Some new chromium(III) complexes of nicotinic acid; a D NMR and EPR study

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Abstract

The synthesis in very mild conditions of three new nicotinic acid complexes of Cr(III) are reported. The D NMR study of the d_2-nicotinic acid complexes reveals that nicotinic acid is bound to chromium(III) through the carboxylic group in all cases. The ternary complex with histidine shows zero field splitting in its EPR spectrum indicating a distorted octahedral geometry for this complex.

Introduction

The interactions of Cr(III) with molecules of biological relevance are of continuing interest because of the implication of this metal ion in a number of biological processes, but the factors leading to its possible beneficial effects or to its harmful consequences are, as yet, rather poorly understood [1]. Within this area of research, there has been a number of reports of complexes of Cr(III) and Cr(II) with nicotinic acid and some related derivatives [2–12].

Because of our investigations into Cr(III) complexes with amino acids [13, 14] we noted, with interest, a report that mixed ligand complexes of Cr(III) with nicotinic acid and some amino acids caused a decreased in triglyceride and cholesterol levels in the serum of rats and also in patients with hyperlipoprotenemia. Moreover, blood sugar levels in 8 of 12 diabetic patients were decreased [15].

We report here the synthesis, in very mild conditions, of a new nicotinic acid complex of Cr(III) and new Cr(III)–nicotinic acid–amino acid ternary complexes with histidine and cysteine, and their characterization by a range of physical measurements, including the useful D NMR method, previously applied to some Cr(III)–nicotinic acid systems by Green *et al.* [3].

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Experimental

Preparations

The nicotinic acid and amino acids (Fig. 1) were obtained from Serva and Merck, and used without further purification. The starting complex $Cr(urea)_6Cl \cdot 3H_2O$ was prepared according to the literature [16].

Deuterated d_2-nicotinic acid was prepared according to the method of Zoltewicz *et al.* [17] from pyridine 2,3-dicarboxylic acid (Merck). The product was purified by sublimation and recrystallization. The H NMR spectra in DMSO-d_6 revealed a 86% degree of deuteration in position 2 of the obtained samples, in good agreement with the results of Zoltewicz *et al.* (78–87%).

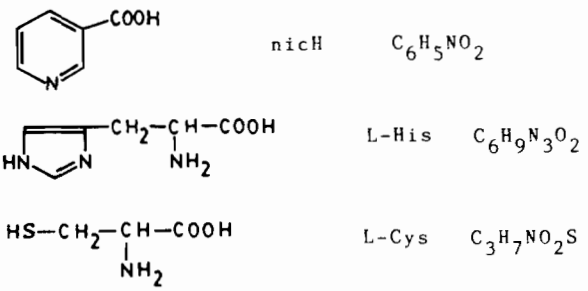

Fig. 1. Formula of the ligands and abbreviations.

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$Cr_2(C_6H_4NO_2)_3(OH)_3 \cdot 4H_2O$ and
$Cr_2(C_6H_5NO_2)_3CL_6 \cdot 6H_2O$

A 20 ml water solution containing 4 mmol of nicotinic acid (0.493 g) was added to a solution of 2 mmol of $Cr(urea)_6Cl_3 \cdot 3H_2O$ in 10 ml of water and the pH adjusted to 7.5 with 2 N NaOH. The resultant green solution was placed in a thermostated bath at 50 °C. Almost immediately a violet precipitate appeared. The mixture was heated for 24 h and then the violet precipitate was filtered off, washed with water and vacuum dried over P_4O_{10} in a desiccator.

Anal. Calc. for $Cr_2(C_6H_4NO_2)_3(OH)_3 \cdot 4H_2O$: C, 36.42; H, 3.88; N, 7.08; Cr, 17.54. Found: C, 36.32; H, 3.67; N, 7.08; Cr, 17.54%. The compound is insoluble in water and common organic solvents.

The blue solution which remained after filtering off the violet complex was concentrated to 5 ml in a rotavapor and eluted through a Sephadex G-10 column (1 cm diameter, 50 cm high). A single blue–grey fraction was obtained. The precipitate obtained on evaporating the solution was vacuum dried over P_4O_{10}.

Anal. Calc. for $Cr_2(C_6H_5NO_2)_3Cl_6 \cdot 6H_2O$: C, 27.20; H, 3.40; N, 5.29; Cr, 13.10. Found: C, 26.99; H, 3.47; N, 5.68; Cr, 12.39%. This compound is very soluble in water (62 mg in 1 ml). The electrolytic conductivity $\Lambda = 1015\ \Omega\ cm^2\ mol^{-1}$ at 20 °C in a 10^{-3} M aqueous solution.

Cr(L-his)(nicH)$Cl_3 \cdot 5H_2O$

A 10 ml water solution containing 1 mmol of L-his and 1 mmol of nicotinic acid was prepared, and the pH adjusted to 7.3 with 2 N NaOH. A 5 ml solution containing 1 mmol of $Cr(urea)_6Cl_3 \cdot 3H_2O$, with an adjusted pH of 7.27, was added and the mixture heated for 3 h at 50 °C (thermostatic bath). The final pH was 3.0.

This solution was concentrated in a rotavapor to 5 ml and was eluted through a Sephadex G 10 column to give a violet fraction (F_1) and a smaller green fraction (F_2) from unreacted chromium urea complex. Evaporation of the F_1 fraction in a rotavapor gave a precipitate which was washed and vacuum dried over P_4O_{10} in a desiccator.

Anal. Calc. for $Cr(C_6H_9N_3O_2)(C_6H_5NO_2)Cl_3 \cdot 5H_2O$: C, 27.34; H, 4.56; Cl, 20.22; Cr, 9.87. Found: C, 27.42; H, 4.18; Cl, 19.72; Cr, 9.01%. This violet complex is very soluble in water (about 60 mg in 1 ml) with a conductivity $\lambda = 482\ \Omega^{-1}\ cm^2\ mol^{-1}$.

Cr(L-cys$^-$)(nicH)$Cl_2 \cdot 4H_2O$

This compound was obtained by the same procedure using L-cys instead of L-his. The initial pH was 7.0 and the reaction time was 5 h.

Anal. Calc. for $Cr(C_3H_6NO_2S)(C_6H_5NO_2)Cl_2 \cdot 4H_2O$: C, 24.64; H, 4.30; N, 6.38; Cr, 11.86; S, 7.30. Found: C, 24.74; H, 3.66; N, 6.97; Cr, 12.12; S, 7.28%. The compound is very soluble in water and has a conductivity value $\Lambda = 363\ \Omega^{-1}\ cm^2\ mol^{-1}$.

Deuterated complexes

These were obtained by the same procedure using d_2-nicotinic acid.

Analyses

Elemental analyses were carried out as described previously [14].

Physical measurements

The deuterium NMR spectra were recorded on aqueous solutions at ambient temperature in a field of 5.87 T on a Brucker WM-250 spectrometer operating at 38.4 MHz. Sample volumes were approximately 2 ml in 10 mm sample tubes containing a capillary of the reference compound ($CDCl_3$). The pH of the sample complex solutions was 2.0. In each experiment, the FID was recorded using 8K data points and a sweep width equivalent to ± 100 ppm, and was multiplied by an appropriate exponential window function before transformation.

The other spectroscopic measurements were carried out as described previously [14].

Results and discussion

The conductivity values of the three soluble complexes agree with non-coordination of the chloride ions to the chromium ion (the data are consistent with 1:6 electrolytes for the nicotinic acid derivative, 1:3 for the L-histidine ternary derivative and 1:2 for the L-cysteine ternary derivative).

For the $Cr(nicH)_3Cl_6 \cdot 6H_2O$ derivative, the appearance of the H-bonded ring deformation band at 1382 cm^{-1} [19] and changes in the ring bands [11, 18–20] from 813, 750, 695 and 683 cm^{-1} in the nicotinic acid to 834, 750, 696 and 673 cm^{-1} in the complex suggests protonation in the nitrogen position of the heterocycle. The broad band at 594–592 cm^{-1} can be tentatively assigned as $\nu(Cl\text{–}OH_2)$ [21] indicating coordination of water molecules to the chromium(III) ion. The coordination to the carboxylic group is also indicated by the shift to lower frequencies of the 1725–1714 cm^{-1} band tentatively assigned as ν^+COO^- that appears at 1625 cm^{-1} in the complex [19], and the splitting of the 642 cm^{-1} band in the nicotinic acid (owing to a combination mode between deformation ring bands and stretching carboxylic bands) that appears at 673 and 624 cm^{-1} in the complex. No Cr–Cl stretching band was observed, in agreement with the conductivity data.

For the ternary derivatives the information obtained from IR spectra is limited owing to the overlapping between some of the nicotinic and amino acid bands. In the ternary cysteine derivative the disappearance of the S–H stretching bands at 2456 and 376 cm^{-1} suggests coordination of the sulfur to chromium(III) [22–24]. The appearance of a band at 1374 (histidine derivative) and 1386 (cysteine derivative) cm^{-1} confirms the protonation of the pyridine nitrogen of the nicotinic acid in these ternary complexes. In the L-histidine derivative the variation of the imidazole ring bands is very small [25–33]. It is possible to assign tentatively bands at 647 (histidine complex) and 624 (cysteine complex) cm^{-1} as stretching Cr–OH_2 bands from coordinated water or librational water.

The electronic spectra (Table 1) agree with coordination of chromium(III) with O donors for the complex $(Cr_2(nicH)_3(H_2O)_6)Cl_6$ with an average $10Dq$ of 17 300 cm^{-1} and with the ternary nature of Cr(L-his)(nicH)$Cl_3 \cdot 5H_2O$ ($10Dq = 18\,700$ cm^{-1}) and Cr(L-cys^-)(nicH)$Cl_2 \cdot 4H_2O$ ($10Dq = 17\,900$ cm^{-1}) suggesting coordination with nitrogens of L-his, either from imidazole or the amino group, and O donors for the former and coordination with S, amino and O donors for the cysteine derivative [34].

The EPR spectra of solid samples of $Cr_2(C_6H_5NO_2)_3Cl_6 \cdot 6H_2O$ and the cysteine ternary complex show simply a broad band $g_{eff} = 2.0$ consistent with a dimeric or polynuclear structure. The spectrum of the histidine ternary complex also has its principal band at $g_{eff} = 2$ but, in this case, there is a shoulder at lower field (Fig. 2) due to zero field splitting, as previously observed for some chromium(III)–amino acid complexes [13, 14], implying that this compound is monomeric.

The D NMR results indicate coordination of nicotinic acid to chromium(III) through the carboxylic group because the d_2 signal appears at 9–10 ppm (Fig. 3) instead of at −70 ppm expected for nitrogen coordination [3].

For the nicotinic acid binary derivative only a single peak appears (Fig. 3) indicating a very symmetrical geometry for the three nicotinic acid molecules. The IR study indicated coordination of chromium with water molecules, the conductivity values are consistent with no coordination by the chloride ions, the EPR spectra suggests a dimeric or polynuclear nature and the electronic spectrum is in accord with only O donors. All these facts are consistent with a dimer (Fig. 4) or a

TABLE 1. Electronic spectra for the complexes (bands in nm)

	$^4T_{2g} \leftarrow {}^4A_{2g}$	$^4T_{1g} \leftarrow {}^4A_{2g}$
$Cr_2(nic)_3(OH)_3 \cdot 4H_2O$[a]	608, 567	430, 390, 358
$Cr_2(nicH)_3Cl_6 \cdot 6H_2O$[b]	576 (97)	404 (107)
Cr(L-his)(nicH)$Cl_3 \cdot 5H_2O$[b]	534 (55)	400 (103)
Cr(L-cys-)(nicH)$Cl_2 \cdot 4H_2O$[b]	560 (42)	404 (64)

[a]In reflectance mode. [b]in water solution indicating the extinction molar coefficient in parentheses. The assignment uses an O_h notation for simplicity.

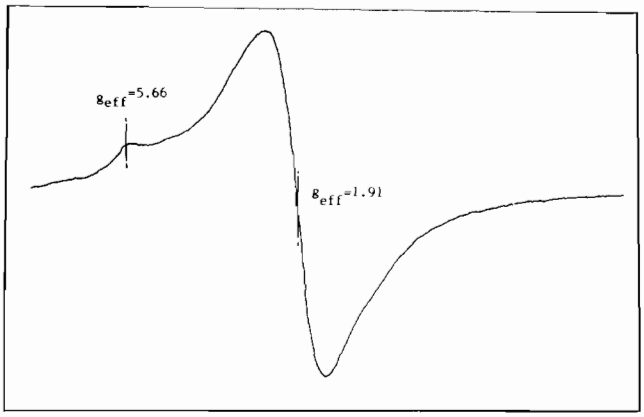

Fig. 2. Room temperature EPR spectra of Cr(L-His)(nicH)$Cl_3 \cdot 5H_2O$.

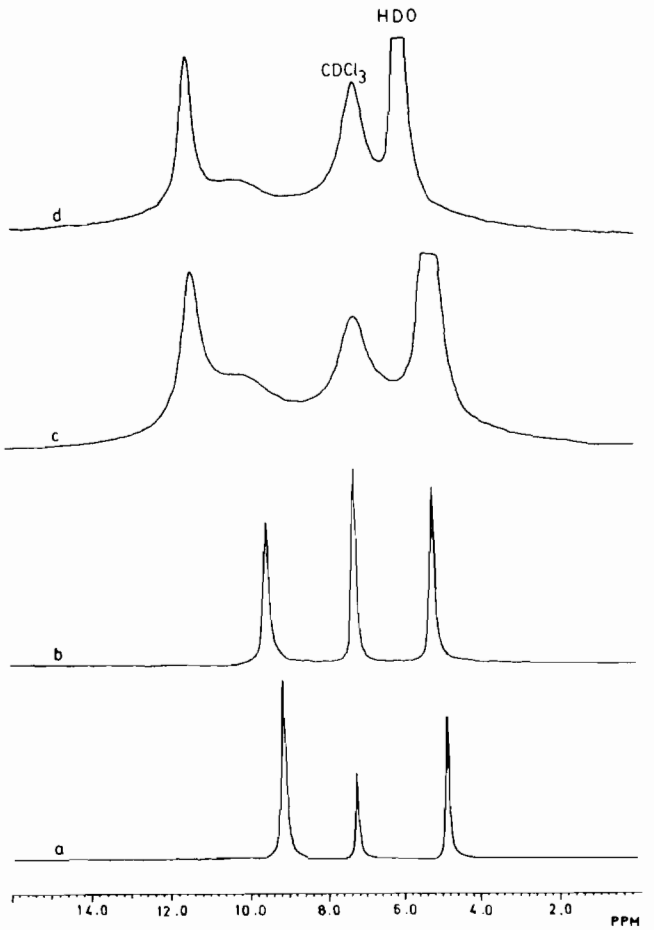

Fig. 3. D NMR spectra of (a) d_2-nicotinic acid, (b) Cr_2 (d_2-nicH)$_3Cl_6 \cdot 6H_2O$, (c) Cr(L-his)(d_2-nicH)$Cl_3 \cdot 5H_2O$, (d) Cr(L-cys)(d_2-nicH)$Cl_2 \cdot 4H_2O$.

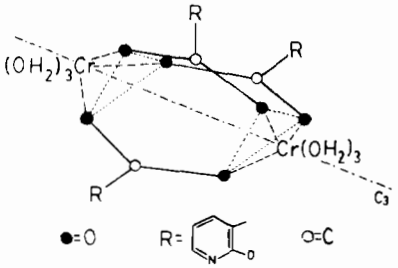

Fig. 4. Proposed structure of $Cr_2(nicH)_3Cl_6 \cdot 6H_2O$.

more extended polymeric array involving bridging carboxylate groups.

In the case of the ternary derivatives two broad peaks are observed (Fig. 3), one of them at 11.32 and 11.45 ppm and a second one as a shoulder at 10.00 and 10.43 for the histidine and cysteine derivative, respectively.

The shifts in band positions as compared with the nicotinic acid binary complex are to be expected as it is known [3] that the band position in Cr(III) nicotinic acid complexes is influenced by the nature of the other ligands bound to the metal ion (e.g. *trans*-$(Cr(1,2pn)_2(HnicO)_2)^{3+}$ at 8.8 ppm, *trans*-$(Cr(NH_3)_4(HnicO)_2)^{3+}$ at 9.0 ppm and $(Cr_3O(nicH)_6(H_2O)_3)^{8+}$ at 6.7 ppm). The presence of two different deuterium NMR bands suggests that solution in water results in the formation of more than one solute species.

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