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Investigations of the reactivity of pyridine carboxylic acids with diazodiphenylmethane in protic and aprotic solvents. Part II. Pyridine mono-carboxylic acid *N*-oxides

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Abstract: The rate constants for the reaction of three isomeric pyridine mono-carbocylic acid *N*-oxides with diazodiphenylmethane were determined at 30 ºC in thirty two protic and aprotic solvents by the well known UV spectrophotometric method. The rate constants are generally higher than for pyridine mono-carboxylic acids in a similar range of solvents, except for picolinic acid *N*-oxide, and also higher in protic than in aprotic solvents. The determined rate constants were correlated with solvent parameters using the Kamlet–Taft solvatochromic equation by means of multiple regression analysis. The sign of the equation coefficients were in agreement with the postulated reaction mechanism. The mode of the influences of the solvent is discussed on the basis of the correlation coefficients, taking into account the specific structures of the pyridine mono-carboxylic acid *N*-oxides.

Keywords: pyridine carboxylic acids, pyridine carboxylic acid *N*-oxides, diazodiphenylmethane, rate constants, solvent parameters, protic and aprotic solvents.

INTRODUCTION

In a previous paper, Part I in this series,[1] an investigation of the reactivity of three isomeric pyridine mono-carboxylic acids with diazodiphenylmethane (DDM) in twenty aprotic solvents was presented. Together with the results of a previously published study of the reactivity of the same acids in eleven alcohols,[2] the rate constants from both series were used to analyse the solvation energy relationship (LSER) by the Kamlet–Taft equation:

$$\log k = \log k_0 + s\pi^* + a\alpha + b\beta \quad (1)$$

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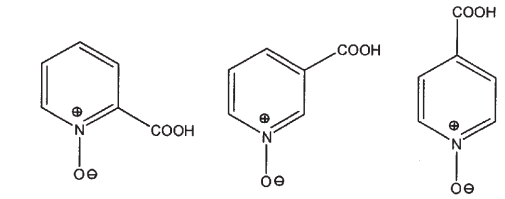
The general conclusion was that the reactivity is highly dependent on the relative positions of the ring nitrogen and the carboxylic group, which was also observed at the very beginning of the study of heterocyclic carboxylic acids in their reaction with ethanol,[3] but the order of reactivity was reversed in some of the solvents, particularly in aprotic ones. Although a large number of solvent–solute interactions could have been considered, it was concluded that the diverse solvent effects could be generally quantified by the use of the Kamlet–Taft equation. However, it was difficult to separate the contribution of particular solvent effects in the initial and transition states, due to the variety of polar and steric interactions in the course of the reaction.



Picolinic acid *N*-oxide Nicotinic acid *N*-oxide Isonicotinic acid *N*-oxide

Fig. 1. Structures of the investigated pyridine carboxylic acid *N*-oxides.

In the present work, the rate constants of three isomeric pyridine mono-carboxylic acid *N*-oxides (Fig. 1) in their reaction with DDM were determined in twenty one aprotic solvents. An initial difficulty was the low solubility of the investigated acids in aprotic solvents, due to the high polarity of the *N*-oxide nuclei. Also a strong intramolecular hydrogen bond in picolinic acid *N*-oxide complicated the direct comparison of the corresponding rate constants with the results for the two other acid *N*-oxides. The processing of the kinetic data was performed using the Kamlet–Taft solvatochromic equation in its two-parameter form (Eq. (1)), very much in the same way as in Part I of this study.[1] Generally, the solvent effects are more pronounced in the *N*-oxide series than in the previously studied carboxylic acid series, due to the higher polarizability of the corresponding molecules.

EXPERIMENTAL

The rate constants for the reaction of isomeric pyridine monocarboxylic acid *N*-oxides with DDM were determined using the spectrophotometric method originally developed by Roberts[4,5] and subsequently extensively used for structure activity relationships, also in our previous investigations.[1–3,6,7] The reactions were performed at 30 ºC, using a DDM concentration of 0.06 mol/dm^3, which is the most suitable for the spectrophotometric determination of pseudo-first order or second order processes. The spectrometer used was a Shimadzu UV-160A. The acids were commercial products from Fluka. DDM was synthesized by the Smith and Howard method.[8]

RESULTS AND DISCUSSION

A kinetic study and discussion of the different influences of protic and aprotic solvents on the reaction rates of pyridine mono-carboxylic acid *N*-oxides with DDM was the objective of this work. Comparison of the kinetic data from this

study with the kinetic data for benzoic acid under the same reaction condition, and also an overall comparative analysis with the reactivity of pyridine mono-carboxylic acids[1] are included in the discussion about the significance of the position of the pyridine nitrogen *N*-oxide group.

The mechanism of the reaction between carboxylic acids and DDM has been thoroughly studied by Roberts,[4,5] Kamlet,[9] Chapman,[10–20] Bowden,[21] and the spectrophotometric method and kinetic approaches were developed. The influence of protic solvents on the reaction involving isomeric pyridine and the corresponding *N*-oxide carboxylic acids,[2] 6-substituted pyridine carboxylic acids,[6] isomeric 3- and 4-pyridine acetic acids and the corresponding *N*-oxide derivatives[7] have been thoroughly investigated in their reaction with DDM. No similar study has hitherto been exclusively devoted to pyridine carboxylic acids *N*-oxides in aprotic solvents.

The mechanism of the reaction in both protic and aprotic solvents was found to involve a rate-determining proton transfer from the acid to DDM, forming a diphenylmethanediazonium carboxylate ion-pair.[14,15,18,22,23]

$$Ph_2CN_2 + RCOOH \xrightarrow{slow} Ph_2CHN_2^{+}\ ^{-}OOCR \qquad (2)$$

The rate constants for all three isomeric pyridine mono-carboxylic acid *N*-oxides determined in the present study are given in Table I, together with the results of a previous study of these acids in protic solvents taken from the literature.[2]

TABLE I. Rate constants ($dm^3mol^{-1}min^{-1}$) for the reaction of nicotinic, isonicotinic and picolinic acid *N*-oxides with DDM in protic and aprotic solvents at 30 ºC

Solvent	Nicotinic acid *N*-oxide		Isonicotinic acid *N*-oxide		Picolinic acid *N*-oxide	
	k_2	log k_2	k_2	log k_2	k_2	log k_2
Methanol**	34.29	1.535	24.15	1.383	1.04	0.015
Ethanol	19.10	1.281	12.90	1.110	0.46	–0.333
Propan-1-ol**	25.53	1.372	12.38	1.093	0.28	–0.547
Propan-2-ol**	18.42	1.265	8.03	0.905	0.19	–0.716
2-Methylpropan-2-ol**	7.65	0.884	4.39	0.642	0.10	–1.000
2-Methylpropan-1-ol**	25.51	1.407	21.04	1.323	0.38	–0.423
Butan-1-ol**	18.98	1.278	10.74	1.031	0.20	–0.694
Butan-2-ol**	15.38	1.187	6.76	0.830	0.181	–0.742
2-Methylbutan-2-ol**	6.20	0.792	2.93	0.467	0.08	–1.081
Pentan-1-ol**	14.50	1.161	10.67	1.028	0.28	–0.553
Benzyl alcohol**	62.48	1.795	54.94	1.740	2.88	0.459
Dimethyl sulfoxide	0.85	–0.071	0.37	–0.431	0.023	–1.638
N,*N*-Dimethylacetamide	0.75	–0.128	0.24	–0.629	0.004	–2.357
1-Methyl-2-pyrrolidone	0.67	–0.174	0.25	–0.602	0.0046	–2.337
N,*N*-Dimethylformamide	1.37	0.137	0.52	–0.284	0.0045	–2.347

Solvent	Nicotinic acid *N*-oxide		Isonicotinic acid *N*-oxide		Picolinic acid *N*-oxide	
	k_2	log k_2	k_2	log k_2	k_2	log k_2
Acetophenone	16.97	1.229	7.89	0.897	0.87	–0.062
2-Pyrrolidinone	0.37	–0.425	0.39	–0.399	0.031	–1.510
N-Methylacetamide	1.66	0.220	0.84	–0.076	0.0019	–2.722
Sulfolan	56.00	1.748	46.00	1.663	–	–
N-Methylformamide	1.26	0.100	1.31	0.117	–	–
Butan-2-one	–*	–	1.15	0.059	0.116	–0.936
Acetone	–	–	4.20	0.623	0.0034	–2.469
Chloroform	–	–	–	–	0.109	–0.962
Ethyl benzoate	–	–	–	–	0.060	–1.221
Acetonitrile	–	–	17.90	1.253	0.014	–1.854
Diethyl carbonate	–	–	–	–	1.035	0.015
Methyl acetate	–	–	–	–	0.0702	–1.154
Butyl acetate	–	–	–	–	0.0367	–1.044
4-Methylpentan-2-one	–	–	0.81	–0.084	0.0942	–1.025
Ethyl acetate	–	–	–	–	0.119	–1.925
Tetrahydrofuran	–	–	0.48	–0.314	0.00047	–3.328
Dioxane	–	–	0.75	–0.125	0.0012	–2.921

* Not soluble; ** Reference 2

The kinetic data show (Table I) that the rate constants increase with increasing polarity of the solvent. The values of the reaction constants in protic and aprotic solvents indicate a slower reaction in aprotic solvents than in protic ones, which is in accordance with the proposed reaction mechanism.

Kamlet *et al.*[9] established that the solvent effect 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 (*iii*) the ability of the solvent to stabilize the proton of the carboxylic acid in initial state by donating an ion pair. The parameter π^* is a suitable measure of the first property, while the second and third properties are governed by the effects of the solvent acidity and basicity, expressed quantitatively by parameters α and β. The solvent parameters (π^*, α and β) for the hydrogen bond donor and non-hydrogen bond donor solvents, (Eq. (1)), are taken from the literature.[24,25]

The results of multiple linear regression correlation for isomeric pyridine carboxylic acid *N*-oxides were compared with the results for benzoic acid, and, finally, an overall comparison was made, including the correlation results from a previous study.[1]

The discussion is based on the quantitative values and the sign of the coefficients in the corresponding equations. As in pyridine mono-carboxylic acids, a possible mode of influence of the solvents on the reactivity of the investigated acids can be observed, in which the solvent acts on the two sites in the initial (Fig. 2) and also in the transition state (Eq. (2)) of the pyridine carboxylic acid *N*-oxide molecules.

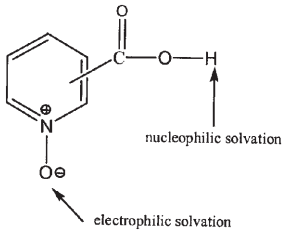


Fig. 2. The mode of the solvent effects in pyridine mono-carboxylic acid *N*-oxides.

Electrophilic solvation of the oxygen atom of the *N*-oxide group can not be neglected, particularly for the protic solvents, and for those aprotic solvents which possess partially acidic character ($\alpha \neq 0$). This means, as it was concluded in a previous paper,[1] that electrophilic solvation does not uniquely affect the reaction rate in the transition state. Instead, this effect can be operative both in the initial and in the transition states through the solvation of the oxygen atom of the *N*-oxide group, contributing thus to the values of the coefficient *a*. The same observation is valid for classic and nucleophilic solvation, but these effects are less complex than electrophilic solvation.

An important fact included in the discussion about the differences between the electronic effects of the pyridine and pyridine *N*-oxide group is the strength of the negative inductive and resonance effect of these groups, as well as the positive resonance effect of the *N*-oxide group, which has a large influence on the reactivity of the acids in the *N*-oxide series. Also, in picolinic acid *N*-oxide, a possible steric arrangement, due to the vicinity of the *N*-oxide and the carboxylic group, creates a stable six-membered intramolecular hydrogen bond in the initial state, which significantly affects the reactivity of this acid.

Protic solvents

The kinetic data for nicotinic acid *N*-oxide from Table I have been correlated with the solvent parameters for protic solvents,[24,25] giving the following result:

$$\log k_2 = (0.57 \pm 0.82) + (0.98 \pm 0.46)\,\pi^* + (0.67 \pm 0.18)\,\alpha + (-0.35 \pm 0.66)\,\beta \quad (3)$$
$$R = 0.960 \quad SD = 0.109 \quad n = 11$$

All the coefficients are in agreement with the reaction mechanism of the investigated reaction but not all of them are statistically correct. The negative value of the coefficient *b* indicates that nucleophilic solvation decreases the reaction rate, which corroborates the established reation mechanism. However, this coefficient is disputable, making three-parameters equation useless for the interpretation of kinetic data, because of the statistical deficiency of the parameters used.

Therefore, the best interpretation of the solvent effects for protic solvents are described by a system of simplified two-parameters equation of the following type:

$$\log k_2 = (0.14 \pm 0.14) + (1.20 \pm 0.18)\,\pi^* + (0.72 \pm 0.15)\,\alpha \qquad (4)$$
$$R = 0.950 \quad SD = 0.10 \quad n = 11$$

The results of the above correlations also corroborate the reaction mechanism, and the influence of the solvent by the effects of classic and electrophilic solvation, the HBD effect, which have the effect of increasing the reaction rate, the transition state being more stabilized than the initial state (positive sign of the coefficients *s* and *a*).

Comparison of the above correlation (Eq. 4) for nicotinic acid *N*-oxide to the correlation for benzoic acid (the values of the kinetic data were taken from the literature[26]),

$$\log k_2 = -2.87 + (0.83 \pm 0.36)\,\pi^* + (3.20 \pm 0.73)\,\alpha \qquad (5)$$
$$R = 0.975 \quad SD = 0.103 \quad n = 7$$

by calculation of the percent contribution[27] of the individual solvent effects, indicates the significance of the following effects: for nicotinic acid *N*-oxide, the classic solvation (π^*) is 62.5 % and HBD effect (α) is 37.5 %, while for benzoic acid they are 20.6 % and 79.4 %, respectively. The effect of electrophilic solvation is the main effect influencing the reaction rate of benzoic acid. The large difference in the percent contributions for the two acids can be explained by the significant increase of the classical solvation of nicotinic acid *N*-oxide, due to its more polarizable transition state. This is caused by the strong negative inductive and resonance effect of the pyridine *N*-oxide group.

The same procedure was performed for isonicotinic acid *N*-oxide:

$$\log k_2 = (-0.33 \pm 0.22) + (1.51 \pm 0.29)\,\pi^* + (0.85 \pm 0.24)\,\alpha \qquad (6)$$
$$R = 0.92 \quad SD = 0.15 \quad n = 11$$

The higher positive value of the coefficient *s* compared to the coefficient *a* in equation (6) indicates that classic solvation in the transition state is the main solvent effect influencing the reactivity of this acid. The transition state is more stabilized than the initial state, more polar solvents lead to an increase in the reaction rate. Percent contributions of the individual solvent effect are 64 % for classic solvation and 36 % for electrophilic solvation.

The correlation of the kinetic data of picolinic acid *N*-oxide determined in protic solvents with the corresponding parameters π^* and α gave the following result:

$$\log k_2 = (-2.20 \pm 0.22) + (2.17 \pm 0.29)\,\pi^* + (0.82 \pm 0.24)\,\alpha \qquad (7)$$
$$R = 0.95 \quad SD = 0.15 \quad n = 11$$

Analysis of equation (7) indicates that classical solvation is the dominant factor influencing the reaction rate and the positive sign of the coefficient *s* indicates better solvation of the transition state than of the initial state. The positive value of the coefficient *a* indicates stabilization of the transition state by the HBD solvent

effect, through stabilization of the emerging carboxylate anion. The percent contributions of the solvent effects for picolinic acid *N*-oxide are 72.6 % for classic solvation and 27.4 % for electrophilic solvation.

A summary of the correlation results for all three acids in protic solvents is given in Table II, which includes the correlation results for pyridine mono-carboxylic acids in the same solvents from a previous study.[1]

TABLE II. The percent contributions of the protic solvent effects (%)

Coefficient (parameter)	s (π^*)	a (α)
Benzoic acid*	20.6	79.4
Nicotinic acid *N*-oxide	62.5	37.5
Isonicotinic acid *N*-oxide	64.0	36.0
Picolinic acid *N*-oxide	72.6	27.4
Nicotinic acid**	66.0	34.0
Isonicotinic acid**	58.0	42.0
Picolinic acid**	59.0	41.0

*Reference 26; **Reference 1

The highest contribution of electrophilic solvation in the transition state appears to be for benzoic acid. According to this result, it follows that the stabilization of the negative charge at the pyridine nitrogen, by the HBD solvent effect, increases the stabilization of the forming carboxylate anion but decreases the reaction rate of all pyridine mono-carboxylic acids and their corresponding *N*-oxides. It is evident that the same solvent effect decreases the nucleophilicity of the carboxylate anion for attack at the diazodiphenylmethane carbocation. Classic solvation is the more important solvent effect for all the isomeric pyridine carboxylic acids and the corresponding *N*-oxides because the structure of these acids is more polarizable, being the most pronounced for picolinic acid *N*-oxide. This is probably the result of electrostatic repulsion of the negatively charged carboxylate anion and the *N*-oxide group (Fig. 4b), preventing a direct electronic interaction of the *N*-oxide group with the carboxylic group. Non-planarity of the carboxylate anion of the picolinic acid *N*-oxide molecule in the transition state causes the more distinct dipolar structure being subjected to a larger influence of the solvent as a dielectric.

Aprotic solvents

The same approach as for protic solvents was utilized for the kinetic results for nicotinic acid *N*-oxide in aprotic solvents (Table I), with the exclusion of 2-pyrrolidinone:

$$\log k_2 = (2.62 \pm 0.46) + (1.08 \pm 0.46)\,\pi^* + (0.83 \pm 0.11)\,\alpha + (-4.94 \pm 0.18)\,\beta \quad (8)$$
$$R = 0.997 \quad SD = 0.065 \quad n = 8$$

The above result indicates that the influence of the solvent on the reaction rate is mainly caused by the strong basic character of the aprotic solvent molecules,

which is reflected in the high values of the coefficient *b* (Table III). Nucleophilic solvation, basicity of the aprotic solvent, decrease the reaction rates of the investigated acid. The percent contribution of the individual solvent effects for nicotinic acid *N*-oxide is 16 % for classical solvation, 12 % for electrophilic solvation and 72 % for nucleophilic solvation. With this acid, the HBD solvent effect and classical solvation also increase the reaction rate.

One equation which includes all three solvent parameters in the correlation for benzoic acid for solvents which allegedly do not possess HBD character has been reported in the literature:[28]

$$\log k_2 = 0.20 + 1.21\,\pi^* + 2.71\,\alpha - 3.70\,\beta \qquad (9)$$
$$R = 0.980 \quad SD = 0.171 \quad n = 44$$

The percent contributions of individual solvent effects calculated from equation (9) are: $\pi^* = 16$ %; $\alpha = 35$ %; $\beta = 49$ %. A comparison of these results with those for nicotinic acid *N*-oxide (Eq. 8) leads to the conclusion that the electrophilic solvation is significantly more pronounced for benzoic acid, while the nucleophilic solvation is significantly more pronounced for benzoic acid, while the nucleophilic solvation, respectively the HBA solvent effect, is more pronounced for nicotinic acid *N*-oxide. For both acids, the basicity of the aprotic solvent, or the nucleophilic solvation of the initial state of the molecules, which decrease the reaction rate, are the main factors affecting their reactivity. This effect is more pronounced in the correlation for nicotinic acid *N*-oxide because of its higher acidity.

The correlation of log *k* for isonicotinic acid *N*-oxide with the solvent parameters π^*, α and β for aprotic solvents gave the following results:

$$\log k_2 = (0.39 \pm 0.31) + (3.32 \pm 0.45)\,\pi^* + (1.34 \pm 0.31)\,\alpha + (-5.28 \pm 0.44)\,\beta \qquad (10)$$
$$R = 0.964 \quad SD = 0.21 \quad n = 15$$

The classic and electrophilic solvation increases the reaction rate of this acid, while the nucleophilic solvation of the initial state decreases the reaction rate. The percent contribution of the individual solvent parameters are: 34 % for classical solvation, 13 % for electrophilic solvation and 53 % for nucleophilic solvation.

Large differences can be noticed between the values of the percent contribution of the coefficients *b* and *s* for isonicotinic and nicotinic acid *N*-oxides (Table III). A higher acidity of the isonicotinic acid *N*-oxide was to be expected, and, consequently, a higher value of the coefficient *b*, because of the strong negative inductive and resonance effects of the *N*-oxide group. This was not experimentally established (Tables I and III), which is undoubtedly due to the positive resonance effect of the *N*-oxide group, which increases the electron density in the pyridine ring and, in this way, decreases the acidity of the isonicotinic acid *N*-oxide, as is presented in Fig. 3a. The higher contribution of this effect causes a smaller contribution of nucleophilic solvation (lower value of percent contribution of coefficient *b*). In the transition state of isonicotinic acid *N*-oxide, this mode of resonance inter-

action is diminished (Fig. 3b) which results in an anion with a more polarizable structure, which is more susceptible to a larger influence of the dipolar structure of the solvent (higher value of the percent contribution of coefficient *s*):

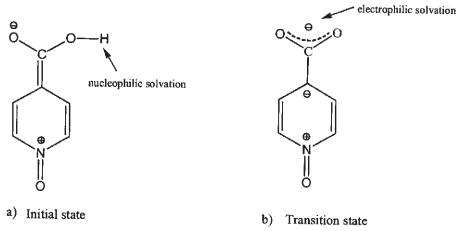


Fig. 3. Mesomeric structures of isonicotinic acid *N*-oxide and isonicotinic acid *N*-oxide carboxylate anion.

As can be seen from the presented mesomeric structures of isonicotinic acid *N*-oxide (Fig. 3), an electron donating resonance effect, acting in the opposite direction to the negative inductive and resonance effect, is transmitted directly to the reaction center, thus causing a decrease in the reaction rate. The same phenomenon is valid for nicotinic acid *N*-oxide, but the electron-donating effect of the *N*-oxide group is not directly transmitted to the reaction center, a fact reflected in a higher value of the percent contribution of coefficient *b*.

Kinetic data for nicotinic and isonicotinic acids *N*-oxides in aprotic solvents (Table I) show interesting results as the rate constants strongly depend on effects of aprotic solvents, which is reflected in the value of coefficient *b*. The values of the percent contribution of electrophilic solvation by the solvent in the transition state for nicotinic and isonicotinic acids *N*-oxides are almost the same, indicating a similar possibility of the solvent to stabilize the carboxylate anion in forming and the negative end of the *N*-oxide group in the initial and transition states.

In a previous paper,[1] the correlation results showed that the values of the percent contribution of the coefficients *s*, *a* and *b* for nicotinic and isonicotinic acids were similar, meaning that the larger differences in the corresponding values for nicotinic and isonicotinic acids *N*-oxides arise, basically, from the positive resonance effect of the *N*-oxide group.

Correlation of the kinetic data for picolinic acid *N*-oxide with the parameters π^*, α and β for aprotic solvent gives the following result:

$$\log k_2 = (-4.93 \pm 0.56) + (8.70 \pm 1.10)\,\pi^* + (-2.45 \pm 0.76)\,\alpha + (-6.92 \pm 0.81)\,\beta \quad (11)$$
$$R = 0.956 \quad SD = 0.24 \quad n = 17$$

The high negative value of coefficient *b* shows that the HBA solvent effect, namely the nucleophilic solvation of the initial state, is important, but less significant than the effect of classic solvation. This is opposed to the results for picolinic acid,[1] where nucleophilic solvation is the main effect. Also the negative sign of the coefficient *a* indicates a better electrophilic solvation of the initial state of this acid. The positive sign and high value of the coefficients *s* indicate that classic solvation

is the most important solvent effect, influencing an increasing in reaction rate. The calculations of the percent contribution of a particular solvent effect gives the following results: $\pi^* = 48$ %; $\alpha = 14$ %; $\beta = 38$ %.

A summary of the correlation results for all the acids in aprotic solvents is given in Table III, which includes the results of the correlations for pyridine mono-carboxylic acids from a previous study.[1]

TABLE III. The percent contributions of the aprotic solvent effects (%)

Coefficient (parameter)	s (π^*)	a (α)	b (β)
Benzoic acid*	16	35	49
Nicotinic acid *N*-oxide	16	12	72
Isonicotinic acid *N*-oxide	34	13	53
Picolinic acid *N*-oxide	48	13	38
Nicotinic acid**	33	15	52
Isonicotinic acid**	29	21	50
Picolinic acid**	29	24	47

*Reference 28; **Reference 1

The values of the percent contributions of the HBD effect of aprotic solvents from Table III are similar, indicating a weak solvation of the transition state of all the three pyridine carboxylic acid *N*-oxides. It is attributed to the joint effect of the electrophilic solvation of the carboxylate anion and the oxygen of the *N*-oxide group in the transition and initial states, giving small overall solvations by the HBD solvent effect. The highest value of the percent contribution of coefficient *a* was found for picolinic acid. The carboxylate anion of picolinic acid in the transition state is close to the pyridine nitrogen, causing, to some extent, a repulsion between the identical negative charges and thereby, to some extent, a perpendicular position of the plane of carboxylate anion with respect to the pyridine ring. Therefore, the carboxylate anion is better subjected to electrophilic solvation by the solvent (Fig. 4a). The same phenomenon could be expected for picolinic acid *N*-oxide in the transition state of this acid, but the steric and electrostatic repulsion between the carboxylate anion and the *N*-oxide group oxygen is more pronounced (Fig. 4b), probably causing a higher percent of perpendicular orientation of the carboxylate anion with respect to the *N*-oxide group. The higher value of coefficient *a* is in accordance with this observation. Oppositely, the low and negative value of this coefficient indicates that the initial state is better solvated by HBD solvent effects than the transition state. This is probably caused by a significant transfer of the carboxylic proton to the oxygen atom of *N*-oxide group, thus creating, to some extent, a carboxylate anion in the initial state (Fig. 5). The highest percent contribution of the HBD solvent effect was observed for benzoic acid, being probably influenced by an exclusive stabilization of the carboxylate ion, when there is no sta-

bilization of the negative charge on the pyridine nitrogen or no *N*-oxide oxygen exists, as is the case for pyridine carboxylic acids and the corresponding *N*-oxides.

In the series of pyridine mono-carboxylic acids,[1] classic solvation (π^*) is a more pronounced solvent effect for nicotinic acid, but the values of the percent contribution of coefficient *s* are very similar. This is probably due to the nicotinic acid molecule having a somewhat more dipolar structure than those of other two pyridine mono-carboxylic acids. In the series of pyridine carboxylic acid *N*-oxides, on the other hand, nicotinic acid has the lowest value of *s*, probably because of the positive resonance effect of the *N*-oxide group, which strongly decreases the polarization of the pyridine *N*-oxide ring as a whole. The high value of the coefficient *s* for picolinic acid *N*-oxide derives from the strong repulsion between the negative charge of the carboxylate anion and the oxygen of the *N*-oxide group, causing a distinct polarization at the pyridine *N*-oxide ring (Fig. 4b) in the transition state.

Fig. 4. Carboxylate anions of picolinic acid and picolinic acid *N*-oxide.

Picolinic acid in the series of pyridine carboxylic acids has the smallest value of the percent contribution of the HBA solvent effect, as established in previous paper.[1] This could be explained by the ability of picolinic acid to create a weak intramolecular hydrogen bond in the initial state, which decreases the influence of the HBA solvent effect. In the pyridine *N*-oxide series, nicotinic acid *N*-oxide has the highest percent contribution of coefficient *b* while it is significantly decrased for isonicotinic acid *N*-oxide, and picolinic acid *N*-oxide has the lowest value of all six acids. As a weak intramolecular hydrogen bond is created within the picolinic acid molecule,[1] from the values of the percent contribution of the coefficient *b* for picolinic acid and picolinic acid *N*-oxide, it follows that a significantly stronger hydrogen bond is created within the picolinic acid *N*-oxide molecule presented in Fig. 5:

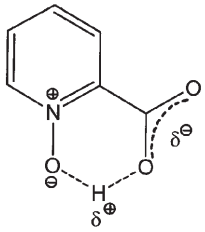


Fig. 5. Intramolecular hydrogen bond in picolinic acid *N*-oxide.

CONCLUSION

The solvatochromic structure–reactivity study of the reactions of the three isomeric pyridine mono-carboxylic acid *N*-oxides with DDM in thirty two solvents,

both protic and aprotic, showed that there are several possible modes of interactions with the solvents, both in the initial and transition states, due to the structural characteristics of the investigated acids.

In a previous investigation of the kinetics of the reaction of pyridine and pyridine *N*-oxide carboxylic acids with DDM in ethanol,[20] it was established that the reactivity of the carboxylic group is highly dependent on its position with respect to the nitrogen and the *N*-oxide group. This is also true, as established here, for the studied *N*-oxide acids, where the order of reactivity is the same: nicotinic>isonicotinic>picolinic in all the employed solvents.

The specific features of the structure of the *N*-oxide acids in comparison to the pyridine carboxylic acids, investigated in the Part I of the series,[1] are the highly polarizable *N*-oxide group and the strong intramolecular hydrogen bond between the carboxylic and *N*-oxide groups in picolinic acid *N*-oxide. As could be seen from the discussion section, the solvent effects are complicated, which is evident from the magnitudes and signs of the coefficients in the corresponding equations and their percent contributions. The most prominent electronic effect which orders the reactivity in the pyridine *N*-oxide nucleus is the positive resonance effect, which operates together with negative inductive and resonance effects. These effects, together with the polar active sites created in the process of breaking the hydrogen bond in picolinic acid *N*-oxide, produce a complicated pattern of solvent effects in the investigated acids.

The results of the present investigations show that those diverse solvent effects could be generally quantified by the use of the Kamlet–Taft equation, although a quantitative separation of these solvent effects applying mathematical treatment, into individual contributions to the transition and initial states was not completely possible, due to the diversity of the polar groups and their position in the studied molecules.

ИЗВОД

ИСПИТИВАЊЕ РЕАКТИВНОСТИ ПИРИДИН-*N*-ОКСИД--МОНОКАРБОНСКИХ КИСЕЛИНА У РЕАКЦИЈИ СА ДИАЗОДИФЕНИЛМЕТАНОМ У ПРОТИЧНИМ И АПРОТИЧНИМ РАСТВАРАЧИМА. ДРУГИ ДЕО

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Константе брзина реакције између диазодифенилметана и изомерних пиридин-*N*-оксид-карбонских киселина одређене у тридесет два протична и апротична растварача на 30 ºC, коришћењем познате UV спектрофотометријске методе, анализиране су у функцији ефеката растварача. Вредности константи брзина су генерално веће за пиридин-*N*-оксид-карбонске киселине у односу на пиридин-монокарбонске киселине, изузев пико-

лин-*N*-оксид-киселине, а такође вредности константи брзина су веће у протичним растварачима у поређењу са апротичним за обе серије киселина. Одређене константе брзина су корелисане са параметрима растварача коришћењем Kamlet–Taft солватохромне једначине изведене методом вишеструке регресионе анализе. Знак коефицијената у добијеним корелацијама је у сагласности са претпостављеним реакционим механизмом. Утицај растварача на вредности реакционих константи је дискутован на основу добијених корелационих резултата, узимајући у обзир специфичну структуру пиридин-*N*-оксид-монокарбонских киселина.

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