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Complexation between Iron(III) and Nicotinamide in Aqueous Dimethyl Sulfoxide

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Abstract—The stability constants of iron(III) complexes with nicotinamide in water–DMSO mixtures (X_{DMSO} = 0–0.75) were determined by potentiometric titration at 25.0 ± 0.1°C and an ionic strength of 0.25 ($NaClO_4$). The contributions from the solvation of the reagents to the Gibbs energy of complexation transfer were analyzed. The stabilities of iron(III), copper(II), and silver(I) complexes with nicotinamide were compared. The observed decrease in the stability constants was attributed to the stabilization of iron(III) solvate complexes as the DMSO content increases.

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Variation in the solvent composition can substantially influence the thermodynamics of a reaction, the chemical affinity of the reactants, and the strengths of newly formed bonds. For instance, transsolvation of the reactants can change their charge distribution and molecular geometries and, ultimately, the stability of the resulting complex. That is why the modern chemistry of solutions is focused on the study of solvent effects during complexation processes in solution.

Only a few studies [1, 2] have been devoted to complexation of iron(III) in aqueous organic solvents. The thermodynamics of equilibria in the systems nicotinamide–copper(II) and nicotinamide–silver(I) have been investigated in [3–5]. The stability constants of iron(III) complexes with nicotinamide in aqueous ethanol at different ethanol contents are cited in [2]. Here we studied the influence of the composition of a water–DMSO solvent on the stability of an iron(III) complex with nicotinamide.

This study is of obvious practical value because the iron(III) complex with nicotinamide is used as the antianemia drug feramid. In the feramid form, iron is absorbed several times better than its ionic forms. In addition, an iron complex with a carrier ligand should be as stable as to provide a therapeutic concentration of iron in blood but prevent excessive (above permissible values) accumulation of its ions in the alimentary canal.

EXPERIMENTAL

The stability constants of iron(III) complexes with nicotinamide were determined by potentiometric titration as described in [2]. A potentiometric cell was charged with 0.0104–0.0294 M $Fe(ClO_4)_3$ and 0.0191–0.0877 M $HClO_4$; 0.1000 ± 0.5% M nicotinamide was used as a titrant. Potential differences between a working glass electrode and a silver-chloride reference electrode were measured to within ±0.1 mV at 25.0 ± 0.1°C and an ionic strength of 0.25 ($NaClO_4$); the mole fraction of DMSO (X_{DMSO}) in the mixed solvent was varied from 0 to 0.75.

The efficiency of the electrode system was checked against standard buffer solutions (pH 1.68–12.50) and perchloric acid solutions with known concentrations. The Nernst slope was 59.3 ± 1.5 mV. To eliminate the diffusion potential, the silver-chloride electrode was filled with 0.1 M LiCl in an appropriate mixed solvent.

Working solutions were prepared from deaerated twice-distilled water. Nicotinamide (special purity grade) was used without additional purification. Sodium perchlorate (high-purity grade) was twice recrystallized and dried at 90°C to a constant weight. Dimethyl sulfoxide was distilled in vacuo. The water content of DMSO was determined using the Fischer titration [6] and taken into account in the preparation of working solutions.

Iron(III) perchlorate was synthesized by adding $HClO_4$ to $Fe(OH)_3$ (prepared from $FeCl_3$ and NaOH). The concentration of iron was determined by spectrophotometry for its colored thiocyanate complex (λ = 490 nm) [6].

The absence of side redox processes was confirmed by the following data: (1) nicotinamide can be oxidized in this system only with strong oxidants (e.g., HNO_3) in a boiling aqueous solvent [7, 8] and (2) DMSO acts as a reducing agent only toward compounds with high oxidative potentials under drastic conditions [9].

Stability constants of FeL^{3+}, CuL^{2+} [3], and AgL^{+} [4] in water–DMSO mixtures

$\log K$	X_{DMSO} *				
	0	0.1	0.3	0.5	0.75
$\log K_{FeL}$	4.17 ± 0.08	3.62 ± 0.10	2.72 ± 0.08	2.50 ± 0.11	2.03 ± 0.07
$\log K_{CuL}$ **	1.55 ± 0.05	1.57 ± 0.05	1.66 ± 0.05	1.56 ± 0.05	1.45 ± 0.05
$\log K_{AgL}$ **	1.67 ± 0.02	1.70 ± 0.02	1.46 ± 0.02	1.09 ± 0.02	0.84 ± 0.02

Notes: * X is the mole fraction of DMSO.

** The data for CuL and AgL are taken from [3] and [4], respectively.

RESULTS AND DISCUSSION

The titration data were used to determine the stability constants of mono- and biligand complexes of iron(III) and the stability constant of iron(III) monohydroxo complex (from a different informative area of the titration curve).

The titration data were processed with the PHMETR program [10] for the following equilibria [11]:

$$H^+ + L \rightleftharpoons HL^+, \quad (1)$$

$$Fe^{3+} + L \rightleftharpoons FeL^{3+}, \quad (2)$$

$$Fe^{3+} + 2L \rightleftharpoons FeL_2^{3+}, \quad (3)$$

$$Fe^{3+} + H_2O \rightleftharpoons FeOH^{2+} + H^+, \quad (4)$$

$$Fe^{3+} + 2H_2O \rightleftharpoons Fe(OH)_2^+ + 2H^+, \quad (5)$$

$$FeOH^{2+} + L \rightleftharpoons FeOHL^{2+}, \quad (6)$$

$$Fe(OH)_2^+ + L \rightleftharpoons Fe(OH)_2L^+. \quad (7)$$

The protonation constants of nicotinamide were taken from [12]. The titration was carried out in the pH range from 1.5 to 2.5. Under these conditions, the yields of $Fe(OH)_2^+$, $Fe(OH)_3$, $FeOHL^{2+}$, and $Fe(OH)_2L^+$ were no higher than 2%. Since the calculation without equilibria (5)–(7) made no significant change in the final result, we excluded them from consideration when constructing an accurate model of the system and finding the absolute minimum. The stability constants of the monohydroxo and bis(nicotinamide) complexes of iron(III) cannot be determined with a sufficient accuracy because of their low yields and are not presented in this study.

Nicotinamide contains two fragments suitable for coordination to metals: the amide group and the N atom of the heterocycle. An analysis of the IR spectra of nicotinamide and its metal complexes revealed its monodentate coordination to metal atoms through the nitrogen heteroatom (the absorption peak of the amide group experiences no shift upon the complexation) [13].

The results obtained and the stability constants of nicotinamide complexes of copper(II) [3] and silver(I) [4] and protonated nicotinamide in water–DMSO are given in table.

The errors in the $\log K_{FeL}$ values constitute a confidence interval calculated from the t-test for three to five runs and a confidence probability of 0.95.

Any of the complexes under consideration (except for CuL^{2+}, which shows a small stability peak at $X_{DMSO} = 0.3$) becomes less stable as X_{DMSO} increases. This is mainly attributable to the stabilization of solvate complexes of metal ions with an increase in X_{DMSO} because DMSO is superior to water in complexing ability and the donor number of the mixed solvent is increased.

An iron(III) ion is a harder Lewis acid than silver and copper ions. Because of this, an interaction of an iron(III) ion with the O atom of DMSO (a hard Lewis base) becomes more probable. Apparently, this interaction additionally stabilizes iron complexes with DMSO and partially decomposes hydrogen-bonded water–DMSO associates (their content in solution decreases with an increase in X_{DMSO}).

Based on thermodynamic data for drugs, one can further test them in vitro and in vivo. For instance, the iron complex with nicotinamide becomes less stable as the DMSO content increases, which makes it possible to employ this complex as an antianemia drug with DMSO as a membranotropic agent.

Using the known thermodynamic relationships

$$\Delta G_r = -RT\ln K,$$

$$\Delta_{tr}G_r = \Delta G_{rS} - \Delta G_{rW},$$

(where ΔG_{rW} and ΔG_{rS} are the Gibbs energies of complexation in water and a mixed solvent, respectively), we calculated the Gibbs energies of complexation transfer from water to a water–DMSO mixture from the stability constants of the nicotinamide complex of iron(III).

Using the Gibbs energies of the transfer of the complexation between iron and nicotinamide [14], one can estimate the Gibbs energy difference between the transfer of the complex ion and the transfer of the complex-

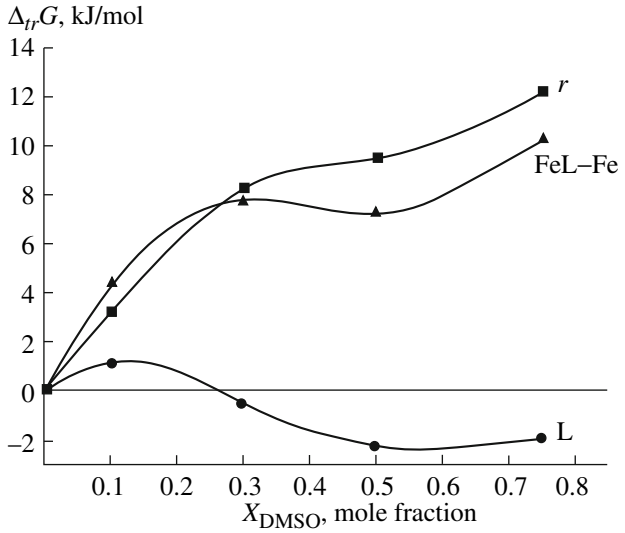

Fig. 1. Gibbs energies of complexation transfer (r) and ligand transfer (L) [14] and the difference between the Gibbs energies of transfer of the complex and central ions (FeL–Fe) from water to water–DMSO mixtures.

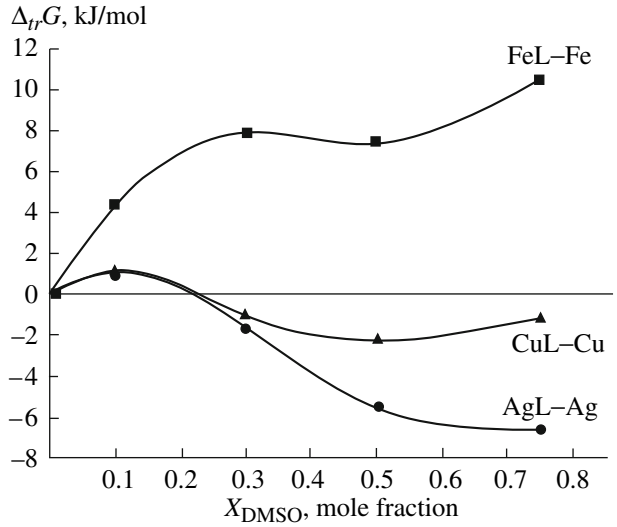

Fig. 2. Difference between the Gibbs energies of transfer of the complex and central ions for iron(III), copper(II) [3], and silver(I) [4].

ing ion (the ionic component of the Gibbs energy of complexation transfer) by the equation

$$\Delta_{tr}G_{\mathrm{FeL}} - \Delta_{tr}G_{\mathrm{Fe}} = \Delta_{tr}G_r + \Delta_{tr}G_{\mathrm{L}}.$$

The results obtained are shown in Fig. 1.

Some stabilization of nicotinamide with an increase in the DMSO content lowers the stability of its complexes. However, the Gibbs energy of complexation transfer for almost any X_{DMSO} is mainly contributed by the ionic component.

It can be seen in Fig. 1 that the solvation difference between the central and complex ion substantially changes with an increase in the DMSO content (compared to water). The fact that the transfer of the iron ion from water to DMSO is thermodynamically more favorable than the transfer of the complex ion can be explained by considerable desolvation of the central ion upon its complexation with nicotinamide in DMSO.

For comparison, analogous dependences of the ionic components of the Gibbs energy of complexation transfer for copper(II) [3] and silver(I) complexes with nicotinamide [4] are shown in Fig. 2.

According to Fig. 2, the increase in the coordination number of the metal ion (Ag < Cu < Fe) favors its transfer from water to water–DMSO mixtures rather than the transfer of the corresponding complex ion. Apparently, the replacement of water by DMSO creates steric hindrances to the construction of the first solvation shell of the complex ion because solvent molecules cannot be accommodated in the octahedral spatial configuration of the iron(III) ion, which already contains a large nicotinamide molecule. Similar steric effects are less characteristic of the square configuration of the copper(II) ion and the linear configuration of the silver(I) ion. This subject has been recently discussed in detail in [15].

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