) clearly show that the electron density at the carbon atom is increased under the influence of electron-donating substituents (increased negative value of $V_{\mathrm{C}}$) such as OH, $OCH_3$, and $NH_2$ and significantly lowered by the effect of electron-withdrawing groups (CN, $CF_3$, $NO_2$, NO). Excellent linear dependence

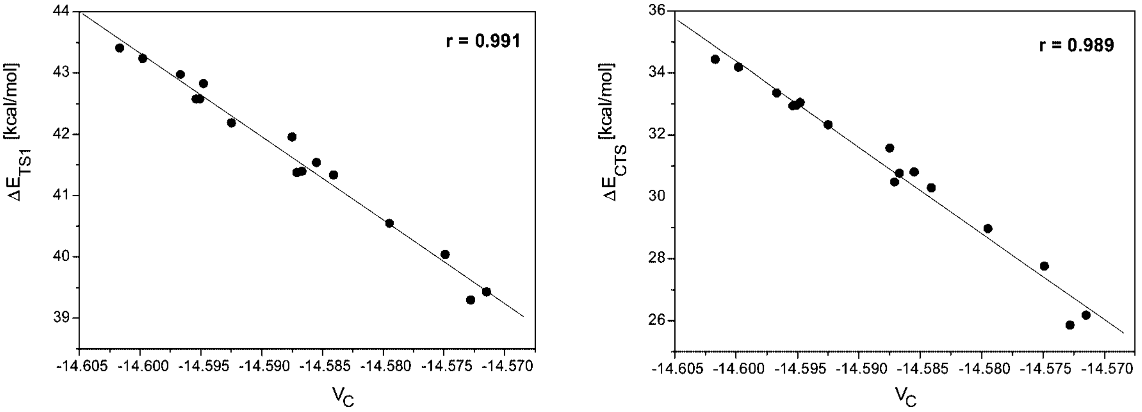


**Figure 2.** Plots between barrier heights for stepwise and concerted pathways of the aminolysis of phenyl acetates and electrostatic potential at the carbonyl carbon atom of reactant esters.

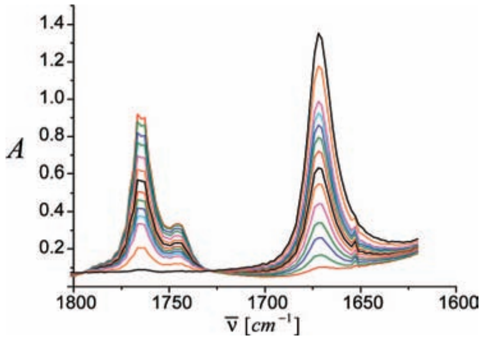
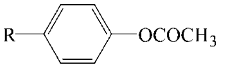


**Figure 3.** Kinetics of the *n*-butylaminolysis of phenyl acetate in acetonitrile at 25°C as followed by FTIR spectroscopy. The ordinate axis is in absorbance units.

### CHART 2: R = H, $CH_3$, $C(CH_3)_3$, $OCH_3$, Cl, $CF_3$, $NO_2$



R = H, $CH_3$, $C(CH_3)_3$, $OCH_3$, Cl, $CF_3$, $NO_2$

**TABLE 3: Measured Experimental Pseudo-First-Order Kinetic Constants at 25°C for the *n*-Butylaminolysis of *p*-Substituted Phenyl Acetates in Acetonitrile**

| substituent R | $k^a$ [$mol^{-1}$ $s^{-1}$] | ln *k* |
|---|---|---|
| H | $1.95 \times 10^{-4}$ | −8.54251 |
| CH3 | $1.15 \times 10^{-4}$ | −9.07058 |
| C(CH3)3 | $0.95 \times 10^{-4}$ | −9.26163 |
| OCH3 | $0.60 \times 10^{-4}$ | −9.71861 |
| Cl | $19.57 \times 10^{-4}$ | −6.23651 |
| CF3 | 0.0199 | −3.91704 |
| NO2 | 0.2137 | −1.54303 |

[a] $k = k_{obs}/[BuNH_2]$.

between barrier heights and EPN values ($V_C$) at the carbonyl carbon in the monomer esters are obtained for both possible mechanisms of the process. The dependences between $\Delta E$ and $V_C$ are illustrated in Figure 2. The obtained relationship between activation energies and $V_C$ values is far superior to any other dependency discussed in the present study. The result is not surprising in view of the fact that the atomic potentials reflect accurately the changing electron densities at the different atomic sites because in their evaluation, no further approximations are made and the values obtained have the same reliability as the molecular wave function employed. The EPN values have the additional advantage to reflect local properties of atomic sites and are thus able to characterize the reactivity of different reaction centers in a molecule.

The discussion of the theoretical results provided some key insights in the intramolecular factors governing the reactivity in the aminolysis of phenyl acetates. However, it is not of lesser interest to assess how these theoretical reactivity descriptors would correlate with experimental kinetic data for the aminolysis of *p*-substituted phenyl acetates.

**3.2. Kinetic Results.** The kinetics of the aminolysis of phenyl acetates by *n*-butyl amine in acetonitrile solvent was followed by IR spectroscopy. The clear separation between the carbonyl-group bands in the reactant esters and the amide products provides a basis for the kinetic measurements (Figure 3). Experiments were carried for seven compounds (Chart 2). As can be seen, the series includes the parent compound as well as three electron-donating and three electron-withdrawing groups. Thus, the derivatives selected are expected to reflect alternative polar influences of the para substituents.

A summary of the kinetic results obtained is given in Table 3. An example of the pseudo-first-order kinetics for the *n*-butylaminolysis of phenyl acetate is illustrated in Figure 3. As mentioned, we established a second-order kinetics for the aminolysis of the parent phenyl acetate. This result indicates that no additional amine molecule is involved in the rate-controlling stage if the reaction and, therefore, general-base catalysis for the process in acetonitrile solution is not present at these conditions. A clean second-order kinetics for the aminolysis of ester groups in various molecular environments in acetonitrile has been experimentally found in a number of studies by Lee and coworkers.[13h,k,m]

The theoretical study of this reaction[29e] showed that the concerted process possesses distinctly lower barrier in acetonitrile solution. Concerted mechanism for the ester aminolysis in acetonitrile was previously reported for various ester derivatives.[12g,13i–l] The obtained ln *k* values are plotted against four reactivity indices: the NBO atomic charges at the carbonyl carbon atom, the global electrophilicity index (*ω*), the experimental Hammett constants (*σ*), and the electrostatic potential at the carbonyl carbon atom ($V_C$) in the reactant phenyl acetates. The obtained plots are illustrated in Figures 4–7.

The NBO charges provide a good description of the experimentally established reactivities of the compounds from the series studied (Figure 4). The electrophilicity index, however, only qualitatively describes the trend of rate-constant variations (Figure 5). As already discussed, the result can be attributed to the global nature of the index. As expected, the experimentally determined Hammett substituent constants correlate very well with the observed rate constants (Figure 6).

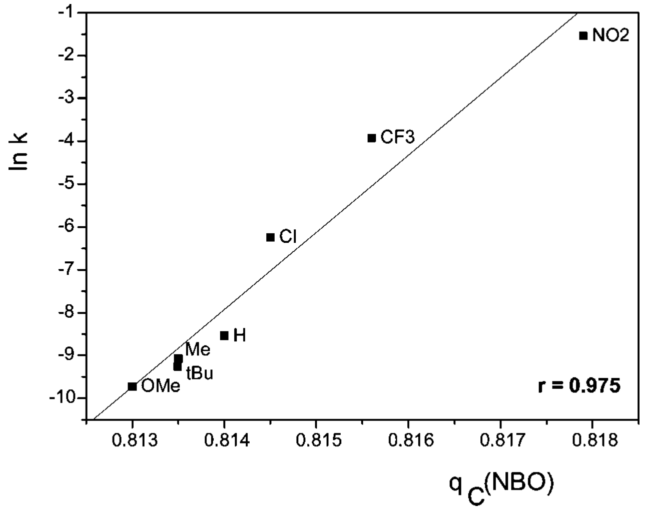


**Figure 4.** Plot between ln *k* values for the *n*-butylaminolysis of phenyl acetates and NBO charges at the carbonyl carbon atom.

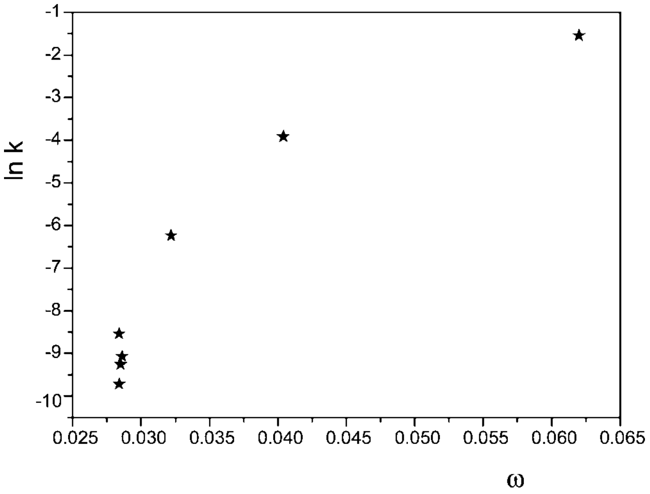


**Figure 5.** Plot between ln *k* values for the *n*-butylaminolysis of phenyl acetates and the global electrophilicity index ($\omega$) for the reactant esters.

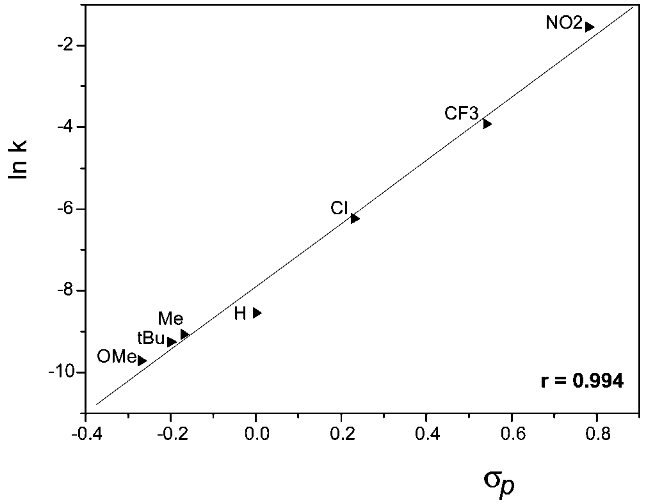


**Figure 6.** Plot between ln *k* values for the aminolysis of phenyl acetates and the Hammett $\sigma_p$ constants.

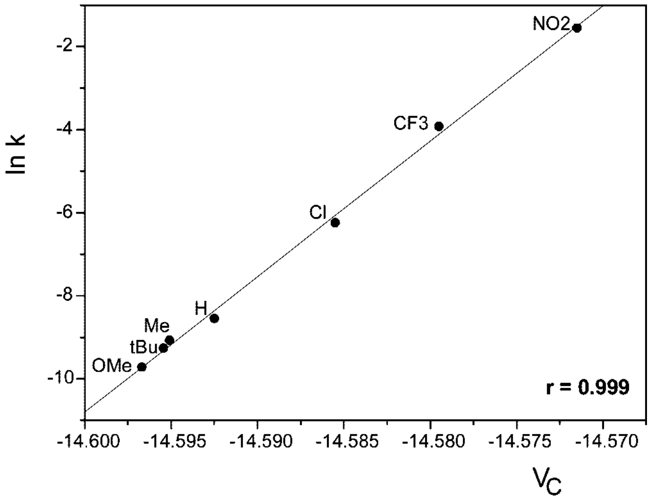


**Figure 7.** Plot between ln *k* values for the *n*-butylaminolysis of phenyl acetates and the electrostatic potential at the carbonyl carbon atom ($V_C$) for the reactant phenyl acetates.

In agreement with the theoretical results discussed in the previous part, the best prediction of reactivity is provided by the EPN values at the carbonyl carbon in the reactant phenyl acetates. Figure 7 illustrates the plot between ln *k* and $V_C$. The respective correlation coefficient is $r = 0.999$. It is indeed somewhat surprising to obtain such perfect theoretical predictions of the experimental reactivities.

In general, the results from the present study support the following conclusions: (1) contemporary electronic structure methods provide reactivity descriptors that can be employed to predict with a good accuracy the rates of chemical reactions, and (2) the atomic electrostatic potential is a highly reliable local reactivity index.

## 4. Conclusions

The aminolysis of a series of para-substituted phenyl acetates is studied by applying DFT as well as experimental kinetic measurements. A number of theoretical indices of reactivity as well as the experimental substituent constants were employed to rationalize the barrier heights for the rate-determining stage of the reaction and the variation of the experimental rate constants. The results show that the electrostatic potentials at the carbon atom of the carbonyl reaction center provide a superb description of reactivities with regards to both theoretical barrier heights and experimental rate constants. The performance of other reactivity indices (Mulliken and NBO atomic charges, electrophilicity index, and Hammett constants) was also assessed.

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**Supporting Information Available:** This material is available free of charge via the Internet at http://pubs.acs.org.

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