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

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The protonation equilibria of cysteine 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 40) % (v/v), and constant ionic strength ($0.1\ \text{mol}\cdot\text{dm}^{-3}$ 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 cysteine and the formation constants of the formed complexes in different media were analyzed in terms of Kamlet, Abboud, and Taft (KAT) parameters. Single-parameter correlations of the formation constants versus α (hydrogen-bond donor acidity), β (hydrogen-bond acceptor basicity), and for 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 the calculated ones, while all the KAT parameters are considered. Finally, the results are discussed in terms of the effect of solvent on protonation and complexation.

Introduction

Thallium compounds have long been known to be poisonous to human beings,[1−4] although radio-thallium is used in monitoring cardiac functions. General population exposure to thallium(I) may occur as a result of atmospheric pollution from coal-burning power plants, cement factories, etc. This metal ion is rapidly and almost completely absorbed following ingestion, inhalation, or skin contact.[5] After absorption in animals, thallium(I) is widely distributed in the body. Both acute and chronic studies show that the highest concentration is found in the kidney.[1] Thallium(I) is very slowly excreted from the body. The metabolic action and fate of thallium(I) is not clear. Nevertheless, experimental evidence suggests that there are some similarities between the ionic transport of thallium(I) and the potassium ion through cell membranes, although intercellular release of thallium(I) seems to be less rapid than the potassium ion.[1] The biological effects of thallium(I) have also been thought to be due to its interference with the metabolism of sulfur-containing compounds.[5] Sulfur-containing compounds have been the main detoxifying drug used in the case of poisoning by the metal ion.[1] To understand thallium(I) sulfur-containing interactions better, an estimation of some stability constant values was attempted on the basis of chemical considerations involving known complex equilibria.

Now, it is understood that, in proteins, active site cavities of enzymes, and in different complexes of nucleotides and nucleosides, the effective dielectric constant is decreased at the ligand−water interface and the activity of water is decreased due to the presence of aliphatic or aromatic side chains of the ligand at the location.[6] 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.

During the past few years, several experimental and theoretical works dealing with the effect of organic solvent on intermolecular reactions have been published. Most of these papers are concerned with the effect of solvent on reaction rates, and a few exclusively deal with complexation of some biologically important ligands. The interaction of solvents with different dielectric constants by biological molecules is of importance for understanding the chemistry of in vivo processes like enzyme interaction, the assembly of lipids in biomembranes, surfactant aggregation, etc.[7]

In previous publications,[8−11] we have reported that the dielectric constant alone (as believed for many years) cannot serve as a quantitative measurement of solvent polarity. This property is often inadequate since the dielectric constant description considers a solvent as a nonstructured continuum, not composed of individual solvent molecules with their own solvent−solvent interactions, and does not take into account specific solute−solvent interactions. To obtain a quantitative method for the determination of solvent effects on physical properties, many empirical solvent scales have been devised during the last two decades.[12] Among these scales (around 40), the most comprehensive are the solvatochromic ones, but only a few of them have found wider application in correlation analysis of solvent effects. A quantitative measurement of the solvent polarity has been introduced by Kamlet et al.[13,14] KAT solvatochromic parameters have been used in one-, two-, or three-parameter correlations involving different combinations of these parameters that are called linear solvation energy relationships. In general, all of these parameters are more comprehensive measures of the solvent polarity than the

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Table 1. Experimental Protonation Constants and Calculated Ones (from Equation 13) of the Carboxylic, K_1, the Sulfydryl, K_2, and the Amino, K_3, Groups of Cysteine at 25 °C, Different Aqueous Solutions of Methanol, and Ionic Strength 0.1 mol·dm^{-3} (NaClO$_4$), Together with the Values Reported in the Literature

methanol % (v/v)	log K_1	log K_2		log K_3		ref
	exp.	exp.	cal.	exp.	cal.	
0.0	1.75 ± 0.03	8.16 ± 0.05	8.17 ± 0.03	10.28 ± 0.06	10.28 ± 0.06	this work
10	1.77 ± 0.03	8.04 ± 0.03	8.04 ± 0.04	10.11 ± 0.04	10.10 ± 0.07	this work
15	1.80 ± 0.01	7.99 ± 0.06	7.98 ± 0.03	10.01 ± 0.07	10.01 ± 0.06	this work
20	1.85 ± 0.04	7.92 ± 0.05	7.92 ± 0.05	9.92 ± 0.05	9.92 ± 0.05	this work
25	1.89 ± 0.04	7.87 ± 0.04	7.86 ± 0.04	9.83 ± 0.04	9.83 ± 0.05	this work
30	1.97 ± 0.02	7.80 ± 0.02	7.80 ± 0.07	9.74 ± 0.04	9.74 ± 0.03	this work
35	2.08 ± 0.02	7.74 ± 0.04	7.74 ± 0.04	9.64 ± 0.05	9.64 ± 0.04	this work
40	2.19 ± 0.04	7.67 ± 0.06	7.68 ± 0.07	9.56 ± 0.06	9.56 ± 0.05	this work
0.0	1.81	7.91		10.04		19
0.0	1.90	7.91		10.36		20
0.0		8.24		10.55		21

Table 2. Average Values of the Experimental and Calculated (from Equation 14) log β_{MH2L}, log β_{MHL} and log β_{ML} for the Tl(I)−Cys System at 25 °C, Different Aqueous Solutions of Methanol, and Ionic Strength 0.1 mol·dm^{-3} (NaClO$_4$)

methanol % (v/v)	log β_{MH2L}		log β_{MHL}		log β_{ML}		ref
	exp.	cal.	exp.	cal.	exp.	cal.	
0.0	2.47 ± 0.04	2.46 ± 0.03	11.02 ± 0.08	11.00 ± 0.06	3.95 ± 0.05	3.96 ± 0.04	this work
10	2.57 ± 0.02	2.57 ± 0.03	11.12 ± 0.08	11.13 ± 0.08	4.07 ± 0.04	4.06 ± 0.05	this work
15	2.62 ± 0.04	2.62 ± 0.02	11.19 ± 0.05	11.19 ± 0.07	4.11 ± 0.05	4.11 ± 0.04	this work
20	2.68 ± 0.03	2.68 ± 0.01	11.25 ± 0.04	11.26 ± 0.06	4.16 ± 0.06	4.16 ± 0.03	this work
25	2.72 ± 0.01	2.73 ± 0.04	11.31 ± 0.06	11.32 ± 0.09	4.21 ± 0.02	4.21 ± 0.02	this work
30	2.78 ± 0.05	2.79 ± 0.05	11.38 ± 0.09	11.38 ± 0.06	4.26 ± 0.05	4.26 ± 0.05	this work
35	2.84 ± 0.02	2.84 ± 0.02	11.46 ± 0.05	11.45 ± 0.05	4.31 ± 0.04	4.31 ± 0.04	this work
40	2.91 ± 0.03	2.90 ± 0.03	11.52 ± 0.07	11.51 ± 0.07	4.37 ± 0.02	4.37 ± 0.05	this work
0.0			11.285		3.262		5
0.0			11.03		3.48		15

dielectric constant or other physical properties alone. They reflect more reliably the complete picture of all intermolecular forces acting between solute and solvent molecules. In this work, we have chosen a well-understood system, complexation of thallium(I) with cysteine[15] in different aqueous solutions of methanol, to show how the solvents and their mixtures with various polarities affect the formation of such complexes. Further, an attempt is performed to describe the variations of the protonation constants of cysteine in different aqueous solutions of organic media. The solvation of amino acids that constitute proteins is closely connected with stabilizing and destabilizing effects of electrolytes on protein structure. Therefore, the study of protonation and solvation processes of amino acids in various organic media is important to elucidate their connection between chemical ability and biological activity, as the polarity and activity of water are expected to be lower in an active site cavity of an enzyme than in bulk water.[12,16]

Experimental Section

Reagents. Methanol was obtained from Merck as an analytical reagent grade material and was used without further purification. L-Cysteine, cys (Fluka, analytical reagent grade), 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 cysteine was freshly prepared daily and was used immediately after preparing the solution avoiding oxidizing to cysteine. The NaOH solution was prepared from titrisol solution (Merck), and its concentration was determined by several titrations with standard HCl. 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. A dilute perchloric acid solution was standardized against standard NaOH solution. All dilute solutions were prepared from double-distilled water with a specific conductance equal to (1.3 ± 0.1) μS·cm^{-1}.

Measurements. All measurements were performed at (25 ± 0.1) °C. The ionic strength was maintained at 0.1 mol·dm^{-3} with sodium perchlorate. An Eyela pH meter, PHM 2000, was used for pH measurements. The hydrogen ion concentration was measured with an Ingold UO 3234 glass electrode and an Ingold UO 3236 calomel electrode. The pH-meter was calibrated for the relevant H$^+$ concentration with a solution of 0.01 mol·dm^{-3} perchloric acid solution containing 0.09 mol·dm^{-3} sodium perchlorate (for adjusting the ionic strength to 0.1 mol·dm^{-3}). For this standard solution, we set $-\log [H^+] = 2.00$, assuming the acid is dissociated 100 %. [17] Junction potential corrections have been calculated from eq 1.

$$-\log [H^+]_{real} = -\log [H^+]_{measured} + a + b[H^+]_{measured} \quad (1)$$

where a and b were determined by measuring the hydrogen ion concentration for two different solutions of HClO$_4$ or NaOH with sufficient NaClO$_4$ to adjust the ionic media.

Spectrophotometric measurements were performed using a UV−vis Shimadzu 2100 spectrophotometer with a Pentium 4 computer and thermostatically matched 10 mm quartz cells. The measurement cell was of the flow type. A Masterflex pump allowed circulation of the solution under study from the potentiometric cell to the spectrophotometric cell, so the absorbance and $-\log [H^+]$ of the solution could be measured simultaneously.

For each experiment, a 50 mL acidic solution of Tl(I) ($1.2 \cdot 10^{-3}$ mol·dm^{-3}) was titrated with an alkali solution, 0.1 mol·dm^{-3} NaOH, of cys, $(5.1 \text{ to } 5.5) \cdot 10^{-3}$ mol·dm^{-3}, both of the same ionic strength and mole fraction of methanol. The absorbance and $-\log [H^+]$ were measured after addition of a few drops of titrant, and the procedure extended up to the required $-\log [H^+]$. In all cases, the procedure was repeated at least three times, and the resulting average values and corresponding deviations from the average are shown in the text and tables. 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.

Calibration of the Glass Electrode. The term pH has significance only in aqueous media. The glass electrode potential in an aqueous solution differs from that in a solution of mixed solvents, and a liquid-junction potential of uncertain magnitude may affect the results. To overcome this difficulty, it was necessary to calibrate the glass electrode in different solvent mixtures. The experimental method proposed in the literature[18] was employed for this purpose. The pH meter reading B in methanol + water media was converted into $[H^+]$ using the equation

$$-\log [H^+] = B + \log \mu H \qquad (2)$$

where the concentration factor $\log \mu_H$ was obtained for the ionic strength 0.1 $mol \cdot dm^{-3}$ $NaClO_4$ from the expression $\log \mu_H = \log \mu°_H + \log \gamma_\pm$. The value of $\mu°_H$ is independent of ionic concentration but is dependent on solvent composition, and $\gamma_\pm$ is the mean activity coefficient of perchloric acid in the solvent mixtures. In this work, the values of B were recorded in various solvent mixtures containing a known concentration of perchloric acid and sufficient sodium perchlorate to give a constant ionic strength of 0.1 $mol \cdot dm^{-3}$. The difference between the logarithm of known hydrogen-ion concentrations and the corresponding values of B was used to calculate values of the correction term $\log \mu_H = \log(\mu°_H \gamma_\pm)$.

Results and Discussion

Protonation of the Amino Acid. The following species of the amino acid may exist in solution at different pH, L^{2-}, HL^-, H_2L, and H_3L^+, where L^{2-} represents the fully dissociated ligand anion. The protonation constants of cysteine have been extensively studied in different kinds of background electrolytes, and the results are reported in the literature.[19−21] The following equilibria were considered.

$$H^+ + H_{2-n}L^{-n} \, \Phi \, H_{3-n}L^{1-n}$$

$$K_{1+n} = [H_{3-n}L^{1-n}]/[H^+][H_{2-n}L^{-n}] \qquad (3)$$

where n is 2, 1, or 0 corresponding to K_3, K_2, and K_1 that refer to protonation of the amino, sulfydryl, and the carboxylic acid groups, respectively.

The protonation constant values have been determined using the potentiometric technique under the same condition of temperature, ionic media, and mole fraction of methanol and calculated using the computer program (Microsoft Excel Solver) which employs a nonlinear least-squares method.[22] The protonation constant values, expressed in log units, are collected in Table 1 together with the values reported in the literature for comparison.[19−21]

Complexation of Thallium(I) by Cysteine. 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 4 is defined by β_{xyz}

$$xM^+ + yH^+ + zL^{2-} \, \Phi \, M_xH_yL_z^{x+y-2z} \qquad (4)$$

$$\beta_{xyz} = [M_xH_yL_z+^{x+y-2z}]/([M^+]^x[H^+]^y[L^{2-}]^z) \qquad (5)$$

Determination of the formation constant was employed using the method mentioned before.[11] 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 (250 to 280) nm (see 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.[23] The stoichiometric formation constants were computed from the data using computer program Squad. The number of experimental points (absorbance versus pH) was more than 30 (maximum 40) for each titration. If we designate m absorption spectra that will be measured at n wavelengths, the individual absorbance readings thus can be arranged in an $m \times n$ matrix $\mathbf{R}$; the m spectra form the rows of $\mathbf{R}$, and the columns consist of the n response curves gathered at the different wavelengths. According to Beer's law, for a system with N absorbing components, $\mathbf{R}$ can be decomposed into the product of a concentration matrix $\mathbf{C}$ ($m \times N$) and a matrix of the molar absorptivities $\mathbf{S}$ ($N \times n$). However, because of the inherent noise in the measured data, the decomposition does not represent $\mathbf{R}$ exactly. The matrix $\mathbf{T}$ of the residuals is given by the difference between $\mathbf{CS}$ and $\mathbf{R}$

$$\mathbf{T} = \mathbf{CS} - \mathbf{R} \qquad (6)$$

In the fitting procedure, those matrices $\mathbf{C}$ and $\mathbf{S}$ are determined which best represent the original matrix $\mathbf{R}$. The task of the fitting procedure is to optimize the matrix $\mathbf{T}$ of the residuals, eq 6, according to the least-squares criterion. In eq 7, U is the sum of the squares of all elements of $\mathbf{T}$. It is the task of the nonlinear least-squares fitting to find the set of parameters that result in a minimum of U.

$$U = \sum_{i=1}^{m} \sum_{j=1}^{n} \mathbf{T}(i,j)^2 = \text{minimize} \qquad (7)$$

Considering eqs 4 and 5, 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 also were MH_2L_2, MHL_2, and ML_2 (the charges are omitted for simplicity). A value for MH_3L species was also calculated by the program; however, the species was not considered further because the estimated error in its formation constant was unacceptable, and its inclusion does not improve the goodness of the fit. The models 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 2.

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)−cys system is shown as a function of $-\log [H^+]$. The calculations are based on the stability constant values given in Table 2. The curves clearly demonstrate that an increase of the pH is accompanied by an increase in the formation of deprotonated complex species, and also the stability of the species depends upon pH. The most stable complex species at pH = 3, 6, and 11 are TlH_2L^+, TlHL, and TlL^-, respectively. However, in the presence of methanol (not plotted here), the complex formation shifted to lower pH values which is possibly due to the higher stability constant of the species formed in the lower dielectric constant mixed solvents.

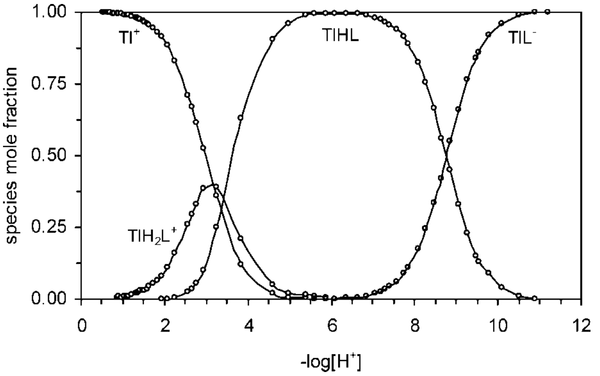

Figure 1. Distribution diagram of complex species of thallium(I) ion−cysteine system at 25 °C, ionic strength 0.1 mol·dm^{-3} NaClO$_4$, and 0 % methanol.

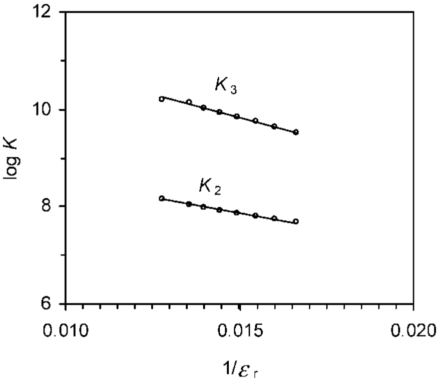

Figure 2. Plots of the experimental values of log K_2 and K_3 versus the reciprocal of dielectric constant of different mixed solvents at 25 °C and ionic strength 0.1 mol·dm^{-3} NaClO$_4$.

Table 3. KAT Solvatochromic Parameters and the Dielectric Constants of Different Methanol−Water Solvent Mixtures

methanol % (v/v)	α^a	β^a	π^{*a}	ε_r^a
0.0	1.17	0.47	1.09	78.36
10	1.15	0.49	1.04	73.79
15	1.14	0.50	1.02	71.51
20	1.13	0.51	0.99	69.22
25	1.12	0.52	0.97	66.94
30	1.11	0.53	0.94	64.65
35	1.10	0.54	0.92	62.36
40	1.09	0.55	0.89	60.08

[a] The pure values of α, β, π*, and ε_r for methanol and water have been obtained from ref 12.

Solvent Effect

Protonation Constant of Cysteine. The three protonation constants of the amino acid in water−methanol mixed solvents have different behavior (Table 1). The protonation constant of the amino, K_3, and the sulfydryl, K_2, groups of the amino acid decreased as the solvent became enriched in the organic component, but the protonation constant of the carboxylic acid group, K_1, increased as methanol increased in the mixtures. It is very difficult to interpret the variation of the protonation constant values of the amino acid 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,[24,25] and a nonelectrostatic term, which includes specific solute−solvent interaction. When the electrostatic effects predominate, then in accordance with the Born equation, eq 8, the plot of log K versus the reciprocal of dielectric constant of the media, ε_r, should be linear.

$$\Delta \log K = (121.6n/r)(1/\varepsilon_r - 0.0128) \tag{8}$$

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

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

Log K_1 values of the amino acid show small changes in the range 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 solute−solvent interaction effects. This effect possibly changes the structure of the mixtures. [25] 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.[25] In this region there are small changes in the log K_1 values of the amino acid. However, the log K_1 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_1 values. This discussion is in accordance with previous results for other aqueous−organic solvent mixtures and in agreement with the present results.[24−27]

To obtain a quantitative method for evaluation of the solute−solvent interaction on protonation or the formation constants, we have used the method introduced by Kamlet, Abboud, and Taft.[13,14] 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 accepter, 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 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.[12] The multiparametric equation, eq 9, has been proposed, using the solvatochromic solvent parameters, α, β, and π*, which have been introduced in previous reports.[8−11]

$$\log K = A_0 + a\alpha + b\beta + p\pi^* \tag{9}$$

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)

Table 4. Percentage Contribution of KAT Parameters00 on the Effect of Different Media on Protonation and Complexation at 25 °C and Ionic Strength 0.1 mol·dm^{-3} (NaClO$_4$)

species	α	β	π*
log K_1	16.5	43.8	39.7
log K_2	10.8	34.3	54.9
log K_3	6.2	35.8	58.0
log β_{MH2L}	23.3	37.6	39.1
log β_{MHL}	10.6	40.7	48.7
log β_{ML}	14.2	38.1	47.7

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. The empirical values of the solvatochromic solvent parameters (α, β, and π*) for pure methanol and water were obtained from the literature.[12] However, the solvatochromic parameters for the different binary aqueous mixtures of methanol were calculated with the procedure proposed in the literature, eq 10[28]

$$P_{\text{mixture}} = P_{\text{MeOH}}\phi_{\text{MeOH}} + P_{\text{H2O}}\phi_{\text{H2O}} \qquad (10)$$

where P is the property of interest and ϕ is the volume fraction of the component in the solution. The calculated values of solvatochromic parameters used for different aqueous mixtures of methanol are listed in Table 3.

In eq 9 the discontinuous polarizability correction term is omitted because of the solvent used in this work containing no chlorine atom. 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 obtained log K values through the KAT solvent parameter, the protonation constants were correlated with solvent properties by means of single and multiple regression analysis by the computer program (Microsoft Excel Solver).[22] 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 11. Single-parameter correlations of log K_1, log K_2, and log K_3 individually with α, β, or π* did not give good results in all cases. As a typical example, the single-parameter correlations of log K_1 are shown by eq 12.

$$S = \sum (\log K_{\text{exp}} - \log K_{\text{cal}})^2 \qquad (11)$$

$$\log K_1 = 8.47(\pm\ 1.54) - 5.81(\pm\ 0.85)\alpha \qquad (12a)$$

$$\log K_1 = -1.06(\pm\ 0.69) + 5.81(\pm\ 1.23)\beta \qquad (12b)$$

$$\log K_1 = 4.13(\pm\ 1.26) - 2.25(\pm\ 0.67)\pi^* \qquad (12c)$$

(n = 8, $r^2 \cong 0.88$ to 0.89 from eq 12).

To indicate the importance of the KAT parameters, for each parameter in eq 12 the uncertainty values from the average are shown in the parenthesis. So, we correlate log K values versus a multiparametric equation involving α, β, and π*. However, the result presented from a multiparametric eq 9 indicates significant improvement with regard to the single-parameter models, eq 13.

$$\log K_1 = 1.82(\pm\ 0.12) + 0.74(\pm\ 0.06)\alpha + 1.96(\pm\ 0.22)\beta - 1.78(\pm\ 0.17)\pi^* \qquad (13a)$$

$$\log K_2 = 6.23(\pm\ 0.28) + 0.37(0.05)\alpha - 1.18(\pm\ 0.14)\beta + 1.89(\pm\ 0.10)\pi^* \qquad (13b)$$

$$\log K_3 = 7.60(\pm\ 0.19) + 0.31(\pm\ 0.04)\alpha - 1.79(\pm\ 0.12)\beta + 2.90(\pm\ 0.11)\pi^* \qquad (13c)$$

(n = 8, r^2 = 0.9289, 0.9965, and 0.9902, respectively).

The coefficients of α, β, and π* in eqs 13a to 13c are different from each other and are in the order of $\pi^* > \beta > \alpha$ for K_2 and K_3, and $\beta > \pi^* > \alpha$ in the case of K_1 for the amino acid. This indicates the hydrogen-bond accepter basicity parameter of the solvent is the most important for K_1, but in the case of K_2 and K_3, the polarity parameter plays a major role. Finally, the hydrogen-bond donor acidity parameter has less significance in the variation of protonation constant values of the amino acid 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 the other aqueous solutions of methanol. It can be seen from Tables 1 and 3 that the dielectric constants of the solvent mixtures decrease as the solutions are enriched in methanol. The values of log K_2 and log K_3 decrease with decreasing dielectric constant of the media, but this is not true in the case of log K_1 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_2 and log K_3 by the KAT equation imply that a decrease in the polarity of the mixed solvent decreases the protonation constant values of the amino and the sulfydryl groups. According to the above discussion, the negative π* coefficient obtained for log K_1 of cysteine represents a decrease in polarity of the solvent mixtures that causes an increase in the protonation constant values of carboxylic acid. In the latter case, the positive coefficient β (with a relatively large difference with the other coefficients, Table 4) suggests the basicity of the solvent mixtures has a major role.

To show the efficiency of the suggested multiparameter correlations, the calculated log K_2 and log K_3 are listed in Table 1 for comparison, and the experimental values of log K_1 were plotted versus their calculated ones for the studied system by eq 13a, for the different aqueous solutions of methanol (Figure 3). It is observed that the experimental and the calculated values of log K_2 and log K_3 are in good agreement with each other, r^2 > 0.99 in both cases. However, as mentioned, the correlation of log K_1 is poor (Figure 3). From the values of the regression

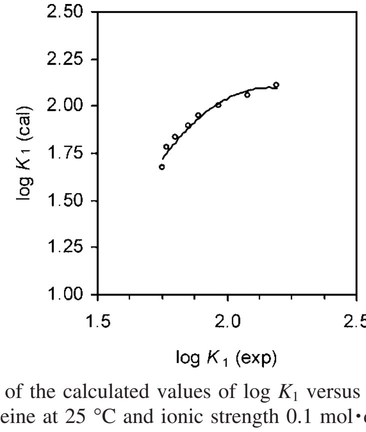

Figure 3. Plot of the calculated values of log K_1 versus the experimental values for cysteine at 25 °C and ionic strength 0.1 mol·dm^{-3} NaClO$_4$.

coefficients, the contribution of each parameter on a percentage basis was calculated and is listed in Table 4.

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. 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 11. 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 14, multiparametric equation, indicates significant improvement with regard to the single-parameter models.

$$\log \beta_{121} = 2.34(\pm 0.09) + 1.16(\pm 0.08)\alpha + 1.87(\pm 0.08)\beta - 1.94(\pm 0.10)\pi^* \quad (14a)$$

$$\log \beta_{111} = 11.92(\pm 0.29) + 0.46(\pm 0.03)\alpha + 1.76(\pm 0.12)\beta - 2.10(\pm 0.11)\pi^* \quad (14b)$$

$$\log \beta_{101} = 4.59(\pm 0.10) + 0.52(\pm 0.04)\alpha + 1.40(\pm 0.14)\beta - 1.75(\pm 0.08)\pi^* \quad (14c)$$

($n = 8$, $r^2 = 0.9965$, 0.9960, and 0.9983, respectively).

In this case, the solvent polarity parameter of the media, π^*, has 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 the other aqueous solutions of methanol. However, the formation constant of the complex species increases with an increase in the solvent hydrogen-bond acceptor basicity parameter, β, and decreases with increasing solvent polarity π^*. They also increase with a decrease in the hydrogen-bond donor acidity parameter, α, of the solvents. The coefficients of π^*, α, and β in eq 14 are in the order of $\pi^* > \beta > \alpha$. This suggests that the polarity parameter power of the solvent is the most important, that the hydrogen-bond acceptor basicity parameter plays a relatively small role, and finally that the hydrogen-bond donor acidity parameter nearly has no significance in changing the formation constants of the Tl(I) + cys system in the various aqueous solutions of methanol. From the magnitude of the coefficients *a*, *b*, and *p*, the percentage contributions of the KAT solvatochromic parameters on the effect of different media on complexation were calculated and are given in Table 4. To show the efficiency of suggested multiparameter correlations, the calculated values of the formation constants are listed in Table 2. It can be seen that the experimental values of log β and the calculated ones are in good agreement.

Conclusions

The combined potentiometric and spectrophotometric measurements were used to characterize the different complex species of the thallium(I)−cysteine system in various aqueous methanol solutions. Our data reveal that three complex species are formed at pH ≅ 3, 6, and 11, respectively. The determined formation constants as well as the protonation constants of cysteine are analyzed in terms of Kamlet, Abboud, and Taft parameters. Single-parameter correlations of the formation and the protonation constants are poor, but multiparameter correlation represents significant improvement with regard to the single-parameter models. The correlations between the protonation constant of the amino and the sulfydryl groups of cysteine in log units with the reciprocal of the dielectric constant of methanol−water mixtures are linear, but this is not true for the protonation of the carboxylic acid group of the amino acid. These findings are in agreement with the Born equation.

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