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OXOVANADIUM COMPLEXES CONTAINING OXYGEN AND NITROGEN DONORS: SYNTHESIS, INFRARED CHARACTERIZATION AND VIRTUAL SCREENING AGAINST HUMAN SPINDLIN 1 CANCER CELL

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ABSTRACT: Oxovanadium (IV) complexes containing oxygen and nitrogen donors were prepared. V_2O_5 was reduced to VO^{2+} in ethanolic sulphuric acid. The melting point and solubility of the complexes were determined. Infrared spectroscopy was used for the characterization of the complexes. Molecular docking studies of the chelated metal complexes were performed with Human SPINDLIN 1 Cancer Cell using Patchdock molecular docking algorithm server. Binding free energy function based on the atomic contact energy was estimated. The best scoring function gave atomic contant energy of -193.90, -135.90 and -225.60 Kcal/mole for oxovanadiumacetylacetonate/bis(1-pyrazolyl)borate, oxovanadium hexafluoroacetylacetonate /tris(1-pyrazolyl)borate and oxovanadiumacetylacetonate/tris(1-pyrazolyl)borate chelate complexes respectively. Negative values of the binding energy indicated that the use of the synthesized metal complexes for Human SPINDLIN 1 inhibition would be feasible. Molecular docking of oxovanadiumbis (trifluoroacetylacetonate), with Human SPINDLIN 1 gave a binding energy with positive value. Inhibition of oxovanadiumbis (trifluoroacetylacetonate) with the receptor would not be feasible. Thus on the basis of the infrared spectra, square pyramidal structures have been proposed for oxovanadiumbis (trifluoroacetylacetonate) and oxovanadiumacetylacetonate/bis(1-pyrazolyl)borate chelate complexes, while octahedral structures were proposed for oxovanadiumhexafluoroacetylacetonate/tris(1-pyrazolyl) borate and oxovanadiumacetylacetonate/tris(1-pyrazolyl)borate metal chelates.

Keywords: Oxovanadium, poly (1-pyrazolyl) borate, complexes, Infra-red spectroscopy, molecular docking

INTRODUCTION

Vanadium is the only element in the periodic table that is named after a goddess (the Nordic goddess Vanadis), and perhaps with this legacy brings to the table a sense of some unpredictable and surprising chemistry[1]. Oxo-bis(acetyl acetonato) vanadium (IV) has probably been studied more extensively than any other VO^{2+} complex and has a heat of combustion of -1276 Kcal/mole[2]. Probably the most characteristics infrared feature of the oxovanadium (IV) complexes is the strong, sharp ν(V=O) band at 985±50cm^{-1} . Previously the low V=O stretching region (985±50cm^{-1}) have been considered to be indicative of oxygen bridging, V-O-V in polymeric chain formation[2]. However x-ray studies by Pasquali[3] demonstrated that solid state interaction can cause this shift. A number of spectroscopic on oxovanadium (IV) complexes have shown that since the crystal field is dominated by strong V=O interaction, interpretation of the spectra has not been easy. The mull infrared data revealed that V=O stretching frequency of ν(5-Cl-hbp)$_2$en and VO(4-CH_3-5-Cl-hbp)$_2$en appear at 881 and 879 cm^{-1} respectively. The most obvious difference between the normal and low frequency

complexes is the presence of electron donating methy group in the ligand of the latter. Similarly V=O stretching frequency have been observed in the vanadyl complexes of salicylideamine, monothio-β-ketone and dithiophosphoric acid with electron donating groups. The V=O stretching frequencies increased with an ability of the Hammeth δ (electron withdrawing ability) of the substituents[4,5] . Compendium of contributions dedicated to vanadium chemistry edited by Chasteen[6], showed the number of publications in the area of vanadium chemistry increased dramatically from the early to the late 1980s. The discoveries of several medicinal properties of vanadium complexes as insulin-mimetic, anticancer, antitumour and antifungal antibacterial activities [7, 8] have stimulated further research in this area. In most cases the active site contains either of these two motifs coordinated by oxygen–nitrogen atoms. The strong affinity of these two motifs towards O, N-donor ligand is probably due to their hard acidic nature and selective stabilization of these two motifs depends upon the basicity of donor atoms. These ligands have a tendency to stabilize the vanadium in its highest oxidation state[9,10,11]. The coordination chemistry of vanadium has great interest since the discovery of vanadium in organisms such as certain ascidians and Amanita mushrooms and as a constituent of the cofactors in vanadate-dependent haloperoxidases and vanadium nitrogenases[12, 13]. Since then, extensive studies have been carried out to explore vanadium chemistry, including the synthesis of novel complexes and their antidiabetic activities both *in vitro* and *in vivo*[14, 15,16]. Many clinical trials of vanadium compounds have also been reported [17,18,19,] in which vanadium salts such as $VOSO_4$ and $NaVO_3$ were administered to diabetic patients. Some oxovanadium(IV) complexes of salicylic acid /sulphosalicylic acid and 5, 10, 15, and 20-meso-tetraphenylporphyrin with unidentate and bidentate nitrogen donors have been synthesized and characterized and were found to possess antibacterial, antifungal anf anticancer properties [20].

SPINDLIN1, a new member of the *SPIN*/*SSTY* gene family, was first identified as a gene highly expressed in ovarian cancer cells. It is involved in the process of spindle organization and chromosomal stability and plays a role in the development of cancer[21]. Nevertheless, the mechanisms underlying its oncogenic role are still largely unknown. Ectopic expression of SPINDLIN1 promotes cancer cell proliferation[21]. The Ser84 and Ser99 amino acids within SPINDLIN1 are the key functional sites in cancer cell proliferation. Mutation of these two sites of SPINDLIN1 would inhibit cancer cell proliferation [21]. SPINDLIN1 is highly expressed in many kinds of malignant tumour tissues, including ovarian tumours, non–small cell lung cancers, and some hepatic carcinomas [22].

EXPERIMENTAL

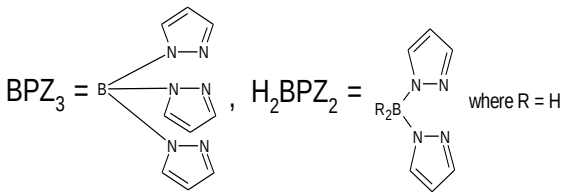
Except for the poly(1-pyrazolyl) borates that were obtained from Colombia Organic Chemicals Co. Inc. Manufacturing and Research Chemists Columbia S.C., all other chemicals used were obtained from the British Drug House (BDH) Chemicals Co.Ltd. Poole England. All the chemicals were used without further purification. The melting points of all the complexes were determined using electrothermal melting point apparatus. The infrared spectra for the complexes were recorded in KBr disc using Pyeunicam Sp 2000 infrared spectrophotometer at the department of chemistry, University of Ilorin, Nigeria.

Synthesis of mixed ligand chelates

5.0 g of V_2O_5 was added to a solution containing 12 cm^3 of distilled water, 9 cm^3 of conc. H_2SO_4 and 25 cm^3 of ethanol. The mixture was then heated on a hot plate in a fume hood. As the reaction proceeded, the colour changed from green to dark blue in which the reduction of V_2O_5 to VO^{2+} was completed (about 30 minutes). The solution was then filtered hot. Equal moles of corresponding chelating agents (TFAC/TFAC, ACAC/H_2BPZ_2, HFAC/$HBPZ_3$, ACAC/$HBPZ_3$) were added to the filtrate. A solution of 20 g Na_2CO_3 in 125 cm^3 of distilled water was finally added. The precipitate

was then filtered using Buckner flask, washed several times with distilled water and dried by drawing air through the filter cake. The product was finally recryatallized in chloroform and kept in a dessicator over $CaCl_2$.

Note :ACAC=Acetylacetonate ion, TFAC = trifluoroacetylacetonate ion, HFAC =hexafluoroacetylacetonate ion,



Molecular docking studies

Structural drawings of the chelated metal complexes were performed with ACD Lab Chem Sketch software. They were saved as PDB file using Argus lab software [23]. PDB file of Human Spindling (Figure 1) was downloaded from protein data bank (2NS2). Molecular docking was performed using Patchdock Molecular Docking Algorithm server [24,25]. The structures were opened using Swiss-PDB viewer 4.1.0 [26, 27].

RESULTS AND DISCUSSION

All the complexes were powdry, coloured and stable. The colours of the $[VO(TFAC)_2]$, $[VO(ACAC/H_2BPZ_2)]$, $[VO(HFAC/HBPZ_3)]$, $[VO(ACAC/HBPZ_3)]$ complexes are lizlit green, greenish yellow, grey and grey respectively. The colours and the melting points of the complexes are shown in Table 1. The complexes were insoluble in water but partially soluble in common organic solvents like acetone, chloroform, methanol, acetonitrile, benzene and toluene.

Table 1: Colour and melting points of the complexes

Complex	Colour	Melting point ^oC
$[VO(TFAC)_2]$	Lizlit green	300
$[VO(ACAC/H_2BPZ_2)]$	Greenish yellow	269 – 272
$[VO(HFAC/HBPZ_3)]$	Grey	169
$[VO(ACAC/HBPZ_3)]$	Grey	300

The infrared spectra of all the complexes were very similar thus implying that the complexes have similar structures. The frequencies of the observed bands are reported in Table 2.

Table 2: Infrared frequencies (cm^{-1}) of the major observed bands

$[VO(TFAC)_2]$	$[VO(ACAC/H_2BPZ_2)]$	$[VO(HFAC/HBPZ_3)]$	$[VO(ACAC/HBPZ_3)]$
3400 vw,br	3160, m	3450, w	2710, w
2700 w,s	3130, m	2720, w	2485, m
2450 w,s	2720, m	2480, m	1845, vw
2250 w	2680, m	1845, vw	1780, vw
1900 br	2430, m	1785, vw	1640, vw
1640 br	1800, w	1680, vw	1465, s
1530, s	1650, m	1645, s	1450, s
1285, s	1540, m	1500, m	1275, m
1220, m	1275, m	1405, m	1212, s
1190, s	1180, s	1310, s	1185, vw
1130, s	1160, s	1250, m	1140, m
1005, m	1130, s	1146, s	1115, m
920, s	1070, s	1201, s	1105, m
855, m	1050, s	1101, s	1092, m
790, s	1000, w	1105, s	1070, w
590,s	960, s	1070, w	1050, s
620, m	742, m	-	1015, w
590, m	760, m	-	1025, w
525, m	640, m	-	980, m
505, w	500, m	543	560, s
-	430, w	465, w	470, w

For structural elucidation purposes, the most important frequencies are those due to V=O, V-N and V-O stretching vibrations and discussions have been limited to those bands. Assignments have been made by comparison of the observed frequencies with those of known complexes in literature[12]. All the complexes showed a strong band at 1005, 1000, 1070 and 980 cm^{-1}. These band has been attributed to υ(V=O) stretching vibration. The frequencies 3400, 3160, 3450 cm^{-1} in $[VO(TFAC)_2]$, $[VO(ACAC/H_2BPZ_2)]$ and

[VO(HFAC/HBPZ$_3$)] complexes indicated the presence of water of crystallization. It was conspicously absent in the spectrum of [VO(ACAC/HBPZ$_3$)] complex which indicated the absence of water of hydration. A weak to medium band between 2400 –2600 cm^{-1} assignable to υ(B-H) mode was observed in [VO(TFAC)$_2$], [VO(ACAC/H$_2$BPZ$_2$)] and [VO(HFAC/HBPZ$_3$)] complexes. The mixed ligand complexes showed a weak band in the region 1680 – 1640 cm^{-1}. This band has been attributed to the ν(C=N) stretching vibration of the pyrazolylmoeity. The bands appearing in the 500–560 cm^{-1} range correspond to υ(V-O) and bands about 430 - 470 cm^{-1} correspond to υ(V-N), respectively.

The crystal structure of Human SPINDLIN 1is presented in Figure 1 while the molecular docking of the metal chelates with Human SPINDLIN 1are presented in Figures 2 – 5. Binding free energy function based on the atomic contact energy was estimated as shown in equation 1 [13] . $\Delta Gcal = \Delta Ec + \Delta Eel - T\Delta Strv$ (*Equation* 1) where Δ*E*c is the change in atomic contact energy. Δ*E*el is the direct electrostatic interaction between protease and its inhibitor. The term Δ*S*trv denotes the entropy change associated with the six degrees of freedom of rotation/translation and vibration [13]. The best scoring function gave atomic contant energy of -193.90, -135.90 and -225.60 Kcal/mole for [VO(ACAC/H$_2$BPZ$_2$)], [VO(HFAC/HBPZ$_3$)] and [VO(ACAC/HBPZ$_3$)] chelate complexes respectively. Negative values of the binding energy indicated that the synthesized metal complexes would inhibit Human SPINDLIN 1proliferation. Molecular docking of [VO(TFAC)$_2$] with Human SPINDLIN 1 gave a binding energy with positive value. Inhibition of [VO(TFAC)$_2$] with the receptor would not be feasible.

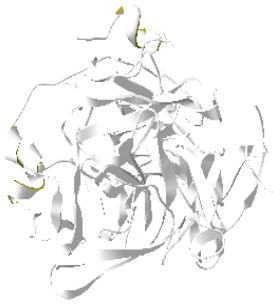


Figure 1: X-ray crystallography of Human SPINDLIN 1

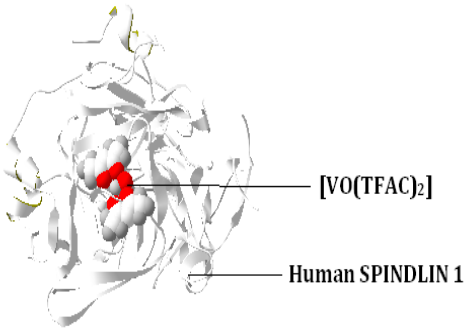


Figure 2 : Molecular docking of [VO(TFAC)$_2$] with Human SPINDLIN 1
Atomic Contact Energy = 3.54 Kcal/mole

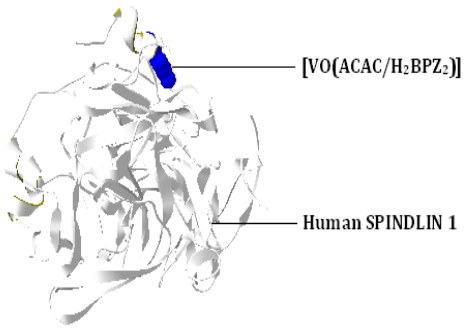


Figure 3: Molecular docking of [VO(ACAC/H$_2$BPZ$_2$)] with Human SPINDLIN 1
Atomic Contact Energy = -193.90 Kcal/mole

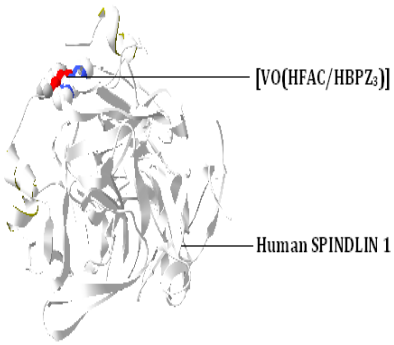


Figure 4: Molecular docking of [VO(HFAC/HBPZ$_3$)] with Human SPINDLIN 1
Atomic Contact Energy = -135.90 Kcal/mole

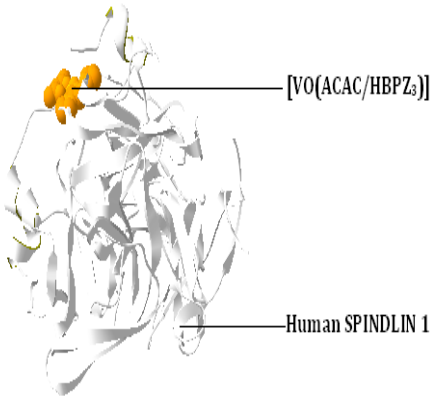


Figure 5: Molecular docking of [VO(ACAC/HBPZ$_3$)] with Human SPINDLIN 1
Atomic Contact Energy = -225.61 Kcal/mole

Thus on the basis of the infrared spectra, square pyramidal structures have been proposed for [VO(TFAC)$_2$], [VO(ACAC/H_2BPZ$_2$)] chelate complexes, while octahedral structures were proposed for [VO(HFAC/HBPZ$_3$)] and [VO(ACAC/HBPZ$_3$)] metal chelates. The proposed structures for the complexes are presented in Figures 6 – 9 respectively.

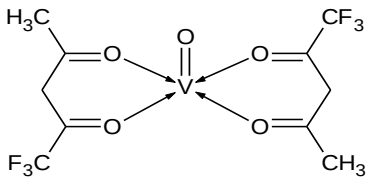


Figure 6: Suggested structure for Oxovanadium Bis(trifluoroacetylacetonate) chelate complex.

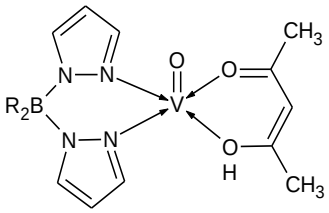


Figure 7: Suggested structure for Oxovanadium acetylacetonate/ Bis (1-pyrazolyl)borate chelate complex.

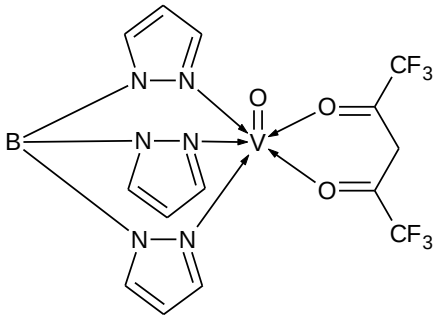


Figure 8: Suggested structure for Oxovanadium hexafluoroacetylacetonate/ tris(1-pyrazolyl) borate chelate complex

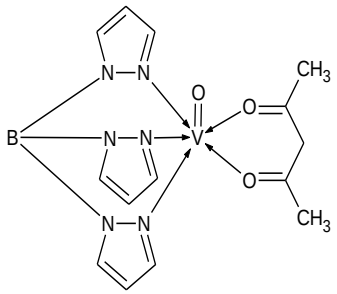


Figure 9: Suggested structure for Oxovanadium acetylacetonate/ tris(1-pyrazolyl) borate chelate complex

CONCLUSION

This reseach work showed that poly(1-pyrozolyl) borate ligands formed air stable and coloured complexes with VO^{2+} species. Most of them are water insoluble but partially soluble in common organic solvents like acetone, methanol, benzene, toluene and chloroform. All the complexes showed infrared absorption characteristics of (V=O) stretching frequencies . Negative values of the binding energy indicated that the use of the synthesized metal complexes for Human SPINDLIN 1 inhibition would be feasible. On the basis of infrared, square pyramidal and octahedral structures were proposed for the chelated metal complexes.

REFERENCES

1. 1. Paresh KM, *Dissertation Submitted in partial fulfillment for the degree of Master of Science in Chemistry*Under The Academic Autonomy National Institute of Technology, Rourkele , 1
2. Jones MM, Journal of American Chemical Society, 1954, **76**: 5995.
3. Pasquil M, Journal of Chemical Society, Dalton Transaction, 1977, **139**: 222.
4. Ginsberg AP, Inorganic Chemistry, 1966, 5: 1656.
5. Pasquil M, Journal of Chemical Society, Dalton Transaction, 1979, **145**: 401.
6. Chasteen ND. *Vanadium in Biological Systems: Physiology and Biochemistry*, Kluwer Academic, Boston, 1990, 2
7. Crans DC, Yang L, Alfano JA, Chi LH, Jin W, Mahroof- Tahir M, Robins K, Toloue MM, Chan LK, Plante AJ, Grayson RZ, Willsky GR, *Coord. Chem. Rev*., 2003, **13**: 237.
8. Butler A and Walker JV, *Chem. Rev*., 1993, **93:** 1937.
9. Pohlmann A, Nica S, Luong TKK and Plass W, *Inorg. Chem. Commun*. , 2005, **8**: 289.
10. Maurya MR, Khurana S, Schulzke C and Rehder D, *Eur. J. Inorg. Chem*., 2001,779.
11. Dinda R, Sengupta P, Ghosh S, Mak TCW, *Inorg. Chem*., 2002, **41:** 1684.
12. RehderD, Inorganic Chemistry Communications, 2003, **6**(5): 604–617.
13. Willkinson G, Ed., Comprehensive Coordination Chemistry, Pergamon Press, Oxford, UK, 1987, 6
14. Tas S, Sarandol E, Ayvalik SZ, Serdar Z, and Dirican M, Archives of Medical Research,2007, **38**(3): 276–283.
15. Shukla R and Bhonde RR, BioMetals, 2008, **21**(2): 205 – 210.
16. 16. Smee JJ, Epps JA, Ooms K Journal of Inorganic Biochemistry, 2009, 103(4) :575–584,
17. Chohan ZH and Sherazi SKA, Metal-Based Drugs, 1997, **4**(6): 327 – 332
18. Halberstam H, Cohen N, Shlimovich P, Rossetti L, and Shamoon H, Diabetes,1996, **45** (5): 659 – 666.
19. Cusi K, Cukier S, DeFronzo RA, Torres M, Puchulu FM, and Redondo JCP, Journal of Clinical Endocrinology and Metabolism, 2001, **86** (3): 1410 – 1417.
20. Gauri DB, Puja S, Ashu K, Madhulika B, Sujata K, and Deepmala G, Journal of Inorganic Chemistry, 2013. **2013**: 1-11
21. Jing-Xue Wang, QuanZeng, Lin Chen, Ji-Chao Du, Xin-Long Yan, Hong-Feng Yuan, Chao Zhai, Jun-Nian Zhou, Ya-Li Jia, Wen

Yue, and Xue-Tao Pei. *Mol Cancer Res, 2012, **10**(3): 326 – 335.*

22. Yue W, Sun LY, Li CH, Zhang LX, Pei XT. Chinese J Cancer, 2004*, **23**:141– 145.*

23. Mark AT, ArgusLab 4.0 Planaria Software LLC, Seattle, WA. http://www.arguslab.com

24. Duhovny D, Nussinov R and Wolfson HJ. Proceedings of the 2'nd Workshop on Algorithms in Bioinformatics(WABI) Rome, Italy, Lecture Notes in Computer Science Springer Verlag, 2002, 2

25. Schneidman-Duhovny D, Inbar Y, Nussinov R and Wolfson HJ. *Nucl. Acids.Res.*, 2005, **33**: 363-367.

26. http://spdbv.vital-it.ch/

27. http://www.expasy.org/spdbv/