

The influence of the solvent on organic reactivity. Part II. Hydroxylic solvent effects on the reaction rates of diazodiphenylmethane with 2-(2-substituted cyclohex-1-enyl)acetic and 2-(2-substituted phenyl)acetic acids

JASMINA B. NIKOLIĆ[#], GORDANA S. UŠĆUMLIĆ^{*#} and VERA V. KRSTIĆ[#]

*Department of Organic Chemistry, Faculty of Technology and Metallurgy, University of Belgrade,
Karnegijeva 4, P. O. Box. 494, 11000 Belgrade, Serbia and Montenegro*

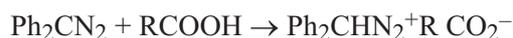
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Abstract: The rate constants for the reaction of diazodiphenylmethane with 2-(2-substituted cyclohex-1-enyl)acetic acids and 2-(2-substituted phenyl)acetic acids, previously determined in seven hydroxylic solvents, were correlated using the total solvatochromic equation, of the form: $\log k = \log k_0 + s\pi^* + a\alpha + b\beta$, the two-parameter model, $\log k = \log k_0 + s\pi^* + a\alpha$, and a single parameter model $\log k = \log k_0 + b\beta$, where π^* is a measure of the solvent polarity, β represents the scale of solvent hydrogen bond acceptor basicities and α represents the scale of solvent hydrogen bond donor acidities. The correlations of the kinetic data were carried out by means of multiple linear regression analysis and the solvent effects on the reaction rates were analysed in terms of initial state and transition state contributions.

Keywords: 2-(2-substituted cyclohex-1-enyl)acetic acids, 2-(2-substituted phenyl)acetic acids, diazodiphenylmethane, kinetic measurements, protic solvents.

INTRODUCTION

The influence of hydroxylic solvents on the reaction rate has always been a point of particular interest to many authors.^{1–3} One of the most representative examples in this field is the reaction of carboxylic acids with diazodiphenylmethane (DDM).^{4–6} The mechanism of this reaction has been thoroughly investigated^{7–10} 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 in subsequent product-determining steps to give esters (or ethers in the case of alcoholic solvents):



* Corresponding author.

Serbian Chemical Society active member.

In our previous work¹¹ the reactivity of 2-(2-substituted cyclohex-1-enyl)acetic acids with DDM in various alcohols was examined, and the rate data for these acids were correlated using the simple and extended Hammett equations. The results showed that linear free energy relationships are applicable to the kinetic data for the 2-(2-substituted cyclohex-1-enyl)acetic acid system. Comparisons were made with the corresponding 2-(2-substituted phenyl)acetic acid system. The solvent effects on the reactivity of cyclohex-1-enylacetic acid are proportional to their influence on that of phenylacetic acid.

In the present work, our study^{12,13} of the hydroxylic solvent effects on the reaction of carboxylic acids with DDM by means of linear solvation energy relationships (LSER) concept developed by Kamlet and Taft¹⁴ have been extended.

Aslan, Collier and Shorter⁵ showed that the correlation analysis of second-order rate constants for the reaction of benzoic acid and DDM in hydroxylic solvents did not give satisfactory results. They came to a conclusion that the possibility of a Koppel-Palm analysis of data related to protic solvents depends on the fitting of the data in a regression with the main lines being determined by a much larger number of aprotic solvents. To the best of our knowledge, the influence of hydroxylic solvents on the reactivity of carboxylic acids with DDM by the Kamlet-Taft treatment has not been systematically presented before.^{16,17}

In a recent paper¹⁵ hydroxylic solvent effects on the reaction of α,β -unsaturated cycloalkenecarboxylic and cycloalkenylacetic acids with DDM by LSER method were examined. The correlation equations obtained by the stepwise regression of all the examined acids showed that the best approach, which helps the understanding of hydroxylic solvent effects in the reaction, lies in the separate correlation of the kinetic data with the hydrogen bond donating (HBD) and hydrogen bond accepting (HBA) ability of a solvent.

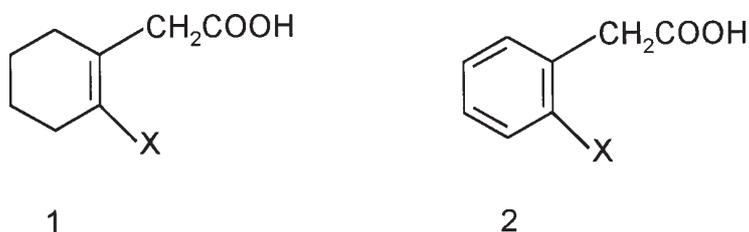
For the first time, the present paper demonstrates how the multiple interacting effects of hydroxylic solvents on the reaction rates of carboxylic acids and DDM can be analysed in terms of initial and transition state contributions.

In the present work, the second order rate constants determined previously^{11,18} for the reaction of 2-(2-substituted cyclohex-1-enyl)acetic acids (system 1) and 2-(2-substituted phenyl)acetic acids (system 2) with DDM in various alcohols at 30 °C were correlated using a total solvatochromic equation¹⁴ of the form:

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

where π^* , α and β are solvatochromic coefficients and $\log k_0$ is the regression values of the solute property in the reference solvent, cyclohexane.¹⁴

According to the structural analogy between the systems 1 and 2, it seemed of interest to compare the obtained results for these acids with identical substituents.



X = H, CH₃, C₂H₅, Cl, Br, I, NO₂

RESULTS AND DISCUSSION

The first comprehensive application of multiple linear regression analysis (MLRA) to kinetic phenomena was that of Koppel and Palm,¹⁹ who listed regression constants for the simple Koppel-Palm equation¹⁹ for various processes. Shorter and co-workers¹ applied correlation analysis to solvent effects on the reaction between DDM and benzoic acid.

In the present work, multiple linear regression analysis has been applied to hydroxylic solvent effects on the reaction between DDM and 2-(2-substituted cyclohex-1-enyl)acetic and 2-(2-substituted phenyl)acetic acids. The reaction rate constants of the examined acids, determined previously,^{11,18} were correlated with the solvent properties using the total solvatochromic Eq. (1).

The solvent parameters are given in Table I (for seven alcohols determined by Kamlet *et al.*²⁰).

TABLE I. Solvent parameters for alcohols²⁰

Solvent	π^*	α	β
Methanol	0.60	0.93	0.62
Ethanol	0.54	0.83	0.77
Propan-1-ol	0.52	0.78	0.83
Propan-2-ol	0.48	0.76	0.95
Butan-1-ol	0.47	0.79	0.88
2-Methylpropan-2-ol	0.41	0.68	1.01
Ethylene glycol	0.92	0.90	0.52

Correlation analysis of the investigated acids with the solvent parameters π^* , α and β , in protic solvents, showed that there were no satisfactory results for correlation coefficients in the three-parameter Eq. (1). For each examined acid the same problem arose – the coefficient related to the HBA parameter (b) had a standard error overriding its value and making the equation unreliable. The equation for 2-methylcyclohex-1-enylacetic acid is given as an example:

$$\log k = -7.08 + (1.38 \pm 0.87) \pi^* + (5.58 \pm 2.86) \alpha + (1.71 \pm 2.04) \beta \quad (2)$$

$$R = 0.972, s = 0.13, n = 7$$

As the solvent effect on the examined reaction could not be clearly presented when all the solvent properties were taken together, an attempt was made to separate them into those that stabilize the transition state and those that influence the ground state. Taking into consideration the reaction mechanism (Fig. 1), it can 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 which also exists in the transition state. On the contrary, the nucleophilic solvating ability can be prominent in the ground state, stabilizing the carboxylic proton and, hence, slowing down the reaction.

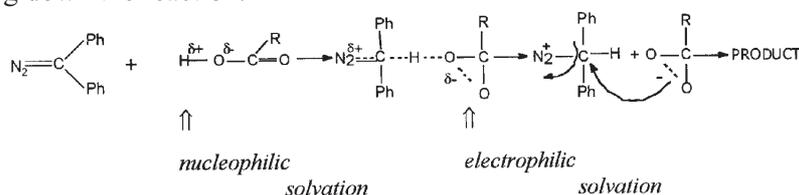


Fig. 1. The mechanism of the reaction of carboxylic acids with DDM.

Further examination, using one- and two- parameter equations with the parameters π^* , α (effects important for the transition state) and β (ground state) gave more convincing results, using the following forms:

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

$$\log k = \log k_0 + b\beta \quad (4)$$

TABLE II. Results of the correlations of $\log k$ for 2-(2-substituted cyclohex-1-enyl)acetic¹¹ and 2-(2-substituted phenyl)acetic acids¹⁸ with Eq. (2)

Acids	$\log k_0$	s	a^a	R^b	sd^c
Cyclohex-1-enylacetic	-3.33	0.75(±0.41)	3.91(±0.94)	0.960	0.14
2-CH ₃ -Cyclohex-1-enylacetic	-3.50	0.73(±0.38)	3.31(±0.58)	0.966	0.13
2-C ₂ H ₅ -Cyclohex-1-enylacetic	-3.44	0.72(±0.39)	3.26(±0.89)	0.963	0.13
2-(2-Cl-Cyclohex-1-enyl)acetic	-2.77	0.62(±0.33)	3.03(±0.75)	0.968	0.11
2-(2-Br-Cyclohex-1-enyl)acetic	-2.72	0.63(±0.33)	3.01(±0.75)	0.968	0.11
2-(2-I-Cyclohex-1-enyl)acetic	-2.64	0.62(±0.32)	3.02(±0.72)	0.971	0.11
2-(2-NO ₂ -Cyclohex-1-enyl)acetic	-1.36	0.45(±0.25)	2.23(±0.57)	0.988	0.08
Phenylacetic	-2.48	0.85(±0.31)	2.59(±0.71)	0.972	0.105
2-CH ₃ -Phenylacetic	-2.82	0.96(±0.35)	2.89(±0.82)	0.971	0.12
2-C ₂ H ₅ -Phenylacetic	-2.82	0.97(±0.37)	2.89(±0.84)	0.969	0.12
2-(2-Cl-Phenyl)acetic	-2.44	0.88(±0.33)	2.66(±0.75)	0.971	0.11

TABLE II. Continued

Acids	$\log k_0$	s	a^a	R^b	sd^c
2-(2-Br-Phenyl)acetic	-2.44	0.88(±0.33)	2.70(±0.76)	0.970	0.11
2-(2-I-Phenyl)acetic	-2.45	0.91(±0.34)	2.72(±0.77)	0.970	0.11
2-(2-NO ₂ -Phenyl)acetic	-1.68	0.69(±0.27)	2.15(±0.61)	0.960	0.09

^acalculated solvatochromic coefficient; ^bcorrelation coefficient; ^cstandard deviation of the estimate

TABLE III. Results of the correlations of $\log k$ for 2-(2-substituted cyclohex-1-enyl)acetic¹¹ and 2-(2-substituted phenyl)acetic¹⁸ acids with Eq. (3)

Acids	$\log k_0$	b^a	r^b	sd^c
Cyclohex-1-enylacetic	1.66	-2.26(±0.36)	0.941	0.15
2-CH ₃ -Cyclohex-1-enylacetic	1.32	-2.17(±0.36)	0.936	0.16
2-C ₂ H ₅ -Cyclohex-1-enylacetic	1.32	-2.15(±0.37)	0.934	0.16
2-(2-Cl-cyclohex-1-enyl)acetic	1.63	-1.98(±0.28)	0.954	0.12
2-(2-Br-Cyclohex-1-enyl)acetic	1.66	-1.98(±0.28)	0.952	0.12
2-(2-I-Cyclohex-1-enyl)acetic	1.73	-1.98(±0.28)	0.954	0.12
2-(2-NO ₂ -Cyclohex-1-enyl)acetic	1.85	-1.43(±0.24)	0.937	0.10
Phenylacetic	1.70	-1.99(±0.27)	0.950	0.12
2-CH ₃ -Phenylacetic	1.85	-2.23(±0.32)	0.953	0.14
2-C ₂ H ₅ -Phenylacetic	1.86	-2.24(±0.33)	0.951	0.14
2-(2-Cl-Phenyl)acetic	1.86	-2.05(±0.29)	0.952	0.13
2-(2-Br-Phenyl)acetic	1.90	-2.07(±0.30)	0.951	0.13
2-(2-I-Phenyl)acetic	1.96	-2.11(±0.30)	0.951	0.13
2-(2-NO ₂ -Phenyl)acetic	1.76	-1.64(±0.24)	0.951	0.10

^acalculated solvatochromic coefficient; ^bcorrelation coefficient; ^cstandard deviation of the estimate

From the results presented in Tables II and III, it can be concluded that the carboxylic acid – DDM reaction is influenced by two opposing effects. The opposite signs of the electrophilic and nucleophilic parameters are in accordance with the described mechanism (Fig. 1). The positive signs of the s and a parameters prove that classical solvation and HBD effects dominate the transition state and increase the reaction rate, and the negative sign of the b parameter indicates that HBA effects (β) stabilize the initial state before the reaction commences and are responsible for a decrease in the reaction rate.

From Table II, it can be seen that the classical solvation effects are more pronounced for the 2-(2-substituted phenyl)acetic acids, contrary to proton-donor solvent effects which are intensive for 2-(2-substituted cyclohex-1-enyl)acetic acids.

The explanation of this fact probably lies in the planarity of the ring of the phenylacetic acid system, which makes it easier for the solvent molecules to approach and arrange themselves around the ionic pair in the transition state (Fig. 1). The solvent molecules cannot solvate the cyclohexene ring so easily which makes the effect of proton-donating ability of a solvent more important. The solvent effects generally decrease with increasing electronegativity of a substituent because a carboxylic acid containing an electron-attracting substituent already has its own way of stabilizing the carboxylic anion in the transition state which makes the solvating ability less important.

Hence, Eqs. (2) and (3) were taken as the most likely explanations of the influence of the solvent on the examined reaction. Therefore, the experimentally obtained rate constants^{11,18} were correlated with those calculated from these two equations. The results are given in Eqs. (5) and (6) using phenylacetic acid as an example.

$$\log k_{\text{exp}} = 0.008 + 1.002 \log k_{\pi^*\alpha} \quad (5)$$

$$r = 0.972, s = 0.09, n = 7$$

$$\log k_{\text{exp}} = 0.0004 + 1.004 \log k_{\beta} \quad (6)$$

$$r = 0.955, s = 0.012, n = 7$$

Judging from the high correlation coefficients R and acceptably low standard errors in the correlations above (Eqs. (5) and (6)), the experimental and calculated data were very much in agreement, but only a comparison of exact values for each solvent could prove which of the two suggested models best describes the solvent effects in this case, given in Table IV for phenylacetic acid.

TABLE IV. Experimental and calculated rate constants for phenylacetic acid

Solvent	k_{exp}	$k_{\pi^*\alpha}$	k_{β}
Methanol	2.540	2.752	2.925
Ethanol	1.140	1.347	1.471
Propan-1-ol	1.320	0.961	1.117
Propan-2-ol	0.808	0.789	0.645
Butan-1-ol	1.180	0.925	0.889
2-Methylpropan-2-ol	0.345	0.427	0.490
Ethylene glycol	5.050	4.955	4.626

As the same regression analysis of $\log k$ with the π^* and α solvent parameters gave the best agreement between the experimental and calculated data for all acids included in this study (Fig. 2), it was concluded that the effects described by it most clearly represent the influence of hydroxylic solvents on this reaction.

Using this correlation, the effects of the hydroxylic solvents can be clearly shown by separating them into those influencing the ground state and those influencing the

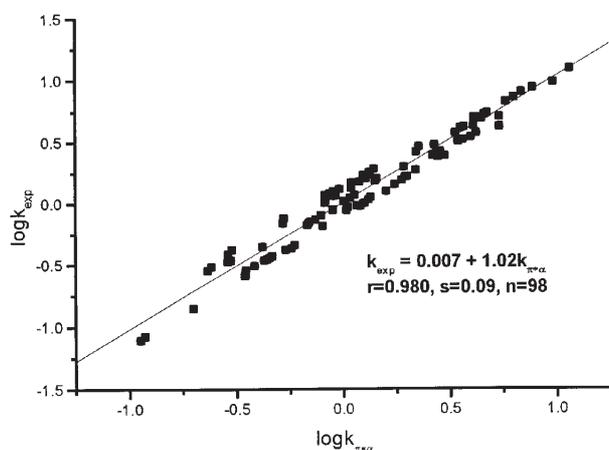


Fig. 2. The plot of $\log k$ observed against the values calculated from the equation $\log k = \log k_0 + s\pi^* + a\alpha$.

transition state. The results presented in this paper are in accordance with the proposed mechanism of the reaction of carboxylic acids with diazodiphenylmethane.⁷⁻¹⁰ The classical solvation and proton-donor (HBD) effects of protic solvents dominate the transition state and increase the reaction rate, by solvating the intimate ion-pair created during the rate-determining step (shown in Fig. 1). The more pronounced these accelerating solvent effects are, the faster is the reaction.²¹

Additional evidence for the solvent effect on the structure-reactivity relationship in the reaction of 2-(2-substituted cyclohex-1-enyl)acetic and 2-(2-substituted phenyl)acetic acids with DDM was obtained from the correlation of the σ_p^0 substituent constant²² with the ratio of the solvatochromic coefficients, a/s (Table V), calculated using the coefficients given in Tables II. The results of the correlations for all the acids are presented in Figs. 3 and 4.

TABLE V. The ratio of solvatochromic coefficients a/s for 2-(2-substituted cyclohex-1-enyl)acetic and 2-(2-substituted phenyl)acetic acids and the corresponding substituent constants σ_p^0 ²²

Substituent	σ_p^0	2-(2-Substituted cyclohex-1-enyl)acetic acids	2-(2-substituted phenyl)acetic acids
		a/s	a/s
H	0	5.21	3.05
CH ₃	-0.14	4.54	3.01
C ₂ H ₅	-0.13	4.54	2.98
Cl	0.24	4.90	3.03
Br	0.27	4.78	3.06
I	0.28	4.89	2.99
NO ₂	0.81	4.95	3.11

The existence of this correlation (Figs. 3 and 4) is strong evidence for the proportionality between the structure characteristics (substituent constants) of the in-

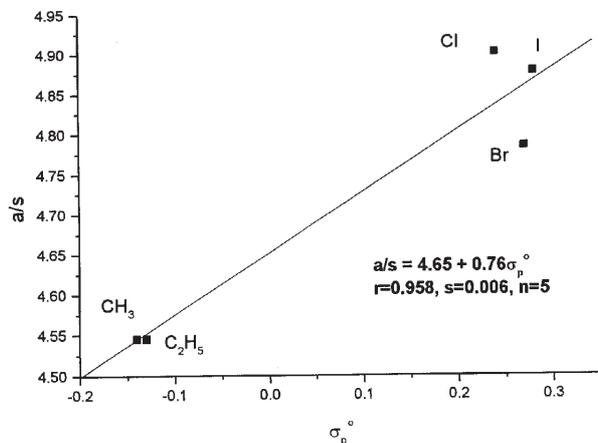


Fig. 3. The plot of ratios of the solvatochromic coefficients a/s vs. the substituent constant σ_p^0 for 2-(2-substituted cyclohex-1-enyl)acetic acids.

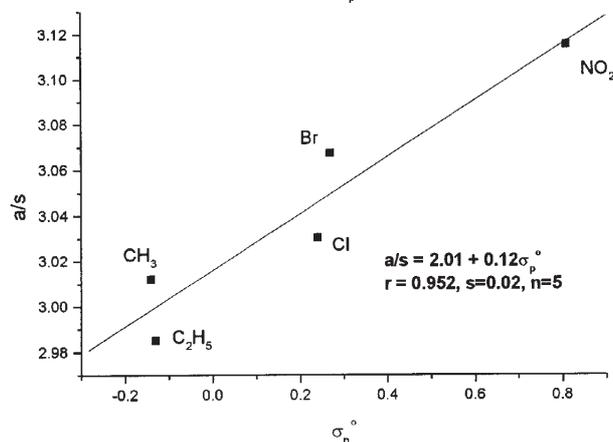


Fig. 4. The plot of ratios of the solvatochromic coefficients a/s vs. the substituent constant σ_p^0 for 2-(2-substituted phenyl)acetic acids.

vestigated acids and the solvatochromic effects in the reaction of carboxylic acids with DDM in different alcohols. These results show that the 2-(2-substituted cyclohex-1-enyl)acetic acid system is more sensitive to the influence of hydroxylic solvents than the 2-(2-substituted phenyl)acetic acid system.

On the basis of all the information presented, it may be concluded that the solvatochromic treatment of Kamlet and Taft is applicable to the kinetic data of the reaction of 2-(2-substituted cyclohex-1-enyl)acetic and 2-(2-substituted phenyl)acetic acids with DDM in various alcohols. The satisfactory results of the correlations of the kinetic data by Eq. (2) indicate that the selected model is correct. This means that this model gives a detailed interpretation of the solvating effect of the carboxylic group in different hydroxylic solvents. For these reasons, in our opinion, the results presented in this work may be used to quantitatively estimate and separate the overall solvent effects into initial-state and transition-state contributions in the reaction of diazodiphenylmethane with carboxylic acids.

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ИЗВОД

УТИЦАЈ ХИДРОКСИЛНИХ РАСТВОРАЧА НА БРЗИНУ РЕАКЦИЈЕ
ДИАЗОДИФЕНИЛМЕТАНА СА 2-(2-СУПСТИТУИСАНИМ
ЦИКЛОХЕКС-1-ЕНИЛ)СИРЋЕТНИМ И 2-(2-СУПСТИТУИСАНИМ
ФЕНИЛ)СИРЋЕТНИМ КИСЕЛИНАМА

ЈАСМИНА Б. НИКОЛИЋ, ГОРДАНА С. УШЋУМЛИЋ И ВЕРА В. КРСТИЋ

*Катедра за орџанску хемију, Технолошко-металуриџки факултет, Универзитет у Беоџраду, Карнеџијева 4,
11000 Беоџрад*

Константе брзина за реакцију између диазодифенилметана и 2-(2-супституисаних циклохексен-1-енил)сирћетних и 2-(2-супституисаних фенил)сирћетних киселина, претходно одређене у седам алкохолних раствараџа на 30 °C, корелисане су тоталном солватохромном једначином облика: $\log k = \log k_0 + s\pi^* + a\alpha + b\beta$, као и двопараметарском $\log k = \log k_0 + s\pi^* + a\alpha$ и једнопараметарском $\log k = \log k_0 + b\beta$, где је π^* мера поларности раствараџа, β представља скалу базности раствараџа као акцептора протона у водоничној вези, α скалу киселости раствараџа као донора протона у водоничној вези. Корелација кинетичких параметара је извршена методом вишеструке линеарне регресионе анализе. Супротни знаџи уз електрофилни и нуклеофилни параметар су у складу са наведеним реакционим механизмом. Слагање експериментално одређених константи брзина са израџунатим вредностима је потврда исправности примењеног модела. Резултати приказани у овом раду омогуђују квантитативно раздвајање и процену укупних ефеката раствараџа на полазно и прелазно стање у реакцији карбонских киселина са DDM-ом у алкохолним раствараџима.

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