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Effects of solvent and structure on the reactivity of 2-substituted nicotinic acids with diazodiphenylmethane in aprotic solvents

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Abstract: The rate constants for the reactions of diazodiphenylmethane (DDM) with 2-substituted nicotinic acids in nine aprotic solvents at 30 °C were determined. The obtained second order rate constants in aprotic solvents were correlated using the Kamlet–Taft solvatochromic equation in the complete form: $\log k = \log k_0 + s\pi^* + a\alpha + b\beta$. The correlations of the kinetic data were realized by means of multiple linear regression analysis. The obtained results were analyzed in terms of the initial and the transition state of the reaction and compared with previously determined kinetic data for nicotinic acid. The signs of the equation coefficients (*s*, *a* and *b*) are in agreement with the reaction mechanism and the influence of the solvent on the reaction rate is discussed based on the correlation results. The mode of the transmission of the substituent effect is discussed in light of the contribution of solute–solvent interaction to the reactivity of the acid. The substituent effect was additionally analyzed by the Hammett equation, $\log k = \rho\sigma + \log k_0$.

Keywords: pyridinecarboxylic acids; diazodiphenylmethane; reaction rate constants; solvatochromic parameters; aprotic solvents.

INTRODUCTION

The relationship between the structure of carboxylic acids and their reactivity with diazodiphenylmethane (DDM) has been studied by many authors, with particular regard to the influence of the solvent.^{1–5} Related to previous studies^{6–10} of the chemical behavior of pyridinecarboxylic acid, the reactivity of 2-substituted nicotinic acids with the following substituents Cl (chloro), OH (hydroxy), CH₃ (methyl), Br (bromo) and SH (mercapto) was studied in its reaction

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with DDM. The kinetics of the reaction of these carboxylic acids with DDM was investigated in a series of aprotic solvents.

Kamlet *et al.*³ established that the effect of a solvent on the reaction rate should be given in terms of the following properties: *i*) the behavior of a solvent as a dielectric facilitating the separation of opposite charges in the transition state, *ii*) the ability of a solvent to donate a proton in a solvent-to-solute hydrogen bond and thus stabilize the carboxylate anion in the transition state and *iii*) the ability of a solvent to donate an electron pair and therefore to stabilize the initial carboxylic acid, through a hydrogen bond between the carboxylic proton and the solvent electron pair. These properties are connected through Eq. (1):

$$\log k = A_0 + s\pi^* + a\alpha + b\beta \quad (1)$$

The parameter π^* is an appropriate measure of the first property, while the second and the third properties are governed by the effects of the solvent acidity and basicity, quantitatively expressed by the parameters α and β , respectively. The linear solvation energy relationship (LSER) of the solvent parameters is used to correlate and predict a wide variety of solvent effects, as well as to provide an analysis in terms of knowledge and theoretical concepts of molecular structural effects.³ Such a correlation indicates the existence of both specific and non-specific solute-solvent interactions in the studied reaction.

The reactivity of the investigated acids with DDM in relationship to the electronic substituent effects was also studied using the Hammett equation (linear free energy relationship – LFER) of the type:

$$\log k = \rho\sigma + \log k_0 \quad (2)$$

where ρ is a reaction constant reflecting the sensitivity of the rate constant to the substituent effect, and σ is the substituent constant, a measure of the electronic effect of a substituent. The analysis of the contribution of electronic substituent effects showed that these effects have a definite influence on the reactivity of the investigated acids.

EXPERIMENTAL

Materials

The acids were commercial samples of *p.a.* quality, used without further purification. Diazodiphenylmethane was prepared by the Smith and Howard method.¹¹ A stock solution of 0.06 mol dm⁻³ was stored in a refrigerator and diluted before use. The solvents were purified as described in the literature.¹² All the solvents used for the kinetic studies were examined by GC and no impurities were detected.

Kinetic measurements

The rate constants, k , for the reactions of the investigated acids with DDM were determined as reported previously by the spectroscopic method of Roberts and co-workers¹³ using a Shimadzu 1700A spectrophotometer. The optical density measurements were performed at 525 nm with 1.0 cm cells at 30±0.05 °C. Three to five measurements were made

with each acid and in every case, the individual second-order rate constants agreed within 3 % of the mean.

RESULTS AND DISCUSSION

The mechanism of the reaction between carboxylic acids and DDM, in both protic and aprotic solvents is known to involve the rate-determining proton transfer from the acids to DDM, and the formation of a diphenylmethanediazonium carboxylate ion-pair (Fig. 1).^{14–21} Chapman *et al.*²² established that the solvent effects are best interpreted in the form of the contributions of the initial and transition state to specific (α and β) and non-specific (π^*) solvent-solute interactions (Fig. 1).

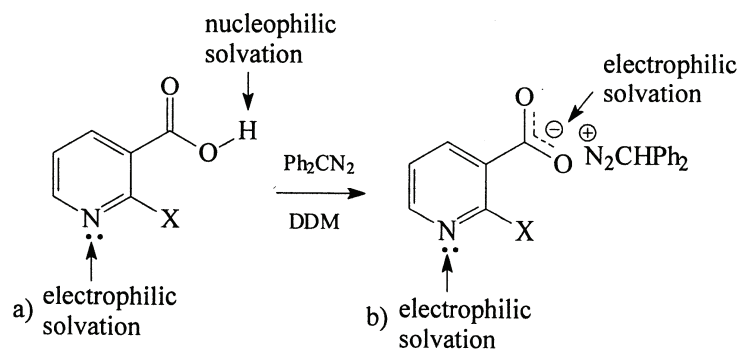


Fig. 1. The mode of the solvent effects in 2-substituted nicotinic acids in a) the initial state and b) the transition state.

The reaction rate constants (as $\log k$) for the reaction of the examined acids with DDM in the applied solvent set are given in Table I.

TABLE I. Logarithm of the second order rate constants ($k / \text{dm}^3 \text{mol}^{-1} \text{min}^{-1}$) for the reaction of 2-substituted nicotinic acids with DDM at 30 °C in aprotic solvents

Solvent/substituent	H ¹⁰	2-Cl	2-OH	2-CH ₃	2-Br	2-SH
Dimethyl sulfoxide	-0.678	0.005	-0.030	-0.611	0.006	-0.044
<i>N,N</i> -Dimethylacetamide	-0.940	-0.259	-0.201	-0.851	-0.240	-0.131
<i>N</i> -Methylpyrrolidone	-0.921	-0.131	0.139	-0.796	-0.138	-0.121
<i>N,N</i> -Dimethylformamide	-0.611	-0.014	0.171	-0.480	-0.016	0.196
<i>N</i> -Methylformamide	-0.027	0.103	-0.354	0.242	0.111	0.378
Acetophenone	0.714	1.343	- ^a	0.751	1.373	1.231
Acetone	0.190	0.451	-	0.524	0.506	0.719
Ethyl benzoate	0.528	1.088	-	0.860	1.082	0.895
Isobutyl methyl ketone	0.143	0.606	-	0.313	0.651	0.751

^aInsoluble

The results from Table I show that the influence of a solvent on the reactivity is rather complex, due to the many types of solvent to solute interactions: dipolarity/polarizability, π^* , proton-donor, α (HBD), and proton-acceptor, β (HBA), effects. Considering the reaction mechanism, it is obvious that polar solvents accelerate the reaction by stabilizing the ion-pair in the transition state. However, their other properties have to be taken into consideration. Solvents of high polarity and of high HBA capability cause a significant decrease in the reaction rate by stabilizing the carboxylic hydrogen in the ground state before commencement of the reaction. For example, the reaction rate constant in dimethyl sulfoxide was lower than in acetophenone – both solvents are of similar polarity, 1.00 and 0.90, respectively, but dimethyl sulfoxide has a higher proton-acceptor ability (0.75) than acetophenone (0.49), and hence the reaction was slower in dimethyl sulfoxide.

Generally, the results of the kinetic studies show that reactions of all acids with DDM are of second order, which was confirmed by the high correlation coefficients, R , which were in the range 0.938–0.990. The exception was 2-hydroxynicotinic acid, which was, because the R -value was only 0.817, excluded from the calculation.

Solvent–reactivity relationship

In order to explain the obtained kinetic results based on the polarity, acidity and basicity of the solvent, the $\log k$ values were correlated with the solvatochromic parameters π^* , α and β using the solvatochromic Eq. (1). The correlation of the kinetic data was realized by means of multiple regression analysis, which was very useful in separating and quantifying the solvent effect on the examined reaction.

The correlation results are presented in the following equations.

Nicotinic acid:

$$\log k = 0.82 + (2.45 \pm 0.85)\pi^* + (1.72 \pm 0.32)\alpha - (5.18 \pm 0.63)\beta$$

$$R = 0.977, s = 0.17, n = 9$$

2-Chloronicotinic acid:

$$\log k = 0.70 + (3.12 \pm 1.23)\pi^* + (0.78 \pm 0.46)\alpha - (4.90 \pm 0.91)\beta$$

$$R = 0.938, s = 0.25, n = 9$$

2-Methylnicotinic acid:

$$\log k = 1.50 + (1.91 \pm 0.60)\pi^* + (1.99 \pm 0.22)\alpha - (5.30 \pm 0.44)\beta$$

$$R = 0.990, s = 0.12, n = 9$$

2-Bromonicotinic acid:

$$\log k = 0.81 + (3.03 \pm 1.21)\pi^* + (0.80 \pm 0.45)\alpha - (4.93 \pm 0.89)\beta$$

$$R = 0.942, s = 0.24, n = 9$$

2-Mercaptonicotinic acid:

$$\log k = 1.31 + (1.79 \pm 0.92)\pi^* + (1.03 \pm 0.35)\alpha - (3.99 \pm 0.68)\beta$$

$$R = 0.955, s = 0.18, n = 9$$

The values for π^* , α and β (Table II) were taken from the literature.²³ Here, the correlation results for nicotinic acid are also given for comparison.

TABLE II. Solvent parameters

Solvent	π^*	α	β
Dimethyl sulfoxide	1.00	0.00	0.75
<i>N,N</i> -Dimethylacetamide	0.88	0.00	0.76
<i>N</i> -Methylpyrrolidone	0.92	0.00	0.77
<i>N,N</i> -Dimethylformamide	0.88	0.00	0.69
<i>N</i> -Methylformamide	0.90	0.62	0.80
Acetophenone	0.90	0.04	0.49
Acetone	0.71	0.08	0.43
Ethyl benzoate	0.74	0.00	0.41
Isobutyl methyl ketone	0.65	0.02	0.48

The correlation equations obtained for all the examined acids confirmed the reaction mechanism described above, as the solvent polarity and its proton-donor (HBD) activity increase the reaction rate constant, and the proton-acceptor (HBA) ability decreases it. It could be noticed that the HBA effect is the most prominent effect in this solvent set.

From the values of regression coefficients (s , a and b), the contribution of each parameter to the reactivity of the investigated compounds on a percentage basis was calculated and the results are listed in Table III.

TABLE III. Percentage contribution of the Kamlet–Taft solvatochromic parameters for the reactivity of the investigated acids in aprotic solvents

Acid	$P_{\pi^*} / \%$	$P_{\alpha} / \%$	$P_{\beta} / \%$
H	26	18	56
2-Cl	35	9	56
2-CH ₃	22	20	58
2-Br	35	9	56
2-SH	26	15	59

It could be noticed that in the case of the electron withdrawing substituents, the values for the HBD parameter (α) were lower than for the unsubstituted acid and for the acid with the electron-donor substituent (CH₃). The negative inductive effect of the electron-acceptor substituents additionally stabilizes the carboxylic anion and hence, the HBD solvent effect is less involved.

The results from Table III, lead to the following conclusions:

a) The rate of the reaction is mostly influenced by the rate-decreasing HBA parameter, as its percentage prevails over the other two rate-increasing parameters.

b) The non-specific interaction have higher influence (higher percentage value) than HBA on the reaction rate in all cases, meaning that the classical or non-specific solute–solvent interactions dominate in the transition state and increase the reaction rate.

When the obtained correlation results were compared with the previously published results for the corresponding 6-substituted nicotinic acids,¹⁰ it was found that the solvent effect disposition was similar considering the dominant HBA effect. However, the percentage values for the non-specific and the HBD interactions were different, as the proton-donor ability had a larger influence on the 6-substituted acids. This can be explained by the strong negative inductive effect of the majority of substituents, which is considerably stronger in the C-2 position, as it is next to the reactive center, than in C-6 position of the ring, with three atoms separating them. Comparing the reaction rate constants for both types of nicotinic acid, it can be noticed that the 2-substituted acids generally react faster, due to the additional stabilization of the anion in the transition state by the negative inductive substituent effect. The fact that the only examined acid with an electron-donor substituent, the methyl group, also reacts faster when it is in the 2-position can be explained by the steric effect of the substituent which twists the carboxylic group out of the plane of the ring and makes it more approachable for the other reactant, the DDM molecule. The higher value of the HBD coefficient (α) shows that electron-donor support from the solvent is necessary to a larger extent in this case, as there is no negative inductive substituent effect to stabilize the transition state. The inductive effect of the substituents in C-2 position, which is in fact based on their electronegativity, is additionally proved by HBD coefficient value for the 2-mercaptonicotinic acid: sulfur is less electronegative than chlorine or bromine, and this compound has a higher α coefficient than the other two acids, but somewhat lower than the unsubstituted and the methyl-substituted acid.

The outlier found in 2-hydroxynicotinic acid with its earlier mentioned unsuccessful correlation also draws attention. 6-Hydroxynicotinic acid, unlike 2-hydroxynicotinic acid, gave a successful correlation in the same solvents, with the expected signs of the arithmetic coefficients.

6-Hydroxynicotinic acid:¹⁰

$$\log k = -1.92 + (2.37 \pm 0.36)\pi^* + (1.99 \pm 0.09)\alpha - (2.20 \pm 0.51)\beta$$

$$R = 0.982, s = 0.26, n = 5$$

Due to the ability of forming strong hydrogen bonds between oxygen and hydrogen of both the carboxylic and the hydroxyl group, both compounds are

insoluble in many solvents; however, a set of five solvents in which both dissolved was found, and this set of solvents was used in this study.

The exception of the unsuccessful correlation for the 2-hydroxynicotinic acid could be explained by its specific structure. As can be seen in Fig. 2, this compound forms a strong intramolecular hydrogen bond, enhanced by the positive resonance effect of the hydroxyl group, which significantly decreases its reactivity in the anionic form. When the carboxylic proton leaves the molecule, the strong hydrogen bond is formed between the carboxylic group and the hydroxylic proton, preventing the anion from further reacting.

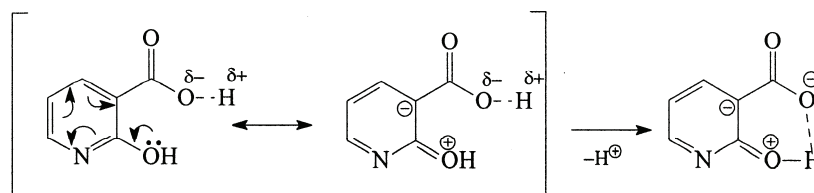


Fig. 2. The resonance effect of a hydroxyl group as substituent at C-2 and the formation of an intramolecular hydrogen bond.

Contrary to this, in case of 6-OH-nicotinic acid, there is a possibility of forming intermolecular hydrogen bonds (Fig. 3) which, as can be concluded from the successful Kamlet-Taft equation, do not interfere significantly with its reactivity in the examined reaction.

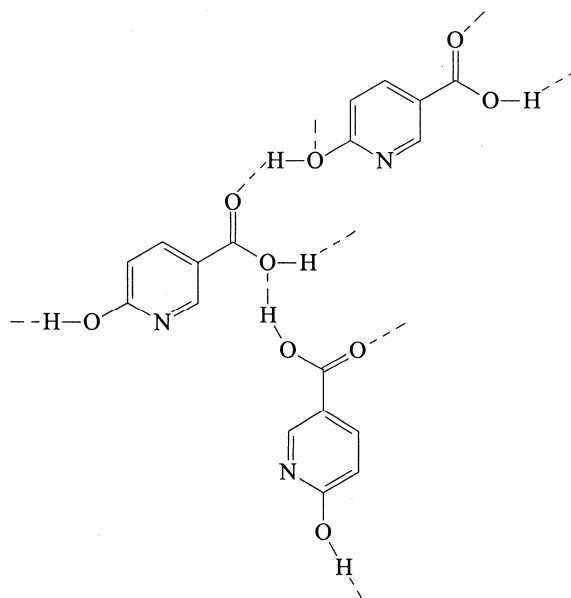


Fig. 3. Intermolecular hydrogen bonds of 6-hydroxynicotinic acid.

It could be concluded that, due to the complex possibilities of the formation of intramolecular hydrogen bonds, 2-hydroxynicotinic acid is not an appropriate compound for the investigation of the reaction mechanism of carboxylic acids with DDM and the effect of the solvent on it; neither can it be analyzed by the Kamlet–Taft equation.

None of the other examined 2-substituted nicotinic acids possesses the ability to form such an intramolecular hydrogen bond, except 2-mercaptynicotinic acid. However, it is obvious that in this case, the strength of the hydrogen bond was not sufficient to influence the reactivity of the compound as it behaved similarly to the other examined compounds in their reaction with DDM.

Structure–reactivity relationship

The relationship between the molecular structure and chemical reactivity gives additional insight into the electronic effect of substituents and the influence of solvent on the electronic distribution in the initial and transition states. Here, the most successful correlations obtained using the Hammett Equation (2) are given:

Dimethyl sulfoxide:

$$\log k = -0.33 + (1.57 \pm 0.13)\sigma_p$$

$$R = 0.992, s = 0.04, n = 4$$

N,N-Dimethylacetamide:

$$\log k = -0.54 + (1.59 \pm 0.44)\sigma_p$$

$$R = 0.931, s = 0.14, n = 4$$

N-Methylpyrrolidone:

$$\log k = -0.48 + (1.71 \pm 0.27)\sigma_p$$

$$R = 0.976, s = 0.09, n = 4$$

Acetophenone:

$$\log k = 1.00 + (1.51 \pm 0.05)\sigma_p$$

$$R = 0.999, s = 0.015, n = 4$$

The values for the σ_p constant were taken from the literature.²⁴

2-Hydroxynicotinic and nicotinic acid had to be excluded from the calculations in order to obtain a successful correlation. From the values of the obtained reaction constants, it could be concluded that the reaction is significantly susceptible to substituent effects. Furthermore, the positive reaction constant confirms that a negative charge is formed during the reaction. All four solvents are of similar properties, high polarity/polarizability and HBA ability and, as could be expected, the examined compounds behaved similarly in them, judging by the similar values of the reaction constants. The high sensitivity of the reaction constant to solvent effects in aprotic dipolar solvents may be explained by the

fact that at high relative permittivity of the surrounding solvent molecules, the energy necessary to bring about charge separation in the transition state is relatively small, which causes higher susceptibility to the electronic substituent effect.

CONCLUSIONS

The overall solvent effects on the reactivity of carboxylic acids in their reaction with DDM are complicate because of intertwined interactions between the solvent, and the reacting acid molecules. The results of the present investigation show that these solvent effects could be generally quantified by use of the Kamlet–Taft equation in the case of 2-substituted nicotinic acids. The quantitative separation of these effects into individual contributions in the initial and transition states showed the domination of the proton acceptor solvent effect. The low contribution of the proton donor solvent effect in the case of acids with electron-acceptor substituents can be explained by the negative inductive effects of these substituents, which draw the excess negative charge in the transition state and make the carboxylic anion more stable. The exception of the failed correlation for 2-hydroxynicotinic can be explained by the existence of the strong intramolecular hydrogen bond that this compound can form. In addition, the higher reaction rates for the 2-substituted nicotinic acids than for the previously investigated 6-substituted nicotinic acids confirm the electronic substituent influence, which is much more prominent in the C-2 position. In the case of 2-methylnicotinic acid, the positive inductive effect of the methyl group decreases the reaction rate, which is contrary to the steric effect. Actually, the steric effect twists the carboxylic group out and facilitates the approach of a DDM molecule, the consequence of which is an increase of the reaction rate.

Additional insight into the electronic effect of the substituents was given by the use of the Hammett equation, which showed that examined compounds behave similarly in solvents of similar properties, judging by the similar values of the reaction constants.

Considering the values of the reaction constants, it could be noticed that the negative charge increased in the transition state, which also confirms the discussed mechanism of the examined reaction. Furthermore, the same values indicate that the reaction is also considerably susceptible to the effects of substituents.

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ИЗВОД

ЕФЕКТИ СТРУКТУРЕ И РАСТВОРАЧА НА РЕАКТИВНОСТ 2-СУСПИТУИСАНИХ НИКОТИНСКИХ КИСЕЛИНА СА ДИАЗОДИФЕНИЛМЕТАНОМ У АПРОТИЧНИМ РАСТВОРАЧИМА

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Константе брзине за реакцију диазодифенилметана (DDM) са 2-супституисаним никотинским киселинама у девет аprotичних растварача су одређене на 30 °C. Добијене константе брзине за реакцију другог реда су корелисане Камлет–Тафтовом тоталном солватохромном једначином у облику: $\log k = \log k_0 + s\pi^* + a\alpha + b\beta$. Корелација кинетичких података извршена је вишеструком линеарном регресионом анализом. Добијени резултати су анализирани у односу на основно и прелазно стање и упоређени са раније одређеним вредностима за несупституисану киселину. Знаци испред коефицијената у једначини су у складу са претпостављеним механизмом реакције. Дискутован је пренос ефеката супституената на реакциони центар узимајући у обзир допринос ефеката растварача на реактивност испитиваних једињења. Ефекат супституената је додатно анализиран Хаметовом једначином: $\log k = \rho\sigma + \log k_0$.

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