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Quantum-Chemical Simulation of Glycine Specific Solvation in the Solvents Water–1,4-Dioxane and Water–2-Propanol

T. P. Kustova, L. B. Kochetova, and N. V. Kalinina

Ivanovo State University,
ul. Ermaka 39, Ivanovo, 153025 Russia
e-mail: kustova_t@mail.ru

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Abstract—Structural and energy characteristics of the solvatocomplexes of glycine molecular and anionic forms with the components of the solvents water–dioxane and water–2-propanol were calculated by the HF/6-31G method. The results of calculation were compared with kinetic data on the glycine reactions with 3-nitrobenzenesulfonyl chloride and benzoyl chloride that allowed to understand the difference in the effect of composition of these binary solvents on the rate of N-acylation of α-aminoacids.

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Earlier we studied the kinetics of reactions of a series of α-aminoacids with 3-nitrobenzenesulfonyl chloride in the solvents water–dioxane and water–2-propanol [1], as well as with benzoyl chloride in aqueous dioxane [2–5]. The results of those investigations show that at the increase in water content in these binary solvents the rate constants of N-acylation of α-aminoacids vary differently. In particular, at the increase in the water mole fraction in aqueous dioxane from 0.15 to 0.32 the rate constant of glycine arenesulfonylation falls monotonically in the range $(4.98 - 2.03)\times10^3$ l mol^{-1} s^{-1}, while when the fraction of water in its mixture with 2-propanol is varied in the range from 0.31 to 0.07 the rate constant of the same reaction grows 40-fold. The rate constant of glycine N-acylation with benzoyl chloride decreases 5-fold when the water fraction in the water–dioxane systems is changed from 0.32 to 0.15. Similar effect of the composition of the solvents water–dioxane and water–2-propanol on the rate of N-acylation occurs in the reactions of all studied α-aminoacids with these acylating agents [1–5].

The effect of the solvent nature and composition on the rate of a reaction can be due to the features of specific solvation of reagents by the binary mixture components. We showed formerly [5] that the rate of the reactions of nucleophilic substitution at the sulfonyl or carbonyl center with participation of amines was mainly affected by the the amine solvation while the solvation of the acylating agent played a minor role.

A widely used approach to the understanding of the effects of specific solvation is the quantum-chemical simulation of the solvatocomplex of the molecules involved in the reaction in a supramolecular approximation. We carried out the simulation of the all possible solvatocomplexes of glycine with the components of the solvents water–dioxane and water–2-propanol. The choice of glycine as a model aminoacid is caused by the simplicity of its structure: The substituent at its α-carbon atom is a hydrogen atom. Depending on the conditions, the acylation can occur either with the uncharged or anionic forms of α-amino-acids having an unprotonated amino group [1–5], therefore the calculations of solvatocomplexes were carried out for both these forms of glycine.

We applied the HF/6-31G* method with complete geometry optimization to the calculation of the structural and energy characteristics of the following complexes: $(Gly)(H_2O)_n$, n = 1–4; $(Gly)(Diox)_m$, m = 1–2; $(Gly)(i\text{-PrOH})_l$, l = 1–2; $(Gly)(H_2O)(Diox)$; $(Gly)\cdot(H_2O)(i\text{-PrOH})$;$(Gly^-)(H_2O)_n$, n = 1–4; $(Gly^-)(Diox)_m$, m = 1–2; $(Gly^-)(i\text{-PrOH})_l$, l = 1–2; $(Gly^-)(H_2O)(Diox)$; $(Gly^-)(H_2O)_n(i\text{-PrOH})$, n = 1–2. The calculations included the vibration spectra of these systems. The minimum on the potential energy surface was characterized by the absence in the calculated spectrum of the

bands with a negative frequency. HyperChem 7.52® program [6] was used for the calculations.

The specified initial geometry of the complexes was taken so as to provide the glycine amino group to behave as H-donor in one or two hydrogen bonds. The structures of the solvatocomplexes obtained in the course of optimization in the most cases differed from the initial ones. Schematic images of these structures and some of geometric, electronic and energy characteristics obtained in the calculations are shown in the Table 1. The values of energy of formation of the complexes ($\Delta E_{complex}$) were taken as the difference of the total energies of the complexes and isolated molecules.

In some investigations, e.g., [7–9], by the methods of IR and UV spectroscopy, NMR, calorimetry and others has been found that at the complexation with a solvent components the amino group can behave as the H-donor and H-acceptor. In the first case complexes of 1:1 or 1:2 composition on account of formation of hydrogen bonds are formed. In the second case a bond with hydrogen atom is formed with participation of the nitrogen lone electron pair.

The results of our calculations indicate substantial difference in the specific solvation of glycine molecules and anions. In the molecular form of glycine (see Table 1, **I–X)** the amino group is capable to form

Table 1. Geometry and electronic and energy characteristics of solvatocomplexes of the glycine molecular and ionic forms with the components of the solvents water–dioxane and water–2-propanol

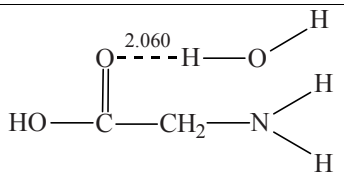
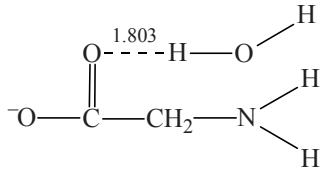
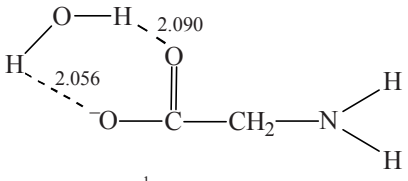
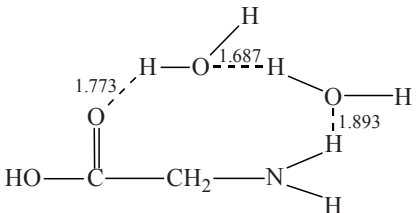
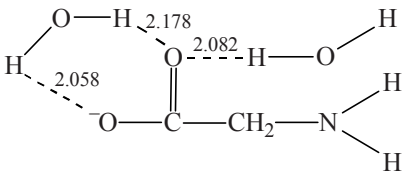
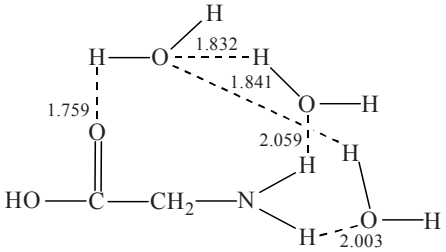
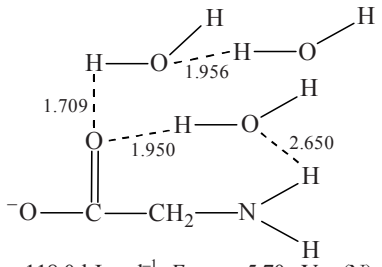
Comp. no.	Glycine molecular form	Comp. no.	Glycinate anion
I		**XIa**	
	$\Delta E_{complex}$ –38.6 kJ mol^{-1}; E_{HOMO} –10.82 eV; q(N) –0.846; q(NH$_2$) –0.111; Cp_z(N) 0.392; $r_{N–H}$ 1.002 Å		$\Delta E_{complex}$ 6.9 kJ mol^{-1}; E_{HOMO} –4.96 eV; q(N) –0.857; q(NH$_2$) –0.209; Cp_z(N) 0.310; $r_{N–H}$ 1.004 Å
		XIb	
			$\Delta E_{complex}$ –14.2 kJ mol^{-1}; E_{HOMO} –5.26 eV; q(N) –0.869; q(NH$_2$) –0.209; Cp_z(N) 1.736; $r_{N–H}$ 1.004 Å
II		**XII**	
	$\Delta E_{complex}$ –80.4 kJ mol^{-1}; E_{HOMO} –9.83 eV; q(N) –0.850; q(NH$_2$) –0.184; Cp_z(N) 1.058; $r_{N–H}$ 1.003 Å		$\Delta E_{complex}$ –69.3 kJ mol^{-1}; E_{HOMO} –6.21 eV; q(N) –0.886; q(NH$_2$) –0.214; Cp_z(N) 0.368; $r_{N–H}$ 1.002 Å
III		**XIII**	
	$\Delta E_{complex}$ –85.1 kJ mol^{-1}; E_{HOMO} –10.03 eV; q(N) –0.941; q(NH$_2$) –0.130; Cp_z(N) 0.214; $r_{N–H}$ 0.995 Å		$\Delta E_{complex}$ –118.0 kJ mol^{-1}; E_{HOMO} –5.70 eV; q(N) –0.873; q(NH$_2$) –0.207; Cp_z(N) 0.644; $r_{N–H}$ 1.003 Å

Table 1. (Contd.)

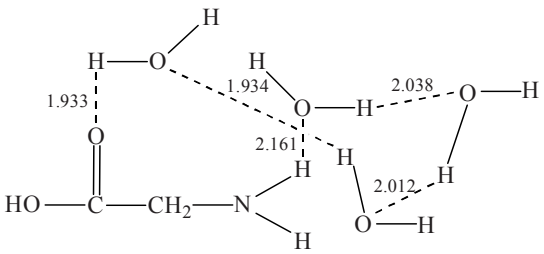
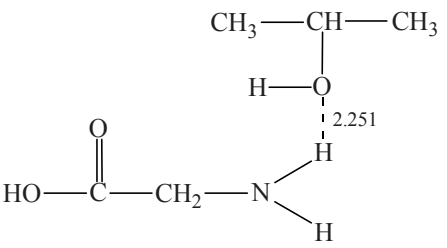
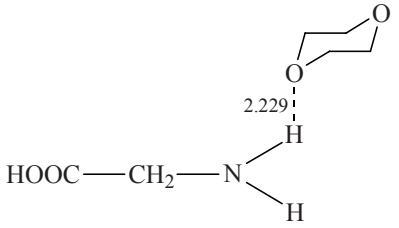
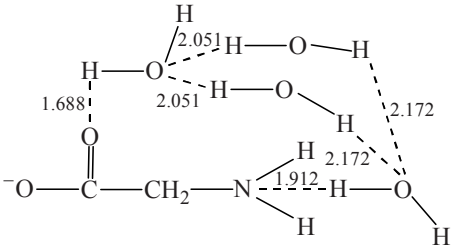
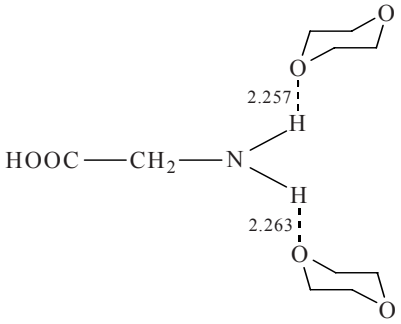
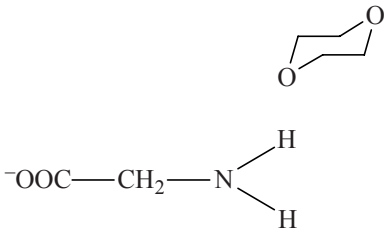
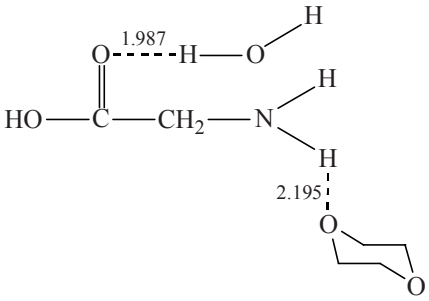
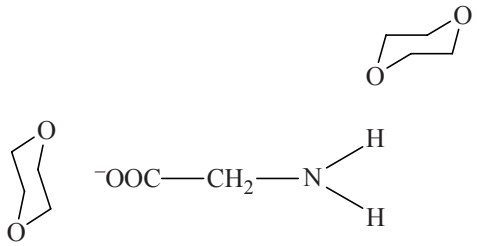
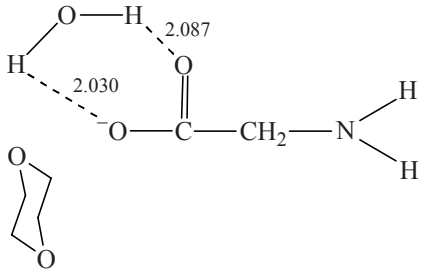
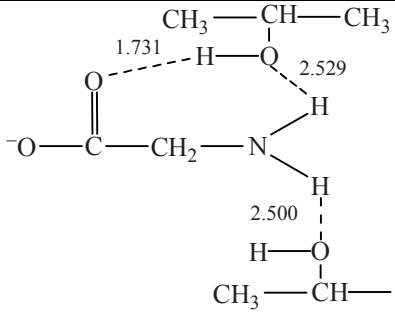
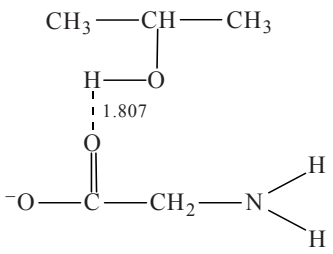
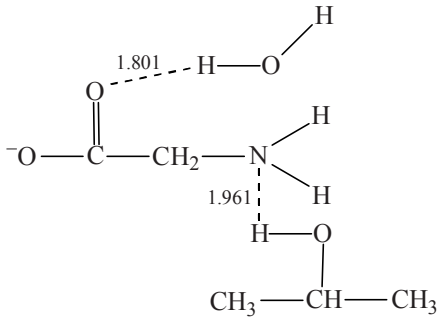
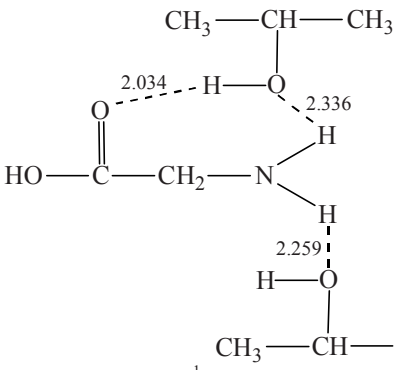
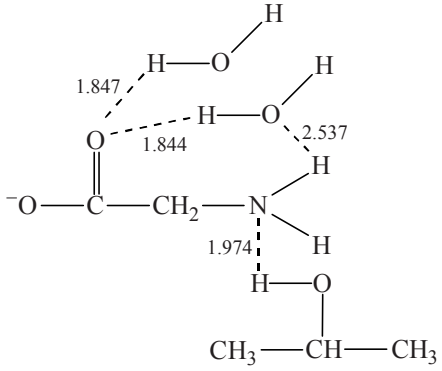
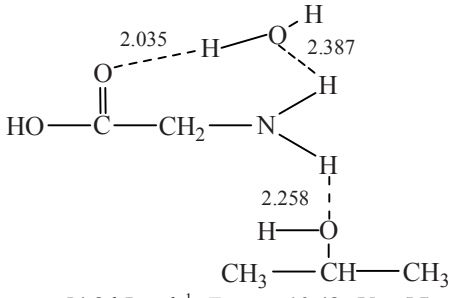
Comp. no.	Glycine molecular form	Comp. no.	Glycinate anion
IV		**VIII**	
	$\Delta E_{complex}$ –148.4 kJ mol^{-1}; E_{HOMO} –10.88 eV; q(N) –0.909; q(NH$_2$) –0.141; Cp$_z$(N) 0.188; $r_{N–H1}$ 1.004 Å; $r_{N–H2}$ 1.002 Å		$\Delta E_{complex}$ –24.7 kJ mol^{-1}; E_{HOMO} –10.52 eV; q(N) –0.857; q(NH$_2$) –0.115; Cp_z(N) 1.808; $r_{N–H}$ 1.003 Å
V		**XIV**	
	$\Delta E_{complex}$ –21.7 kJ mol^{-1}; E_{HOMO} –10.62 eV; q(N) –0.857; q(NH$_2$) –0.122; Cp_z(N) 0.734; $r_{N–H}$ 1.002 Å		$\Delta E_{complex}$ –158.4 kJ mol^{-1}; E_{HOMO} –5.72 eV; q(N) –0.926; q(NH$_2$) –0.210; Cp_z(N) 0.236; $r_{N–H}$ 1.004 Å
VI		**XV**	
	$\Delta E_{complex}$ –35.5 kJ mol^{-1}; E_{HOMO} –10.32 eV; q(N) –0.892; q (NH$_2$) –0.125; Cp_z(N) 1.372; $r_{N–H}$ 1.002 Å		$\Delta E_{complex}$ 45.6 kJ mol^{-1}; E_{HOMO} –4.77 eV; q(N) –0.881; q(NH$_2$) –0.215; Cp_z(N) 0.756; $r_{N–H}$ 1.005 Å
VII		**XVI**	
	$\Delta E_{complex}$ –55.6 kJ mol^{-1}; E_{HOMO} –10.44 eV; q(N) –0.874; q(NH$_2$) –0.116; Cp_z(N) 0.144; $r_{N–H}$ 1.002 Å		$\Delta E_{complex}$ 5.8 kJ mol^{-1}; E_{HOMO} –4.06 eV; q(N) –0.951; q(NH$_2$) –0.222; Cp_z(N) 0.390; $r_{N–H}$ 1.005 Å

Table 1. (Contd.)

Comp. no.	Glycine molecular form	Comp. no.	Glycinate anion
XVII	 $\Delta E_{complex}$ –44.0 kJ mol^{-1}; E_{HOMO} –5.67 eV; q(N) –0.864; q(NH$_2$) –0.201; Cp_z(N) 1.148; $r_{N–H}$ 1.004 Å	**XIX**	 $\Delta E_{complex}$ –5.6 kJ mol^{-1}; E_{HOMO} –5.10 eV; q(N) –0.908; q(NH$_2$) –0.219; Cp_z(N) 0.550; $r_{N–H}$ 1.003 Å
XVIII	 $\Delta E_{complex}$ –10.5 kJ mol^{-1}; E_{HOMO} –5.31 eV; q(N) –0.868; q(NH$_2$) –0.206; Cp_z(N) 0.434; $r_{N–H}$ 1.004 Å	**XX**	 $\Delta E_{complex}$ –46.4 kJ mol^{-1}; E_{HOMO} –5.48 eV; q(N) –0.930; q(NH$_2$) –0.211; Cp_z(N) 0.056; $r_{N–H}$ 1.004 Å
IX	 $\Delta E_{complex}$ –54.8 kJ mol^{-1}; E_{HOMO} –10.46 eV; q(N) –0.887; q(NH$_2$) –0.126; Σ Cp_z(N) 0.848; $r_{N–H}$ 1.002 Å	**XXI**	 $\Delta E_{complex}$ –103.7 kJ mol^{-1}; E_{HOMO} –5.93 eV; q(N) –0.944; q(NH$_2$) –0.206; Cp_z(N) 0.202; $r_{N–H}$ 1.004 Å
X	 $\Delta E_{complex}$ –54.8 kJ mol^{-1}; E_{HOMO} –10.48 eV; q(N) –0.886; q(NH$_2$) –0.126; Cp_z(N) 1.938; $r_{N–H}$ 1.002 Å		

the complexes of 1:1 or 1:2 composition by hydrogen bonding with water, 2-propanol, and dioxane. But it does not form complexes where it would be the H-acceptor. Among the studied solvatocomplexes with uncharged form of glycine the most stable one is the complex with four water molecules **IV**, the least advantageous energetically one is the complex with one dioxane molecule **V**. The complex with dioxane of 1:2 composition **VI** is more stable. When one dioxane molecule was replaced by a molecule of water the solvatocomplex **VII** of higher stability formed. In this case the hydrogen bond involved the carbonyl oxygen atom like in the case of glycine complex with one water molecule **I**. The increase in the number of water molecules in the solvatocomplexes of molecular form of glycine **I**–**IV** leads to the stabilization that is revealed in a sharp increase in the complex energy of formation (negative). In the systems **II**–**IV** a tendency was observed to form cyclic structures by formation of hydrogen bonds with involvement of carbonyl oxygen atom, water molecules, and hydrogen atom of the amino group.

The 1:1 complex of glycine molecule with 2-propanol **VIII** is less stable than the complex of the same composition with water **I**, but more stable than the complex with dioxane **V**. The complex (Gly)(*i*-PrOH)$_2$ **IX** includes a seven-membered ring formed due to binding of the 2-propanol hydrogen by carbonyl oxygen. Replacement of one alcohol molecule by water molecule in **X** does not alter the complex structure and does not affect the complex energy of formation.

The solvatocomplexes of glycinate ion (Table 1, **XI**–**XXI**) are of great interest from a viewpoint of reactivity because existing experimental observations show that in water–organic media the rate of reaction of acylating agents with the glycine anion is much higher than with its unionized molecule [1–5].

Our calculations show that the glycine anionic form unlike the molecular one forms with one and two dioxane molecules relatively unstable structures **XV** and **XVI**, respectively, with $\Delta E_{complex} > 0$. Among the complexes with dioxane **XV**–**XVII** listed in Table 1 the stable one is **XVII** containing a ring with the deprotonated carboxylic group formed by water molecule in the presence of dioxane ($\Delta E_{complex}$ = –44 kJ mol^{-1}). Interestingly in the absence of dioxane the glycinate ion forms with one water molecule complex **XIb** of similar structure with $\Delta E_{complex}$ = –14.2 kJ mol^{-1}. According to the calculations, the dioxane molecule is not involved into hydrogen bonding. A significant increase in the energy of formation of complex **XVII** over that of the complex **XIb** can originate from the weak interaction of the hydrogen bond type between water and dioxane molecules [10].

Two water molecules form with glycinate anion rather stable complex **XII**, therewith one water molecule forms cyclic structure like in the complex **XVII**. The complexes of glycinate ion **XIII** and **XIV** consist of complex cycles whose stability grows with the increase in the number of water molecules in the solvate shell from 3 to 4.

2-Propanol forms with the glycine anione form complexes **XVIII** and **XIX** of respectively 1:1 and 1:2 composition with relatively low values of $\Delta E_{complex}$ (–10.5 and –5.6 kJ mol^{-1}, respectively). The involvement of water molecules into the complex formation increases stability of complexes **XX**, **XXI**: for the structure (Gly$^-$)(H$_2$O)$_2$(*i*-PrOH), $\Delta E_{complex}$ = –103.7 kJ mol^{-1}.

The results of calculations lead to some conclusions. As known [5], a series of the reactions of acyl transfer, e.g., acylation of aromatic and alkylaromatic amines, arenecarbohydrazines etc. proceed under orbital control, that is, the rate of these reactions is defined by the interaction of the amine HOMO and acylating agent LUMO. The data listed in Table 1 shows that E_{HOMO} of the studied solvatocomplexes of glycine molecule vary in the range –9.83 to –10.88 eV while for the glycinate ion this value fall to the range –5.1 to –6.2 eV. The energy gap $\Delta E = |E_{HOMO}(\text{amine}) - E_{LUMO}(\text{acylating agent})|$ for the reactions of the glycine anionic form is much smaller than for the uncharged form confirming the conclusion made on the basis of kinetic experiment about higher rate of N-acylation of the glycinate anion as compared with unionized molecule. As seen from Table 1, the N–H bond lengths in the glycinate anion amino group are practically independent of the complex composition: r_{N-H} = 1.002–1.005 Å. The charge on the amino group $q(NH_2)$ in the considered complexes of glycinate ion also alter insignificantly: –0.201 to –0.222. More significant is the variation of the charge on the nitrogen atom: q(N) is –0.857 to –0.951, but the latter does not depend on the nature and stoichiometric composition of the complex. Thus, the above listed parameters cannot be considered as characterizing the reactivity of these complexes.

The decrease in the rate constant of glycine anion N-acylation at the increase of the water fraction in its mixture with dioxane can be understood as follows.

Inasmuch as dioxane does not form complexes with the glycine anionic form prevailingly entering into the acylation, the complex formation occurs with the second component of the binary solvent (water). The energtically most advantageous are the glycinate anion complexes with three and four water molecules **XIII** and **XIV**. However, the reactivity of complex **XIV** should be diminished because the formation of the hydrogen bond with the fourth water molecule occurs on account of the nitrogen lone electron pair. The necessity of the cleavage of this bond at the formation of the transition state leads to the increase in activation energy and decrease in the rate constant. Therefore among the studied complexes of the glycinate ion the most reactive one should be the complex of 1:3 composition **XIII**.

As shown earlier [11], the main role in the formation of HOMO of amines plays the nitrogen $2p_z$ orbital. Therefore its contribution to HOMO (Cp_z) can be considered as a characteristic of the solvato-complexes reactivity. Decrease in the contribution of the nitrogen $2p_z$ orbital to HOMO in going from complex **XIII** to **XIV** also points to the diminished reactivity of the latter. One can suggest that with increase in the water fraction in the water–dioxane system the number of reactive complexes **XIII** falls while that of unreactive complexes **XIV** grows resulting in diminished rate of the N-acylation.

When this reaction is carried out in aqueous 2-propanol, the existence of the complexes of glycinate ion both with water and with 2-propanol in equilibrium is possible. The increase in the water content in the binary solvent can shift this equilibrium to the side of the complexes containing more water molecules.

Noteworthy is the tendency in the case of glycinate ion solvatocomplexes with water and 2-propanol to increase in Cp_z at the increase in water fraction in the complex within the series: **XX**, **XXI**, **XII**, **XIII**. Hence the same sequence should exist for the reactivity of the complexes in acylation reaction, that is, the reactivity should increase with the increase in the water fraction in the solvent water–2-propanol, in agreement with the experimental observations [1–5]. From this consideration and from the existing kinetic data it is possible to conclude that in the studied range of composition of the water–2-propanol system the unreactive complex **XIV** is not formed in a significant amount.

Resuming the above said we have to note that the medium effects in the reaction of α-aminoacids display some features connected with their bifunctional nature. As show our results, unlike aromatic, alkylaromatic and aliphatic amines whose reactivity is defined by the specific solvation of the amino group, in the case of the α-aminoacids the complexes with the solvent molecules are formed with the involvement of the carboxy group, and this is reflected in the reaction kinetics.

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