Chemometric Investigation of Complex Equilibria in the Solution Phase. 3. Chemical Models for the Complexation of Ni(II) with Adipic Acid Dihydrazide and 2-Furoic Acid Hydrazide in Water–*N,N′*-Dimethylformamide and Water–Dioxane Media. Correlation with Solvent Parameters

A. Ravindra Babu and R. Sambasiva Rao*

School of Chemistry, Andhra University, Visakhapatnam 530003, India

The stability constants of binary complexes of adipic acid dihydrazide or 2-furoic acid hydrazide with Ni(II) in water–*N,N′*-dimethylformamide or water–dioxane (10–60% (vol/vol)) were determined pH metrically. The titrand consists of the mineral acid, ligand, and metal ion solutions in water–cosolvent mixtures. The hydrogen ion activities were measured using sodium hydroxide as titrant. The chemical models which gave the best fit were judged using residual analysis. The different trends for the distribution of species (MLH, ML, ML₂H, and ML₂) in the presence of varying amounts of cosolvent were explained on the basis of electrostatic interactions and specific solute–solvent and solvent–solvent contributions. In order to ascertain the accuracy of stability constants, the simultaneous effect of errors in the ingredient concentrations and electrode parameters was studied using three-dimensional plots. It was found that perturbation in pK_w and total initial volume has a negligible effect. The robustness of the computer program MINIQUAD75 to refine the stability constants for wild initial guess values was investigated.

Introduction

Acid hydrazides have biological importance (*1*) and are used in industry, agriculture, and synthesis. Adipic acid dihydrazide has been widely used for coatings of epoxy resins and in varnishes. Further it is employed as a latent hardener, curing agent, and cross-linker in many industrial products such as semiconductor devices (*2*). 2-Furoic acid hydrazide is one of the reactants in the synthesis of fungicides, nervous stimulants, and low density foams (*3*). In this work we study the effect of cosolvent on the formation constants of complexes of Ni(II) with adipic acid dihydrazide and 2-furoic acid hydrazide using a glass electrode. Due to difficulties, earlier studies were limited to the determination of log β values of mononuclear, unprotonated, and unhydrolyzed complexes. But conclusions drawn by neglecting minor species are in error. We have used a nonlinear least-squares program (MINIQUAD75 (*4*)) which makes it possible to search for all possible species.

Experimental Section

Aqueous solutions of adipic acid dihydrazide and 2-furoic acid hydrazide (Fluka AG, Switzerland) of concentration 0.1 mol dm⁻³ were prepared without further purification in doubly distilled water. BDH AnalaR nickel(II) chloride was used to prepare a 0.1 mol dm⁻³ stock solution which was rendered slightly acidic to repress the hydrolysis of metal ion. Its concentration was determined by complexometric titrations against a standard solution of EDTA. The free hydrogen ion concentration in the stock solution was determined by estimating the acid released on passing a known volume through a column of amberlite IR-120 resin. The result was in good agreement with that obtained by measuring the pH of a dilute solution of the metal ion in the presence of a background electrolyte, when the appropriate correction factor was used. All other solutions, including hydrochloric acid, sodium hydroxide, and sodium chloride, were prepared using degassed doubly glass distilled deionized water through which nitrogen gas was purged to expel any dissolved oxygen or carbon dioxide. Since even small systematic errors in concentrations affect the calculated formation constants, the

pessimistic errors in solution concentrations were calculated by COSWT (*5*) (concentration of solution by weight method). The random errors in the concentrations of alkali solutions were assessed by COST (*5*) (concentration of solution by titration). The very high *F* (Fischer variance ratio) value (1.567) indicates good precision of the titrimetric results. *N,N′*-Dimethylformamide (E. Merck) was purified by drying over calcium hydroxide and distilling twice at 0.5–3.0 mmHg (*6*). The fraction at 55 °C was collected as the substance decomposes at higher temperatures. The criteria (*7, 8*) for purity were resistance (>10 000 Ω) and refractive index (1.48). Dioxane (E. Merck) was purified by refluxing over KOH and drying with barium oxide. The equilibration of the glass electrode and details of the titration assembly have been described previously (*9*).

Experimental Design for Complex Equilibria in Aquo-Organic Media. The standard deviations in log β values calculated by any algorithm depend on the optimization function and convergence criteria. To enhance the signal to noise ratio, we used the recommendations of the IUPAC Commission on Equilibrium Data (*10*). A research pH meter (PHM 64) (radio meter) in conjunction with a 0–14 pH range combination electrode (GK 2401B) was employed in the present study. Potassium acid phthalate or Borax solutions were used for preliminary calibration of the electrode. Because of the inherent disadvantages in adopting only two buffers for calibration of glass electrodes, Gran (*11*) analysis of the titration of a strong acid with alkali solution was used. In this method a plot of 10⁻ᵖᴴⁱ($V_0 + v_i$) versus v_i intersects the volume axis at the equivalence point (v_e) where V_0 is the initial total volume of titrand and v_i is the volume of alkali solution added. No appearance of curvature indicates that the pH metric response is Nernstian and activity coefficients and electrode junction potentials are invariant during the titration. The electromotive force (emf) measured in aquo-organic media is affected (eq 1) by the liquid junction potential

$$E = E° + s \log F_{Hi} + s \log \delta_{H^+} + E_j + E_{Na^+} \quad (1)$$

(E_j), standard electrode potential ($E°$), and change in potential

due to the sodium ion error (E_{Na^+}). F_{Hi} is the equilibrium hydrogen ion concentration and s the Nernstian slope. Since we monitored pH meter dial readings in the present study, a correction factor (log F) taking into account the cumulative effects of these terms is employed to calculate pH_i from the equation

$$PH_i = B_i + \log F \qquad (2)$$

The magnitudes of log F values were obtained by the linear least-squares analysis of PH_i versus B_i.

Relative concentrations of metal complex species depend not only on the equilibrium constants but also on the ratio of ligand to metal and the judicious selection of other conditions like temperature, cosolvent content, and surfactant concentration. Hence, a chemometric experimental design is necessary to obtain a good knowledge of the system from the minimum number of experiments. Another reason to maximize the concentration of some of the species is to prepare complexes of desired stoichiometry with minimum interference from other species and to reduce the number of overlapping equilibria. In this study, the hydrazide to Ni(II) ratio was varied from 2:1 to 5:1 so that, at the lowest ratio, high concentrations of MLH_h species would be formed, while at the other extreme ratio, ML_2H_h would be formed. In order to investigate the effect of water-miscible cosolvents on the speciation, 10–60% (vol/vol) aquo-N,N'-dimethylformamide (or dioxane) media were employed and the change in the free concentration of hydrogen ion was monitored during alkalimetric titrations. The details of ingredient concentrations and ambient conditions are given in Table I.

Results and Discussion

Chemical Modeling. A chemical model in complex equilibria represents the stoichiometric coefficients of the species and their equilibrium constants. It is a data reduction technique. The interaction of a metal ion with most anionic forms of the ligand and proton(s) in aqueous or aquo-organic mixtures results in NB complexes. The formation constants of the species for the equilibrium in eq 3 is given by eq 4,

$$m(j)M + l(j)L + h(j)H \rightleftharpoons M_{m(j)}L_{l(j)}H_{h(j)} \qquad (3)$$
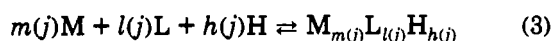
$$\beta_{m(j)l(j)h(j)} = [M_{m(j)}L_{l(j)}H_{h(j)}]/F_M^{m(j)}F_L^{l(j)}F_H^{h(j)} \qquad (4)$$

where F_M and F_L are the free concentrations of metal ion and ligand at the experimental point and $h(j)$ is negative for hydroxyl ions while positive for protons. We have used the computer program MINIQUAD75 in this investigation which employs the sum of the squares of residuals in all mass balance equations (U) as the optimization function:

$$U = \sum_{i=1}^{n_p} (T_{MEi} - T_{MCi})^2 + (T_{LEi} - T_{LCi})^2 + (T_{HEi} - T_{HCi})^2 \qquad (5)$$

$$T_{MCi} = F_{Li} + \sum_{j=1}^{n_p} \beta_{m(j)l(j)h(j)} F_M^{m(j)} F_L^{l(j)} F_H^{h(j)} \qquad (6)$$

Similar equations can be written for T_{LCi} and T_{HCi}.

Necessity of Approximate Stability Constants. Although wild constants which are far away from true values should converge in principle, recent studies by Sylva et al. (*12*) and Larsson and Pardue (*13*) advocate the necessity of fairly good initial estimates especially in complex systems (more than two overlapping equilibria). Otherwise the species that really exist may be rejected or the model leads to an ill-conditioned matrix. We employed Lagrange interpolation (LIFSC) (*14*) and linear least-squares analysis of pruned data

(SCPHD) (*15*) for the determination of the guess values for ML_n-type complexes. The guess constants for protonated and hydroxylated species were based on a knowledge of β values of proton–ligand complexes and refined values of stability constants for ML_n complexes. The limits of log β_{110} and log β_{120} by this program (MINIQUAD75) were investigated, and the results clearly indicated that for the chemical model (log β_{011} = 2.508, log β_{110} = 3.707, and log β_{120} = 6.455) the approximate/guess values of log β_{110} and log β_{120} can be 2 log units on either side.

Selection of Best Fit Model. Almost all the programs available in complex equilibria output the refined values of stability constants from only a given set of stoichiometric coefficients and initial estimates of stability constants of the species. Thus, the selection of the species has been a matter of subjective decision, based on auxiliary functions (average number of ligands bound per metal ion, average number of protons released per mole of metal or ligand). Of the two popular approaches, forward selection and backward elimination (*16*), the former method is used to develop models containing an increasing number of species from a base model (ML and ML_2). The best fit chemical models are derived (Table II) on the basis of minimum U (sum of the squares of deviations in metal ion, ligand, and hydrogen ion concentrations), the standard deviation in log β, and other statistics pertaining to residuals (χ^2, mean and standard deviation of residuals). Since values of χ^2 for residuals in our study (6–60) are less than $\chi^2_{\nu,0.5}$ (ν is the degree of freedom) (*17*), the chemical models reported now represent a good fit to experimental data. Residual plots for a typical system (Ni-(III)–2-furoic acid hydrazide in 10% dioxane) show that the model containing ML and ML_2 species represents the complex equilibria better than the one-parameter model, and further over-ambitious modeling has not been performed as the deviations of calculated values of pH from experimental data are far greater than the accuracy of the data acquisition system.

Concentration Profiles of Metal–Ligand Complexes. In the pH region for metal complexation the reactive forms of the ligand are LH_2 and LH, indicating the possibility of the detection of $M(LH)_n$ in addition to ML_n-type species by the pH metric technique. On the basis of the distribution of various species, the formation of different metal complexes may be represented by the following equilibria:
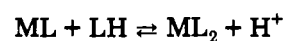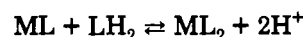
$$M(II) + LH_2 \rightleftharpoons MLH + H^+ \qquad (7)$$

$$M(II) + LH_2 \rightleftharpoons ML + 2H^+ \qquad (8)$$

$$MLH \rightleftharpoons ML + H^+$$

$$M(II) + 2LH_2 \rightleftharpoons ML_2H + 3H^+ \qquad (9)$$

$$ML + LH_2 \rightleftharpoons ML_2H + H^+$$

$$MLH + LH_2 \rightleftharpoons ML_2H + 2H^+$$

$$ML_2H \rightleftharpoons ML_2 + H^+ \qquad (10)$$

$$ML + LH_2 \rightleftharpoons ML_2 + 2H^+$$

$$ML + LH \rightleftharpoons ML_2 + H^+$$
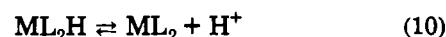
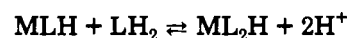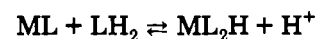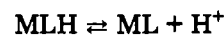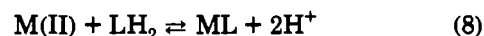**Table I. Total Initial Concentrations of Components[a]**

% of cosolvent DMF/DIOX (vol/vol)	TLO/(10^{-3} mol dm^{-3})						TMO:TLO
	N,N'-dimethylformamide			dioxane			
	AADH	FAH	log F	AADH	FAH	log F	
10.0	5.985	6.002	−0.19	6.030	5.912	−0.04	1:2
	9.986	10.005		10.051	9.854		1:3
	14.964	15.007		15.076	14.781		1:5
20.0	6.161	6.067	−0.28	6.030	6.061	+0.02	1:2
	10.270	10.111		10.051	10.101		1:3
	15.400	15.167		15.076	15.152		1:5
30.0	6.161	5.797	−0.38	6.136	6.150	+0.08	1:2
	10.269	9.662		10.227	10.250		1:3
	15.403	14.493		15.141	15.375		1:5
40.0	6.160	5.797	−0.51	6.136	6.034	+0.12	1:2
	10.270	9.662		10.227	10.057		1:3
	15.400	14.493		15.341	15.086		1:5
50.0	6.160	5.894	−0.48	6.441	6.056	+0.22	1:2
	10.270	9.823		10.736	10.094		1:3
	15.400	14.736		16.104	15.140		1:5
60.0	5.953	5.973	−0.75	6.111	6.061	+0.35	1:2
	9.922	9.956		10.186	10.101		1:3
	14.883	14.933		15.279	15.152		1:5

[a] Titrand $T_{Mo(Ni^{2+})}$ = 3.482 × 10^{-3}, E_o = 21.85 × 10^{-3} mol dm^{-3}, μ = 0.10 mol dm^{-3} (NaCl), V_o = 50.0 cm^3, T = 301 K, titrant [NaOH] = 0.390 163 mol dm^{-3}.

Table II. Best Fit Chemical Models with Statistical Parameters for Ni(II)–Adipic Acid Dihydrazide (or 2-Furoic Acid Hydrazide) in Aquo-N,N'-Dimethylformamide (or Dioxane) Media

% (vol/vol)	log β_{mlh} (SD)				pH range	N_E:n_p	$U/(n_p - m) \times 10^8$	χ^2	kurtosis	skewness	$\sigma \times 10^4$	mean $\times 10^6$
	110	120	111	121								
	Ni(II)–Adipic Acid Dihydrazide in Dimethylformamide											
10	4.962 (4)	6.409 (6)	5.716 (8)	9.824 (8)	1.8–4.6	3:89	1.7374	49.94	3.07	−0.91	3.15	−5.45
20	5.175 (1)	6.639 (3)	5.510 (9)	9.711 (12)	1.8–4.6	3:90	2.8233	31.06	4.79	0.04	1.13	−3.11
30	4.857 (6)	6.951 (8)	5.182 (11)	9.362 (4)	1.8–4.6	3:87	5.4866	43.95	7.49	−1.74	1.56	−1.89
40	4.309 (4)		5.392 (5)	9.646 (11)	1.8–4.6	3:90	6.4826	39.04	9.31	−1.86	1.88	−1.48
50	4.052 (7)		5.694 (13)	10.306 (11)	1.8–4.6	3:91	2.3694	51.13	5.43	−1.49	3.06	−1.02
60	3.712 (5)		6.126 (9)	10.892 (12)	1.8–4.6	3:90	1.9959	43.10	3.15	0.07	0.95	−1.49
	Ni(II)–Adipic Acid Dihydrazide in Dioxane											
10	4.155 (1)	6.742 (8)		9.695 (7)	1.7–4.8	3:80	1.1134	59.78	14.15	2.91	0.59	9.24
20	4.304 (4)	7.222 (4)		9.912 (9)	1.7–4.8	3:78	0.0886	31.01	3.75	0.06	0.16	−0.25
30	4.715 (5)	7.463 (6)		10.256 (9)	1.7–4.8	3:81	1.3261	56.03	3.19	0.02	0.65	−1.34
40	5.174 (3)	7.739 (3)		10.517 (12)	1.7–4.8	3:82	6.9288	18.12	7.31	2.04	4.71	0.71
50	4.133 (2)	6.349 (3)		9.351 (9)	1.7–4.8	3:84	0.2468	16.26	4.06	−0.23	0.28	−1.97
60	3.835 (8)	5.832 (7)		8.964 (4)	1.7–4.8	3:84	2.5695	29.14	5.85	−1.25	1.49	−9.12

% (vol/vol)	log β_{mlh} (SD)		pH range	N_e:n_p	$U/(n_p - m) \times 10^8$	χ^2	kurtosis	skewness	$\sigma \times 10^4$	mean $\times 10^6$
	110	120								
	Ni(II)–2-Furoic Acid Hydrazide in Dimethylformamide									
10	3.345 (8)	6.042 (15)	2.0–2.6	3:22	24.4812	5.67	3.55	−0.77	3.19	−33.73
20	3.556 (2)	6.267 (10)	2.0–2.5	3:16	24.2087	8.67	3.47	0.02	2.65	15.54
30	3.635 (5)	6.455 (9)	1.8–2.6	3:65	26.8428	7.28	4.89	−1.27	2.90	−33.46
40	3.707 (3)	6.455 (17)	1.8–2.7	3:67	25.6153	8.31	5.02	−1.30	2.87	−32.26
50	3.977 (4)	6.803 (3)	1.8–3.2	3:51	32.6551	12.91	4.01	−1.00	3.23	−36.62
60	3.411 (3)	6.094 (12)	2.0–6.0	3:35	23.6828	64.52	5.60	1.26	2.73	4.36
	Ni(II)–2-Furoic Acid Hydrazide in Dioxane									
10	2.986 (7)		1.8–3.2	3:70	11.7159	6.30	4.29	−1.04	1.93	−2.03
20	2.240 (3)		1.8–4.0	3:82	0.7437	25.37	4.00	−1.00	0.88	−21.57
30	2.709 (10)		1.8–4.0	3:80	13.5136	50.87	5.95	0.44	2.08	−24.09
40	2.804 (2)		1.8–2.3	3:41	0.4805	22.38	5.10	−0.21	0.65	−1.42
50	2.890 (3)		1.8–3.2	3:54	1.4111	23.93	5.21	−0.03	1.15	−12.91
60	3.116 (2)		1.6–3.2	3:75	23.0669	15.46	2.91	−0.40	2.71	−4.63

Figure 1 indicates the percentage of species that exhibit different trends with addition of the cosolvent which is a manifestation of the cumulative effect of various solute–solvent interactions and solvent–solvent equilibria.

Chemometric Inspection of the Reliability of log β Values of the Best Model. The accuracy of the stability constants refined by any of the existing algorithms depends not only on the initial estimates but also on the number of overlapping equilibria in a particular pH range and correlation of stability constants. The cumulative effect of errors which crept into the final model due to inaccuracies in the proton–ligand stability constants is not transparent as the residual statistics indicate only the unexplained variation in pH in terms of explanatory parameters (stoichiometric coefficients of species and stability constants).

The effect of systematic errors of different magnitudes up to pessimistic limits in magnitudes of proton–ligand stability constants and concentrations of ingredients (strong acid, alkali solution, and ligand) on log β values was studied using factorial design.

Little effect was observed in the magnitude of the stability constants (log β_{11h}) when an error of ±3σ was introduced into the best fit model for acid–base equilibria. It indicates the high precision of the stability constants reported in this
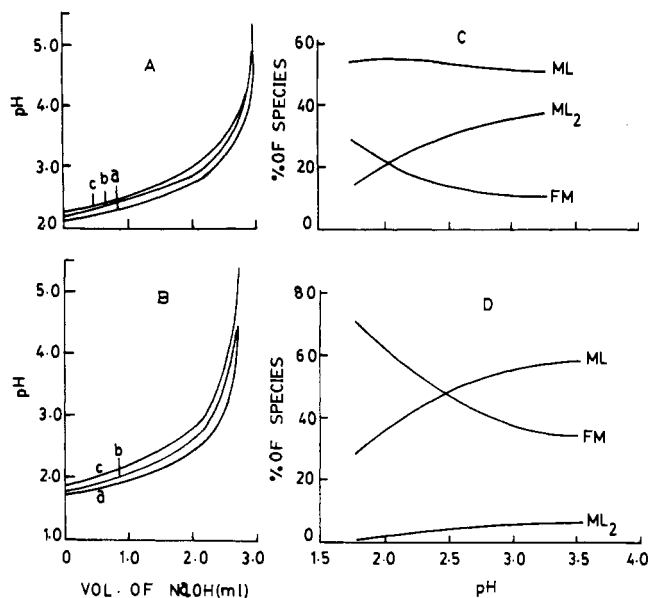
Figure 1. Alkalimetric titration curves and species distribution diagrams of the Ni(II)-2-furoic acid hydrazide system: (A) pH metric titration curves in 30% water-N,N'-dimethylformamide medium, concentrations of the ligand a, b, and c are 5.797, 9.662, and 14.493 × 10^{-3} M; (B) pH metric titration curves in 30% water-dioxane medium, a, b, and c are 6.150, 10.250 and 15.375 × 10^{-3} M; (C) and (D) species distribution diagrams in 30% water-N,N'-dimethylformamide and 30% water-dioxane mixtures, respectively.

investigation. However, a large amount of error in log β_{01h} leads to invalidating some chemical models or log β_{1lh} whose magnitudes are considerably far from those reported in the best fit chemical model.

A few typical 3D plots depicted in Figure 2 represent the simultaneous effect of some of the combinations of these dangerous parameters on the change in log β_{110} values (Δ log β). It is interesting that even a large error in the initial volume (V_0) has a negligible effect which throws light on the effect of mixing volumes in aquo-organic media. It is found that errors in E_0 and [alk] have a more pronounced effect than those in T_{L0} and T_{M0}. However, the chemical models proposed are accurate to 0.02 units in log β as the errors in ingredient concentrations are less than 1%.

In an attempt to check whether any equilibria have been ignored in the present modeling study, the stability constants of acidic-basic equilibria are refined, keeping the corresponding constants for metal-ligand complexes fixed. The good agreement of the constant log β_{011} = 2.517 (2) for Ni(II)-2-furoic acid hydrazide in 40% N,N'-dimethylformamide with that obtained earlier (log β_{011} = 2.508 (3)) in separate experiments designed for acidic-basic investigation shows very clearly that no other solution equilibria exist which change the hydrogen ion concentration.

Results of simultaneous refinement of proton-ligand and metal-ligand complexes for Ni(II)-2-furoic acid hydrazide in 40% N,N'-dimethylformamide (log β_{011} = 2.626 (8), log β_{110} = 3.526 (3), log β_{120} = 6.722 (2)) show that log β values are altered due to the existence of several overlapping equilibria.

Solute-Solvent Interactions. The nonlinear change in the formation constants of complexes of adipic acid dihydrazide-2-furoic acid hydrazide with Ni(II) in 10-60% (vol/vol) of dioxane or N,N'-dimethylformamide indicates that both electrostatic and nonelectrostatic factors contribute due to the cumulative effect. The transfer free energy ΔG^t of a solute from water to aquo-organic medium is given by eq 11

$$\Delta G^t = \Delta G^t_{el} + \Delta G^t_{nel} \tag{11}$$

ΔG^t is related to the mole fraction (n_x) of the solvent by eq 12, where μ_t is a constant for each solvent concentration of the solute.

$$\Delta G^t = n_x \mu_t \tag{12}$$

If the electrostatic interactions alone operate, ΔG^t is proportional to the reciprocal of the dielectric constant (D_M) of the medium by eq 13, where D_W is the dielectric constant

$$\Delta G^t \propto 1/D_M - 1/D_W \tag{13}$$

of water. In order to understand the relative importance of electrostatic and nonelectrostatic forces, a detailed analysis of the variation of the logarithm of the equilibrium constant with $1/D_M$ and n_x is carried out.

Analysis Using n_x and $1/D$. The various approximate equilibria models are based on $1/D$, n_x, and/or functions of [H_2O] in aquo-organic media. From the visual inspection of log K^M vs n_x plots, an orthogonal polynomial fit (18) has been attempted. Typical plots (Figure 3) indicate a quadratic trend and cubic ones in rare cases. Use of higher order equations is not required in view of the errors in log K^M and statistical parameters of the fit. Since $1/D$ and $(D-1)/(2D+1)$ are found to be perfect linear functions of n_x in the case of aquo-N,N'-dimethylformamide, no further analysis is made with other functions of D.

The linear trends observed for the variation of log K^M_{ML} with n_x or $1/D$ of aquo-cosolvent mixtures in the case of Ni(II)-glycine (19) and acetylacetone-salicyladehyde complexes of divalent metal ions in aquo-dioxane (20) were interpreted on the basis of predominance of the O-M bond as compared to the N-M bond. However, McBryde (21) observed apparently anomalous behavior (sometimes exhibiting multiple extrema) for Cu(II) or Ni(II) complexes of nitrilotriacetic acid or iminodiacetic acid when methanol was used as the cosolvent. This behavior was rationalized on the basis of multiple solution processes of varying importance and changes in the solvation shell. However, no simple relationship was found for chelates containing N-M bonds, and conflicting results were reported. For example, an increase in cosolvent content has little influence on the stabilities of complexes of ammonia (22), ethylenediamine (23), etc. Pelletier (24) obtained thermodynamic data for amino acid complexes of Ni(II), Cu(II), and Zn(II) which were difficult to interpret. Although Irving and Rossotti (25) proposed the possibility of predicting the relative importance of O-M and N-M bonds for metal complexes of multisite donors, it led to contradictory and inconclusive results. After a thorough investigation of 5-substituted, 8-hydroxyquinoline complexes with Ca(II), Mg(II), Mn(II), and Zn(II) in aquo-dioxane, Steger and Corsini (26) concluded that it is hazardous to interpret deviations from expected behavior due to N-M bond importance. In our case N,N'-dimethylformamide is a cation stabilizer, and even the protonated ligands are cations wherein the relative stabilities will decide the cumulative effect.

Analysis Based on the Complete Equilibrium Constant. Faraglia et al. (27) proposed a chemical model for the interpretation of the changes in equilibrium constants in binary solvent mixtures wherein the eliminated coordinated water is also considered. Extension of Marshall's (28) concept of the complete equilibrium constant ($K^{M'}_{ML}$) to aquo-organic media leads to

$$K^{M'}_{ML} = K^M_{ML}[H_2O]_M \tag{14}$$

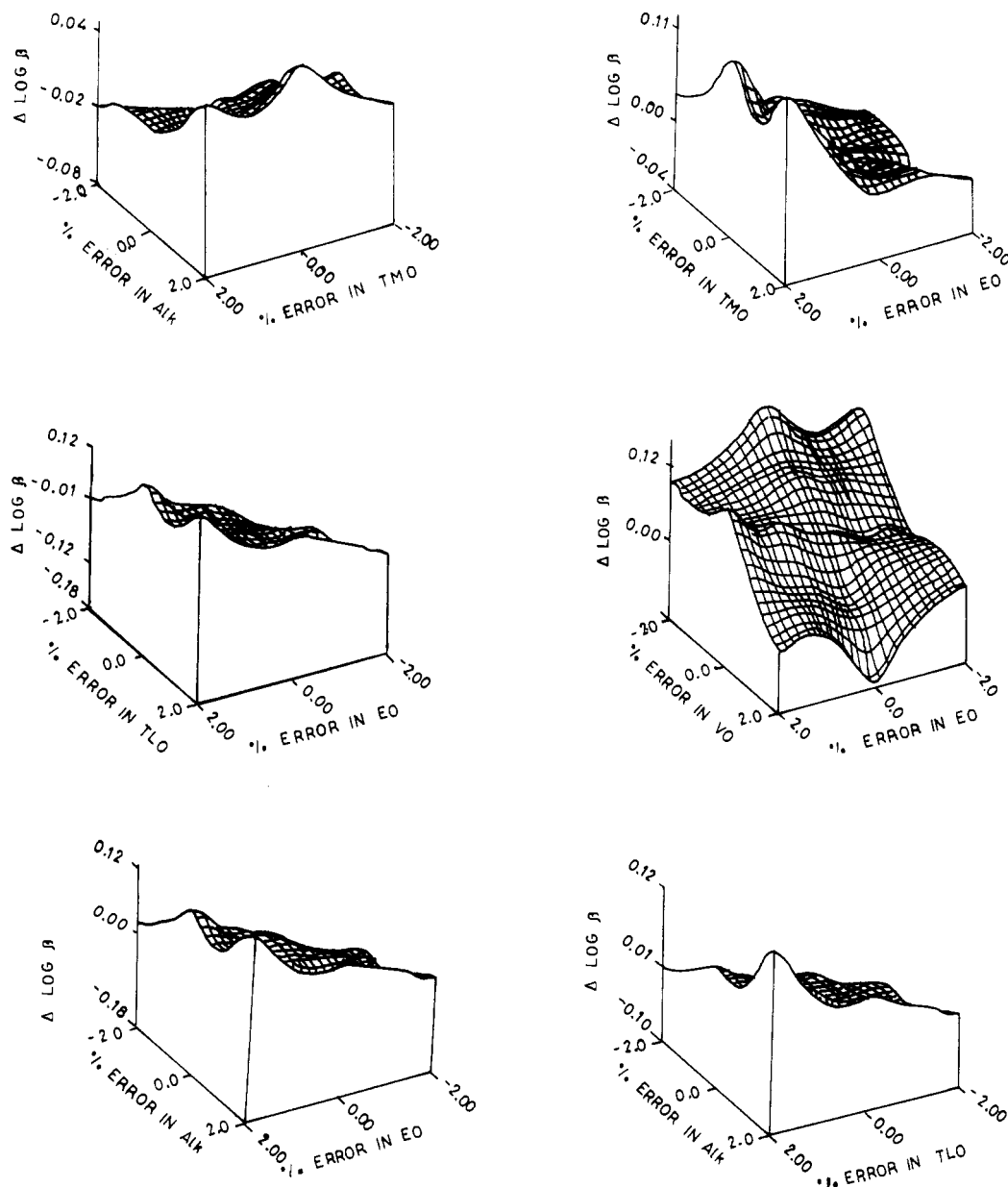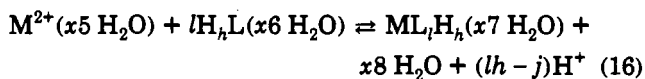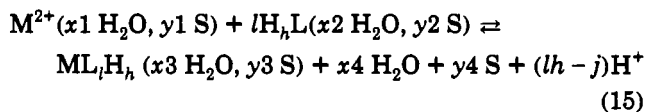where [H_2O]$_M$ is the concentration of water in binary solvent

Figure 2. 3D representation of $\Delta \log \beta_{110}$ (Ni(II)–2-furoic acid hydrazide in 40% N,N'-dimethylformamide) for errors in ingredient concentrations.

media and $K^M{}_{ML}$ is the equilibrium constant calculated at that solvent composition. This equation is based on the implicit assumption that species are hydrated only which is in contradiction with the established fact that metal ions, ligands, and complex species are highly solvated under favorable conditions. From the idea of the change in the number of water and solvent molecules for formation of a metal complex (eqs 15 and 16) x's and y's are the number

$$M^{2+}(x1\ H_2O, y1\ S) + lH_hL(x2\ H_2O, y2\ S) \rightleftharpoons$$

$$ML_lH_h\ (x3\ H_2O, y3\ S) + x4\ H_2O + y4\ S + (lh - j)H^+ \quad (15)$$

$$M^{2+}(x5\ H_2O) + lH_hL(x6\ H_2O) \rightleftharpoons ML_lH_h(x7\ H_2O) +$$

$$x8\ H_2O + (lh - j)H^+ \quad (16)$$

of water and solvent molecules in the coordination sphere of the species. The ΔG^t for the process can be calculated by eq 17.

The above equation has two unknown parameters, w and j. w is calculatable from a plot of j log [S] + log K^M vs log
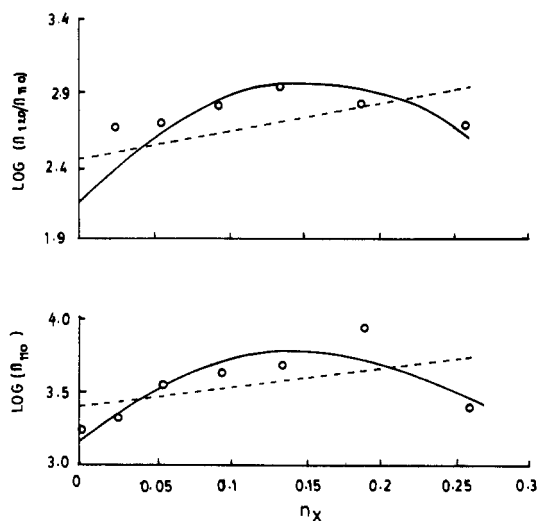

Figure 3. Orthogonal polynomial fit of log β with mole fraction: (O) experimental points; (—) quadratic; (- - -) linear.
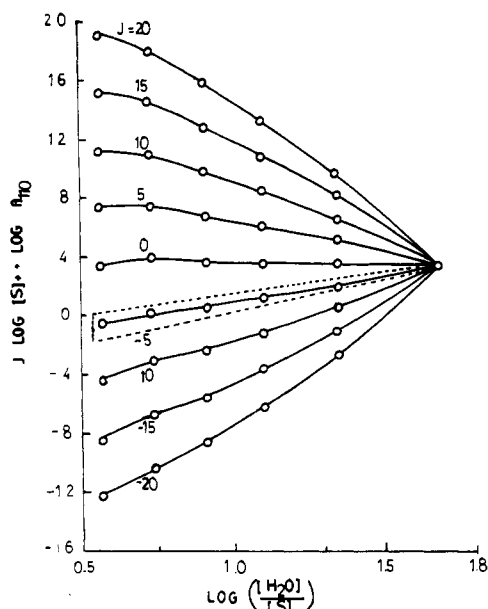
Figure 4. Effect of j on the linearization of j log [S] + log β^M vs log ([H_2O]/[S]). The straight line corresponding to j = −5 enclosed in dashed box represents the best fit.

$$(j \log [S] + \log K^M_{ML}) - \log K^W_{ML} = \Delta G^t/2.303RT -$$
$$w \log ([H_2O]_M/[S]_M) + j \log [H_2O]_M \quad (17)$$

([H_2O]$_M$/[S]$_M$) provided the total number of water (w) and solvent molecules (s) released is assumed. [S] is the concentration of cosolvent. Mui and McBryde (22) chose the best straight line on the basis of statistical parameters, varying j (=$w + s$) in integral increments or in fractions. We studied the variation of j from −8 to +8 with unit increments and the change in the number of water (w) and solvent (s) molecules was found to be −5 (Figure 4). The linear relationship is established by visual inspection, residuals in log K^M, and rigorous statistical parameters like the corrected correlation coefficient, Exner Ψ (29), and Ehreuson ϕ (30) applicable for a small number of data points ($n < 6$). It implies that the total change of water and cosolvent molecules associated with the equilibrium is invariant over the composition range investigated. The empirical quadratic model is not only instrumental in the prospective prediction of log K^M for homologous compounds or those in similar solvents but also in shedding light on the effective dielectric constant (31) at the biological active site.

Acknowledgment

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Abbreviations and Symbols

$\beta_{m(j)l(j)h(j)}$	overall formation constant defined by eq 4
F_M, F_L, F_H	equilibrium concentrations of free metal, free ligand, and free hydrogen ion
U	sum of the squares of residuals in all mass balance equations (eq 5)
$T_{MEi}, T_{LEi}, T_{HEi}$	total concentrations of metal, ligand, and hydrogen ion
$T_{MCi}, T_{LCi}, T_{HCi}$	calculated concentrations of total metal, ligand, and hydrogen ion
n_p	number of experimental points
$\bar{n}$	average number of ligands bound per mole of metal ion
ΔG^t	change in transfer free energy
n_x	mole fraction of the solvent

D	macroscopic dielectric constant
w, s, j	number of water molecules, solvent molecules, and their sum released in equilibrium (eq 10)
E_o	initial concentration of mineral acid
V_o	initial volume of titrand
N_E	number of titration curves
μ	ionic strength
T_{Mo}, T_{Lo}, T_{Ho}	total initial concentration of metal, ligand, and hydrogen ion
SD	standard deviation
R_i	$=[(T_{MEi} - T_{MCi}) + (T_{LEi} - T_{LCi}) + (T_{HEi} - T_{HCi})]$
mean	$=(\sum_{i=1}^{n} R_i)/n_p$
variance	$=(\sum(R_i)^2)/(n_p - m)$
kurtosis	$=(\sum(R_i)^4)/n_p(var)^2$
χ^2	$=\sum(R_i)^2/(T_{XEi})^2$
σ	$=(var)^{1/2}$
skewness	$=(\sum(R_i)^3)/n_p(var)\sigma$

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Registry No. H^+, 12408-02-5; dimethylformamide, 68-12-2; dioxane, 123-91-1.