Solvent Effects on Protonation and Complexation of Penicillamine and Thallium(I) in Different Aqueous Solutions of Methanol

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The protonation equilibria of penicillamine and its complex formation with the Tl(I) ion were studied over a wide range of pH (1 to 11), using a combination of spectrophotometric and potentiometric methods at constant temperature, 25 °C, different methanol−water mixtures [(0 to 45) % v/v], and constant ionic strength (0.1 mol·dm^{-3} sodium perchlorate). Least squares regression calculations are consistent with the formation of TlH_2L^+, TlHL, and TlL^- species, where L^{2-} represents the fully dissociated ligand. The protonation of penicillamine and the formation constants of the formed complexes in different media were analyzed in terms of Kamlet, Abboud, and Taft (KAT) parameters. A single-parameter correlation of the formation constants versus α (hydrogen-bond donor acidity), β (hydrogen-bond acceptor basicity), and π^* (dipolarity/polarizability) are relatively poor in all solutions, but multiparameter correlations represent significant improvements with regard to the single-parameter model. Linear correlation is observed when the experimental log β_{xyz} values are plotted versus calculated ones, while all of the KAT parameters are considered. Finally, the results are discussed in terms of the effect of solvent on protonation and complexation.

Introduction

Thallium compounds are very toxic. They can be released into the environment from industrial operations such as the manufacturing of electronic components, optical lenses, semiconductor materials, alloys, γ radiation detection equipment, coal-burning power plants, cement factories, and so forth.[1−3] Atmospheric thallium contaminates surface soils by deposition allowing for the exposure of humans by oral, dermal, or inhalation routes.[4] The most common nonoccupational sources of thallium exposure are contaminated food crops and tobacco.[5] The dietary intake of thallium(I) has been estimated to be about 2 μg per day,[6] and polluted atmospheres may contribute as much as or more than a normal human diet.[7] After absorption in animals, the thallium ion is widely distributed in the body. Both acute and chronic studies show that the highest concentration in humans is found in the kidney.[8] With chronicity, the centers of concentration shift to include the central nervous system and hair.[8] Little information on the metabolism of thallium has been given.[9] However, experimental evidence suggests that there are some similarities between the ionic transport of the thallium(I) and potassium ions through cell membranes.[10]

The biological effects of thallium(I) have also been thought to be due to its interference with the metabolism of sulfur-containing compounds.[8] Actually, diets high in sulfur-containing compounds, such as penicillamine, cysteine, and so forth, protect rats against chronic thallium(I) poisoning.[11] Sulfur-containing compounds have been the main detoxifying drugs used in the case of poisoning.[8] On the other hand, thallium(I) does not seem to interfere with enzymes that contain sulfur, and the metal ion does not block sulfydryl groups in the skin.[12] Thus, a greater understanding of thallium(I) binding by sulfur-containing compounds would give some insight of the toxicity mechanisms of this ion.

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Now, it is understood that, in proteins, active site cavities of enzymes, and different complexes of nucleotides and nucleosides, the effective dielectric constant is decreased at the ligand−water interface and the activity of water is decreased because of the presence of aliphatic or aromatic side chains of the ligand at the location.[13] Therefore, the interaction of a metal ion with a ligand increases considerably when decreasing the solvent polarity of the medium. This effect is well-established for most metal ion complexes of biological ligands. Hence, knowledge of the physicochemical properties of a solvent to understand the intermolecular interactions between solute−solvent and also solvent−solvent molecules is required for proper laboratory work.

In this work, we have chosen a well-understood system, complexation of thallium(I) with penicillamine[14] in different aqueous solutions of methanol, to show how the solvents and their mixtures with various polarities affect the formation of such complexes. Furthermore, an attempt is performed to describe the variations of the protonation constants of penicillamine in different aqueous solutions of organic media.

Experimental Section

Reagents. Methanol was obtained from Merck as an analytical reagent grade material and was used without further purification. L-Penicillamine (Fluka, analytical reagent grade), $(CH_3)_2C(SH)$-$CH(NH_2)COOH$, was recrystallized from hot water, washed with ethanol, and dried over P_2O_5. Equivalent weights were checked by titration against a standard alkali solution. The stock solution of penicillamine was freshly prepared daily. The NaOH solution was prepared from titrisol solution (Merck). Perchloric acid and thallium(I) nitrate were supplied from Merck (analytical reagent grade) and were used without further purification. Sodium perchlorate (Merck, analytical reagent grade) was vacuumed at room temperature at least 72 h before use. All dilute solutions were prepared from double-distilled water with a specific conductance equal to (1.3 ± 0.1) μS·cm^{-1}.

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Apparatus. The electromotive force, E, was measured using a Metrohm model 781 pH ion meter. The combined glass/pH electrode (model 6.0258.000) was modified by replacing its aqueous KCl solution with 0.01 mol·dm^{-3} NaCl and 0.09 mol·dm^{-3} $NaClO_4$ saturated with AgCl. The electrode was soaked for (15 to 20) min in the water−methanol mixture before potentiometric measurements. All titrations were carried out in a 80 mL thermostatted double-walled glass vessel.

Spectrophotometric measurements were performed on a UV−vis Shimadzu 2100 spectrophotometer with a Pentium 4 computer and using thermostatted matched 10 mm quartz cells. The measurement cell was of a flow type. A peristaltic pump allowed circulation of the solution under study from the potentiometric cell to the spectrophotometric cell, so the absorbance and the electromagnetic force (emf) of the solution could be measured simultaneously. To exclude carbon dioxide from the system, a stream of purified nitrogen was passed through a sodium hydroxide solution and then bubbled slowly through the reaction solution.

Procedure. All measurements were performed at 25 °C and constant ionic strength (0.1 mol·dm^{-3} sodium perchlorate−perchloric acid). The protonation constants were evaluated from measurements of the emf by titration of 25 mL of penicillamine ($5.0 \cdot 10^{-3}$ mol·dm^{-3}) with 0.1 mol·dm^{-3} sodium hydroxide solution both in the same ionic strength and mole fraction of methanol [(0 to 45) % by v/v]. The stability constants of the Tl(I)−penicillamine system were determined from the measurements of absorbance versus emf by titration of a 50 mL acidic solution of Tl(I) ($1.25 \cdot 10^{-3}$ mol·dm^{-3}) with an alkali solution (0.1 mol·dm^{-3} NaOH) of penicillamine [(5.0 to 5.5)·10^{-3} mol·dm^{-3}] both with the same ionic strength and mole fraction of methanol [(0 to 45) % by v/v].

In the first step, the electrode system calibration was performed by Gran's method.[15] For this purpose a measured amount of an acidic solution, at the same conditions of temperature, ionic strength, and solvent composition to be used in later experiments, was placed in the double-wall thermostatted vessel. The electrode was immersed in the solution in the vessel, and the acidic solution was titrated with a strong base (0.1 mol·dm^{-3} NaOH). The potential was allowed to stabilize after each addition of the titrant, and the recorded emf values were then used to obtain $E°$. The procedure was continued to pH ≅ 2. In the second step, 25 mL of an acidic solution (0.01 mol·dm^{-3} $HClO_4$) of penicillamine [(4.0 to 4.5)·10^{-4} mol·dm^{-3}] at the same conditions of temperature, ionic strength, and solvent composition was titrated with a sodium hydroxide solution (0.1 mol·dm^{-3}). In the third step, 50 mL of an acidic solution of Tl(I) ($1.25 \cdot 10^{-3}$ mol·dm^{-3}) was titrated with an alkali solution of the ligand [(5.0 to 5.5)·10^{-3} mol·dm^{-3}], again in the same conditions, and the emf and the absorbance values [in the interval of (250 to 300) nm] were then determined. The procedure was continued up to the required p_cH (around 11).

The recorded emf values were then converted to p_cH (−log [H$^+$]) using the method described in the literature.[16] In acidic solution, the measured potential of the cell, E_{cell}, glass electrode/$HClO_4$, $NaClO_4$ (0.1 M), water−organic solvent//NaCl (0.01 M), $NaClO_4$ (0.09 M)/AgCl, Ag, can be written as

$$E_{cell}\,(\mathrm{mV}) = E°_{cell} + k\log[\mathrm{H^+}] + k\log\gamma_{\mathrm{H^+}} + E_{LJ} \quad (1)$$

where $E°_{cell}$ is the standard potential of the cell, E_{LJ} is the liquid junction potential, $k = 2.303RT/F$ in which R, T, and F have the usual meaning, and γ_{H+} is the activity coefficient of the hydrogen ion, respectively. Difficulties in computing the activity coefficients of hydrogen ion in various aqueous mixtures of organic solvents lead to the measurement of emf versus H$^+$ concentration in solution. Because the ionic strength of the solution is kept constant, so the activity coefficient of hydrogen ion is constant too. The nonideality of solutions is then included in E'_a (the specific constant of the potentiometric cell in the acidic region), so

$$E_{cell} = E'_a + k\log[\mathrm{H^+}] \quad (2)$$

where $E'_a = E°_{cell} + k\log\gamma_{H^+} + E_{LJ}$. The use of a glass electrode (with an aqueous inner solution) in nonaqueous media introduces a deviation from ideality. But, it has been shown that the deviation is negligible and the glass electrode is always usable in such media to measure H$^+$ concentrations with a linear relation of E_{cell} versus log [H$^+$].[17]

In the acidic region the hydrogen ion concentration can be expressed as

$$[\mathrm{H^+}] = (M_{HClO_4}V_0 - M_{NaOH}V_1)/(V_0 + V_1) \quad (3)$$

where M_{HClO_4} and M_{NaOH} are the molarities of perchloric acid and sodium hydroxide and V_0 and V_1 are the initial volume of perchloric acid and the added volume of sodium hydroxide solution, respectively. In basic solution, the measured potential of the cell can be written as

$$E_{cell}\,(\mathrm{mV}) = E°_{cell} + k\log a_{ClO_4^-} - k\log[\mathrm{OH^-}] - k\log\gamma_{OH^-} + E_{LJ} \quad (4)$$

so

$$E_{cell} = E'_b - k\log[\mathrm{OH^-}] \quad (5)$$

where E'_b (the specific constant of the potentiometric cell in the basic region) $= E°_{cell} + k\log a_{ClO_4^-} - k\log\gamma_{OH^-} + E_{LJ}$ and a_{OH^-} and γ_{OH^-} are the activity and the activity coefficient of the hydroxyl ion, respectively. E'_b can be calculated from the intercept of the linear plot of E_{cell} versus −log[OH$^-$]. In the basic region hydroxyl ion concentration is expressed as:

$$[\mathrm{OH^-}] = (M_{NaOH}V_1 - M_{HClO_4}V_0)/(V_0 + V_1) \quad (6)$$

The autoprotolysis constant of water is then calculated from eq 7 and listed in Table 1 for different aqueous methanol solutions together with the values reported in the literature for comparison.[18]

$$pK_{ap} = (E'_a - E'_b)/k \quad (7)$$

There are some differences between the autoprotolysis constants determined in this work and those reported in the

Table 1. Values of pK_{ap} of Different Aqueous Solutions of Methanol at 25 °C and an Ionic Strength of 0.1 mol·dm^{-3} ($NaClO_4$)

methanol % (v/v)	pK_{ap}	ref
0	13.71 ± 0.08	this work
10	13.75 ± 0.07	”
15	13.81 ± 0.06	”
20	13.86 ± 0.09	”
25	13.90 ± 0.08	”
30	13.93 ± 0.07	”
35	14.00 ± 0.09	”
40	14.07 ± 0.07	”
45	14.12 ± 0.09	”
0	13.69 ± 0.03	18
10	13.75 ± 0.01	”
20	13.73 ± 0.03	”
30	13.70 ± 0.02	”
40	13.73 ± 0.01	”

Table 2. Experimental Protonation Constants and Calculated Ones (from Equation 19) of the Carboxylic Acid, K_3, and the Sulfydryl, K_2, and the Amino, K_1, Groups of Penicillamine at 25 °C, Different Aqueous Solutions of Methanol, and an Ionic Strength of 0.1 mol·dm^{-3} ($NaClO_4$), Together with the Values Reported in the Literature

	log K_3	log K_2		log K_1		
methanol % (v/v)	expt	expt	calc	expt	calc	ref
0.0	1.94 ± 0.02	7.97 ± 0.04	7.97 ± 0.03	10.65 ± 0.04	10.66 ± 0.04	this work
10	1.94 ± 0.02	7.92 ± 0.05	7.92 ± 0.02	10.61 ± 0.05	10.60 ± 0.03	”
15	1.95 ± 0.03	7.87 ± 0.03	7.87 ± 0.03	10.57 ± 0.04	10.56 ± 0.04	”
20	1.96 ± 0.02	7.81 ± 0.02	7.81 ± 0.04	10.49 ± 0.06	10.50 ± 0.05	”
25	1.97 ± 0.03	7.78 ± 0.04	7.76 ± 0.05	10.45 ± 0.05	10.45 ± 0.04	”
30	2.03 ± 0.04	7.68 ± 0.05	7.69 ± 0.05	10.39 ± 0.04	10.39 ± 0.06	”
35	2.06 ± 0.03	7.62 ± 0.04	7.64 ± 0.03	10.33 ± 0.03	10.34 ± 0.04	”
40	2.13 ± 0.04	7.59 ± 0.03	7.58 ± 0.04	10.29 ± 0.05	10.28 ± 0.05	”
45	2.27 ± 0.03	7.50 ± 0.03	7.50 ± 0.02	10.21 ± 0.05	10.21 ± 0.04	”
0.0		8.01 ± 0.08		10.50 ± 0.12		14
0.0		7.95		10.45		20
0.0	1.9 ± 0.02	7.85 ± 0.04		10.55 ± 0.06		21
0.0	1.92 ± 0.03	8.0 ± 0.01		10.74 ± 0.02		22
0.0	2.19 ± 0.03	7.91 ± 0.06		10.35 ± 0.06		23
0.0	1.66 ± 0.007	7.75 ± 0.005		10.64 ± 0.004		24

literature especially when the percentage of methanol is enriched in the mixed solvents. The main differences are due to the purity of the organic solvent used, the experimental method, and the use of a background electrolyte.

Results and Discussion

Protonation of Penicillamine. The following species of the ligand may exist in solution at different pH, L^{2-}, HL^-, H_2L, and H_3L^+, where L^{2-} represents the fully dissociated ligand anion. From eq 8, the protonation constants of penicillamine (K_1, K_2, and K_3) corresponding to $n = 1$, 2, or 3 refer to protonation of the amino, sulfydryl, and the carboxylic acid groups of the ligand, respectively.

$$H_{n-1}L^{n-3} + H^+ \rightleftharpoons H_nL^{n-2} \quad (8)$$

The protonation constant values of penicillamine were determined potentiometrically by titration of appropriate solutions of the ligand in different water−methanol mixtures. In this way, penicillamine was fully protonated at the beginning of a titration by adding a certain amount of perchloric acid at first and then using sodium hydroxide solution (0.1 mol·dm^{-3}) as titrant. The protonation constants were obtained from systematic emf measurements of the following cell: GE/$HClO_4$−$NaClO_4$, $H_3L^+ + H_2L + HL^- + L^{2-}$ in water−methanol/NaCl−$NaClO_4$/Ag−AgCl.

The fraction of protons still bound to the amino acid, $\bar{n}$, can be written as:[19]

$$\bar{n}_{cal} = (C_H - [H^+])/C_L \quad (9)$$

where C_H and C_L are the total concentrations of protons and penicillamine, respectively. Substituting C_L and C_H in eq 9 leads to

$$\bar{n}_{cal} = (K_1[H^+] + 2K_1K_2[H^+]^2 + 3K_1K_2K_3[H^+]^3)/(1 + K_1[H^+] + K_1K_2[H^+]^2K_1K_2K_3[H^+]^3) \quad (10)$$

On the other hand, during a titration, electrical neutrality demands that the concentration of the cations should equal the concentration of the anions at all times, and hence, substituting $[L^{2-}]$ from C_L in eq 9 and simplification leads to

$$\bar{n}_{exp} = (2C_L + [ClO_4^-] - [Na^+] - [H^+] + [OH^-])/C_L \quad (11)$$

In eqs 10 and 11, $[Na^+]$ originates from the titrant used, and $[ClO_4^-]$ is introduced from the perchloric acid added; $[H^+] = 10^{(E_{cell}-E'_a)/k}$ and $[OH^-] = K_{ap}/[H^+]$. Using a suitable computer program (Microsoft Excel Solver),[23] the data from eqs 10 and 11 were fitted for estimating the protonation constant values of penicillamine in different aqueous solutions of methanol. We used the Gauss−Newton nonlinear least-squares method in the computer program to refine the $\bar{n}$ values by minimizing the error square sum from eq 12.

$$U = \sum (\bar{n}_{exp} - \bar{n}_{cal})^2 \quad (12)$$

where $\bar{n}_{exp}$ is the experimental $\bar{n}$ and $\bar{n}_{cal}$ is the calculated one. The calculated protonation constant values of penicillamine in different water−methanol mixtures are listed in Table 2 together with the values reported in the literature for comparison.[14,20−24] With some differences, the protonation constant values obtained in this work are in agreement with those reported before. The main differences are due to the different experimental method and the fact that a different background electrolyte has been employed to determine the values.

Complexation of Thallium(I) with Penicillamine. The complex $M_xH_yL_z^{x+y-2z}$ that formed is characterized by its stoichiometry (x:y:z), where M and L represent the metal ion and ligand, respectively. To determine the formation constant of the complexation, eq 13 is defined by β_{xyz}:

$$xM^+ + yH^+ + zL^{2-} \rightleftharpoons M_xH_yL_z^{x+y-2z} \quad (13)$$

$$\beta_{xyz} = [M_xH_yL_z^{x+y-2z}]/([M^+]^x[H^+]^y[L^{2-}]^z) \quad (14)$$

Determination of the formation constant was employed using the method mentioned before.[25] Absorbance, A, and $-\log[H^+]$ were measured by successive addition of an alkali solution of the ligand to the acidic metal ion solution in the UV range of (250 to 280) nm; see the Experimental Section. Treatment of the spectrophotometric data (every 0.5 nm) obtained during the titrations, as a function of H^+ concentration, was conducted with the computer program Squad.[26] The stoichiometric formation constants were computed from the data using the same computer program. The number of experimental points (absorbance versus p_cH) was more than 30 (maximum of 50) for each titration.

Considering eq 14, different models including MH_2L, MHL, and ML and several polynuclear and protonated species were tested by the program. As expected, polynuclear complexes were systematically rejected by the computer program, as were MH_2L_2, MHL_2, and ML_2 also (the charges are omitted for simplicity). A value for the MH_3L species was also calculated by the program, but the species was not considered further,

Table 3. Average Values of the Experimental and Calculated (from Equation 20) log β_{MH_2L}, log β_{MHL}, and log β_{ML} for the Tl(I)−Penicillamine System at 25 °C, Different Aqueous Solutions of Methanol, and an Ionic Strength of 0.1 mol·dm^{-3} ($NaClO_4$)

	log β_{MH_2L}		log β_{MHL}		log β_{ML}		
methanol % (v/v)	expt	calc	expt	calc	expt	calc	ref
0.0	2.54 ± 0.02	2.54 ± 0.02	12.17 ± 0.06	12.19 ± 0.05	4.02 ± 0.02	4.03 ± 0.02	this work
10	2.61 ± 0.03	2.61 ± 0.03	12.27 ± 0.05	12.26 ± 0.04	4.08 ± 0.02	4.07 ± 0.02	”
15	2.67 ± 0.02	2.67 ± 0.02	12.32 ± 0.05	12.32 ± 0.06	4.12 ± 0.03	4.11 ± 0.02	”
20	2.75 ± 0.04	2.75 ± 0.04	12.43 ± 0.04	12.41 ± 0.05	4.16 ± 0.02	4.17 ± 0.03	”
25	2.81 ± 0.05	2.81 ± 0.03	12.48 ± 0.07	12.48 ± 0.04	4.19 ± 0.03	4.21 ± 0.02	”
30	2.90 ± 0.02	2.89 ± 0.04	12.57 ± 0.06	12.56 ± 0.05	4.28 ± 0.04	4.27 ± 0.04	”
35	2.95 ± 0.04	2.95 ± 0.05	12.61 ± 0.05	12.64 ± 0.04	4.32 ± 0.05	4.32 ± 0.03	”
40	3.01 ± 0.05	3.03 ± 0.03	12.72 ± 0.07	12.73 ± 0.06	4.38 ± 0.03	4.39 ± 0.03	”
45	3.12 ± 0.04	3.11 ± 0.03	12.86 ± 0.06	12.85 ± 0.05	4.47 ± 0.02	4.47 ± 0.02	”
0.0			12.81 ± 0.10		1.27 ± 0.05		14
0.0			12.05 ± 0.03		3.57 ± 0.01		27

because the estimated error in its formation constant was unacceptable, and its inclusion does not improve the goodness of the fit. The model finally chosen, formed by MH_2L, MHL, and ML for the studied system, resulted in satisfactory numerical and graphical fitting. The calculated average values of the stability constants for different experiments are listed in Table 3 together with the values reported in the literature for comparison.[14,27]

With some differences, the stability constant values obtained in this work are in agreement with those reported before. The main differences are due to the postulation of a new complex species, TlH_2L^+, and some are possibly due to the different experimental method and the fact that a different background electrolyte has been employed to determine the values.

In Figure 1 the equilibrium distribution of various species in the Tl(I)−penicillamine system is shown as a function of p_cH. The calculations are based on the stability constant values given in Table 3. The curves clearly demonstrate that an increase of p_cH is accompanied by an increase in the formation of deprotonated complex species and also the fact that the stability of the species depends upon p_cH. The most stable complex species at $p_cH = 3.1$, 6.1, and 10.8 are TlH_2L^+, TlHL, and TlL^-, respectively. However, in the presence of methanol (not plotted here), the complex formation shifted to lower p_cH values, which is possibly due to the higher stability constant of the species formed in the lower dielectric constant of the mixed solvents.

Solvent Effect

Protonation Constant of Penicillamine. The three protonation constants of penicillamine in water−methanol mixed solvents have different behavior (Table 2). The protonation constant of the amino, K_1, and the sulfydryl, K_2, groups of the ligand decreased as the solvent became enriched in the organic component, but the protonation constant of the carboxylic acid group, K_3, increased as methanol increased in the mixtures. It is very difficult to interpret the variation of the protonation constant values of penicillamine with respect to the percentage of methanol in the mixtures using the dielectric constant of the solutions as a single parameter.

In general, the standard free energy of protonation equilibria consists of two terms: an electrostatic term, which can be estimated by the Born equation,[28,29] and a nonelectrostatic term, which includes specific solute−solvent interactions. When the electrostatic effects predominate, then in accordance with the Born equation, eq 15, a plot of log K versus the reciprocal of the dielectric constant of the media, ε_r, should be linear.

$$\Delta \log K = (121.6z/r)(1/\varepsilon_r - 0.0128) \qquad (15)$$

where r is the common radius of the ions and z is the square summation of the charges involved in the protonation equilibria. For example $z = 4$ for the charge type $L^{2-} \rightleftharpoons HL^-$, $z = 2$ for the charge type $HL^- \rightleftharpoons H_2L$ and $z = 0$ for the charge type $H_2L \rightleftharpoons H_3L^+$.

The correlation between log K_1 and log K_2 with the reciprocal of the dielectric constant of methanol−water mixtures is linear, with correlation coefficients of more than 0.99 (Figure 2). However, there is no change in the number of charges involved in the protonation equilibria of the zwitterionic form of penicillamine, K_3. In this case, the correlation between log K_3 values and $1/\varepsilon_r$ is poor (Figure 3), and so the protonation possibly depends on the solute−solvent interaction of the different species in the mixtures. Therefore, it is essential to

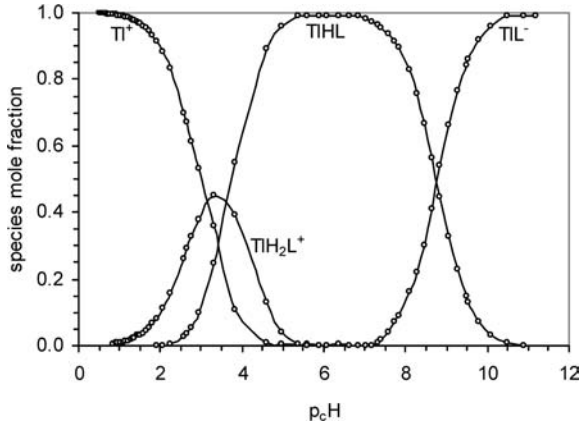

Figure 1. Distribution diagram of complex species of thallium(I)−penicillamine system at 25 °C, an ionic strength of 0.1 mol·dm^{-3} ($NaClO_4$), and 0 % methanol.

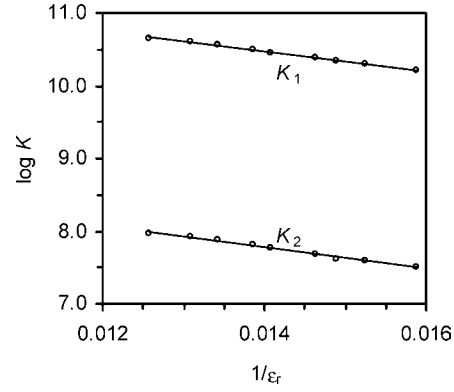

Figure 2. Plots of the experimental values of log K_1 and log K_2 versus the reciprocal of the dielectric constant of different mixed solvents at 25 °C and an ionic strength of 0.1 mol·dm^{-3} ($NaClO_4$).

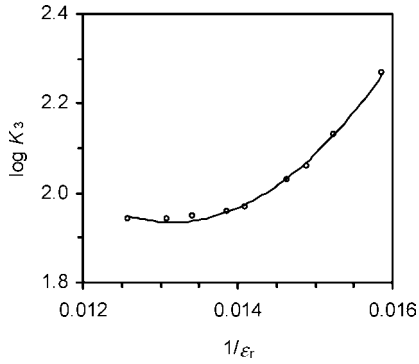

Figure 3. Plot of the experimental values of log K_3 versus the reciprocal of the dielectric constant of different mixed solvents at 25 °C and an ionic strength of 0.1 mol·dm^{-3} ($NaClO_4$).

elucidate the nature of solute−solvent interactions for a better understanding of solvent effects.

log K_3 values of penicillamine show small changes in the range of (0 to about 20) % (v/v) of methanol and a larger increase when the mixture is richer in methanol. This variation with the percentage of the organic solvent is due to the solute−solvent interaction effects. This effect possibly changes the structure of the mixtures.[29] In fact, the water structure remains intact in the water-rich region, and the methanol molecules occupy the cavities between water molecules without changing the water structure.[29] In this region there are small changes in the log K_3 values of penicillamine. However, the log K_3 values change by larger amounts when the percentage of methanol increases to higher values. In this region the influence of methanol on water structure is high, and the solute−solvent interactions cause a greater variation in log K_3 values. This discussion is in accordance with previous results for other aqueous−organic solvent mixtures and in agreement with the present results.[28−31]

To obtain a quantitative method for the evaluation of the solute−solvent interaction on protonation or the stability constants, we used the method introduced by Kamlet, Abboud, and Taft (KAT).[32,33] The KAT equation contains nonspecific as well as specific solute−solvent interactions separately, and the latter could be subdivided into solvent Lewis acidity interactions (hydrogen-bond acceptor, HBA solute, and hydrogen-bond donor, HBD solvent) and solvent Lewis basicity interactions (HBD solute−HBA solvent). In general, all of these parameters constitute more comprehensive measures of solvent polarity than the dielectric constant or any other single physical characteristic alone, because they reflect more reliably the complete picture of all intermolecular forces acting between solute and solvent molecules. In general, this approach has been widely and successfully applied in the correlation analysis of all kinds of solvent-dependent processes.[34] The multiparametric equation, eq 16, has been proposed, using the solvatochromic solvent parameters, α, β, and π^*, which have been introduced in previous reports.[35−37]

$$\log K = A_0 + a\alpha + b\beta + p\pi^* \qquad (16)$$

where A_0 represents the regression value and π^* is the index of the solvent dipolarity/polarizability, which is a measure of the ability of a solvent to stabilize a charge or a dipole by its own dielectric effects. The π^* scale was selected to run from 0.0 for cyclohexanone to 1.0 for dimethylsulfoxide. The α coefficient represents the solvent hydrogen-bond donor (HBD) acidity; in other words it describes the ability of a solvent to donate a proton in a solvent to a solute hydrogen bond. The α scale extends from 0.0 for non-HBD solvents to about 1.0 for methanol. The β coefficient is a measure of a solvent hydrogen-bond acceptor (HBA) basicity and describes the ability of a solvent to accept a proton in a solute to solvent hydrogen bond. The β scale was selected to extend from 0.0 for non-HBA solvents to about 1.0 for hexamethylphosphoric triamide.

Table 4. KAT Solvatochromic Parameters and the Dielectric Constant of Different Methanol−Water Solvent Mixtures at 25 °C

methanol % (v/v)	α^a	β	π^*	ε_r
0.0	1.23	0.49	1.14	79.50
10	1.19	0.51	1.13	76.40
15	1.17	0.53	1.12	74.49
20	1.14	0.54	1.10	72.10
25	1.11	0.56	1.09	70.98
30	1.08	0.57	1.07	68.13
35	1.06	0.59	1.06	67.15
40	1.04	0.60	1.04	65.16
45	1.02	0.62	1.02	63.00

The regression coefficients a, b, and p measure the relative susceptibilities of the solvent dependence of log K to the indicated solvent parameters. To explain the determined log K values through the KAT solvent parameter, the protonation constants were correlated with the solvent properties by means of single and multiple regression analysis by a suitable computer program (Microsoft Excel Solver and Linest).[38] We used the Gauss−Newton nonlinear least-squares method in the computer program to refine the log K by minimizing the error squares sum from eq 17.

$$U = \sum (\log K_{exp} - \log K_{cal})^2 \qquad (17)$$

The procedure used in the regression analysis involves a rigorous statistical treatment to find out which parameter in eq 16 is best suited to the water−organic mixed solvents. So, a stepwise procedure and least-squares analysis were applied to select the significant solvent properties to be influenced in the model and to obtain the final expression for the protonation constants. Therefore, the KAT equation, eq 16, was used as single- and multiparameters for correlation analysis of log K in various solvent mixtures. The computer program used can give the values of A_0, a, b, p and some statistical parameters including the r^2 coefficient, the uncertainty value of any parameter (given in brackets), and the overall standard error (ose) of log K. The KAT parameters and the dielectric constant values for all of the water−methanol mixtures used in this work were obtained from the plot of each property versus the mole fraction of the organic solvent of the values that were reported in the literature for some other percentages of aqueous solutions of methanol,[39,40] those are listed in Table 4. The expressions of the KAT equation thus obtained for each property and are given as single- and multiparameters as follows:

$$\log K_3 = 3.47(\pm 0.34) - 1.29(\pm 0.30)\alpha \quad (N = 9,\ r^2 = 0.72,\ \text{ose} = 0.03) \qquad (18a)$$

$$\log K_3 = 0.77(\pm 0.26) + 2.27(\pm 0.47)\beta \quad (N = 9,\ r^2 = 0.77,\ \text{ose} = 0.02) \qquad (18b)$$

$$\log K_3 = 4.74(\pm 0.43) - 2.50(\pm 0.39)\pi^* \quad (N = 9,\ r^2 = 0.85,\ \text{ose} = 0.01) \qquad (18c)$$

Although the solvent polarity is identified as the main reason for the variation of log K values in water−methanol mixtures, the results show that any single-parameter correlations of log K_1, log K_2, and log K_3 values individually with π^*, α, and β did not give good results in all cases. However, the correlation

analysis of log K_1, log K_2, and log K_3 values with multiparameter equations indicate significant improvement with regard to the single-parameter models. To indicate the importance of the KAT parameters, the uncertainty values for each term in eqs 18a and 19a are shown in the brackets using the Linest program.

$$\log K_3 = 1.47(\pm 0.18) + 4.90(\pm 0.77)\alpha + 4.27(\pm 1.37)\beta - 6.67(\pm 0.81)\pi^* \quad (19a)$$
$$(N = 9,\ r^2 = 0.98,\ \text{ose} = 1.2\cdot 10^{-3})$$

$$\log K_2 = 4.92(\pm 0.19) + 0.17(\pm 0.08)\alpha - 0.74(\pm 0.14)\beta + 2.81(\pm 0.09)\pi^* \quad (19b)$$
$$(N = 9,\ r^2 = 0.993,\ \text{ose} = 1.4\cdot 10^{-3})$$

$$\log K_1 = 7.47(\pm 0.11) + 0.29(\pm 0.05)\alpha - 0.45(\pm 0.08)\beta + 2.67(\pm 0.05)\pi^* \quad (19c)$$
$$(N = 9,\ r^2 = 0.997,\ \text{ose} = 4.7\cdot 10^{-4})$$

The coefficients of α, β, and π^* in eqs 19a to 19c are different from each other and are in the order of $\pi^* > \beta > \alpha$ for K_1 and K_2 and $\pi^* > \alpha > \beta$ in the case of K_3. This indicates that the polarity parameter plays a major role in all cases, but the HBA basicity parameter of the solvent has less significance in the correlation analysis of K_3 and the HBD acidity parameter in the case of K_1 and K_2 in the variation of protonation constant values of penicillamine in the proposed various aqueous solutions of methanol.

If the dielectric constant of the media was the only factor for the solvent effect on the protonation, it may be expected that the log K in a solution with the higher dielectric constant should be greater than those of all of the other aqueous solutions of methanol. It can be seen from Table 4 that the dielectric constants of the solvent mixtures decrease as the solutions are enriched in methanol. The values of log K_1 and log K_2 decrease with decreasing dielectric constant of the media, but this is not true in the case of log K_3 values. It is impossible to explain this variation using the dielectric constant approach as a single parameter. However, a multiparametric approach according to the KAT equation was applied to find out which parameter is responsible for this behavior. The positive π^* coefficients in the correlation analysis of log K_1 and log K_2 by the KAT equation imply that a decrease in the polarity of the mixed solvents decreases the protonation constant values of the amino and the sulfydryl groups. According to this discussion, the negative π^* coefficient obtained for log K_3 represents a decrease in polarity of the solvent mixtures, which causes an increase in the protonation constant values of the carboxylic acid. This indicates that the polarity parameter, π^*, is the most important (with a relatively large difference with the other coefficients, Table 4) in the correlation analysis of the protonation constants of penicillamine. In a previous work, in correlation analysis of the protonation constants of cysteine in aqueous solutions of methanol, almost the same results were obtained.[25] Furthermore, the positive coefficient β in the correlation of log K_3, negative in the case of log K_1 and log K_2, suggests that the increasing basicity of the solvent mixtures increases the protonation constant of the carboxylic group of penicillamine and decreases the protonation constants of the sulfydryl and the amino groups of the compound. This could be due to the charges involved in the protonation equilibria. An increase in the basicity of the mixtures increases the solvation of the cationic species of penicillamine and therefore makes protonation equilibrium more likely. However, this is not true in the case of K_1 and K_2 that have a negative coefficient of β.

Table 5. Percentage Contribution of KAT Parameters on the Effect of Different Media on Protonation and Complexation at 25 °C and an Ionic Strength of 0.1 mol·dm^{-3} ($NaClO_4$)

species	α	β	π^*
log K_3	30.9	27.0	42.1
log K_2	4.6	19.9	75.5
log K_1	8.5	13.2	78.3
log β_{MH2L}	9.0	24.3	66.7
log β_{MHL}	9.7	30.6	59.7
log β_{ML}	15.3	30.7	54.0

Complexation Constant. To explain the obtained log β values through the KAT equation, the formation constants were correlated with the solvent properties by means of single and multiple linear regression analysis using the same computer program (Microsoft Excel Solver and Linest). We again used the Gauss−Newton nonlinear least-squares method in the computer program to refine the log β by minimizing the error squares sum from eq 17. Single-parameter correlations of log β individually with α, β, or π^* again did not give a good result. However, the result presented in eq 20a, a multiparametric equation, indicates significant improvement with regard to the single-parameter models.

$$\log \beta_{121} = 5.81(\pm 0.10) - 0.39(\pm 0.04)\alpha + 1.06(\pm 0.08)\beta - 2.90(\pm 0.05)\pi^* \quad (20a)$$

$$\log \beta_{111} = 15.16(\pm 0.23) + 0.70(\pm 0.09)\alpha + 2.21(\pm 0.17)\beta - 4.31(\pm 0.10)\pi^* \quad (20b)$$

$$\log \beta_{101} = 5.65(\pm 0.16) + 0.95(\pm 0.06)\alpha + 1.91(\pm 0.12)\beta - 3.36(\pm 0.07)\pi^* \quad (20c)$$

$N = 9$, $r^2 = 0.999$, 0.995, and 0.995, respectively, and ose < $1.8\cdot 10^{-3}$ in all cases.

In this case the solvent polarity parameter of the media, π^*, has again a major role and increases with increasing mole fraction of water in aqueous solutions of methanol. If the π^* of the media was the only factor for describing the solvent effect on complexation, it may be expected that the log β in water should be greater than those of all of the other aqueous solutions of methanol. However, the formation constant of the complex species increases with an increase in the solvent HBA basicity parameter, β, and decreases with increasing solvent polarity π^*. They also increase with a decrease in the HBD acidity parameter, α, of the mixed solvents. The coefficients of π^*, α, and β in eq 20b are in the order of $\pi^* > \beta > \alpha$. This suggests that the polarity parameter power of the solvent is the most important, the HBA basicity parameter plays a relatively small role, and finally the HBD acidity parameter nearly has little significance in changing the formation constants of the Tl(I) + penicillamine system in the various aqueous solutions of methanol. From the magnitude of the coefficients *a*, *b*, and *p* the percentage contribution of the KAT solvatochromic parameters on the effect of different media on complexation was calculated and is given in Table 5. To show the efficiency of the suggested multiparameter correlations, the calculated values of the formation constants are listed in Table 3. It can be seen that the experimental values of log β and the calculated ones are in very good agreement.

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