

Scientific paper

Synthesis, Characterization and Crystal Structures of Oxidovanadium(V) Complexes with Schiff Base and Pyrone Ligands and Their Antimicrobial Activity

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Abstract

Two oxidovanadium(V) complexes, [VOLL^a] (1) and [VOLL^b] (2), where L is the dianionic form of the Schiff base ligand 2-(((2-hydroxyethyl)imino)methyl)-6-methylphenol (H₂L), L^a and L^b are the deprotonated forms of 3-hydroxy-2-methyl-4H-pyran-4-one (HL^a) and 2-ethyl-3-hydroxy-4H-pyran-4-one (HL^b), respectively, have been prepared and characterized by elemental analyses, IR, UV-Vis, ¹H NMR and single-crystal X-ray crystallographic determination. The V atoms in the complexes are in octahedral coordination, with the Schiff base ligand mer-coordinated to the metal atoms through the phenolate O, imino N and hydroxyl O atoms, and with the pyrone ligands coordinated to the metal atoms through the two O atoms. The effect of the compounds on the antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* was studied.

Keywords: Schiff base; pyrone; vanadium complex; crystal structure; antimicrobial activity

1. Introduction

Schiff bases with typical imine group, C=N, are interesting ligands in coordination chemistry.¹ In recent years, metal complexes of Schiff bases have attracted remarkable attention due to their versatile biological activity, such as antifungal, antibacterial and antitumor.² Schiff base complexes derived from salicylaldehyde and its derivatives with primary amines, bearing the NNO, NNS, NOO or NSO donor sets, have particular biological activities.³ Pyrone compounds are bidentate ligands in various metal complexes.⁴ Most complexes with pyrone ligands have interesting biological properties.⁵ In the present work, two oxidovanadium(V) complexes, [VOLL^a] (1) and [VOLL^b] (2), where L is the dianionic form of the Schiff base ligand 2-(((2-hydroxyethyl)imino)methyl)-6-methylphenol (H₂L), L^a and L^b are the deprotonated form of 3-hydroxy-2-methyl-4H-pyran-4-one (HL^a; maltol) and 2-ethyl-3-hydroxy-4H-pyran-4-one (HL^b; ethyl maltol), respectively, are reported.

2. Experimental

2.1. Material and Methods

3-Methylsalicylaldehyde, 2-aminoethanol, 3-hydroxy-2-methyl-4H-pyran-4-one and 2-ethyl-3-hydroxy-

4H-pyran-4-one were purchased from Fluka. Other reagents and solvents were analytical grade and used without further purification. Elemental (C, H, and N) analyses were made on a Perkin-Elmer Model 240B automatic analyser. Infrared (IR) spectra were recorded on an IR-408 Shimadzu 568 spectrophotometer. UV-Vis spectra were recorded on a Lambda 35 spectrometer. ¹H NMR spectra were recorded on a Bruker 300 MHz instrument. X-ray diffraction was carried out on a Bruker SMART 1000 CCD area diffractometer.

2.2. Synthesis of Complex 1

3-Methylsalicylaldehyde (13.6 mg, 0.1 mmol) was dissolved in methanol (10 mL), to which was added dropwise a methanol solution (10 mL) containing 2-aminoethanol (6.1 mg, 0.1 mmol). The mixture was stirred at ambient temperature for 1 h. Then, 3-hydroxy-2-methyl-4H-pyran-4-one (12.6 mg, 0.1 mmol) and VO(acac)₂ (26.5 mg, 0.1 mmol) dissolved in methanol (10 mL) was added. The mixture was stirred for 1 h at ambient temperature to give a deep brown solution. Brown block-shaped single crystals suitable for X-ray diffraction were formed by slow evaporation of the solution in air for several days. The yield is 32% (based on V). IR data (KBr, cm⁻¹): 1628 (C=O), 1597

(C=N), 958 (V=O). UV–Vis data in methanol [λ_{\max} (nm), ϵ (L · mol⁻¹ · cm⁻¹): 218, 14,352; 280, 7,765; 407, 2,230. Anal. Calcd. (%) for C₁₆H₁₆NO₆V: C, 52.0; H, 4.4; N, 3.8. Found (%): C, 52.2; H, 4.3; N, 3.9. ¹H NMR (300 MHz, *d*⁶-DMSO) δ , ppm: 8.94 (s, 1H, CH=N), 8.20 (d, 1H, ArH), 7.43 (d, 1H, ArH), 7.36 (d, 1H, ArH), 6.80 (t, 1H, ArH), 6.41 (d, 1H, ArH), 4.80 (d, 1H, CH₂), 4.70 (t, 2H, CH₂), 4.40 (t, 1H, CH₂), 2.46 (s, 3H, CH₃), 1.99 (s, 3H, CH₃).

2. 3. Synthesis of Complex 2

Complex 2 was prepared by the same method as described for complex 1, with 3-hydroxy-2-methyl-4H-pyran-4-one replaced by 3-hydroxy-2-ethyl-4H-pyran-4-one (14.0 mg, 0.1 mmol). The yield is 37% (based on V). IR data (KBr, cm⁻¹): 1626 (C=O), 1596 (C=N), 961 (V=O). UV–Vis data in methanol [λ_{\max} (nm), ϵ (L · mol⁻¹ · cm⁻¹): 220, 15,120; 280, 8,210; 409, 2,545. Anal. Calcd. (%) for C₁₇H₁₈NO₆V: C, 53.3; H, 4.7; N, 3.7. Found (%): C, 53.2; H, 4.9; N, 3.5. ¹H NMR (300 MHz, *d*⁶-DMSO) δ , ppm: 8.94 (s, 1H, CH=N), 8.23 (d, 1H, ArH), 7.43 (d, 1H, ArH), 7.36 (d, 1H, ArH), 6.80 (t, 1H, ArH), 6.41 (d, 1H, ArH), 4.80 (d, 1H, CH₂), 4.72 (t, 2H, CH₂), 4.35 (t, 1H, CH₂), 2.85 (m, 2H, CH₂), 1.98 (s, 3H, CH₃), 1.23 (t, 3H, CH₃).

2. 4. X–Ray Structure Determination

Data were collected from selected crystals mounted on glass fibres. The data for the two complexes were processed with SAINT⁶ and corrected for absorption using SADABS.⁷ Multi-scan absorption corrections were applied with ψ -scans.⁸ The structures were solved by direct methods using the program SHELXS-97 and were refined by full-matrix least-squares techniques on F^2 using anisotropic displacement parameters.⁹ The structures were refined by SHELXL-97 program.¹⁰ All hydrogen atoms were placed at the calculated positions. Idealized H atoms were refined with isotropic displacement parameters set to 1.2 (1.5 for methyl groups) times the equivalent isotropic U values of the parent atoms. The crystallographic data for the complexes are listed in Table 1, selected bond lengths and bond angles for compounds 1 and 2 are given in Table 2.

2. 5. Antimicrobial Assay

Qualitative determination of antimicrobial activity was done using the disk diffusion method as described in the literature.¹¹ Suspensions in sterile peptone water from 24-h cultures of microorganisms were adjusted to 0.5 Mc-

Table 1. Crystallographic data and refinement parameters for complexes 1 and 2

Parameters	1	2
Habit, color	Block, brown	Block, brown
Molecular formula	C ₁₆ H ₁₆ NO ₆ V	C ₁₇ H ₁₈ NO ₆ V
Formula weight	369.24	383.26
Temperature, K	298(2)	298(2)
Crystal size, mm	0.31 × 0.27 × 0.26	0.32 × 0.30 × 0.30
Radiation (λ , Å)	MoK α (0.71073)	MoK α (0.71073)
Crystal system	Triclinic	Monoclinic
Space group	<i>P</i> 1	<i>P</i> 2 ₁ / <i>c</i>
Unit cell dimensions:		
<i>a</i> , Å	7.654(2)	7.5888(7)
<i>b</i> , Å	14.692(3)	25.1559(13)
<i>c</i> , Å	14.692(3)	9.5310(9)
α , °	89.640(3)	90
β , °	81.053(3)	107.309(1)
γ , °	81.053(3)	90
<i>V</i> , Å ³	1611.9(6)	1737.1(2)
<i>Z</i>	4	4
ρ_{calcd} , g cm ⁻³	1.521	1.465
<i>F</i> (000)	760	792
Absorption coefficient, mm ⁻¹	0.647	0.604
θ Range for data collection, deg	1.97–25.50	2.76–25.49
Index ranges, <i>h</i> , <i>k</i> , <i>l</i>	–9 ≤ <i>h</i> ≤ 9; –17 ≤ <i>k</i> ≤ 10; –17 ≤ <i>l</i> ≤ 14	–9 ≤ <i>h</i> ≤ 9; –30 ≤ <i>k</i> ≤ 30; –11 ≤ <i>l</i> ≤ 11
Reflections collected	3971	12701
Independent reflections	2606	3139
Data/parameters	2083/437	2625/228
Restraints	0	0
Final <i>R</i> indices (<i>I</i> > 2 σ (<i>I</i>))	<i>R</i> ₁ = 0.0419, <i>wR</i> ₂ = 0.1029	<i>R</i> ₁ = 0.0660, <i>wR</i> ₂ = 0.1321
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0519, <i>wR</i> ₂ = 0.1084	<i>R</i> ₁ = 0.0802, <i>wR</i> ₂ = 0.1371
Goodness-of-fit on <i>F</i> ²	0.967	1.200

Table 2. Selected bond lengths (Å) and bond angles (°) for complexes 1 and 2

1			
V1–O1	1.890(3)	V1–O2	1.829(3)
V1–O3	2.292(3)	V1–O4	1.920(3)
V1–O6	1.606(3)	V1–N1	2.140(4)
V2–O7	1.880(3)	V2–O8	1.835(3)
V2–O9	2.279(3)	V2–O10	1.917(3)
V2–O12	1.597(3)	V2–N2	2.130(4)
O6–V1–O2	98.52(17)	O6–V1–O1	96.53(16)
O2–V1–O1	157.72(14)	O6–V1–O4	94.97(15)
O2–V1–O4	95.55(14)	O1–V1–O4	99.41(14)
O6–V1–N1	108.63(16)	O2–V1–N1	77.73(13)
O1–V1–N1	81.96(13)	O4–V1–N1	156.10(13)
O6–V1–O3	171.28(16)	O2–V1–O3	85.00(14)
O1–V1–O3	82.51(14)	O4–V1–O3	76.69(11)
N1–V1–O3	79.87(12)	O12–V2–O8	99.40(17)
O12–V2–O7	95.71(16)	O8–V2–O7	157.75(15)
O12–V2–O10	95.74(16)	O8–V2–O10	95.36(15)
O7–V2–O10	99.30(13)	O12–V2–N2	106.87(17)
O8–V2–N2	77.60(15)	O7–V2–N2	82.44(13)
O10–V2–N2	157.08(15)	O12–V2–O9	171.99(15)
O8–V2–O9	84.90(15)	O7–V2–O9	82.19(14)
O10–V2–O9	77.05(11)	N2–V2–O9	80.58(13)
2			
V1–O1	1.867(3)	V1–O2	1.838(3)
V1–O3	1.909(3)	V1–O4	2.303(3)
V1–O6	1.591(3)	V1–N1	2.120(4)
O6–V1–O2	97.60(17)	O6–V1–O1	97.82(16)
O2–V1–O1	157.86(14)	O6–V1–O3	95.40(15)
O2–V1–O3	98.51(14)	O1–V1–O3	95.75(14)
O6–V1–N1	107.45(16)	O2–V1–N1	77.86(14)
O1–V1–N1	82.42(14)	O3–V1–N1	157.13(13)
O6–V1–O4	172.29(14)	O2–V1–O4	83.49(14)
O1–V1–O4	83.36(14)	O3–V1–O4	76.89(11)
N1–V1–O4	80.26(12)		

Farland. Muller–Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10 µL of the substance to be tested (at a concentration of 2048 µg/mL in DMSO) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37 °C for 18–24 h. Reading of the results was done by measuring the diameters of the inhibition zones generated by the test substance. Tetracycline was used as a reference substance. Determination of MIC was done using the serial dilutions in liquid broth method. The materials used were 96–well plates, suspensions of microorganism (0.5 McFarland), Muller–Hinton broth (Merck) and stock solutions of each substance to be tested (2048 µg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96–well plates: 1024, 512, 256, 128, 64, 32, 16, 8, 4 and 2 µg/mL. After incubation at 37 °C for 18–24 h, the MIC for each tested substance was determined by microscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited.

3. Results and Discussion

3.1. Chemistry

The Schiff base compound H₂L was prepared by the condensation of equimolar quantities of 3-methylsalicylaldehyde with 2-aminoethanol in methanol. Complexes 1 and 2 were readily synthesized by reaction of the Schiff base compound H₂L with VO(acac)₂ in methanol in the presence of 3-hydroxy-2-methyl-4*H*-pyran-4-one and 2-ethyl-3-hydroxy-4*H*-pyran-4-one, respectively (Scheme 1). All the compounds are very stable at room temperature in the solid state, and soluble in common organic solvents, such as methanol, ethanol, and acetonitrile. The results of

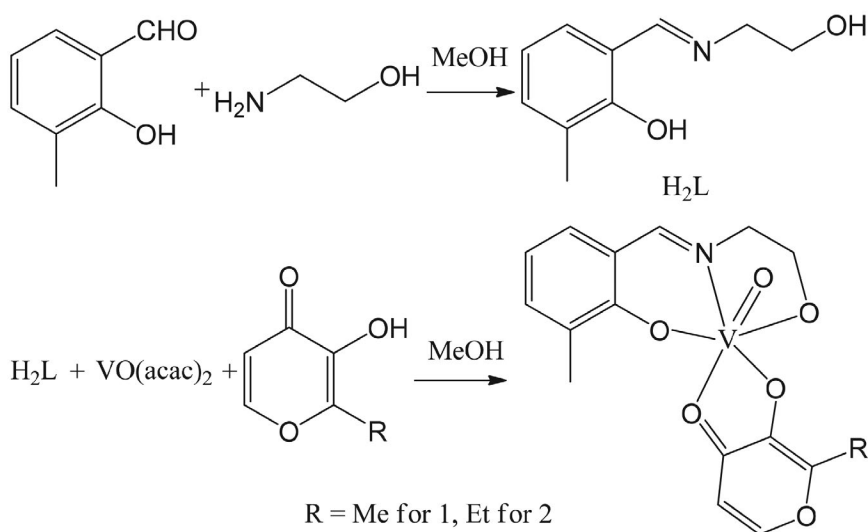
**Scheme 1.** The synthetic procedure of the complexes.

Table 3. MIC values ($\mu\text{g/mL}$) for the antimicrobial activities of the tested compounds

Compounds	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Candida albicans</i>
H ₂ L	128	64	> 512
1	4.0	1.0	32
2	4.0	1.0	32
Tetracycline	0.32	2.12	> 1024

hances the penetration of the complexes into lipid membrane and blocks the metal binding sites on enzymes of microorganisms.

From the results, it is obvious that the two complexes have higher antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* when compared to the free Schiff base. This phenomenon is in accordance with those reported in literature.¹⁵ The two complexes have in general the same activities against all the bacteria and fungi strains. The complexes have strong activity against *Escherichia coli*, with MIC value of 1.0 $\mu\text{g/mL}$, which is superior to Tetracycline. The complexes have strong activity against *Staphylococcus aureus*, yet, they are weaker than Tetracycline. It is interesting that both complexes have medium activity against *Candida albicans*, which is rarely seen in metal complexes.

4. Material

CCDC 1880706 for 1, and 1880707 for 2 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/const/retrieving.html> or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or email: deposit@ccdc.cam.ac.uk.

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Povzetek

Sintetizirali smo dve kompleksni spojini oksidovanadija(V), [VOLL^a] (1) in [VOLL^b] (2), kjer je L dianionska oblika liganda Schiffove baze 2-(((2-hidroksietil imino) metil)-6-metilfenola (H₂L), L^a in L^b sta deprotonirani obliki 3-hidroksi-2-metil-4H-piran-4-ona (HL^a) in 2-etil-3-hidroksi-4H-piran-4-ona (HL^b). Spojini smo karakterizirali z naslednjimi metodami: infrardečo spektroskopijo (IR), UV-Vis spektroskopijo, NMR spektroskopijo in rentgensko strukturno analizo monokristalov. Atomi vanadija v spojinah so okatedrično koordinirani z atomi kisika in dušika, ki pripadajo obema ligandoma. Preučevali smo tudi protimikrobno učinkovitost spojin napram *Staphylococcus aureus*, *Escherichia coli* in *Candida albicans*.