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Binary and Ternary Complexes of Sulphamethoxazole

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Summary. The complex formation equilibria involved in the binary and ternary systems *M*(II)-*sulpha* and *M*(II)-*phen-sulpha* were investigated by potentiometric titrations at 25 °C and a ionic strength of 0.1 *N* $NaNO_3$ (*M* = Cu, Ni, Co, Zn; *sulpha* = sulphamethoxazole; *phen* = phenanthroline). The stability constants of the binary and ternary complexes follow the order of *Irving* and *William*. The formation of the ternary complex is discussed in terms of the binary species. The mode of chelation was ascertained by conductivity measurements.

Keywords. Sulphamethoxazole; Binary and ternary complexes; Potentiometric studies.

Binäre und ternäre Komplexe von Sulphamethoxazol

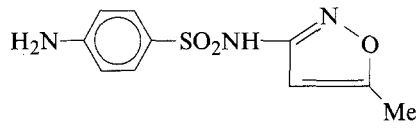
Zusammenfassung. Die an den binären und ternären Systemen *M*(II)-*sulpha* und *M*(II)-*phen-sulpha* (*M* = Cu, Ni, Co, Zn; *sulpha* = Sulphamethoxazol; *phen* = Phenanthrolin) beteiligten Komplexbildungsgleichgewichte wurden bei 25 °C und einer Ionenstärke von 0.1 *N* $NaNO_3$ mittels potentiometrischer Titration untersucht. Die Stabilitätskonstanten der binären und ternären Komplexe gehorchen der Reihenfolge von *Irving* und *William*. Die Bildung der ternären Komplexe wird auf der Basis der binären Spezies diskutiert. Die Art der Chelatbildung wurde durch Leitfähigkeitsmessungen ermittelt.

Introduction

In recent years, considerable attention has been paid to the investigation of the complex forming properties of sulpha drugs because of their outstanding biological significance. Some sulpha drugs are used in the treatment of cancer [1], malaria [2], leprosy [3], and tuberculosis [4]. They are of proven therapeutic importance and are used against a wide spectrum of bacterial ailments [3, 5, 6].

Binary and ternary complexes of transition metals are commonly found in biological media and may play important roles in processes as diverse as the catalytic interaction of drugs with biomolecules, the uptake of irons by living organisms, the interaction of viruses with bacterial cell walls, the transport and storage of oxygen, *etc.* [7]. As a continuation of our research program directed to

study binary and ternary complexes of biological significance [8–10], the present paper traces the formation and characterization of binary and ternary complexes involving some transition metal ions, sulphamethoxazole and phenanthroline.



Sulphamethoxazole

Results and Discussion

The acid dissociation constant (pk_a) of sulphamethoxazole was determined by direct potentiometric measurements. The pk_a value was found to be 5.91 ± 0.00. The proton may be released from the $-SO_2NH-$ group as shown below:

$$R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-NH-R' \rightleftharpoons R-\overset{\overset{OH}{|}}{\underset{\underset{O}{\|}}{S}}=N-R' \rightleftharpoons R-\overset{\overset{O^-}{|}}{\underset{\underset{O}{\|}}{S}}=N-R' + H^+$$

In the potentiometric titration of metal(II)-*sulpha* (mixture B, Fig. 1) the first buffer region was identical with that of free *sulpha*, corresponding to the neutral-

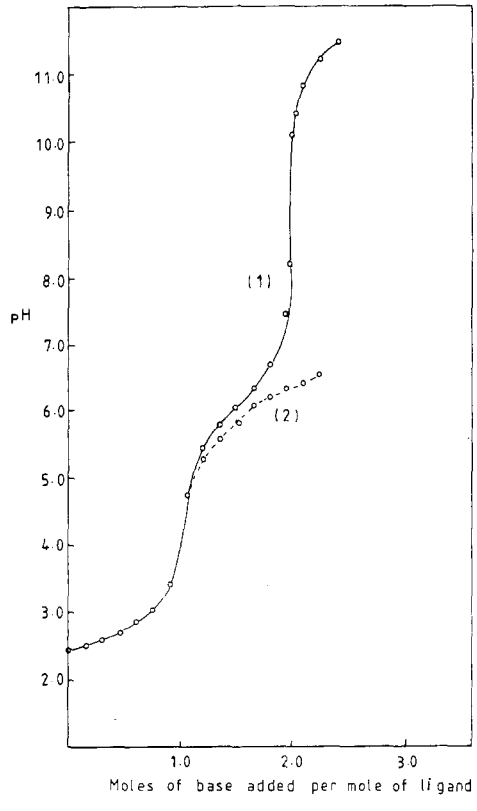


Fig. 1. Potentiometric titration curves of the Cu(II)-sulphamethoxazole system: (1) *sulpha*; (2) Cu-*sulpha*

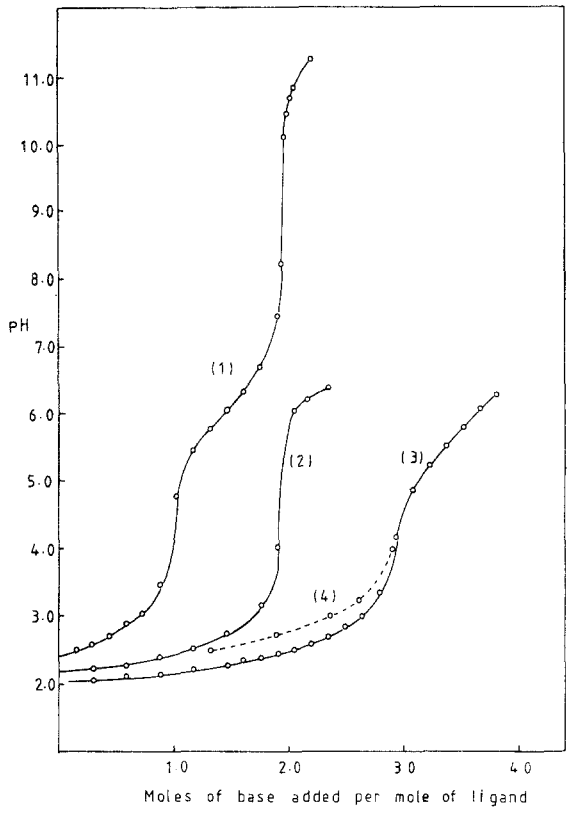


Fig. 2. Potentiometric titration curves of the Cu(II)-*phen-sulpha* system: (1) *sulpha*; (2) Cu-*phen*; (3) Cu-*phen-sulpha*; (4) composite curve

ization of HNO_3. In the second buffer region there was a lowering of the titration curve with respect to that of free *sulpha*, indicating the formation of a complex through the release of a proton. The model that best fits the potentiometric data is found to consist of the 1:1 complex. The stability constants (Table 1) follow the order Co(II) < Ni(II) < Cu(II) > Zn(II) which is in accordance with *Irving-William*'s order [14].

The tendency of sulphamethoxazole to form mixed ligand complexes with the above mentioned metal ions and phenanthroline was studied. The titration curves of the Copper(II) complexes, taken as representative, are presented in Fig. 2. The Cu(II)-*phen* (1:1) mixture titration curve starts at *pH* 2.2 and has a low *pH* buffer region followed by a sharp inflection at $a = 2$ (a = moles of base added per mole of ligand), corresponding to complete formation of the 1:1 complex. The mixed Cu(II)-*phen-S* (1:1:1) solution does not show this sharp inflection at $a = 2$. The formation of the mixed ligand complex is ascertained by comparison of the mixed ligand titration curve with the composite curve, obtained by graphical addition of the free *sulpha* curve to the 1:1 Cu(II)-*phen* titration curve. The experimental titration curve of the mixed ligand system is quite different from the composite curve, indicating the formation of the mixed ligand complex.

Let us now consider the ability of metal ions to form mixed ligand complexes with sulphamethoxazole. This tendency may be appreciated by examining the specific increments of stability which account for the formation of mixed ligand species relative to the corresponding parent ones. The calculation of these

Table 1. Formation constants of binary and ternary complexes of sulphamethoxazole

System	γ	p	q[a]	log B[b]		S[c]	n[d]	$\Delta \log K$	% proportion	pH
				Binary complexes						
sulpha	0	1	1	5.91	(0.00)	1.3×10^{-7}	65		–	–
Cu-*sulpha*	1	1	0	2.69	(0.07)	2.6×10^{-6}	62		53	6.3
Ni-*sulpha*	1	1	0	2.32	(0.10)	3.1×10^{-6}	62		39	6.8
Co-*sulpha*	1	1	0	2.13	(0.05)	5.6×10^{-7}	62		32	6.8
Zn-*sulpha*	1	1	0	2.04	(0.03)	7.1×10^{-8}	25		28	6.9
				Ternary complexes						
Cu-*phen-sulpha*	1	1	0	3.36	(0.06)	7.2×10^{-6}	57	0.67	63	5.9
Ni-*phen-sulpha*	1	1	0	2.44	(0.08)	8.1×10^{-6}	57	0.12	36	6.4
Co-*phen-sulpha*	1	1	0	2.31	(0.11)	8.0×10^{-6}	57	0.18	30	6.4
Zn-*phen-sulpha*	1	1	0	2.65	(0.05)	3.3×10^{-6}	57	0.61	43	6.3

[a] γ, p, and q refer to the $M_1(sulpha)_pH_q$ for the binary complexes; γ refers to $[M(phen)]$ for the ternary complexes; [b] Standard deviations are given in parentheses; [c] sum of square of residuals; [d] number of data points

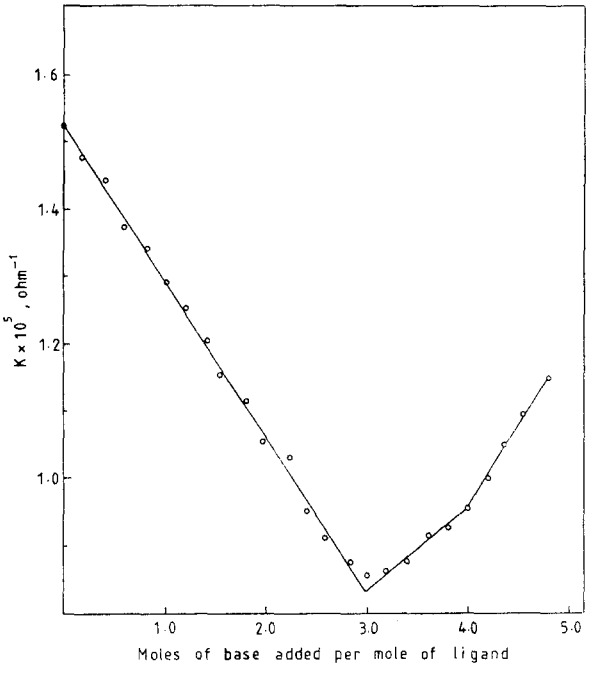


Fig. 3. Conductometric titration of the Cu(II)-*phen-sulpha* system

increments is possible using the following equation [15]:

$$\Delta \log K = \log k^{M(phen)}_{M(phen)(S)} - \log k^{(M)}_{(M)(S)} \qquad 3$$

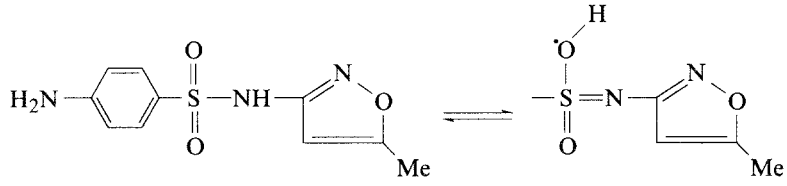
Thus, *M-phen-S* systems uniformly show positive $\Delta(\log K)$ in all cases as expected when the primary ligand is an aromatic amine like phenanthroline and the secondary ligand is a potential oxygen donor. This is attributed to π back-bonding from the metal ion to the aromatic amine [16], which is in accordance with the

previous study of the ternary complexes involving aromatic amines like 2,2′-bipyridyl [17].

The concentration distribution of various complex species in solution as a function of *pH* was calculated by the MINIQUAD-75 program. The extent of complex formation is *pH* dependent. The maximum degrees of formation of the sulphamethoxazole complexes are given in Table 1.

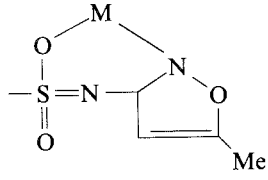
The conductometric titration curve for the ternary complex of Copper(II) with 1,10-phenanthroline and sulphamethoxazole (Fig. 3) shows an initial decrease and an inflection at $a = 3$. This probably corresponds to the neutralization of H^+ ions originating from the formation of Cu(II)-*phen* as well as from HNO_3 used for the dissolution of *sulpha*. In the $4 \geq a \geq 3$ range, the conductance increases slightly due to the formation of a ternary complex associated with the release of a H^+ ion from *sulpha*. Beyond $a = 4$, the conductance increases appreciably due to the presence of an excess of NaOH.

Based on the above findings, the complex formation ability of *sulpha* could be ascribed by the tautomeric shift of the sulfonamide hydrogen to the sulfonyl oxygen (**I** ⇌ **II**), and the participation of the sulfonyl oxygen and the oxazole nitrogen in



I **II**

the complex formation with the formation of a six-membered strainless chelate ring(III).



III

Experimental

Reagents

Sulphamethoxazole was obtained from Kahira Pharm. and Chem. Ind. Co. (Egypt); 1,10-phenanthroline monohydrate was supplied by Merck Chem. Co. *Sulpha* solutions were prepared immediately before use by exact weighing of the substance which was then dissolved in aqueous equimolar nitric acid solution. Phenanthroline was used in the diprotonated form. The metal salts were provided by BDH as nitrates. All solutions were prepared in deionized water. The metal ion solutions were standardized by *EDTA* using suitable indicators [11].

Measuring Techniques

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosmiat (Switzerland). The *pH* meter and electrode were calibrated with standard buffer solutions

prepared according to NBS specifications [12]. Conductance of solutions was measured with a WTW LBR conductivity bridge.

Procedures

The following mixtures were prepared for the determination of acid dissociation constants of *sulpha* and formation constants of the binary and ternary complexes:

(A) 10 ml of 0.02 *N* *sulpha* (*HS*) + 30 ml of 0.13 *N* $NaNO_3$
(B) 10 ml of 0.01 *N* metal ion + 10 ml of 0.02 *N* *sulpha* + 20 ml of 0.2 *N* $NaNO_3$
(C) 10 ml of 0.02 *N* metal ion + 10 ml of 0.02 *N* phenanthroline + 20 ml of 0.20 *N* $NaNO_3$
(D) 10 ml of 0.02 *N* metal ion + 10 ml of 0.02 *N* phenanthroline + 10 ml of 0.02 *N* *sulpha* + 10 ml of 0.40 *N* $NaNO_3$
(E) 10 ml of 0.02 *N* Cu(II) + 10 ml of 0.02 *N* phenanthroline + 10 ml of 0.02 *N* *sulpha*

Mixtures (A)–(E) were titrated against 0.305 *N* NaOH solution at 25 °C in a purified N_2 atmosphere.

Formation constants were evaluated from titration data according to equation 1 (for binary complexes) and equation 2 (for mixed ligand complexes).

$$HS \rightleftharpoons H + S$$

$$M + S \rightleftharpoons MS \qquad 1$$

$$M(phen) + S \rightleftharpoons M(phen)S \qquad 2$$

(Charges are omitted for simplicity)

Calculations were made with the aid of the MINIQUAD-75 computer program [13] on an IBM-4331 computer. The model selected was that which gave the best statistical fit and was consistent with chemical logic. The formation constant $K^{M(phen)}_{M(phen)S}$ of the mixed ligand complex was calculated assuming the complex *M*(*phen*) to be undissociated in the region of mixed ligand complex formation. The results are listed in Table 1.

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