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Inorganica Chimica Acta 229 (1995) 253–260

Inorganica Chimica Acta

Bisperoxovanadium compounds: synthesis and reactivity of some insulin mimetic complexes ☆

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Received 28 June 1994; revised 28 September 1994

Abstract

A series of bisperoxovanadium complexes (bpV) of the general formula $K_3[VO(O_2)_2(L\text{–}L')]$ has been prepared and characterized, where L–L′ is a pyridinedicarboxylate (2,3-pdc, 2,4-pdc, 2,5-pdc) or 3-acetatoxypicolinate (3-acetpic). Two structures have been determined: bpV(2,4-pdc), $P2_1$, $a=7.1018(12)$ Å, $b=38.187(5)$ Å, $c=11.4088(8)$ Å, $\beta=90.546(9)°$, $V=3093.8(7)$ Å^3, $Z=8$, $R/R_w=0.049/0.055$, and bpV(3-acetpic), $P\bar{1}$, $a=7.4037(13)$ Å, $b=10.709(3)$ Å, $c=10.9569(19)$ Å, $\alpha=110.742(16)°$, $\beta=95.600(19)°$, $\gamma=100.195(19)°$, $V=787.4(3)$ Å^3, $Z=2$, $R/R_w=0.036/0.026$. The oxygen atom of the 2-carboxylate group and the oxo ligand are situated in apical positions of a pseudotrigonal plane formed by the nitrogen atom and the centres of the two peroxo groups. The compounds rapidly oxidize sodium tris(3-sulfonatophenyl)phosphine, in water, to the corresponding oxide. The results are discussed with reference to the reported insulin mimetic activity of this class of compounds.

Keywords: Crystal structures; Vanadium complexes; Peroxo complexes; Insulin mimetic complexes

1. Introduction

Diabetes mellitus is a serious metabolic disease that is characterized by elevated blood glucose levels [1]. It is estimated that up to 5% of the population of industrialized countries may suffer from diabetes mellitus. In recent years there has been a great interest in the insulin mimetic effects of complexes of vanadium(IV) [2–5] and vanadium(V) [6–13]. The mechanism by which vanadium exerts its insulin mimetic effect is poorly understood; however, the ability of orally administered vanadate to reduce blood glucose levels in rats has created much interest [14]. The design of ligand systems facilitating the uptake of vanadium(IV) for use in oral administration is also an area of intense current activity [2,3]. Vanadium complexes may become alternative treatments for diabetes mellitus and are useful probes into the pathology of this disease.

Peroxovanadium (pV) complex anions of the type $[VO(O_2)_xL\text{–}L']^{n-}$, where $x=1$ or 2 and L–L′ is a bidentate ligand such as picolinic acid anion, form a new class of powerful insulin mimics [15]. They activate the insulin receptor kinase (IRK) of cultured hepatoma cells, stimulate lipogenesis in adipocytes, and inhibit the in situ dephosphorylation of autophosphorylated IRs and epidermal growth factor receptors (EGFR) of rat liver endosomes. The phosphotyrosine phosphatase (PTP) inhibitory and IRK activating potencies of these compounds are linearly correlated, decay in parallel in solution and vary considerably with the ancillary ligands. Moreover, compounds with different ancillary ligands often display relative specificity as PTP inactivators by inhibiting IR dephosphorylation to a significantly different degree than EGFR dephosphorylation. This inhibition results in an enhanced insulin effect, since the activity of the IRK is maintained for a greater period of time without being inactivated by its associated PTP [15]. The mechanism of the inactivation of PTP by pV compounds has not yet been determined.

In this paper we present the synthesis and characterization of a series of bisperoxovanadium compounds differing only in the structure of their pyridine dicarboxylato ligands. In this way differences in activity of

☆ This paper is dedicated to Professor F.A. Cotton on the occasion of his 65th birthday.

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SSDI 0020-1693(94)04252-Q

the complexes can be attributed to the substitution pattern of the ligand. Two representative complexes were characterized by single crystal X-ray diffraction and their structures are reported. These compounds oxidize sodium tris(3-sulfonatophenyl)phosphine, which is of interest as a possible model of their ability to inhibit PTP.

2. Experimental

2.1. General

Infrared spectra were measured on an Analect Instruments AQS-18 FT–IR spectrometer with the samples as KBr pellets. Typical abbreviations for the infrared bands are: vs, very strong; s, strong; m, medium; w, weak. ^{51}V NMR spectra of solutions of the complexes in D_2O (98% D purity, MSD Isotopes) were obtained at ambient temperature on a Varian XL-300 NMR spectrometer operating at 78.891 MHz. Vanadium-51 chemical shifts were measured in parts per million (± 1 ppm) using $VOCl_3$ as an external standard at 0.00 ppm; upfield shifts are considered negative. ^{31}P NMR spectra were obtained in a D_2O/H_2O mixture at ambient temperature on a Varian XL-300 NMR spectrometer operating at 121.4 MHz. Phosphorus-31 chemical shifts were referenced externally to H_3PO_4 (85%) at 0.00 ppm. ^1H NMR spectra of samples in D_2O or in DMSO-d_6 (99.9% D, Isotec Inc.) were obtained with a Varian Gemini 200 MHz NMR spectrometer using HOD at 4.63 ppm or residual protons in DMSO-d_6 at 2.49 ppm as references, respectively. Abbreviations for nmr spectra are: s, singlet; m, multiplet; d, doublet; br, broad. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario, Canada.

2.2. Chemicals

The compounds V_2O_5 (99.99%), pyridine-2-carboxylic acid (picolinic acid), 3-hydroxypyridine-2-carboxylic acid (3-hydroxypicolinic acid), ethyl bromoacetate (98%), 2,5-pyridinedicarboxylic acid (98%), 2,4-pyridinedicarboxylic acid monohydrate (98%) and 2,3-pyridinedicarboxylic acid (99%) were supplied by Aldrich and used as received. The compound tris(3-sulfonatophenyl)phosphine tetrahydrate sodium salt (10–15% oxide) was supplied by Strem and used as received. Solutions of H_2O_2 (30% by volume) were purchased from ACP Chemicals. Distilled water was used in all preparations.

2.3. Phosphine oxidation

Solutions (0.16 M) of the peroxovanadium compounds bpV(2,3-pdc), bpV(2,4-pdc), bpV(2,5-pdc) and bpV(3-acetpic) were prepared in deoxygenated H_2O. Aliquots (0.35 ml) of each of these solutions were placed into NMR tubes and to each of these tubes was added 0.35 ml of a solution of sodium tris(3-sulfonatophenyl)phosphine tetrahydrate (0.16 M) in deoxygenated D_2O. After a reaction time of approximately 5 minutes a ^{31}P NMR spectrum was obtained for each of the samples. A control sample containing 0.35 ml of the phosphine solution and 0.35 ml of D_2O was also prepared and its ^{31}P NMR spectrum observed both before and after all other spectra had been obtained to ensure that no aerial oxidation had occurred.

2.4. $K_3[VO(O_2)_2(2,3\text{-pyridinedicarboxylato})]\cdot 2H_2O$, bpV(2,3-pdc)

The compound V_2O_5 (0.9 g, 5 mmol) was added to a solution of KOH (0.9 g, 16 mmol) in water (15 ml). The mixture was stirred with gentle heating until a clear, nearly colourless solution was obtained. To the cooled solution was added approximately 1 ml H_2O_2 (30%), which resulted in a change of colour to yellow and a small amount of precipitate. After stirring for 5 min, the solution was filtered through a medium-porosity glass frit and the precipitate left on the frit was dissolved in H_2O_2 (approx. 9 ml, 30%). The combined filtrates were then slowly added to a solution of 2,3-pyridinedicarboxylic acid (2.0 g, 12 mmol) and KOH (1.0 g, 18 mmol) in water (15 ml). After stirring for approximately 2 h the solution was adjusted to pH 8 by addition of 6 M HCl. Ethanol was then added until a persistent precipitate was observed and the solution was maintained at 5 °C for 20 h. The solution was filtered and the white, water-insoluble precipitate left on the frit was discarded. The filtrate was kept at 5 °C for an additional 18 h, and a fluffy yellow precipitate was collected by vacuum filtration and dried in vacuo (1.1 g, 2.4 mmol). Two additional crops of yellow precipitate were collected from the filtrate upon further addition of ethanol and standing at 5 °C. The total yield was 3.05 g (67%). IR (KBr): ν(CO) 1635 (s), 1397 (s); ν(VO) 940 (m); ν(OO) 867 (s), 838 (m) cm^{-1}. ^{51}V NMR (D_2O): δ −742. ^1H NMR (D_2O): δ 9.1 (br, 1H), 7.9 (br, 1H), 7.7 (br, 1H). *Anal.* Calc. for $C_7H_7NO_{11}K_3V$: C, 18.71; H, 1.57; N, 3.12. Found: C, 18.69; H, 1.55; N, 3.12%.

2.5. $K_3[VO(O_2)_2(2,4\text{-pyridinedicarboxylato})]\cdot 3.25H_2O$, bpV(2,4-pdc)

The compound V_2O_5 (2.3 g, 13 mmol) was added to a solution of KOH (2.8 g, 50 mmol) in water (20 ml). The mixture was stirred and heated gently until a clear, nearly colourless solution was obtained (approx. 15 min). To the cooled solution (cold water bath, 8 °C) was added 4 ml of H_2O_2 (30%), resulting in the

formation of a yellow slurry. The mixture was stirred for approximately 5 min and filtered through a medium-porosity glass frit. The precipitate left on the frit was dissolved in H_2O_2 (approx. 25 ml). The combined filtrates were stirred for 5 min and the formation of additional precipitate was noted. More KOH (0.2 g, 3.6 mmol) was added to the reaction mixture prior to its slow addition to a solution of 2,4-pyridinedicarboxylic acid monohydrate (5.0 g, 27 mmol) and KOH (3.0 g, 53 mmol) in water (25 ml). After stirring for 30 min the solution was filtered and ethanol (30 ml, absolute) was added. The solution was maintained at 5 °C for 12 h and filtered again. The water-insoluble precipitate was dissolved on the frit in H_2O_2 (20 ml, 30%) and all the filtrates combined. Ethanol (150 ml, absolute) was added and the solution kept at 5 °C for 3 h. The solution was then filtered and the residue discarded. Additional ethanol (50 ml, absolute) was added to the filtrate and the solution was maintained at 5 °C for 12 h to give yellow crystals, which were collected on a frit and dried in vacuo (2.5 g, 5.3 mmol). Prolonged cooling of the mother liquor at 5 °C gave a second crop of yellow crystals. The total yield was 3.5 g (57%). IR (KBr): ν(CO) 1669 (br, s), 1373 (s); ν(VO) 940 (s); ν(OO) 865 (s), 852 (s) cm^{-1}. ^{51}V NMR (D_2O): δ −743. ^1H NMR (D_2O): δ 9.15 (br, 1H), 8.21 (s,1H), 7.93 (br, 1H). *Anal.* Calc. for $C_7H_{9.5}NO_{12.25}K_3V$: C, 17.82; H, 1.79; N, 2.97. Found: C, 18.18; H, 1.79; N, 2.96%.

2.6. $K_3[VO(O_2)_2(2,5\text{-pyridinedicarboxylato})]\cdot 2H_2O$, bpV(2,5-pdc)

The compound V_2O_5 (2.3 g, 13 mmol) was added to a solution of KOH (2.8 g, 50 mmol) in water (20 ml). The mixture was stirred for 15 min until a clear, almost colourless solution was obtained. The solution was cooled to 0 °C and filtered. To the filtrate was added 6.5 ml of H_2O_2 (30%), which gave a change of colour to yellow and a precipitate. The mixture was stirred for 10 min, then filtered through a medium-porosity glass frit to collect the precipitate, which was then dissolved in H_2O_2 (30%, 18.5 ml). The combined filtrates were added, over a period of 10 min, to a slurry of 2,5-pyridinedicarboxylic acid (5.0 g, 30 mmol) in a solution of KOH (3.5 g, 62 mmol) and water (22 ml). The resulting yellow solution was stirred for 1 h, then filtered, and absolute ethanol (45 ml) was slowly added to the solution until a persistent precipitate was observed. The mixture was kept at 5 °C for 18 h to give a precipitate, which was collected on a frit. The precipitate was dissolved in a small amount of H_2O (10 ml) and the solution was filtered. The insoluble residue was discarded. Absolute ethanol (200 ml) was added to the filtrate and the solution was kept at 5 °C for 48 h to give a yellow precipitate, which was collected on a frit and washed with ethanol (5 ml) and dried in vacuo. The total yield was 5.28 g (93%). IR (KBr): ν(CO) 1617 (s), 1362 (s); ν(VO) 932 (s); ν(OO) 890 (s), 860 (s) cm^{-1}. ^{51}V NMR (D_2O): δ −742. ^1H NMR (D_2O): δ 9.46 (br, 1H), 8.44 (br, d, 1H), 8.01 (br, d, 1H). *Anal.* Calc. for $C_7H_7NO_{11}K_3V$: C, 18.71; H, 1.57; N, 3.12. Found: C, 18.60; H, 1.29; N, 2.98%.

2.7. Potassium 3-acetatoxypicolinate

The compound ethyl-2-(2-ethoxycarbonyl-3-pyridyl-oxy)acetate (11 g, 43 mmol), prepared by the literature method [16], was added to a solution of KOH (5.1 g, 91 mmol) in H_2O (100 ml) and the mixture was refluxed for 3 h. The solution was washed with CH_2Cl_2 (2×25 ml), reduced to approximately half volume by rotary evaporation and cooled to 5 °C. Ethanol (approx. 10 ml) was added to give a sand-coloured precipitate, which was collected by filtration. The total yield (not optimized) was 6.8 g (58%). The compound (5.1 g, 19 mmol) was purified by dissolution in a mixture of hot CH_3OH (75 ml) and H_2O (13 ml) and filtered. The filtrate was cooled to 5 °C, and absolute ethanol was added (2 ml) to give crystals which were collected by vacuum filtration and dried in vacuo. The total yield (not optimized) was 3.3 g (65%). ^1H NMR (D_2O): δ 7.88 (d, 1H), 7.18 (m, 2H), 4.38 (s, 2H). ^{13}C NMR (D_2O): δ 177, 175, 151, 148, 141, 126, 122, 69.

2.8. $K_3[VO(O_2)_2(3\text{-acetatoxypicolinato})]\cdot 2H_2O$, bpV(3-acetpic)

The compound V_2O_5 (0.80 g, 4.4 mmol) was added to a solution of KOH (1.0 g, 18 mmol) in H_2O (20 ml) and the mixture was stirred for 10 min until a clear, almost colourless solution was obtained. The solution was cooled to approximately 8 °C and 2 ml of H_2O_2 (30%) was added to give a yellow slurry. After stirring for approximately 20 min the precipitate was collected on a medium-porosity glass frit and then was dissolved in H_2O_2 (30%, 6 ml). Potassium 3-acetatoxy-picolinate (2.2 g, 8.0 mmol) was added to the filtrate and the pH adjusted to 7 with KOH. The solution was stirred for approximately 1.5 h, then filtered, and absolute ethanol (4 ml) was added to the filtrate, which was cooled at 5 °C for 3 h; the solution was then filtered again. The pale yellow, water-insoluble precipitate that remained on the frit was discarded. The filtrate was maintained at 5 °C for a further 20 h, filtered, and allowed to stand at 5 °C for a further 8 days to give yellow-orange crystals (1.1 g, 2.3 mmol), which were collected by filtration and dried in vacuo. A second crop of crystals (0.20 g, 0.42 mmol) was collected upon addition of absolute ethanol to the mother liquor at 5 °C. The total yield was 1.3 g (34%). IR (KBr): ν(CO) 1619 (s), 1401 (s); ν(VO) 912 (s); ν(OO) 860 (s), 875 (s) cm^{-1}. ^{51}V NMR (D_2O): δ −745.

^{1}H NMR (D_2O): δ 8.8 (br, 1H), 7.5 (br, 2H), 4.5 (s, 1H). *Anal.* Calc. for $C_8H_9NO_{12}K_3V$: C, 20.04; H, 1.89; N, 2.92. Found: C, 20.28; H, 2.00; N, 2.80%.

2.9. Structure determinations

2.9.1. $K_3[VO(O_2)_2(2,4\text{-pdc})]\cdot 3.25H_2O$

Yellow thin plate crystals of bpV(2,4-pdc) ($0.4\times0.17\times0.1$ mm), obtained as described above, were mounted on a glass fibre and coated with epoxy. Cell dimensions were obtained from 25 reflections with $80°\leq 2\theta\leq 100°$. A total of 4355 reflections having $2\theta\leq 110°$ was collected on a Rigaku AFC6S diffractometer using the ω–2θ scan mode with graphite-monochromated Cu Kα radiation ($-7\leq h\leq 7$; $0\leq k\leq 40$; $0\leq l\leq 12$); of these, 3978 were unique and 3389 having $I\geq 2.5\sigma(I)$ were employed in the solution and refinement of the structure using the NRCVAX system of crystallographic software [17]. The data were corrected for absorption (psi scans). The structure was solved by direct methods, which gave the positions of the potassium, vanadium and some oxygen atoms coordinated to the vanadium. Remaining nonhydrogen atoms were found by successive difference maps. Single residues were assigned as oxygen for water. The hydrogen atom positions for the 2,4-pdc ligand were calculated at idealized geometries (C–H = 1.08 Å, $U_{iso}(H) = 0.01 + U_{eq}(C)$). Hydrogens on water were not included in the model. Refinement on $|F|$ was carried out in blocks of two molecules at a time; weights used were based on counting statistics.

Refinement of chirality η gave a value of 0.113; hence the minimum data set available does not discern between the two mirror images [18]. The anions themselves are not chiral and are present as two copies of each mirror image. Chirality comes from the packing; the odd number of water molecules (13) implies that the simplest nondisordered model contains four anions.

2.9.2. $K_3[VO(O_2)_2(3\text{-acetpic})]\cdot 2H_2O$

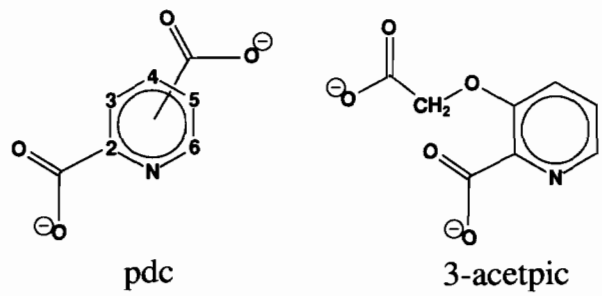
Yellow needles of bpV(3-acetpic) ($0.33\times0.1\times0.1$ mm), obtained as described above, were mounted on a glass fibre and coated with epoxy. Cell dimensions were obtained from 25 reflections with $30°\leq 2\theta\leq 35°$. A total of 2251 reflections having $2\theta\leq 45°$ was collected on a Rigaku AFC6S diffractometer using the ω–2θ scan mode with graphite-monochromated Mo Kα radiation ($-7\leq h\leq 7$; $0\leq k\leq 11$; $-11\leq l\leq 11$); of these 2060 were unique and 1537 having $I\geq 2.5\sigma(I)$ were employed in the solution and refinement of the structure using the NRCVAX system of crystallographic software [16]. Merging R for 191 pairs of symmetry-related reflections was 1.9%. The structure was solved by direct methods which gave the positions of all nonhydrogen atoms; the hydrogen atom positions were found by difference maps. Refinement was on $|F|$ with weights based on counting statistics. All nonhydrogen atoms were refined anisotropically; hydrogens were refined isotropically (except HW1B, which was fixed at the difference map position). Scattering factors and anomalous dispersion were from the usual sources [19].

3. Results

The following bisperoxo complex anions (bpV) have been prepared as their potassium salts: $[VO(O_2)_2L\text{–}L']^{3-}$, where L–L′ is a pyridinedicarboxylate (2,3-pdc, 2,4-pdc, 2,5-pdc) and 3-acetatoxypicolinate (3-acetpic) (Scheme 1). These complexes were isolated as yellow crystals or crystalline powders which displayed no visible decomposition upon prolonged storage (months). They are very water soluble. The ν(O–O) stretching vibration appears in the range 838–890 cm^{-1} in their infrared spectra [20,21]. A strong singlet was observed in the range -742 to -745 ppm in the ^{51}V NMR spectra of the compounds [22]. An additional, much weaker peak was always observed at approximately -700 ppm, which is assigned to the diaquo anion $[VO(O_2)_2(H_2O)_2]^-$ formed by dissociation of the ancillary ligand [22]. The ratio of the diaquo species to the ligand-bound species varies depending on the concentration and the nature of the ancillary ligand (5–10% for the pdc compounds and 30–50% for the bpV(3-acetpic)). The ^{1}H NMR spectra were consistent with this, showing signals due to roughly the same proportions of bound and unbound ligands, as expected.

The reactions of the pV compounds in water with approximately equimolar amounts of sodium tris(3-sulfonatophenyl)phosphine tetrahydrate were monitored by ^{31}P NMR. In all cases, after a reaction time of 5 minutes the phosphine had been completely oxidized to the corresponding oxide [23]; no change was observed in a control solution containing only the phosphine.

The crystal data for bpV(2,4-pdc) and bpV(3-acetpic) are listed in Table 1, and the structures of the anions are shown in Figs. 1 and 2, respectively, along with selected bond lengths and angles. The parameters listed for bpV(2,4-pdc) are the average of those found in the four independent but very similar molecules in the



Scheme 1. The structures of pdc and 3-acetpic.

Table 1
Crystallographic parameters for bpV(2,4-pdc) and bpV(3-acetpic)

	bpV(2,4-pdc)	bpV(3-acetpic)
Formula	$C_7H_3K_3NO_9V \cdot 3.25H_2O$	$C_8H_5K_3NO_{10}V \cdot 2H_2O$
Formula weight	471.88	479.39
Crystal system	monoclinic	triclinic
Space group	$P2_1$	$P\bar{1}$
Temperature (°C)	20 ± 1	20 ± 1
ρ_{calc} (g cm^{-3})	2.026	2.022
λ (Å)	1.54056	0.70930
a (Å)	7.1018(12)	7.4037(13)
b (Å)	38.187(5)	10.709(3)
c (Å)	11.4088(8)	10.9569(19)
α (°)		110.742(16)
β (°)	90.546(9)	95.600(19)
γ (°)		100.195(19)
V (Å^3)	3093.8(7)	787.4(3)
Z	8	2
R [a]	0.049	0.036
R_w [b]	0.055	0.026
S	1.97	1.47
K	0.0001	0
μ (mm^{-1})	13.47 (Cu Kα)	1.47 (Mo Kα)
Transmission range	0.095 to 0.199	
Secondary extinction	0.67(4)	0.025(7)
No. variables	486×2	263
No. measured	4355	2251
No. observed ref.	3389	1537
Scan (°)	$0.97 + 0.30 \tan \theta$	$1.5 + 0.30 \tan \theta$
Scan speed (° min^{-1}) (rescans)	8 (7)	8 (7)

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $R_w = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{1/2}$; $w = 1/(\sigma^2(F_o) + KF_o^2)$.

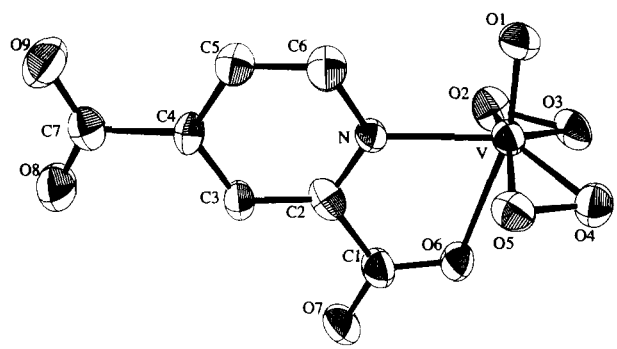


Fig. 1. ORTEP diagram of bpV(2,4-pdc) excluding the potassium ions and the H_2O molecules. Selected average bond lengths (Å) and angles (°): V–O(1), 1.622(9); V–O(2), 1.894(10); V–O(3), 1.894(9); V–O(4), 1.862(10); V–O(5), 1.909(10); V–N, 2.144(11); O(2)–O(3), 1.460(14); O(4)–O(5), 1.452(13); O(1)–V–O(2), 101.2(5); O(1)–V–O(3), 101.2(5); O(1)–V–O(4), 102.4(5); O(1)–V–O(5), 99.2(5); O(1)–V–O(6), 166.3(4); O(1)–V–N, 93.1(4); O(2)–V–N, 110.1(4); O(2)–V–O(3), 45.3(4); O(3)–V–O(4), 110.9(5); O(4)–V–O(5), 45.3(4); O(5)–V–N, 87.2(4).

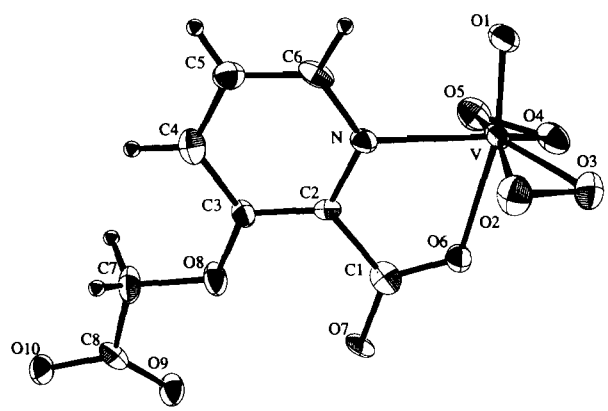


Fig. 2. ORTEP diagram of bpV(3-acetpic) excluding the potassium ions and the H_2O molecules. Selected bond lengths (Å) and angles (°): V–O(1), 1.621(3); V–O(2), 1.917(4); V–O(3), 1.866(4); V–O(4), 1.878(4); V–O(5), 1.941(4); V–N, 2.179(4); O(2)–O(3), 1.461(5); O(5)–O(4), 1.480(5); O(1)–V–O(2), 98.32(17); O(1)–V–O(3), 103.39(17); O(1)–V–O(4), 104.84(17); O(1)–V–O(5), 97.78(17); O(1)–V–O(6), 166.04(15); N–V–O(1), 93.39(16); N–V–O(2), 89.97(15); O(2)–V–O(3), 45.41(15); O(3)–V–O(4), 88.04(16); O(5)–V–O(4), 45.56(15); N–V–O(5), 85.59(15).

asymmetric unit. The final atomic coordinates for both compounds are listed in Tables 2 and 3, respectively. The structures of the molecules approximate distorted trigonal bipyramids if one assigns one coordination site to each peroxo ligand [24]. The inner coordination spheres of the vanadium atoms consist of one nitrogen and six oxygen atoms. The vanadyl oxo ligand and the carboxylate oxygen atom occupy the two axial positions, with the nitrogen atom and the two peroxo groups forming the trigonal plane. All five atoms of the equa-

Table 2
Fractional atomic coordinates for bpV(2,4-pdc) excluding the potassium ions and water molecules

Atom	x	y	z	B_{eq} [a]
V(A)	0.87408(35)	0.55226(6)	0.48952(20)	2.56(10)
O(1A)	0.9141(15)	0.5185(2)	0.5690(8)	3.7(5)
O(2A)	1.1245(14)	0.5634(3)	0.4426(9)	3.8(5)
O(3A)	1.0185(14)	0.5428(2)	0.3582(8)	3.6(4)
O(4A)	0.6577(14)	0.5403(2)	0.4072(8)	3.6(4)
O(5A)	0.6095(13)	0.5571(2)	0.5147(8)	3.1(4)
O(6A)	0.8270(13)	0.6086(2)	0.4212(7)	3.1(5)
O(7A)	0.8510(17)	0.6656(2)	0.4760(9)	4.3(6)
O(8A)	1.0131(17)	0.6890(3)	0.9031(9)	4.5(6)
O(9A)	1.0327(18)	0.6436(3)	1.0204(9)	4.9(6)
N(A)	0.9100(16)	0.5870(3)	0.6371(9)	2.4(5)
C(1A)	0.8590(22)	0.6335(4)	0.4968(12)	3.2(7)
C(2A)	0.9034(19)	0.6213(3)	0.6200(11)	2.7(6)
C(3A)	0.9341(21)	0.6453(4)	0.7094(11)	3.0(7)
C(4A)	0.9635(18)	0.6324(3)	0.8235(11)	2.3(5)
C(5A)	0.9637(20)	0.5964(4)	0.8395(11)	2.7(6)
C(6A)	0.9366(22)	0.5746(4)	0.7461(11)	3.2(6)
C(7A)	1.0067(21)	0.6576(4)	0.9261(13)	3.1(7)
V(B)	1.14423(31)	0.41281(5)	0.20784(17)	2.33(9)
O(1B)	1.2111(14)	0.4470(2)	0.2814(7)	2.9(4)
O(2B)	0.8820(13)	0.4124(2)	0.2438(7)	3.1(4)
O(3B)	0.9237(13)	0.4288(2)	0.1314(7)	3.0(4)
O(4B)	1.2719(14)	0.4187(2)	0.0671(7)	3.2(5)
O(5B)	1.3826(13)	0.3984(2)	0.1504(8)	3.2(4)
O(6B)	1.0717(12)	0.3577(2)	0.1407(7)	2.2(4)
O(7B)	1.1041(17)	0.3015(2)	0.1852(8)	4.0(5)
O(8B)	1.2492(15)	0.2727(2)	0.6113(7)	3.3(5)
O(9B)	1.2628(18)	0.3171(3)	0.7365(8)	4.5(6)
N(B)	1.1830(16)	0.3781(3)	0.3542(9)	2.5(5)
C(1B)	1.1062(19)	0.3324(4)	0.2109(11)	2.7(6)
C(2B)	1.1599(19)	0.3441(3)	0.3339(11)	2.3(6)
C(3B)	1.1759(21)	0.3193(3)	0.4238(11)	2.6(6)
C(4B)	1.2190(20)	0.3311(3)	0.5377(11)	2.6(6)
C(5B)	1.2420(20)	0.3661(3)	0.5543(11)	2.8(6)
C(6B)	1.2190(21)	0.3891(3)	0.4606(11)	2.6(6)
C(7B)	1.2478(20)	0.3049(4)	0.6362(12)	2.7(6)
V(C)	0.76715(32)	0.40732(5)	0.78005(18)	2.50(9)
O(1C)	0.7286(13)	0.4432(2)	0.7027(7)	3.2(4)
O(2C)	0.6257(13)	0.4165(2)	0.9150(7)	3.5(4)
O(3C)	0.5169(12)	0.3974(2)	0.8274(8)	3.5(4)
O(4C)	0.9856(12)	0.4189(2)	0.8650(7)	2.9(4)
O(5C)	1.0305(12)	0.4026(2)	0.7536(7)	2.8(4)
O(6C)	0.8113(12)	0.3510(2)	0.8463(6)	2.5(4)
O(7C)	0.7788(14)	0.2959(2)	0.7893(7)	3.6(4)
O(8C)	0.6279(15)	0.2733(2)	0.3643(7)	4.1(5)
O(9C)	0.6253(16)	0.3180(3)	0.2398(7)	4.5(5)
N(C)	0.7300(17)	0.3742(3)	0.6327(9)	3.3(5)
C(1C)	0.7775(20)	0.3280(3)	0.7713(11)	3.2(6)
C(2C)	0.7369(17)	0.3396(3)	0.6468(9)	2.1(5)
C(3C)	0.7041(17)	0.3169(3)	0.5548(10)	2.3(5)
C(4C)	0.6740(20)	0.3296(3)	0.4435(10)	2.8(6)
C(5C)	0.6766(21)	0.3658(3)	0.4275(10)	3.3(6)
C(6C)	0.7029(19)	0.3868(3)	0.5231(10)	2.9(6)
C(7C)	0.6410(19)	0.3054(3)	0.3404(11)	3.3(6)
V(D)	0.50018(32)	0.54501(0)	1.05914(17)	2.49(9)
O(1D)	0.4329(13)	0.5111(2)	0.9850(7)	3.2(4)
O(2D)	0.7216(12)	0.5295(2)	1.1332(7)	3.1(4)
O(3D)	0.7639(13)	0.5465(2)	1.0202(7)	3.3(4)
O(4D)	0.3734(12)	0.5391(2)	1.1995(7)	3.2(4)
O(5D)	0.2619(13)	0.5604(2)	1.1167(7)	3.4(4)
O(6D)	0.5779(13)	0.5999(2)	1.1246(6)	3.1(4)
O(7D)	0.5786(17)	0.6569(2)	1.0753(8)	4.8(5)
O(8D)	0.3780(15)	0.6862(2)	0.6641(8)	4.2(5)
O(9D)	0.3725(15)	0.6438(2)	0.5305(7)	4.1(5)
N(D)	0.4603(15)	0.5805(2)	0.9145(8)	2.6(4)
C(1D)	0.5522(20)	0.6250(3)	1.0505(11)	3.1(6)
C(2D)	0.4892(17)	0.6144(3)	0.9306(10)	2.4(5)
C(3D)	0.4693(17)	0.6391(3)	0.8442(11)	2.8(6)
C(4D)	0.4160(18)	0.6284(3)	0.7319(10)	2.6(5)
C(5D)	0.3909(19)	0.5930(3)	0.7126(9)	2.9(6)
C(6D)	0.4135(19)	0.5699(3)	0.8072(10)	2.6(5)
C(7D)	0.3881(21)	0.6551(3)	0.6324(11)	3.4(6)

(*continued*)

Table 2 (*continued*)

[a] B_{eq} is the mean of the principal axes of the thermal ellipsoid.

Table 3
Fractional atomic coordinates for bpV(3-acetpic) excluding the potassium ions and water molecules

Atom	x	y	z	B_{eq}
V	0.77355(13)	0.87285(9)	0.27465(8)	1.49(4)
K(1)	0.50755(18)	0.55017(12)	0.26844(12)	2.19(6)
K(2)	1.23110(18)	0.87597(12)	0.40930(12)	2.31(6)
K(3)	0.95528(18)	0.46427(13)	0.24376(12)	2.57(7)
N	0.7224(6)	0.9204(4)	0.0985(4)	1.47(20)
O(1)	0.9343(5)	1.0116(3)	0.3516(3)	2.15(18)
O(2)	0.5637(5)	0.9427(3)	0.3352(3)	2.45(20)
O(3)	0.6335(5)	0.8623(3)	0.4048(3)	2.31(19)
O(4)	0.8772(5)	0.7321(3)	0.2951(3)	2.51(19)
O(5)	0.9298(5)	0.7589(3)	0.1784(3)	2.72(21)
O(6)	0.5472(5)	0.7082(3)	0.1352(3)	2.22(18)
O(7)	0.3513(5)	0.6286(3)	−0.0552(3)	2.23(18)
O(8)	0.4634(5)	0.7328(3)	−0.2316(3)	2.38(20)
O(9)	0.2684(5)	0.5143(3)	−0.4329(3)	2.33(20)
O(10)	0.2605(5)	0.6291(3)	−0.5679(3)	2.03(19)
C(1)	0.4896(8)	0.7089(5)	0.0231(5)	1.95(27)
C(2)	0.6006(7)	0.8250(5)	−0.0063(5)	1.24(25)
C(3)	0.5788(7)	0.8380(5)	−0.1286(4)	1.48(25)
C(4)	0.6768(8)	0.9565(5)	−0.1388(5)	2.13(29)
C(5)	0.7930(7)	1.0552(5)	−0.0282(5)	1.96(28)
C(6)	0.8153(7)	1.0330(5)	0.0877(5)	1.89(26)
C(7)	0.4341(8)	0.7478(5)	−0.3566(5)	2.35(30)
C(8)	0.3080(7)	0.6181(5)	−0.4606(5)	1.73(27)

torial ligands (one nitrogen and four oxygen atoms) lie in this plane. The bond lengths and angles in the inner coordination sphere are nearly identical for the two structures and correspond closely to those reported for similar compounds [22]. The 2,4-pdc ligand is planar, with O(8) being on average the farthest away from the planar pyridine ring (range 0.14(2)–0.33(2) Å). The 3-acetpic also exhibits a high degree of planarity. The plane formed by the acetatoxy moiety (C(7), C(8), O(8), O(9) and O(10)) is tilted by only 10.0(3)° from the plane formed by the rest of the ligand and the vanadium atom.

Fig. 3 of the supplementary material shows a packing diagram of the unit cell of bpV(2,4-pdc). The asymmetric

unit contains two layers of anions oriented in the AC plane. These layers are at $y \approx 0.4$ and 0.6 (equivalent layers at 0.9 and 1.1). The plane of the 2,4-pdc ligand is perpendicular to this layer and the ligands themselves lie alternately above and below the vanadium layers. The potassium cations can be divided into three types based on the environments in which they exist. The first two types of cations form thin layers between the anion layers described above. One type of potassium cation (K_1, K_4, K_{11} and K_{12}) lies between the layers at 0.6 and 0.9 and interacts with the carboxylate oxygens of pdc ligands, whereas the second type of potassium cation (K_2, K_9, K_7 and K_{10}), found between the layers at 0.4 and 0.6, interacts with the oxo and peroxo ligands on vanadium. The third type of potassium cation is found in the layers formed by the vanadium anions: K_3 and K_8 are in the 0.6 layer and K_5 and K_6 are in the 0.4 layer. This potassium type interacts with oxygens from peroxo ligands and two water molecules (OW3 at the 0.6 layer and OW6 at the 0.4 layer). The remaining water molecules are distributed between the potassium layers and serve to bridge the cationic and anionic layers.

For the structure of bpV(3-acetpic) the potassium counter ions K(1), K(2) and K(3) are extensively coordinated, with 8, 9 and 6 bonds, respectively, shorter than 3.1 Å. Coordination is to both the solvent molecules and the oxygen donors of the anion. Details of the coordination of potassium atoms and hydrogen bonding are found in the supplementary material.

4. Discussion

The three complexes containing the pdc ligands constitute an interesting series differing only in the position which the 'free' carboxylate group occupies on the pyridine ring. If the two carboxylate groups occupy the 2- and 6-positions (i.e., 2,6-pdc) this results in the pseudo-octahedral monoperoxovanadium complex $NH_4[VO(O_2)(2,6\text{-pdc})(H_2O)]\cdot H_2O$ [25]. Both carboxylate ligands and the nitrogen atom are bonded to the vanadium together with the oxo group, a peroxo ligand and a water molecule. In the three pdc complexes reported here only one of the carboxylate groups is bonded to the vanadium, leading to the formation of bisperoxo complexes of pseudo-trigonal-bipyramidal geometry. The complexes bpV(2,3-pdc), bpV(3-acetpic), bpV(3-OHpic) [22] and bpV(pic) [22] form another structurally similar series wherein the substituent at the 3-position of the picolinic acid ligand is CO_2^-, $OCH_2CO_2^-$, OH and H, respectively. All of the complexes mentioned above are powerful inhibitors of the PTP associated with the insulin receptor. The effects that the various substitution patterns of these ancillary ligands have on the activity is currently under study.

The mode of inhibition of the PTP by pV compounds is not completely understood. Simple vanadate ion is thought to inhibit phosphatase enzymes by coordinating to the active site to form a stable trigonal bipyramidal transition state analogue of the binding of a phosphate ester during hydrolysis [26]. The combination of distorted trigonal bipyramidal geometry and strong oxidizing properties [27–29] observed for peroxovanadium compounds may enable them to inhibit PTP not only through a competitive mechanism but also by modifying the active site of the enzyme via oxidation. The oxidative chemistry of pV compounds has recently been reviewed by Butler et al. [30]. In organic solvents peroxovanadium compounds in the presence of excess peroxide act as highly effective oxidative catalysts. As a class, pV compounds are effective oxidants of sulfides to sulfoxides [31,32] and thiolatocobalt complexes (CoSR) to sulfinate species $[CoS(O)_2R]$ [33].

Catalytic oxidation in aqueous solutions has been studied as a means of modelling halide oxidation by vanadium bromoperoxidase [30]. There has, however, been less research into noncatalytic oxidations in aqueous solutions. We have shown that pV compounds oxidatively couple cysteine to give cystine [2]. As an alternative model of oxidations that may occur in the active site of PTPase, sodium tris(3-sulfonatophenyl)phosphine was chosen because of its water solubility and oxophilicity. The rapid oxidation of sodium tris(3-sulfonatophenyl)phosphine by the pV complexes further demonstrates a potential role of this class of compounds as efficient biological oxidants. Alternative and more accurate models for PTPase oxidation are currently being investigated.

5. Supplementary material

Packing diagrams including the potassium ions and water molecules (Figs. 3 and 4), full tables of final fractional atomic coordinates (Tables 4 and 5), listings of anisotropic temperature factors (Tables 6 and 7), full tables of bond lengths and angles, least square plane calculations, potassium coordination and hydrogen bonding interactions (Tables 8 and 9) and listings of observed and calculated structure factors (Tables 10 and 11) for bpV(2,4-pdc) and bpV(3-acetpic) are available upon request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK. Any request should be accompanied by the full literature citation for this communication.

Acknowledgements

Financial support for this work was provided by the Medical Research Council (MRC) of Canada, the De-

partment of Education of Quebec, and Nordic Merrell Dow Research Inc. of Montreal.

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