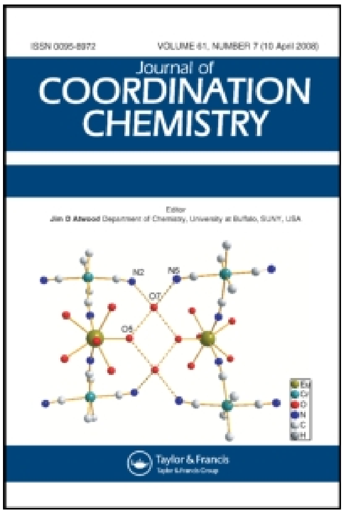

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POTENTIOMETRIC STUDY OF COMPLEX FORMATION OF SOME DIVALENT METAL IONS WITH 2-AMINOOXYACIDS[1]

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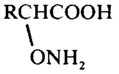
By using the potentiometric method, complexation equilibria have been studied in aqueous solution containing metal ions and selected 2-aminooxyacids. The measurements were carried out at 25° and at a constant ionic strength of 0.5 M. The systems studied included Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Cd(II), Pb(II) and 2-aminooxyacids of the general formula



$$\underset{\displaystyle \backslash\ ONH_2}{RCHCOOH}$$

where R = H, CH_3, C_2H_5, C_4H_9, $CH_3CH(CH_3)CH_2$ and $C_6H_5CH_2$ The 2-aminooxyacids have been found to form 1:1 complexes with each of the metal ions. Stability constants for the complexes were determined and the nature of bonding in the complexes is discussed. The pKa_1 and pKa_2 values of the ligands were also determined.

INTRODUCTION

It has long been known that aminooxyacids are substances of biological importance.[3] They have found use as antibiotics, anticancer agents and fungicides. Thus, the antibiotic cycloserine, a cyclised derivative of 2-amino-3-aminooxypropanoic acid, displays a broad spectrum of antibacterial activity.[4] Less complex structurally, aminooxyethanoic acid inhibits distinct bacteriostatic activity against several organisms.[5] It also inhibits transamination of β-alanine and ornithine in the liver and is likely to inhibit transamination of γ-aminobutyric acid in the brain.[6]

It may thus be useful in treatment of neurological diseases[6] and many papers have been confined to the study of its bioactivity.[7,8] Physical and chemical properties of 2-aminooxyacids and their derivatives have also been extremely investigated.[9–13] According to an early suggestion[14] 2-aminooxyacids do not form complexes with metal ions. Contrary to this statement a deep blue copper(II) complex of aminooxyethanoic acid has been isolated.[15] To our knowledge this is the only report on complexes formed by this type of acid. This finding, together with the known pharmacological behaviour of these types of compounds, prompted us to study the complexation of metal ions with 2-aminooxyacids. In this paper the results of potentiometric investigations of the complexes in aqueous solution are reported. The results of investigations of the complexes in the solid state are being prepared for publication.

EXPERIMENTAL

Reagents

The 2-aminooxyacids were synthesized by using the scheme reported by Testa and *et al.*[14] The starting reagents were commercially available amino acids. Freshly

TABLE I
Chemical analyses of the 2-aminooxyacid hydrochlorides.

	Calculated (%)			Found (%)		
Acid hydrochloride	C	H	N	C	H	N
aminooxyethanoic	18.83	4.74	10.98	18.80	4.71	10.79
2-aminooxypropanoic	25.45	5.69	9.89	25.62	5.75	10.03
2-aminooxybutanoic	30.87	6.48	9.00	30.49	6.39	9.03
2-aminooxypentanoic	35.40	7.13	8.26	35.92	7.27	8.30
2-aminooxy-3-methylbutanoic	35.40	7.13	8.26	35.24	7.18	8.32
2-aminooxyhexanoic	39.24	7.68	7.63	39.47	7.81	7.84
2-aminooxy-4-methylpentanoic	39.24	7.68	7.63	39.39	7.85	7.72
2-aminooxy-3-phenylpropanoic	49.66	5.56	6.43	49.36	5.48	6.58

prepared monohydrochlorides of 2-aminooxyacids were used for measurements. Elemental analyses are collected in Table I.

All the remaining reagents used to synthesize the ligands were either the best commercially available grade or were purified by common procedures.

Solutions of potassium hydroxide were prepared and standardized using the usual method.[16] The metal ion content in nitrate salt stock solution was determined by direct titration with EDTA and gravimetrically.[17]

General procedure

The pH-metric measurements were carried out by using a Radiometer PHM-52 pH Meter which had been previously calibrated against three standard buffer solutions covering the pH range 2–7. The electrode system consisted of a G 202C glass electrode and a K 401 calomel electrode.

A common technique of titration was employed for the determination of the ligand dissociation constants pKa_1 and pKa_2.[18] Starting aqueous solutions (50 cm^3) containing the monohydrochloride of the 2-aminooxyacids (0.03 M), were titrated with potassium hydroxide solution (0.1 M). The mean ligand number, $\bar{n}$, and the equilibrium ligand concentration [L], were determined by a similar titration in the presence of copper(II) ions.

To establish the stability constants of the complexes a series of solutions containing known concentrations of 2-aminooxyacid hydrochloride, potassium hydroxide, metal nitrate and potassium nitrate were prepared and their pH measured.[16,19]

The ratios of the three first components were close to 1:1:1 and fall within the 10^{-3}–10^{-34} M range. A constant ionic strength was maintained with a potassium nitrate. All measurements were carried out in a water-jacketted reaction vessel, thermostated at 25 ± 0.2°. Nitrogen was continually passed over the solutions.

Calculations

The values of the acid dissociation constants, Ka_1 and Ka_2, were determined by employing a published method.[20] The mean ligand number and equilibrium ligand concentration were established using known methods.[21]

The stability constants for the complexes were calculated on a ODRA 1204 computer, using the DECFAM program. This program minimizes the sum of the squares of the differences between theoretical (resulting from parameters such as equilibrium constants) and measured electromotive forces. The calculations were performed iteratively; initially guessed equilibrium constants were improved in several cycles until the differences between the constant in successive cycles were less than required tolerance. The algorithm is described in detail elsewhere.[22]

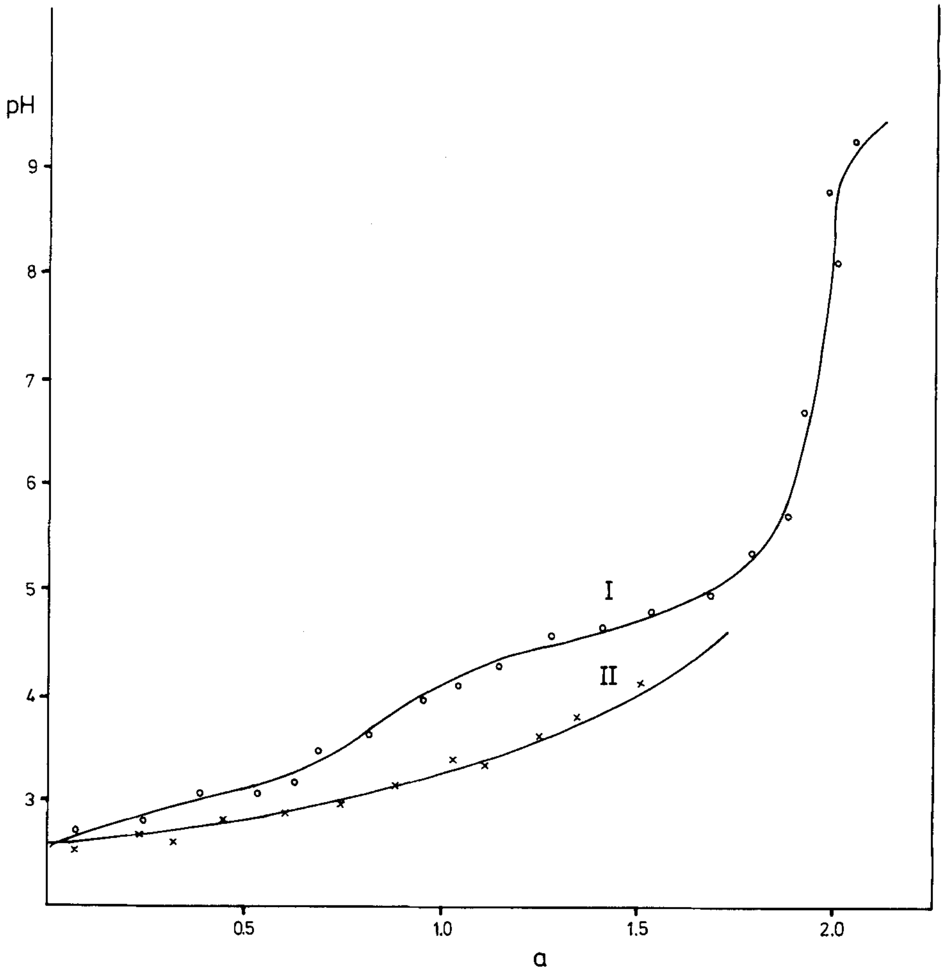


FIGURE 1 Titration curves for 2-aminooxyethanoic acid hydrochloride (curve I) and its copper(II) complex (curve II).

RESULTS AND DISCUSSION

The investigations were started with measurements which allowed us to establish values for the dissociation constants of the ligands.

The available literature data are very incomplete and concern the basicity of the aminooxy group.[11,14] The only exception is for aminooxyethanoic acid, for which Ka_1 and Ka_2 have been evaluated.[23] Results reported here cover eight 2-aminooxyacids. Both the first and second dissociation constants of these ligands have been determined. An illustrative example of a typical titration curve is shown in Figure 1 (curve I). Its shape shows a very weak inflection after the addition of one equivalent of base and a sharp rise in pH when the degree of neutralization, a, approaches 2, corresponding to the behaviour of a dibasic ligand with close pKa_1 and pKa_2 values. The separation of the constants may be less than 2.7 log units. To obtain their accurate numerical values a previously described method was utilized.[20] The experimental

TABLE II
Dissociation constants of the 2-aminooxyacids.

Compound	pKa_1 -COOH	pKa_2 $R = -ONH_2$	pKa_2 $R = -NH_2$	Ref.
CH_2COOH R	2.80	4.58		this work
	2.87	4.67		23
	2.33		9.61	24
$CH_3CHCOOH$ R	2.75	4.62		this work
	2.33		9.73	24
$CH_3CH_2CHCOOH$ R	2.73	4.54		this work
	2.30		9.66	24
$CH_3(CH_2)_2CHCOOH$ R	2.70	4.50		this work
	2.31		9.68	24
$CH_3(CH_2)_3CHCOOH$ R	2.70	4.48		this work
	2.30		9.70	24
$CH_3CH(CH_3)CHCOOH$ R	2.68	4.47		this work
	2.28		9.50	25
$CH_3CHCH_2CHCOOH$ CH_3 R	2.66	4.45		this work
	2.39		9.71	26
$C_6H_5CH_2CHCOOH$ R	2.49	4.25		this work
	2.20		9.11	24

results averaged from three or more determinations are listed in Table II. For comparison, some related data concerning 2-aminoacids are also included. From these data it results that the acidity constants of the carboxyl group of 2-aminooxyacids are slightly higher, as compared with those of analogous 2-aminoacids. On the other hand, the basicity of the aminooxy groups is markedly lower than the basicity of the amino group of the related aminoacids. This can be rationalized in terms of the presence of a strongly electronegative oxygen atom linked with the nitrogen atom in 2-aminooxyacids.

An examination of the pKa_2 values for various 2-aminooxyacids shows that they are comparable and fall within the range 4.62–4.45, with the exception of the pKa_2 value for 2-aminooxy-3-phenylpropanoic acid, which is appreciably lower (4.25). It might be noted that the alkyl groups and phenyl group effect the dissociation constants of the ligands to the extent observed in 2-aminoacids.[24]

Potentiometric investigations of the complexation equilibria were started with solutions containing copper(II) ions. An example of the titration curve is shown in Figure 1 (curve II). In the course of the measurements it was found that precipitates appeared at markedly higher hydrogen ion concentrations than in systems containing aminoacids. For this reason the measurements were confined to a narrow pH range, not exceeding pH 4. To make sure that only mononuclear complexes were present a series of solutions containing three different concentrations of metal ion (10, 20 and 30 mM) were investigated. Under these conditions $\bar{n}$ approach unity (Figure 2). The shape of the formation curves is independent of the metal ion concentration and thus confirms that

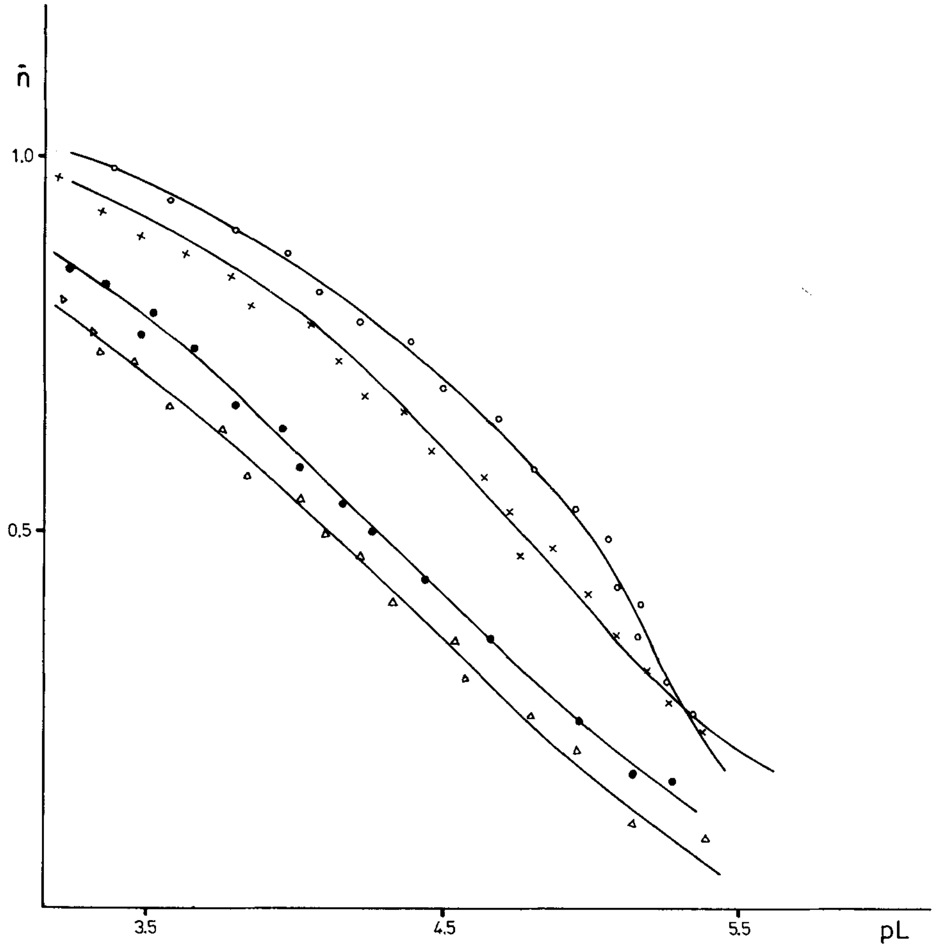


FIGURE 2 Formation curves for copper(II) and the 2-aminooxyacids: 2-aminooxy-ethanoic (○ ○ ○), 2-aminooxypropanoic (x x x), 2-aminooxybutanoic (● ● ●) and 2-aminooxy-3-phenyl propanoic (△ △ △).

only mononuclear, 1:1, complexes exist in the solutions (for clarity n̄ for systems containing only 0.02 M copper(II) is depicted in Figure 2).

From the Irving-Williams stability order it is expected that copper(II) forms the most stable complexes of all the metals studied.[27] Accordingly, it was expected that the remaining ions would not form more than one complex. Consequently, during further measurements the above noted procedure of investigation was employed.[16,19] This technique has an advantage over the former because it prevents the formation of hydroxcomplexes. The possibility of formation of protonated complexes or species with a greater number of ligands was also taken into account. However, small values for the equilibrium concentrations of complexes other than ML were obtained and the minimized sum of squares did not reduce to any extent upon their inclusion. One can therefore consider that assumption of the presence of 1:1 complexes alone is a good approximation for these systems. The calculated stability constants are summarized in Table III. The data indicate that the relative stabilities of the complexes are Cu > Ni > Pb > Co > Cd > Zn > Mn in agreement with the usual Irving-Williams order.[27] A

TABLE III

Stability constants for the complexes of the 2-aminooxyacids with the divalent metal ions.

Acid	Metal ion	log K	Metal ion	log K
Aminooxyethanoic	Cu	5.02 ± 0.03	Cd	2.98 ± 0.05
	Ni	3.41 ± 0.01	Zn	2.90 ± 0.04
	Pb	3.09 ± 0.03	Mn	1.94 ± 0.01
	Co	3.04 ± 0.03		
2-aminooxypropanoic	Cu	4.88 ± 0.04	Co	2.43 ± 0.03
	Ni	3.18 ± 0.04	Cd	2.42 ± 0.04
	Pb	2.52 ± 0.02	Zn	2.34 ± 0.05
2-aminooxybutanoic	Cu	4.23 ± 0.03	Zn	1.95 ± 0.01
	Ni	2.81 ± 0.04	Mn	1.53 ± 0.04
	Co	2.36 ± 0.05		
2-aminooxyhexanoic	Cu	4.09 ± 0.02	Co	1.73 ± 0.04
	Ni	2.10 ± 0.03	Cd	1.52 ± 0.03
	Pb	1.75 ± 0.03	Zn	1.48 ± 0.05
2-aminooxy-4-methylpentanoic	Cu	4.07 ± 0.02		
	Ni	2.08 ± 0.02		
	Co	1.71 ± 0.05		
2-aminooxy-3-phenylpropanoic	Cu	4.07 ± 0.02	Co	1.71 ± 0.04
	Ni	2.06 ± 0.05	Cd	1.51 ± 0.04
	Pb	1.72 ± 0.02	Zn	1.47 ± 0.02

relatively stable complex is formed by lead (II). The same phenomenon was observed in many cases involving other O and N type ligands.[28,29] This is consistent with the orders in which non-transition metals are involved.[30]

The data collected in Table III reveal that the stability constants are also sensitive to the size of the ligands and decrease in the order 2-aminooxyethanoic > 2-aminooxypropanoic > 2-aminooxybutanoic > 2-aminooxyhexanoic > 2-aminooxy-4-methylpentanoic > 2-aminooxy-3-phenylpropanoic acids.

Thus, the stability of the complexes is proportional to the pKa_2 of the acids. This means that the complexation capabilities of aminooxyacids are analogous to those of corresponding aminoacids.[24] However, the stability constants of the former are much lower than those of the 2-aminoacids. For instance, the log K value for the copper(II) complex of 2-aminooxypropanoic acid is 4.88, whereas the value for the analogous complex of 2-aminopropanoic acid is 8.15.[25] Such large differences in the log K values of the complexes can be attributed to the lower basicity of the aminooxy groups. In order to draw conclusions as to the nature of the bonding of the ligands with the central ions, it was expedient to compare them with the bonding in complexes of monocarboxylic acids, such as, for instance, chloroethanoic acid. Its pKa is equal to 2.63.[31] The pKa value of this acid matches the pKa_1 values of the 2-aminooxy acids (Table II). The experimentally determined log K value for the copper(II) complex with chloroethanoic acid is equal to 1.07.[31] On the other hand, the pKa value of ethanoic acid is 4.56, *i.e.*, it is close to the pKa_2 values of the 2-aminooxyacids.

Similar differences are observed in the case of the other metal ion complexes.

It might also be useful to compare our results with hydroxylamine data. Its pKa is equal to 6.12 and the log K values for the stability constants, for instance, of copper(II), nickel(II) and zinc(II) complexes are 2.4, 1.5 and 0.5, respectively.[32] These values are still markedly lower as compared to those concerning 2-aminooxyacids. Hydroxylamine

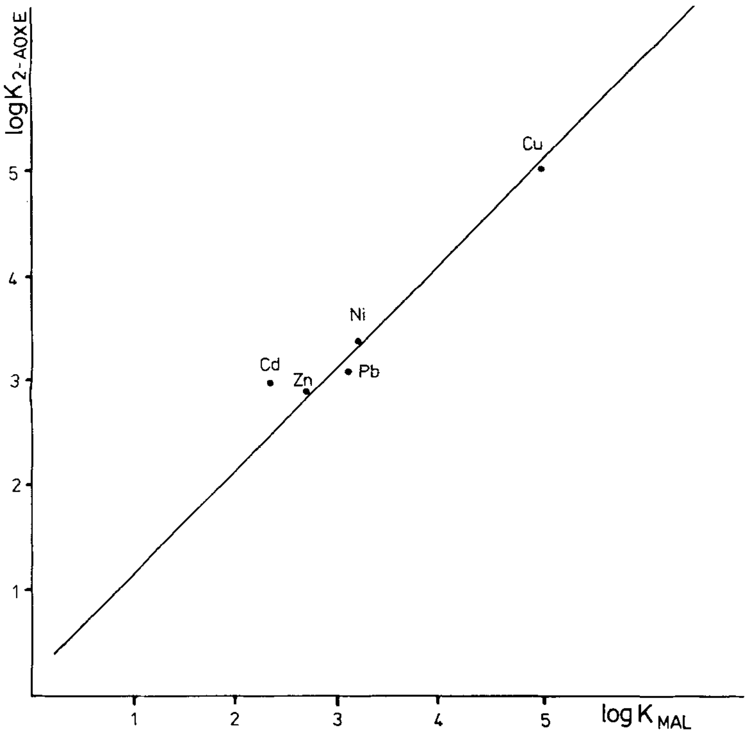


FIGURE 3 Correlation between the stabilities of the complexes of malonic acid (MAL) and 2-aminooxyethanoic acid (2-AOXE).

acts as monodentate ligand too, and is bonded to the central atom through the nitrogen atom of the $-ONH_2$ group.

The above findings suggest that the 2-aminooxyacids form chelates with divalent metal ions. This conclusion receives further support from the stability constants for complexes of malonic and methylmalonic acids. The pKa_1 and pKa_2 values of these ligands are equal to 2.57, 2.78 and 5.11, 5.18, respectively.[33] The values are comparable with the magnitudes of those for 2-aminooxyacids. It is well known that there is often a linear relationship between the dissociation constants of ligands and the stability constants of their complexes.[34] If so, the stability constants of the dicarboxylic acids and the 2-aminooxyacids should also be comparable. The literature data provide such evidence. For instance, the log K values for the copper(II) complexes with malonic and methylmalonic acids are 5.02 and 4.89, respectively.[35,36]

The values are again very close to the corresponding data for the 2-aminooxyacids. The dicarboxylic acids have been found to form chelate complexes with metal ions. The comparable stabilities of the 2-aminooxyacid complexes to those of malonic and methylmalonic acids also implies that the former likewise form chelate compounds.

It has been shown that if two very similar ligands A and B form complexes MA and MB with a series of metals such that the size, the number and the geometry of chelated rings is essentially the same, a plot of log K_{MA} against log K_{MB} should be straight line of unit slope.[37] For the pair, for example, of malonic acid (MAL) and 2-aminooxyethanoic acid (2-AOXE) this seems to hold for some metals (Figure 3). This also seems to confirm the validity of the suggesting that the 2-aminooxyacids act as bidentate ligands.

REFERENCES

1. This work was supported by the Polish Academy of Sciences under Grant No. 70/53/81.
2. To whom inquiries should be addressed.
3. K. Undheim, P. Bramberg and B. Sjöber, *Acta Chem. Scand.*, **19,** 317 (1965).
4. A.C. Cuckler, L. Forst, L. McClelland and M. Solotorovsky, *Antibiot. Chemother.*, **5,** 191 (1955).
5. D. McHale, J. Green and P. Mamalis, *J. Chem. Soc. A.*, 225 (1960).
6. T.L. Perry and S. Hansen, *J. Neurochem.*, **30,** 679 (1978).
7. J. Cott and J. Engel, *J. Neurol. Transm.*, **40,** 253 (1977).
8. J.D. Wood, E. Karylo and J.D. Newstood, *Can. J. Biochem.*, **56,** 667 (1978).
9. J. Tamás, J. Hegedüs-Vajda, L. Dancsi and L. Kisfaludy, *Org. Mass Spectrom.*, **7,** 341 (1973); **9,** 672 (1974).
10. P. Sohár, L. Dancsi and L. Kisfaludy, *Acta Chim. Acad. Sci. Hung.*, **83,** 391 (1974).
11. L. Kisfaludy, I. Schön and S. Görög, *Acta Chim. Acad. Sci. Hung.*, **95,** 315 (1977).
12. Z. Warnke, J . Szafranek, Cz. Trojanowska and A. Wiśniewski, *Biomed. Mass Spectrom.*, **11,** 231, (1984).
13. L. Kisfaludy, M. Löw, I. Schön and O. Nyéki, *Acta Chim. Acad. Sci. Hung.*, **100,** 101 (1979).
14. E. Testa, B.I.R. Nicolaus, L. Mariani and G. Pogoni, *Helv. Chim. Acta*, **46,** 766 (1963).
15. G. Zvilichovsky, *Tetrahedron*, **22,** 1445 (1966).
16. A. McAuley and G.H. Nancollas, *J. Chem. Soc. A.*, 2215 (1961).
17. A.I. Vogel, Quantitative Inorganic Analysis, (Longman, London and New York, 1978), pp. 324, 456–488.
18. J.J. Farrell, *J. Chem. Educ.*, **54,** 445 (1977).
19. Y.S.K. Nair and G.H. Nancollas, *J. Chem. Soc.*, 4367 (1961).
20. A. Albert and E.P. Serjeant, Ionization Constants of Acids and Bases, (John Wiley and Sons Inc., London, 1962), p. 51.
21. J. Inczédy, Analytical Applications of Complex Equilibria, (Akadémiai Kiadó, Budapest, 1976), p. 116.
22. J. Kostrowicki and A. Liwo, *Comput. Chem.*, in press.
23. E. Borek and H.T. Clarke, *J. Biol. Chem.*, **125,** 479 (1938).
24. A. Gergely, I. Sóvágó, I. Nagypal and R. Kiraly, *Inorg. Chim. Acta*, **6,** 435 (1972).
25. T.P.I. Nancollas and G.H. Nancollas, *Inorg. Chem.*, **11,** 2414 (1972).
26. S. Morazzani-Pelletier and S. Mariaux, *J. Chim. Phys.*, **63,** 278 (1966).
27. H. Irving and R.J.P. Williams, *Nature*, **162,** 746 (1948).
28. C.B. Monk, *Trans. Faraday Soc.*, **47,** 285, 297 (1951).
29. V. Simeon and O.A. Weber, *Croat. Chem. Acta*, **38,** 161 (1966).
30. M. Yasuda, K. Yamasaki and H. Ohtaki, *Bull. Chem. Soc. Japan*, **33,** 1067 (1960).
31. J.W. Bunting and K.M. Thong, *Can. J. Chem.*, **48,** 1654 (1970).
32. I. Szilard, *Acta Chem. Scand.*, **17,** 2674 (1963).
33. A. Vanni, G. Ostacoli and E. Roletto, *Annali di Chimica*, **59,** 847 (1969).
34. V.T. Athavale, N. Mahadevan, P.K. Mathur and R.M. Sathe, *J. Inorg. Nucl. Chem.*, **29,** 1947 (1967).
35. J.E. Powell and D.K. Johnson, *Chromatography*, **44,** 212 (1969).
36. G. Ostacoli, A. Vanni and E. Roletto, *Ricerca Sci.*, **38,** 318 (1968).
37. H. Irving and H.S. Rossotti, *Acta Chem. Scand.*, **10,** 72 (1956).