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Effect of substituent groups (R= $-CH_3$, $-Br$ and $-CF_3$) on the structure, stability and redox property of $[Cr(R\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ complexes

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ABSTRACT

Complexes $[Cr(3\text{-}CH_3\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**1**), $[Cr(5\text{-}Br\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**2**) and $[Cr(5\text{-}CF_3\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**3**) were synthesized (pic = pyridine-2-carboxylic acid) and characterized by X-ray crystal diffraction. Crystal structure indicates that two bidentate ligands occupy equatorial position and two H_2O occupy axial positions in *trans*-configuration. (i) Decomposition of complexes **1**, **2** and **3** in different medium (phosphate buffered saline (PBS), apo-ovotransferrin (apootf) and EDTA) indicates that decomposition rate constants of these complexes follow the sequence of **1** < **2** < **3**. (ii) The redox potential of Cr(III)/Cr(II) by cyclic voltammetry follows the sequence of **1** (−1.20 V) > **3** (−1.29 V) > **2** (−1.31 V). (iii) In addition, ·OH-generation of the new synthesized complexes was determined by Fenton-like reaction in comparison with $Cr(pic)_3$, and it may be related to the reduction potential of the complexes. (iv) Moreover, Hammett substituent constants σ_p (inductive) and σ_m (resonance) (R = 3-CH_3, 5-Br, 5-CF_3) were introduced to evaluate the impact of substituent groups on the bond length and decomposition kinetics. The substituent group on the ligand has great effect on the properties of the complexes.

1. Introduction

Significant efforts have been made in the last decade to investigate Cr(III) supplements [1], and these efforts focused on the essentiality and safety of Cr(III) as a health product additive [2,3]. Cr(III) has been proposed to be essential and beneficial at long durations for its efficacy in the metabolism of carbohydrates and lipid [4–6]. However, Cr(III) is verified to be a second artificial messenger other than essential element for it is able to amplify insulin signaling at supranutritional level [7]. Some studies have also show that administration of Cr(III) have no effect on various indexes of mice [8,9]. Besides, as the most acceptable transport mechanism, binding of Cr(III) to transferrin is dimed to be detoxication of dietary chromium(III) other than transport of an essential trace element [10]. Hence, the safety of Cr(III) is still pendent.

As the most bioavailable form of trivalent chromium [11–14], $Cr(pic)_3$ (pic = pyridine-2-carboxylic acid) has been the most popular Cr(III) supplements for many years. Previous research indicated that $Cr(pic)_3$ is absorbed from the gastrointestinal tract by cells as intact form [13]. $Cr(pic)_3$ may be reduced to Cr(II) by biological reductants with the generation of hydroxyl radical (·OH), which causes chromosome damage in Chinese hamster chromosome ovary cells [15]. It indicates that decomposition kinetics and redox properties of Cr(III) complexes may have great influence on the bioavailability and safety of Cr(III) complexes. Hence, it is hopeful to develop new efficient and hypotoxic $Cr(pic)_3$ additives through changing substituent groups of picolinate (pic).

In this report, three new Cr(III) complexes $[Cr(3\text{-}CH_3\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**1**), $[Cr(5\text{-}Br\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**2**) and $[Cr(5\text{-}CF_3\text{-}pic)_2(H_2O)_2]NO_3\cdot H_2O$ (**3**) were synthesized and characterized by X-ray crystal diffraction. In order to improve the bioactivity of $Cr(pic)_3$, a well-accepted trifluoromethyl substituent group in medical and structural chemistry was employed in **3** to increase the lipophilicity of the complex [16–19]. The decomposition kinetics in different medium (phosphate buffered saline (PBS, 50 mM, pH 7.4), apo-ovotransferrin (apootf, equivalent with the complexes) and EDTA (100 equivalent of complexes in PBS)), redox potential and ·OH-generation of complexes **1**–**3** were evaluated by UV–vis spectroscopy, cyclic voltammetry, and Fenton-like reaction. Besides, the effect of substituent groups was also assessed, and the

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results may help to develop new high-efficiency and hypotoxic Cr(III) complexes as nutritional additives.

2. Experimental

2.1. Materials and methods

All reagents and solvents were obtained commercially and used without further purification. Apo-ovotransferrin (apootf) was obtained in Sigma-Aldrich. Crystallographic data of Cr(III) complexes were collected on a D8 Venture X-ray diffractometer (Bruker, Germany). The cyclic voltammetry were recorded on an electrochemical workstation (Shanghai Chenhua Instruments, China). Elemental analyses of the complexes **1**–**3** for C, H, and N were conducted on a Vario EL III analyzer. The infrared spectra were collected on a Bruker TENSOR 27 FT-IR spectrometer as KBr pellets in the range of 400–4000 cm^{-1}. UV–vis spectra were recorded on a Varian Cary 50 Bio UV–visible Spectrophotometer.

2.2. Synthesis of the complexes

2.2.1. $[Cr(3\text{-}CH_3\text{-}pic)_2(H_2O)_2]NO_3{\cdot}H_2O$ (**1**)

Complex **1** was prepared according to the literature [16]. A mix solution of 3-CH_3-pic (0.14 g, 1.0 mmol), concentrated nitric acid (15.0 μL, 15.0 M) and $Cr(NO_3)_3{\cdot}9H_2O$ (0.20 g, 0.50 mmol) in distilled water (20 mL) was heated to 100 °C for 2 h and then cooled to room temperature slowly. The solution turned purple from green during the process, and the X-ray quality purple crystals were obtained after standing the filtrate for 5 days at room temperature. Anal. Calcd for $C_{14}H_{16}CrN_3O_9$ (%): C, 38.19; H, 4.12; N, 9.54. Found (%): C, 38.50; H, 3.88; N, 9.67. Selected IR data (KBr pellet, cm^{-1}, Fig. S1): 3600–3294 (br), 3095 (w), 2933 (w), 1670 (s), 1643 (s), 1589 (w), 1458 (w), 1384 (w), 1326 (w), 1276 (w), 1243 (w), 880 (m), 694 (s), 641 (m), 443 (w). $P2_1/c$ space group, $a = 9.535(3)$, $b = 10.3839(3)$, $c = 18.9591(6)$ Å, β=102.4250(10) ° (CCDC: 1500278).

2.2.2. $[Cr(5\text{-}Br\text{-}pic)_2(H_2O)_2]NO_3{\cdot}H_2O$ (**2**)

Similarly, the reaction of 5-Br-pic (0.20 g, 1.0 mmol), $Cr(NO_3)_3{\cdot}9H_2O$ (0.20 g, 0.50 mmol) with nitric acid (15.0 μL, 15.0 M) resulted in purple crystal **2**. Anal. Calcd for $C_{12}H_{10}Br_2CrN_3O_9$ (%): C, 25.28; H, 2.12; N, 7.37. Found (%): C, 25.19; H, 1.98; N, 7.36. Selected IR data (cm^{-1}, Fig. S2): 3449 (br), 3423 (br), 3367 (w), 3099 (w), 3058 (br), 2892 (br), 2511 (br), 1678 (s), 1650 (s), 1592 (m), 1554 (w), 1474 (w), 1425 (m), 1380 (m), 1340 (m), 1299 (m), 1255 (m), 1162 (m), 1093 (m), 1048 (m), 863 (m), 796 (m), 682(s), 518 (m), 428 (w). $P2_1/c$ space group, $a = 6.2984(5)$, $b = 31.040(3)$, $c = 9.2279(9)$ Å, β=97.933(2) ° (CCDC: 1500348).

2.2.3. $[Cr(5\text{-}CF_3\text{-}pic)_2(H_2O)_2]NO_3{\cdot}H_2O$ (**3**)

Refluxing of 5-CF_3-pic (0.19 g 1.0 mmol), $Cr(NO_3)_3{\cdot}9H_2O$ (0.20 g, 0.50 mmol) and concentrated nitric acid (15.0 μL, 15.0 M) in distilled water resulted in purple crystal **3**. Anal. Calcd for $C_{14}H_{10}CrF_6N_3O_9$ (%): C, 30.67; H, 2.21; N, 7.66. Found (%): C, 30.60; H, 2.38; N, 7.73. Selected IR data (cm^{-1}, Fig. S3): 3408 (br), 3126 (br), 3092 (br), 3058 (br), 2935 (s), 2454 (br), 1657 (s), 1621 (s), 1586 (m), 1493 (w), 1427 (s), 1407 (s), 1385 (m), 1363 (s), 1328 (s), 1194 (s), 1162 (s), 1134 (s), 1078 (s), 1049 (m), 1031 (s), 892 (m), 694 (s), 513 (m), 428 (w). $P\bar{1}$ space group, $a = 6.244$, $b = 8.406$, $c = 9.575$, 82.21 Å, α=82.21, β=97.933(2), γ=85.76°, (CCDC: 1500279).

2.3. X-ray crystallography

X-ray single-crystal data of complexes **1**–**3** were recorded on a Bruker D8 Venture X-ray diffractometer with graphite monochromated Mo Ka radiation. The structures were solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-2014 [20]. All non-hydrogen atoms were refined anisotropically and the H atoms were located from difference Fourier maps and geometrically calculated positions. The ORTEP diagram and hydrogen bonding interaction network of complexes **1**, **2** and **3** were demonstrated as Figs. 1–3. Crystallographic data of structure refinements, bond lengths, angles and hydrogen bonds for complexes **1**–**3** were listed in Tables 1–3. The IR spectra of these complexes and corresponding ligands were shown in the supporting information (Figs. S1–S6).

2.4. Decomposition kinetics in PBS

To evaluate the decomposition kinetics of new synthetic complexes, hydrolysis rate constants of **1**–**3** and $Cr(pic)_3$ (5.0×10^{-4} M) were evaluated in PBS (pH 7.4). The UV–vis spectra of these complexes during the process were recorded along with the time and all the samples were kept in water bath (37 °C). First-order reaction rate constants of all the complexes were obtained by fitting the absorption of the complexes at 540 nm (**1**–**3**) or 535 nm ($Cr(pic)_3$) vs. time with the first order reaction rate equation. The UV–vis spectra of the complexes and hydrolysis rate constants were given in Fig. 4 and Table 4. Besides, ligand substitution reaction of three complexes (5.0×10^{-4} M) with EDTA (0.05 M) was also measured in PBS, and the results were given in Fig. S7.

2.5. Interaction with apootf

The mixture solutions of apootf (1.0×10^{-5} M, PBS), $NaHCO_3$ (25 mM, PBS) and complexes **1**, **2** or **3** (1×10^{-5} M, PBS) were kept in water bath (37 °C) and the UV difference spectra were recorded along with time. The Cr-apootf complexes were time dependent and the ultraviolet difference spectra of them turned to be constant after standing for 12 h. The second-order reaction rate constants were obtained by fitting the $(A_\infty - A_0)/[a(A_t - A_0)]$ (293 nm) with time by second-order rate equation [21].

2.6. Cyclic voltammetry

The redox properties of $Cr(NO_3)_3$ and complexes **1**–**3** were investigated by cyclic voltammetry (CV). CV of complexes **1**–**3** (1.0 mM) and corresponding ligands (2.0 mM) were carried with a three-electrode cell in DMSO, where $Cr(NO_3)_3$ (1.0 mM) was used as source comparison. In this experiment, glassy carbon electrode, mercurous chloride electrode and platinum net were used as working electrode, reference electrode and counter electrode, respectively. The redox process were recorded in the potential range of −0.8 to −2.3 V with the scan rate of 50 mV/s, and tetrabutylammonium perchlorate (TBAP, 0.10 M) was used as supporting electrolyte.

2.7. Generation of hydroxyl radical

The mixture of 2-deox-D-ribose (4.0×10^{-3} M) and ascorbic acid (1.0×10^{-4} M) were put into water bath (37 °C) for 10 min with the addition of PBS (pH 7.4) buffer, Fe(EDTA) (1×10^{-4} M), complexes **1**–**3** or $Cr(pic)_3$, respectively. Then hydrogen peroxide (1.0×10^{-4} M) was added and the solutions were kept in thermostated bath (37 °C) continuously for 3 h. After the addition of 2-thiobarbituric acid (2.8% w/V, 300 μL) and trichloroacetic acid (1% w/V, 5 mL) to the reaction mixture (2 mL) consecutively, two spectrally equivalent tautomeric structures I and II (Scheme S1) with the maximum absorbance at 532 nm were obtained after 30 min in water bath (90 °C) [22]. In this experiment, PBS and Fe(EDTA) act as blank and control group, and complexes act as experimental groups.