

Substituent and structural effects on the kinetics of the reaction of *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with diazodiphenylmethane

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Abstract: The rate constants for the reaction of twenty-two *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with diazodiphenylmethane were determined in absolute ethanol at 30 °C. The effects of substituents on the reactivity of the investigated compounds were interpreted by correlation of the rate constants with LFER equations. The results of quantum mechanical calculations of the molecular structure together with experimental results gave a better insight into the effects of structure on the transmission of electronic effects of the substituents. New σ constants for substituted benzylideneamino group were calculated.

Keywords: rate constants; substituent and structural effects; geometry optimization.

INTRODUCTION

It has been reported that *N*-benzylidenealdimines are important intermediates for the synthesis of a number of pharmacologically active compounds.^{1–4} Numerous former investigations of the molecular structures of *N*-benzylideneanilines^{5–9} showed that substituents in the aniline and benzylidene moiety largely influence the deflection of the angles θ_N or θ_C by their electronic and/or steric effects, and, therefore, determine the conformation of the corresponding molecules (Fig. 1, the torsion angle around the C=N double bond is labeled as θ_D).

The aim of the present study was to investigate the effects of substituents at the benzylidene ring on the reactivity of the carboxylic group in *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with diazodiphenylmethane (DDM). It is a continuation of the investigation of the effects of substituents on the ¹³C-NMR chemical shifts of the same acids.¹⁰

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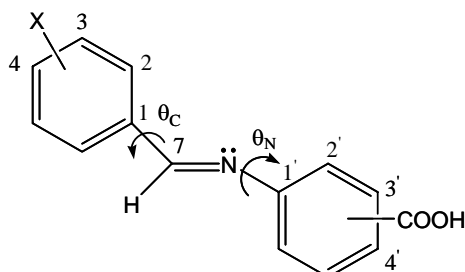


Fig. 1. Structure of *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with the descriptors of their geometry.

EXPERIMENTAL

All of the *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids were synthesized by heating equimolar amounts of the corresponding *m*- or *p*-aminobenzoic acids and the corresponding substituted aldehydes in appropriate solvents.¹⁰ As an example: 1.37 g (0.01 mol) *p*-aminobenzoic acid and 1.06 g (0.01 mol) benzaldehyde were refluxed in 10 ml absolute ethanol for two hours. After crystallization, the crude product was filtered and recrystallized from absolute ethanol. The structure and purity of the obtained compounds were controlled by melting points, elemental analysis, ¹H- and ¹³C-NMR spectroscopy, which were in agreement with literature data.

Diazodiphenylmethane was prepared by the Smith and Howard method.¹¹ A stock solution of *ca.* 0.06 mol dm⁻³ was stored in a refrigerator and diluted immediately before use. Kinetic measurements of the reaction rate in absolute ethanol were performed by the spectroscopic method of Roberts and coworkers,¹² using a Shimadzu 160A UV spectrophotometer. Optical density measurements were performed at 525 nm with 1-cm cells at 30±0.05 °C. Three determinations were made for each acid and in every case the individual second order or pseudo-first-order rate constants agreed within 3 % of the mean. All regression analyses in this work were performed with the Microsoft Excel® program package.

Method of calculation

The MNDO-PM3 method has proved to be highly reliable for investigating the molecular properties of molecules, ions^{13,14} and zwitterions.¹⁵ The MOPAC program package, Version 7.01, was used. The initial structures of the compounds were generated by PC MODEL, version 4.0,¹⁶ which involves an MMX force field¹⁷ and were saved as MOPAC input files for MNDO-PM3 semi-empirical calculations.^{18,19} The geometries of all molecular species, corresponding to the energy minima in vacuum, were optimized by the PM3 method. As the conformers may have different stabilities in vacuum and in the condensed state, the conformational space was also systematically searched for local energy minima, starting from various conformations differing from the most stable one. The simulation of the polar medium, with full geometry optimization, was performed using the COSMO facility in MOPAC.²⁰

RESULTS AND DISCUSSION

The reaction of carboxylic acids with DDM has been used by numerous authors for quantitative structure–reactivity studies.^{21–23} The mechanism of this reaction, suggested by Roberts and later proved,^{12,24} involves proton transfer from the acids to DDM in the rate-determining step.

The values of second-order rate constants for the reaction of *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with DDM in absolute ethanol at 30 °C are given in Table I, together with corresponding $\sigma_{m/p}$ substituent constants.²⁵

TABLE I. The second-order rate constants, k_2 , for the reaction of *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids with DDM at 30 °C in absolute ethanol

Substituent (X)	$k_2 / \text{dm}^3 \text{mol}^{-1} \text{min}^{-1}$		$\sigma_{m/p}$
	<i>N</i> -(Substituted phenylmethylene)- <i>m</i> - -aminobenzoic acids	<i>N</i> -(Substituted phenylmethylene)- <i>p</i> - -aminobenzoic acids	
H	1.086	0.386	0
<i>p</i> -N(CH ₃) ₂	0.945	0.284	-0.83
<i>p</i> -OCH ₃	1.045	0.354	-0.27
<i>p</i> -CH ₃	1.063	0.387	-0.17
<i>p</i> -Br	1.151	0.455	0.23
<i>p</i> -Cl	1.135	0.442	0.23
<i>p</i> -NO ₂	1.282	0.571	0.78
<i>p</i> -CN	1.228	0.520	0.66
<i>m</i> -CH ₃	1.078	0.384	-0.07
<i>m</i> -OCH ₃	1.130	0.425	0.12
<i>m</i> -Cl	1.160	0.470	0.37

For quantitative assessment of the substituent effects on the rate constants, the simple Hammett Equation was used:

$$\log k_2 = \log k_0 + \rho \sigma_{m/p} \quad (1)$$

where ρ is a reaction constant reflecting the sensitivity of the rate constants to substituents effects and k_0 is the rate constant of the parent (unsubstituted) compound of the series. The following correlation parameters were obtained using the data from Table I for *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids:

$$\log k_2 = 0.039 + 0.079 \sigma_{m/p} \quad (2)$$

$(r = 0.995; s = 0.004; n = 11)$

while the corresponding correlation for *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids is:

$$\log k_2 = -0.396 + 0.184 \sigma_{m/p} \quad (3)$$

$(r = 0.993; s = 0.009; n = 11)$

where r is the correlation coefficient, s the standard deviation and n the number of data included in the correlation.

The low values of the reaction constant ρ for both series of acids indicate a significant attenuation effect of the imino group diminishing the transmission of electronic effects of the substituents through that group. The lower value of ρ for *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids leads to the conclusion that the rate constants of these acids are significantly less sensitive to the substituent effects than is the case of *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids.

Applying the Taft dual substituent-parameter Equation (DSP) in the form:

$$\log k_2 = \log k_0 + \rho_I \sigma_I + \rho_R \sigma_R \quad (4)$$

the overall substituent effect is separated into inductive, σ_I , and resonance, σ_R or σ_R^+ , contribution. This approach gives the following results for *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids:

$$\log k_2 = 0.04 + 0.085\sigma_I + 0.074\sigma_R \quad (5)$$

$(r = 0.992; s = 0.015; n = 8)$

$$\log k_2 = 0.04 + 0.085\sigma_I + 0.040\sigma_R^+ \quad (6)$$

$(r = 0.992; s = 0.014; n = 8)$

and for *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids:

$$\log k_2 = -0.40 + 0.198\sigma_I + 0.175\sigma_R \quad (7)$$

$(r = 0.992; s = 0.015; n = 8)$

$$\log k_2 = -0.41 + 0.198\sigma_I + 0.093\sigma_R^+ \quad (8)$$

$(r = 0.993; s = 0.013; n = 8)$

In these correlations only acids with substituents in the *para* position at the phenylmethylene ring were included and σ_I , σ_R and σ_R^+ were taken from the literature.²⁵

The relative contribution of inductive and resonance substituent effects were quantitatively estimated by calculating the parameter λ as the ratio of ρ_R and ρ_I , giving values of $\lambda_m = \rho_{Rm}/\rho_{Im} = 0.872$ and $\lambda_m^+ = \rho_{Rm}^+/\rho_{Im} = 0.471$ for *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids, and $\lambda_p = \rho_{Rp}/\rho_{Ip} = 0.884$ and $\lambda_p^+ = \rho_{Rp}^+/\rho_{Ip} = 0.470$ for *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids. It is evident that the contribution of the resonance substituent effect is less significant compared to the inductive one. The lower values of parameters λ^+ calculated from correlations (6) and (8) indicate that the contribution of direct conjugation (π, π -conjugation) of the substituent, and carboxylic group as the reaction centre, across the investigated molecules, was attenuated because of inadequate molecular geometry for this type of conjugation. A more important resonance interaction all the way through the molecules of *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids, than that in the molecules of *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids, could have been expected, but the values of the parameters λ show that the differences between the two series of acids are negligible. This obvious leveling effect could be explained by the relatively high electronegativity of the nitrogen atom, causing a considerable localization of the π -electrons.

There are two experimental facts which could be inferred from Table I and Eqs. (1)–(8). The rate constants for the *m*-carboxy series are 2.2–3.2 times higher than those for the *p*-carboxy series. On the other hand, the better transmission of the variation in the electronic effects in the *p*-carboxy series results in the higher value of the reaction constant ρ . In the *m*-carboxy series, the absence of direct conjugation with the reaction centre, together with the facts established in a former study¹⁰ about an electron deficiency at the azomethine carbon and, consequently, a limited transmission of the variation in the electron acceptor effect, causes the lower value of the constant ρ .

Specific electronic interactions within the *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acid molecules found in both a previous¹⁰ and the present study, prompted us to calculate the σ_m and σ_p substituent constants for the substituted benzylideneamino groups, which have not been previously reported. The kinetic data from Table I were used for the calculation of these new $\sigma(\text{exp})$ constants on the basis of the Hammett Equation, given by Eq. (1) in the form $\log k_2 = \log k_0 + \rho\sigma$ (for $\log k_0 = 0.039$ and $\rho = 0.937$), for benzoic acids for the same reaction conditions.¹²

All $\sigma_p(\text{exp})$ constants (Table II) of *p*-substituted benzylideneamino groups are negative, which means that these groups, according to their electronic effects, are electron-donating. This indicates that the *n*, π -conjugation in the aniline part of *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids is the dominant effect, because of the electron-accepting carboxylic group. Electronic effects of substituents from the benzylidene part influence only an increase or decrease of this conjugation. The *n*, π -conjugation in the aniline part of *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids has a weaker effect in comparison to that in the previous *p*-series of acids, as reflected in the $\sigma_m(\text{exp})$ values of the corresponding substituted benzylideneamino groups (Table II). The electronic effect is negative for electron-donating and positive for electron-accepting substituents. On the basis of the calculated values of the σ constants for *p*- and *m*-substituted benzylideneamino groups, two opposite effects could be identified. One is the electronic effect of the substituents in the benzylidene ring and the other is electronic conjugation interactions in the aniline part of the molecule. Generally, it can be said that the balance of these two effects produces the overall effect of these groups on the reactivity of the investigated acids.

TABLE II. The substituent constants, $\sigma(\text{exp})$, of *m*- and *p*-substituted benzylideneamino groups

Substituent (X)	$\sigma_m(\text{exp})$	$\sigma_p(\text{exp})$
H	-0.003	-0.478 ^a
<i>p</i> -N(CH ₃) ₂	-0.068	-0.639
<i>p</i> -OCH ₃	-0.022	-0.533
<i>p</i> -CH ₃	-0.014	-0.492
<i>p</i> -Br	0.024	-0.406
<i>p</i> -Cl	0.017	-0.397
<i>p</i> -NO ₂	0.074	-0.312
<i>p</i> -CN	0.054	-0.345
<i>m</i> -CH ₃	-0.006	-0.490
<i>m</i> -OCH ₃	0.015	-0.444
<i>m</i> -Cl	0.027	-0.391

^aValue: -0.55²⁶

In order to get rationalized the transmission of electronic substituent effects in the investigated acids we searched for a method to determine their geometry,

and as the result semi-empirical calculations were performed using the MOPAC program package. Full optimization of the molecular geometry of the investigated acids was performed by the MNDO-PM3 method.^{18,19} As major descriptors of their geometry, the following structural elements were selected (see Fig. 1): a) *Z/E* isomerization about the C=N double bond; b) rotation of the carboxylic group by a certain degree about the C_{carbonyl}-C_{phenyl} bond; c) rotation of the hydroxyl group around the C-O bond, d) the torsional angle C(2')-C(1')-N-C(7), marked as θ_N ; e) torsional angle C(1')-N-C(7)-C(1), marked as θ_D ; f) torsional angle N-C(7)-C(1)-C(2), marked as θ_C for the molecular structures with a minimum potential energy.

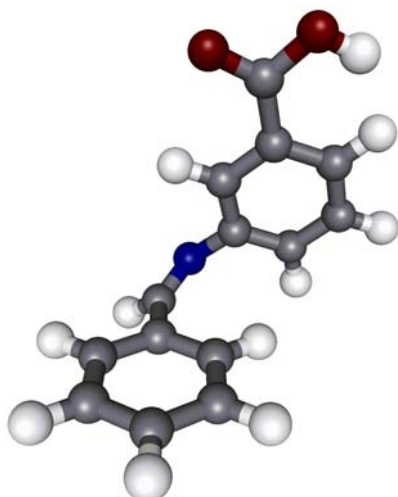
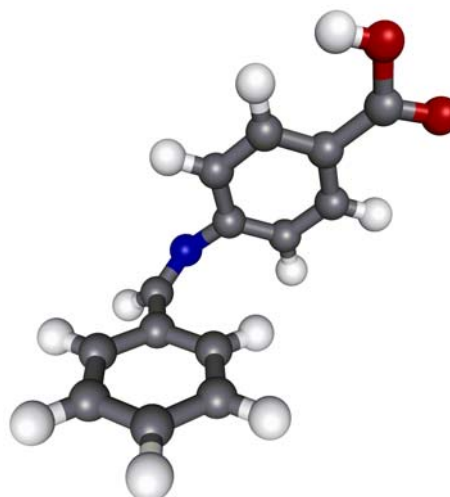
The calculated energies of the two possible *Z/E* geometrical isomers for both series of acids are very similar, indicating that an appropriate equilibrium of isomers of acids may exist in solution. It was assumed that a corresponding contribution of the isomers conforms to the statistical Boltzman distribution, thus the weighted average values of the molecular energies and corresponding angles were calculated. It was assumed that the inductive effect should not be markedly affected by conformational variations of the molecule. The opposite is true for the resonance effect, which is strongly dependent on the conformational arrangement. The resonance effect is proportional to \cos^2 of the corresponding torsional angle between the reaction centre and the substituent. Following this procedure and multiplying σ_R substituent constants²⁵ with the corresponding calculated values of the angle in the form $\cos^2\theta = \cos^2\theta_N \cos^2\theta_D \cos^2\theta_C$, a new resonance constants $\sigma_R \cos^2\theta$ for the *m*- and *p*-substituted benzylideneamino groups were obtained. Finally, the $\sigma_{m/p}(\text{calcd.})$ constants of these groups for both series of acids were obtained according to the formula $\sigma_{m/p}(\text{calcd.}) = \sigma_I + \sigma_R \cos^2\theta$, the calculated values of which are given in Tables III and IV. Examples of the most stable conformers of *N*-(substituted phenylmethylene)-*m*- and -*p*-aminobenzoic acids are shown in Figs. 2 and 3, respectively.

TABLE III. The values of angles θ_N , θ_D and θ_C of *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids and $\sigma_m(\text{calcd.})$ constants of substituted benzylideneamino groups

Substituent	θ_N	θ_D	θ_C	$\sigma_m(\text{calcd.})$
H	64.157	0.349	35.253	0.035
<i>p</i> -N(CH ₃) ₂	62.296	0.566	30.061	-0.024
<i>p</i> -OCH ₃	62.869	0.740	31.534	0.015
<i>p</i> -CH ₃	63.774	0.371	34.144	0.031
<i>p</i> -Br	63.732	0.321	38.125	0.062
<i>p</i> -Cl	62.143	0.501	34.559	0.059
<i>p</i> -NO ₂	61.838	0.439	40.400	0.101
<i>p</i> -CN	62.792	0.333	38.838	0.092
<i>m</i> -CH ₃	64.661	0.417	36.240	0.030
<i>m</i> -OCH ₃	63.426	0.466	38.235	0.050
<i>m</i> -Cl	62.889	0.354	35.938	0.069

TABLE IV. The values of angles θ_N , θ_D and θ_C of *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids and σ_p (calcd.) constants of substituted benzylideneamino groups

Substituent	θ_N	θ_D	θ_C	σ_p (calcd.)
H	66.917	0.353	36.577	-0.402
<i>p</i> -N(CH ₃) ₂	65.910	0.563	31.579	-1.012
<i>p</i> -OCH ₃	65.941	0.754	32.623	-0.455
<i>p</i> -CH ₃	66.252	0.375	34.075	-0.429
<i>p</i> -Br	66.916	0.327	38.669	-0.342
<i>p</i> -Cl	66.300	0.419	35.636	-0.348
<i>p</i> -NO ₂	64.303	0.292	41.033	-0.247
<i>p</i> -CN	64.799	0.550	39.373	-0.272
<i>m</i> -CH ₃	67.429	0.705	34.816	-0.420
<i>m</i> -OCH ₃	68.356	0.547	39.956	-0.372
<i>m</i> -Cl	67.504	0.391	36.550	-0.325

Fig. 2. Structure of the most stable conformer of *N*-(phenylmethylene)-*m*-aminobenzoic acid calculated by the MNDO-PM3 method.Fig. 3. Structure of the most stable conformer of *N*-(phenylmethylene)-*p*-aminobenzoic acid calculated by the MNDO-PM3 method.

The results from Tables III and IV indicate a large out of plane deviation of the aniline ring, while the deviation of benzylidene ring has a lower value, but the deviations are significant for both series of acids. Regularity can be observed for the values of the angles θ_C , *i.e.*, for electron-donor substituents, these values are lower and for electron-acceptors higher for higher values of the substituent constant. This is in agreement with a previous study,¹⁰ as a good correlation was obtained with σ_I for electron-acceptor and with the electrophilic substituent constant σ_p^+ for electron donors. These results show that electron-donor substituents induce planarity of the benzylidene part of the molecules, while electron-acceptors cause a deviation from planarity. Therefore, only the inductive part of their substituent effect is transmitted to the reaction center. Since no regularity in the va-

riation of the values of angle θ_N were observed, this probably means that complex electronic effects involving both π,π - and n,π -conjugation in aniline part influence the values of the angle θ_N .

Intercorrelation of the experimental $\sigma_m(\text{exp})$ values (Table II) and the calculated $\sigma_m(\text{calcd.})$ (Table III) for *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids gave the following result:

$$\sigma_m(\text{exp}) = -0.004 + 1.072\sigma_m(\text{calcd.}) \quad (9)$$

$$(r = 0.999; s = 0.004; n = 11)$$

having the y-axis interception close to zero.

Also, intercorrelation of the $\sigma_p(\text{exp})$ (Table II) and $\sigma_p(\text{calcd.})$ (Table IV) values for *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids gives the following correlation:

$$\sigma_p(\text{exp}) = -0.034 + 1.099\sigma_p(\text{calcd.}) \quad (10)$$

$$(r = 0.996; s = 0.004; n = 11)$$

where $\sigma_{m/p}(\text{exp})$ (Table II) are the values of the substituent constants calculated on the basis of experimental data and $\sigma_{m/p}(\text{calcd.})$ (Tables III and IV) are data calculated according to the optimization of molecular geometry. It can be seen, on the basis of the correlation results, that the modeling of the geometry of the investigated molecules by quantum mechanical calculation is a reliable method for an estimation of their structure.

CONCLUSIONS

The excellent Hammett correlations obtained with $\sigma_{m/p}$ substituent constants (Eqs. (2) and (3)) and low values of the reaction constants indicate a moderate transmission of electronic effects through the whole system of the investigated acids. The separation of the electronic substituent effect into a resonance and inductive part by the Taft equation shows a smaller contribution of resonance interaction. As a consequence, when electron-donating substituents are present in the benzyli-dene ring, there is a substantial decrease of the angle θ_C and, consequently, the molecules tend to attain a planar conformation. Thus, a better transmission of the resonance substituent electronic effects through the molecules is achieved.

The above correlations and the results of a previous study¹⁰ show that the effects of substituents on the variations of the angles θ_N and θ_C are a significant feature of the geometry of the investigated molecules. Therefore, it can be concluded that the conformation of the molecules is determined by a balance of n,π -conjugation in the aniline part of the molecule and inductive and resonance effects of substituents in the benzyli-dene ring. Consequently, the carboxylic group in the *para* position causes the values of the angles θ_N and θ_C to have slightly higher values than when that group is in the *meta* position. This is corroborated by a mathematical (quantum-mechanical) optimization of the structure of the investigated

molecules, whereby the changes of the values of the angle follow the above-stated principles. Also, the higher values of the rate constants for the *N*-(substituted phenylmethylene)-*m*-aminobenzoic acids indicate a stronger conjugation in the series of *N*-(substituted phenylmethylene)-*p*-aminobenzoic acids, due to the better electron donating power of the benzyldeneamino groups, thus decreasing the acidity of these acids.

It should be pointed out that the excellent intercorrelation of the experimentally determined and calculated $\sigma_{m/p}$ values for the substituted benzyldeneamino groups verify the credibility of both approaches.

ИЗВОД

ЕФЕКТИ СУПСТИТУЕНАТА И СТРУКТУРЕ НА КИНЕТИКУ РЕАКЦИЈЕ
N-(СУПСТИТУИСАНИХ)-*m*- И -*p*-АМИНОБЕНЗОЕВИХ КИСЕЛИНА
 СА ДИАЗОДИФЕНИЛМЕТАНОМ

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Константе брзина реакџија између двадесет две *N*-(супституисане фенилметилеи)-*m*- и -*p*-аминобензоеве киселине и диазодифенилметана одређене су у апсолутном етанолу на 30 °C. Ефекти супституената на реактивност испитиваних једињења су интерпретирани корелацијом реакционих константи помоћу LFER једначина. Резултати квантно-механичких рачунања молекулске структуре заједно са експерименталним резултатима омогућили су боље разумевање утицаја структуре на пренос електронских ефеката супституената. Израчунате су нове σ константе за супституисане бензилиденамино групе.

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