

Study of Binary Complexes of Several Transition Metal Ions with D-Naproxen in Methanol—Water Medium by Potentiometry

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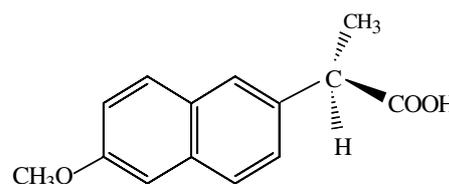
Binary complexes of D-naproxen (HL) with several transition metal ions M(II) (M = Cd, Co, Ni, Cu, and Zn) were studied potentiometrically in 60 vol. % methanol—water at 25°C and $I(\text{KNO}_3) = 0.2 \text{ mol dm}^{-3}$. The stability constant of binary complexes was estimated by using the computer programs MINIQUAD and MIQUV. For the ligand, the protonation constant increased, while the content of methanol increased in mixed solvent. The results show that the stability constants of the binary complexes ML_2 for the different metal ions, which were found to be $\beta_{\text{CdL}_2} < \beta_{\text{CoL}_2} < \beta_{\text{NiL}_2} < \beta_{\text{CuL}_2} > \beta_{\text{ZnL}_2}$, have an Irving—Williams order.

As a nonsteroidal antiinflammatory analgesic, D-naproxen (HL) was used extensively in the clinical practice for treatment of arthritis and chronic and acute pain states [1]. Many studies have shown that metal ions play a vital role in a vast number of widely different biological processes and some diseases are related to the lack of some metallic elements vital to life. It has been observed that a copper supplement is desirable in the treatment of rheumatoid arthritis [2]. Although the metal complexes of naproxen have been investigated because of the application in medicine [3], less attention has been paid in solution system to its coordinative behaviour and the stability. In order to understand the interaction between drug and metal ion, it is worthwhile to undertake the ascertainment of the complexes species and the estimation of the stability constants.

In the present research, the formation and stability of the binary complexes of ligand naproxen with several transition metal ions M(II) were considered by potentiometry in 60 vol. % methanol—water at $(25 \pm 0.1)^\circ\text{C}$ and $I(\text{KNO}_3) = 0.2 \text{ mol dm}^{-3}$.

EXPERIMENTAL

D-Naproxen (medically pure, Southwest Second Pharmaceutical Factory, China) (Formula 1) was dissolved with an equimolar amount of NaOH solution in water. The reaction mixture was stirred until clear, and then acidified; the white product was separated out by filtration and dried over a molecular sieve under vacuum. M.p. = 153—155°C (the literature [4] value



Formula 1. Structural formula of D-naproxen.

is 155.3°C). For $\text{C}_{14}\text{H}_{14}\text{O}_3$ ($M_r = 230.26$) $w_i(\text{calc.}): 73.03\% \text{ C}, 6.13\% \text{ H}$; $w_i(\text{found}): 72.92\% \text{ C}, 6.12\% \text{ H}$.

The other reagents, obtained from Shanghai Chemical Reagents Supplier, were of anal. grade or high purity, and the water for preparing solutions was deionized by means of ion-exchanger equipment. For the stock solutions, the contents of metal ions M(II) (M = Cd, Co, Ni, Cu, and Zn) in nitrate form were determined by complexometric titration against EDTA. The stock solution of naproxen was prepared by weighing and kept out of sunlight. Carbonate-free titrant NaOH was prepared by diluting the saturated stock solution, and then standardized with potassium hydrogen phthalate (dried at 120°C for 4 h).

A model PXS-215 pH/mV-meter (accuracy: $\pm 0.2 \text{ mV}$) assembled with model 231 glass electrode and model 232 calomel electrode (Shanghai Rex Instruments Factory, China) was employed for all potentiometric measurements. A model DAB-1B digital automatic burette (Jiangsu Electroanalytical Instruments Factory, China, accuracy: $\pm 0.003 \text{ cm}^3$) was used to

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deliver titrant base. Sample solutions were titrated in a double-walled glass cell maintained at $(25 \pm 0.1)^\circ\text{C}$ by means of water circulation from a water thermostat (TB-85 Thermo Bath, Shimadzu) and were stirred magnetically under a continuous flow of pure nitrogen.

The calibration of glass electrode was followed by the procedure of our earlier works [5, 6] employing the computer program MAGEC [7].

For the valuation of the protonation constant of ligand, four sample solutions in which φ_m (the volume fraction of methanol in mixed solvent) was changed from 50 to 80 vol. % were used. The concentration of naproxen was changed in the range of $(1.0\text{--}3.0) \times 10^{-3} \text{ mol dm}^{-3}$. Every sample solution was titrated with a standard NaOH solution in the pH range 4.2—6.5.

The pH titrations of the binary systems were carried out with initial 50.0 cm^3 sample solutions, which had a content of 60 vol. % methanol and a ratio of $n(\text{metal ion}):n(\text{ligand}) = 1:1, 1:2,$ and $1:3$, respectively. The concentration of naproxen was fixed to $3.0 \times 10^{-3} \text{ mol dm}^{-3}$ and that of metal ions was changed. The pH range for data collection was 4.2—7.1. All the calculations were performed with the aid of computer programs MINQUAD and MIQUV [8], which were based on the least squares. The procedure included the preliminary refinement of the formation constants with MINQUAD, as well as the refinement with MIQUV using the $\log \beta$ values obtained by MINQUAD as starting values. With this cycle, the computed result is more precise and reliable.

The notation β_{pqs} (concentration constants) was defined as follows (charges are omitted for simplicity)



$$\beta_{pqs} = \frac{[MpLqHs]}{[M]^p [L]^q [H]^s}$$

where $p, q,$ and s denote the numbers of moles of $M(\text{II})$ ions, deprotonated naproxen (L^-), and proton (the negative value of s denotes the hydroxyl-containing complexes), respectively. The complexes species are simply referred to as the combination of pqs and the formation constant is expressed as β_{pqs} .

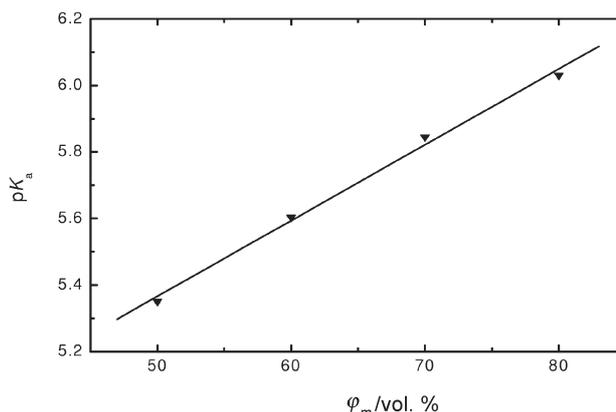


Fig. 1. The relationship between the protonation constant (pK_a) of D-naproxen and the volume fraction of methanol in mixed solvent (φ_m).

RESULTS AND DISCUSSION

The protonation constants pK_a of naproxen were estimated 5.351(2) (50 vol. %) (the first parenthesis presents the standard deviation, the second one the volume fraction of methanol), 5.604(2) (60 vol. %), 5.845(3) (70 vol. %), and 6.030(2) (80 vol. %), respectively.

It is obvious that the pK_a value of naproxen increased with the increase of φ_m . In fact, the methanol solvent has a relatively lower polarity than water, so decreasing the polarity of mixed solvent will lead to the increase of the bonding force between the ions with different charge. That is to say that the deprotonation ability of naproxen is decreased in a medium with the higher φ_m . This result is similar to the reports by Hosny *et al.* [9] about the effect of organic solvent on the protonation constant of tetracycline.

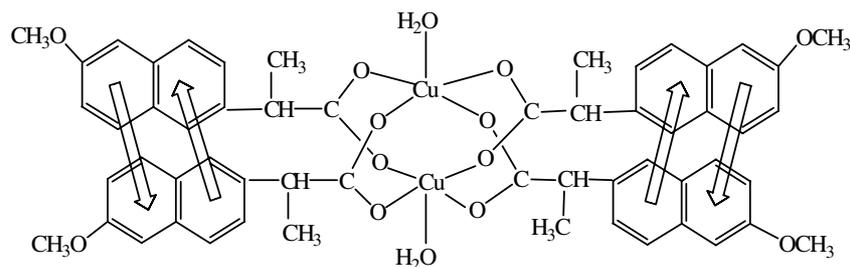
A linear relationship between pK_a and φ_m was found (Fig. 1), and it can be expressed as an equation: $pK_a = 4.227 + 0.0228\{\varphi_m\}$. Based on this function relationship, we can deduce the protonation constant of naproxen with a random φ_m in the 50—80 vol. % range.

For the binary systems $M(\text{II})\text{—HL}$ we fixed the titration solutions in $\varphi_m = 60\%$, and the ascer-

Table 1. The Stability Constants of the Binary System $M(\text{II})\text{—HL}$ ($\varphi_m = 60\%$)

Stability constants	Cd(II)	Co(II)	Ni(II)	Zn(II)	Cu(II)
$\log \beta_{ML} (\log K_1)$	1.73(5)*	1.36(2)	—	—	2.29(1)
$\log \beta_{ML_2}$	4.72(2)	4.81(2)	4.91(5)	4.84(2)	5.35(1)
$\log K_2$	3.09(2)	3.45(2)	—	—	3.06(1)
$\log \beta_{ML(OH)}$	−5.22(3)	−5.67(6)	—	—	—
$\log \beta_{M_2L_4}$	—	—	13.56(4)	12.63(6)	—
pH range	4.7—6.9	4.7—7.1	4.7—6.3	4.4—6.7	4.2—5.3

*The standard deviation is in parenthesis.



Formula 2. The structure of dimeric complex $\text{Cu}_2\text{L}_4 \cdot 3\text{H}_2\text{O}$ ($\text{L} = \text{C}_{14}\text{H}_{13}\text{O}_3^-$) (one water is the crystal).

tained complex species and estimated stability constants in logarithm are shown in Table 1. Complex species ML_2 existed for all, whereas species ML also for Cd(II) , Co(II) , and Cu(II) . In addition, the complex in dimeric form M_2L_4 was found in Ni(II) - and Zn(II) -containing systems. These results suggest that the complex M_2L_4 is the most stable while there is the increase in pH of sample solutions.

Comparing the step stability constants of Cd(II) , Co(II) , and Cu(II) , they follow the order of $\log K_2 > \log K_1$. According to this result, which conflicts with the general rule, it can be concluded that the formation of complex species ML_2 is easier than that of ML . On one hand, the natural complex is more stable than the fundamentally charged one; on the other hand, this could be attributed to the hydrophobic interaction [10] between ligands of complex ML_2 . The stability constants of the complexes ML_2 have the order $\beta_{\text{CdL}_2} < \beta_{\text{CoL}_2} < \beta_{\text{NiL}_2} < \beta_{\text{CuL}_2} > \beta_{\text{ZnL}_2}$, which is also in accord with the order of Irving—Williams [11].

As mentioned above, complexes Ni_2L_4 and Zn_2L_4 are the dimeric forms of their parent complexes NiL_2 and ZnL_2 . For the dimerization reaction $2\text{ML}_2 \rightleftharpoons \text{M}_2\text{L}_4$, the calculated equilibrium constant K_e ($K_e = \beta_{\text{M}_2\text{L}_4} / \beta_{\text{ML}_2}^2$) for Ni(II) and Zn(II) is 5.5×10^3 and 8.9×10^2 , respectively, and this suggests that the complexes NiL_2 and ZnL_2 could be converted almost to dimeric forms. Herein we assume that the hydrophobic interaction is still the main drive of dimerization.

For the binary system containing Cu(II) ion, a large amount of green deposit formed when the pH of titration solution was close to 5.3. The deposit was separated, washed-up with methanol and then dried. For $\text{Cu}_2\text{L}_4 \cdot 3\text{H}_2\text{O}$ ($\text{C}_{56}\text{H}_{58}\text{O}_{15}\text{Cu}_2$, $M_r = 1098.16$) w_i (calc.): 61.25 % C, 5.32 % H, 11.57 % Cu; w_i (found): 61.22 % C, 5.14 % H, 11.48 % Cu (obtained by EDTA complexometry). The formation of solid compound $\text{Cu}_2\text{L}_4 \cdot 3\text{H}_2\text{O}$ is in accord with the early report [3], and this implies that the dimerization is caused by an extra interaction of intramolecular aromatic-ring stacking or hydrophobic adducts, with a structure as shown in the formula, between ligands in the complex (Formula 2). For the other systems, the deposit was also formed when the pH of titration solutions was close to 7.0, and we assume that the de-

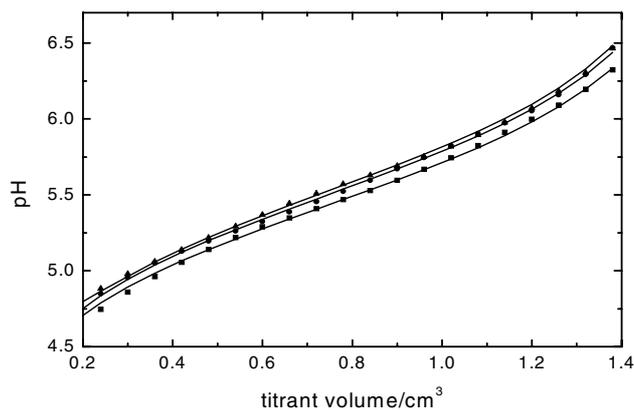


Fig. 2. Comparison of experimental titration curves (■ 1:1 ($n(\text{metal}):n(\text{ligand})$), ● 1:2, ▲ 1:3) and simulated ones (—) of the $\text{Ni(II)}\text{—HL}$ system. $c_{\text{Ni}} = (1.0\text{—}3.0) \times 10^{-3} \text{ mol dm}^{-3}$, $c_{\text{HL}} = 3.0 \times 10^{-3} \text{ mol dm}^{-3}$.

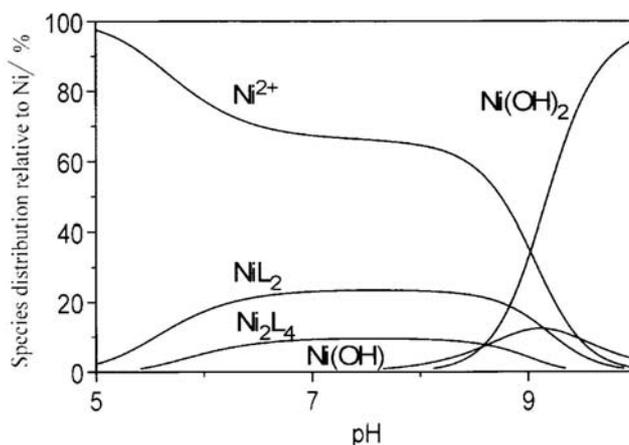


Fig. 3. Species distribution curves for the $\text{Ni(II)}\text{—HL}$ system at a mole ratio of 1:3 ($n(\text{metal}):n(\text{ligand})$). $c_{\text{Ni}} = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$, $c_{\text{HL}} = 3.0 \times 10^{-3} \text{ mol dm}^{-3}$. The stability constants of species Ni(OH) and Ni(OH)_2 were from the literature [13].

posits are mixtures of complexes and hydrolysis products.

The experimental and simulated titration curves of the Ni(II) -containing system are shown in Fig. 2. It is obvious that the simulated curve is matchable to the experimental one. This result supports the validity

of species model selected in the Ni(II)—HL system. In addition, the species distribution curves (Fig. 3) of the system were also obtained by employing the program HYSS [12]. By analyzing the species distribution of M(II)—HL systems at a mole ratio of 1:3 ($n(\text{metal}):n(\text{ligand})$), it is clear that the maximum content of complex ML_2 is about 27 % (CdL_2), 29 % (CoL_2), 20 % (NiL_2), 16 % (ZnL_2), and 35 % (CuL_2) while $\text{pH} \approx 6.5$, respectively. On the other hand, the content of complex ML_2 is almost unchanged in the 7.0—8.0 pH range.

Complex species $\text{ML}(\text{OH})$ was only ascertained in the binary system containing Cd(II) and Co(II). The formation of hydrolysis form may be explained by the fact that the relatively higher pH than in the other systems was achieved in experiment.

CONCLUSION

There is a linear relationship between the protonation constant ($\text{p}K_{\text{a}}$) of naproxen and the content of methanol in methanol—water mixed solvent (φ_{m}), which can be expressed as an equation: $\text{p}K_{\text{a}} = 4.227 + 0.0228\{\varphi_{\text{m}}\}$. In the binary M(II)—HL systems, complexes species ML_2 was found for investigated transition metal ions, and its stability constants coincide with the Irving—Williams order. The formation of complexes M_2L_4 , the dimeric form of binary species ML_2 , hints that the aromatic-ring stacking or hydrophobic interaction exists between ligands in the complexes.

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