Reactivity of phenyl *N*-phenylcarbamates in the alkaline hydrolysis reaction

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In the present study, we explore the application of several theoretically estimated indices that characterize the reactivity of a series of phenyl *N*-phenylcarbamates in the alkaline hydrolysis reaction. The rate constants (at 25 °C) for the hydrolysis of several derivatives were spectrophotometrically determined. The obtained kinetic data in this study, combined with literature data for other derivatives, were then correlated with theoretically estimated reactivity indices: Hirshfeld and NBO atomic charges, the Parr electrophilicity index (ω), and the electrostatic potential at the carbon and oxygen atoms of the reaction centre (V_C, V_O). The predictive ability of these quantities is discussed in a comparative context. Copyright © 2011 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: alkaline hydrolysis; phenyl *N*-phenyl substituted carbamates; reactivity indices; reactivity of organic compounds

INTRODUCTION

The principal aim of the present study is to assess the quality of reactivity predictions coming from alternative theoretical approaches for the alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates. Carbamates are well-known class of compounds that can be synthesized by various methods.[1–4] The interest for studying their properties is determined mostly by the biological activities of carbamate derivatives.[1–11] Various carbamates find application in the agrochemical industry[5–9] as herbicides, fungicides and pesticides, in the pharmaceuticals industry[5,6,10] as drug intermediates, and in the polymer industry[5,6,11] for the synthesis of polyurethane and peptides. In the course of studying the biological activity of carbamates it was established that for some representatives the mode of decomposition during hydrolysis is a factor influencing their effects.[3] Therefore, the detailed understanding of the chemistry of the hydrolysis process, the theoretical prediction of kinetic parameters as well as the achievement of quantitative compliance with experimental reactivity trends is of particular importance. These objectives provided the motivation for carrying out theoretical evaluation of reactivity descriptors as well as experimental kinetic studies on the hydrolysis of a series of phenyl *N*-phenylcarbamates. The bulk of experimental kinetic data for the studied reaction was taken from the work of Williams,[12] who reported carefully determined kinetic constants for the alkaline hydrolysis of twelve compounds from the series examined. The series was expanded in the present study with four more derivatives, following the kinetic procedure of Williams.[12] We determined experimentally the rate constants for the following derivatives: *m*-CH$_3$, *p*-NO$_2$, *m*-N(CH$_3$)$_2$, and *p*-C(CH$_3$)$_3$ phenyl *N*-phenylcarbamates substituted in the O-phenyl ring. The series of compounds studied is presented in Scheme 1. These derivatives contain both electron donating and electron withdrawing groups, thus allowing to reflect alternative polar influence of the substituents. Experimental kinetic data for such a representative series of derivatives provided a solid basis for a reliable assessment of the factors governing reactivity.

The experimental kinetic constants were rationalized in terms of global and local reactivity indices derived from density functional theory. Thus the predictive power of the theoretically evaluated reactivity descriptors was assessed by direct comparison with experimental results.

## KINETIC EXPERIMENTS AND THEORETICAL COMPUTATIONS

Kinetic experiments

Substituted carbamates were obtained through condensation of the corresponding phenols with equivalent amount of phenyl isocyanate in the presence of small amount of triethylamine as catalyst.[13]

The kinetic measurements on the alkaline hydrolysis of a series of phenyl *N*-phenylcarbamates were carried out using UV spectroscopy. We strictly followed the kinetic procedure used by Williams[12] in his study on the alkaline hydrolysis of phenyl *N*-phenylcarbamates. Thus, it was possible to combine his experimental data with the kinetic constants determined in the present study for several additional derivatives. In his work Williams has provided a detailed justification of the adopted kinetic procedure. For three of the molecules studied in the present work the rate of hydrolysis was measured at the

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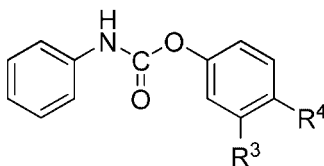
3-N(CH$_3$)$_2$, 3-CH$_3$, 3- CHO, 3-Cl, 3-COOC$_2$H$_5$, 3-NO$_2$, 3-CH$_3$-4-NO$_2$,

4-OCH$_3$, 4-CH$_3$, 4-C(CH$_3$)$_3$, 4-Cl, 4-COCH$_3$, 4-CN, 4-CHO, 4-NO$_2$

Scheme 1. Carbamates under consideration

absorption maximum of the respective final products. In the case of *p-tert*-butylphenyl *N*-phenylcarbamate the kinetic of the reaction was followed through the absorption maximum of the initial carbamate. The rate constants were measured on a Shimadzu UV-1800 spectrophotometer using 1 cm path length quartz cells. The temperature was kept constant at 25 ± 0.1 °C by thermostated cell compartment. The hydrolysis of diphenyl carbamates was performed in water solution with different buffers (pH varied in the 7–9 range, 0.1 ionic strengths). The final concentration of the respective carbamates was about 1×10^{-4} M.

The reactions exhibited pseudo-first-order kinetics, because of the constant concentration of hydroxide ions. Kinetic data were generated to estimate the rate constants, k_{obs}, by plotting $\ln(A_\infty - A_t)$ versus time. The correlation coefficients in the kinetic plots were in the range 0.9980–0.9997. The slope of the line yielded k_{obs}. As an illustration, experimental spectral data and the kinetic chart for the hydrolysis of 3-methylphenyl *N*-phenylcarbamate is presented in Fig. 1. The spectral data and plots for several other derivatives are shown in Figs. S1–S3 in the Supporting Information. The experimentally measured k_{obs} values are given in Table 1. Each rate constant was determined by three independent measurements. Further details for the kinetic measurements are provided in the Supporting Information.

Computational methods

All computations were performed using Gaussian 03[14] suite of programs. Geometries were optimized at DFT level with B3LYP[15–17] functional in combination with 6-311+G(2d,2p)[18,19] basis set. All optimized structures were characterized by analytic computations of harmonic vibrational frequencies at the same level/basis sets. When a molecule has more than one stable conformation, all conformers were examined, and the ones with the lowest energy were employed in the subsequent analysis.

Electrostatic potentials (V_C, V_O),[20,21] natural bond orbital (NBO) charges,[22,23] Hirshfeld charges[24,25,26] at the atoms of the reaction centre as well as the Parr electrophilicity index (ω)[27] were computed with tight self-consistent field convergence. The electrostatic potential at a nucleus Y can be expressed as follows (in atomic units, bold font denotes vector quantities)[21]:

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

In this relation, Z_A is the charge on nucleus A with radius vector $\mathbf{R_A}$, $\rho(\mathbf{r})$ is the electronic density function. Equation (1) contains a summation over all atomic nuclei, treated as positive point charges, as well as integration over the continuous distribution of the electronic charge. Unlike atomic charges, which depend strongly on their definition and additional approximations, the EPN values reflect the variations of electron densities rigorously. The dominant contribution to V_Y comes from the local densities around the respective atomic sites. More negative V_Y values indicate greater electron densities. The EPN index was defined by Wilson[20] in 1962. This quantity was first introduced as a reactivity index for organic compounds in the works of Galabov et al.[28–34] In previous studies[28–30] it was shown that
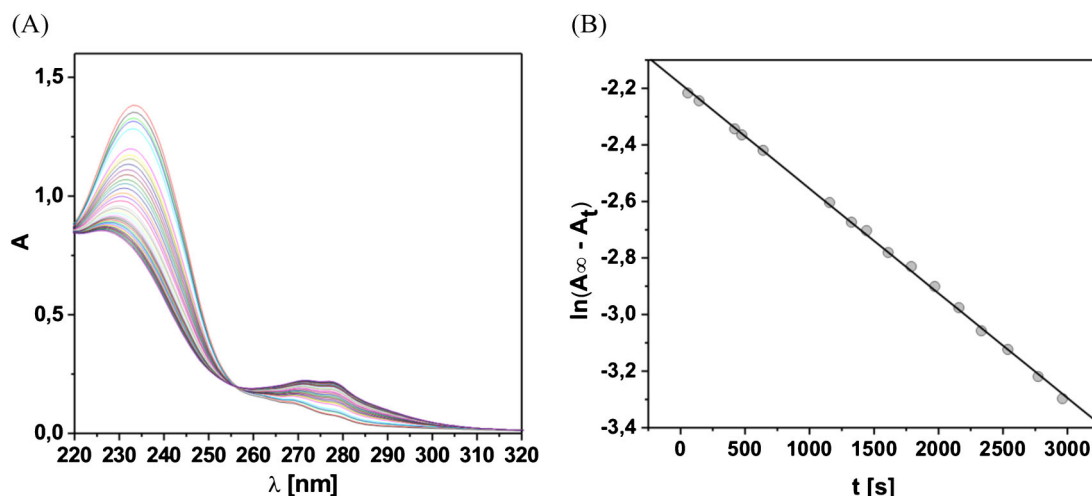
(A)

(B)

Figure 1. (A) The change in the UV spectrum of 3-methylphenyl phenylcarbamate as a function of time (in buffer solution with pH 9). (B) The plot between $\ln(A_\infty - A_t)$ at $\lambda = 271$ nm and time ($r = 0.9996$)

Table 1. Experimentally determined rate constants at 25 °C for the alkaline hydrolysis of phenyl *N*-phenylcarbamates and Hammett substituent constants

R	k_{obs} [s^{-1}]	k^a [s^{-1} M^{-1}]	log k	σ^{-b}
H^c	—	5.48×10^1	1.74	0
3-N(CH$_3$)$_2$^{d}	5.02×10^{-4}	5.02×10^1	1.70	−0.16
3-CH$_3$^{d}	3.71×10^{-4}	3.71×10^1	1.57	−0.07
3-CHO^c	—	1.64×10^3	3.22	0.35
3-Cl^c	—	1.83×10^3	3.26	0.37
3-COOC$_2$H$_5$^{c}	—	1.26×10^3	3.10	0.37
3-NO$_2$^{c}	—	1.32×10^4	4.12	0.71
3-CH$_3$, 4-NO$_2$^{d}	2.47×10^{-2}	2.47×10^5	5.39	1.20^e
4-OCH$_3$^{c}	—	2.52×10^1	1.40	−0.26
4-CH$_3$^{c}	—	3.62×10^1	1.56	−0.17
4-C(CH$_3$)$_3$^{d}	7.60×10^{-4}	4.58×10^1	1.66	−0.13
4-Cl^c	—	3.07×10^2	2.49	0.19
4-COCH$_3$^{c}	—	4.23×10^4	4.63	0.84
4-CN^c	—	4.11×10^4	4.68	1.00
4-CHO^c	—	6.60×10^4	4.82	1.03
4-NO$_2$^{c}	—	2.71×10^2	5.43	1.27
Correlation coefficient r				0.994

^{a} $k = k_{obs}/[OH^-]$.
^{b} From Ref.[49]
^{c} From Ref.[12]
^{d} From the present study.
^{e} Sum of σ(3-CH$_3$) and σ^-(4-NO$_2$).

the electrostatic potential at nuclei (EPN) can be applied as a highly accurate descriptor of the ability of molecules to form hydrogen bond complexes either as proton donors or proton acceptors. EPN proved also a reliable reactivity index for chemical reactions.[31,32] The electrostatic potential at nuclei found recently further successful applications as a reactivity descriptor and provided solutions to various chemical problems.[35–45]

The electrophilicity index ω, proposed by Parr *et al.*,[27] was considered as well. It is defined by the relationship,

$$\omega = \mu^2/2\eta \tag{2}$$

where μ is the electronic chemical potential and η is the total hardness.

There is a continuing interest in applying the Hammett equation[46–48] in characterizing of the reactivity of organic system. The Hammett relationships were recently substantiated theoretically by electronic structure computations on a variety of systems.[41,49–55]

RESULTS AND DISCUSSION

Literature data[12,56–58] revealed that the favoured mechanism of the alkaline hydrolysis of phenylcarbamates follows an E1cB elimination–addition stepwise pathway (Scheme 2). Studies on the effect of substituents indicated[56] that the reaction rate is controlled by the second stage of the process associated with the release of a phenolate. As discussed, Williams[12] has studied the kinetics of the alkaline hydrolysis of a series of twelve substituted phenyl *N*-phenylcarbamates. He established good correlations between the logarithm of the rate constants and the Hammett σ^- constants. The conclusions from this work
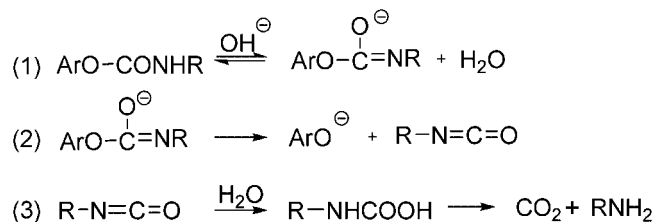
Scheme 2. General scheme for the mechanism of the alkaline hydrolysis of aromatic carbamates

supported previous studies and confirmed the second stage of the process, namely formation of an aryl isocyanate and release of phenolate, as rate controlling.

In the present study we rationalize the reactivity of aryl carbamates in the alkaline hydrolysis with the aid of electronic parameters. We tested the quality of theoretical reactivity descriptors by comparisons with a set of kinetic constants, which combines the data reported by Williams[12] with those obtained in the present study. The extended set of experimental kinetic data provided a valuable basis for analysing critically the reactivity trends for the reaction studied and the predictive power of theoretical indices.

We examined the effects of structural changes on several theoretical quantities that characterize the variations of electron densities at particular atomic sites of the functional group involved in the hydrolysis process. As already discussed, three types of local reactivity descriptors were evaluated: NBO atomic charges[22,23]; Hirshfeld atomic charges[24–26]; electrostatic potential at nuclei values (EPN).[20,21] In addition we also evaluated the
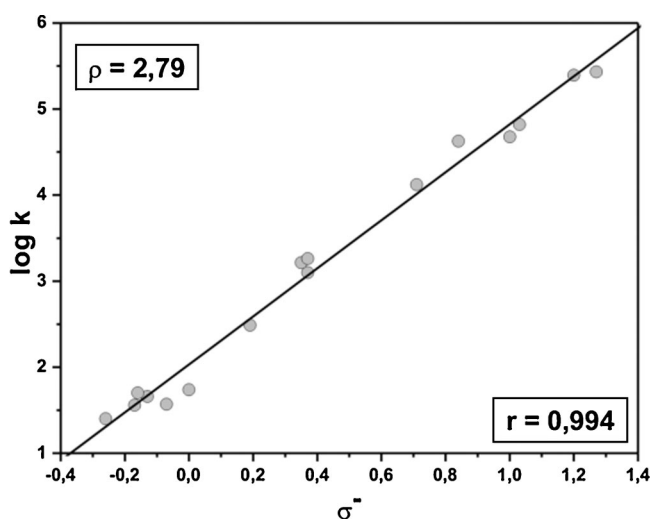
Figure 2. Dependence between experimental rate constants (log *k*) for the alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates and σ^- substituent constants ($r = 0.994$)

Parr electrophilicity index ω. This quantity is expected to characterize the global electrophilicity of the molecule considered.

The kinetic data employed in the analysis are summarized in Table 1. The second column contains the four rate constants determined in this study. The influence of polar groups in the aromatic ring is reflected by the variations of the electrostatic potential values as well as the NBO and Hirshfeld charges at the atoms of the electrophilic centre. The electron withdrawing substituents favour the interaction between the two reactants. Inversely, electron donating substituents, such as CH_3, OCH_3 and

$N(CH_3)_2$, hamper the reaction with the electronegative hydroxide ion. The final column contains the σ^- constants of the respective substituents. An excellent correlation (Fig. 2) between log *k* and σ^- constants is established ($r = 0.994$), in accord with the earlier findings of Williams.[12] This result has been interpreted as a clear indication that a transition state with well expressed phenolate character controls the rate of the alkaline hydrolysis of phenylcarbamates.[12]

We conducted correlation analysis for the dependences between log *k* values and the four theoretical reactivity indices evaluated in the present work. Table 2 compares the derived electronic parameters with the experimental log *k*. The last row of the table contains the correlation coefficients for the dependences between log *k* and the reactivity indices considered. Since the hydrolysis of aryl carbamates involves breaking of the ester –CO–O– bond we focused our analysis on the variation of electronic structure around the carbonyl carbons and ester oxygens. Highest correlation coefficients are obtained with the set of Hirshfeld atomic charges at the carbonyl carbon atom ($r = 0.980$). Somewhat unexpectedly, the electrostatic potentials V_C and V_O did not perform quite well. The global electrophilicity index did not correlate with the experimental rate constants ($r = 0.888$). All correlation coefficients obtained are, however, distinctly lower than correlation with the σ^- constants. These results should not be regarded as too surprising. As already discussed, the first stage of the reaction involves the elimination of hydrogen from the NH group (Scheme 2). The rate-determining second stage involves the formation of an isocyanate grouping and the release of phenolates, which contain the substituents. The structure of the rate-controlling transition state as obtained from B3LYP/6-31+G(d,p) computations is shown in Fig. 3. The leaving group has well expressed phenolate ion character. Thus, the electronic structure of the

Table 2. Experimental rate constants and theoretical reactivity indices at B3LYP/6-311+G(2d,2p) for reactant phenyl *N*-phenylcarbamates

| R | log *k* | Hirshfeld charges [e] | | NBO charges [e] | | EPN [a.u.] | | ω [eV] |
		q_C	q_O	q_C	q_O	V_C	V_O	
H	1.74	0.2443	−0.1322	0.9389	−0.5792	−14.6087	−22.3106	2.25
3-N(CH$_3$)$_2$	1.70	0.2433	−0.1324	0.9397	−0.5798	−14.6148	−22.3187	1.86
3-CH$_3$[a]	1.57	0.2440	−0.1324	0.9394	−0.5792	−14.6103	−22.3129	2.19
3-CHO[a]	3.22	0.2452	−0.1314	0.9380	−0.5779	−14.5988	−22.2987	4.46
3-Cl[a]	3.26	0.2457	−0.1296	0.9386	−0.5775	−14.6023	−22.3025	2.53
3-COOC$_2$H$_5$[a]	3.10	0.2447	−0.1315	0.9385	−0.5778	−14.6044	−22.3055	3.45
3-NO$_2$[a]	4.12	0.2468	−0.1279	0.9378	−0.5747	−14.5936	−22.2921	6.14
3-CH$_3$, 4-NO$_2$	5.39	0.2476	−0.1255	0.9378	−0.5742	−14.5929	−22.2913	5.48
4-OCH$_3$[a]	1.40	0.2429	−0.1347	0.9393	−0.5792	−14.6123	−22.3149	2.09
4-CH$_3$[a]	1.56	0.2438	−0.1330	0.9392	−0.5788	−14.6109	−22.3132	2.17
4-C(CH$_3$)$_3$	1.66	0.2436	−0.1335	0.9393	−0.5793	−14.6114	−22.3139	2.15
4-Cl[a]	2.49	0.2449	−0.1312	0.9382	−0.5779	−14.6028	−22.3032	2.52
4-COCH$_3$[a]	4.63	0.2469	−0.1264	0.9388	−0.5748	−14.5994	−22.2991	3.84
4-CN	4.68	0.2472	−0.1267	0.9376	−0.5754	−14.5931	−22.2914	4.77
4-CHO[a]	4.82	0.2473	−0.1259	0.9383	−0.5748	−14.5963	−22.2953	4.26
4-NO$_2$[a]	5.43	0.2481	−0.1246	0.9375	−0.5737	−14.5905	−22.2879	5.85
Correlation coefficient *r*		0.980	0.973	0.832	0.972	0.949	0.947	0.888

[a] From Ref.[12]

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1169

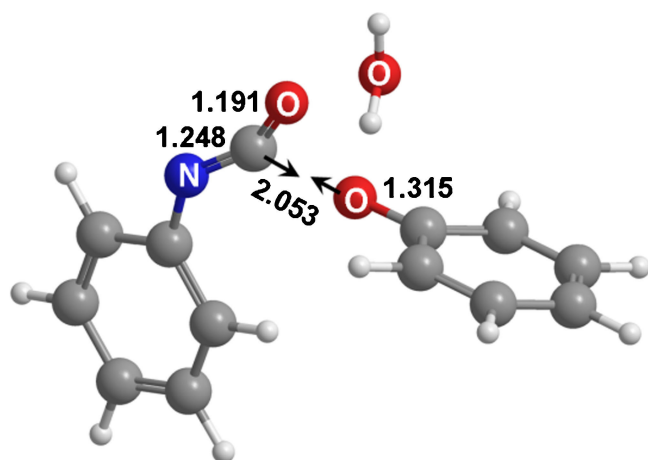**Figure 3.** B3LYP/6-31+G(d,p) optimized structure of the rate-controlling transition state in the alkaline hydrolysis of phenyl *N*-henylcarbamate

Figure 4. Dependence between experimental rate constants ($\log k$) and EPN values for product phenolates (V_O) for the alkaline hydrolysis of phenyl *N*-phenylcarbamates

initial reactants, as reflected in the theoretical reactivity indices included in Table 2, may not be so well related to the electronic structure of the transition state for the rate-controlling stage. It is, therefore, reasonable to analyse the variations of the electronic structure in the phenolate ions, which form at the rate-determining transition state. We examined the correlations between kinetic constants and the evaluated reactivity indices for the phenolate ions. The theoretical data are presented in Table 3 and are compared with the $\log k$ values. The last row contains the correlation coefficients for the dependences between NBO and Hirshfeld atomic charges as well as the respective EPN values (V_O) with $\log k$. Survey of the data obtained reveals that the best correlation between theoretical reactivity parameters and experimental
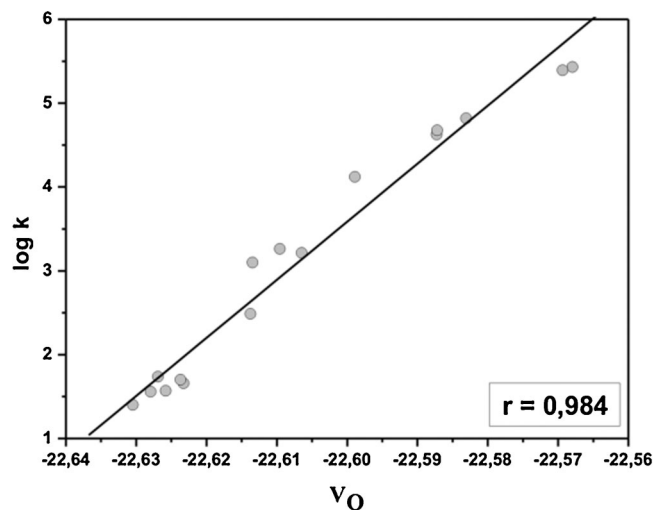
constants is obtained with the EPN values ($r = 0.984$). The plot between $\log k$ and EPN is shown in Fig. 4. The results obtained illustrate once more the accuracy of theoretical description of local properties provided by the electrostatic potential at nuclei.

The present results provide an opportunity to compare the predictive power of experimental (σ^-) and theoretically derived (atomic charges, EPN, ω) reactivity indices. Quite clearly the best correlation is achieved between the experimental rate constants and the σ^- constants (Fig. 2). Studies on other reactions have shown, however, that theoretically derived reactivity parameters can provide competitive, and in a number of cases, superior than

Table 3. Experimental rate constants for the alkaline hydrolysis of phenyl *N*-phenylcarbamates and theoretical reactivity indices for product phenolates at B3LYP/6-311+G(2d,2p)

R	$\log k$	Hirshfeld charges [e] q_O	NBO charges [e] q_O	EPN [a.u.] V_O
H[a]	1.74	−0.4749	−0.7947	−22.6269
3-N(CH$_3$)$_2$	1.70	−0.4707	−0.7903	−22.6237
3-CH$_3$[a]	1.57	−0.4730	−0.7922	−22.6258
3-CHO[a]	3.22	−0.4618	−0.7798	−22.6065
3-Cl[a]	3.26	−0.4566	−0.7733	−22.6096
3-COOC$_2$H$_5$[a]	3.10	−0.4663	−0.7861	−22.6135
3-NO$_2$[a]	4.12	−0.4520	−0.7697	−22.5989
3-CH$_3$, 4-NO$_2$	5.39	−0.4075	−0.7117	−22.5694
4-OCH$_3$[a]	1.40	−0.4862	−0.8080	−22.6305
4-CH$_3$[a]	1.56	−0.4783	−0.7980	−22.6279
4-C(CH$_3$)$_3$	1.66	−0.4739	−0.7929	−22.6233
4-Cl[a]	2.49	−0.4659	−0.7844	−22.6138
4-COCH$_3$[a]	4.63	−0.4265	−0.7354	−22.5873
4-CN	4.68	−0.4324	−0.7438	−22.5872
4-CHO[a]	4.82	−0.4218	−0.7299	−22.5831
4-NO$_2$[a]	5.43	−0.4065	−0.7109	−22.5680
Correlation coefficient r		0.960	0.952	0.984

[a] From Ref.[12]

experimental indices description of chemical reactivity.[31–33,55] The current results revealed that the theoretical quantities can be most closely associated with the actual mechanism of the reaction (in our case with properties of the leaving group). In aromatic systems, appropriate reactivity constants for polysubstituted derivatives are not available, while there are no limitations in evaluating theoretical indices for such systems. In general, the application of both experimental and theoretical quantities in describing reactivity is desirable wherever possible.

Chemical reactivity is usually discussed in terms of properties of the initial reactants. The example of alkaline hydrolysis of aryl carbamates, however, shows that such an approach may not always be correct. For the systems studied, the electronic properties of the leaving group are better descriptors of reactivity because of their closeness to the structure of the rate-controlling transition state. Thus, knowledge on the mechanism of the process is essential for the correct analysis of reactivity and the comparisons between theoretical descriptors and experimental kinetic data.

CONCLUSIONS

A number of reactivity indexes were explored in describing the reactivity of 16 substituted in the aromatic ring phenyl *N*-phenylcarbamates in the alkaline hydrolysis reaction. An extended set of experimental kinetic constants were correlated with Hirshfeld and NBO charges at the atoms of the reaction centre, the electrostatic potential at nuclei at the same atoms, and the Parr electrophilicity index. The theoretical indices were evaluated for both reactants and the leaving groups. The best correlation between theory and experiment was obtained with the EPN index ($r = 0.984$) for the leaving group (phenolate ions). This result is in accord with literature findings, indicating that the rate of the hydrolysis process is governed by the second transition state, which has a well-expressed phenolate character.

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