Synthesis of the First Stable Nitrogen-Coordinated Nicotinic Acid–Chromium(III) Complexes: *cis*- and *trans*-H[Cr(mal)$_2$(nic-*N*)$_2$]

Sir:

Chromium has been shown to be an essential trace element associated with the maintenance of normal glucose metabolism.[1] The biologically active form of chromium, although not well-defined, has been proposed as minimally a complex of chromium and nicotinic acid, since nicotinic acid is apparently essential for maximal activity of complexes in in vitro testing.[1b] Therefore, a thorough knowledge of the coordination chemistry of chromium and nicotinic acid is fundamental to an understanding of the biological role of chromium. Recently we reported the synthesis of the first stable (at physiological pH) carboxyl-bound chromium(III)–nicotinic acid complex, *trans*-[Cr(1,3-pn)$_2$(nic-*O*)$_2$]Cl (1,3-pn = 1,3-propanediamine; nic = nicotinate).[2] Currently, our attention is focused on the synthesis of stable pyridyl-nitrogen-coordinated chromium(III)–nicotinic acid complexes, which to our knowledge has not yet been demonstrated. Apparently, classical ligand substitution synthetic schemes using chromium(III) starting materials favor the formation of O-coordinated nicotinic acid complexes[2,3] or unstable nitrogen-coordinated nicotinic acid complexes.[4] The synthesis of *trans*-[Cr^{II}(nic-*N*)$_2$(H$_2$O)$_4$] (nic = nicotinate) via aqueous chromium(II) was recently reported,[5] indicating an affinity of chromium(II) for the pyridyl nitrogen of nicotinic acid. This is surprising, in light of the numerous dinuclear chromium(II)–carboxylato complexes known.[6] This observation, coupled with the knowledge of the intrinsic reducibility of nicotinic acid by aqueous chromium(II) reported by Gould and Taube,[7] prompted us to investigate synthetic schemes for producing nitrogen-coordinated chromium(III)–nicotinic acid complexes from chromium(II). But, since Taube and co-workers[7,8] showed that pyridyl-nitrogen-coordinated chromium(III)–nicotinic acid or –nicotinamide complexes were not produced by chromous reduction of pentaamminecobalt(III) complexes of these ligands, we tried ligand reduction "redox trapping"[9] as a method of synthesizing the desired complexes. Presently, we wish to communicate the synthesis of *cis*- and *trans*-H[Cr^{III}(mal)$_2$(nic-*N*)$_2$] (mal = malonate) using such a method.

Experimental Section. The complexes *cis*- and *trans*-H[Cr(mal)$_2$(nic-*N*)$_2$] were synthesized via chromium(II) as follows: Nicotinic acid (4.0 g, 0.032 mol) and malonic acid (1.7 g, 0.016 mol) were dissolved in 50 mL of distilled water, and the pH was adjusted to 6 with 20% KOH. The ligand solution was transferred to a 100-mL 24/40 Schlenk flask fitted with a rubber septum. A semi-micro Orion pH electrode was carefully pushed through a small hole (ca. 3–4 mm) bored in the septum. The ligand solution was deoxygenated in this flask by repeated evacuation and subsequent flushing with chromous-scrubbed argon. An aliquot of a stock chromium(II) solution[10] (0.008 mol) was added to the stirred ligand solution with use of a gastight Hamilton syringe. This dark red solution was shielded from the light and stirred for 1 h while the pH rose to 6.9. Next, the reaction solution was exposed to air and added to a 4.5 × 40 cm column of QAE-Sephadex (A-25, Cl$^-$) in the dark at 4 °C. After the solution was loaded on the column bed and the column was washed with water, elution with 0.1 M KCl yielded a single blue-violet band (band I). Changing the eluent to 0.2 M KCl yielded two bands, a salmon-colored band (band II) and a red-purple band (band III) closely following band II. Elution with 0.3 M KCl resulted in a pink band (band IV), which was cleanly resolved from a red-pink band (band V). Bands IV and V were each rotary evaporated to near-dryness at 25 °C in the dark, and the resulting KCl was filtered off and washed with methanol until colorless. Ethanol was added to each filtrate until the solutions turned cloudy, and then ether was added (100 mL) to precipitate the compounds. These cloudy mixtures were cooled for 1 h at 0 °C, and the precipitate was filtered and air dried. The crude solid obtained for each band was dissolved in a small amount of distilled water (ca. 10 mL), and the solutions were cooled on ice and acidified to pH 1 (while they were being stirred) with concentrated HCl. Stirring was continued until a precipitate formed, which was filtered, washed with acetone, and dried in vacuo. Analytical results[12] are consistent with the bis(malonato) bis(nicotinic acid) formulation for bands IV and V. Chromatograpic behavior is also consistent with this formulation since bands IV and V eluted similarly to −3 species at neutral pH but were found to migrate similarly to −1 species when eluted with 0.1 M HCl. The previously prepared chromium complexes[13] Cr(mal)$_3^{3-}$ and Cr(mal)$_2$(H$_2$O)$_2^-$ were used for comparison.

Deuteron NMR spectroscopy was used to establish that the coordination mode of the nicotinic acid ligands is through the pyridyl nitrogen. Nicotinic acid was deuterated at the 2-carbon (nic-2-*d*) as previously reported[14] and used in the synthesis described above. The deuterated complexes (250 mg) were dissolved in 3.5 mL of water by adjusting the pH to 5 with 20% KOH.

Table I. Deuteron NMR Spectral Data

complex	δ (ω)[a]	conditions
trans-H[Cr(mal)$_2$(nic-*N*-2-*d*)$_2$]·1.5H$_2$O	−73 (890)	pH 5
cis-H[Cr(mal)$_2$(nic-*N*-2-*d*)$_2$]·3.5H$_2$O	−75 (1000)	pH 5
trans-[Cr(mal)$_2$(py-2-*d*)$_2$]$^-$ [b]	−70 (500)	in MeOH
trans-[Cr(Me-nic-2-*d*)$_2$(H$_2$O)Cl$_2$] [c]	−70 (1650)	in EtOH
trans-[Cr(1,3-pn)$_2$(nic-*O*-2-*d*)$_2$]$^+$ [c]	9.1 (70)	pH 7.2

[a] δ = chemical shift with respect to CDCl$_3$ assigned as δ +7.2; ω = band width at half-height in Hz. [b] References 2 and 13. [c] Reference 2.

Table II. Visible–Ultraviolet Spectra in Aqueous Solution

complex	λ_{max}, nm (ϵ, L mol^{-1} cm^{-1})		
cis-H[Cr(mal)$_2$(nic-*N*)$_2$]·3.5H$_2$O[a]	263 (6800)	400 (60.0)	537 (67.6)
trans-H[Cr(mal)$_2$(nic-*N*)$_2$]·1.5H$_2$O[b]	263 (6570)	382 (34.0)	536 (33.8)
syn-cis-[Cr(edda)mal]$^-$ [c]		399 (53.2)	540 (68.9)
trans-Li[Cr(mal)$_2$(py)$_2$]·2H$_2$O[d]		382 (25.5)	536 (30.0)

[a] pH 3.5. [b] pH 4.5. [c] Reference 16. [d] Reference 13.

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(10) Chromium(II) solutions were prepared as follows: Electrolytically pure amorphous chromium metal (Gallard-Schlesinger) was dissolved in 2 equiv of 6 N HCl under a stream of chromous scrubbed argon. After evolution of hydrogen ceased, deoxygenated, doubly distilled water was added to this chromium(II) concentrate to the desired volume. Purities of these solutions were checked by UV–vis spectroscopy, and analysis was performed by the basic peroxide procedure as chromate.[11] These solutions are stable for months under argon, especially if a slight excess of pure crystalline chromium metal is added in the initial step above. (The crystalline metal dissolves much more slowly than amorphous chromium metal.)

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(12) Anal. Calcd for band IV, *trans*-H[Cr(mal)$_2$(nic-*N*)$_2$]·1.5H$_2$O: C, 40.76; H, 3.42; N, 5.28. Found: C, 41.15; H, 3.50; N, 5.24. Calcd for band V, *cis*-H[Cr(mal)$_2$(nic-*N*)$_2$]·3.5H$_2$O: C, 38.17; H, 3.91; N, 4.94. Found: C, 38.27; H, 3.83; N, 4.81.

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Spectra were recorded with a Nicolet NT-200 WB spectrometer, as previously described.[13,15]

Results and Discussion. The ^2H NMR spectra for *cis*- and *trans*-H[Cr(mal)$_2$(nic-*N*-2-*d*)$_2$], summarized in Table I, show broad resonances centered at −75 and −73 ppm, respectively. Related methylnicotinate and pyridine complexes deuterated at the 2-carbon show similar resonances consistent with the ligand coordination mode assignment (Table I). Carboxyl coordination of nicotinate-*2-d* gives rise to a distinctly narrower resonance centered at ca. +9 ppm (Table I).[2]

Table II summarizes the electronic spectra of *cis*- and *trans*-H[Cr(mal)$_2$(nic-*N*)$_2$], bands V and IV, respectively. The ligand field spectra are consistent with a Cr(N_2-O_4) formulation by comparison with the previously characterized Cr(N_2-O_4) complexes listed in Table II. The striking similarity of band maxima and molar absorptivities for band IV and previously characterized *trans*-Li[Cr(mal)$_2$(py)$_2$][13] is the basis for the assignment of band IV as *trans*-H[Cr(mal)$_2$(nic-*N*)$_2$]. Therefore, since band V is also a bis(malonato) bis(nicotinic acid) complex, it must be assigned the cis configuration as this is the only other geometrical isomer possible. The larger molar absorptivities for the d–d transitions of this isomer are consistent with the cis assignment, due to the lower symmetry associated with the cis relative to the trans configuration. The geometrical assignments could be made directly from ^2H NMR spectra for the complexes with deuterium-labeled malonate,[13] but so far we have not succeeded in obtaining the desired spectra. Deuteration of the coordinated malonates was carried out as described previously for *trans*-Li[Cr(mal)$_2$(py)$_2$][13] and was confirmed by IR spectroscopy. Apparently, the malonate protons (deuterons) undergo facile exchange in solution. This may be due to intramolecular general-base catalysis promoted by the pyridyl carboxyl group, since this facile exchange is not observed in *trans*-Li[Cr(mal)$_2$(py)$_2$], which was assigned the trans configuration by malonate ^2H NMR studies.[13]

Experiments are in progress to determine the mechanism of what appears to be an intriguingly simple reaction. There is little question, though, that nicotinic acid is the oxidant in the reaction. The reduction of nicotinic acid most likely proceeds through a ligand radical ion intermediate,[7] but how the observed chromium(III)–nicotinic acid species are produced is uncertain. Disproportionation of the ligand radical complex or a mechanism similar to the "bleaching reaction" observed by Dunne and Hurst[17] for "pyrazine green", Cr(pyzH)$^{3+}$, as shown in eq 1 below, are plausible pathways for the production of the observed N-coordinated chromium(III)–nicotinic acid species.

$$Cr(pyzH)^{3+} + pyzH^+ \leftrightarrow Cr(pyz)^{3+} + pyzH_2^+ \quad (1)$$

The complexes reported are stable for many hours in aqueous solution at physiological pH, although aquation at the nicotinic acid ligand sites occurs more rapidly on prolonged exposure to light.[18] Thus, if nicotinic acid is essential to the biological role of chromium in glucose metabolism, as has been proposed,[1] the involvement of pyridyl-nitrogen-coordinated nicotinic acid complexes of Cr(III) cannot be ruled out on the basis of instability.

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Department of Chemistry and Program in Biochemistry and Biophysics
Washington State University
Pullman, Washington 99164-4630

William E. Broderick
J. Ivan Legg*

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Catecholate Coordination to Copper: Structural Characterization of a Tetrachloro-*o*-catecholate-Bridged Dicopper(II) Complex as a Model for Intermediates in Copper-Catalyzed Oxidation of Catechols

Sir:

Investigations of the interactions and reactivity of catechols, *o*-semiquinones, and *o*-benzoquinones with transition metals have received considerable recent attention.[1-5] Copper-catalyzed oxidative C–C bond cleavage reactions of phenols and catechols have been examined in synthetic procedures,[6] copper(II) catecholate complexes have been studied in model pyrochatechase reactions,[7] and Cu(II)–catecholate and Cu(II)–*o*-semiquinone complexes have recently been studied in connection with the interest in redox chemistry of metal–quinone species.[2-5] Such complexes are also relevant to the two-electron oxidation of catechols to *o*-benzoquinones,[5,6,8,9] which is also an important reaction catalyzed by a binuclear copper ion center in the copper protein tyrosinase.[10] In this protein, it has been proposed[10a,11]

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