Journal of Molecular Structure 1001 (2011) 111–117

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Comparison of two binuclear vanadium–catecholate complexes: Synthesis, X-ray structure and effects in cancer cells

Zixiang Chi, Linli Zhu, Xiaoming Lu *

Department of Chemistry, Capital Normal University, Beijing 100048, PR China

ARTICLE INFO

Article history:
Received 18 February 2011
Received in revised form 21 June 2011
Accepted 21 June 2011
Available online 29 June 2011

Keywords:
Binuclear
Vanadium
Catecholate
Crystal structure
Anti-cancer effect

ABSTRACT

Two binuclear vanadium–catecholate complexes $[Et_3NH]_2[V^VO_2(\mu\text{-cat})]_2$(**1**) and $[Et_3NH]_2[V^VO_2(\mu\text{-N-2,3-D})]_2$(**2**) (cat = catechol, N-2,3-D = naphthalene-2,3-diol) have been synthesized and characterized by X-ray diffraction, IR, UV–vis spectroscopy and cyclic voltammetry (CV). X-ray analysis reveals that the structures of complexes **1** and **2** are both in the anion form of $\left[V_2^VO_4(L)_2\right]^{2-}$. Et_3N works as counter-ions and connects the main frame by hydrogen bonding. The electrochemical behavior of the two complexes is studied in comparison to that of the free ligands and the two complexes display different redox potentials. Pharmaceutical screenings of complexes **1** and **2** have been made against two representative cancer cell-lines A-549 (lung cancer) and Bel-7402 (liver cancer) by MTT assay. The inhibition of cell proliferation was determined 72 h after cells were exposed to the tested compounds at a concentration of 5 μg/mL. Complex **1** exhibits well inhibition ratio against both two cell-lines (76.28% and 75.94%), while **2** displays positive and negative effect (65.36% and −68.82%) respectively. In association with X-ray and electrochemistry, a preliminary analysis about the possible inhibitory mechanism is provided.

1. Introduction

The various biological and pharmacological activities of vanadium compounds are well known and have driven a considerable amount of research, especially on their insulin-simulating action and anticancer activity [1–4]. Between them, anticancer activity currently focuses even more increasing attentions. Successful studies over the past few decades have advanced the anticancer research on vanadium compounds into the preclinical stage, such as breast cancer, colon cancer, liver cancer and leukemia [5]. However, among various reported vanadium compounds with potential applications on anticancer area, whether vanadium–catecholate systems possess such activities has not been discussed.

Vanadium compounds containing catecholate ligands are of great contemporary research interests [6–8]. Most of these interests stem from the tunicate chemistry, studied decades ago [9–16]. Cooper et al. [17] presented the well study of the redox and complexation chemistry of catechols and vanadium ions, in which crystal structures of three mono-vanadium–catechol models were obtained for the first time, with the stoichiometric ratio of metal to catechol 1:2 and 1:3. Later, several authors [18–26] made further researches and the number of vanadium–catecholate complexes was greatly expanded. As a homologue of catechol, naphthalene-2,3-diol is extremely similar on the coordination environment, except the number of the aromatic rings (Scheme 1). However, there is nearly no previous studies involved with vanadium-N-2,3-D compounds so far.

In this work, we describe the binding of two catecholate-type ligands (cat and N-2,3-D) to different vanadium salts (V^{III} and V^{IV}), and report the synthesis and X-ray determination of two binuclear vanadium complexes $[Et_3NH]_2[V^VO_2(\mu\text{-cat})]_2$(**1**) and $[Et_3NH]_2[V^VO_2(\mu\text{-N-2,3-D})]_2$(**2**). The two complexes are also characterized by IR, UV–vis spectroscopy and CV. In an attempt to explore the anti-cancer effect of this series of compounds, as well as to test if most of vanadium compounds exhibit potential anti-cancer bioactivity, we carried out the MTT assay and the inhibition ratio of these two complexes against two representative cancer cells is preliminarily evaluated.

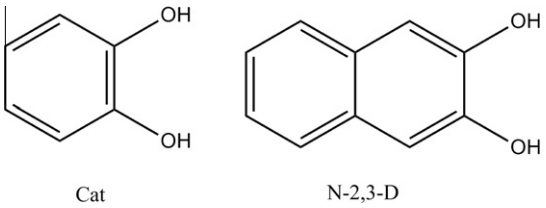
2. Experimental

2.1. Materials and measurements

All reagents and materials used for synthesis were reagent grade and used without further purification. Single-crystal structure determination was performed on Bruker APEX CCD area detector device with Mo Kα radiation (λ = 0.71073 Å) by the Φ–ω scan method. Element alanalyses (C, N, and H) were performed with a Perkin–Elmer 2400 elemental analyzer. FT-IR spectra were

* Corresponding author.
E-mail address: lxm6896@126.com (X. Lu).

0022-2860/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2011.06.026



Scheme 1.

recorded in the range 4000–400 cm^{-1} with an EQUINOX-55 spectrometer using KBr pellets. UV–vis spectra were recorded in 10 mm quartz cell in the scan range 300–900 nm on a Shimadzu UV-2550 instrument. Electrochemical measurements were carried out on a PARC model-273 Potentiostat.

2.2. Synthesis of $[Et_3NH]_2[VO_2(\mu\text{-cat})]_2$(**1**)

A 0.31 g VCl_3 (2 mmol) was added to a mixed solvent of 15 ml CH_3OH and 15 ml CH_3CN. The mixture was stirred continuously till VCl_3 powder was completely dissolved and a lightgreen solution was obtained. Then 0.11 g catechol (1 mmol) was added, and the color of the solution darkened a little to grass green. After stirring for 2 h, 4 ml Et_3N was added to the system. Upon addition of the amine the color became much darker and turned to intense dark green. Stirred for about 12 more hours at room temperature, then the solution was filtered. The dark green filtrate was carefully layered with Et_2O and stood away from light for 2 weeks. Needle-shaped green block crystals suitable for X-ray diffraction were obtained and the yield was about 60%. *Anal. Calc.* C, 49.15; H, 6.87; N, 4.78; V, 17.37. Found: C, 49.21; H, 6.82; N, 4.82; V, 17.31%.

2.3. Synthesis of $[Et_3NH]_2[VO_2(\mu\text{-N-2,3-D})]_2$(**2**)

Addition of 0.6g$VOSO_4$ (3.7 mmol) in the mixed solvent of 15 ml CH_3OH and 15 ml CH_3CN affords a blue solution, to which 0.20 g naphthalene-2,3-diol (1.25 mmol) was added and the blue color deepened a little. After stirring for about 2 h, 8 ml Et_3N was added, and the color of the solution turned to deep brown. Continuously stirring for 12–20 more hours at room temperature, the solution was filtered, and the filtrate was layered with Et_2O and stood away from light for 8 weeks. Green needle crystals suitable for X-ray diffraction were obtained and the yield was about 45%. *Anal. Calc.* C, 55.98; H, 6.46; N, 4.08; V, 14.84. Found: C, 56.03; H, 6.51; N, 4.11; V, 14.78%.

2.4. X-ray crystallography

Intensity data collection was carried out with a Bruker Smart APEXII diffractometer equipped with a CCD detector using Mo Kα monochromated radiation (λ = 0.71073 Å) at room temperature. All data were corrected for absorption using SADABS [51]. The structure was solved by direct method and refined by full-matrix least-squares on F^2 using the SHELXTL-97 and Olex 2 software packages [52,53]. All non-hydrogen atoms in complexes **1** and **2** were refined anisotropically. Positions of hydrogen atoms attached to carbon were fixed at their ideal positions. A summary of the crystallographic data and structure determinations for compounds **1** and **2** is provided in Table S1, and the lengths and angles are presented in Table S2.

CCDC-735788 (for **1**) and 750877 (for **2**) contain the Supplementary Crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.5. MTT assay

The anticancer tests of both the two complexes against two human cancer lines: A-549 (lung cancer) and Bel-7402 (liver cancer) were evaluated by MTT assay. The cells in logarithmic growth were cultured in a RPMI 1640 medium with 10% fetal bovine serum (FBS). The cell suspension of approximate density 5000 cells/ml was redistributed into equivalently in 96-well microplates, 100 μl per well. After preincubation (24 h at 37 °C, 5% CO_2), 10 μl test complex solution (dissolved in DMSO, and then diluted to 5 μg/ml by saline) was added to each well and then each well was finally complemented to 200 μl by RPMI 1640 medium. Incubation of cells with test compound lasted for 72 h at 37 °C, in a humilified atmosphere of 5% CO_2. Abandon the supernatant, and 100 μl MTT (3-(4,5-dimethylthiazoyl-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well. After 4 h incubation at 37 °C, the supernatant was removed again and the formazan precipitates formed was dissolved with 200 μl of DMSO by sonic oscillation. The optical density of each well was measured at 544 nm wavelength using a microplate reader. The inhibition ration (%) was calculated according to the following equation:

$$\text{Inhibition ratio } (\%) = [(OD_c - OD_t)/(OD_c - OD_0)] \times 100\%$$

where OD_c represents the absorbance in the presence of the contrast sample; OD_t represents the absorbance in the presence of the test compound; OD_0 represents the absorbance in the absence of the contrast and test compound (blank solution).

3. Result and discussion

3.1. Synthesis

Parallel experiments show that vanadium source and the counter-ion used are crucial for isolation complexes **1** and **2**. Single crystals of complexes **1** and **2** are obtained by taking V(III) and V(VI) salts as starting materials. Vanadium (V) salts such as $NaVO_3$, NH_4VO_3 and Na_3VO_4 cannot help obtain single crystals but mostly dark brown powders, probably due to the redox reaction mainly happened instead of coordination one. Catechols and its derivatives can reduce V(V) to V(IV) [17,27] and be oxidized by V(V) to semiquinone and quinone, which is difficult to coordinate with vanadium at mild conditions. The type of counter-ions is also an important determining factor. We have tried NaOH, $NH_3{\cdot}H_2O$, Et_3N, ethanediamine, 1, 2-PDA and 1, 3- PDA as the role of counter-ions. Parallel experiments reveal that Et_3N helps yield bi-vanadium complexes as described in this work, whereas 1, 3- PDA gives mono-vanadium ones (will be published later), probably due to the different steric hindrance of aromatic rings and amines. By adopting other bases mentioned above, either a mixture of powders or nothing could be obtained. Scheme 2 sketchily concludes the synthesis procedure of complexes **1** and **2**.

3.2. IR spectra

The IR spectra of the two complexes mainly exhibit three groups of characteristic peaks, separately corresponding to the presence of metal, aromatic ring and amine. Both the two complexes have the nearly same characteristic peaks in the range 930–940 cm^{-1} (935 for **1**, 942 for **2**), which are expected for the presence of V=O bonds, almost in agreement with $[VO(cat)_2]^{2-}$ (V=O 950 cm^{-1}) reported in Cooper's work [17]. For characteristic peaks of ligands, strong peaks shown at around 3000–3100, 1650 and 1480 cm^{-1}, belong to the stretch of ν(=CH) and ν(C=C) of aromatic rings. Peaks near 3410 and 1280–1330 cm^{-1} are attributed to the ν(NH) and ν(C—N), showing the presence of amine in the