Kinetic and mechanism of the addition of piperidine and benzylamine to the aroylacrilic acid phenylamides

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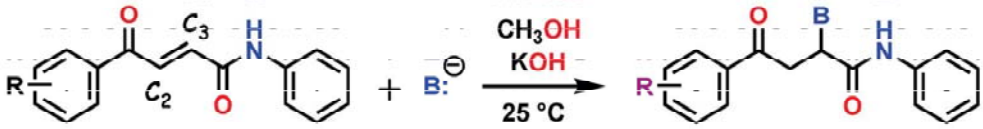
Introduction

The nucleophilic 1,4- Michael addition of amines or thiols to the activated double bonds of the xenobiotics has been suggested as a primary outcome responsible for their biological activity.[1] Knowledge on the mechanism of aza Michael addition to such compounds is important contribution for understanding their biological effects.

Results and discussion

Spectrophotometrically, under the pseudo-first order conditions, second order rate constants (k_2) for the Michael addition of piperidine and benzylamine to compounds **1-13**, in methanol, were obtained (**Table 1**).

*Table 1. Addition of deprotonated amines (piperidine and benzylamine, **B:**$^-$) to compounds **1-13**. Structures, reaction sheme, calculated charges and the Hammmett substituent constants.*



Comp N°	R-	k_2 ($M^{-1}s^{-1}$) (piperidine)	k_2 ($M^{-1}s^{-1}$) (benzylamine)	SP charge* (vacuum)	SP charge* (MeOH)	σ^2
1	tetralinil	0.64 (±0.05)	0.45 (±0.06)	−0.15233	−0.15499	−0.48
2	3,4-di-Cl	3.87 (±0.27)	1.84 (±0.22)	−0.14684	−0.14939	0.52
3	3,4-di-Me	0.74 (±0.13)	0.25 (±0.01)	−0.15228	−0.15515	−0.14
4	2,4-di-*i*-Pr	0.57 (±0.01)	0.53 (±0.03)	−0.14291	−0.14037	/
5	4-H	0.79 (±0.09)	0.50 (±0.01)	−0.15054	−0.15347	0
6	4-OMe	0.35 (±0.03)	0.23 (±0.03)	−0.15281	−0.15567	−0.27
7	2,5-di-Me	1.58 (±0.12)	0.84 (±0.04)	−0.14233	−0.13922	/
8	4-F	1.52 (±0.12)	0.76 (±0.08)	−0.14952	−0.15274	0.06
9	4-Br	1.84 (±0.15)	1.31 (±0.05)	−0.14884	−0.15026	0.23
10	4-*n*-Bu	0.43 (±0.05)	0.33 (±0.03)	−0.15189	−0.15452	−0.16
11	4-*t*-Bu	0.62 (±0.06)	0.45 (±0.02)	−0.15168	−0.15286	−0.20
12	4-*i*-Pr	0.47 (±0.05)	0.39 (±0.01)	−0.15165	−0.15279	−0.15
13	4-Cl	2.05 (±0.19)	1.25 (±0.13)	−0.14890	−0.15056	0.23

* SP- Mulliken charges, as obtained by single-point calculations in vacuum, or implicit solvent model for methanol.

Addition of amines proceeds exclusively to the activated C_3 atom, not to the C_2 (Table 1), as confirmed by the HMBC spectrum of the addition product of piperidine to compound **13**. The 3D depiction of the addition products of piperidine and benzylamine to compound **5**, are given in Figure 1.

Rate constants were determined by pseudo-first order kinetics,[3] following the decrease of absorbance on ~ 310 nm, using the 20-fold excess of amine (Figure 1).

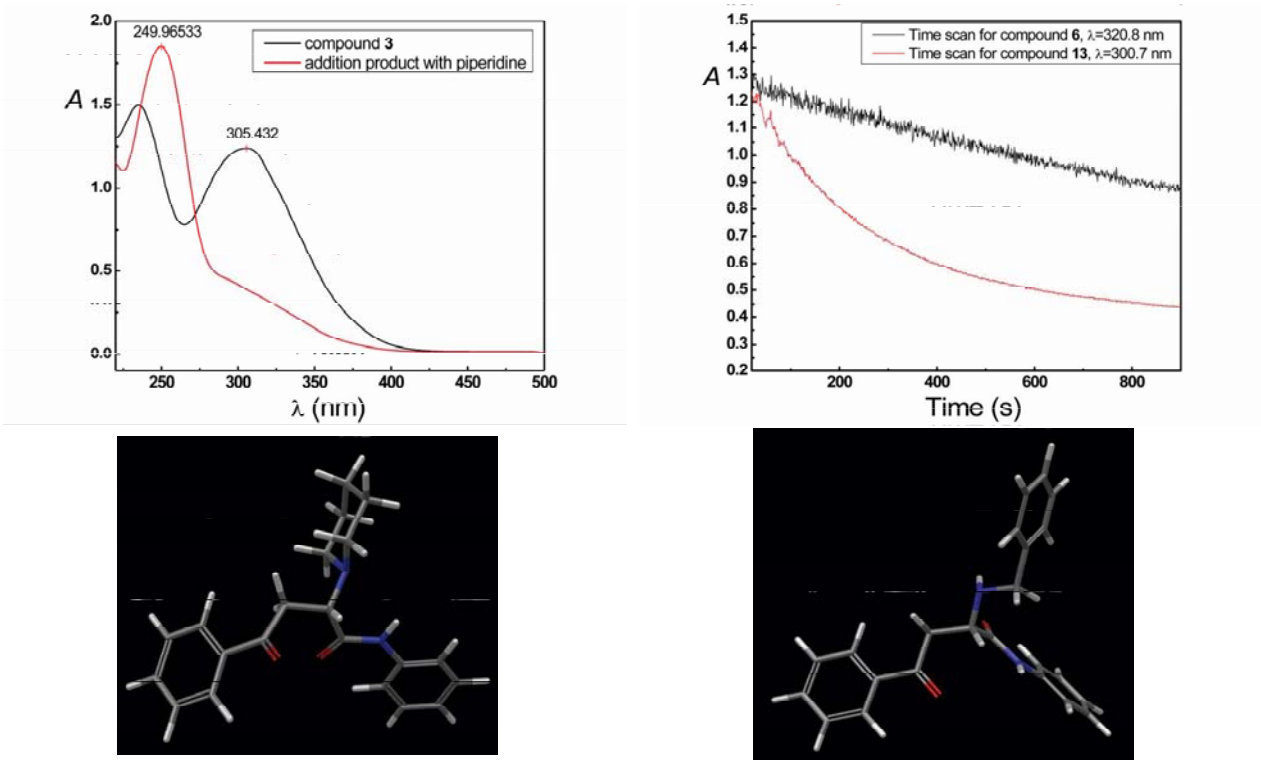


*Figure 1. The UV-VIS spectra of **3**, and its addition product with piperidine (upper left);*
*The difference in time scan curves obtained after the addition of piperidine to compounds **6** and **13** (upper right).*
*The 3D depiction of the addition products of piperidine (lower left) and benyzlamine (lower right) to **5**.*

Amines were deprotonated with the stoichiometric amount of stronger base (KOH) prior to addition, in order to generate the more nucleophilic amine anion. All measurements were done using Cintra 40 UV/VIS spectrophotometer, on the temperature of 25 ± 2 °C.

Rate constants for the addition of piperidine are higher than those for addition of benzylamine, as is expected, concerning basicity of amines used. Rate constants depend on substituent changes on the aroyl ring of the **1-13**. The substituent effects were quantified by using the Hammett substituent parameters (σ_x), as given by Equation 1:

$$\log\frac{k_x}{k_0} = \rho \cdot \sigma_x \qquad (1)$$

Where k_x is the rate constant of the *meta* or *para* X-substituted phenyl derivative, and k_0 is the rate constant for the unsubstituted derivative.

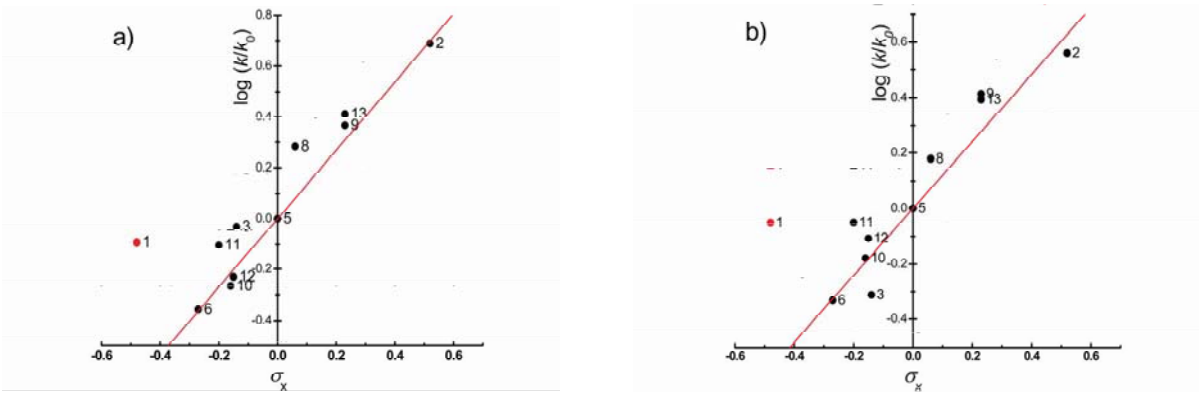


*Figure 2. Hammett plot for the second order rate constants of the addition of piperidine (a) and benzylamine (b) to compounds **1-13**.*

The least squares line fitting through zero gave the following equations:

Piperidine:

$$\log\left(\frac{k_x}{k_0}\right) = 1.35(\pm 0.15)\cdot\sigma_x$$

$$r = 0.96, s = 0.11, N = 10, P < 0.0001$$

Benzylamine:

$$\log\left(\frac{k_x}{k_0}\right) = 1.21(\pm 0.15)\cdot\sigma_x$$

$$r = 0.95, s = 0.11, N = 10, P < 0.0001$$

Reaction constant can be calculated as the slope of Hammett plots (Figure 2a and 2b). Reaction constant, ρ, represents the relative sensitivity of reaction under consideration upon the change of substituents on the aromatic ring. The sign and the magnitude of the reaction constants depend upon the nature of the reactants and the mechanism of reaction. Positive signs of the reaction constants for the addition of piperidine and benzylamine (ρ = 1.35, and ρ = 1.21, respectively) to **1-13** indicate that electron-withdrawing substituents increase the rate of addition. Numerical values of rate constants indicate the formation of the charged species in the rate-limiting step, which is in accordance with proposed mechanism of the formation of carbanionic intermediate, and subsequent rapid protonation of it.[4] Polar solvents are capable to stabilize charged species in the transition state, and lead to the formation of amino adduct. Reaction product was not observed in CCl_4 after 24^h, confirming the importance of polar/charged intermediates in reaction mechanism.

The geometries of the **1-13**, and the addition products of **5** with piperidine and benzylamine were optimized on a semiempirical MO level, using PM6 method,[5] as implemented in MOPAC 2009.[6] In this way obtained geometries were used for the single-point calculations at the DFT level[7] (B3LYP/6-311G**), with and without implicit solvent model (CH_3OH). DFT Calculations were performed by Gaussian03. Mulliken atomic charges, obtained from DFT calculations, were used to examine correlation between k_2 and atomic charges on an electrophilic center. Results are shown on Figure 3.

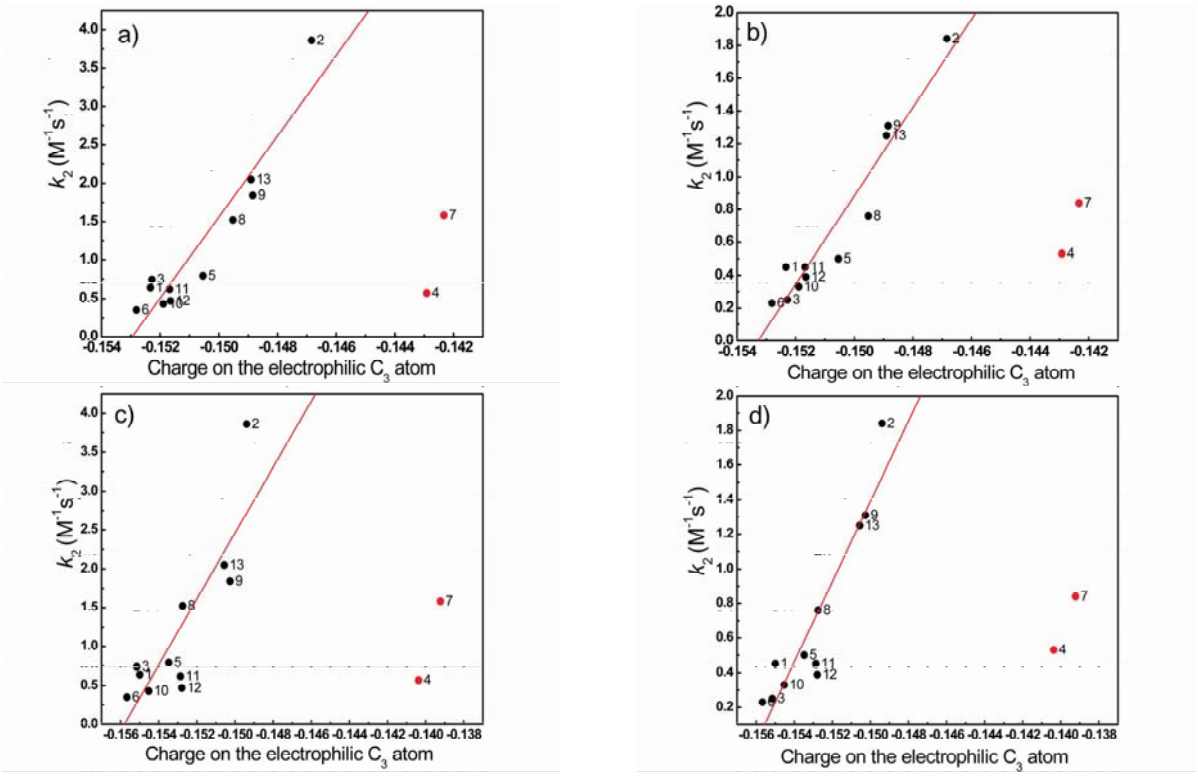


*Figure 3. Correlation of the rate constants for the addition of piperidine and benzylamine to compounds **1-13** with the calculated Mulliken atomic charges; a) Charges obtained without implicit solvent model and the rate constant for piperidine (r = 0.94) and b) benzylamine (r = 0.96); c) Charges obtained with the implicit solvent model (CH_3OH) in correlation with the rate constant for piperidine (r = 0.85) and d) benzylamine (r = 0.93).*

Statistically superior correlations were found for the Mulliken charges obtained in vacuum, compared to implicit solvent model. Compounds **4** and **7** having *ortho*- substituents were omitted from Hammett corelations, because corresponding σ_o values could not be defined. Simillarly, the same compounds were outliers in correlations with atomic charges.

Molecular electrostatic potential (MEP) maps, with charges obtained on DFT level, show difference in the charge distribution around electrophylic center among **2, 4** and **6** (**Figure 4**). Pictures are created by MOLEKEL software,[8] and Maestro.[9]

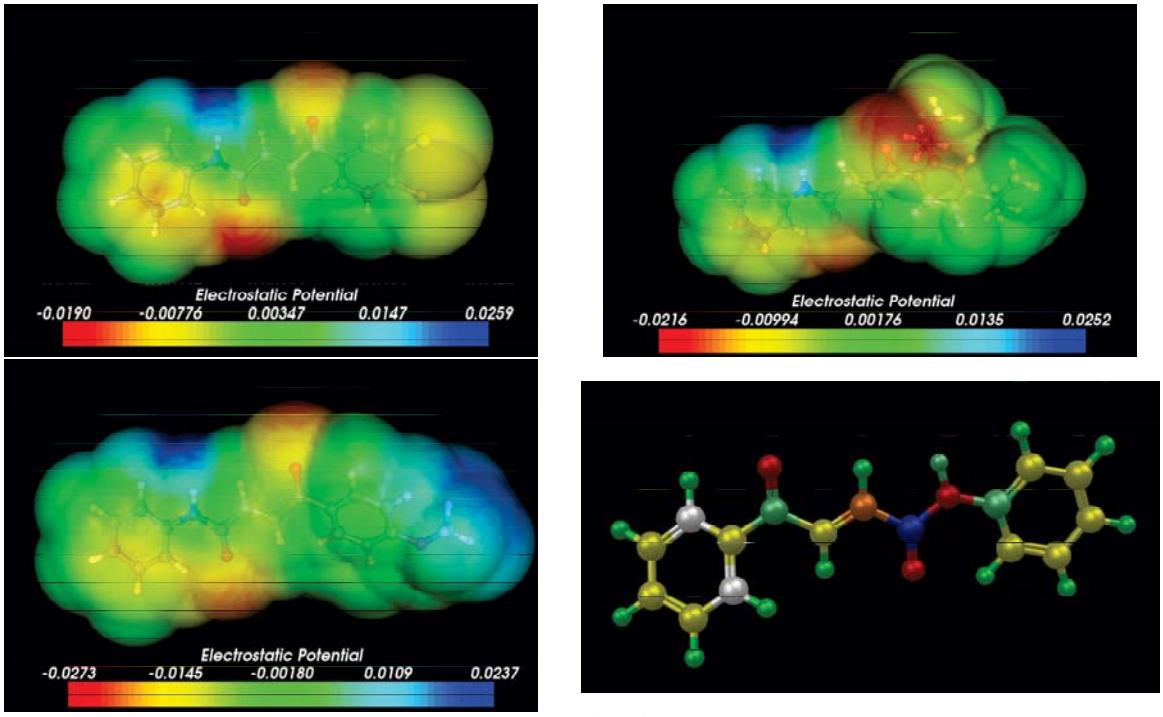


*Figure 4. Molecular electrostatic potential (MEP) mapped on solvent accessible area (1.4 Å probe - water) of **2** (upper left), **4** (upper right) and **6** (lower left). Lower right picture represents molecule **5** colored by Mulliken atomic charge; blue color- charge ≥ 0.25, red color- charge ≤ -0.25.*

Conclusion

Rate constants of the addition of piperidine and benzylamine to compounds **1-13** were determined spectrophotometrically. The addition product of **13** with piperidine was isolated and characterized. Rate constants were well correlated with the Hammett substituent constants and calculated charges on C_3 atom. MEP Maps provided insight on the differences in electron density around reaction center. Hammett reaction constants, ρ, gave an indication of the possible mechanism of conjugated 1,4- addition of amines to the aroylacrilic acid phenylamides. The further experimental and theoretical investigation of this biologically and synthetically important reaction will be conducted.

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Кинетика и механизам адиције пиперидина и бензиламина на фениламиде ароилакрилних киселина

Константе брзине реакције адиције депротонованог пиперидина и бензиламина на конгенерну серију фениламида ароилакрилних киселина у метанолу одређене су помоћу UV-VIS спектрофотометрије, под условима псеудо-првог реда. Утицај супституената на константе брзина реакције квантификован је помоћу Хаметових константи супституената и наелектрисања израчунатих за електрофилни угљеников атом (са и без модела имплицитног растварача), употребом DFT метода. Вредности Хаметових реакционих константи и испитивање реакције у различитим растварачима дају индикације о вероватном механизму ове реакције.

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