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Effects of solvent and structure on the reactivity of 6-substituted nicotinic acids with diazodiphenylmethane in aprotic solvents

SAŠA Ž. DRMANIĆ*#, ALEKSANDAR D. MARINKOVIĆ#
and BRATISLAV Ž. JOVANOVIĆ#

Department of Organic Chemistry, Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, P.O. Box 3503, 11121 Belgrade, Serbia

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Abstract: The rate constants for the reactions of diazodiphenylmethane (DDM) with 6-substituted nicotinic acids in aprotic solvents at 30 °C were determined. The obtained second order rate constants in aprotic solvents, together with literature data for benzoic and nicotinic acids in protic solvents, were used for the calculation of solvent effects, employing the Kamlet-Taft solvatochromic equation (linear solvation energy relationship – LSER) in the form: $\log k = \log k_0 + s\pi^* + a\alpha + b\beta$. The correlations of the kinetic data were performed by means of multiple linear regression analysis taking appropriate solvent parameters. The sign of the equation coefficients (s, a and b) were in agreement with the postulated reaction mechanism, and the mode of the solvent influences on the reaction rate is discussed based on the correlation results. A similar contribution of the non-specific solvent effect and electrophilic solvation was observed for all acids, while the highest contribution of nucleophilic solvation was influenced by their high acidity. Correlation analysis of the rate data with substituent σ_p parameters in an appropriate solvent using the Hammett equation was also performed. The substituent effect on the acid reactivity was higher in aprotic solvents of higher dipolarity/polarizability. The mode of the transmission of the substituent effect is discussed in light of the contribution of solute–solvent interaction on the acid reactivity.

Keywords: pyridine carboxylic acids; diazodiphenylmethane; rate constants; solvatochromic parameters; aprotic solvents.

INTRODUCTION

The relationship between the structure of carboxylic acids and their reactivity with diazodiphenylmethane (DDM) has been studied by many authors, with particular regard to the influence of the solvent.[1–5] Related to previous studies[6–9]

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[*] Corresponding author. E-mail: drmana@tmf.bg.ac.rs
[#] Serbian Chemical Society member.

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of the transmission of substituent effects in pyridine carboxylic acids, this paper describes the transmission of those effects in 6-substituted nicotinic acids, with the following substituents: Cl (chloro), OH (hydroxy), CH_3 (methyl), Br (bromo) and SH (mercapto). The kinetics of these acids was studied in a series of aprotic solvents and the results were compared with the data for nicotinic and benzoic acid in protic solvents.

The kinetic data were correlated with the solvatochromic parameters π^*, α and β corresponding to the solvents used, in the form of the following LSER equation:

$$\log k = \log k_0 + s\pi^* + a\alpha + b\beta \tag{1}$$

where π^* is an index of the solvent dipolarity/polarizability, which measures the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect, the α parameter is the HBD acidity (hydrogen bond donor), and the β parameter is the HBA basicity (hydrogen bond acceptor) of the solvent in a solute to solvent hydrogen bond and $\log k_0$ is the regression value of the solute property in a reference solvent. The regression coefficients s, a, and b measure the relative susceptibilities of the solvent-dependent solute property (rate constant) to the indicated solvent parameter. The rate data for all the compounds studied show a satisfactory correlation with solvent parameter *via* the above LSER equation (Eq. (1)). Such a correlation indicates the existence of both specific and non-specific solute–solvent interactions in the studied reaction.

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

$$\log k_2 = \rho\sigma + \log k_0 \tag{2}$$

where ρ is a reaction constant reflecting the sensitivity of the rate constant to the substituent effect, and σ is the substituent constant. The analysis included in the discussion concerning the contribution of the electronic substituent effects shows that these effects have a definite influence on the reactivity of the investigated acids. Some other factors, such as the coplanarity of nicotinyl ring and the carboxylic group could be significant for the reactivity and therefore geometry optimization of all investigated acids in three solvents was preformed.

EXPERIMENTAL

Materials

The acids were commercial samples of *p.a.* quality, used without further purification. Diazodiphenylmethane was prepared by the Smith and Howard method.[10] A stock solution of *ca*. 0.06 mol dm^{-3} was stored in a refrigerator and diluted before use.

The solvents were purified as described in the literature.[11] All the solvents used for the kinetic studies were examined by GC and no impurities were detected.

Kinetic measurements

The rate constants, *k*, for the reactions of the investigated acids with DDM were determined as reported previously by the spectroscopic method of Roberts and co-workers[12] using a Shimadzu 1700A spectrophotometer. The optical density measurements were performed at 525 nm with 1 cm cells at 30±0.05 °C.

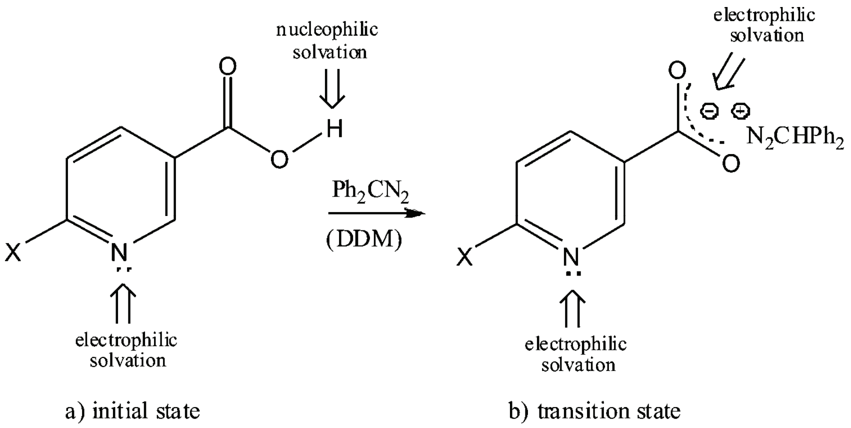
Three to five rate determinations were made on each acid and in every case, the individual second-order rate constants agreed within 3 % of the mean.

Geometry optimization

The reported conformations of the molecular forms were obtained by the semi-empirical MO PM6 method,[13] with implicit chosen solvent solvation (COSMO) (keywords: EF, GNORM = 0.01, EPS = 48 (DMSO), EPS = 4.8 ($CHCl_3$), EPS = 37.5 (acetonitrile) and NSPA = 92) using the MOPAC2009^{TM} program package. A VEGA ZZ 2.3.2 was used as the graphical user interface (GUI).[14]

RESULTS AND DISCUSSION

The mechanism of the reaction between carboxylic acids and DDM, in both protic and aprotic solvents was found to involve the rate-determining proton transfer from the acids to DDM, thereby forming a diphenylmethanediazonium carboxylate ion-pair (Fig. 1.).[15–22] Chapman *et al.*[23] established that the solvent effects are best interpreted in the form of the contributions of the initial and transition state to the specific (α and β) and non-specific (π*) solvent–solute interactions (Fig. 1).



a) initial state b) transition state

Fig. 1. The mode of the solvent effects in 6-substituted nicotinic acids in a) the initial state and b) the transition state.

The reaction rate constants (as log k_2) for the reaction of the examined acids with DDM in the employed solvents are given in Table I.

The results from Table I 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 at the electrophilic and nucleophilic acid sites (Fig. 1), but also they could cause modifications of electronic properties of a substituent. Solvents of high dipolarity/polarizability and/or high proton-acceptor capability cause a significant decrease of the reaction rate. The highest value of the reaction rates in chloroform could be explained by the highest proton-donor ability of this solvent ($\alpha = 0.2$), as well as by the lowest proton--acceptor capability ($\beta = 0.1$).[24]

TABLE I. Logarithm of the second order rate constants ($dm^3 mol^{-1} min^{-1}$) for the reaction of 6-substituted nicotinic acids with DDM at 30 °C in aprotic solvents (NMF: *N*-methylformamide; DMSO: dimethyl sulfoxide; DMAC: *N*,*N*-dimethylacetamide; DMF: *N*,*N*-dimethylformamide; NMP: *N*-methylpyrrolidone)

Solvent	H[a]	6-Cl	6-OH	6-CH_3	6-Br	6-SH
Acetophenone	0.714	0.878	–[b]	0.350	0.920	0.790
Acetone	0.190	0.370	–	0.142	0.400	0.320
Chloroform	1.610	2.320	–	1.500	2.450	2.200
Ethyl benzoate	0.528	0.640	–	0.450	0.653	0.482
Isobutyl methyl ketone	0.143	0.550	–	–0.052	0.614	0.350
NMF	–0.027	0.180	–0.310	–0.117	0.150	0.008
DMSO	–0.678	–0.379	–1.200	–0.900	–0.350	–0.380
DMAC	–0.940	–0.600	–1.500	–1.120	–0.560	–0.460
DMF	–0.611	–0.238	–1.280	–0.780	0.200	–0.160
NMP	–0.921	–0.480	–1.370	–1.070	–0.303	–0.450

[a]From reference 1; [b]insoluble

As was stated in the literature,[19] 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.[19] Being a solvent of low polarity, chloroform influences a weaker stabilisation 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.

Generally, the results of the kinetic studies show that reaction rates for all acids with DDM were of second order, which was confirmed by the high correlation coefficients, *r*, which were in the range 0.95–0.99.

Solvent–reactivity relationship

In order to explain the obtained kinetic results based on the polarity, acidity and basicity of the solvent, the log k_2 were correlated with the solvatochromic parameters π^*, α and β using the solvatochromic Eq. (1). The correlation of the kinetic data was realized by means of multiple regression analysis, which is very useful in separating and quantifying such interactions in the examined reaction. The correlation results are presented in Table II. The values for π^*, α and β were taken from the literature.[24]

TABLE II. Statistical results for the correlations of the reaction rate constants (log k_2) of 6-substituted nicotinic acids with DDM with the Kamlet–Taft solvatochromic parameters

Acid	$s(\pi^*)$	$a(\alpha)$	$b(\beta)$	log k_0	R^b	F^c	SD^d	n
NA	2.05±1.08	1.61±0.39	−(4.63±0.67)	0.80±0.60	0.974	38	0.22	10
Cl–NA	1.70±0.70	1.58±0.27	−(4.77±0.47)	1.48±0.41	0.990	91	0.16	10
HO–NA	2.37±0.36	1.99±0.09	−(2.20±0.51)	−1.92±0.37	0.999	320	0.03	5^a
CH_3–NA	1.35±0.97	1.73±0.35	−(4.34±0.61)	1.02±0.54	0.980	49	0.20	10
Br–NA	1.68±0.77	1.50±0.28	−(4.91±0.48)	1.64±0.42	0.989	92	0.16	10
HS–NA	1.89±0.77	1.40±0.28	−(4.56±0.48)	1.18±0.43	0.986	72	0.16	10

[a]See Table I; [b]correlation coefficient; [c]Fischer's test; [d]standard error

The correlation equations obtained by polylinear regression for all the examined acids showed that the best approach, which aids in the understanding of the effects of aprotic solvents in the reaction, could be the usual correlation of the kinetic data with the contribution of the hydrogen bond donating (HBD) and hydrogen bond accepting (HBA) ability of a solvent to the transition and initial states. 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 III.

TABLE III. Percentage contribution of the Kamlet–Taft solvatochromic parameters (*P*) to the reactivity of the investigated acids in aprotic solvent

Acid	P_{π^*} / %	P_α / %	P_β / %
NA	27	23	60
Cl–NA	21	20	59
HO–NA	36	30	34
CH_3–NA	18	23	59
Br–NA	21	19	60
HS–NA	24	18	58

The results from Tables II and III, 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 (see 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.

One correlation was found in the literature[25] which includes all three solvent parameters in a correlation for benzoic acid for solvents that do not possess HBD character:

$$\log k_2 = 0.20 + 1.21\pi^* + 2.71\alpha - 3.70\beta \qquad (3)$$

$$R = 0.980;\ SD = 0.171;\ n = 44$$

The correlation coefficients for this equation also indicate a high contribution of the HBD solvent effect or electrophilic stabilization of the carboxylate anion in forming. The calculated percent contributions of particular solvent effects for benzoic acid are P_{π^*} (16 %), P_α (35 %) and P_β (49 %).

Generally, 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 aprotic solvents. Classical solvation has a higher influence on the reactivity of 6-hydroxynicotinic acid, while the electrophilic stabilization, respectively 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 aprotic solvents, 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 at 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 favour acid ionisation and charge separation, and the created carboxylate anion–diazodiphenylmethane cation ion pair could be stabilized by aprotic 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 hydroxy group, causing stabilization and a definite modification of the electron-donating properties of that group.

A better understanding of the contribution of solvent effects could be attained by comparing the results from the present study with correlation results of data published for nicotinic and benzoic acids[8] in protic solvents.

The kinetic data for nicotinic acid from a previous paper[8] were correlated with the solvent parameter for eleven protic solvents, giving the following results:

$$\log k_2 = (-0.14\pm0.20) + (1.34\pm0.52)\pi^* + (0.78\pm0.21)\alpha - (0.51\pm0.76)\beta \quad (4)$$
$$R = 0.960;\ SD = 0.12;\ n = 11$$

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

Therefore, the best interpretation of solvent effects in protic solvents is described by a simplified system of a two-parameter equation of the following type:

$$\log k_2 = (-0.76\pm0.17) + (1.65\pm0.22)\pi^* + (0.85\pm0.16)\alpha \quad (5)$$
$$R = 0.960;\ SD = 0.11;\ n = 11$$

The results of the above correlation corroborate the reaction mechanism, and the influence of solvent by classical solvation and electrophilic solvation. It is evident that the HBD effect increases the reaction rate, stabilizing the transition state more than the initial state.

The calculation of the percent contribution of particular solvent effects gave the following results: for nicotinic acid P_{π^*} (66 %) and P_{α} (34 %); for benzoic acid the effect of electrophilic solvation is the main effect (21 and 79 %, respectively). The large differences in the contributions of the same solvent effects for these two acids can be explained by the significant increase in the influence of classical solvation because of the more polar structure of nicotinic acid in the transition state, caused by the negative inductive and resonance effects of the pyridine nitrogen.

Structure–reactivity relationship

The relationship between the molecular structure and chemical reactivity gives additional insight into the electronic effect of substituents and the influence of solvent on the electronic distribution in the initial and transition states. Correlation results obtained using the Hammett equation (2) are given in Table IV for aprotic solvents.

The magnitude of the obtained reaction constants indicates that the reaction is significantly susceptible to substituent effects. Furthermore, the positive reaction constant suggests that the positive charge at the reaction centre may disappear. Generally, the Hammett equation predicts[27] that the reaction constant for this type of reaction appears to increase with decreasing relative permittivity of the medium. In the present study, however, there is a very marked deviation from the relationship between ρ and the relative permittivity of the medium (ε_r) (macroscopic solvent parameter). This suggests that the ρ values are influenced by both non-specific and specific solvent effects.

TABLE IV. Hammett ρ values for the reaction of 6-substituted nicotinic acids with DDM in aprotic solvents at 30 °C (σ values for Cl, OH, CH_3, Br and SH are from literature[26])

Solvent	ρ	log k_0	*r*	*SD*	*F*	*n*
Acetophenone	0.96±0.17	0.65±0.17	0.94	0.06	32	5
Acetone	1.29±0.26	0.32±0.05	0.93	0.09	26	5
Chloroform	1.91±0.42	1.84±0.08	0.92	0.16	20	5
Ethyl benzoate	1.13±0.23	0.53±0.05	0.93	0.09	24	5
Isobutyl methyl ketone	1.62±0.14	0.10±0.03	0.98	0.05	128	5
NMF	1.37±0.17	0.03±0.04	0.96	0.09	61	6
DMSO	2.09±0.24	–0.66±0.05	0.97	0.12	77	6
DMAC	2.25±0.32	–0.82±0.07	0.95	0.16	48	6
DMF	2.11±0.24	–0.56±0.05	0.97	0.12	78	6
NMP	2.36±0.29	–0.83±0.06	0.96	0.15	64	6

Taking into consideration the assumption of similarity in the transmitting cavities for 6-substituted nicotinic acids and benzoic acid, the differences in the transmission of substituent effects through the benzene and pyridine ring depend on the polarizability of these ring systems and also on the contribution of electrons from the pyridine nitrogen. The higher sensitivity of the reaction constant to solvent effects in aprotic dipolar solvent may be explained in the way that at high relative permittivities of the surrounding solvent molecules, the energy necessary to bring about charge separation in the transition state is relatively small, which gives rise to a higher susceptibility to the electronic substituent effect. Aprotic highly dipolar solvents (DMSO, DMF, DMAC and NMP) tend to be poor anion solvators, while they are usually better for larger and softer anions. The extended conjugated system of the investigated acids, considering their planarity shown by the semi-empirical PM6 method, having delocalized electronic densities could be more susceptible to the influence of substituents on reactivity. The classical solvent effect is not necessarily only achieved through dipolar attraction but also by the repulsion of the negative end of solvent dipole and, consequently, the π-electronic densities could have more influence on the reactivity of the acids. An exception is NMF which contributes less to the substituent influences, probably because of its possibility of hydrogen bonding and self-association. Other aprotic dipolar solvents (acetophenone, acetone and ethyl benzoate) of lower dipolarity/polarizability and HBA basicity show lower substituent influence on reactivity, primarily because of their lower polarizability.[25]

The consideration of the influences of solvent and substituent is based on the macroscopic solvent and substituent characteristics, which do not separate specific reactant/solvent interaction and the contribution of substituent/solvent interactions. The interaction modes presented in Fig. 1 approximate the regiospecific interactions of the solvent with the actual electrophilic and nucleophilic sites in an acid. The overall solvent effect is achieved by the joint interactions, presented in Fig. 1, of the contribution of non-specific and specific solvent effects to the electron density at the site. The solvent or substituent causes electron density changes of the most polarisable molecular orbitals, which indeed transmit these effects to the reaction centre. The reasons why some irregularities were observed in the correlation results may be associated with the choice and analysis of the HOMO molecular orbitals, occupied with electrons, available for reactant/solvent interactions. The optimized geometries of all 6-substituted nicotinic acids show small or no deviation from planarity and thus electron transfer could be achieved without suppression of these effects. Analysis of the three highest occupied levels showed that only HOMO orbitals give an adequate explanation of the interaction and transmission modes of solvent and substituent effects to the reaction centre. The HOMO orbitals for 6-hydroxynicotinic and nicotinic acid are presented in Fig. 2.

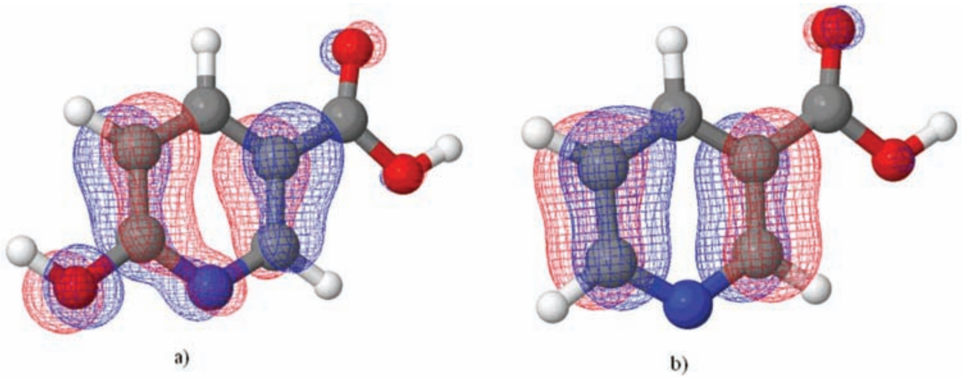


Fig. 2. HOMO orbitals of 6-hydroxynicotinic (a) and nicotinic acid (b) obtained by the semi-empirical MO PM6 method, with implicit DMSO solvation using the MOPAC2009^{TM} program package.

Electron densities of the most polarized HOMO orbitals in both acids show some important differences which indeed have the highest contribution to the transmission of the substituent effect and influence of solvent on the reactivity. The pyridine nitrogen in 6-hydroxynicotinic acid belongs to the π-polarized system with a C_5–C_6 double bond, which is susceptive to electronic shifts, being sensitive to substituent and solvent influences at these atoms. The electronic effects of the pyridine nitrogen, as a part of this π-polarisable system, have a significant contribution to the solvent and substituent effects on the reactivity of the investigated nicotinic acids. Aprotic solvents of high dipolarity/polarizability interfere with the electron-accepting capability of the pyridine nitrogen, causing lower acidity of the investigated acids. Opposed to this, solvents of lower dipolarity/polarizability and higher proton-donor ability contribute to the higher electrophilic solvation of the nitrogen in both the initial and transition state, enhancing the electron-accepting power and thus increasing the acidity of the acids.

CONCLUSIONS

The overall solvent effects on the reactivity are complicated by several possible modes of interactions between the solvent, either protic or aprotic, with several active sites on the reacting acid molecules. The results of the present investtigation show that these diverse solvent effects could be generally quantified by use of the Kamlet–Taft equation. The quantitative separation of these effects into individual contributions in the initial and transition states is not completely possible. Secondary solvent effects are operative, causing modifications originating from both the pyridine ring and substituent electronic effects on the reactivity of the investigated acids. Generally, the pyridine nitrogen has a significant influence on the reactivity of 6-substituted nicotinic acids, considering the possibilities of different solvent interactions with this atom. Thus, for example, a stronger electrophilic solvation of the pyridine nitrogen in the transition state causes a decrease of the electrophilic solvation of the carboxylate anion in forming. In addition, the high contribution of nucleophilic solvation of the carboxylic hydrogen in the initial state is caused by the strong electron-accepting character of the pyridine nitrogen. The substituent electronic effect on the reactivity is of greatest influence in highly dipolar aprotic solvents which interfere with the strong electron-accepting character of the pyridine nitrogen.

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ИЗВОД

УТИЦАЈ РАСТВАРАЧА И СТРУКТУРЕ НА РЕАКТИВНОСТ 6-СУПСТИТУИСАНИХ НИКОТИНСКИХ КИСЕЛИНА СА ДИАЗОДИФЕНИЛМЕТАНОМ У АПРОТИЧНИМ РАСТВАРАЧИМА

САША Ж. ДРМАНИЋ, АЛЕКСАНДАР Д. МАРИНКОВИЋ и БРАТИСЛАВ Ж. ЈОВАНОВИЋ

Кашедра за органску хемију, Технолошко-мешалуршки факулшеш, Универзишеш у Београду, ш. шр. 3503, Карнегијева 4, 11120 Београд

Константе брзина 6-супституисаних никотинских киселина са диазодифенилметаном (ДДМ) су одређене у различитим протичним и апротичним растварачима на 30 °C. Израчунате константе брзина, као и литературни подаци, коришћени су за израчунавање ефеката растварача коришћењем Kamlet–Taft-ове солватохромне једначине. Константе брзина су корелисане са параметрима растварача коришћењем Kamlet–Taft-ове једначине облика: log *k*

= log k_0 + + $s\pi^*$ + $a\alpha$ + $b\beta$. Корелације добијених кинетичких резултата са одговарајућим параметрима растварача су изведене применом методе вишеструке линеарне регресионе анализе. Знак коефицијената (*s*, *a* и *b*) у добијеним корелацијама је у сагласности са реакционим механизмом. Сличан допринос неспецифичних ефеката и електрофилне солватације растварача је уочен за све испитиване киселине, а највећи допринос нуклеофилне солватације полазног стања је последица високе киселости испитиваних киселина. Утицај растварача на вредности реакционих константи је дискутован на основу добијених корелационих резултата. Корелациона анализа константи брзина са σ_p константама супституената, у испитиваном растварачу, извршена је применом Hammett-ове једначине. Ефекти супституената на реактивност испитиваних киселина су значајнији у апротичним растварачима високе диполарности/поларизабилности. Начин преноса ефеката супституената је дискутован у светлу доприноса интеракција растворак–растварач на реактивност испитиваних киселина.

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