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Complexes of Aluminium(III) with Picolinic and Pipecolinic Acids: An ^{27}Al-NMR Investigation

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Summary. Aluminium-27 NMR has been employed for the study of the interaction of Al(III) with picolinic (*pic*-H) and pipecolinic (*pip*-H) acids in aqueous solution at variable *pH*. In the reaction with picolinic acid distinct peaks for hydrated Al(III), 1 : 1 and 1 : 2 Al-picolinate complexes, as well as a mixed hydroxo-picolinato complex Al(*pic*)$_2$OH are observed. An insoluble 1 : 3 picolinate complex is formed at *pH* 3. Pipecolinic acid forms 1 : 1 and 1 : 2 Al-pipecolinate complexes. No hydroxy-pipecolinate species are formed, however, and the 1 : 2 complex is deprotonated above *pH* 4.5 to colin- (*pic*-H) und Pipecolinsäure (*pip*-H) in wäßriger Lösung bei verschiedenen *pH* angewandt. Bei Al(*pip*)(H$_{-1}$*pip*) have been isolated and characterized by elemental analysis, IR and ^{1}H-NMR.

Keywords. Picolinic acid; Pipecolinic acid; Aluminium; ^{27}Al-NMR.

Komplexe von Aluminium(III) mit Picolin- und Pipecolinsäure: Eine ^{27}Al-NMR-Untersuchung

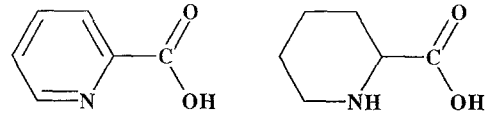
Zusammenfassung. ^{27}Al-NMR wurde zur Untersuchung von Wechselwirkungen von Al(III) mit Picolin- (*pic*-H) und Pipecolinsäure (*pip*-H) in wäßriger Lösung bei verschiedenen *pH* angewandt. Bei der Reaktion mit Picolinsäure wurden separate Signale für hydratisiertes Al(III), 1 : 1 und 1 : 2 Al-Picolinat-Komplexe und auch für gemischte Hydroxo-picolinat-Komplexe Al(*pic*)$_2$OH beobachtet. Bei *pH*3 wird unlöslicher Picolinat-Komplex gebildet. Pipecolinsäure geht 1 : 1 und 1 : 2 Al-Pipecolinat-Komplexe ein. Es werden keine Hydroxo-Pipecolinat-Komplexe gebildet. Der 1 : 2 Komplex wird über einem *pH* von 4.5 deprotoniert und ergibt den unlöslichen Komplex Al(*pip*)(H$_{-1}$*pip*). Die [3, 4] as well as those undergoing dialysis treatment for chronic renal failure [5]. taranalyse, IR und ^{1}H-NMR charakterisiert.

Introduction

During the past decade an ever increasing volume of evidence has been presented to associate aluminium with a variety of neuro-toxic conditions [1, 2]. Increased aluminium levels have been detected in patients suffering from Alzheimer's disease [3, 4] as well as those undergoing dialysis treatment for chronic renal failure [5]. The toxicity of Al^{3+} raises questions concerning the possible route of its absorption into the body and its binding modes after ingestion. The coordination chemistry of Al(III) with ligands having biological significance has, therefore, attracted widespread interest [6].

Picolinic acid (**A**; 2-pyridinecarboxylic acid) is a tryptophane metabolite [7] and has been associated with the formation of soluble complex in the uptake and

passage of Zn(II) through the intestinal membrane [8]. Owing to the expected connection between Zn(II) and Al(III) in the biochemical pathways [9], the study of the various aluminium(III) picolinates in aqueous solutions seems appropriate. On the other hand, pipecolinic acid (**B**; 2-piperidinecarboxylic acid) is an intermediate in the transformation of *L*-lysine to acetyl *CoA*, and is produced by the conversion of Δ′-piperidine-2-carboxylic acid by its reductase [10]. Pipecolinic acid is also connected with *L*-lysine metabolism in the brain [11, 12] as well as with several metabolic disorders and brain irregularities [13].



A B

Aluminium-27 NMR has previously been successfully used to provide structural information for complexes in aqueous solutions [14–17]. The aim of the present study is to investigate the *pH* dependance of the complexes of aluminium(III) formed with the above mentioned ligands (Picolinic acid = *pic*-H; pipecolinic acid = *pip*-H).

Experimental

Reagent-grade $Al(NO_3)_3 \cdot 9\,H_2O$ (Mallinckrodt), picolinic and *D,L*-pipecolinic acids (Aldrich) were used without further purification. Microanalyses were performed by Oneida Research Services, Whitesboro NY. The IR spectra (4000–700 cm^{-1}) were recorded on a Perkin-Elmer 137 grating spectrometer as Nujol mulls. NMR spectra were recorded on Bruker AM-250 (^1H) and Bruker WM-300 (^{27}Al) spectrometers {δ in ppm relative to $SiMe_4$, external (^1H) and $[Al(H_2O)_6]^{3+}$, external (^{27}Al)}. The *pH* measurements were made using a Corning 245 *pH*-meter with a Ag/AgCl type M-M12 microcombination electrode (Microelectrodes Inc., Londonderry, NH). Thermogravometric analysis were carried out on ca. 3 mg of sample, heated at a rate of 10°C per minute under nitrogen atmosphere, in an automated Seiko 200 TG/DTA.

Variable pH-^{27}Al NMR

To a D_2O solution of $Al(NO_3)_3 \cdot 9\,H_2O$ and either picolinic or pipecolinic acid (200–400 m*M*), in a molar ratio 1:1, 1:2 or 1:3 was added a known volume of standard NH_4OH, or HNO_3, solutions. The solution was allowed to equilibrate for at least 3 h at 25°C, and the *pH* measured before and after the NMR spectra was collected. The ^{27}Al-NMR spectra were obtained with a spectral range of 20 kHz, line broadening 1 Hz and a pulse width of 20 ms at 297 K.

Tris(picolinato)aluminium(III); $Al(pic)_3$

To a solution of $Al(O^iPr)_3$ (0.64 g, 3.14 mmol) in benzene (50 ml) was added picolinic acid (1.16 g, 9.43 mmol). The reaction mixture was heated under reflux on a fractionating column. The isopropanol liberated during the reaction was fractionated out until the refluxing temperature reached 80°C at the top of the column. The excess solvent was removed under vacuum to give a white solid, yield 1.20 g, 97%.

M.p. 333°C (dec.). Anal. Calcd. for $C_{18}H_{12}AlN_3O_6$. C 54.96, H 3.05, N 10.68. Found: C 55.00, H 3.07, N 10.65. IR: 1890 (w), 1580 (s), 1340 (s), 1290 (m), 1255 (m), 1245 (m), 1150 (s), 1095 (m), 1045 (m), 860 (m), 1020 (m), 750 (w), 710 (w), 690 (w).

Bis(picolinato)hydroxyaluminium(III); Al(*pic*)$_2$OH

To an aqueous solution (30 ml) of $Al(NO_3)_3 \cdot 9\,H_2O$ (0.93 g, 2.48 mmol) and picolinic acid (0.92 g, 7.45 mmol) was added NH_4OH solution until precipitation occurred at *pH* 4. The solid was removed by filtration and NH_4OH solution added to the filtrate until a further precipitation occurred at *pH* 5.5. The solid was collected by filtration and dried under vacuum, yield 0.32 g, 45%.

M.p. 300°C (dec.) Anal. Calcd. for $C_{12}H_9AlN_2O_5$: C 50.0, H 3.13, N 9.72. Found: C 50.05, H 3.13, N 9.77. IR: 3 510 (br), 1 890 (w), 1 600 (s), 1 560 (s), 1 320 (s), 1 280 (m), 1 145 (s), 1 080 (m), 1 015 (s), 855 (s), 825 (m), 755 (s), 705 (m), 685 (s), 645 (m).

Tris(D,L-pipecolinato)aluminium(III), Al(*pip*)$_3$

To a solution of $Al(O^iPr)_3$ (0.64 g, 3.14 mmol) in benzene (80 ml) was added pipecolinic acid (1.21 g, 9.38 mmol). The reaction mixture was refluxed on a fractionating column until 40 ml of solvent had been removed. The excess solution was removed by filtration and the white solid washed with pentane (2 × 30 ml) then dried under vacuum, yield 1.18 g, 91%.

M.p. 211°C (dec.) Anal. Calcd. for $C_{18}H_{30}AlN_3O_6$. C 52.2, H 7.24, N 10.1. Found C 52.9, H 7.30, N 10.3. IR: 3 800 (br, w), 1 600 (s), 1 570 (s), 1 400 (m), 1 315 (m), 1 280 (m), 1 170 (w), 1 125 (w), 1 040 (m), 1 020 (m), 970 (w), 920 (m), 900 (m), 760 (m), 710 (m).

(D,L-pipecolinato)(H_{-1}*-D,L-pipecolinato)aluminium(III),* Al(*pip*)(H_{-1}*pip*)

To an aqueous solution (5 ml) of $Al(NO_3)_3 \cdot 9\,H_2O$ (1.13 g, 3.01 mmol) and *D,L*-pipecolinic acid (1.55 g, 12.0 mmol) was added a solution of NaOH (0.1 *M*). The *pH* was raised to 4.0 when a small quantity of a gelatinous precipitate appeared. On raising the *pH* to 9.0 no augumentation or disappearance of the precipitate occurred. The solution was filtered and the solid dried under vacuum, after which the solid was washed with *Et*OH (20 ml) and acetone (25 ml). Yield: 0.16 g, 18%.

M.p. 290°C (dec.). Anal. calcd. for $C_{12}H_{19}AlN_2O_4$: C 51.0, H 6.73, N 9.92. Found: C 50.1, H 6.69, N 9.85. IR: 1 600 (br s), 1 390 (m), 1 315 (s), 1 270 (m), 1 120 (m), 1 045 (m), 1 020 (s), 910 (s), 760 (m), 680 (w).

Results and Discussion

Picolinic Acid

The ^{27}Al-NMR spectrum of an equimolar solution of aluminium nitrate and picolinic acid, at *pH* 0.2, consists of the $[Al(H_2O)_6]^{3+}$ peak at 0 ppm [15, 16] and another broader band of lesser intensity at 8 ppm. The 8 ppm peak is consistent with the 1 : 1 aluminium picolinate complex, $[Al(pic)]^{2+}$ with waters of hydration occupying the remaining coordination sites. Peaks of similar chemical shift have been observed previously for other 1 : 1 aluminium carboxylate systems [16, 17]. The signal at 8 ppm gradually increases in intensity as the *pH* is raised; the peak at 0 ppm decreases concomitantly.

At *pH* 1.0 a third band is observed at 15 ppm, presumably due to the 2 : 1 complex $[Al(pic)_2]^+$. As the *pH* is increased the peak at 15 ppm is enhanced while the one at 0 ppm decreases until *pH* 3.0 when precipitation occurs. The peak at 8 ppm remains essentially constant between *pH* 1.0 and 3.0.

The precipitate formed at *pH* 3.0 is the hydrated tris(picolonato)aluminium complex $[Al(pic)_3] \cdot 1/2\,(H_2O)$ which has been characterized by elemental analysis, IR and thermogravimetric analysis (see Experimental). The anhydrous complex, Al(*pic*)$_3$, can be prepared via the stoichiometric reaction of aluminium

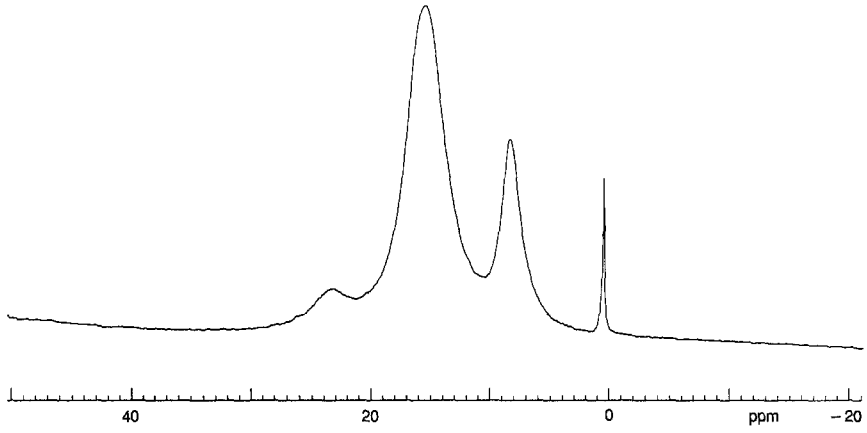


Fig. 1. ^{27}Al-NMR spectrum of aluminium-picolinic acid (1 : 1) at *pH* 3.8 after filtration of precipitated Al(*pic*)$_3$

tris(isopropoxide) with picolinic acid. Refluxing the anhydrous complex in H_2O results in a hydrated complex analytically identical to that precipitated from the aluminium/picolinic acid system above. The insolubility of Al(*pic*)$_3$ in both H_2O and common organic solvents suggests that it has a polymeric structure similar to that found for other aluminium tris-carboxylates [18].

Raising the *pH* of the filtrate results in the appearance of a fourth peak at 23 ppm (Fig. 1), which gains in intensity at the expense of those at 0, 8 and 15 ppm. At *pH* 5.0 a second precipitate is formed. As the *pH* is further increased above 5.0 the peaks at 0, 8 and 15 ppm disappear while the one at 23 ppm remains constant, although additional precipitate is formed with each change in *pH*.

The second precipitate is the neutral bis(picolinato) hydroxyaluminium complex, Al(*pic*)$_2$OH, which has been characterized by elemental analysis IR, ^{1}H-NMR and thermogravimetric analysis. The ^{27}Al-NMR of Al(*pic*)$_2$OH gives a single peak at 23 ppm indicating that Al(*pic*)$_2$OH is the species present in aqueous solution at high *pH*, although with limited solubility.

From the preceding, a series of *pH* dependent equilibria can be proposed for the aluminium – picolinic acid system [Eqs. (1)–(4)]. The variable *pH* ^{27}Al-NMR of solutions of aluminium nitrate and picolinic acid in 1 : 2 and 1 : 3 metal to ligand ratios are essentially the same as that described above for the 1 : 1 system.

$$Al^{3+} + pic\text{-}H \rightleftharpoons Al(pic)^{2+} + H^+, \quad (1)$$

$$Al(pic)^{2+} + pic\text{-}H \rightleftharpoons Al(pic)_2^+ + H^+, \quad (2)$$

$$Al(pic)_2^+ + H_2O \rightleftharpoons Al(pic)_2OH + H^+, \quad (3)$$

$$Al(pic)_2^+ + pic\text{-}H \rightleftharpoons Al(pic)_3 + H^+. \quad (4)$$

Equations (1)–(3) agree with the results of a potentiometric study [19]. The observation of Al(*pic*)$_3$ in our studies is a result not present in the potentiometric study, presumably due to the low concentration (0.001 *M*) employed in the latter. Both our results and those from potentiometric titrations [19] predict the neutral compound, Al(*pic*)$_2$OH, to be the species present at *pH* values relevant for the

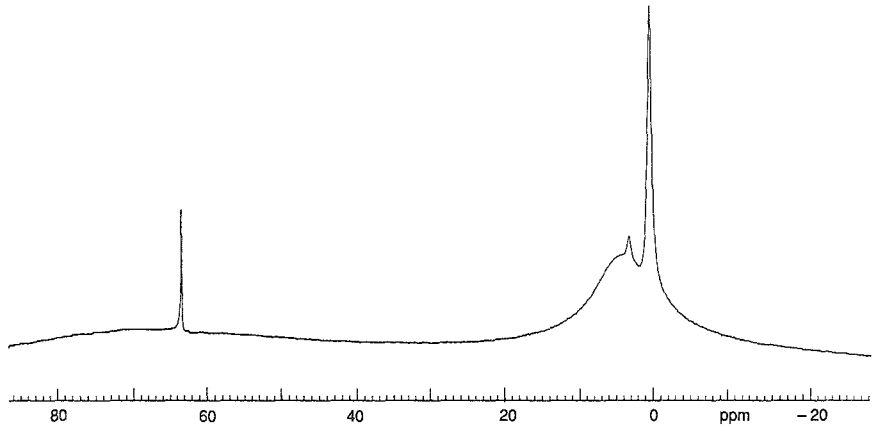


Fig. 2. ^{27}Al-NMR spectrum of aluminium-pipecolinic acid (1 : 1) at *pH* 3.7

region in the gastrointestinal tract where aluminium is absorbed [20]. Such a low molecular weight uncharged species is suitable for passage through the lumenal mucosa.

Pipecolinic Acid

The ^{27}Al-NMR spectrum of an equimolar solution of aluminium nitrate and pipecolinic acid in the acidic region, *pH* 0.2–1.5 consists of only one peak at 0 ppm due to $[Al(H_2O)_6]^{3+}$. On raising the *pH* above 1.5 a new broad band is observed at 4 ppm, the intensity of which increases at the expense of the peak at 0 ppm. The broad band is probably a composite one consisting of the signals of $[Al(pip)]^{2+}$ and $[Al(pip)_2]^{+}$, as the peak shifts downfield and becomes broader at higher *pH* [16].

The band at 4 ppm increases in intensity while the one at 0 ppm decreases until *pH* 3.5, at which point a small peak is observed at 63 ppm, due to the isopolyanion $[Al_{13}(OH)_{24}O_4]^{7+}$ [16] (Fig. 2). The intensities of this latter peak and the one at 4 ppm increase with increasing *pH*. Precipitation starts ca. *pH* 4.5 after which only the peak at 63 ppm remains.

The precipitate formed is not tris(pipecolinato)aluminium, $Al(pip)_3$ but the neutral complex $Al(pip)(H_{-1}pip)$ in which one of the amine protons has been removed. $Al(pip)_3$ can be synthesized directly from $Al(O^iPr)_3$ and pipecolinic acid (see Experimental), it disproportionates on refluxing in H_2O to give the insoluble $Al(pip)(H_{-1}pip)$ and pipecolic acid (Eq. (5)). A series of *pH* dependant equilibria can be proposed to account for the species observed in aqueous solution for the aluminium-pipecolinic acid system (Eqs. (6)–(8)).

$$Al(pip)_3 \rightleftharpoons Al(pip)(H_{-1}pip) + pip\text{-}H, \tag{5}$$

$$Al^{3+} + pip\text{-}H \rightleftharpoons [Al(pip)]^{2+} + H^+, \tag{6}$$

$$[Al(pip)]^{2+} + pip\text{-}H \rightleftharpoons [Al(pip)_2]^{+} + H^+, \tag{7}$$

$$[Al(pip)_2]^{+} \rightleftharpoons Al(pip)(H_{-1}pip) + H^+. \tag{8}$$

From the above result it can be concluded that at physiological *pH* and even at low concentrations the major aluminium containing species would be the neutral complex Al(*pip*)(H_{-1}*pip*) which, unlike Al(*pic*)$_2$OH appears to have practically no solubility in H_2O. This raises the possibility of the use of pipecolinic acid as a sequestering agent of aluminium from aqueous solution. Our initial studies have shown that addition of an excess of pipecolinic acid to a buffered *pH* 7 solution of aluminium nitrate results in the precipitation from solution of 80–85% of the aluminium.

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References

[1] Driscoll C. T., Baker J. P., Bisogni J. J., Schofield C. L. (1980) Nature **284**: 161
[2] Alfrey A. C. (1983) Adv. Clin. Chem. **23**: 69
[3] Crapper D. R., Krishnan S. S., Dalton A. J. (1973) Science **180**: 511
[4] Crapper D. R., Krishnan S. S., Quirrkat S. (1976) Brain **99**: 67
[5] Alfrey A. C., Legendre G. R., Kaehny W. D. (1976) N. Engl. J. Med. **294**: 184
[6] Martin R. B. (1988) Bioinorganic Chemistry of Aluminium. In: Siegel H., Siegel A. (eds.) Aluminium and Its Role in Biology (Metal Ions in Biological Systems, Vol. 24). Marcel Dekker, New York Basle, p. 1
[7] Mehler H. H. (1956) J. Biol. Chem. **218**: 241
[8] Evans G. W., Johnson E. C. (1981) J. Nutr. **111**: 68
[9] Greger J. L., Gum E. T., Bula E. N. (1986) Biol. Trace Elem. Res. **9**: 67
[10] Grobelaar N., Sterward F. C. (1953) J. Am. Chem. Soc. **75**: 4341
[11] Giacobimi E., Gutierrez M. del C. (1983) Neurol. Neurobiol.: 571
[12] Chang Y. F. (1978) J. Neurochem. **30**: 347, 355
[13] Trijbels J. M. F., Momnens L. A. H., Bakkeren J. A. J. M., Van Raay-Selten A. H. J., Corstiezmsemien J. M. B. (1979) J. Inherited Metab. Dis. **2**: 39
[14] Haraguchi H., Fujiwara S. (1969) J. Phys. Chem. **73**: 3462
[15] Toy A. D., Smith T. D., Pilbrow J. R. (1973) Austr. J. Chem. **76**: 1889
[16] Karlik S. J., Tarien E., Elgarish G. A., Eichhorn G. L. A. (1983) Inorg. Chem. **72**: 22
[17] Feng T. L., Gurian P. L., Healy M. D., Barron A. R. (in press) Inorg. Chem.
[18] Goel S. C., Jain N. C., Parashar G. K. (1982) Synth. React. Inorg. Met.-Org. Chem. **12**: 739
[19] Jøns O., Johansen E. S. (1988) Inorg. Chim. Acta **151**: 129
[20] Kaehny W. D., Hegg W. D., Alfrey A. C. (1977) N. Engl. J. Med. **296**: 1389

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