Formation of Aluminium and Zinc Complexes with Picolinic Acid. A Potentiometric Investigation

OLE JØNS* and ERIK SYLVEST JOHANSEN

Royal Danish School of Pharmacy, Department of Pharmaceutical Chemistry AD, 2, Universitetsparken, DK-2100 Copenhagen, Denmark

(Received July 7, 1987)

Abstract

Complex formation between picolinate (HL = picolinic acid) and aluminium(III) or zinc(II) in 0.15 M KNO_3 was investigated in the pH range 3 to 7. The experiments were carried out as potentiometric titrations using glass electrodes. The experimental data can be explained by formation of the complexes ZnL^+, ZnL_2 and ZnL_3^- for the zinc–picolinate system and AlL^{2+}, AlL_2^+ and $Al(OH)L_2$ for the aluminium–picolinate system. The equilibrium constants were refined by the least squares computer program TITRER. A plotter program, DISTPLOT, displayed the distribution of aluminium(III) and zinc(II) picolinate species and illustrated the possible biological competition between the two metal ions for the ligand.

Introduction

Aluminium has long been regarded to be biologically inert, but is now known to be toxic at high or prolonged intake. The disease known as dialysis encephalopathy discovered in patients with uremia undergoing dialysis was found to be the result of high concentrations of aluminium in the grey matter of the brain [1]. Aluminium intoxication has also been implicated in various neurological disorders such as Alzheimer dementia [2]. The aluminium absorption and consequent accumulation in the brain of patients with dialysis dementia is well documented by analytical and clinical investigations. Patients with renal failure absorb aluminium from orally administrated aluminium gels used as phosphate binder; while receiving hemodialysis they may also be exposed to aluminium in the domestic water supply. In connection with the increased aluminium uptake a slight decrease in zinc concentration in plasma is observed [3]. Little is known about the mechanism of aluminium uptake. It is supposed that only dissolved aluminium is able to cross the mucosa barrier in the gastrointestinal tract [4]. The accumulation and effects of aluminium in the central nervous system may be influenced by the homeostatis of essential metals. Experiments with rats fed on diets containing suboptimal levels of zinc and elevated levels of aluminium showed increased aluminium concentrations in their brains [5]. Probably the absorption of aluminium in gut occurs by competing for binding sites on zinc or iron binding ligands. In a recent investigation elevated aluminium concentrations were observed in the cerebral cortex and in bones of rats fed with aluminium citrate [6].

The absorption process of the essential metal zinc has been investigated by Evans *et al.* [7, 8] showing that picolinic acid (2-pyridiniumcarboxylic acid) probably plays an important role. Picolinic acid is a tryptophane metabolite. The hypothesis is that the picolinic acid produced in the pancreas and secreted into the intestine, coordinates to zinc forming a complex that facilitates the passage of zinc through the luminal membrane. Rats fed on a diet supplemented with picolinic acid showed an increased zinc absorption. On the contrary, experiments using isolated rat intestines gave no enhanced transfer of zinc through the intestine membrane with picolinic acid additions [9], and the zinc absorption was not enhanced in calves, whose diet was supplemented with picolinic acid [10].

In the present work we have investigated the ability of aluminium to form complexes with picolinate ions. Such studies are complicated by the forming of polynuclear species in aqueous solutions of aluminium [11] and by slow attainment of equilibrium. However, our experiences with molybdate systems has convinced us that it should also be possible to handle the aqueous aluminium system [12, 13], since preliminary titrations indicated that equilibrium was fast in the ternary mixtures, probably because experimental conditions forced nearly all aluminium to form complexes with picolinate. Having obtained equilibria data for the zinc– and aluminium–picolinate systems computer simulations will demonstrate the competition between the two systems [14].

*Author to whom correspondence should be addressed.

0020-1693/88/$3.50

Experimental

Chemicals and Analysis

2-Picolinic acid, Fluka, was recrystallized twice from ethanol and dried at 105 °C. Standard stock solutions of the metal ions were prepared from their nitrate salts (Aluminiumnitrat zur Analyse, Merck and Zinc nitrate hexahydrate, Aldrich) and analyzed by EDTA complexometric titrations for metal ion concentrations after AnalaR [15]. Standardized nitric acid diluted from Merck Suprapur nitric acid, and sodium hydroxide carefully prepared free from carbonate were used as titrants. The ionic strength was kept constant at 0.150 by means of potassium nitrate, Suprapur, Merck.

Apparatus and Procedure

The automatic system for precise EMF titrations with burettes, pH-meter, electrodes and process controller has been described earlier [13]. An ABU 13 (Radiometer) autoburette was used for addition of a known amount of nitric acid to the titration mixtures before titration with sodium hydroxide.

Potentiometric titrations were performed at 25.0 °C, $I = 0.150$ M KNO_3, with pure nitrogen used as an inert atmosphere. In the metal–ligand systems the concentration for each component were of the order 10^{-3} M. The metal-to-ligand ratio was varied between 1:2 to 1:15 in the mixtures which were titrated in the pH range 3 to 7. Titrations were stopped as soon as any precipitate appeared in the solutions, as evidenced by drifting potential readings. Only stable data were employed in equilibrium computations. Separate titrations of picolinic acid in the concentration range 0.004–0.012 M and on an extended pH range were used to determine the acidity constants.

Calculations

All computer calculations were performed with the ALGOL program TITRER on the RC 8000/15 at this Institution as outlined earlier [13].

The equilibria considered in the present study are:

(a) the binary picolinic acid equilibria

$$L^- + H^+ = HL; \qquad \beta_{011}$$

$$L^- + 2H^+ = H_2L; \qquad \beta_{012}$$

where L^- = picolinate ion

(b) the ternary metal–ligand equilibria of the general form

$$pM + qL^- + rH^+ = M_pL_qH_r; \qquad \beta_{pqr}$$

The distribution diagrams visualizing the relative amount of different species have been produced by means of the computer program DISTPLOT and a HP 7475A plotter.

Results and Discussion

The Acidity Constants of Picolinic Acid

The protonation constants of the picolinate ion were evaluated with $I = 0.150$ M (KNO_3). The data comprises 7 titrations with 87 experimental points. The analysis of the data ended up with a weighted variance of 0.84 giving $\log(\beta_{011} \pm 3\sigma) = 5.184 \pm 0.001$ and $\log(\beta_{012} \pm 3\sigma) = 6.066 \pm 0.017$. The variance is satisfactorily small, as it ought to be for a simple system with a known model. We found no comparable values in the literature for the same ionic medium.

The Zinc–Picolinate Complexes

The investigation on the zinc–picolinate system comprises 6 titrations with 69 experimental points. The analysis of the data ended up with a weighed variance of 1.59, comfortably low for a three component system. The equilibrium analysis showed that a series of stepwise mononuclear complexes are formed in the pH range investigated. As illustrated in Fig. 1. the system is very regular. From pH equal to the second pK_a value of picolinic acid and higher zinc and picolinate form the complex species in a fixed ratio. No zinc hydroxy species are formed even if the pH range is extended to about pH ~ 9.

The stability constants found are given in Table I together with the values reported by Anderegg [16]. The agreement with these values is very close considering the different techniques applied.

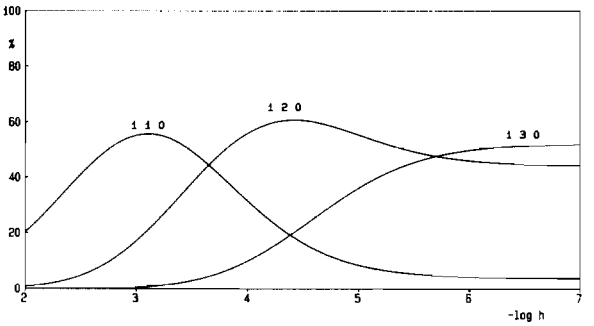

Fig. 1. The distribution diagram for the zinc–picolinate system [Zn(II)] = 0.001 M and [picolinate] = 0.003 M. The calculations have been performed using the computer program DISTPLOT.

TABLE I. Stability Constants, $\log(\beta \pm 3\sigma)$ of the Zinc–Picolinate System

	Present work	Reference 16
	$I = 0.15(KNO_3)$; 25 °C	$I = 0.10(NaNO_3)$; 20 °C
$\log \beta_{110}$	5.177 ± 0.006	5.30
$\log \beta_{120}$	9.539 ± 0.006	9.63
$\log \beta_{130}$	12.90 ± 0.014	12.92

The Aluminium–Picolinate System

The measurements performed for the aluminium–picolinate system comprise 26 titrations including 503 experimental points. This system is not entirely analogous to the corresponding zinc–picolinate system, a consequence of the tendency of aluminium to form hydrolyzed species.

In the analysis of three component experimental data we normally start considering the binary complex models to be known and held fixed. For the picolinate system the constants are already mentioned. However, the binary aluminium hydroxide equilibria are not easy to evaluate. To attain stable potentials very long equilibration times are needed in the titrations [17, 18]. Especially in the reverse titrations (decreasing pH) the rate of equilibration is low. Even at the very low concentrations used in this work slow polymerization could pose a problem. We made several titrations on the binary aluminium hydroxide system and examined the data obtained but no conclusive model emerged, presumably due to lack of equilibrium.

Instead it was attempted to circumvent these problems by avoiding low ratios of picolinate/aluminium coincident with high pH values. This turned out to be quite feasible since (i) titrations indicated fast equilibration, very good repeatability and reversibility, and (ii) simulations of the system showed clearly that hydrolyzed aluminium species were absent under the present experimental conditions.

A non-linear regression analysis of the titration data resulted in a very reasonable and simple model. The variance equal to 1.17 is very satisfactory for a ternary system. The species distribution diagrams for a 1:3 molar ratio of aluminium and picolinate is shown in Fig. 2. As can be seen from Fig. 2 all species of the model contribute significantly in the pH interval examined. It is possible to lower the variance including more species in the model e.g. $AlL(OH)_2$, $\log \beta_{11-2} = 21.73 \pm 0.08$ with a variance 0.95.

Examination of the distribution of this species reveals that its occurence is mainly in the pH range >6, *i.e.* outside the range of this work. Since the lowering of variance is not significant our conclusion

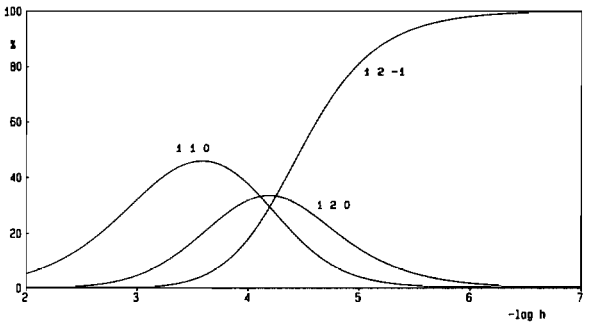

Fig. 2. Distribution diagrams of species as function of pH for 0.001 M Al(III) + 0.003 M picolinate.

is that no further species can be added to the model using experiments in this investigation.

No other results are available for comparison with this particular system, but a system: aluminium salicylate investigated by Öhman and Sjöberg [19], could be compared to the present because of the analogous structure of picolinic acid and salicylic acid. Öhman and Sjöberg found in their investigation working mostly with ratios of aluminium to salicylate greater than 1:5, the major species AlA^+, AlA_2^- and $Al(OH)A_2^{2-}$, where H_2A = salicylic acid. These are analogous to the species we find in the picolinate system. The aluminium–salicylate complexes have a higher stability than the corresponding picolinate complexes in agreement with the expected trend, where aluminium prefers oxygen to nitrogen donor atoms.

The model predicts neutral species for both aluminium and zinc, $Al(OH)L_2$ resp. ZnL_2, at pH values relevant for the region in the gastrointestinal tract where both metals are absorbed. Such low molecular weight uncharged species will be suspected to be able to pass the luminal mucosa.

The species found can be used to evaluate the competition between the zinc and aluminium. With excess of picolinate both aluminium and zinc are completely bound to picolinate. Examination of the distribution of species in solutions with equal concentrations of the metals shows that $Al(OH)L_2$ is the complex present in the greatest amount at pH greater than 5.

TABLE II. Stability Constants ($\log \beta_{pqr}$) of Complex Species $M_pL_qH_r$ (M = Aluminium(III), L = Picolinate and H = Proton) in 0.15 M KNO_3 at 25 °C

System	Species *p q r*	$\log \beta_{pqr} \pm 3\sigma$	Variance
Proton–picolinate	0 1 1	5.184 ± 0.001	0.84
	0 1 2	6.066 ± 0.017	
Aluminium–picolinate	1 1 0	4.487 ± 0.014	
	1 2 0	8.419 ± 0.017	1.14
	1 2 −1	17.589 ± 0.017	

The zinc ion binds to picolinate to a greater extent than does the aluminium ion, in agreement with the concept of hard and soft acids and bases. Aluminium as a hard acid prefers oxygen donors, while zinc is more of a nitrogen acceptor, so the winning complex is dependent on the uptake of a hydroxyl ion. Competitive interactions between essential and toxic metal ions are important factors in trace element requirements and toxicities. The antagonism between calcium and lead is well known. The present systems show that competitive interactions between aluminium and zinc are also possible here.

References

1 A. C. Alfrey, G. R. LeGendre and W. D. Kaehny, *N. Engl. J. Med., 294*, 184 (1976).
2 D. P. Perl, *Environ. Health Perspect., 63*, 149 (1985).
3 H. Zumkley, H. P. Bertram, A. Lison, O. Knoll and H. Losse, *Clin. Nephrol., 12*, 18 (1979).
4 W. D. Kaehny, W. D. Hegg and A. C. Alfrey, *N. Engl. J. Med., 296*, 1389 (1977).
5 G. L. Wenk and K. L. Stemmer, *Brain Res., 288*, 393 (1983).
6 P. Slanina, Y. Falkeborn, W. Frech and A. Cedergren, *Food Chem. Toxicol., 22*, 391 (1984).
7 G. W. Evans, *Nutr. Rev., 38*, 137 (1980).
8 G. W. Evans and E. C. Johnson, *J. Nutr., 111*, 68 (1981).
9 P. Oestreicher and R. J. Cousins, *J. Nutr., 112*, 1978 (1982).
10 T. Flagstad, *J. Nutr., 111*, 1996 (1981).
11 A. G. Sharpe, 'Inorganic Chemistry', Longman, New York, 1981.
12 E. S. Johansen and O. Jøns, *Acta Chem. Scand., Ser. A, 35*, 233 (1981).
13 E. S. Johansen and O. Jøns, *Talanta, 31*, 743 (1984).
14 D. D. Perrin and R. P. Agarwal, in H. Sigel (ed.), 'Metal Ions in Biological Systems', Marcel Dekker, New York, 1973, p 168–206.
15 'AnalaR Standards for Laboratory Chemicals', 6th edn., AnalaR, London, 1967.
16 G. Anderegg, *Helv. Chim. Acta, 52*, 414 (1960).
17 C. F. Baes and R. E. Mesmer, 'The Hydrolysis of Cations', Wiley, New York, 1976.
18 G. Biedermann, *Svensk Kem. Tidsskr., 76*, 362 (1964).
19 L.-O. Öhman and S. Sjöberg, *Acta Chem. Scand., Ser. A, 37*, 875 (1983).