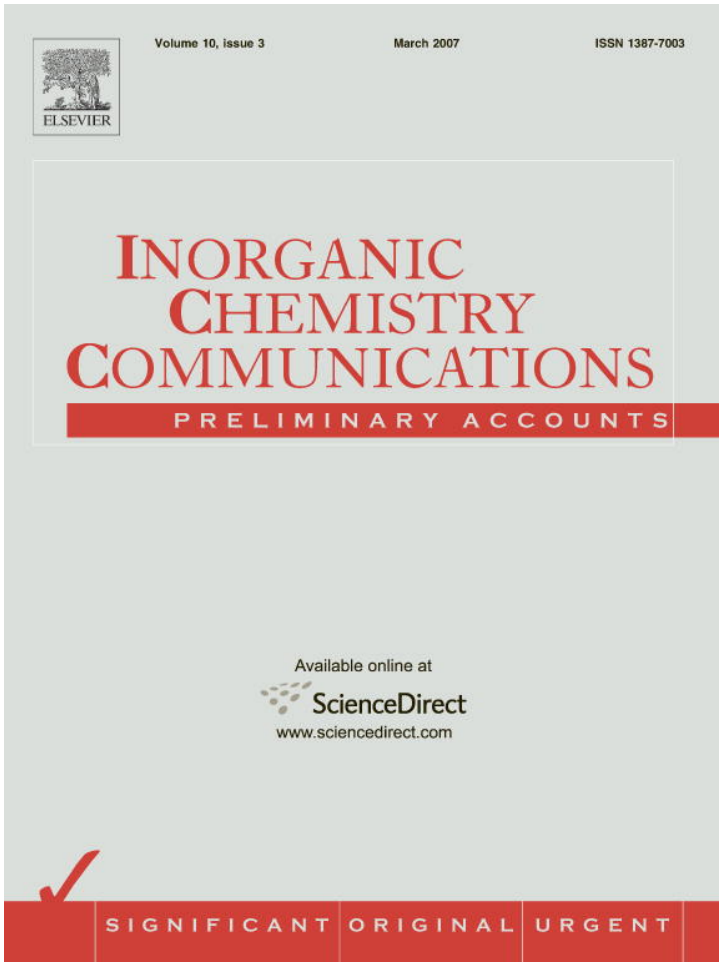

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Synthesis, characterization and kinetics properties of chromium(III) complex $[Cr(3\text{-}HNA)(en)_2]Cl \cdot H_2O \cdot CH_3OH$

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Abstract

The reaction of chromium(III) chloride, 3-hydroxy-2-naphthoic acid (3-HNA) and ethylenediamine (en) led to the formation of complex $[Cr(3\text{-}HNA)(en)_2]Cl \cdot H_2O \cdot CH_3OH$, Bis(ethylenediamine-$\kappa^2N,N'$)(3-hydroxy-2-naphthoic acid-κ^2O,O') chromium(III) monochloride monohydrate monomethanol. The kinetics of transfer of Cr(III) from the title compound to the low-molecular-mass chelator EDTA and to the iron-binding protein apoovotransferrin (apoOTf) were carried out by means of UV–Visible (UV–Vis) and fluorescence spectra in 0.01 M Hepes at pH 7.4. The second-order rate constants were calculated, respectively. The results show that Cr(III) can be transferred from the complex to apoovotransferrin.

Keywords: Chromium(III); Crystal structure; Apoovotransferrin; Kinetics

Chromium is thought to play a key role in normal carbohydrate and lipid metabolism in mammals [1–4]. Clinical trials have demonstrated that supplementation with chromium(III) compounds can lower blood glucose levels in diabetic patients [5]. Chromium(III) picolinate, $Cr(pic)_3$, has been the most thoroughly studied of these synthetic products and become a very popular nutritional supplement [6]. It is reported that $Cr(pic)_3$ can efficiently cleave DNA in the presence of biological reducing agents [7–9]. Recently, Cr(III) oxidation to Cr(V) and/or Cr(VI) in biological systems came into consideration as a possible reason of anti-diabetic activities of some Cr(III) complexes, as well as of long-term toxicities of such complexes [10]. A search has been under way to identify the biologically active form of chromium and to seek other safely synthetic chromium complex [11,12].

The mechanisms of absorption of chromic ions are still uncertain. Little is known of the fate of Cr(III) intake orally. Essentially no data exist on the form of chromium(III) in food as a result of its very low concentration [13]. The iron-transport protein transferrin (Tf) has been proposed to serve as the major chromium transport agent [6]. The transfer of chromium from its complex to the blood serum proteins transferrin was examined [14,15]. We tried to develop novel chromium complexes and study the mechanism for the action of chromium. In this paper the crystal structure, spectroscopic properties and kinetics studies of one newly synthesized chromium complex are reported.

The reaction of chromium(III) chloride, 3-hydroxy-2-naphthoic acid (3-HNA) and ethylenediamine (en) in molar ratio of 1:1:5 in methanol led to the formation of the chromium complex $[Cr(3\text{-}HNA)(en)_2]Cl \cdot H_2O \cdot CH_3OH$. The structure was determined by X-ray crystallography. The perspective structure and the atomic numbering schemes for the chromium complex are shown in Fig. 1. The chromium(III) ion is at the centre of a compressed octahedron formed by four N atoms [Cr–N, 2.056(4)–2.101(4) Å] from two en molecules, one phenolate O atom [Cr–O, 1.908(3) Å] and a carboxylate O atom [Cr–O, 1.940(3) Å] from the 3-HNA ligand. These two

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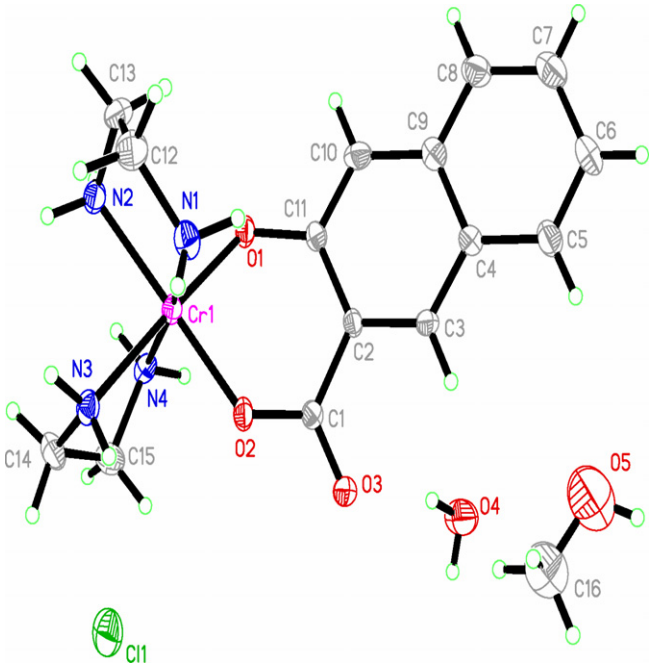


Fig. 1. The structure of the title compound, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level for non-H atoms.

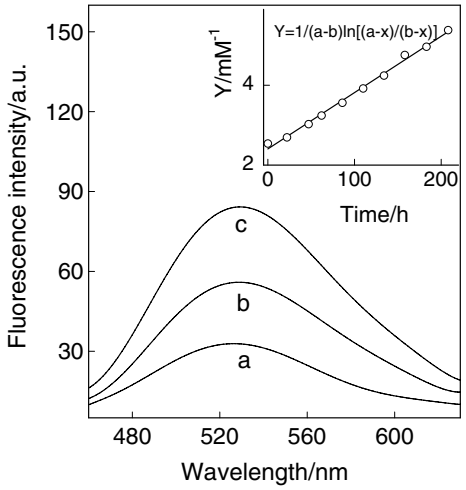


Fig. 2. Fluorescence changes with time (a → c) for the mixture of 85 μM $[Cr(3\text{-HNA})(en)_2]^+$ with 850 μM EDTA at 37 °C in 0.01 M Hepes, pH 7.4, time: a, 10; b, 30; c, 50 h. λ_{ex}, 280 nm. Inset: A plot of $\ln[(a-x)/(b-x)]/(a-b)$ vs. time, $a = 85$ μM, $b = 10a$, $x = a(F_0 - F_t)/(F_0 - F_\infty)$, $r = 0.995$.

O atoms and two of N atoms occupy the equatorial positions and the remaining N atoms occupy the axial positions. There are four kinds of intermolecular hydrogen bonds formed which stabilize the conformation with the distances in the ranges of 2.763 Å for O–H ⋯ O, 3.148 Å for O–H ⋯ Cl, 2.905–3.370 Å for N–H ⋯ O and 3.282–3.659 Å for N–H ⋯ Cl, respectively.

The characteristic absorption peak of 3-HNA occurs at 352 nm, while in the complex this peak exhibits considerable red shift to 372 nm. In addition, 3-HNA displays relatively strong fluorescence intensity with a maximum emission peak near 530 nm. When coordinated with Cr(III), its fluorescence is quenched. In other words, the title complex has hardly any fluorescence in the same condition.

Chromium(III) because of its d^3 electronic configuration forms stable and substitutional inert metal complexes, which is usually required many days for the kinetics studies [15]. In order to research the interaction of the complex with transferrin, EDTA was employed as a simple competitive ligand first. The interaction of 85 μM $[Cr(3\text{-HNA})(en)_2]^+$ with 850 μM EDTA in 0.01 M, pH 7.4 Hepes buffer at 37 °C was monitored by UV–Visible (UV–Vis) spectra and fluorescence spectra. The changes of UV–Vis spectra show that the absorption peaks at 372 nm for coordinated 3-HNA decrease and the peaks at 352 nm for free 3-HNA increase gradually. There are three isosbestic points at 325, 365 and 433 nm. The second-order rate constant k was obtained using standard fitting procedures, $k = (3.8 \pm 0.1) \times 10^{-3}\ M^{-1}\ s^{-1}$.

The fluorescence spectra are shown in Fig. 2. Sample was excited at 280 nm and the emission was monitored from 450 nm to 630 nm. The fluorescence peaks of 3-HNA at 530 nm increased with time gradually. The second-order rate constant k is calculated to be $(3.9 \pm 0.3) \times 10^{-3}\ M^{-1}\ s^{-1}$. It indicated that the free 3-HNA is gradually released from the complex. The results from the two methods are in good agreement. The control experiment for the EDTA experiment with the complex alone and in the absence of EDTA shows that the complex is stable in Hepes buffer at pH 7.4 at 37 °C. It can be concluded that Cr(III) was combined by EDTA and the 3-HNA or en ligands were competitively replaced. This procedure is briefly illustrated by the following scheme:

$$[Cr(3\text{-HNA})(en)_2]^+ \xrightarrow{EDTA} Cr(EDTA) + 3\text{-HNA} + 2en$$

The iron-transport protein transferrin has been proposed to serve as the major chromium transport agent. In this paper, apoovotransferrin (apoOTf) was utilized in place of serum transferrin because of its ready availability in quantity and its cost; the binding properties of apoOTf are nearly identical to serum transferrin [14]. ApoOTf can bind Fe^{3+} and other metal ions tightly [16,17] in the presence of synergistically bound anion that is usually carbonate. The UV–Vis spectra of Cr-OTf reported previously are similar to that of Cr-saturated transferrin [15]. Furthermore, titration of $CrCl_3$ to apoOTf monitored by fluorescence spectra shows the fluorescence intensity of apoOTf decreased to about 50% [18]. The control experiment shows that quenching was scarcely observed in the titration of 3-HNA to apoOTf in the same conditions.

To monitor the transfer of Cr(III)from $[Cr(3\text{-HNA})(en)_2]^+$ to apoOTf, solution of 42 μM $[Cr(3\text{-HNA})(en)_2]^+$ with 42 μM apoOTf in 0.01 M Hepes at pH 7.4 was stored at 37 °C for one week. Both the difference UV–Vis spectra and the fluorescence spectra were monitored as a function of time throughout the course. The fluorescence of apoOTf at 336 nm (characteristic of tryptophan residue) is quenched

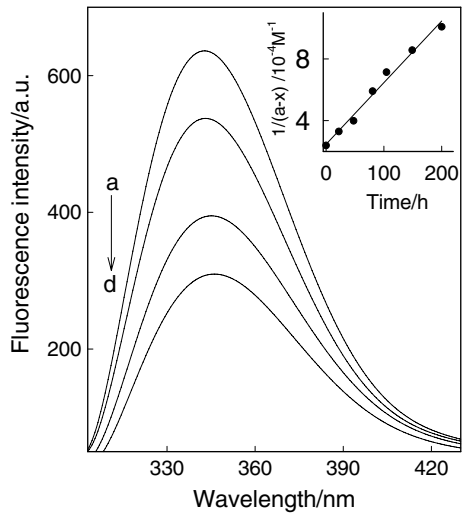


Fig. 3. Fluorescence spectra at different time for the reaction of 42 μM $[Cr(3\text{-}HNA)(en)_2]^+$ with 42 μM apoOTf at 37 °C in 0.01 M Hepes at pH 7.4, time, a → d: a, 25, 50, 100, 200 h, $\lambda_{ex} = 280$ nm. Inset: A plot of $1/(a - x)$ vs. time, $a = 42$ μM, $x = a(F_0 - F_t)/(F_0 - F_\infty)$, $r = 0.987$.

with time slowly (a → d), as shown in Fig. 3. The kinetics of the reaction followed a second-order rate law. The plot in Fig. 3 inset is almost linear within experiment error. The rate constant k is calculated to be $(109.7 \pm 2.4) \times 10^{-3}$ M^{-1} s^{-1}. The fluorescence peak of free 3-HNA appeared when the solution was excited at 320 nm. These phenomenon result from coordination of Cr(III) to the protein and decomposition of the complex.

Fig. 4 shows the difference UV spectra of the mixture, blanked as the same concentration of apoOTf. The peaks at 372 nm increasingly decreased and the peaks at 352 nm increased, just as the reaction with EDTA. The rate constant k is $(111.1 \pm 1.2) \times 10^{-3}$ M^{-1} s^{-1}. It is well consistent

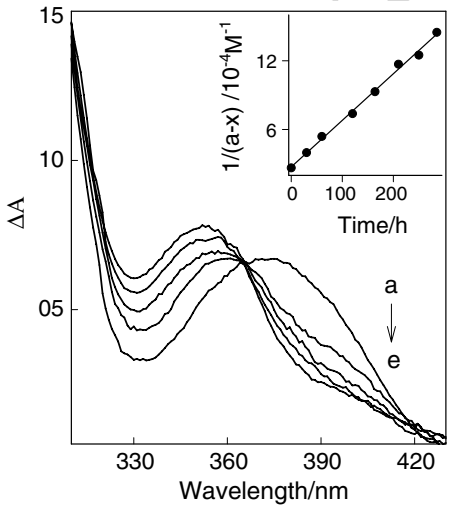
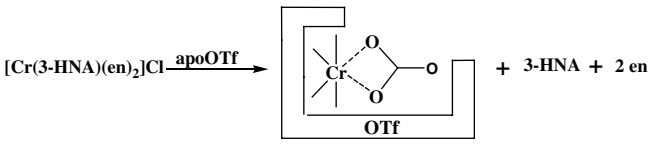


Fig. 4. Difference UV spectra for the reaction of 42 μM $[Cr(3\text{-}HNA)(en)_2]^+$ with 42 μM apoOTf at different time, 37 °C, 0.01 M Hepes, pH 7.4, time, a → e: 0, 60, 100, 150, 280 h. Inset: A plot of $1/(a - x)$ vs. time, $a = 42$ μM, $x = a(A_0 - A_t)/(A_0 - A_\infty)$, $r = 0.996$.



Scheme 1.

with data from fluorescence spectra, which shows that the complex is decomposed and Cr(III) has been transferred to apoOTf.

A number of literatures have indicated that dozens of organic anions (including salicylate) could substitute for carbonate as the synergistically bound anions in iron-transferrin complex [19–21]. Recently we studied the reaction of $[Cr(SA)(en)_2]Cl$ with apoOTf (SA = salicylic acid) [18]. It shows that Cr(III) can be transferred into apoOTf with the retention of SA, SA acted as the synergistically bound anion. However, the results in this paper show that 3-HNA could not transfer into apoOTf together with Cr(III). 3-HNA could not serve as synergistically bound anion; probably it is due to the bigger molecular structure then salicylic acid. In this case, carbonate act as the synergistically bound anion in the combination of Cr(III) to OTf and this summing-up can be illustrated in Scheme 1.

In contrast, $Cr(pic)_3$ is an amazing stable complex. Vincent has studied the interaction of $Cr(pic)_3$ with apoOTf by UV–Vis spectrum [14]. There was no evidence for transfer of chromium to apoOTf unless the metal is reduced to the Cr^{2+} level.

In conclusion, the synthesis and characterization and kinetics properties of one novel chromium(III) complex was reported here. The combination of UV–Vis and fluorescence spectra is used to study the transfer of Cr(III) from the title complex to EDTA and apoOTf, and the second-order rate constants were obtained. The bigger molecular structure of 3-HNA prevents it from serving as the synergistically bound anion.

Acknowledgements

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Appendix A. Supplementary data

CCDC 289526 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2006.11.013.

Appendix B. Note

Analysis: Calcd. for $CrC_{16}H_{28}O_5N_4Cl$ (%): C, 43.26; H, 6.36; N, 12.61. Found (%): C, 43.19; H, 6.33; N, 12.64. Crystal data: monoclinic, space group P2(1), $M_r = 443.87$, $a = 8.390(5)$ Å, $b = 10.162(7)$ Å, $c = 11.842(8)$ Å, $\beta = 97.164(9)°$, $V = 1001.7(11)$ Å^3 and $Z = 2$, $D_c = 1.472$ Mg/m^3, $F(000) = 466$, $T_{max} = 0.9298$, $T_{min} = 0.7565$, $S = 1.094$, $\Delta\rho_{max}/\Delta\rho_{min}$ (e A^{-3}) $= 0.46/-0.23$, $\mu = 0.739$ mm^{-1}. Diffraction intensities were collected at 293 K on a Bruker Apex CCD diffractometer (Mo Kα, $\lambda = 0.71073$ Å). The structure was solved with the direct methods and refined with full-matrix least-squares technique (SHELX-97) [22]. H atoms attached to O atoms (water) were located in a difference Fourier map and their geometry idealized; they were then treated as riding. The other H atoms were also treated as riding atoms. The final R_1 value is 0.0554 and the final wR_2 is 0.0580.

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