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MODELLING CHROMIUM BIOCHEMISTRY: SYNTHESIS AND CHARACTERIZATION OF $[NEt_3H][Cr_4^{III}O_2(O_2CPh)_7(pic)_2]\cdot CH_2Cl_2$ (Hpic = PICOLINIC ACID)

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Abstract—Reaction of $[Cr_3O(O_2CPh)_6(H_2O)_3]NO_3$ in PhCN with NEt_3 and picolinic acid followed by recrystallization of the resulting solid from CH_2Cl_2–hexanes affords green crystals of $[NEt_3H][Cr_4O_2(O_2CPh)_7(pic)_2]$ (**1**). The X-ray crystal structure reveals the presence of a di(μ-oxo) tetrachromium(III) core in the anion, which combines two structural elements previously proposed as important for the biological activity of chromium.

Nearly 40 years ago, chromium was recognized to be an essential trace element in mammals.[1] Since this time, chromium has been demonstrated to be required for normal carbohydrate and lipid metabolism. However, despite the apparent importance of chromium, essentially nothing is known about the composition and structure of its biologically active form.[2] Currently, the best candidate for the biologically active form of chromium is low-molecular-weight chromium-binding substance (LMWCr). Isolated from rabbit liver, LMWCr is a glutamate/aspartate-rich oligopeptide which binds four chromic ions.[3] Charge and size considerations suggest that the chromic ions occur in an anion-bridged tetranuclear assembly supported by carboxylate ligands provided by the oligopeptide.[4] Yet, other recent investigations have identified an apparent biological activity associated with chromic/picolinate complexes. Administration of chromium/picolinate supplements to mammals (including humans) has been reported to result in decreases in serum glucose and cholesterol while increasing the rate of lean body mass development.[5] In this communication, this laboratory describes the preparation of a chromium complex which incorporates both elements proposed to be essential for biological activity, i.e. an anion-bridged tetranuclear carboxylate assembly and picolinate ligands.

EXPERIMENTAL

Synthesis

All manipulations were performed under aerobic conditions, and all chemicals were used as received. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, U.S.A. $[Cr_3O(O_2CPh)_6(H_2O)_3]NO_3$[6] was available from previous work.

$[Cr_4O_2(O_2CPh)_7(pic)_2]$ (1)

A green solution of $[Cr_3O(O_2CPh)_6(H_2O)_3]NO_3$[6] in 50 cm^3 PhCN was treated with 1.29 g picolinic acid (Hpic) and 1.06 g NEt_3. The mixture was heated to reflux for 2 h and the resulting blue–green

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Table 1. Crystallographic data for complex **1**

$C_{67}H_{59}O_{20}N_3Cr_4$
$M_r = 1434.20$
$a = 14.066(5)$ Å
$b = 16.407(8)$ Å
$c = 15.077(6)$ Å
$\beta = 104.63(3)°$
$V = 3367(2)$ Å^3
$Z = 2$
$\rho_{calc} = 1.415$ g cm^{-3}
$\mu = 7.04$ cm^{-1}

Space group $P2/n$
$T = 296$ K
$\lambda = 0.71073$ Å
Range $4° \leqslant 2\theta \leqslant 50.0°$
Unique data 5877
Observed data 3170
$F > 6.0\sigma(F)$
$R = 4.56\%$
$R_w = 5.94\%$

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solution was allowed to cool. The solution was then filtered to remove red crystals of Cr(pic)$_3$ and layered with diethyl ether. After several days, the resulting blue–green solid was collected and dissolved in CH_2Cl_2. This solution was layered with hexanes to give, after several days, blue–green crystals of the desired product in *ca* 30% isolated yield (based on chromium). Found: C, 54.0; H, 3.7; N, 3.6; Cr, 13.3. Calc. for $C_{68}H_{61}N_3O_{20}Cl_2Cr_4$:* C, 53.8; H, 4.1; N, 2.8; Cr, 13.7%. IR: 1615 (s), 1580 (m), 1560 (m), 1180 (m), 1160 (m), 1070 (w), 1055 (w), 1030 (w), 855 (w), 720 (vs), 675 (m), 630 (m), 500 (m).

X-ray crystallography and structure solution

Data were collected on a Siemens R3m/V Diffractometer equipped with Mo-K_α graphite monochromated radiation in the 2θ range of 3.0–50.0°. Data collection parameters are collected in Table 1. The structure was solved using direct methods (SHELXTL) and refined by least squares analysis, giving values of $R = 4.56$ and $R_w = 5.94$ for 3170 observed ($F_0 > 6\sigma F$) reflections from 5877 independent reflections. Hydrogen atoms were placed in their calculated positions and refined with a common isotropic U.

The nitrogen of the NEt_3H cations rests on a two-fold axis; subsequently, the cation is disordered.

Other physical measurements

Infrared spectra (Nujol mull) and electronic spectra were recorded on a Perkin–Elmer 283B spectrophotometer and a Hewlett–Packard 8451A spectrophotometer, respectively. ^1H NMR spectra were obtained using a Bruker AM-360 spectrometer at *ca* 23°C. Chemical shifts are reported on the δ scale (shifts downfield are positive) using the solvent protio-impurity signal as reference. Solution susceptibility measurements were obtained using the Evans NMR method,[7] employing hexamethyldisiloxane as the reference peak; solid state susceptibilities were acquired using a Johnson–Matthey susceptibility balance. Diamagnetic corrections were employed using Pascal's constants.

RESULTS AND DISCUSSION

Synthesis and structure

The reaction of trinuclear Cr^{III} cations of the general form $[Cr_3O(O_2CR)_6(L)_3]^+$ (where L represents a terminal ligand such as H_2O or pyridine) with neutral bidentate ligands (L—L) including 1,10-phenanthroline and 2,2′-bipyridine has been shown to give rise to cations of the form $[Cr_4O_2(O_2CR)_7(L—L)_2]^+$.[8] A similar reaction in refluxing PhCN with the potential anionic, bidentate picolinate readily gives rise to a new tetranuclear species, the anion of complex **1**, in *ca* 30% yield. The relatively low yield results from the formation of the by-product Cr(pic)$_3$.[9] Use of lower picolinate : chromium ratios does not appreciably hinder formation of the mononuclear material. Crystallographic studies confirmed the tetranuclear nature of the anion. The structure of the anion (Fig. 1) consists of a $[Cr_4(\mu\text{-}O)_2]^{8+}$ core peripherally ligated by seven bridging benzoate ligands and two chelating pic groups. An imposed C_2-axis relates the two halves to the anion. Charge considerations indicate that all the metals are Cr^{III}. The anion is thus a member of a rapidly growing class of tetranuclear complexes of the form $[M_4^{III}O_2(O_2CR)_7(L—L)_2]^{n\pm}$, where L—L represents a bidentate ligand and M = Cr, Fe or Mn;[10] only one previous complex of this form with chromium has been reported.[11] The Cr_4O_2 unit can be described in terms of its parentage, i.e. as two edge-fused triangular Cr_3O units; however, the Cr_4 rhombus is no longer planar but has a butterfly type arrangement, where Cr(1) and Cr(1a) occupy the "hinge" sites and Cr(2) and Cr(2a) occupy the "wingtip" sites. This compound represents the fourth Cr^{III} picolinate species characterized by X-ray crystallography; previous examples comprise a mononuclear, a dinuclear and a trinuclear species.[12]

Selected bond distances and angles are collected in Table 2. The two hinge chromium atoms are

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*The crystals as isolated are suitable for X-ray crystallography but are not satisfactory for elemental analysis. Multiple recrystallization from CH_2Cl_2–hexanes gives material suitable for elemental analysis but introduces a CH_2Cl_2 solvate molecule. All spectroscopic and magnetic studies used the multiply recrystallized material.

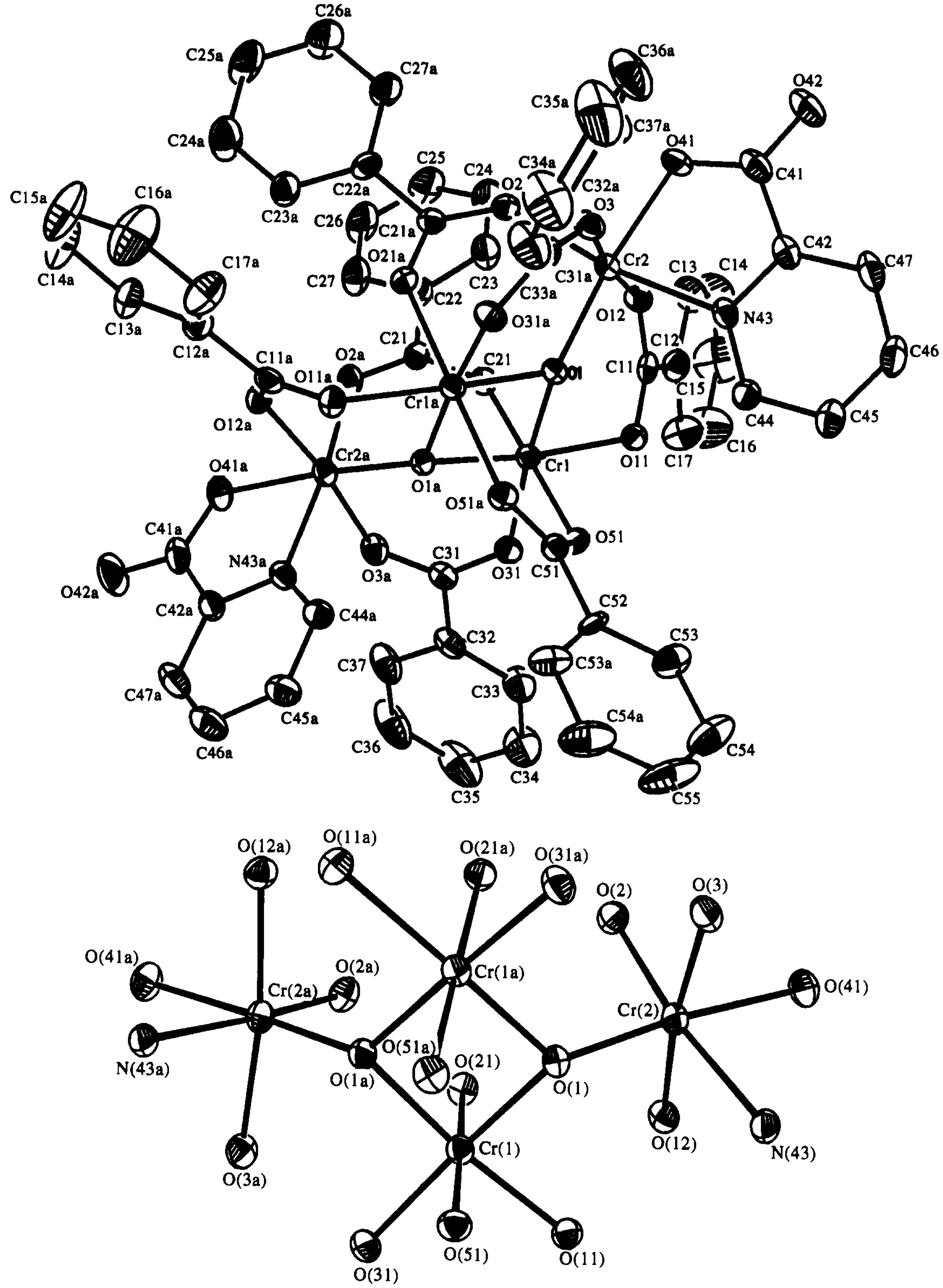

Fig. 1. Structure of the anion $[Cr_4O_2(O_2CPh)_7(picolinate)_2]^-$ and its Cr_4O_2 core (with peripheral atoms).

bridged by two oxide ligands, giving rise to a short Cr- - -Cr separation of 2.774(2) Å. The μ-oxygen atoms bridge asymmetrically with the bond to the wingtip chromium being somewhat shorter than the others [1.864(3) versus 1.908(4) and 1.894(3) Å]. This asymmetry is also manifested in the bond angles about O(1) with Cr(1)—O(1)—Cr(1A) [93.7(1)°] being much smaller than the others,

Table 2. Selected bond distances (Å) and angles (°) for complex **1**

Cr(1)—O(1)	1.908 (4)	Cr(2)—O(1)	1.864 (3)
Cr(1)—O(11)	2.023 (3)	Cr(2)—O(2)	1.986 (4)
Cr(1)—O(21)	1.997 (4)	Cr(2)—O(3)	1.987 (4)
Cr(1)—O(31)	1.994 (4)	Cr(2)—O(12)	2.001 (4)
Cr(1)—O(51)	2.010 (3)	Cr(2)—O(41)	2.007 (4)
Cr(1)—O(1A)	1.894 (3)	Cr(2)—N(43)	2.069 (4)
Cr(1)···Cr(1A)	2.774 (2)		
Cr(1)—O(1)—Cr(2)	130.6 (2)	O(1)—Cr(2)—O(2)	94.7 (1)
Cr(1)—O(1)—Cr(1A)	93.7 (1)	O(1)—Cr(2)—O(3)	92.9 (2)
Cr(2)—O(1)—Cr(1A)	124.6 (2)	O(1)—Cr(2)—O(12)	92.6 (2)
O(1)—Cr(1)—O(11)	90.0 (1)	O(1)—Cr(2)—O(41)	173.2 (2)
O(11)—Cr(1)—O(21)	84.9 (1)	O(2)—Cr(2)—O(41)	92.0 (2)
O(11)—Cr(1)—O(31)	89.7 (1)		
O(1)—Cr(1)—O(51)	177.5 (2)	O(1)—Cr(2)—N(43)	93.5 (2)
O(11)—Cr(1)—O(1A)	173.6 (2)	O(12)—Cr(2)—O(41)	86.6 (2)
O(31)—Cr(1)—O(1A)	95.1 (1)	O(3)—Cr(2)—N(43)	88.0 (2)
O(1)—Cr(1)—O(21)	96.7 (2)	O(41)—Cr(2)—N(43)	79.7 (2)
O(1)—Cr(1)—O(31)	173.3 (1)	O(12)—Cr(2)—N(43)	87.2 (2)
O(21)—Cr(1)—O(31)	89.9 (2)	O(3)—Cr(2)—O(12)	172.9 (1)
O(11)—Cr(1)—O(51)	94.2 (1)	O(2)—Cr(2)—N(43)	171.7 (2)
O(31)—Cr(1)—O(51)	87.7 (2)	O(2)—Cr(2)—O(12)	93.5 (2)
O(1)—Cr(1)—O(1A)	85.8 (1)	O(3)—Cr(2)—O(41)	87.3 (3)
O(21)—Cr(1)—O(1A)	90.7 (1)	O(2)—Cr(2)—O(3)	90.4 (2)
O(51)—Cr(1)—O(1A)	90.4 (1)		

Cr(1)—O(1)—Cr(2) [130.6(2)°] and Cr(1A)—O—Cr(2) [124.6(2)°].

Spectroscopic and magnetic studies

Room temperature magnetic susceptibility measurements in the solid state ($\mu_{\mathrm{eff/Cr}} = 2.56\ \mu_B$) and in $CDCl_3$ solution (Evans' method, $\mu_{\mathrm{eff/Cr}} = 2.65\ \mu_B$) reveal that the chromic ions of complex **1** are antiferromagnetically coupled and that the anion maintains its integrity in solution. These values are similar or slightly lower than those reported previously for $\mathrm{Cr_4^{III}O_2}$ complexes.[8,11]

Recent investigations in this laboratory with antiferromagnetically-coupled $\mathrm{Cr^{III}}$ assemblies have demonstrated the utility of NMR in the characterization of these materials.[13] The ^{1}H NMR spectrum of complex **1** is also consistent with the anion maintaining its integrity in $CDCl_3$ solution (Fig. 2). At least three paramagnetically broadened and shifted resonances can be identified at 1.5, 8.1 and *ca* 33 ppm. The first two, which occur in approximately a 1 : 2 ratio, can readily be assigned to the *para* and *meta* protons of the benzoate ligands by comparison of the spectra with those of previously reported multinuclear $\mathrm{Cr^{III}}$/benzoate complexes.[13] The *ortho* proton resonance is expected to be very broad or even non-resolvable and may represent the broad feature which appears to underlie features between 0 and 4 ppm. Identification of resonances associated with the picolinate (2-pyridinecarboxylate) ligands is less straightforward. The 3-position and 6-position protons for the chelating ligands are expected to be broadened beyond detection.[13] Thus, the remaining proton resonance at ~ +33 ppm must result from either the 4- or 5-position proton.

The electronic spectrum of the anion in CH_2Cl_2 is distinctive, consisting of two distinct bands with maxima at 338 nm (ε/Cr = 1.44×10^4 M^{-1} cm^{-1}) and 564 nm (ε/Cr = 89.8 M^{-1} cm^{-1}). The former, from its intensity, is assigned to a picolinate to chromium charge transfer band, the latter to a *d–d* transition. The former band is absent in the electronic spectrum of the cation $[\mathrm{Cr_4^{III}O_2(O_2CPh)_7(2,2'\text{-bipyridine})_2}]^+$.[11] The position of the latter band's maximum appears to be characteristic of the $\mathrm{Cr_4^{III}O_2}$ core, as it is present in the spectra of all previously reported complexes containing $\mathrm{Cr_4O_2}$ cores.[11]

Biological relevance

Recent studies on the addition of chromium picolinate complexes to the diet of mammals[5] suggest that they have an insulin-potentiating nutritional

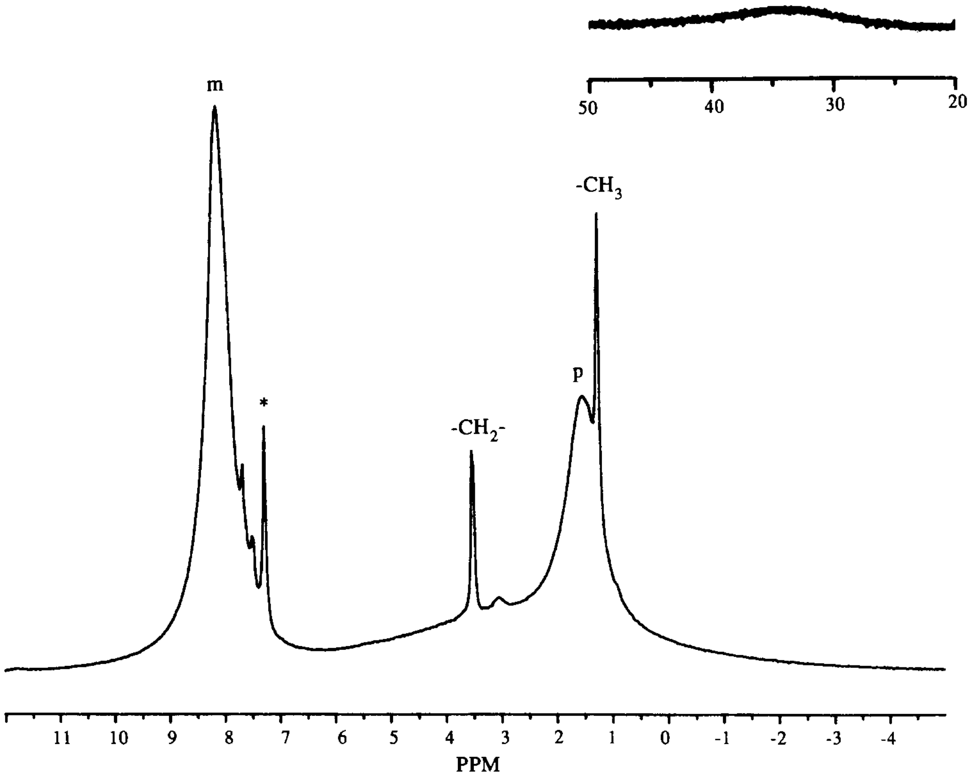

Fig. 2. ^{1}H NMR of $[NEt_3H][Cr_4O_2(O_2CPh)_7(picolinate)_2]$ in $CDCl_3$. Asterisks denote bands due to solvent. Resonances labelled —CH_2— and —CH_3 arise from the cation.

action, reflecting an ability to deliver chromium effectively to important tissues (reviewed in Ref. 14). This may result from an increased ability of the complexes to cross cell membranes;[5] cell membranes appear virtually impermeable to hydrated chromic ions.[15] Consequently, the attachment of picolinate ligands to preformed multinuclear chromium assemblies may allow accelerated transport of the assemblies across cell membranes; these preformed assemblies could then be primed for direct insertion into LMWCr.

CONCLUSIONS

This laboratory has been striving to produce a series of synthetic complexes which contain elements proposed to be essential to the biological activity of chromium; an important member of this series is the anion $[Cr_4O_2(O_2CPh)_7(pic)_2]^-$, which contains both elements recently proposed as important to such activity. Efforts to test the synthetic complexes for biological activity are underway.

Supplementary material available

Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre.

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