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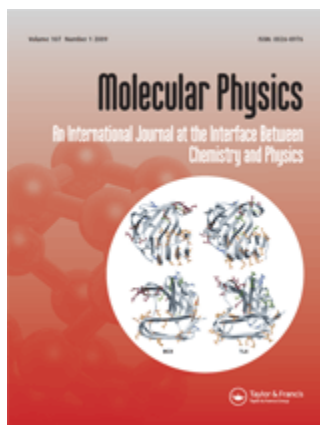
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Theory vs. Experiment**

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Reactivity of Acetanilides in the Alkaline Hydrolysis Reaction: Theory vs. Experiment

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Dedicated to Prof. Henry F. Schaefer III, on the occasion of his 65th anniversary

Abstract

The rate constants (at 25 °C) for the alkaline hydrolysis of a series of seven acetanilide derivatives were experimentally determined. The series included the parent compound of acetanilide and the following para substituents: CH₃, OCH₃, NH₂, CHO, COCH₃, NO₂. The obtained kinetic data were then correlated with the following theoretically estimated reactivity indices: Mulliken and NBO atomic charges, the Parr electrophilicity index (ω), and the electrostatic potential at the carbon and nitrogen atoms of the reaction center (V_C , V_N). A very good correlation between the logarithm of the rate constant, $\ln k$, and ω values was established. Excellent correlations between V_C and V_N with $\ln k$ were found. The data obtained show that the model-independent electrostatic potential at the nuclei (EPN) provides a reliable quantitative approach in describing the reactivity of organic compounds.

Keywords: alkaline hydrolysis, amides, anilides, kinetics, reactivity indices

Introduction

The chemistry of organic reactions requires knowledge on the mechanism of the processes, the energy profile, the solvent influence, the potential role of catalysts, as well as the factors governing reactivity. Such data are usually obtained from kinetic and

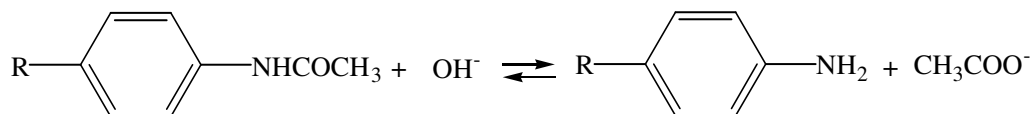
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4 spectroscopic studies and, in last times, from theoretical computations. The quantitative
5 characterization of the reactivity of organic compounds in various chemical interactions
6 is, therefore, of key importance. It emphasizes the conceptual link between properties of
7 reactants and their behavior in chemical reactions and supports the notion of organic
8 chemistry as a fully quantitative science. Since the pioneering works of Hammett [1,2]
9 the interpretation of organic reactivities has been in the focus of numerous studies.
10 Quantum chemistry has open new perspectives in elucidating the factors governing
11 chemical reactivity [3-23]. The introduction of reactivity indices, defined in the
12 framework of density functional theory, has contributed to significant advances in the
13 field [6-8, 10-16]. In spite of the impressive progress, achieving a quantitative accord
14 between theoretical predictions and experimental kinetic data is still a challenging task. It
15 is, therefore, paramount to characterize chemical reactivity by analyzing the agreement
16 between theory and experiment.
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27 We explore in the present study the application of several alternative theoretically
28 estimated indices, which characterize the reactivity of ring-substituted acetanilides in the
29 alkaline hydrolysis reaction. In a previous computational study [21] we evaluated several
30 electronic structure parameters and tested their ability to predict the theoretically
31 determined energy changes accompanying the same process. The quantities tested
32 included two types of atomic charges, the electrophilicity index (ω) of Parr, Szentpály
33 and Liu [12] as well as the electrostatic potential at nuclei (EPN) [24, 25]. In the present
34 work we determined experimentally the rate constants for the alkaline hydrolysis of
35 acetanilide and six para substituted derivatives. The experimental kinetic data were
36 rationalized using the reactivity descriptors determined in our previous study [21].
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45 The reaction and the compounds studied are shown in Scheme I.

46
47 Scheme I



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4 The series includes a balanced number of derivatives containing electron donating and
5 electron withdrawing substituents. The para-substitution is preferred in order to minimize
6 possible steric influences on the reaction rates.
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10 The amide hydrolysis has been the subject of numerous experimental [26-36] and
11 theoretical studies [37-57] because it is regarded as a model process for the cleavage of
12 peptide bonds [58]. In a recent combined kinetic and computational study [57] we
13 showed that the rate of the alkaline hydrolysis of three secondary amides - N-
14 methylbenzamide, N-methylacetamide and acetanilide – is governed by the second stage
15 of the reaction. This stage involves the breakdown of the initially formed tetrahedral
16 intermediate to products. The computational and kinetic results provided a detailed
17 picture of the variations of the free energy barriers for the reactions of the three amides
18 studied.
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26 In the present work we examine how different electronic structure parameters
27 obtained from quantum mechanical computations predict the relative rates of the alkaline
28 hydrolysis of substituted acetanilides. On the experimental side rate constants for the
29 alkaline hydrolysis of a series of acetanilides at 25 °C were experimentally determined.
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34 **Computational Results and Kinetic Experiments**

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36 The rates of hydrolysis of the studied acetanilides were measured
37 spectrophotometrically. The change in absorbance due to the reactant amides and the
38 products, were followed on a Unicam UV500 spectrometer at the λ_{max} for the respective
39 final products (anilines) or initial acetanilides. The hydroxide ion concentration was 0.9
40 M and the ionic strength was maintained constant at 0.9 M (NaCl). The initial
41 concentrations of amides were about 1.10^{-4} M. The hydroxide concentration was in a
42 large excess, so the reactions exhibited pseudo-first-order kinetics. Kinetic data were
43 generated to estimate the rate constants, k_{obs} , by plotting $\ln(A_{\infty}-A_t)$ vs. time, where A_{∞}
44 is the absorbance of the respective aniline at time $t=\infty$ or the pure aryl amine. The slope of
45 the line yielded k_{obs} . Alternatively, in the cases where changes in the concentration of
46 initial reactants were followed the relation $\ln(A/A_0)$ vs. time was applied. The kinetic
47 measurements were carried out at 25 ± 0.1 °C. Temperatures were kept constant by a
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thermostat. The reactions were followed to over 80% transformation of the initial amides. In every case k_{obs} is the average of three independent measurements. The linear dependence of $\ln(A_{\infty}-A_t)$ or $\ln(A/A_0)$ vs. time showed that the reactions had obeyed pseudo-first-order kinetics. Dividing the values by the concentration of the hydroxide ions normalized the obtained pseudo-first-order constants. Bender and Thomas [26] have shown that the alkaline hydrolysis of acetanilides follows second order kinetics. Details of the kinetic experiments are provided in the Supporting Information.

The acetanilide and two of the *p*-substituted acetanilides ($R = \text{H}, \text{NH}_2, \text{NO}_2$) were synthesized by known methods via amidation of acetic acid or acetic anhydride with the respective *p*-substituted anilines [59, 60]. The rest of the *p*-substituted acetanilides from the studied series are commercial products.

The following theoretical quantities employed as reactivity indices were applied in rationalizing the rates of alkaline hydrolysis:

- (i) Mulliken atomic charges [61] at the carbonyl carbon atom, which is the reaction center for the attack by the hydroxide ion.
- (ii) Natural Bond Orbital (NBO) atomic charges [62, 63]. These charges have proved a superior tool for population analysis.
- (iii) The electrophilicity index (ω) of Parr, Szentpály and Liu [12] defined by the relationship: $\omega = \mu^2/2\eta$ was considered as well. μ is the electronic chemical potential and η is the total hardness.
- (iv) The electrostatic potential at nuclei was also applied. This quantity is defined by Eqn. 1, where the singular term $\mathbf{R}_A = \mathbf{R}_Y$ has been excluded [24,25]:

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

In this relation, 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 EPN index was defined and introduced by

Wilson [25] in the distant 1962. However, it was first applied as a reactivity index for organic compounds much later in the works of Galabov et al. [20-22].

The values of the theoretical indices tested, including Mulliken and NBO atomic charges, V_C and ω , are taken from our previous work on the reactivity of acetanilides [21]. These quantities were determined by computations at the B3LYP/6-31+G(d,p) level of theory.

Results and Discussion

As already emphasized, the principal aim of this study was to analyze the correlations between theoretically evaluated reactivity indices for the studied series of acetanilides and the experimentally determined rate constants for the reaction of alkaline hydrolysis. The obtained rate constants (at 25 °C) for the hydrolysis of the seven acetanilides are presented in Table 1. It should be mentioned that kinetic data for the alkaline hydrolysis of acetanilide as well as the respective p-CH₃, p-OCH₃, and p-Cl derivatives were previously reported by Bender et al. [26]. In another study Sorci and Macalady [36] provided experimental kinetic results for the alkaline hydrolysis of para substituted acetanilides. The series of seven acetanilides of these authors included several different substituents compared to the series considered in the present research.

The experimentally determined in the present study rate constants were juxtaposed to theoretical reactivity indices, which were determined in our previous computational study on this reaction [21]. The respective values for these electronic parameters are given in Table 2. Table 2 contains also the usual Hammett constants for the substituents. In the bottom row of the table are shown the linear regression correlation coefficients (r) for the dependences between the $\ln k$ values and the respective reactivity parameters. It is seen that the Mulliken charges do not correlate linearly with the $\ln k$ values. A better correlation, though far from satisfactory, is obtained when the NBO charges on the carbonyl carbon are applied. This dependence is illustrated in Figure 1. The plot between ω and $\ln k$ is presented in Figure 2. It is seen that for this reaction the global electrophilicity index provides very good predictions for the relative reaction rates. The plot between the electrostatic potential at the carbonyl carbon atom (V_C) and $\ln k$ is shown in Figure 3. This linear plot is characterized by the highest correlation coefficient ($r =$

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4 0.990). Surprisingly, the standard Hammett sigma constants do not provide satisfactory
5 results for this reaction.
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8 The variations of the electrostatic potential values as well as the NBO charges at
9 the electrophilic center reflect clearly the influence of polar groups at the para position in
10 the aromatic ring. The increased partial positive charge at the carbonyl carbon under the
11 influence of electron withdrawing substituents favors the interaction between the two
12 reactants. Inversely, electron donating substituents, such as CH₃, OCH₃ and NH₂, lead to
13 increased electron density at the site of the electrophilic center, thus hampering its
14 interaction with the electronegative hydroxide ion.
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20 As we have recently discussed [57], the rate-limiting stage of the reaction studied
21 is associated with the second transition state (TS2). This stage involves simultaneous
22 breaking of the amide C-N bond and the transfer of a proton to the emerging amine anion.
23 The significantly increased negative charge at the amide nitrogen in TS2 reflects in the
24 lower values of V_N in TS2 compared to reactants seen in Table 2. The nascent negative
25 charge at the nitrogen atom can be stabilized by electron delocalisation toward the
26 aromatic ring. This process is strongly favoured by electron withdrawing substituents, such
27 as CHO, COCH₃ and NO₂ groups. It is, therefore, not surprising that acetanilides
28 containing these substituents react much faster than the unsubstituted acetanilide or
29 derivatives with electron donating groups. The linear dependences between rate constants
30 and the electrostatic potential at the nitrogen atom in both reactants and transition state are
31 characterized by high correlation coefficients. The plot between $\ln k$ and V_N in reactants is
32 illustrated in Fig. 4.
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43 The excellent correlations between the electrostatic potential at nuclei and $\ln k$
44 values are not surprising. We have shown in a series of papers [20-22] that EPN provides
45 superb quantitative predictions of reactivities for a number of charge-controlled processes.
46 This index has two characteristics that are behind its successful applications in describing
47 the chemical reactivity: (1) It is a *local* index, characterizing the reactivity of atoms in
48 particular reaction center in molecules; (2) No further assumptions or approximations with
49 respect to the wave function considered are introduced. Thus the electrostatic potential at
50 nuclei reflects accurately fine variations in the electron density at particular atomic sites
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4 caused by structural changes. Further studies in other laboratories [64-71] have
5 emphasized the usefulness at this proposed reactivity index.
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8 It is especially important that V_C and V_N work so well with respect to both
9 theoretically estimated barrier heights and in predicting quantitatively the experimental
10 reaction rates. In a recent experimental and computational study within a series of phenyl
11 acetates [20] the electrostatic potential at nuclei of the carbonyl reaction center provided
12 spectacular quantitative prediction of the rate constants. The data obtained in this study
13 further emphasize the wider applicability of this quantity. In a more general perspective,
14 the present results show also that current theoretical computations provide a basis for a
15 future fully quantitative description of the properties of organic compounds.
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22 Summary

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24 The kinetic constants (at 25 °C) for the alkaline hydrolysis of a series of seven
25 para-substituted acetanilides were experimentally determined. The kinetic data were then
26 correlated with several reactivity indices estimated theoretically. The theoretical
27 quantities included Mulliken and NBO atomic charges, the Parr electrophilicity index
28 (ω), and the electrostatic potential at the carbon and nitrogen atoms of the reaction center
29 (V_C , V_N). Very good linear dependence between $\ln k$ and ω values was established. This
30 result emphasizes the usefulness of ω in discussing the chemical reactivity of organic
31 system. Excellent linear correlations between V_C and V_N with $\ln k$ were found. The data
32 obtained show that the model-independent EPN values provide reliable quantitative
33 approach in describing the reactivity of organic compounds studied up to now.
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Table 1. Experimentally determined rate constants at 25 °C for the alkaline hydrolysis of acetanilide and p-substituted acetanilides.

Substituent	k_{obs} [s^{-1}]	$k^{[\text{a}]}$ [$\text{s}^{-1}\text{M}^{-1}$]	$\ln k$
H	6.38E-06	7.09E-06	-11.8564
CH ₃	5.91E-06	6.57E-06	-11.9335
OCH ₃	6.34E-06	7.04E-06	-11.8633
NH ₂	1.95E-06	2.16E-06	-13.0438
COCH ₃	4.61E-05	5.12E-05	-9.8798
CHO	1.45E-04	1.61E-04	-8.7343
NO ₂	6.17E-04	6.86E-04	-7.2847

^[a] $k = k_{\text{obs}}/[\text{OH}^-]$.

Table 2. Theoretical reactivity indices from B3LYP/6-31+G(d,p) computations^[a] and Hammett constants for acetanilide and p-substituted derivatives.

Substituent	q_{C} MPA	q_{C} NBO	ω	V_{C} [au] Reactant	V_{N} [au] Reactant	V_{N} [au] TS2	Hammett σ constants ^[b]	$\ln k$
H	0.7285	0.6782	1.11	-14.6199	-18.2891	-18.5326	0.000	-11.8564
CH ₃	0.7453	0.6767	1.04	-14.6228	-18.2917	-18.5377	-0.170	-11.9335
OCH ₃	0.7926	0.6747	0.94	-14.6243	-18.2926	-18.5360	-0.268	-11.8633
NH ₂	0.7361	0.6725	0.87	-14.6283	-18.2965	-18.5444	-0.660	-13.0438
COCH ₃	0.7958	0.6818	1.91	-14.6089	-18.2771	-18.4916	0.502	-9.8798
CHO	0.7556	0.6829	2.10	-14.6051	-18.2729	-18.4877	0.420	-8.7343
NO ₂	0.7492	0.6847	2.86	-14.5978	-18.2647	-18.4549	0.778	-7.2847
Correlation coefficient^[c]	0.173	0.952	0.985	0.990	0.993	0.986	0.947	

^[a] Values are taken from ref. 21.

^[b] From ref. 74.

^[c] Correlation coefficients for the linear plots between reactivity indices and $\ln k$.

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4 **Figure 1.** Plot of $\ln k$ vs. carbonyl carbon NBO charges (q_C^{NBO}) for the alkaline
5 hydrolysis of the series of acetanilides studied.
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8 **Figure 2.** Plot of $\ln k$ vs. global electrophilicity index (ω) for the alkaline hydrolysis of
9 the series of acetanilides studied.
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11 **Figure 3.** Plot of $\ln k$ vs. the electrostatic potential at carbonyl carbon atom (V_C) for the
12 alkaline hydrolysis of the series of acetanilides studied.
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15 **Figure 4.** Plot of $\ln k$ vs. the electrostatic potential at the nitrogen atom (V_N) for the
16 alkaline hydrolysis of the series of acetanilides studied.
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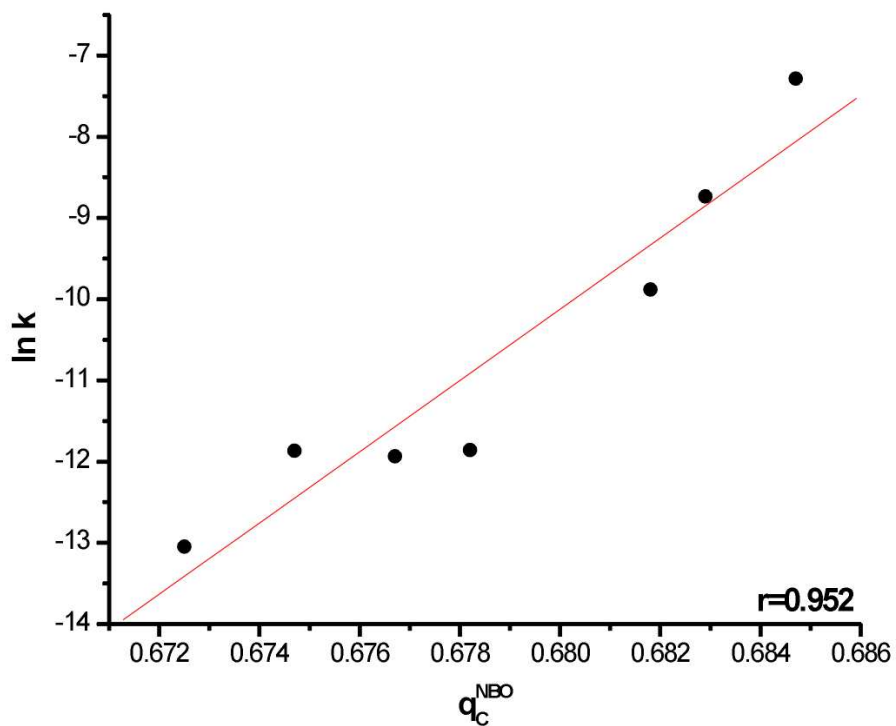


Figure 1. Plot of $\ln k$ vs. carbonyl carbon NBO charges for the alkaline hydrolysis of the series of acetanilides studied.

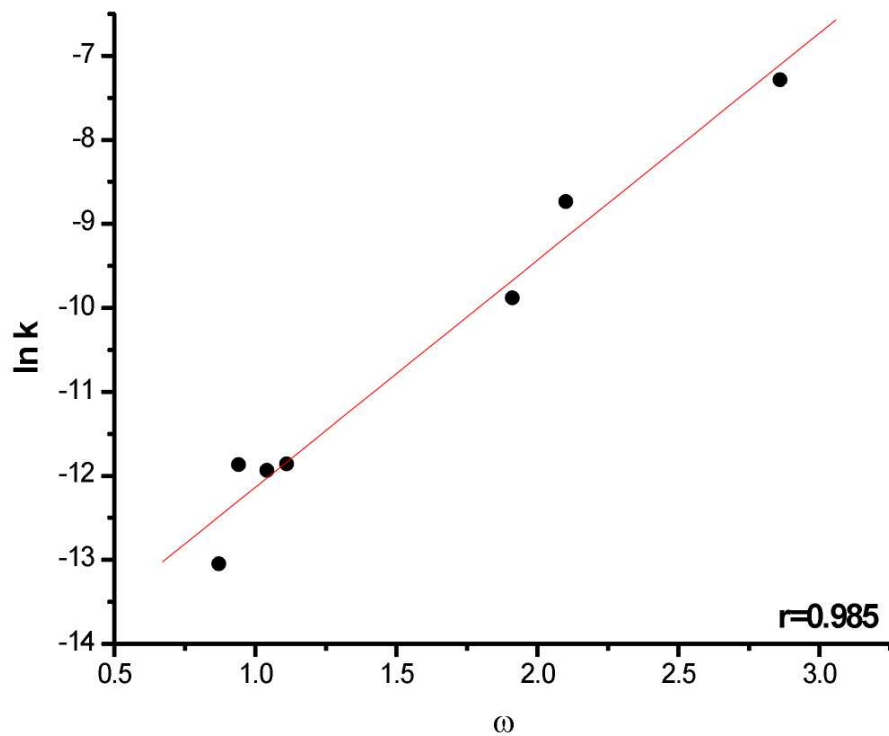


Figure 2. Plot of $\ln k$ vs. global electrophilicity index (ω) for the alkaline hydrolysis of the series of acetanilides studied.

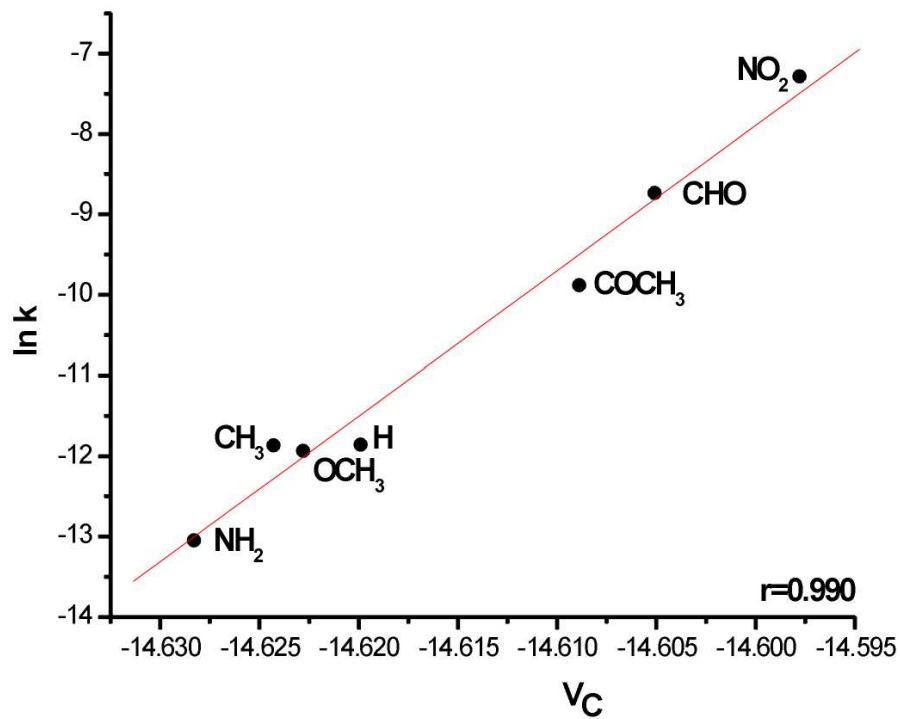


Figure 3. Plot of $\ln k$ vs. the electrostatic potential at carbonyl carbon atom (V_C) for the alkaline hydrolysis of the series of acetanilides studied.

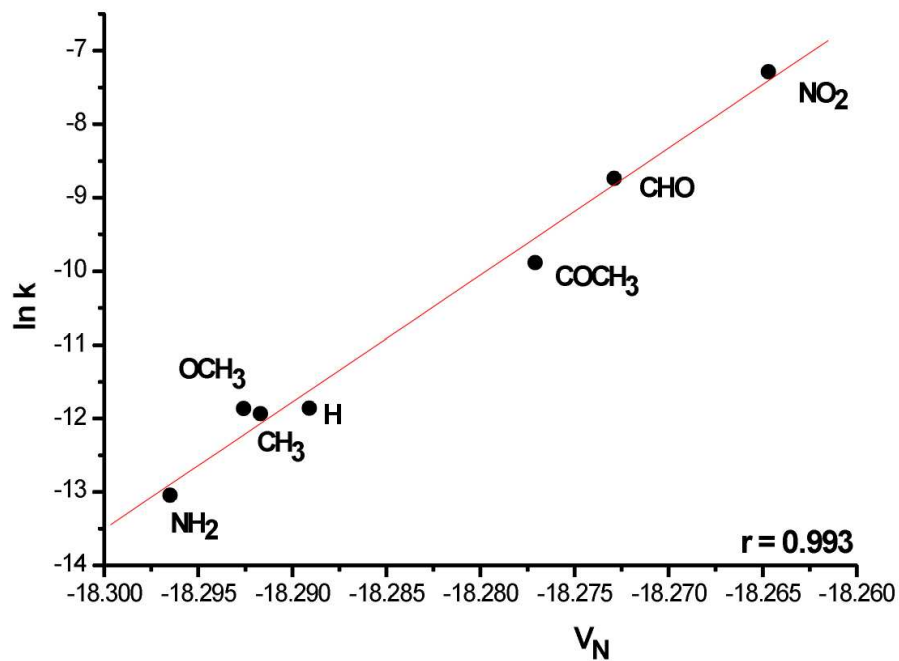


Figure 4. Plot of $\ln k$ vs. the electrostatic potential at the nitrogen atom (V_N) for the alkaline hydrolysis of the series of acetanilides studied.

Supporting information

Reactivity of Acetanilides in the Alkaline Hydrolysis Reaction: Theory vs. Experiment

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Dedicated to Prof. Henry F. Schaefer III, on the occasion of his 65th anniversary

Table of Contents

(1) Tables S1 – S7. Summary of rate constants at $25^{\circ} \pm 0.1^{\circ}\text{C}$ for the seven studied
acetanilides. In all the cases $[\text{OH}^-] = 0.9\text{M}$ ------(S2 – S3)

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Table S1. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of acetanilide at $25^{\circ} \pm 0.1^{\circ} \text{C}$.

Sample #	k [s ⁻¹]	R
I	6.51E-06	0.9956
II	6.39E-06	0.9971
III	6.26E-06	0.9953

Table S2. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of p-methylacetanilide at $25^{\circ} \pm 0.1^{\circ} \text{C}$.

Sample #	k [s ⁻¹]	R
I	5.83E-06	0.9965
II	6.02E-06	0.9953
III	5.87E-06	0.9973

Table S3. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of p-methoxyacetanilide at $25^{\circ} \pm 0.1^{\circ} \text{C}$.

Sample #	k [s ⁻¹]	R
I	6.38E-06	0.9987
II	6.33E-06	0.9987
III	6.33E-06	0.9989

Table S4. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of p-aminoacetanilide at $25^{\circ} \pm 0.1^{\circ} \text{C}$.

Sample #	k [s ⁻¹]	R
I	1.89E-06	0.9948
II	1.96E-06	0.9974
III	1.99E-06	0.9956

Table S5. Summary of rate constants from the separate measurements for the alkaline hydrolysis of p-acetylacetanilide at $25^{\circ} \pm 0.1^{\circ} \text{C}$.

Sample #	k [s ⁻¹]	R
I	4.49E-05	0.9988
II	4.73E-05	0.9984

Table S6. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of p-acetamidobenzaldehyde at $25^{\circ} \pm 0.1^{\circ}\text{C}$.

Sample #	k [s ⁻¹]	R
I	1.48E-04	0.9937
II	1.42E-04	0.9972
III	1.44E-04	0.9966

Table S7. Summary of rate constants from the three separate measurements for the alkaline hydrolysis of p-nitroacetanilide at $25^{\circ} \pm 0.1^{\circ}\text{C}$.

Sample #	k [s ⁻¹]	R
I	6.36E-04	0.9996
II	6.35E-04	0.9994
III	5.81E-04	0.9873