Acidic and alkaline bimolecular hydrolysis of substituted formanilides. Computational analysis and modelling of substitution effects

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Abstract: In this article, the study of 67 compounds representing various *para-*, *meta-* and *ortho-* substituted formanilides is presented. These molecules and the products of their acidic and alkaline hydrolysis were studied using DFT quantum chemical methods in order to calculate the reaction enthalpies. These enthalpies are correlated with the hydrolysis rate constants, k_H, published for the acid-catalysed acyl cleavage bimolecular ($A_{AC}2$) mechanism and the modified base-catalysed acyl cleavage bimolecular ($B_{AC}2$) mechanism. The found linear dependences can be used for the prediction of rate constants of non-synthesised formanilide derivatives.

Keywords: Substituent Effect; Chemical Kinetics; Model Compound; Thermodynamic, *Trans* Isomer, *Cis* Isomer

1. Introduction

Amides are versatile organic compounds since atoms in the amide group (—NH—CO—) can be attacked by an electrophile. This is a result of the π-electrons delocalisation along the amide moiety, yielding hybrid ground state structure of the two resonance forms. Biologically active compounds possess amide groups with hydrophobic residue in their close vicinity (Krátky et al., 2011; Dank et al., 2015). These compounds are able to interact and bind with various enzymes/receptors and affect the biological response. Therefore, the reason for the widespread occurrence of amides in modern pharmaceuticals and biologically active compounds is obvious (Pesko et al., 2015). Formanilides represent a suitable group of model compounds as the simplest aromatic molecules with a peptide bond (Marochkin et al., 2013). Formanilides are not as stable as acetanilides, but the amide moiety can be easily modified by various substitutions in order to improve their hydrolytic stability and other properties. On the other hand, a study of the hydrolysis requires only mild experimental conditions.

The amide bond in the formanilides and acetanilides is isolated, freely rotating, and it does not have any significant steric restrictions due to the acyl component of the moiety. Hydrolytic reactivity of formanilide and its 28 ring substituted derivatives with respect to the selected monosubstituted positions in acidic and alkaline environments was studied experimentally (Desai et al., 2015). In di-lute hydrochloric acid (0.01−8 M, 20−60 °C), the hydrolytic degradation runs *via* the acid catalysed acyl cleavage bimolecular $A_{AC}2$ mechanism. This mechanism involves protonation of the amide at the carbonyl oxygen. The carbonyl carbon is then attacked by water to form the tetrahedral intermediate which can degrade to products through a series of fast proton transfers or revert to the initial substrate. The modified base-catalysed acyl cleavage bimolecular $B_{AC}2$ mechanism was also reported for sodium hydroxide solutions (0.01−3 M, 25 and 40 °C). The reaction solutions were quenched and analysed by high performance liquid chromatography to identify the reaction products. Dependences of the evaluated hydrolysis rate constants on the Hammett constants were also discussed. The authors observed simple linear correlations only for the *meta-* and *para-*substituted derivatives, while multilinear regression was used for the *ortho* substitution effect description. A theoretical view on the alkaline amide hydrolysis of acetanilides including a series of six *para-*substituted acetanilides was suggested (Cheshemdzhieva et al., 2009). The authors tried to correlate the reactivity with the NBO atomic charges and electrostatic potentials at the atoms of the reaction centre.

With respect to the published works, we decided to present a systematic theoretical study of reaction enthalpies for both proposed bimolecular reaction schemes (Scheme 1). The main goal was to perform a quantum chemical thermodynamic study of formanilide and its 66 monosubstituted derivatives
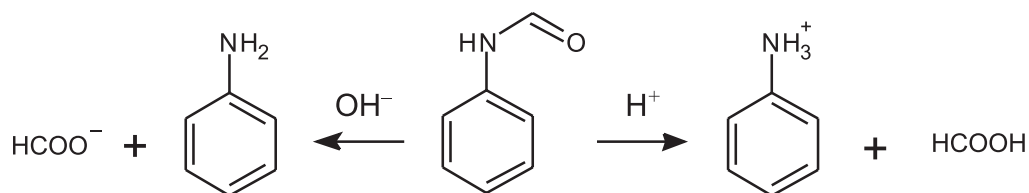
Scheme 1. Cumulative reaction scheme for the acidic and alkaline hydrolysis of formanilides.
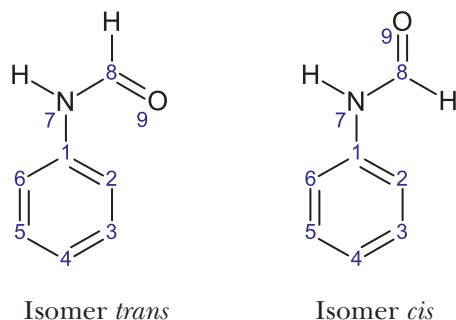

Isomer *trans*   Isomer *cis*

Fig. 1. Schematic structure of formanilide derivatives with atom numbering.

in *ortho*, *meta* and *para* positions (Fig. 1). The evaluated reaction enthalpies were correlated with the experimentally obtained kinetic rate constants of hydrolysis. The obtained dependences were used for the prediction of the hydrolysis rate constants.

2. Computational details

The quantum chemical calculations were performed using the Gaussian 09 program package (Frisch et al., 2009). Optimal geometries of the studied molecules in the neutral and ionic forms were calculated in water using the DFT method with B3LYP (Becke's three parameter Lee–Yang–Parr) functional (Lee et al., 1988; Becke, 1988) without any constraints (energy cut-off of 10^{-5} kJ×mol^{-1}, final RMS energy gradient below 0.01 kJ×mol^{-1}×A^{-1}). For all calculations, the 6-311++G(d,p) basis set was employed (Hariharan et al., 1973; Rassolov et al., 1998). The influence of the solvents was approximated by the continuum Solvation Model based on the quantum mechanical charge Density (SMD) (Marenich et al., 2009) of a solute molecule interacting with a continuum. The optimised structures were confirmed to be real minima by a frequency analysis (no imaginary frequencies). The reaction enthalpies, $\Delta_r H(A_{AC}2)$, for acidic hydrolysis were calculated based on total enthalpies, H, obtained from Eq. 1

$$\Delta_r H(A_{AC}2) = H(R\text{—}NH_3^+) + H(HCOOH) -$$
$$- H(R\text{—}NHCO) - H(H_3O^+) \tag{1}$$

Symbol $H(R\text{—}NH_3^+)$ stands for the total enthalpy of

the anilinium ion, $H(HCOOH)$ is the total enthalpy of formic acid (–189.800086 hartree) and $H(R\text{—}NHCO)$ represents the total enthalpy of the parent molecule. The B3LYP(SMD)/6-311++G(d,p) value for hydronium H_3O^+ in water is –76.846887 hartree. Reaction enthalpies, $\Delta_r H(B_{AC}2)$, for alkaline hydrolysis were calculated according to Eq. 2

$$\Delta_r H(B_{AC}2) = H(R\text{—}NH_2) + H(HCOO^-) -$$
$$- H(R\text{—}NHCO) - H(OH^-) \tag{2}$$

Symbol $H(R\text{—}NH_2)$ stands for the total enthalpy of aniline, while $H(HCOO^-)$ is the total enthalpy of deprotonated formic acid (–189.360285 hartree) and the enthalpy of the hydroxyl anion $H(OH^-)$ is –75.966655 hartree. The enthalpies were evaluated for $T = 298.15$ K.

3. Results and Discussion

In case of the parent formanilide molecule, the possible mutual orientation of the carbonyl C8═O group with respect to the N7—H pair leads to two possible conformations (see Fig. 1). The B3LYP calculation for the parent molecule indicates that the *trans* conformer is practically planar, while the dihedral angle between the aromatic ring and the amide group is 27° for the *cis*-isomer. The electronic energy difference is 0.5 kJ×mol^{-1}, suggesting similar population of the *trans* and *cis* conformers. *Ortho* substitution influences the mutual orientation of the aromatic ring and the terminal —NH—COH moiety, resulting in a more populated *trans* conformation. The energy differences between *trans* and *cis* conformations are in the range from 0.27 to 11.35 kJ×mol^{-1}. Therefore, the calculations were performed for the *trans* conformations.

As already emphasised, the principal aim of this study was to analyse the correlations between the calculated reaction enthalpies for the studied series of formanilides and the experimentally determined rate constants for acidic and alkaline hydrolysis. Under the conditions studied, all investigated molecules were essentially non-dissociated substrates. The obtained Hammett plots are not linear and they display a downward curvature. For *meta*-substituted formanilides, deactivating groups (e.g. nitro-, cyano- and carboxyl-) led to an increase

Tab. 1. Hammett substituent constants (σ_p, σ_m) (Hansch et al., 1991), acidic hydrolysis rate constants (k_H) (Desai et al., 2015) and corresponding B3LYP(water) reaction enthalpies ($\Delta_r H$).

| Substituent	Hammett constants		k_H/hr^{-1}			$\Delta_r H(A_{AC}2)$/kJ mol^{-1}			$\Delta_r H(B_{AC}2)$/kJ mol^{-1}		
	σ_p	σ_m	*para*	*meta*	*ortho*	*para*	*meta*	*ortho*	*para*	*meta*	*ortho*
—NO$_2$	0.78	0.71	27.30	11.30	24.9	−42.394	−48.503	−71.078	−103.114	−89.267	−138.180
—COOH	0.45	0.37	18.20	8.21	24.6	−50.108	−54.988	−95.621	−93.129	−84.875	−133.698
—Br	0.23	0.39	8.32	10.80	2.57	−55.566	−53.615	−70.833	−83.449	−85.838	−115.798
—Cl	0.23	0.37	7.04	9.65	7.24	−56.152	−53.715	−76.512	−83.192	−85.691	−115.136
—H	0.00	0.00	7.39	7.39	7.39	−60.302	−60.302	−60.302	−81.159	−81.159	−81.159
—Ph	−0.01	0.06	7.53	–	3.17	−59.334	−59.814	−92.546	−81.889	−81.551	−114.388
—C$_2$H$_5$	−0.15	−0.07	4.60	6.21	2.07	−62.366	−61.576	−99.220	−78.411	−80.632	−116.357
—isoC$_3$H$_7$	−0.15	−0.05	5.42	6.05	1.39	−62.264	−62.151	−102.234	−78.555	−80.233	−118.841
—CH$_3$	−0.17	−0.07	5.06	6.58	2.57	−62.080	−61.198	−97.910	−77.859	−80.335	−115.874
—OCH$_3$	−0.27	0.12	2.95	8.59	5.23	−63.857	−59.418	−91.302	−75.919	−82.483	−111.006
—OH	−0.37	0.12	2.67	7.80	3.81	−63.285	−56.293	−105.984	−75.420	−83.126	−125.614

a)

b)

c)
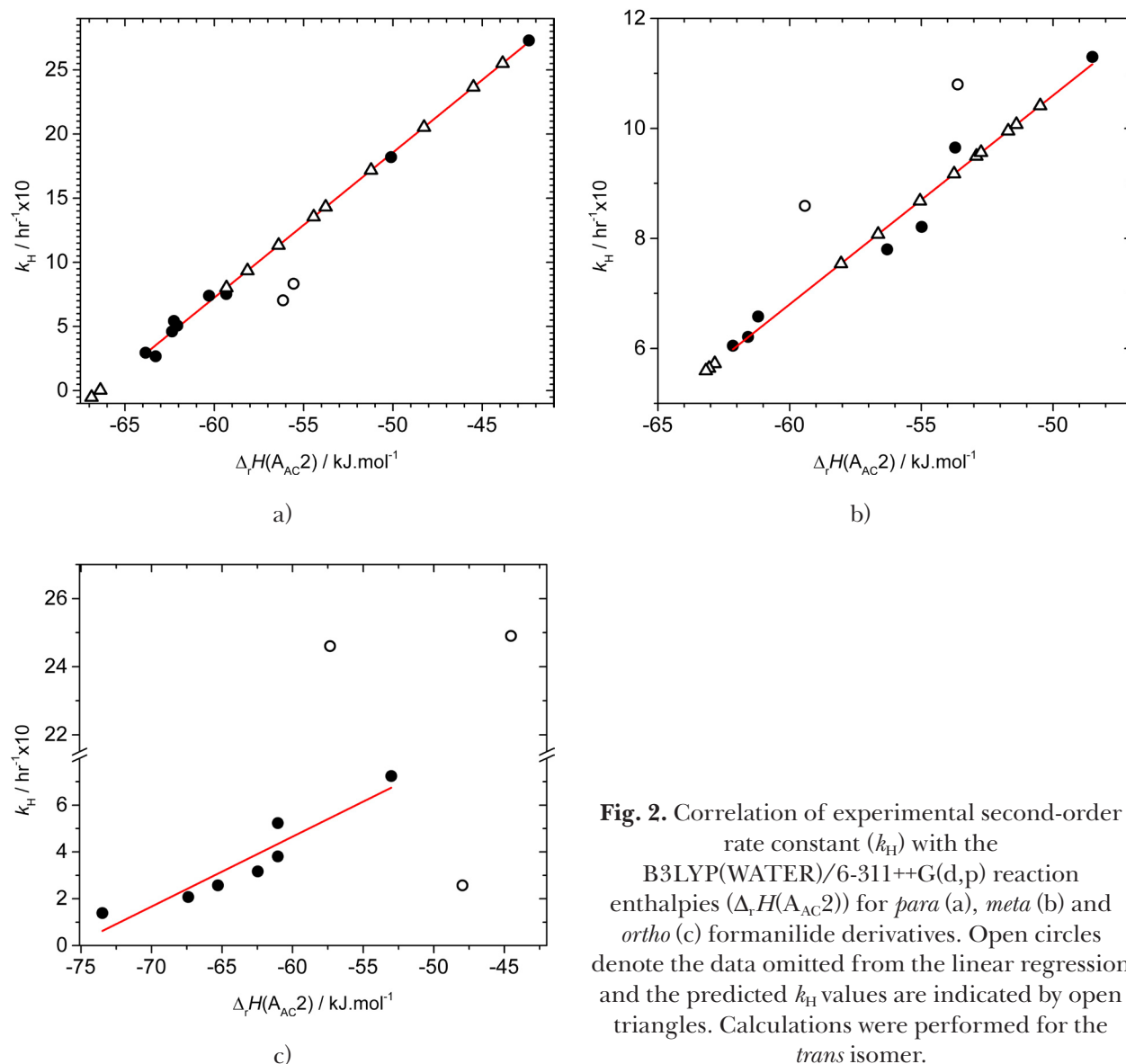
Fig. 2. Correlation of experimental second-order rate constant (k_H) with the B3LYP(WATER)/6-311++G(d,p) reaction enthalpies ($\Delta_r H(A_{AC}2)$) for *para* (a), *meta* (b) and *ortho* (c) formanilide derivatives. Open circles denote the data omitted from the linear regression and the predicted k_H values are indicated by open triangles. Calculations were performed for the *trans* isomer.

Tab. 2. Hammett substituent constants (σ_p, σ_m) (Hansch et al., 1991) predicted acidic hydrolysis rate constants (k_H) and corresponding B3LYP(water) reaction enthalpies ($\Delta_r H$).

Substituent	Hammett constants		k_H/hr^{-1}		$\Delta_r H(A_{AC}2)$/kJ mol^{-1}			$\Delta_r H(B_{AC}2)$/kJ mol^{-1}		
	σ_p	σ_m	*para*	*meta*	*para*	*meta*	*ortho*	*para*	*meta*	*ortho*
—NO	0.91	0.62	31.0	10.4	–38.997	–50.488	–42.034	–108,606	–87,382	–106,309
—CN	0.66	0.56	23.7	10.0	–45.500	–51.696	–46.839	–90,926	–86,833	–98,002
—COCl	0.61	0.51	25.5	10.1	–43.862	–51.389	–47.432	–100,528	–87,067	–106,309
—CF$_3$	0.54	0.43	14.3	9.5	–53.765	–52.904	–51.447	–91,942	–85,599	–95,952
—CCl3	0.46	0.40	17.2	9.6	–51.221	–52.728	–46.574	–89,918	–85,402	–96,306
—CHO	0.42	0.35	20.5	8.7	–48.265	–55.049	–52.851	–95,959	–86,143	–96,695
—CCH	0.23	0.21	13.5	8.1	–54.434	–56.643	–61.665	–86,539	–84,142	–97,653
—SH	0.15	0.25	8.0	7.5	–59.326	–58.050	–54.458	–79,500	–83,709	–86,437
—CH$_2$F	0.11	0.33	11.3	5.7	–56.398	–62.841	–59.945	–85,132	–87,710	–87,030
—F	0.06	0.34	9.3	9.2	–58.150	–53.757	–55.382	–80,566	–84,449	–90,296
—NH$_2$	–0.66	–0.16	–0.5	5.6	–66.871	–63.059	–62.605	–71,521	–80,288	–76,867
—NMe$_2$	–0.83	–0.15	0.0	5.6	–66.386	–63.177	–64.267	–72,136	–79,140	–80,650

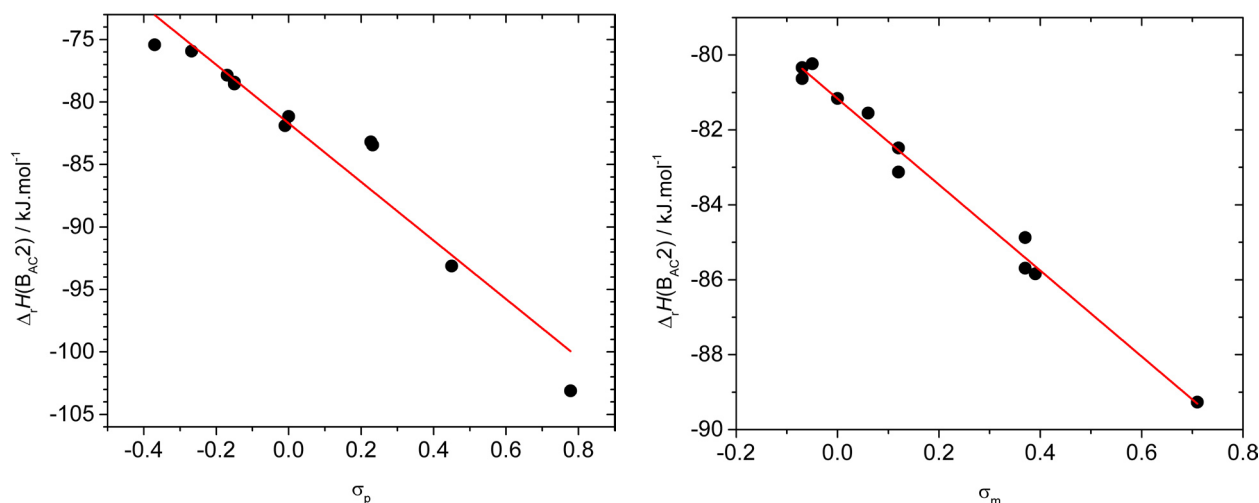**Fig. 3.** Correlation of B3LYP(WATER)/6-311++G(d,p) reaction enthalpies $\Delta_r H(B_{AC}2)$ for *para* (a) and *meta* (b) formanilide derivatives with Hammett constants. Enthalpies were calculated for alkaline hydrolysis at 25 °C and *trans* isomers.
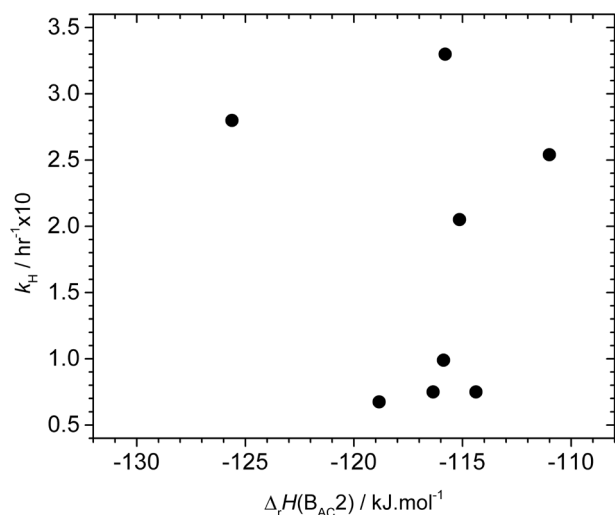

Fig. 4. Dependence of experimental rate constants of alkaline hydrolysis at 25 °C (k_H) on the B3LYP(WATER)/6-311++G(d,p) reaction enthalpies ($\Delta_r H(B_{AC}2)$) for *ortho* formanilide derivatives. Calculations were performed for the *trans* isomer.

in the rate constant (k_H), whereas activating substituents (e.g. amino-, methyl-, isopropyl-) caused a slight decrease of k_H which increased the electron donating capability. A similar trend can be observed for *para* substituents except for the strong electron-withdrawing substituents capable of resonance interactions (p-NO$_2$ and p-COOH) (see Fig. 2a).

The data collected in Tab. 1 and depicted in Fig. 2 enable the comparison of the substituent effect on the k_H values with respect to the reaction enthalpy, $\Delta_r H(A_{AC}2)$. Linear dependences with $R = 0.998$ (Fig. 2a) and 0.981 (Fig. 2b) were found, showing better linearity than the Hammett type dependences for rate constants. From the linear regression depicted in Fig. 2, the following equations were obtained

$$k_H = 75.1(1.5) + 1.131(25)\,\Delta_r H(A_{AC}2) \quad (3)$$

$$k_H = 29.6(1.7) + 0.380(30)\,\Delta_r H(A_{AC}2) \quad (4)$$

Based on Eqs. 3 and 4, k_H values for the non-synthesised derivatives were predicted and are shown in Fig. 2 as open triangles.

A similar linear dependence observed for the *ortho* derivatives yielded correlation coefficient $R = 0.940$ (Fig. 2c). From the linear regression, the following equation was obtained

$$k_H = -22.6(3.1) + 0.298(49)\,\Delta_r H(A_{AC}2) \quad (5)$$

For 0.1 M sodium hydroxide solutions, Desai and Kirsch (2015) reported that the Hammett plots for hydrolysis of *meta*- and *para*-substituted formanilides do not indicate any substituent effect. On the other hand, direct comparison of the reaction enthalpy, $\Delta_r H(B_{AC}2)$, for *para* and *meta* derivatives with the Hammett constants (see Tab. 2) indicates linear dependences with correlation coefficients $R = 0.966$ for *para*- and 0.994 for *meta*-substituents

$$\Delta_r H(B_{AC}2)/kJ \cdot mol^{-1} = -81.70(69) - 23.4(2.1)\,\sigma_p \quad (6)$$

$$\Delta_r H(B_{AC}2)/kJ \cdot mol^{-1} = -81.17(13) - 11.47\,\sigma_m \quad (7)$$

From Fig. 3, the substituent effect on the reaction enthalpy is evident. The dependence of the rate constants on the reaction enthalpies of *para* and *meta* derivatives for alkaline hydrolysis exhibits no linearity, similarly as in case of the *ortho* derivatives (see Fig. 4). Correlation coefficients evaluated for the linear regressions are lower than 0.70. As it was reported by Desai and Kirsch (2015), the possible linear dependence can be evaluated only between $\log k_{obs}$ and the Taft-Kutter-Hansch steric substituent values, E$_s$.

4. Conclusions

A series of compounds representing various *para*-, *meta*- and *ortho*-substituted formanilides were studied. Reaction enthalpies for acidic and alkaline hydrolysis were evaluated using the DFT quantum chemical method and correlated with the hydrolysis rate constants published for the bimolecular ($A_{AC}2$) mechanism of acid-catalysed acyl cleavage. The obtained linear dependences can be employed to predict rate constant of non-synthesised formanilide derivatives. For the modified base-catalysed acyl cleavage, the bimolecular ($B_{AC}2$) mechanism, the reaction enthalpies were correlated with the Hammett constants. In case of the *ortho* derivatives, no linear dependence between k_H and $\Delta_r H(B_{AC}2)$ was found due to the synergic and antagonistic influence of the steric and solvent effects on the molecular electronic structure. Finally, we would like to note that the quantum chemical calculations provide also additional microscopic properties, which can be potentially used to describe the substitution effect, e.g. energies of frontier orbitals, partial charges on selected atoms, dipole moments and the selected bond distances. However, correlations of these quantities with the experimental rate constants were not satisfying. The results obtained can be useful for the development of novel formanilide derivatives.

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