Synthesis and Structure of a Trinuclear Chromium(III)–Nicotinic Acid Complex

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Received October 31, 1981

The reaction of nicotinic acid (nic), chromic perchlorate hexahydrate, and sodium perchlorate in aqueous solution affords a Cr(III)–vitamin complex whose composition has been established to be Na-$[Cr_3O(nicH)_6(H_2O)_3][ClO_4]_8 \cdot nicH \cdot 6H_2O$, based on analytical data and a single-crystal X-ray analysis. In the $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$ ion a central oxygen atom is bonded to three chromium atoms. The nicotinic acid zwitterions bridge these chromium centers through the carboxylate oxygen atoms. On each chromium atom a water oxygen, trans *to the central oxygen atom, completes the octahedral coordination. The ion has crystallographically imposed symmetry $\bar{6}$. The binding of nicotinic acid in this Cr(III)–nicotinic acid complex is significantly different from that currently proposed for the glucose tolerance factor.*

Introduction

Schwarz and Mertz identified an organic complex of chromium that promotes cellular utilization of glucose in chromium-deficient rats. They designated this complex as a 'glucose tolerance factor' (GTF) [1]. Partial characterization of GTF from brewers' yeast indicated that this ionic complex may contain Cr(III), nicotinic acid (nic), glycine, glutamate, and cysteine [2]. Although a structure has been proposed, GTF is still not a well-defined chemical entity [3, 4]. Many attempts have been made to synthesize GTF, but yields have been low and proposed structures remain highly speculative [5]. We have undertaken a systematic study of the synthesis of compounds of chromium(III) with nicotinic acid as part of a program to determine whether N- or O-coordinated nic confers functionality on chromium in biological systems. We have already reported [6] the synthesis and metabolic studies of a chromium(III)–nic–pyridoxylidene ternary complex in which nic is coordinated to the metal through the ring nitrogen atom, as in the structure proposed by Mertz [2]. Although we have not addressed bioavailability (promotion of glucose tolerance) in these studies, we have shown that absorption and biodistribution of such complexes is similar to GTF analogues. We now report the synthesis and structure of a new O-coordinated trinuclear chromium complex of nic, the first such Cr(III)–vitamin complex to be fully characterized.

Experimental

Nicotinic acid (0.246 g, 2 mmol) was dissolved in 50 ml of water at 80 °C, and chromic perchlorate hexahydrate (0.458 g, 1 mmol) was added. The solution was slowly evaporated to dryness on a steam bath. Excess chromic perchlorate was extracted with ethanol. The crude green material was crystallized by dissolving equal amounts of $NaClO_4$ and the complex in a minimal amount of hot water. The solution was immediately filtered and cooled. The resulting small emerald-green crystals were filtered, washed several times with ethanol, and air dried. Crystals sufficiently large and well formed for X-ray analysis were obtained by recrystallization from 50% methanol. A yield of 60% of the original starting materials was obtained.

The material crystallizes in space group $P6_3/m$ or $P6_3$ of the hexagonal system in a cell of dimensions a = 13.565(6), c = 24.89(1) Å at −150 °C. A total of 4789 diffracted intensities (+h, +k ±l; $2\theta(MoK\alpha_1) < 48°$) was collected at −150 °C by diffractometer methods standard in this laboratory [7]. The crystal used was a hexagonal needle of total volume 0.0061 mm^3. No correction for absorption was necessary. Examination of Friedel pairs provided no evidence for the noncentrosymmetric space group. Accordingly, the intensities were

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TABLE I. Positional and Thermal Parameters for the Atoms of $Na[Cr_3O(nicH)_6(H_2O)_3[ClO_4]_8$.

Atom	x	y	z	B, Å^2
Cr	−0 48836(52)	0.21433(51)	¼	1.00(12)
Cl(1)	0.02346(64)	0.22104(65)	0.08081(29)	2.29(15)
Cl(2)	−1/3	1/3	0 05038(48)	1.58(24)
Na	0	0	0	1 0
O(1)	−0.5354(14)	0.2821(15)	0.19192(69)	1.33(36)
O(2)	−0.4694(14)	0.1248(14)	0.19276(64)	1.19(36)
O(3)	−1/3	1/3	¼	0.58(76)
O(4)	−0.6555(20)	0.0864(20)	¼	0.89(48)
O(5)	0.0828(17)	0.1595(15)	0.08805(75)	2.31(40)
O(6)	0.1033(16)	0.3378(17)	0.06744(76)	2.42(43)
O(7)	−0.0614(17)	0.1671(18)	0.03914(81)	2.71(46)
O(8)	−0.0385(17)	0.2181(18)	0.12952(81)	2.67(45)
O(9)	−0.4478(18)	0.2968(18)	0 03250(75)	2.82(44)
O(10)	−1/3	1/3	0.1098(15)	3.19(82)
C(1)	−0.4877(26)	0.3834(26)	0.1735(12)	2.24(60)
C(2)	−0.5423(23)	0.3986(24)	0.1248(11)	1.51(54)
C(3)	−0.6255(21)	0.3047(21)	0.10016(96)	0 78(49)
N	−0.6748(19)	0.3219(20)	0.05475(87)	1.56(45)
C(4)	−0.6435(25)	0.4248(25)	0.0380(11)	1.94(61)
C(5)	−0.5592(25)	0.5248(25)	0.0613(11)	1.87(58)
C(6)	−0.5076(30)	0.5094(30)	0.1094(12)	3.10(71)

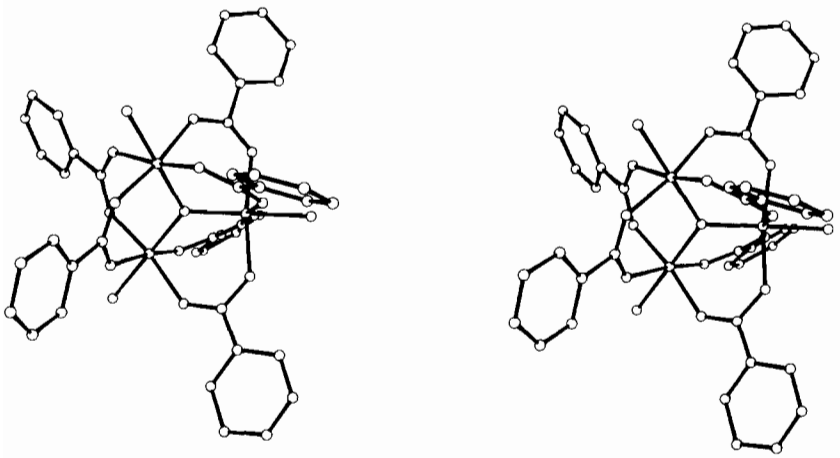

Fig. 1. A stereo drawing of the $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$ ion. The ion has crystallographically imposed symmetry $\bar{6}$. In this and the following figure hydrogen atoms are omitted for clarity.

averaged for Laue group 6/m to yield 1030 unique reflections having $F^2 > 3\sigma(F^2)$. These were used in subsequent calculations. The structure was solved by a combination of Patterson and direct methods.

Refinement of the structure in space group C_{6h}^2–$P6_3/m$ yields two formula units of $Na[Cr_3O(nicH)_6(H_2O)_3][ClO_4]_8 \cdot x nicH \cdot y H_2O$ in the cell (nicH = HNC_4H_4COO = zwitterion of nicotinic acid). The Na^+, $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$, and ClO_4^- ions are well defined by the refinement, although the isotropic thermal parameter on Na does not stay positive. Accordingly, B(Na) was fixed at 1.0 Å^2 for the final refinement (Table I). The disposition of the ions in the cell leaves large holes. The occupants of these holes, presumably nicH and H_2O, must be severely disordered as their positions cannot be discerned from difference electron density maps, despite the fact that such maps yield the positions of the H atoms on the pyridine ring. Because of these difficulties, the R index for isotropic refinement is 12% and

TABLE II. Distances (Å) and Angles (deg) for $Na[Cr_3O(nicH)_6(H_2O)_3][ClO_4]_8 \cdot nicH \cdot 6H_2O$.

Cr–O(1)	1.98(2)	O(1)–Cr–O(2)	86.0(7)
Cr–O(2)	1.97(2)	O(1)–Cr–O(3)	94.7(5)
Cr–O(3)	1.906(6)	O(1)–Cr–O(4)	85.2(7)
Cr–O(4)	2.05(2)	O(2)–Cr–O(3)	95.4(5)
O(1)–C(1)	1.28(3)	O(2)–Cr–O(4)	84.8(7)
O(2)–C(1)	1.24(3)	O(3)–Cr–O(4)	179.8(7)
C(1)–C(2)	1.49(4)	Cr–O(1)–C(1)	131(2)
C(2)–C(3)	1.35(3)	Cr–O(2)–C(1)	132(2)
C(3)–N	1.39(3)	O(1)–C(1)–O(2)	127(3)
N–C(4)	1.31(3)	C(3)–C(2)–C(6)	124(3)
C(4)–C(5)	1.39(4)	C(2)–C(3)–N	117(3)
C(5)–C(6)	1.45(4)	C(3)–N–C(4)	121(2)
C(6)–C(2)	1.39(4)	N–C(4)–C(5)	125(3)
		C(4)–C(5)–C(6)	115(3)
Cl(1)–O(5)	1.43(2)	C(4)–C(6)–C(2)	117(3)
Cl(1)–O(6)	1.44(2)		
Cl(1)–O(7)	1.45(2)	O(5)–Cl(1)–O(6)	109.7(12)
Cl(1)–O(8)	1.46(2)	O(5)–Cl(1)–O(7)	109.4(13)
Cl(2)–O(9)	1.44(2)	O(5)–Cl(1)–O(8)	111.2(12)
Cl(2)–O(10)	1.48(4)	O(6)–Cl(1)–O(7)	111.1(12)
		O(6)–Cl(1)–O(8)	109.1(12)
		O(7)–Cl(1)–O(8)	106.2(12)
		O(9)–Cl(2)–O(9)′	110.9(8)
		O(9)–Cl(2)–O(10)	107.9(9)

the X-ray data provide no direct information on the values of x and y. Our best estimate of x = 1 and y = 6 comes from the analytical data and the measured density, with the value of y being less secure as it rests almost entirely on the H analysis. The calculated formula weight of 2014 amu is consistent with that of 1976 amu obtained from the measured density of 1.62 g/cm^3 and the unit cell volume at room temperature of 4049 Å^3. $Na[Cr_3O(nicH)_6(H_2O)_3][ClO_4]_8 \cdot nicH \cdot 6H_2O$. *Anal.* Calcd.: C, 25.02; H, 2.65; Cr, 7.74; N, 4.86; Na, 1.14. Found: C, 25.09; H, 2.61; Cr, 7.75; N, 4.72; Na, 1.10%.

Results and Discussion

Despite difficulties in establishing the exact composition of the solid material, the nature of and the metrical details for the Cr–nicotinic acid species, $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$, are secure. A stereo drawing of the ion is shown in Fig. 1; labeling is shown in Fig. 2. Important bond distances and angles are tabulated in Table II. The ion has crystallographically imposed symmetry $\bar{6}$. It is similar to the corresponding Cr(III)–acetate [8] and Fe(III)–glycine species [9]. In the present structure the octahedrally coordinated Cr(III) center has Cr–O distances of 1.98(2), 1.97(2), 1.906(6), and 2.05(2) Å to atoms O(1) through O(4), respectively. The bond angles within the octahedron range from 85 to 95°.

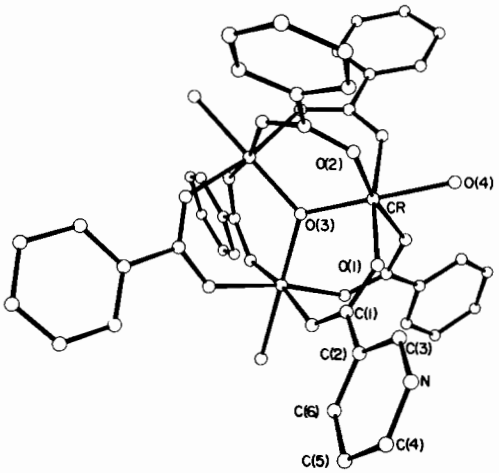

Fig 2. A sketch of the $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$ ion, showing the labeling scheme.

The nature of the present Cr(III)–nicotinic acid complex, namely the $[Cr_3O(nicH)_6(H_2O)_3]^{+7}$ ion, is significantly different from that proposed for GTF by Mertz and co-workers [1, 3] in that the binding of the nicotinic acid is through the carboxylate-O rather than the pyridine-N function and the complex is not mononuclear. Thus, the possibility arises that GTF may be a trinuclear chromium compound bridged by the carboxylic groups of nicotinic acid and amino acids. But we make no claim for the synthesis of a GTF analogue, as the poor solubility at neutral pH of the present trinuclear complex precludes testing of its biological activity in many systems. Doisy *et al.* [10] have speculated that amino acids may be necessary to make GTF water soluble, and that the unique coordination of nic to Cr – still undecided may be responsible for its biological activity.

Acknowledgements

We thank the National Council of Science and Technology (CONACYT-Mexico) for fellowship support of E.G.-V. This work was supported at the University of California by USPHS Grant AM 12386 from the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases and at Northwestern University by Grant HL 13157 of the National Institutes of Health.

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