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Authors' review

AUTHORS' REVIEW

A comparative study of the linear solvation energy relationship for the reactivity of pyridine carboxylic acids with diazodiphenylmethane in protic and aprotic solvents

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Abstract: The effects of protic and aprotic solvents on the reactivity of picolinic, nicotinic and isonicotinic acid, as well as of some substituted nicotinic acids, with diazodiphenylmethane (DDM) were investigated. In order to explain the kinetic results through solvent effects, the second-order rate constants for the reaction of the examined acids with DDM were correlated using the Camlet–Taft Solvatochromic Equation. The correlations of the kinetic data were realized by means of multiple linear regression analysis and the solvent effects on the reaction rates were analyzed in terms of the contributions of the initial and the transition state. The signs of the coefficients of the Equation support the already known reaction mechanism. Solvation models for all the investigated acids are suggested and related to their specific structure.

Keywords: pyridine carboxylic acids; linear solvation energy relationship; diazodiphenylmethane; protic and aprotic solvents.

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1. INTRODUCTION

The effect of different solvents on the rates of chemical changes was one of the earliest kinetic problems to be studied[1–3] and the development of the correlation analysis in the area of solvent effects has recently proved to be one of the most efficient ways to perform this task. The application of the techniques of multiple regressions has proved quite successful and has considerably increased the understanding of the role of solvents. The reaction rate constant (usually expressed as log k) or the standard Gibbs energy of the transition state in the examined reaction ($\Delta G^{\#}$) may be correlated with a physical parameter describing some characteristic of the solvent, for example, dielectric constant, solubility parameter, viscosity, *etc*., or with an empirical solvent parameter, such as *Y*, *Z*, *Et*, *etc*.[4–6] This manner of analysis was extended to multiple linear correlations with a number of solvent parameters, notably by Mather and Shorter[7] for the reaction of diazodiphenylmethane (DDM) and benzoic acid, and more generally by Koppel and Palm[8] and by Kamlet and Taft and their co-workers.[9–11] The modification of this approach was to separate the solvent effect on log k or $\Delta G^{\#}$ into contributions of the reactants (initial state) and the transition state, followed, where possible, by a comparison of effects of a solvent on the transition state with the effects of the solvent on solutes that might function as suitable models for the transition state. This method has proved itself efficient enough for application to a number of standard organic reactions and also to organometalic reactions and inorganic reactions.

Two groups of workers set out the general equations for the correlations of solvent effects through multiple regression analysis. Koppel and Palm[8] used the four-parameter equation (1):

$$\log k = \log k_0 + gf(\varepsilon) + pf(n) + eE + bB \quad (1)$$

in which $f(\varepsilon)$ is a dielectric constant function, usually $Q = (\varepsilon - 1)/(2\varepsilon + 1)$, $f(n)$ is a refractive index function $(n^2 - 1)/(n^2 + 2)$ and E and B are measures of the electrophilic solvation ability and the nucleophilic solvation ability of the solvent, respectively. Koppel and Palm[8] and later Mather and Shorter[7] applied Eq. (1) quite successfully to a variety of reaction types.

The Kamlet and Taft group of workers[11] used the alternative equation (2):

$$\log k = A_0 + s\pi^* + a\alpha + b\beta \quad (2)$$

in which π^* is a measure of solvent dipolarity/polarizability, β represents the scale of the solvent hydrogen bond acceptor basicity, and α represents the scale of solvent hydrogen bond donor acidity, and A_0 is the regression value of the

solute property in the reference solvent, cyclohexane. The regression coefficients *s*, *a* and *b* measure the relative susceptibilities of the solvent-dependent solute property (log *k* or as $\Delta G^{\#}$) to the corresponding solvent parameters.

Both Eq. (1) and (2) are general enough to be applied to almost any type of reaction.

This review demonstrates how the linear solvation energy relationship (LSER) method can be used to explain and present the multiple interacting effects of the solvent on the reactivity of pyridine carboxylic acids in their reaction with DDM. The solvent effects on the reaction rates were analyzed in terms of the initial and the transition state contributions, and are expressed quantitatively and discussed.

2. SOLVENT EFFECTS ON THE KINETICS OF THE REACTION OF PYRIDINE CARBOXYLIC ACIDS WITH DIAZODIPHENYLMETHANE

The reactivity of all carboxylic acids, including also pyridine carboxylic acids, with diazodiphenylmethane (DDM) is closely related to the molecular structure of the acid and the solvent present. The main advantage that makes this esterification appropriate for examining the influence of solvent and structure on the carboxylic acid reactivity is that a catalyst is not required for this reaction. It may vary in rate, but occurs without any additional support and in protic and aprotic solvents, it follows the second-order kinetics.[12–14] The mechanism of this reaction has been thoroughly examined[15–17] and it was established that the rate-determining step involves a proton transfer from the carboxylic acid to DDM to form a diphenylmethanediazonium–carboxylate ion pair, which rapidly reacts to give esters in the subsequent product-determining step in aprotic solvents, or ethers in the case of hydroxylic solvents:

$$Ph_2CN_2 + RCOOH \rightarrow Ph_2CHN_2^+O_2^-CR$$

Taking into consideration the reaction mechanism, it could be noticed that, because of the charge separation in the transition state, a solvent of high polarity can stabilize this state, making the reaction faster; the electrophilic ability of a solvent can have a similar effect, affecting the carboxylic anion that also exists in the transition state. On the contrary, nucleophilic solvating ability could be prominent in the initial state, stabilizing the carboxylic proton and hence, retarding the reaction.

Multiple linear regression analysis (MLRA) is very useful in separating and quantifying such interactions on the examined reactivity. The first comprehensive application of multiple linear regression analysis to kinetic phenomena was that of Koppel and Palm,[8] who listed regression constants for the simple Koppel–Palm Equation for various processes. Aslan *et al.*[14] showed that correlation analysis of the second-order rate constants for the reaction of benzoic acid with DDM in hydroxylic solvents did not give satisfactory results with the Koppel–Palm Model. They concluded that the possibility of Koppel–Palm analysis of data re-

lated to protic solvents depends on the fitting of data in a regression with the main lines being determined by a much larger number of aprotic solvents.

The influence of hydroxylic solvents on the rate constants of the reaction between carboxylic acids and DDM is rather complex. In these amphiprotic solvents, complications can arise from self-association, type AB hydrogen bonding, and multiple type A and type B interactions. In type A hydrogen bonding, the solute acts as an HBA base and the solvent as an HBD acid. In type B hydrogen bonding, the roles are reversed. Type AB represents hydrogen bonding in which the solute acts as both an HBD acid and an HBA base, associating thereby with at least two molecules of amphiprotic solvent in a probably cyclic complex. Under these circumstances where both solvent and solute are hydrogen bond donors, it was proven to be quite difficult to untangle solvent dipolarity/polarizability, type B hydrogen bonding and variable self-association effects from usual multiple type A hydrogen bonding interactions.

Aprotic solvents influence the reaction mainly by their polarity/polarizability, which has an accelerating effect and the HBA activity, which causes a decrease in the reaction rate. The general effect of an aprotic solvent depends on the prevailing solvent property. Some of the aprotic solvents can even show HBD activity (*e.g.*, chloroform) which additionally increases the reaction rate.

In already published studies,[18–23] the reactivity of various substituted and unsubstituted pyridine carboxylic acids with DDM in various solvents were investigated.

The interesting observation for all the investigated acids was the possible modes of influence of the solvent on their reactivity, considering the two sites in the initial and in the transition states of the pyridine carboxylic acids molecules, which are presented in Fig. 1.

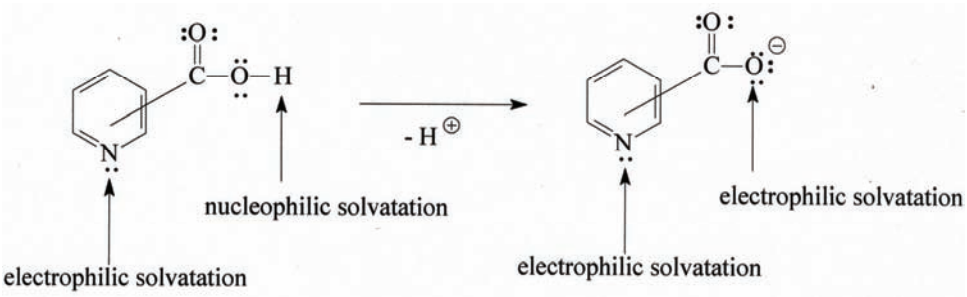

Fig. 1. The structure of a pyridine carboxylic acid and its anion.

Both electrophilic and nucleophilic solvation are present in the initial state, however only electrophilic solvation is present in the anion that exists in the transition state of the examined reaction. The effect of the electrophilic solvation of the pyridine nitrogen exists in both states, especially if a protic solvent is used.

Electrophilic solvation also plays a dominant role in the transition state, due to the structure of the molecule with two electrophilic centers. As electrophilic solvation is present in both the initial and the transition state, its influence may be complicated. Nucleophilic solvation is present only in the initial state and the classical solvation is present in both states, however it is more prominent in the transition state due to the charge increase.

The rate data for the examined acids were correlated with the Kamlet–Taft Equation. The results showed that linear free energy relationships (LFER) are applicable to the kinetic data for the investigated acid systems.

The correlation equations obtained by stepwise regression for all the examined acids showed that the best approach, which helps in the understanding of the effects of hydroxylic solvents on the reaction, lies in the separate correlations of the kinetic data with the hydrogen bond donating (HBD) and hydrogen bond accepting (HBA) ability of a solvent. For aprotic solvents, it is often the case that the effects can be considered together.

3. THE KAMLET–TAFT METHOD FOR THE EXAMINATION OF SOLVENT EFFECTS ON THE REACTIVITY OF CARBOXYLIC ACIDS WITH DIAZODIPHENYLMETHANE

Kamlet *et al.*[9] established that the effect of a solvent on the reaction rate should be given in terms of the following properties: *i*) the behavior of the solvent as a dielectric, facilitating the separation of opposite charges in the transition state, *ii*) the ability of the 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 the solvent to donate an electron pair and therefore stabilize the initial carboxylic acid, by way of a hydrogen bond between the carboxylic proton and the solvent electron pair. 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 solvent parameters (π^*, α and β) for hydrogen bond donor and non-hydrogen bond donor solvents (Eq. (2)), taken from the literature,[11] are given in Table I. The linear dependence (LSER) on the solvent parameters were used to correlate and predict a wide variety of solvent effects, as well as to provide an analysis in the terms of knowledge and the theoretical concepts of molecular structural effects.[9]

TABLE I. Solvent parameters[11]

Solvent	π^*	β	α
Methanol	0.60	0.62	0.93
Ethanol	0.54	0.77	0.83
Cyclopentanol	0.45	0.84	0.66
Butan-2-ol	0.40	0.80	0.69
2-Methylbutan-2-ol	0.40	0.93	0.28

TABLE I. Continued

Solvent	π^*	β	α
Pentan-1-ol	0.40	0.86	0.84
Benzyl alcohol	0.98	0.52	0.60
Dimethyl sulfoxide	1.00	0.75	0.00
N,*N*-Dimethylacetamide	0.88	0.76	0.00
N-Methylpyrrolidone	0.92	0.77	0.00
N,*N*-Dimethylformamide	0.88	0.69	0.00
N-Methylformamide	0.90	0.80	0.62
Acetophenone	0.90	0.49	0.04
Acetone	0.71	0.43	0.08
Ethyl benzoate	0.74	0.41	0.00
Isobutyl methyl ketone	0.65	0.48	0.02
2-Pyrrolidinone	0.85	0.77	0.36
Sulfolan	0.98	0.39	0.00
Butan-2-one	0.67	0.48	0.06
Chloroform	0.58	0.00	0.44
Acetonitrile	0.19	0.31	0.85
Diethyl carbonate	0.45	0.40	0.00
Methyl acetate	0.60	0.42	0.00
Ethyl acetate	0.55	0.45	0.00
Butyl ethanoate	0.46	0.45	0.00
Tetrahydrofuran	0.58	0.55	0.00
Dioxane	0.55	0.37	0.00

The present review demonstrates how the linear solvation energy relationship method can be used to quantify, correlate and rationalize the multiple interacting effects of the selected solvent set on the reactivity parameters of pyridine carboxylic acids in their reaction with DDM.

3.1. Pyridine carboxylic acids

Protic solvents

The values of second-order rate constants for the reaction of the picolinic (**1**), nicotinic (**2**) and isonicotinic acid (**3**), Fig. 2, in a protic solvent set are given in Table II.

TABLE II. Rate constants (dm^3 mol^{-1} min^{-1}) for the reaction of nicotinic, isonicotinic and picolinic acid with DDM at 30 °C in various alchols[18,19]

Solvent	Picolinic acid	Nicotinic acid	Isonicotinic acid
Methanol	10.96	10.69	19.95
Ethanol	7.24	5.37	12.02
Butan-2-ol	4.36	3.46	5.75
Cyclopentanol	3.74	3.67	5.82
2-Methylbutan-2-ol	1.26	0.87	1.86
Pentan-1-ol	4.26	3.71	7.24
Benzyl alcohol	28.18	26.53	42.94

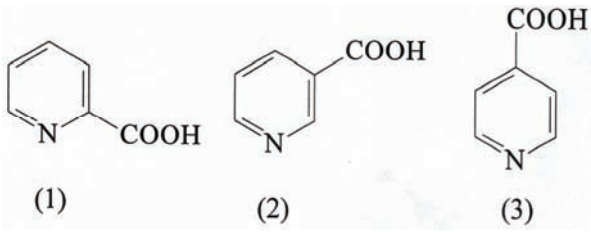

Fig. 2. The structures of the examined compounds.

The observation that isonicotinic acid exhibits the highest reaction rates and picolinic and nicotinic acid have rather similar lower values can be explained by the negative inductive and resonance effects (electron-withdrawing effects) of the present nitrogen, which stabilize the carboxylic anion of the isonicotinic acid and enhances the acidity. In the case of nicotinic acid, which has the lowest reaction rate constants, the nitrogen exerts an inductive effect, which could stabilize the anion, however the same effect is stronger in the molecule of picolinic acid. For picolinic acid, there is a possibility of the formation of an intramolecular hydrogen bond between the carboxylic proton and the neighboring nitrogen; such a hydrogen bond could hinder the removal of the proton, but as picolinic acid react faster than nicotinic acid, it obviously does not prevail over the electron-withdrawing effects of the nitrogen. The fact that the described hydrogen bond exists can be seen from the comparison of picolinic and isonicotinic reaction rate constants. These two compounds have the same resonance and inductive effects, but there is hydrogen bond that decreases the reaction rate only in the case of picolinic acid, Fig. 3.

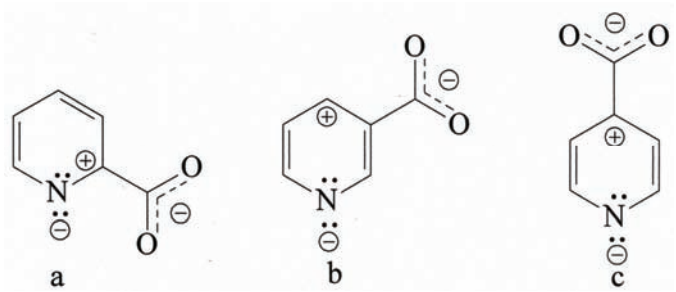

Fig. 3. The carboxylic anions of a) picolinic, b) nicotinic and c) isonicotinic acid.

The Kamlet–Taft parameters of the applied solvent set are given in Table I. The set of seven solvents was chosen to match the solubility of all the examined compounds, so that all the results could be clearly and reliably compared.

In order to separate the effects that influence the initial and the transition state in the examined reaction in protic solvents, the total solvatochromic equation was divided into two parts:

$$\log k = \log k_0 + s\pi^* + a\alpha \quad (3a)$$

$$\log k = \log k_0 + a\alpha + b\beta \quad (3b)$$

Equation (3a) describes the solvent effects influencing the transition state and (3b) the initial state, electrophilic solvation (HBD) exists in the initial state for nicotinic acids because of the presence of the nitrogen in the ring.

By this approach, the following results were obtained:

Nicotinic acid:

$$\log k = -1.02 + (1.83\pm0.18)\pi^* + (1.04 \pm 0.17)\alpha \quad (4a)$$

$$R = 0.987,\ s = 0.09,\ n = 7$$

$$\log k = 2.61 + (0.23\pm0.21)\alpha - (2.70 \pm 0.31)\beta \quad (4b)$$

$$R = 0.979,\ s = 0.103,\ n = 7$$

For all three compounds examined in this chapter, there appeared to be the similar problem, the low significance of the HBD coefficient parameter in the initial state. As the value for the HBA solvent effect was much higher and completely reliable, it could be concluded that the HBA effects dominate in the initial state and mask the electrophilic solvation directed to the nitrogen. In order to obtain clear results, α was excluded from the correlation for the initial state and the equation was given in the following form, for nicotinic acid:

$$\log k = 3.01 - (3.05 \pm 0.43)\beta \quad (4c)$$

$$R = 0.953,\ s = 0.15,\ n = 7$$

This is not to say that electrophilic solvation does not exist in the initial state for nicotinic acids, it is just not prominent enough to be compared with the HBA solvation in the given solvent set.

Therefore, the following results were taken into consideration:

Picolinic acid:

$$\log k = -0.79 + (1.71\pm0.14)\pi^* + (0.91 \pm 0.13)\alpha \quad (5a)$$

$$R = 0.990,\ s = 0.07,\ n = 7$$

$$\log k = 2.90 - (2.81 \pm 0.37)\beta \quad (5b)$$

$$R = 0.958,\ s = 0.13,\ n = 7$$

Isonicotinic acid:

$$\log k = -0.70 + (1.74\pm0.05)\pi^* + (1.04 \pm 0.05)\alpha \quad (6a)$$

$$R = 0.999,\ s = 0.03,\ n = 7$$

$$\log k = 3.15 - (2.89 \pm 0.42)\beta \quad (6b)$$

$$R = 0.950,\ s = 0.15,\ n = 7$$

The results of the above correlations confirm the reaction mechanism and describe the influence of the solvent by classic electrophilic and nucleophilic solvation. It is evident that the solvent polarity/polarizability and HBD effect increased the reaction rate by stabilizing the transition state, which was proved by the positive signs of the coefficients *s* and *a*.

The correlation with the HBA parameter (β) proved also to be successful and from these correlations, it can be seen that this property decreased the reaction rate, which is in agreement with the assumption that this solvent property stabilizes the initial state.

With the intention of analyzing the effect of the presence of nitrogen in the ring, the described results were compared to those for benzoic acid:[18]

$$\log k = -1.99 + (2.25 \pm 0.26)\pi^* + (1.15 \pm 0.25)\alpha \quad (7a)$$

$$R = 0.980,\ s = 0.130,\ n = 7$$

$$\log k = 2.81 - (3.66 \pm 0.55)\beta \quad (7b)$$

$$R = 0.948\ s = 0.190,\ n = 7$$

The higher value of the coefficient of polarity/polarizability parameter signifies a difference in the solvation between the benzoic and the pyridine carboxylic acids. This can be explained by the higher demand for the solvent polarity/polarizability effect as the anion of the benzoic acid is more polarizable. The presence of nitrogen in the ring decreases the difference in the electronic density in the anion of the pyridine carboxylic acids, in comparison with that of the anion of benzoic acid.

The quantitative analysis of solvent effects showed that in all cases, classical solvation prevails over the proton-donor solvent activity, but that the proton-acceptor (HBA) activity was also significant.

The HBA activity was somewhat higher for benzoic acid as in this case, there is no electronegative nitrogen in the ring that could facilitate the removal of the proton.

The HBD activity was also slightly higher for benzoic acid, as it is directed only to the reactive center, the carboxylic group in the transition state. In the case of pyridine carboxylic acids, it is divided between the carboxylic group and the nitrogen, which is not directly involved in the reaction mechanism.

Regarding the solvent parameter coefficients for the pyridine carboxylic acids, it could be noticed that the picolinic acid had the lowest value of the HBA (β) coefficient. It could be explained by the formation of a hydrogen bond between the carboxylic proton and the neighboring nitrogen, which stabilizes the proton in the initial state; hence, nucleophilic stabilization by solvent is not so necessary (Fig. 4).

Considering that there is only the inductive effect of nitrogen in the case of nicotinic acid, the nucleophilic solvent effect will act the strongest on this compound. As the anion of nicotinic acid is the least stable of the three examined compound because of the absence of the electron-withdrawing effect of nitrogen, it has the highest demand for classical solvation, Fig. 3b.

For isonicotinic acid, the coefficients of which lie in the middle, it could be concluded that there is no intramolecular hydrogen bond. A negative inductive effect of the nitrogen exists that is weaker than for the other two examined com-

pounds, but also an electron-withdrawing effect of the nitrogen, which can make the carboxylic anion more stable, Fig. 3c.

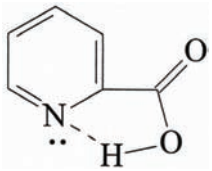

Fig. 4. Hydrogen bond in the molecule of picolinic acid.

The high positive value of the coefficient *s* indicates that the effect of classical solvation is the main solvent effect influencing the transition state of the reaction of the examined pyridine carboxylic acids with DDM. According to the smaller value of the coefficient *a*, electrophilic solvation of the transition state is less pronounced than classic solvation, but also increases the reaction rate.

Various solvents containing no hydroxyl group

The same approach as for protic solvents was applied to the kinetic data of nicotinic acid in various solvents containing no hydroxyl group (Table III).

TABLE III. Rate constants (dm^3 mol^{-1} min^{-1}) for the reaction of nicotinic, isonicotinic and picolinic acids with DDM at 30 °C in various solvents[19]

Solvent	Picolinic acid	Nicotinic acid	Isonicotinic acid
Dimethyl sulfoxide	0.21	0.35	0.10
N,*N*-Dimethylacetamide	0.12	0.21	0.04
N-Methylpyrrolidone	0.12	0.22	0.037
N,*N*-Dimethylformamide	0.25	0.44	0.098
Acetophenone	5.17	1.69	1.36
2-Pyrrolidinone	0.15	0.11	0.14
Sulfolan	14.79	Insoluble	3.97
N-Methylformamide	0.94	1.12	1.35
Butan-2-one	2.51	1.49	0.19
Acetone	1.56	3.52	0.19
Chloroform	40.36	Insoluble	13.24
Ethyl benzoate	3.37	Insoluble	6.25
Acetonitrile	12.80	Insoluble	1.76
Diethyl carbonate	Insoluble	Insoluble	0.049
Methyl acetate	1.39	Insoluble	0.88
Butyl ethanoate	0.72	Insoluble	0.16
Isobutyl methyl ketone	1.39	0.98	0.21
Ethyl acetate	1.22	0.88	0.16
Tetrahydrofuran	1.83	0.30	Insoluble
Dioxane	0.24	0.58	Insoluble

In order to obtain a reliable correlation, tetrahydrofuran, butyl ethanoate and ethyl acetate were excluded from the calculations for nicotinic acid, Eq. (8):

$$\log k = 0.13 + (3.22\pm0.64)\pi^* + (1.53\pm 0.41)\alpha - (5.14 \pm 0.48)\beta \quad (8)$$
$$R = 0.955,\ s = 0.26,\ n = 16$$

The above result indicates that the influence of the solvent on the rate is mainly the result of the strong basic character of applied solvent molecules, which is reflected in the high values of the coefficient *b*. Nucleophilic solvation, the basicity of the applied solvent, is the main solvent effect that af-fects a decrease in the reaction rate of the investigated acid with DDM. The percentage contributions of the individual solvent effects for nicotinic acid are 33 % classical solvation, 15 % electrophilic solvation and 52 % nucleophilic solvation. In this case, the HBD solvent effect and classical solvation increase the reaction rate. One correlation was found in the literature[24] that includes all three solvent parameters in the correlation for benzoic acid in solvents not allegedly possessing HBD character:

$$\log k = 0.20 + 1.21\ \pi^* + 2.71\alpha - 3.70\beta \quad (9)$$
$$R = 0.980,\ s = 0.17,\ n = 44$$

The percentage contributions of the individual solvent effects calculated from the Eq. (9) are: π^* = 16 %, α = 35 %, β = 49 %. A comparative study of these results (Eq. (9)) with those for nicotinic acid (Eq. (8)) leads to the conclusion that classical solvation is more important for nicotinic acid, while electrophilic stabilization, *i.e.*, the HBD solvent effect, is more important for benzoic acid. For both acids, the basicity of a solvent, or the nucleophilic stabilization of the initial state of the molecules, which decreases the reaction rate, is the main factor affecting their reactivity. This effect is more pronounced in the correlation for nicotinic acid because of its higher acidity.

The surprisingly high values of the coefficient *a* for applied solvents in the two previous equations, especially the one for benzoic acid, indicate the important role of the HBD effect of applied solvents, which increases the reaction rate by stabilizing the acid anion.

The correlation of the log *k* values for isonicotinic acid with the parameters π^*, α and β for applied solvents gave the following results:

$$\log k = 0.075 + (1.67\pm0.43)\pi^* + (1.26 \pm 0.23)\alpha - (2.87 \pm 0.47)\beta \quad (10)$$
$$R = 0.953,\ s = 0.12,\ n = 9$$

Classical and electrophilic solvation increase the reaction rate of this acid, while nucleophilic solvation of the initial state decreases it. The percentage contributions of the individual solvent parameters are: 29 % for classical solvation, 21 % for electrophilic solvation and 50 % for nucleophilic solvation.

Although a better solvation of the carboxylic group proton of isonicotinic acid in the initial state was expected because it is more acidic than nicotinic acid, there is only a small difference between the values of the contribution of coef-

ficient *b* for isonicotinic and nicotinic acids, due to negative inductive and electron-withdrawing effects.

The kinetic data for nicotinic and isonicotinic acids in applied solvents (Table III) show interesting results as the rate constants strongly depend on the effects of solvents which is reflected in the value of coefficient *b*. The higher value of electrophilic solvation in the transition state for isonicotinic acid can be explained by the joint effect of solvation of either the forming carboxylate anion or the partial negative charge on the nitrogen of the pyridyl group. The better classical solvation of nicotinic acid is caused, probably, by a less pronounced direct resonance interaction than in isonicotinic acid, leading to a more polarizable structure, resulting in better solvation by the dipolar solvent effect.

The correlation of the log *k* values for picolinic acid with the parameters π^*, α and β for applied solvents gave the following results:

$$\log k = -0.46 + (2.80 \pm 0.43)\pi^* + (2.27 \pm 0.37)\alpha - (4.44 \pm 0.41)\beta \qquad (11)$$
$$R = 0.956,\ s = 0.24,\ n = 17$$

The high negative value of coefficient *b* shows that solvation by the HBA solvent effect, namely nucleophilic solvation of the initial state, is a more important effect than the other two. The positive signs of the coefficients *s* and *a* indicate significant classical and electrophilic solvation, but they are of less significance than nucleophilic solvation. The calculations of the percentage contributions of the partial solvent effect gave the following results: π^* = 29 %; α = 24 % and β = 47 %.

The overall comparison of the results of solvent effects on the reactivity of the pyridine carboxylic acids is presented in Table IV.

TABLE IV. Percentage contribution of the Kamlet–Taft solvatochromic parameters to the reactivity of the investigated acids in variuos solvents

Acids	P_{π^*} / %	P_α / %	P_β / %
Nicotinic	33	15	52
Picolinic	29	21	50
Isonicotinic	29	24	47
Benzoic	16	35	49

The data from Table III indicate that the HBD solvent effect (acidity) significantly affected the stabilization of the transition state, and that this solvent effect is more important for picolinic than for isonicotinic and nicotinic acids. The higher value of the HBA parameter, which expresses the effect of electrophilic solvation, for picolinic acid can, most probably, be explained in the following way: the carboxylate anion forming in the transition state is very close to the pyridine nitrogen, causing, to some extent, a repulsion between the identical negative charges, resulting in the planar carboxylate anion being in a perpendicular

position with respect to the pyridine ring, which is therefore subjected to a better electrophilic solvation. As can be seen, the highest value of the HBD effect for benzoic acid is most probably influenced by the exclusive stabilization of the carboxylate ion, with no stabilization of the negative charge on the pyridine nitrogen, as is the case for the isomeric pyridine carboxylic acids.

Classical solvation (π^*) is more pronounced for nicotinic acid because its molecule has a more distinct dipolar structure than the molecules of the other two investigated pyridine mono-carboxylic acids.

The percentage contribution of the HBA solvent effect shows a small decrease for picolinic acid. This can be explained, probably, by the ability of picolinic acid to create an intramolecular hydrogen bond in the initial state, which decreases the influence of solvents.

3.2. Substituted nicotinic acids

In order to analyze the effect of substituents on the reactivity of pyridine carboxylic acids with DDM, two types of substituted nicotinic acids were examined in the same solvent set.

3.2.1. 2-Substituted nicotinic acids

Protic solvents

The second order rate constants for the reaction of 2-substituted nicotinic acids with DDM in various alcohols at 30 °C are given in Table V. The results show that the rate constants increased with the polarity of the solvents. This is in accordance with the already described reaction mechanism.

TABLE V. Rate constants ($dm^3\ mol^{-1}\ min^{-1}$) for the reaction of 2-substituted nicotinic acids with DDM at 30 °C in various alcohols[20]

Solvent	H	Cl	OH	CH_3
Methanol	10.70	38.10	44.80	9.77
Ethanol	5.40	22.20	28.30	4.80
Butan-2-ol	3.45	9.40	12.10	2.70
Cyclopentanol	3.67	9.27	10.70	2.70
2-Methylbutan-2-ol	1.26	3.42	4.72	0.76
Pentan-1-ol	3.72	11.10	15.90	3.00
Benzyl alcohol	26.50	100.90	137.10	23.10

All investigated 2-substituted nicotinic acids are more reactive than the correspondingly substituted benzoic acids in the same solvent set.[24] This is understandable considering the highly electron attracting pyridine nucleus. In both reaction series, the hydroxyl-substituted acids were more reactive than the other substituted acids.[24] This is generally accepted to be due to the existence of a hydrogen bond between the hydrogen from the hydroxyl group and the oxygen from the carboxylic anion. This interaction is potentially possible in both salicylic acid

and 2-hydroxynicotinic acid, and is probably responsible for enhanced acidity by facilitating the release of the carboxylic proton.

It can be also noticed that the reaction rate constants increase in the presence of electron-acceptor substituents, which stabilize the negative charge in the transition state, such as chlorine in this case. The only investigated compound with an electron-donor substituent (methyl group) has the lowest reaction rates, and the rate constants for the unsubstituted compound lie in the middle, as could have been expected.

The rate constants were examined using the solvatochromic equation (Eq. (2)), and the parameters given in Table I.

The correlation analysis of investigated acids with solvent parameters π^*, α and β in protic solvents showed that there were no satisfactory results for the three-parameter equation (Eq. (2)). Further examination by dividing the solvent effects into those supporting the transition state (π^* and α) and the one supporting the initial state before the reaction starts (β), as in the previous chapter, proved to be successful.

Nicotinic acid:

$$\log k = -1.02 + (1.83 \pm 0.18)\pi^* + (1.04 \pm 0.17)\alpha \quad (4a)$$
$$R = 0.987,\ s = 0.09,\ n = 7$$
$$\log k = 3.01 - (3.05 \pm 0.43)\beta \quad (4c)$$
$$R = 0.953,\ s = 0.15,\ n = 7$$

2-Chloronicotinic acid:

$$\log k = -0.54 + (2.01 \pm 0.06)\pi^* + (0.97 \pm 0.06)\alpha \quad (12a)$$
$$R = 0.995,\ s = 0.032,\ n = 7$$
$$\log k = 3.67 - (3.23 \pm 0.37)\beta \quad (12b)$$
$$R = 0.976,\ s = 0.130,\ n = 7$$

2-Hydroxynicotinic acid:

$$\log k = -0.39 + (2.02 \pm 0.09)\pi^* + (0.91 \pm 0.09)\alpha \quad (13a)$$
$$R = 0.985,\ s = 0.097,\ n = 7$$
$$\log k = 3.75 - (3.15 \pm 0.38)\beta \quad (13b)$$
$$R = 0.965,\ s = 0.890,\ n = 7$$

2-Methylnicotinic acid:

$$\log k = -1.14 + (1.89 \pm 0.12)\pi^* + (1.05 \pm 0.12)\alpha \quad (14a)$$
$$R = 0.994,\ s = 0.063,\ n = 7$$
$$\log k = 3.02 - (3.16 \pm 0.38)\beta \quad (14b)$$
$$R = 0.965,\ s = 0.136,\ n = 7$$

Judging by the similar coefficient values for the compounds with different substituents, it could be stated that the nature of substituent does not considerably change the solvent effect. From a comparison with the unsubstituted acid (Eq.

(4)), it can be seen that the influence of the solvent polarity was higher on all the substituted nicotinic acids than on the unsubstituted one. This observation could be explained by the higher polarity of the substituted acids molecules than of the unsubstituted one. The only compound with an alkyl substituent (2-methylnicotinic acid) should differ the least in polarity from nicotinic acid; this is supported by the polarity/polarizability solvent parameter coefficient (*s*) being the most similar to those of nicotinic acid.

The kinetic results show that in all cases the polarity/polarizability parameter (π^*) was the dominating factor supporting the transition state and increases the reaction rate, which is in agreement with the known mechanism.

The sign of the α coefficient is also positive in all equations, which means that electrophilic stabilization of the transition state existed. This stabilization is explained by a hydrogen bond interaction between the carboxylate anion and the proton of the protic solvent molecule. The effect of both inductive and resonance stabilization of the negative charge on the carboxylate anion by a substituent decreases the necessity of electrophilic solvation, in this way decreasing the influence of the solvent on the reactivity of these acids.

The sign of the coefficients of the β term in all equations is negative, which could be expected considering that this parameter defines the nucleophilic stabilization of the initial state, which slows down the examined reaction.

A comparison with the corresponding 2-substituted benzoic acids[21] revealed that the signs are also in agreement with the reaction mechanism, as can be seen from Eqs. ((15)–(17)):

2-Chlorobenzoic acid:

$$\log k = -1.19 + (2.20 \pm 0.23)\pi^* + (1.04 \pm 0.22)\alpha \quad (15a)$$
$$R = 0.984,\ s = 0.120,\ n = 7$$
$$\log k = 3.44 - (3.59 \pm 0.39)\beta \quad (15b)$$
$$R = 0.972,\ s = 0.140,\ n = 7$$

2-Hydroxybenzoic acid:

$$\log k = -0.45 + (2.01 \pm 0.20)\pi^* + (0.49 \pm 0.20)\alpha \quad (16a)$$
$$R = 0.972,\ s = 0.120,\ n = 7$$
$$\log k = 3.04 - (3.04 \pm 0.33)\beta \quad (16b)$$
$$R = 0.965,\ s = 0.890,\ n = 7$$

2-Methylbenzoic acid:

$$\log k = -2.22 + (2.85 \pm 0.23)\pi^* + (1.32 \pm 0.22)\alpha \quad (17a)$$
$$R = 0.987,\ s = 0.114,\ n = 7$$
$$\log k = 2.85 - (3.82 \pm 0.55)\beta \quad (17b)$$
$$R = 0.965,\ s = 0.136,\ n = 7$$

The most prominent difference between the 2-substituted nicotinic and the 2-substituted benzoic acids is again the coefficient of the solvent polarity/pola-

rizability parameter, with higher values for the latter. This confirms the tentative explanation from the previous chapter. The higher polarizability of the anion of benzoic acids causes a greater demand for stabilization by the solvent polarity.

Considering the coefficient of the HBD parameter, the values are similar for both sets of acids, except for the OH-substituted acid for which it is considerably lower for benzoic than for nicotinic acid (0.49 and 0.91, respectively). As a strong hydrogen bond in the transition state exists in both compounds (Fig. 5), the demand for electrophilic stabilization should be about the same. However, in the molecule of 2-hydroxynicotinic acid, the nitrogen also requires electrophilic stabilization and hence the higher value for the HBD effect (Fig. 5).

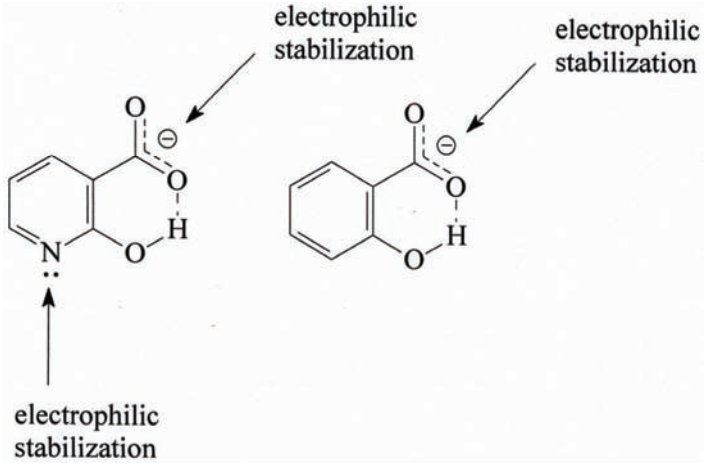

Fig. 5. The electrophilic stabilization of the anion of 2-hydroxynicotinic and 2-hydroxybenzoic acid.

The sign of the HBA parameter coefficient is negative in all equations, as expected considering the known reaction mechanism – the solvation of the proton in the initial state is responsible for the decrease in the reaction rate. The somewhat lower values of the β coefficients for the nicotinic acids could be understood as the lower demand for nucleophilic stabilization by the solvent in the presence of the pyridine nitrogen, which, by its electron-acceptor effect increases the acidity. Therefore, the carboxylic proton is more easily detached from the acid molecule and less stabilized by the HBA solvent effect.

Various solvents containing no hydroxyl group

In order to explain the solvent effect on the reactivity of the 2-substituted nicotinic acids with DDM, the reaction rate constants of the examined compounds were determined in a set of nine various solvents (Table I). The reaction rate constants are given in Table VI.

TABLE VI. Rate constants (dm^3 mol^{-1} min^{-1}) for the reaction of 2-substituted nicotinic acids with DDM at 30 °C in various solvents[21]

Solvent	H	2-Cl	2-OH	2-CH_3	2-Br	2-SH
Dimethyl sulfoxide	0.21	1.011	0.93	0.24	1.01	0.90
N,*N*-Dimethylacetamide	0.11	0.55	0.63	0.14	0.57	0.74
N-Methylpyrrolidone	0.12	0.74	1.38	0.16	0.73	0.76
N,*N*-Dimethylformamide	0.24	0.97	1.48	0.33	0.96	1.57
N-Methylformamide	0.94	1.26	0.44	1.74	1.29	2.38
Acetophenone	5.18	22.03	Insoluble	5.64	23.60	17.02
Acetone	1.55	2.824	Insoluble	3.34	3.21	5.24
Ethyl benzoate	3.37	12.25	Insoluble	7.24	12.08	7.85
Isobutyl methyl ketone	1.39	4.04	Insoluble	2.05	4.477	5.64

The correlation results are presented in the following equations. Here, the correlation results for the nicotinic acid are also given for comparison.

Nicotinic acid:

$$\log k = 0.82 + (2.45\pm0.85)\pi^* + (1.72\pm0.32)\alpha - (5.18\pm0.63)\beta \quad (18)$$
$$R = 0.977,\ s = 0.17,\ n = 9$$

2-Chloronicotinic acid:

$$\log k = 0.70 + (3.12\pm1.23)\pi^* + (0.78\pm0.46)\alpha - (4.90\pm0.91)\beta \quad (19)$$
$$R = 0.938,\ s = 0.25,\ n = 9$$

2-Methylnicotinic acid:

$$\log k = 1.50 + (1.91\pm0.60)\pi^* + (1.99\pm0.22)\alpha - (5.30\pm0.44)\beta \quad (20)$$
$$R = 0.990,\ s = 0.12,\ n = 9$$

2-Bromonicotinic acid:

$$\log k = 0.81 + (3.03\pm1.21)\pi^* + (0.80\pm0.45)\alpha - (4.93\pm0.89)\beta \quad (21)$$
$$R = 0.942,\ s = 0.24,\ n = 9$$

2-Mercaptonicotinic acid:

$$\log k = 1.31 + (1.78\pm0.92)\pi^* + (1.03\pm0.35)\alpha - (3.99\pm0.68)\beta \quad (22)$$
$$R = 0.955,\ s = 0.18,\ n = 9$$

The correlation equations obtained by multiple linear regressions for all the examined acids confirmed the supposed reaction mechanism, as the solvent polarity and its proton-donor (HBD) activity increased the reaction rate constant and the proton-acceptor (HBA) ability decreased it. It could be noticed that the HBA effect was the most prominent one in this solvent set.

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

It could be noticed that the in case of the electron withdrawing substituents, the values for the HBD parameter (α) were lower than for the unsubstituted acid

and the acid with the electron-donor substituent (CH_3). The negative inductive effect of the electron-acceptor substituents additionally stabilizes the carboxylic anion, and so the HBD solvent effect is less involved.

TABLE VII. Percentage contribution of the Kamlet–Taft solvatochromic parameters to the reactivity of the investigated acids in various solvents

Acid	P_{π^*} / %	P_{α} / %	P_{β} / %
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

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

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

b) The non-specific interaction has a greater influence (higher percentage value) than HBD 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 correlation results obtained here were compared with the previously published results for the corresponding 6-substituted nicotinic acids,[10] 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; the proton-donor ability had a higher influence on the 6-substituted acids. This could be explained by the strong negative inductive effect of most of the substituents present that is considerably stronger in the C-2 position, as it is next to the reactive center, than in the C-6 position of the ring, with three atoms separating them from the reactive center. Comparing the reaction rate constants for both types of nicotinic acid, it could be noticed that the 2-substituted acids generally reacted faster, due to the additional stabilization of the anion in the transition state by the negative inductive substituent effect. The fact that of the only examined acids with an electron-donor substituent, the methyl group, the 2-substituted acid also reacted faster than the 6-substituted one 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 DDM molecule. The higher value of the HBD coefficient (α) shows that electron-donor support from the solvent is more necessary 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 based on their electronegativity, is additionally proved by the value of the HBD coefficient for 2-mercaptonicotinic acid; sulfur

is less electronegative than chlorine and bromine, and this compound has an α coefficient higher than the other two acids, but also somewhat lower than the unsubstituted and the methyl-substituted acids.

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

6-Hydroxynicotinic acid:[22]

$$\log k = -1.92 + (2.37\pm0.36)\pi^* + (1.99\pm0.09)\alpha - (2.20\pm0.51)\beta \quad (23)$$
$$R = 0.982,\ s = 0.26,\ n = 5$$

Due to the ability of forming strong hydrogen bonds between the oxygen and nitrogen on both carboxylic acids and the hydroxyl group, both compounds are insoluble in many solvents; however, the set of five solvents given here, in which they both dissolve, was found.

The exception of the unsuccessful correlation for 2-hydroxynicotinic acid could be explained by its specific structure. As can be seen in Fig. 5, this compound forms a strong intramolecular hydrogen bond, helped by the electron-donor resonance effect of the hydroxylic group, which significantly decreases its reactivity in the form of the anion. 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 reaction in the chosen solvent set.

Contrary to this, in case of 6-hydroxynicotinic acid, there is also a possibility of the formation of intermolecular hydrogen bonds that, as can be concluded from the successful application of the Kamlet–Taft Equation, does not interfere significantly with its reactivity in the examined reaction.

It could be concluded that, because of its complex possibilities for the formation of intramolecular hydrogen bonds, 2-hydroxynicotinic acid is not an appropriate compound for an investigation of the reaction mechanism of carboxylic acids with DDM and the effect solvent on it, as it cannot be analyzed by the Kamlet–Taft Equation.

None of the other examined 2-substituted nicotinic acid possesses an ability to form such an intramolecular hydrogen bond, except for 2-mercaptonicotinic acid. However, it is obvious that in this case, the hydrogen bond is not strong enough to influence the reactivity of the compound as it has a similar behavior to that of the other examined acids in their reaction with DDM.

3.2.2. 6-Substituted nicotinic acids

Protic solvents

The analysis of the kinetics of the reaction of the 6-substituted nicotinic acids with DDM gave the following results.

In accordance to previous results, as it could be seen in Eqs. (24)–(26), the signs of the solvatochromic parameters are again in agreement with the reaction mechanism.

Nicotinic acid:

$$\log k = -1.02 + (1.83 \pm 0.18)\pi^* + (1.04 \pm 0.17)\alpha \quad (4a)$$
$$R = 0.987,\ s = 0.09,\ n = 7$$
$$\log k = 3.01 - (3.05 \pm 0.43)\beta \quad (4c)$$
$$R = 0.953,\ s = 0.15,\ n = 7$$

6-Chloronicotinic acid:

$$\log k = -0.58 + (1.77 \pm 0.09)\pi^* + (0.71 \pm 0.09)\alpha \quad (24a)$$
$$R = 0.995,\ s = 0.047,\ n = 7$$
$$\log k = 2.97 - (2.76 \pm 0.33)\beta \quad (24b)$$
$$R = 0.966,\ s = 0.116,\ n = 7$$

6-Hydroxynicotinic acid:

$$\log k = -1.28 + (1.95 \pm 0.12)\pi^* + (1.00 \pm 0.11)\alpha \quad (25a)$$
$$R = 0.994,\ s = 0.060,\ n = 7$$
$$\log k = 2.86 - (3.15 \pm 0.43)\beta \quad (25b)$$
$$R = 0.956,\ s = 0.151,\ n = 7$$

6-Methylnicotinic acid:

$$\log k = -1.09 + (1.92 \pm 0.13)\pi^* + (0.94 \pm 0.12)\alpha \quad (26a)$$
$$R = 0.993,\ s = 0.065,\ n = 7$$
$$\log k = 2.93 - (3.07 \pm 0.43)\beta \quad (26b)$$
$$R = 0.954,\ s = 0.151,\ n = 7$$

Once again, the solvent polarity/polarizability is the dominating effect in the transition state. The effect supporting the initial state, the HBA solvent activity, was in the range similar to those of the previous investigations in this study. The positive sign of the HBD solvent parameter once again describes the support this effect gives to the transition state and the increase in the reaction rate. The somewhat lower value of this parameter coefficient for the chloro-substituted acid may be explained by its acidity, higher than those of the other examined compounds because of the presence of the electronegative chlorine, which additionally stabilizes the anion. Such a structure has a lower demand for electrophilic stabilization.

Contrary to 2-hydroxynicotinic acid, 6-hydroxynicotinic acid displays the lowest reaction rate constants. This observation could be explained by the decrease in its acidity because of the electron-donor resonance effect of the hydroxyl group. The increase of the electronic density in the ring destabilizes the carboxylic anion (Fig. 6).

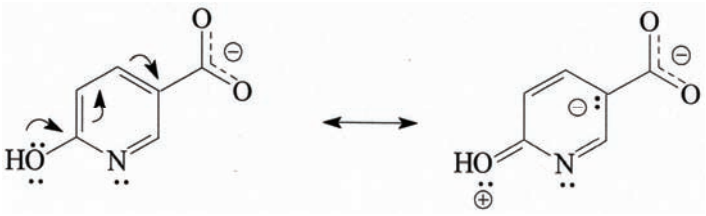

Fig. 6. The carboxylic anion of 6-hydroxynicotinic acid.

The highest value of the π^* coefficient for the 6-hydroxy-substituted acid could be explained by its additional need for stabilization of the anion by the solvent, because the charge separation in the transition state is the highest for this acid. The same compound also has the highest coefficients for the HBD and HBA solvent parameters. The strongest solvent influence on 6-hydroxynicotinic acid is due to lowest stability of the anion of this acid, considering the series examined in this chapter. The negative inductive effect of the oxygen atom seems to be negligibly weak in comparison to the positive resonance one (electron-donor effect).

6-Methylnicotinic acid has lower reaction rate constants than nicotinic and 6-chloronicotinic acids, which is probably due to the positive inductive effect of the methyl group. However, it seems that its anion is more stable than the one of the 6-hydroxynicotinic acid, as 6-hydroxynicotinic has even lower reaction rate constants. The solvent effect on this compound is slightly higher than on the unsubstituted and chloro-substituted nicotinic acids, but lower than on 6-hydroxynicotinic acid, meaning that its demand for stabilization by solvent effects is intermediate between them.

For comparison, the same equations were determined for the same substituted benzoic acids in the same solvent set[23], as in the previous section:

6-Chlorobenzoic acid

$$\log k = -1.48 + (1.96 \pm 0.22)\pi^* + (0.99 \pm 0.22)\alpha \quad (27a)$$
$$R = 0.980,\ s = 0.116,\ n = 7$$
$$\log k = 2.71 - (3.21 \pm 0.43)\beta \quad (27b)$$
$$R = 0.957,\ s = 0.153\ ,\ n = 7$$

6-Hydroxybenzoic acid

$$\log k = -2.59 + (2.42 \pm 0.22)\pi^* + (1.37 \pm 0.21)\alpha \quad (28a)$$
$$R = 0.988,\ s = 0.113,\ n = 7$$
$$\log k = 2.73 - (4.02 \pm 0.58)\beta \quad (28b)$$
$$R = 0.950,\ s = 0.207,\ n = 7$$

6-Methylnicotinic acid

$$\log k = -2.09 + (2.19 \pm 0.23)\pi^* + (1.17 \pm 0.23)\alpha \quad (29a)$$
$$R = 0.984,\ s = 0.119,\ n = 7$$

$$\log k = 2.64 - (3.59 \pm 0.54)\beta \quad (29b)$$
$$R = 0.948,\ s = 0.191,\ n = 7$$

Again the major difference between the two acids systems analyzed in this chapter is the value of the coefficient of the π^* parameter. Once more it was proved that the benzoic acids, although substituted at a different position from the set considered in the previous chapter, have more polarizable anions, which demand additional stabilization by the polarity/polarizability solvent effect. Furthermore, the somewhat higher values for the HBD solvent parameter, in other words more pronounced electrophilic stabilization of the benzoic acids, can again be explained by the fact that it is directed only to the reactive center, the carboxylic group in the transition state.

Various solvents containing no hydroxyl group

The reaction rate constants for the chosen series of 6-substituted nicotinic acids are given in Table VIII.

TABLE VIII. Rate constants ($dm^3\ mol^{-1}\ min^{-1}$) for the reaction of 6-substituted nicotinic acids with DDM at 30 °C in various solvents[22]

Solvent	H	6-Cl	6-OH	2-CH_3	6-Br	6-SH
Acetophenone	5.17	7.55	Insoluble	2.24	8.32	6.16
Acetone	1.55	2.34	Insoluble	1.38	2.51	2.09
Chloroform	40.73	208.92	Insoluble	31.62	281.8	158.5
Ethyl benzoate	3.37	4.36	Insoluble	2.82	4.49	3.04
Isobutyl methyl ketone	1.39	3.55	Insoluble	0.88	4.11	2.24
N-Methylformamide	0.94	1.51	0.49	0.76	1.41	1.20
Dimethyl sulfoxide	0.85	0.42	0.76	0.12	0.45	0.42
N,*N*-Dimethylacetamide	0.11	0.25	0.71	0.76	0.27	0.35
N,*N*-Dimethylformamide	0.24	0.58	0.05	0.16	1.58	0.69
N-Methylpyrrolidone	0.12	0.33	0.04	0.08	0.49	0.35

The results from Table VIII show that the influence of a solvent on the reactivity is complex, due to the many types of solvent to solute interactions (dipolarity, HBD and HBA effects), acting not only on the electrophilic and nucleophilic acid sites (Fig. 1), but also on the substituents, where they could cause modifications of the electronic properties. Solvents of high dipolarity/polarizability and/or high proton-acceptor capability caused a significant decrease in the reaction rate. The highest value of the reaction rates in chloroform could be explained by the highest proton-donor ability of this solvent, as well as by its lowest proton-acceptor capability, considering its values of the α and β parameters from Table I.

As stated in the literature,[25] carboxylic acids dissolved in chloroform exist in the form of dimers. A dimer could appear in two forms, cyclic and open, the latter being a very reactive form because it can easily lose a proton and convert into a resonance-stabilized anion. As the carboxylic anion is the reacting species in this system, it is continuously converted into the product and this is a probable

reason why the open chain dimer, which stabilizes the anion, is the dominant form.[25] Being a solvent of low polarity, chloroform influences a weaker stabilization of the ion-pair intermediate, making it easily convertible into the final product. Solvation of an ion-pair intermediate with a solvent of lower polarizability could have a higher contribution than with one of higher polarizability to a less negative activation entropy and thus to a more spontaneous reaction.

The results of the correlations of the reaction rate with the solvatochromic parameters π^*, α and β using the solvatochromic Eq. (2) are presented in the following equations.

Nicotinic acid:

$$\log k = 0.80 + (2.05\pm1.08)\pi^* + (1.61\pm0.39)\alpha - (4.63\pm0.67)\beta \quad (30)$$
$$R=0.974\ s=0.22\ n=10$$

6-Chloronicotinic acid:

$$\log k = 1.48 + (1.70\pm0.71)\pi^* + (1.58\pm0.27)\alpha - (4.77\pm0.47)\beta \quad (31)$$
$$R = 0.990,\ s = 0.16,\ n = 10$$

6-Hydroxynicotinic acid:

$$\log k = -1.92 + (2.37\pm0.36)\pi^* + (1.99\pm0.09)\alpha - (2.20\pm0.51)\beta \quad (23)$$
$$R = 0.982,\ s = 0.26,\ n = 5$$

6-Methylnicotinic acid:

$$\log k = 1.02 + (1.35\pm0.97)\pi^* + (1.73\pm0.35)\alpha - (4.34\pm0.61)\beta \quad (32)$$
$$R = 0.980,\ s = 0.20,\ n = 10$$

6-Bromonicotinic acid:

$$\log k = 1.64 + (1.68\pm0.77)\pi^* + (1.50\pm0.28)\alpha - (4.91\pm0.48)\beta \quad (33)$$
$$R = 0.989,\ s = 0.16,\ n = 10$$

6-Mercaptonicotinic acid:

$$\log k = 1.18 + (1.89\pm0.77)\pi^* + (1.40\pm0.28)\alpha - (4.56\pm0.48)\beta \quad (34)$$
$$R = 0.986,\ s = 0.16,\ n = 10$$

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

TABLE IX. Percentage contribution of the Kamlet–Taft solvatochromic parameters to the reactivity of the investigated acids in various solvents

Acid	P_{π^*} / %	P_α / %	P_β / %
H	27	23	60
6-Cl	21	20	59
6-OH	36	30	34
6-CH_3	18	23	59
6-Br	21	19	60
6-SH	24	18	58

The results from Table IX lead to the following conclusions:

1) The rate of the reaction is strongly influenced by specific solute–solvent interactions, as indicated by the percentage contributions of the α and β parameters ($P_\alpha + P_\beta$).

2) The positive sign of the coefficient of the α term suggests that the specific interaction between the transition state and the solvent (Fig. 1), through HBD properties is stronger than that between the reactant and solvent, *i.e.*, the HBD solvent effect or electrophilic solvation increases the reaction rate.

3) The negative sign of the coefficient of the β term suggest that the specific interaction between the reactant and solvent, through HBA properties, is stronger than that between the transition state and the solvent, *i.e.*, the HBA effect or nucleophilic solvation decreases the reaction rate.

4) The solvent dipolarity/polarizability, as indicated by P_{π^*} also plays an appreciable role in governing the reactivity. The positive sign of the coefficient of this term proves that classical or non-specific solute–solvent interactions dominate in the transition state and increase the reaction rate.

From a comparison with the already mentioned Eq. (9) for benzoic acid, it could be observed that the higher contribution of the HBA solvent effect for substituted nicotinic acids is affected by their higher acidity and the strong proton accepting character of some of the aprotic solvents. Classical solvation has a higher influence on the reactivity of 6-hydroxynicotinic acid, while the electrophilic stabilization, *i.e.* the HBD solvent effect, is more pronounced for benzoic acid. The significant contribution of the HBD solvent effect, reflected in value of the coefficient *a* for the chosen solvent set, in all previous equations, and especially for benzoic acid, indicate an important role of the HBD solvent effect. The proton donor ability of a solvent to stabilize nucleophilic sites on an acid anion in forming increases the reaction rate, while stabilization of the initial state decreases it. These results could be supported by the observation that dipolar non-HBD solvents, in spite of their high relative permittivities and dipole moments, could favor acid ionization and charge separation, and the created carboxylate anion–diazodiphenylmethane cation ion pair could be stabilized by applied solvents. Furthermore, the significantly higher value of P_α for benzoic acid leads to the conclusion that the strong electron-accepting character of the pyridine nitrogen has an undesirable contribution to HBD solvent stabilization in the transition state. The small and definitely increased contribution of the HBD solvent effect for 6-hydroxynicotinic acid could probably be a manifestation of the specific solvation of the acidic hydrogen of the hydroxyl group, causing stabilization and a definite modification of the electron-donating properties of this group.

4. CONCLUDING REMARKS

From the presented results, the conclusion can be drawn that the Kamlet–Taft Total Solvatochromic Equation can be applied to analyze the solvent effect on the reaction of pyridine carboxylic acids with DDM in both protic and aprotic solvents. A set of seven protic solvents in which all the examined compounds are soluble was chosen in order to obtain clear and comparable results. The arithmetic signs of the equation parameters are in agreement with the known reaction mechanism. The different demands for solvation and stabilization of the examined compounds, which are a consequence of their structure, reflected themselves in the coefficient values. Hence, it could be stated that the applied equation, apart from a quantitative description of the solvent effect on reactivity, also displays the structure effect on reactivity of the examined compounds to some extent, in the given solvent set.

It could be concluded that in the applied solvent set, the classical solvation effect dominates the reaction; it is the main effect that causes an increase in the reaction rate. The proton-donor (HBD) solvent effect has two electrophilic centers available for attack, the nitrogen in the initial state, and the nitrogen and carboxylic anion in the transition state; however, its principal influence is on the carboxylic anion in the transition state. The electrophilic solvent effect on nitrogen in the initial state seems to be masked by the stronger nucleophilic solvent effect. This proton-acceptor solvent effect (HBA) is present in the initial state before the reaction commences and it is directed to the carboxylic proton, decreasing the reaction rate.

The presence of the nitrogen in the ring of the pyridine carboxylic acids could also be noticed by the lower polarizability of its anion. The smaller difference in the electron density of the anion of pyridine carboxylic acids, than in the anion of the corresponding benzoic acids, was proved by the lower values of the coefficients of the solvent polarity/polarizability parameter for the pyridine carboxylic acids. The pyridine ring has a greater electron density than the benzene ring, therefore the anion of the carboxylic acid containing the latter ring has a more polarizable structure and higher demands for stabilization by the polarity/polarizability solvent effect.

The observation that isonicotinic acid has higher reaction rate values than, picolinic and nicotinic acid, which have rather similar values, could be explained by the electron-withdrawing effects of the nitrogen in isonicotinic acid that stabilize the carboxylic anion and increase its acidity. In the case of nicotinic acid, which reacts the slowest, there is only the inductive effect of nitrogen, which gives weaker support than for isonicotinic acid. In the molecule of picolinic acid, an intramolecular hydrogen bond can be formed between the carboxylic proton and the neighboring nitrogen and make the removal of the proton more difficult, but, as picolinic acid reacts faster than nicotinic acid, it obviously does not pre-

vail over the electron-withdrawing effects of the nitrogen. However, the presence of the mentioned hydrogen bond cannot be neglected, judging from a comparison of reaction rate constants for picolinic and isonicotinic acids. These two compounds have the same electron-withdrawing effects, but a hydrogen bond exists only in the case of picolinic acid, which decreases the reaction rate.

The 2-substituted nicotinic acids have higher reaction rate constants than the unsubstituted acid, except for 2-methylnicotinic acid. The strong negative inductive effect increases the acidity in the case of 2-chloronicotinic acid. In the case of the 2-hydroxy-substituted acid, a hydrogen bond between the carboxylic anion and the hydroxylic proton can stabilize the anion and enhance the acidity, therefore the reactivity of this compound with DDM. For the 2-methyl substituted acids, it was observed that the electron-donor effect of the methyl group reduces the acidity, as the reaction rate constants were lower than those of nicotinic acid were.

When comparing 2- and 6-substituted acids, it could be noticed that the negative inductive effect of chlorine was less prominent when coming from C-6. Therefore, 6-chloronicotinic acid has lower reaction rate constants than 2-chloronicotinic acid, however it was still the fastest in the 6-substituted acids series.

Contrary to 2-hydroxynicotinic acid, 6-hydroxynicotinic acid displays the lowest reaction rate constants. This observation could be explained by the decrease of its acidity because of the electron-donor resonance effect of the hydroxyl group. The increase of the electron density in the ring destabilizes the carboxylic anion. There is no possibility for an intramolecular hydrogen bond, as in the case of 2-hydroxynicotinic acid. 2-Hydroxynicotinic acid has high values of the reaction rate constants because of the existence of the hydrogen bond between the hydrogen from the hydroxyl group and the carboxylic anion. This interaction is probably responsible for enhanced acidity of the 2-hydroxynicotinic acid, because it facilitates the release of the carboxylic proton.

The difference between 2- and 6-substituted acids was the smallest in the case of the methyl-substituted acids, which could be expected, as it is the substituent with the weakest electronic effect of all the examined substituents. The positive inductive effect of the methyl group reduces the acidity and the reactivity of these acids with DDM. It could be expected that this effect would be more prominent for 2-methylnicotinic acid, however, 6-methylnicotinic had the lower reaction rate constants. This could be explained by the steric effect that could exist in the case of 2-methylnicotinic acid, which could slightly enhance its reactivity in comparison with 6-methylnicotinic acid. The steric interaction between the methyl group and the carboxylic group can twist out the carboxylic group and make it more accessible for DDM, thereby increasing the reactivity. There is no possibility that such an effect could oppose the positive inductive effect of the methyl group in the case of 6-methylnicotinic acid.

In various solvents containing no hydroxyl group, the Kamlet–Taft Equation could be employed in its full three-parameter form, however it was not possible to find a mutual solvent set for all the examined series of pyridine carboxylic acids. The three-parameter equation makes the solvent properties influence easily comparable, and it can be concluded that the proton acceptor solvent activity, which decreases the reaction rate, is the dominant factor for all the compounds. The interesting difference in reactivity between 2-hydroxynicotinic acid and 6-hydroxynicotinic acid in aprotic solvents could be explained by the presence of an intramolecular hydrogen bond in the molecule of the former. The mentioned hydrogen bond could reverse the effect on the reactivity of the hydroxyl substituent of 2-hydroxynicotinic acid depending on the solvent. In protic solvents, it makes the anion stable and the compound more reactive toward DDM and in aprotic solvents, where there is no stabilization by the proton-donor solvent effect, it blocks the anion and prevents it from reacting further.

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ИЗВОД

КОМПАРАТИВНА СТУДИЈА ЛИНЕАРНЕ КОРЕЛАЦИЈЕ СЛОБОДНИХ ЕНЕРГИЈА ЗА РЕАКТИВНОСТ ПИРИДИН-КАРБОКСИЛНИХ КИСЕЛИНА СА ДИАЗОДИФЕНИЛ-МЕТАНОМ У ПРОТИЧНИМ И АПРОТИЧНИМ РАСТВАРАЧИМА

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У овом раду анализиран је утицај протичних и апротичних растварача на реактивност пиколинске, никотинске и изоникотинске киселине, као и неколико супституисаних никотинских киселина са диазодифенилметаном (DDM). Да би се добијени кинетички подаци могли објаснити помоћу ефеката растварача, константе другог реда за реакцију испитиваних киселина и DDM-а су корелисане Камлет–Тафтовом тоталном солватохромном једначином. Корелација кинетичких података урађена је вишеструком линеарном регресионом анализом и ефекат растварача је посматран са стране основног стања, односно реактаната, и прелазног стања у реакцији. Аритметички знаци испред коефицијената у једначини су у складу са познатим механизмом испитиване реакције. Солватациони модели за све испитиване киселине су предложени и повезани са специфичностима њихових структура.

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