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Effect of Solvation on the Complexation of 18-Crown-6 with Amino Acids in Aqueous–Organic Media

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Abstract—Our own and published data on the effect of mixed solvents on the thermodynamic parameters of molecular complexation of 18-crown-6 with glycine, D,L-alanine, and L-phenylalanine in aqueous ethanol, dimethyl sulfoxide, and acetone have been generalized. In all cases, decrease of the water fraction in mixed solvents increases the exothermic effect of complex formation. The change in the reaction enthalpy is determined mainly by variation of the enthalpies of solvation of the molecular complex and 18-crown-6, whereas the contribution of solvation of the amino acid is insignificant.

Keywords: amino acids, binary solvents, molecular complex formation, solvation, 18-crown-6

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Nowadays, the concept of molecular recognition [1] underlies purposeful syntheses of molecular complexes with a desired combination of properties. Quantitative estimation of the effects of the solvent nature and composition on the stability and energy parameters of the complexes and detection of correlations between the energy parameters of complex formation, dissociation, and solvation, on the one hand, and structure and biological activity of the reactants, on the other, constitute the basis for appropriate choice of solvents to ensure preparation of new molecular complexes with required properties.

Studies on the complexing properties of synthetic macrocycles such as crown ethers capable of recognizing other species make it possible to simulate intricate molecular recognition processes occurring in biological systems [2], as well as to design various molecular devices for modern science and technology [3].

The results of numerous studies on the thermodynamics of molecular complexation with crown ethers in water [4] and pure nonaqueous solvents [5, 6] have been reported. The complexation with crown ethers in water often leads to the formation of unstable molecular complexes, which complicates their study. By contrast, molecular complexes formed by crown ethers in nonaqueous solvents are stable, but experimental studies may be limited due to low solubility of the reactants. Purposeful selection of a binary solvent is expected to ensure optimal conditions for the preparation of crown ether complexes via variation of the solvation parameters of species involved in the complexation equilibrium.

Solov'ev [7] generalized a huge array of relevant thermodynamic data and proposed prognostic mathematic models for the estimation of the stability constants and enthalpies of formation of ionic complexes of crown ethers and cryptands in pure solvents on the basis of the ligand structure in going from one solvent to another and from one cation to another. A correlation was revealed between the change in the Gibbs energy of complex formation and the Gibbs energy of cation transfer from water to a given solvent, and this correlation was used to predict variation in the stability of complexes formed by crown ethers and their macrocyclic and acyclic analogs with alkali and alkaline earth metal and ammonium cations in pure solvents. It was also noted that the solvent effect is related to the electron-donor power of its molecules.

Correlations between various physicochemical properties of aqueous–organic solvents, on the one hand, and thermodynamic parameters of complex formation of crown ethers with metal ions and reactant solvation, on the other, were also analyzed in [8, 9].

We previously studied the complexation of *d*-metal ions with amine and carboxylate ligands [10, 11] and

Table 1. Enthalpies, Gibbs energies, and entropy contributions of the Gibbs energies for the formation of molecular complexes [Gly18C6], [Ala18C6], and [Phe18C6] in aqueous ethanol at 298.15 K

x_{EtOH}, mole fraction	$-\Delta_rH^0$, kJ/mol	$-\Delta_rG^0$, kJ/mol	$-T\Delta_rS^0$, kJ/mol
[Gly18C6]			
0.00	10.83±0.08 [4] 7.3±0.2 [14]	4.5 [4] 4.2 [14]	3.2 [4] 3.1 [14]
0.12 [14]	19.7±0.3	6.8	12.9
0.25 [14]	21.5±0.3	9.3	12.2
0.50 [14]	25.1±0.4	13.0	12.1
0.74 [14]	29.1±0.5	17.2	11.9
0.91 [14]	41.0±0.6	19.9	21.1
1.0 [6]	64.95±0.98	21.71	43.24
[Ala18C6]			
0.0	7.7± 0.5 [15] 5.2 [16] 8.17±0.04 [4]	1.8 [15,16] 2.28 [4]	3.4 [16] 5.9 [4, 15]
0.1 [15]	16.6±0.5	4.6	11.9
0.2 [15]	22.6±0.5	6.6	16.0
0.4 [15]	24.8±0.5	9.9	14.9
0.6 [15]	33.3±0.5	12.1	21.2
1.0 [6]	54.52±2.87	21.06	33.45
[Phe18C6]			
0.0	12.56±1.42 [17, 18] 18.45±1.20 [4]	1.31 [17, 18] 3.82 [4]	11.25 [17, 18] 14.61 [4]
0.1 [17]	11.7±0.3	4.46	7.27
0.2 [17]	15.4±0.4	6.86	8.50
0.4 [17]	24.7±0.2	8.34	16.36
0.6 [17]	27.5±0.2	11.05	16.43
1.0 [6]	56.67±1.08	19.18	37.48

18-crown-6 [12] in mixed aqueous and nonaqueous solvents and found some correlations between the reactant solvation and the stability of the complexes and energy parameters of complexation. In particular, variation of the stability of complexes and complexation enthalpy in transfer from water to aqueous–organic mixtures was shown to be determined by change of the ligand solvation.

We also analyzed how the composition and nature of mixed aqueous–organic solvents affects the stability of molecular complexes between 18-crown-6 and some amino acids [13]. While developing studies in this line [10–13], in the present article we report the results of analysis of our own and published data on the thermodynamics of molecular complex formation between amino acids and 18-crown-6 and solvation of the reactants in aqueous–organic solvents.

Thermodynamic parameters of the complexation. The standard thermodynamic parameters (Δ_rG^0, Δ_rH^0, $T\Delta_rS^0$) for the formation of molecular complexes [Gly18C6], [Ala18C6], and [Phe18C6] in binary mixtures H_2O–EtOH, H_2O–MeAc, and H_2O–DMSO are collected in Tables 1–3.

Table 2. Enthalpies, Gibbs energies, and entropy contributions of the Gibbs energies for the formation of molecular complexes [Gly18C6], [Ala18C6], and [Phe18C6] in aqueous dimethyl sulfoxide at 298.15 K

x_{DMSO}, mole fraction	$-\Delta_rH^0$, kJ/mol	$-\Delta_rG^0$, kJ/mol	$-T\Delta_rS^0$, kJ/mol
[Gly18C6] [19]			
0.1	17.3±1.0	7.3	10.0
0.2	26.5±1.0	10.3	16.2
0.25	30.0±1.0	11.0	19.0
[Ala18C6] [20]			
0.08	15.5±0.5	4.2	11.3
0.17	22.0±0.5	7.7	14.3
0.25	34.0±0.9	8.0	26.0
0.30	35.2±0.9	9.0	26.2
[Phe18C6] [18]			
0.05	7.3±0.5	4.34±1.14	3.0±0.5
0.15	11.9±0.5	7.36±1.14	4.5±0.5
0.25	26.7±0.5	6.85±0.91	19.8±0.5
0.30	30.9±0.5	7.65±0.91	23.3±0.5
0.40	30.6±0.5	6.28±0.91	24.3±0.5

The effects of solvent mixtures H_2O–EtOH, H_2O–DMSO, and H_2O–MeAc on the variation of the thermodynamic parameters for the formation of molecular complexes [Gly18C6], [Ala18C6], and [Phe18C6] are almost similar. Increase in the concentration of the nonaqueous solvent is accompanied by increase of the complexation enthalpy (Tables 1–3); the maximum exothermic effect is observed in H_2O–DMSO, and the minimum, in H_2O–EtOH with analogous composition. The exothermic effect of the formation of complexes [Gly18C6] and [Ala18C6] increases in the series H_2O–EtOH < H_2O–MeAc < H_2O–DMSO.

The Gibbs energy (Δ_rG^0) and its entropy contribution ($T\Delta_rS^0$) increase in absolute value in going from water to aqueous–organic solvents. In all cases, the complexation of 18-crown-6 with the examined amino acids is characterized by predominant enthalpy contribution to the Gibbs energy over the entropy contribution.

The enthalpy–entropy correlations for the formation of molecular complexes [Gly18C6], [Ala18C6], and [Phe18C6] in H_2O–EtOH, H_2O–DMSO, and H_2O–MeAc (Fig. 1) can be approximated by linear dependences $T\Delta_rS^\circ = \alpha\Delta_rH^0 + T\Delta S^0$ with slopes of 0.62 (H_2O–EtOH), 0.80 (H_2O–DMSO), and 0.70 (H_2O–MeAc), regardless of the guest molecule. These findings reflect partial compensation of the enthalpy contribution by entropy, which is referred to as *compensation effect* [4, 21–25].

The effect of the solvent composition on the enthalpy–entropy correlation is obvious. In all cases, the least negative values of Δ_rH^0 and $T\Delta_rS^0$ correspond to binary mixtures with high water content, while the largest negative values are typical of mixtures enriched in nonaqueous component. However, the observed correlations reflect the overall effect on both solvation of the reactants and thermodynamics of complex formation. In order to distinguish the contributions of reactant solvation, which are responsible for the state of the complexation equilibrium, it was necessary to analyze the ratios of the contributions of solvation of 18-crown-6 and amino acids to the change of the thermodynamic parameters in going from water to aqueous–organic mixtures.

Table 3. Enthalpies, Gibbs energies, and entropy constituents of the Gibbs energies for the formation of molecular complexes [Gly18C6] and [Ala18C6] in aqueous acetone at 298.15 K

x_{MeAc}, mole fraction	$-\Delta_r H^0$, kJ/mol	$-\Delta_r G^0$, kJ/mol	$-T\Delta_r S^0$, kJ/mol
[Gly18C6] [14]			
0.08	16.0±0.4	5.81	10.19
0.14	21.0±0.5	7.35	13.65
0.21	23.5±0.5	8.60	14.90
[Ala18C6] [16]			
0.08	15.0±0.5	3.6	11.4
0.17	20.5±0.5	6.1	14.4
0.22	22.0±0.5	7.6	14.4
0.30	28.0±0.5	7.7	20.3

Analysis of the contributions of reactant solvation to the enthalpy of complex formation of 18-crown-6 with amino acids. The enthalpy parameters of the reactants and complexation process were analyzed in keeping with the solvation–thermodynamic approach [10, 11, 26]. The changes in the reaction enthalpy ($\Delta_{tr}H_r^0$) and enthalpies of solvation of the molecular complex {$\Delta_{tr}H^0$([AA18C6])}, amino acid {$\Delta_{tr}H^0$(AA)}, and crown ether {$\Delta_{tr}H^0$(18C6)} upon variation of the solvent composition can be described by Eq. (1), which may be used to calculate $\Delta_{tr}H^0$([AA18C6]) and analyze the ratio of the enthalpy contributions if the reactants to $\Delta_{tr}H_r^0$.

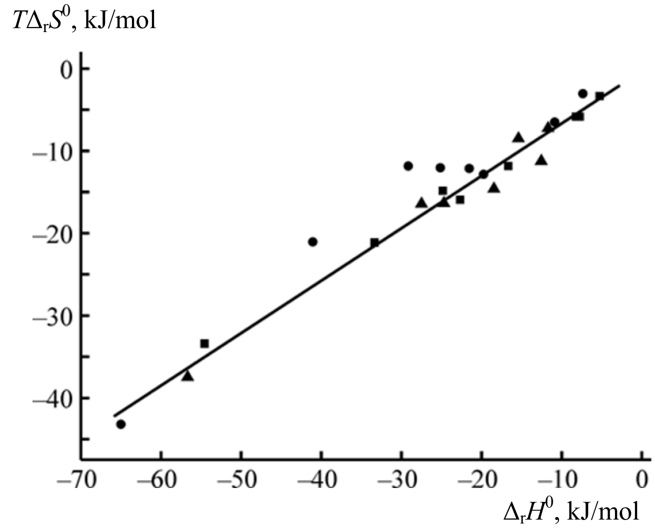

Fig. 1. Example of the enthalpy–entropy compensation effect for the formation of complexes [Gly18C6] (circles), [Ala18C6] (squares), and [Phe18C6] (triangles) in the system H_2O–EtOH.

$$\Delta_{tr}H_r^0 = \Delta_{tr}H^0([\mathrm{AA18C6}]) - \Delta_{tr}H^0(\mathrm{AA}) - \Delta_{tr}H^0(\mathrm{18C6}). \quad (1)$$

Figures 2 and 3 illustrate the dynamics of the contributions of reactant solvation to the enthalpy of formation of molecular complexes [Gly18C6] and [Ala18C6] in H_2O–EtOH, H_2O–DMSO, and H_2O–MeAc. In all binary mixtures, increase in the concentration of the organic component leads to increase of the positive values of the enthalpy of transfer of the macrocycle and molecular complex, and the $\Delta_{tr}H^0$(18C6) value grows more rapidly than does $\Delta_{tr}H^0$[AA18C6], while the change in $\Delta_{tr}H^0$(AA) is close to zero; as a result, the reaction becomes more exothermic.

Analysis of the dependences for the enthalpy parameters of formation of molecular complexes [Gly18C6] and [Ala18C6] (Fig. 2, 3) shows that the main contribution to the change of the reaction enthalpy is provided by different variations of the enthalpies of solvation of the molecular complex and crown ether {$\Delta_{tr}H^0$([AA18C6]) – $\Delta_{tr}H^0$(18C6)} and that the contribution of variation in the solvation of the amino acid is insignificant.

It was also interesting to compare the ratio of the contributions of reactant solvation to the change of the Gibbs energy [13, 15, 17] and the enthalpy of formation of complexes [Gly18C6] and [Ala18C6] in H_2O–EtOH and H_2O–DMSO. In both binary mixtures, the positive values of $\Delta_{tr}Y^0$(AA) and $\Delta_{tr}Y^0$(18C6) ($\Delta_{tr}Y^0$ = $\Delta_{tr}G^0$, $\Delta_{tr}H^0$) increased in parallel with the concentration of the organic component. This indicates

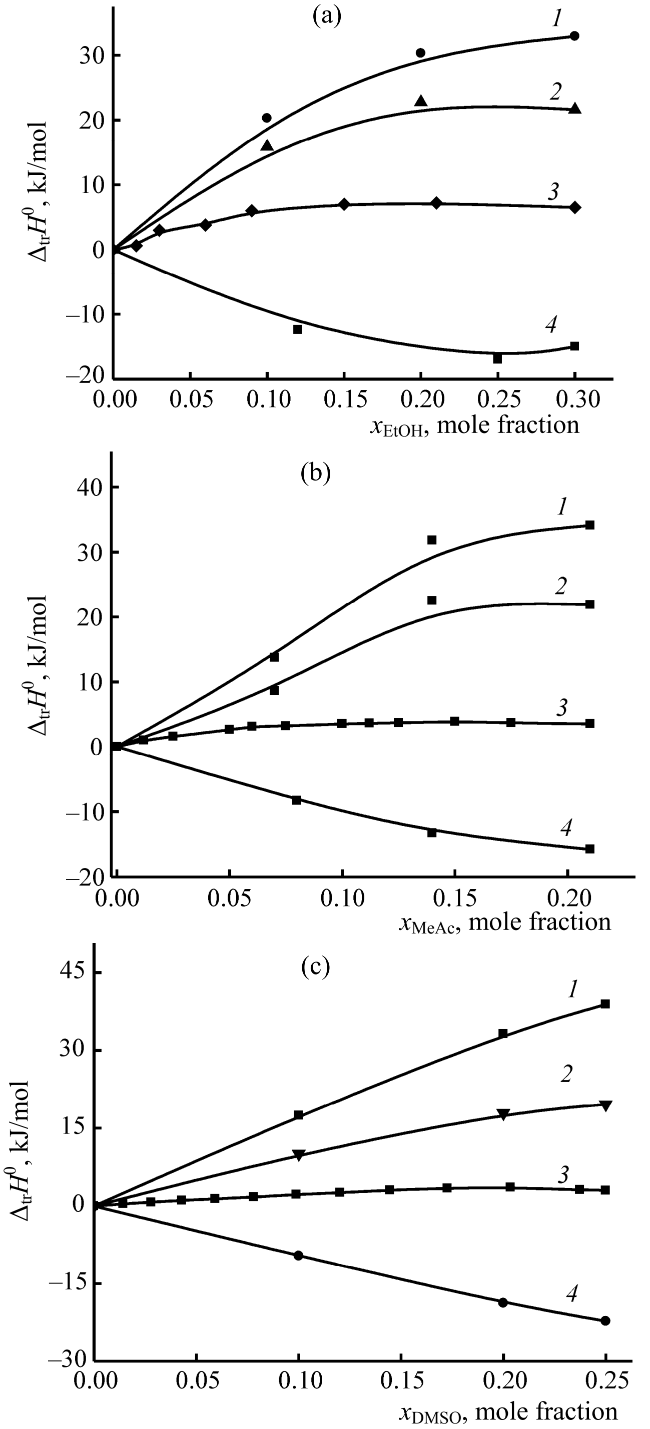

Fig. 2. Enthalpy parameters for the formation of complex [Gly18C6] and reactant solvation in the systems (a) H_2O–EtOH, (b) H_2O–MeAc, and (c) H_2O–DMSO: (*1*) $\Delta_{tr}H^0$(18C6) [27–30], (*2*) $\Delta_{tr}H^0$([Gly18C6]), (*3*) $\Delta_{tr}H^0$(Gly) [31–33], (*4*) $\Delta_{tr}H^0_r$ [14, 19].

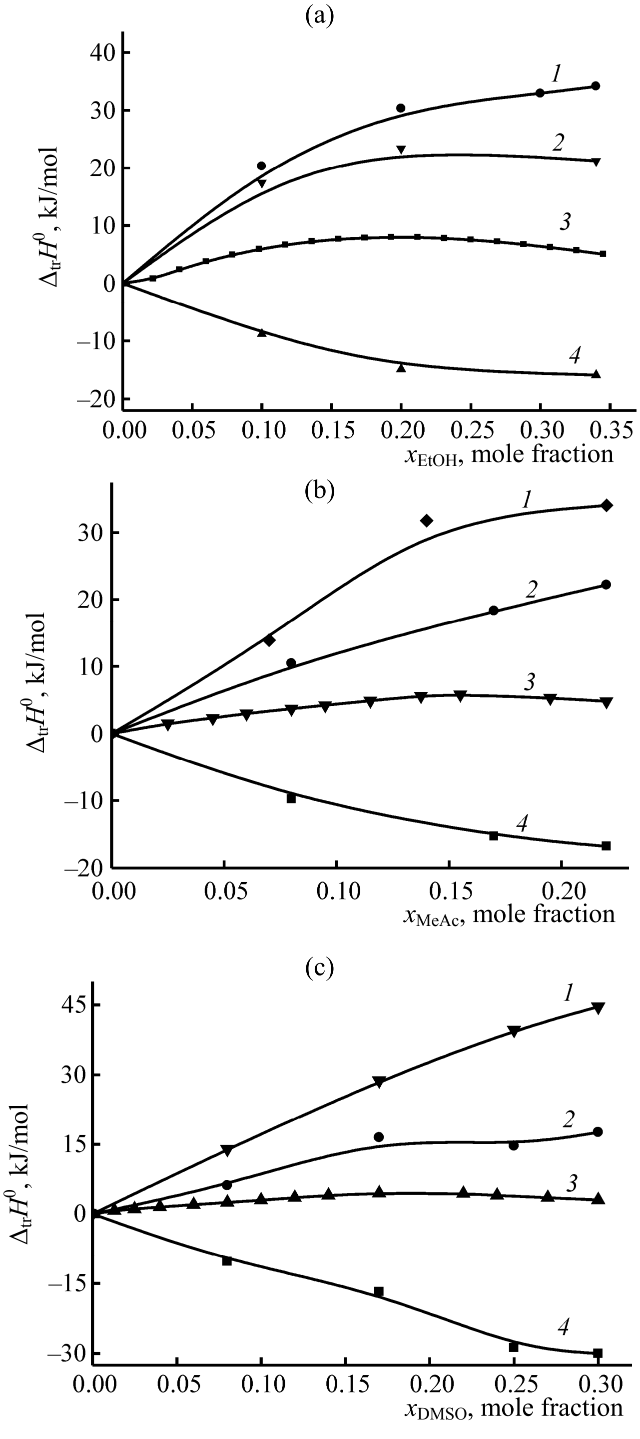

Fig. 3. Enthalpy parameters for the formation of complex [Ala18C6] and reactant solvation in the systems (a) H_2O–EtOH, (b) H_2O–MeAc, and (c) H_2O–DMSO: (*1*) $\Delta_{tr}H^0$(18C6) [27–30], (*2*) $\Delta_{tr}H^0$([Ala18C6]), (*3*) $\Delta_{tr}H^0$(Ala) [34–36], (*4*) $\Delta_{tr}H^0_r$ [15, 16, 20].

weaker solvation of the initial reactants (amino acid and crown ether) in H_2O–EtOH and H_2O–DMSO as compared to pure water, which leads to increase in the stability of the complexes and heat effect of the complex formation. Close values of $\Delta_{tr}Y^0$([AA18C6]) and $\Delta_{tr}Y^0$(18C6) suggest the determining role of the macrocycle solvation shell in the formation of the solvation shell of the complex.

Unlike $\Delta_{tr}H_r^0$, the ratio of the thermodynamic contributions of the reactants to $\Delta_{tr}G_r^0$ is determined by the solvation of amino acid, whereas the contribution of the Gibbs energy of macrocycle transfer is almost zero. As concerns reactant solvation effect on the reaction enthalpy, increase in the endothermicity of the amino acid transfer is insignificant as compared to the change of $\Delta_{tr}H^0$(18C6). Presumably, considerable energy consumption for decomposition of the macrocycle solvation shell, which is accompanied by transfer of molecules of water and organic solvent from the macrocycle solvation shell to bulk solution, is completely compensated by increase of the entropy contribution in the Gibbs energy of solvation of 18-crown-6 [37, 38]. As a result, the change in the Gibbs energy of crown ether transfer is close to zero.

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