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Hydrophilicity and Acid Hydrolysis of Water-Soluble Antibacterial Iron(II) Schiff Base Complexes in Binary Aqueous Solvents[1]

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Abstract—Kinetics of acid hydrolysis of seven antibacterial iron(II) Schiff base complexes has been studied. The Schiff base ligands were derived from sodium 2-hydroxybenzaldehyde-5-sulfonate and a series of amino acids. The hydrolysis rate is studied by spectrophotometric method and compared with complex hydrophilicity. Addition of the organic co-solvent, dimethylsulfoxide or *n*-propanol, significantly accelerates the hydrolysis.

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Recently, the Schiff bases have been recognized as important agents in homogeneous and heterogeneous catalysis [1]. In particular, they catalyze reactions of epoxidation of alkenes [2], cyclopropanation [3], asymmetric hydrosilylation of ketones [4], selective oxidation of alcohols into corresponding carbonyl compounds [5], controlled ring-opening polymerization [6], hydrogenation of benzene under mild conditions [7], hydrogenation of ketones [8], Suzuki cross-coupling reaction under ambient condition [9], and enantioselective oxidation of methyl aryl sulfides [10]. Furthermore, transition metal complexes of the Schiff bases have attracted attention due to their potential biological activity (antifungal, antibacterial, anticancer, and herbicidal) [11]. It has been found that complexes of the Schiff bases derived from salicylic aldehyde can specifically cleave DNA [12–14]. Water-soluble complexes of the sulfonate-substituted Schiff bases act as catalytic antioxidants [15]. Complexes of the Schiff bases composed of amino acids and salicylic aldehyde have gained remarkable attention as intermediates of many metabolic reactions (transamination, decarboxylation, elimination, racemization, and C–C bond cleavage) [16, 17].

Despite the importance of iron complexes with the Schiff bases as synthetic models of the iron-containing enzymes [18–20] and oxidation catalysts, the information available on their acid hydrolysis has been quite scarce [21]. Such kinetic data should allow estimation of the complexes reactivity and will further extend their applications. Substituent and solvent effects on the reactivity of these widely applied chelates are of great interest as well. In this paper, we report on the study of acid hydrolysis kinetics of a series of iron(II) complexes with the amino acid Schiff bases.

The suggested structures of the prepared complexes are given in the Experimental section. Decoloration of their solutions induced by hydrochloric acid indicated the hydrolysis reaction occurring. The typical spectral changes in the presence of HCl are illustrated in Figs. 1 (**I**) and 2 (**VII**).

In order to estimate the complexes hydrophilicity, their solubility in water and aqueous methanol was determined assuming that the ratio of mean activity coefficients in the aqueous and aqueous organic phases was close to unity. The solubility values are reported in Table 1, along with values of the chemical potential of the complex transfer from water into aqueous methanol ($\delta_m\mu^\varphi$). The latter was determined as follows:

$$\delta_m\mu^\varphi = -RT \ln (S_s/S_w),$$

where S_s, solubility in aqueous methanol and S_w, solubility in water. According to the data in Table 1, the complexes hydrophobicity followed the series **I** < **II** < **VI** < **III** < **IV**< **V** < **VII**.

The calculated first-order rate constants of the complexes acid hydrolysis (k_{obs}) are reported in Table 2. The plots of k_{obs} as function of $[H^+]$ (Fig. 3) were linear, $k_{obs} = k_2[H^+]$ (k_2 being the true second-order rate

[1] The text was submitted by the authors in English.

Table 1. Solubility and transfer chemical potential $\delta_m\mu^\varphi$ of complexes **I–VII** in water and water–methanol mixtures at 25°C

Complex	Solubility (g/L)				$\delta_m\mu^\varphi$, kJ/mol		
	MeOH in the solvent, vol %						
	0	10	30	50	10	30	50
I	0.52	0.44	0.37	0.30	0.38	0.83	1.39
II	0.48	0.41	0.34	0.26	0.39	0.83	1.52
III	0.35	0.29	0.21	0.17	0.45	0.61	1.82
IV	0.39	0.33	0.27	0.20	0.41	0.92	1.61
V	0.33	0.28	0.24	0.22	0.41	0.76	1.05
VI	0.40	0.34	0.31	0.20	0.43	0.65	1.77
VII	0.28	0.23	0.18	0.14	0.48	1.04	1.67

Table 2. The observed first-order rate constants ($k_{obs}\times10^5$, s^{-1}) and the calculated second-order rate constants k_2 of the complexes hydrolysis in aqueous solution at varied $[H^+]$. [Complex] = 1.67×10^{-3} mol/L, [I] = 0.5 mol/L, and 298 K

$[H^+]$, mol/L	Complex						
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**
0.050	3.30	3.10	2.99	3.13	3.24	3.62	2.53
0.080	5.56	4.95	4.86	4.93	4.84	6.07	4.27
0.100	6.59	6.27	5.93	6.05	5.81	7.30	5.16
0.133	8.82	8.20	7.88	8.13	7.78	9.61	6.75
0.150	9.84	9.30	8.92	9.15	8.69	11.11	7.63
0.167	11.13	10.48	9.98	10.16	9.69	12.13	8.49
0.183	12.08	11.37	10.70	11.03	10.60	13.42	9.48
$k_2\times10^4$, mol L^{-1} s^{-1}	6.60	6.30	5.09	6.04	5.61	7.34	5.14

constant). Thus, the hydrolysis rate equation was indeed reduced to the pseudo first-order kinetics as follows:

$$r = k_2[H^+][\text{complex}] = k_{obs}[\text{complex}].$$

The derived second-order rate constants increased in the following series: **VII** < **V** < **IV** < **III** < **II** < **I** < **VI.** That series was almost in line with the order of increasing hydrophilicity (see above). Thus, in general, the reactivity towards hydrolysis was lower in the cases of more hydrophobic complexes; we therefore suggested that the hydrolysis rate was controlled by the hydrophobic/hydrophilic characteristics and by hydration of the complexes. The only exception of the observed trend was complex **VI**, showing the fastest hydrolysis but not the highest hydrophilicity. This was due to additional polarization of CH_2OH group (and, therefore, increased hydrophilicity of the complex) in the acidic medium (hydrolysis conditions) as compared to the neutral pH (solubility test conditions).

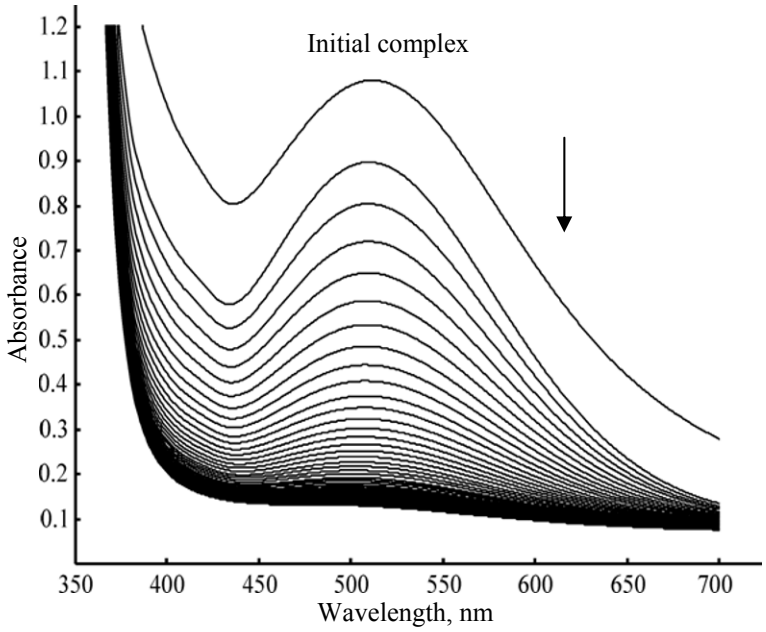


Fig. 1. Spectra of **I** in aqueous solution in the course of acid hydrolysis by HCl. [Complex] = 1.67×10^{-3} mol/L, [HCl] = 0.1 mol/L, [I] = 0.5 mol/L, T = 298 K; scans taken with 1 min intervals.

Table 3. The observed first-order rate constants ($k_{obs}\times10^5$, s^{-1}) of the complexes hydrolysis in DMSO–water media at [complex] = 1.67×10^{-3} mol/L, [HCl] = 0.13 mol/L, and 298 K

DMSO, vol %	Complex						
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**
0	10.82	10.28	9.40	10.01	8.93	12.14	7.72
5	14.26	13.08	11.60	12.37	10.86	15.71	9.15
10	17.30	16.28	14.94	15.43	13.88	18.96	11.60
20	21.50	20.61	17.44	19.78	16.12	23.74	13.51
30	27.08	25.06	21.37	24.68	19.89	29.97	16.45
40	34.47	32.68	26.17	30.61	23.99	37.65	19.66
60	41.94	39.64	32.35	36.59	29.36	46.29	22.77

Table 4. The observed first-order rate constants ($k_{obs}\times10^5$, s^{-1}) of the complexes hydrolysis in *n*-PrOH–water media at [complex] = 1.67×10^{-3} mol/L, [HCl] = 0.13 mol/L, and 298 K

n-PrOH, vol %	Complex						
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**
0	10.82	10.28	9.40	10.01	8.93	12.14	7.72
5	11.77	10.99	9.87	10.65	9.18	12.75	7.90
10	12.29	11.75	10.40	11.16	9.70	13.59	8.10
20	13.09	12.33	10.90	11.93	10.10	14.72	8.37
30	13.69	13.09	11.49	12.58	10.70	15.28	8.91
40	14.58	13.95	12.09	13.28	11.29	16.25	9.39
60	15.40	14.77	12.73	14.15	12.02	17.52	10.51

To elucidate the role of the organic co-solvent in the acid hydrolysis of the studied complexes, the reaction was carried out in a number of binary solvents, mixtures of dimethylsulfoxide DMSO or *n*-propanol PrOH with water, at $[H^+]$ = 0.13 mol/L and 298 K. The respective data are shown in Tables 3 and 4 and in Figs. 4 and 5.

As followed from the collected data, hydrolysis was accelerated in the presence of the both organic co-solvents. The increase of complexes reactivity towards hydrolysis was more pronounced in DMSO as compared with *n*-PrOH; that could be ascribed to the stronger hydrogen bonding of water with DMSO and, therefore, the enhanced chemical potential of water molecules in DMSO–water mixtures.

EXPERIMENTAL

The complexes were prepared as reported elsewhere [22]. Briefly, aqueous solution of iron(II) ammonium sulfate and the amino acid (glycine, L-alanine, L-leucine, L-isoleucine, DL-methionine, DL-serine, or L-phenylalanine) (1:1, mol/mol) was mixed with hot aqueous solution of sodium 2-hydroxybenzaldehyde-5-sulfonate in the presence of

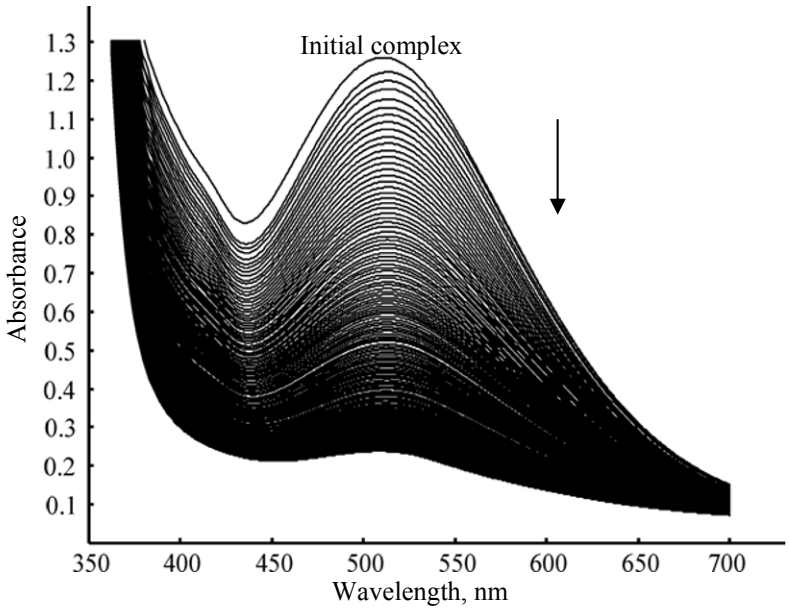


Fig. 2. Spectra of **VII** in aqueous solution in the course of acid hydrolysis by HCl. [Complex] = 1.67×10^{-3} mol/L, [HCl] = 0.1 mol/L, [I] = 0.5 mol/L, T = 298 K; scans taken with 1 min intervals.

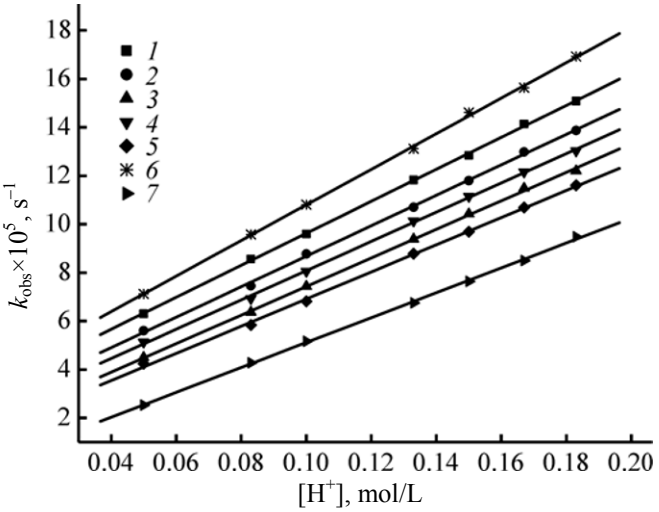


Fig. 3. Hydrolysis rate constant k_{obs} as function of the medium acidity. Aqueous solution, [complex] = 1.67×10^{-3} mol/L, [I] = 0.5 mol/L, and 298 K. Each curve is shifted vertically by an arbitrary increment for better representation. (*1*) complex **I**, (*2*) complex **II**, (*3*) complex **III**, (*4*) complex **IV**, (*5*) complex **V**, (*6*) complex **VI**, and (*7*) complex **VII**.

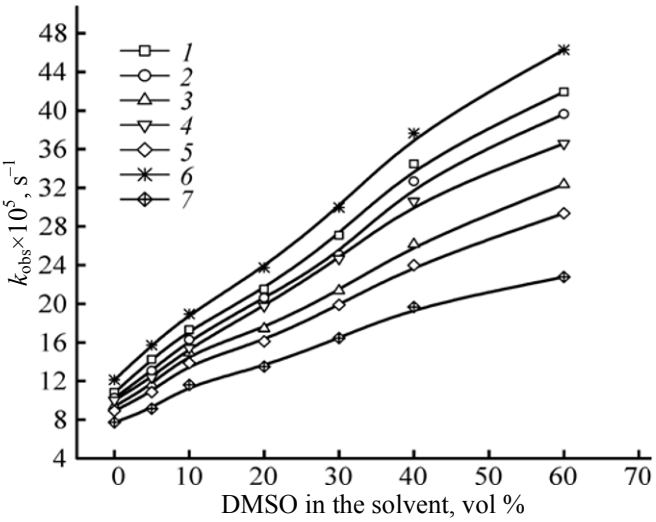
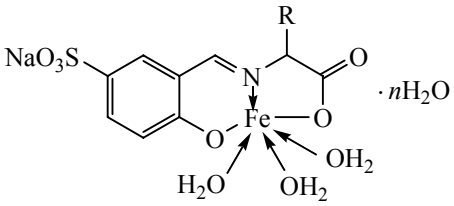


Fig. 4. The rate of acid hydrolysis of complexes **I–VII** as function of the solvent composition. [H$^+$] = 0.13 mol/L, [complex] = 1.67×10^{-3} mol/L, and 298 K. The hydrolyzed complexes are indicated near the respective curves. (*1*) complex **I**, (*2*) complex **II**, (*3*) complex **III**, (*4*) complex **IV**, (*5*) complex **V**, (*6*) complex **VI**, and (*7*) complex **VII**.

glacial acetic acid [to avoid Fe(II) oxidation]. The complexes structure and composition are reported in the scheme below. The characteristics of the complexes including their antibacterial activity were reported previously [22].



R, *n*: H, 1 (**I**); CH_3, 1 (**II**); $(CH_3)_2CHCH_2$, 1 (**III**); $CH_3CH_2CH(CH_3)$, 1 (**IV**); $CH_3SCH_2CH_2$, 3 (**V**); $HOCH_2$, 3 (**VI**); $PhCH_2$, 3 (**VII**).

Kinetic studies were performed under conditions of the pseudo-first order reaction: at 0.05 mol/L ≤ [H$^+$] ≤ 0.183 mol/L, [complex] = 1.67×10^{-3} mol/L, ionic strength of 0.50 mol/L, and T = 298 K. The hydrolysis was monitored by following the decrease in absorbance A with time t at λ_{max} of the respective complex (Perkin Elmer Lambda 35 spectrophotometer). The observed first-order rate constants k_{obs} were calculated via least squares linear fitting of ln $A - t$ data. The effect of organic solvent on the reaction rate was studied in the presence of 0 to 60 vol % of the co-solvent in binary aqueous mixtures, at [H$^+$] = 0.13 mol/L and [complex] = 1.67×10^{-3} mol/L.

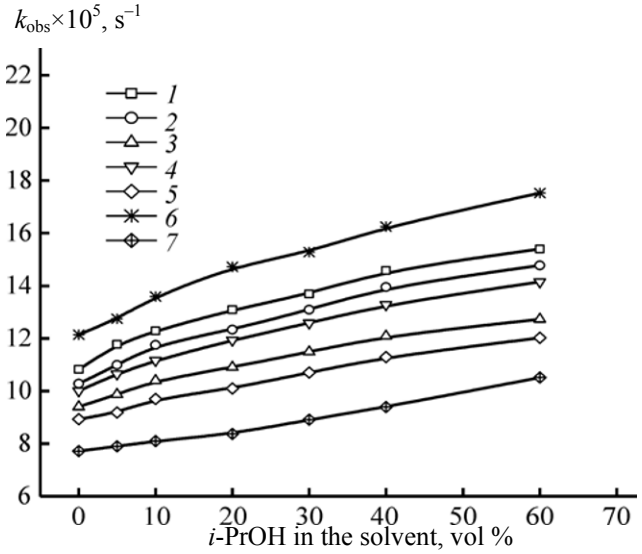


Fig. 5. The rate of acid hydrolysis of complexes **I–VII** as function of the solvent composition. [H$^+$] = 0.13 mol/L, [complex] = 1.67×10^{-3} mol/L, and 298 K. The hydrolyzed complexes are indicated near the respective curves. (*1*) complex **I**, (*2*) complex **II**, (*3*) complex **III**, (*4*) complex **IV**, (*5*) complex **V**, (*6*) complex **VI**, and (*7*) complex **VII**.

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