Selective recognition and binding of arsenate over phosphate†

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A divanadium complex shows remarkable selectivity for arsenate in substitution reactions with oxoanions.

Arsenate and phosphate present challenging tests of anion recognition and selectivity within both biology and chemistry. For example, marine algae have evolved uptake pathways to acquire essential phosphate from seawater, but these processes are not able to distinguish arsenate from phosphate, resulting in high concentrations of arsenic in algae.[1] Non-selectivity is also a factor in determining the human toxicity of arsenic through the accidental incorporation of arsenate into biochemical pathways designed for phosphate with resultant uncoupling of essential oxidative phosphorylation processes.[2] Chemical distinction between arsenate and phosphate is also a difficult task – both oxoanions are tetrahedrally shaped, of similar size (ionic radii of $H_2AsO_4^-$ and $H_2PO_4^-$ are 2.48 Å and 2.38 Å, respectively[3]), and have similar acid strengths (pK_a 2.21, 7.21, and 12.67 for the phosphorus species compared with 2.25, 6.77, and 11.60 for arsenic), and hence they have the same net charge at most pH values.

Supramolecular recognition of oxoanions by synthetic systems has focused principally on H-bonding interactions.[4–6] There are no reports of solution state competition experiments involving isoelectronic and isomorphous anions. Anion concentration by crystallisation with a selectivity order $SO_4^{2-} > SeO_4^{2-} > CO_3^{2-} > SO_3^{2-}$ has recently been shown to occur during the crystallisation of rigid H-bonded capsule frameworks.[7] In this process, the tetrahedral *vs.* trigonal shapes and the differences in anionic radii, even if small, are likely to be important in determining the solid-state phase due to crystal packing effects. Specific direction of intermolecular interactions in solution, however, cannot be assumed through such an observation.

Despite the fact that metal complexes containing coordinated oxoanions are numerous, the use of coordinative binding in solution for oxoanion recognition is largely unexplored. We report that a divanadyl complex of {2,6-bis[*N*,*N*-bis(2-pyridylmethyl)-amino]methyl}-4-*tert*-butylphenolato (bpbp$^-$, Scheme 1)[8] displays marked selectivity for arsenate over phosphate in competitive reactions with these two oxoanions.

The labile aqua ligands of $[(VO)_2(bpbp)(OH_2)_2](ClO_4)_3\cdot H_2O$ ($\mathbf{1}\cdot(ClO_4)_3\cdot H_2O$)[9] undergo facile substitution by a range of oxoanions, including $CH_3CO_2^-$, HCO_2^-, $(C_6H_5O)_2PO_2^-$, $H_2PO_4^-$, $H_2AsO_4^-$, $(C_6H_5O)PO_3^{2-}$, SO_4^{2-}, SeO_4^{2-}, HPO_4^{2-} and $HAsO_4^{2-}$, to give the μ_2-η^1:η^1-oxoanion-bridged complexes $[(VO)_2(bpbp)(\mu_2\text{-}\eta^1\text{:}\eta^1\text{-oxoanion})]^{+/2+}$.[10] One exception is the perchlorate anion which does not replace the water ligands – hence the use of perchlorate as counteranion for isolation of the reactive starting compound **1**. While substitution of two neutral water ligands by a bridging oxoanion is hardly surprising, the striking revelation of this study is that a preference for certain oxoanions over their isoelectronic counterparts is observed. In addition to the expected oxoanion selectivity on the basis of charge (dianionic oxoanions out-compete monoanionic oxoanions), there is a remarkable selectivity when $[(VO)_2(bpbp)]^{3+}$ binds oxoanions having the same charge and shape, *e.g.* SO_4^{2-} *vs.* SeO_4^{2-} or HPO_4^{2-} *vs.* $HAsO_4^{2-}$. The latter anion pair particularly fascinated us because of their contrasting roles in biological systems (essentiality *versus* toxicity). We have thus investigated the structure, rate of formation, and stability of the phosphato- and arsenato-bridged complexes, $[(VO)_2(bpbp)(HPO_4)]^+$ (**2**) and $[(VO)_2(bpbp)(HAsO_4)]^+$ (**3**).

The single-crystal X-ray structure of the phosphato-bridged complex suggests formulation as a double salt $[(VO)_2(bpbp)(HPO_4)][(VO)_2(bpbp)(H_2PO_4)](ClO_4)_3\cdot x\text{MeOH/H}_2\text{O}$ ($\mathbf{2}\cdot\mathbf{2}\text{H}\cdot(ClO_4)_3\cdot x\text{MeOH/H}_2\text{O}$) in the solid state.[11] The structure contains two crystallographically distinct cationic complexes with essentially identical conformations (Fig. 1), which form an H-bonded dimer through a P–O–H···O–P bridge about a crystallographic inversion centre. The centrosymmetry implies disorder of the bridging H atom between two symmetry-related complexes so that the structure formally contains 1+ and 2+

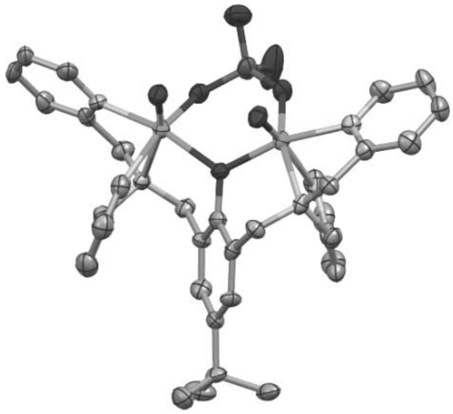

Fig. 1 X-Ray crystal structure of one of the two crystallographically distinct cations in $\mathbf{2}\cdot\mathbf{2}\text{H}\cdot(ClO_4)_3\cdot x\text{MeOH/H}_2\text{O}$. Displacement ellipsoids are shown at 50% probability and H atoms are omitted. The second crystallographically distinct cation in $\mathbf{2}\cdot\mathbf{2}\text{H}\cdot(ClO_4)_3\cdot x\text{MeOH/H}_2\text{O}$ is essentially identical, and the cationic complex in $\mathbf{4}\cdot(ClO_4)_2\cdot x\text{MeOH/H}_2\text{O}$ is also closely comparable.

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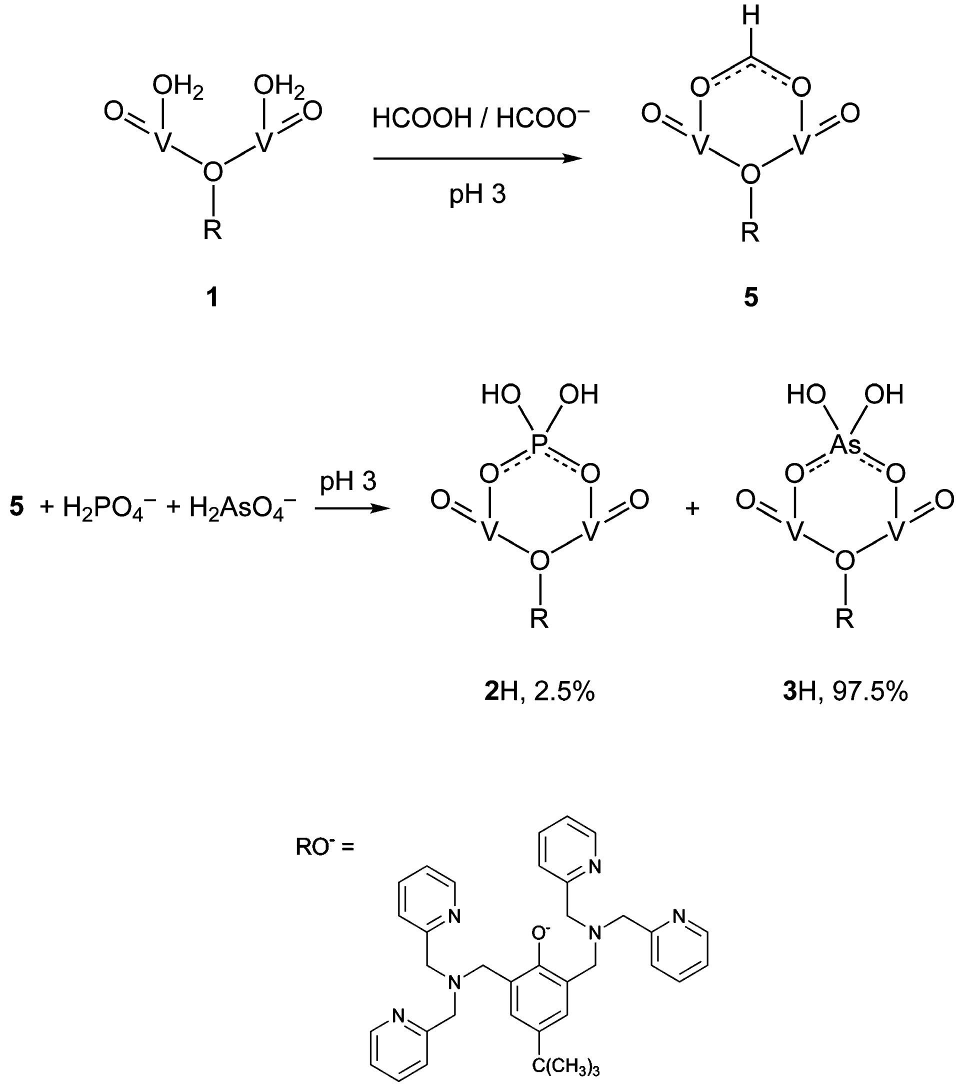

Scheme 1 Summary of the reactions of **1** with formate, phosphate and arsenate. For simplicity, only the bridging phenolate oxygen atom of the dinucleating ligand bpbp⁻ (RO⁻) is depicted and the overall cationic charges are not shown.

cations incorporating HPO_4^{2-} and $H_2PO_4^-$ bridging groups, respectively. The X-ray structure of the arylated derivative of **2**, the diphenylphosphato-bridged compound $[(VO)_2(bpbp)((C_6H_5O)_2PO_2)](ClO_4)_2 \cdot x$MeOH/$H_2O$ (**4**·$(ClO_4)_2 \cdot x$MeOH/H_2O)[11] was examined in order to remove the protonation, charge, and oxidation state ambiguity in the characterisation of **2**. Inspection of these structures show that there is a rearrangement of the complex geometry on going from the diaqua complex **1** to the phosphate-bridged complex **2** or **4**: the $N(CH_2py)_2$ arms of the bpbp⁻ ligand are *fac* coordinated in all three structures, but the V=O groups are twisted further away from each other in **1** compared to **2** or **4**: the magnitude of the O=V···V=O torsion angle in **1** is 98.3(1)°, compared to 13.9(1)/14.2(1)° in **2** and 15.0(1)° in **4**. Consequently, the amine N atoms both lie *trans* to the V=O groups in **1**, while only one amine N is *trans* to a V=O group in **2** or **4**, the other being *trans* to a phosphate O atom. The $V–O_{phen}–V$ angles of 117.92(17)/118.90(18)° in **2** and 118.34(7)° in **4** are smaller than the corresponding angle 125.69(10)° in **1**. Single crystals suitable for X-ray analysis were not forthcoming for the arsenato-bridged complex, however its elemental analysis, suggest a similar double salt formulation, (**3**·**3**H·$(ClO_4)_3 \cdot x$MeOH/H_2O) in the solid state. One isostructural μ_2-η^1:η^1-HPO_4^{2-} and μ_2-η^1:η^1-$HAsO_4^{2-}$ bridged matched pair of dinuclear complexes can be found in the literature, $[(VO)_2(\mu_2\text{-}O)_2HEO_4)(bipy)_2] \cdot xH_2O$ (E = P, x = 1,[12] As, x = 2,[13,14]). Incidentally these are also vanadium complexes, however in the V(V) oxidation state. A comparison of interatomic distances in these complexes, even though the core structures are different to the bpbp⁻ system here (di-μ-oxo-oxoanion triply-bridged *vs.* doubly-bridged phenoxo-oxoanion bridged), is poignant. For instance the interatomic O···O distance (bite) between the two coordinated oxygen atoms of the oxoanion are 2.787 Å for the arsenato complex *vs.* 2.510 Å for the phosphato complex. The corresponding interatomic V···V distances are 3.184 Å *vs.* 3.089 Å. These differences stem from the approximately 0.11 Å longer As–O bonds compared with P–O bonds. A difference of 0.277 Å in bite as observed in these V(V)bipy complexes could lead to selectivity for the slightly larger anion in competition reactions for the $[(VO)_2(bpbp)]^{3+}$ core. Comparison of the rates of formation of these bipy complexes, even if this information had been provided, is not relevant in comparisons with our work, since their formation does not involve a preformed divanadium reagent, and As_2O_3 was the source of arsenate for the arsenato-bridged system.[15]

The formation of complexes **2** and **3** from the reaction of **1** with NaH_2EO_4 (E = P, As) was tested at pH values from 1.0 to 9.0, adjusted in formic acid/aqueous ammonia buffers. In these solutions, **1** is not stable and the formato-bridged divanadium complex $[(VO)_2(bpbp)(HCO_2)]^{2+}$ (**5**) is formed immediately. Compound **5**$\cdot(ClO_4)_2$ was characterised in the solid state and there were no differences in the results described below if this compound was used instead of **1**$\cdot(ClO_4)_3$ to make up the reaction solutions. Using electrospray ionisation mass spectrometry (ESIMS) to follow the reactions, we found that in both cases binding of the oxoanion in its $H_2EO_4^-$ (E = P, As) form by the divanadium complex to give [**2**H]$^{2+}$ and [**3**H]$^{2+}$ peaked at about pH 3.[16] One factor in the stability of the phosphato- and arsenato-bridged complexes compared to the formato-bridged complex is presumably the bite angle required for the bridging groups; larger bite angles are to be expected for bidentate *O*,*O*′-bridging carboxylates compared to bidentate *O*,*O*′-bridging tetraoxoanions.

Further experiments were performed in 50 mM ammonium formate buffer at pH 3.0. In this medium, the phosphato- and arsenato-bridged complexes are stable despite a large excess of formate buffer (up to 5000-fold for diluted solutions of the oxoanion used for ESIMS). Reactions of **1** with either phosphate or arsenate indicated that the latter is bound at a significantly faster rate. This large difference in the rate of binding of the oxoanions by $[(VO)_2(bpbp)]^{3+}$ was also demonstrated by competitive experiments when equimolar amounts of **1**, phosphate and arsenate were mixed. During the first 30 min **1** binds arsenate avidly and almost exclusively, reaching >60% theoretical maximum yield with a 40-fold excess of arsenato complex over phosphato complex (Fig. 2). The speed of reaction and the subsequent timescale of exchange is such that a solution-based molecular sensor for arsenate could potentially be constructed using the $[(VO)_2(bpbp)]^{3+}$ unit. Scheme 1 summarizes the observed reactions.

Hydration enthalpies have been used to rationalise selectivity of arsenate in adsorption studies of phosphate and arsenate into goethite,[17] and in their electro-insertion into organic redox liquids.[18] Together with the interatomic distance and bite angle differences found for matched pairs of μ_2-arsenato and μ_2-phosphato bridged complexes discussed above, perhaps the selectivity for $[(VO)_2(bpbp)]^{3+}$ to bind arsenate may be further enhanced by hydration enthalpy differences for the free anions.

Finally, it is interesting to consider possible practical applications for the observed selective binding. Arsenate is a proven human carcinogen and its presence in drinking water sources, as a consequence of natural geological processes, is a worldwide environmental health issue.[19] The problem is particularly severe in under-developed countries, for example Bangladesh, where water supplies are decentralised, resulting in a need for field-based analytical methods to determine arsenate concentrations in water at the source. The results reported here offer opportunities for the development of supramolecular systems based on vanadium coordination complexes to sense and measure dissolved arsenate anions directly using simple devices.

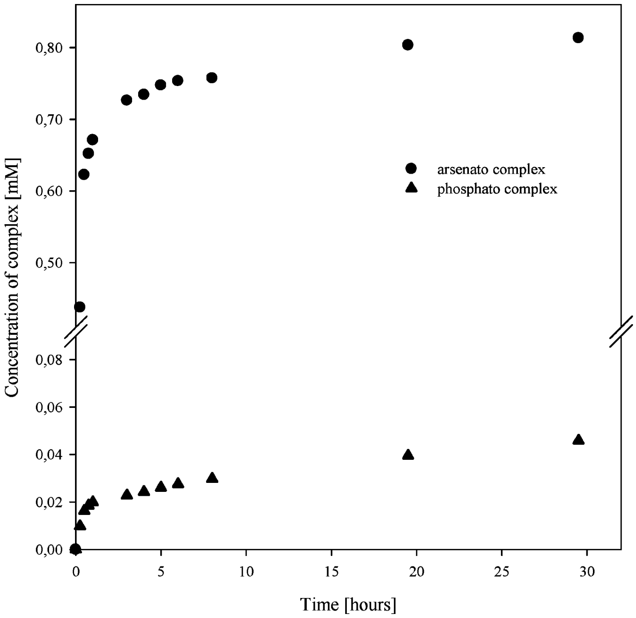

Fig. 2 Selective binding of arsenate over phosphate by $[(VO)_2(bpbp)]^{3+}$. A solution containing equimolar concentrations (each 1 mM) of arsenate, phosphate, and **1** in 50 mM ammonium formate buffer (pH 3.0) was prepared and the formation of complexes was monitored over time by ESIMS. The calculated concentration for complete formation of oxoanion complex was 1 mM. Each data point represents the mean of three ESI-MS measurements of the doubly charged $[(VO)_2(bpbp)(EO_4H_2)]^{2+}$ ions (relative SD was always <2%; for clarity, error bars are not shown).

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10 Complexes **2**, **3**, **4** and **5**, isolated as their perchlorate salts, were prepared by reaction of **1** with one equivalent of Na_2HPO_4, Na_2HAsO_4, $Na(C_6H_5O)_2PO_2$ or $NaHCO_2$, respectively, in methanol–water mixtures. They were isolated in 70–80% yields as lilac crystals. Elemental analyses (C, H, N), ESIMS, and IR spectroscopy were used to verify composition. **CAUTION**: Although we experienced no problems when carrying out the syntheses, perchlorates are potentially explosive and should be treated with care.

11 Crystal data: **2**·**2**H·(ClO$_4$)$_3$·xMeOH/H$_2$O, C$_{72}$H$_{81}$Cl$_3$N$_{12}$O$_{26}$P$_2$V$_4$, M_r = 1902.54, violet plate, 0.25 × 0.20 × 0.06 mm, triclinic, $P\bar{1}$, a = 10.3735(4), b = 21.3057(10), c = 21.9212(10) Å, α = 71.600(2), β = 77.945(1), γ = 87.094(2)°, V = 4495.2(3) Å^3, Z = 2, ρ_c = 1.406 g cm^{-3}, μ(Mo-Kα) = 0.606 mm^{-1}, 2θ_{max} = 25.03, 57173 measured reflections, 15467 independent reflections, R_{int} = 0.091, R_1 = 0.070 (7840 reflections with $I > 2\sigma(I)$), wR_2 = 0.196 (all data), S = 0.95. **4**·(ClO$_4$)$_2$·xMeOH/H$_2$O, C$_{48}$H$_{49}$Cl$_2$N$_6$O$_{15}$PV$_2$, M_r = 1153.68, blue block, 0.20 × 0.20 × 0.12 mm, trigonal, $R\bar{3}$, a = b = 34.3754(12), c = 24.9569(7) Å, α = β = 90, γ = 120°, V = 25539.7(15) Å^3, Z = 18, ρ_c = 1.350 g cm^{-3}, μ(Mo-Kα) = 0.518 mm^{-1}, 2θ_{max} = 28.00, 40700 measured reflections, 13547 independent reflections, R_{int} = 0.039, R_1 = 0.051 (10499 reflections with $I > 2\sigma(I)$), wR_2 = 0.134 (all data), S = 1.04. CCDC 722650 and CCDC 722651 contain the supplementary crystallographic data. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b918143c.

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15 [(VO)$_2$(μ$_2$-O)$_2$HAsO$_4$)(bipy)$_2$]·2H$_2$O was made *via* a hydrothermal synthesis using As$_2$O$_5$.[12] [(VO)$_2$(μ$_2$-O)$_2$HPO$_4$)(bipy)$_2$]·2H$_2$O was made *via* a hydrothermal synthesis using V$_2$O$_5$.[11].

16 ESIMS was performed by flow injection analysis with an Agilent LC/MS system (single quadrupole). Analyses were performed with a mixture of acetonitrile and 50 mM ammonium formate pH 1 to 9, (1+4, v/v) at a flow of 0.2 mL min^{-1}. Measurements were taken in selected ion monitoring mode (150 V fragmentor voltage) at m/z 845 ([(VO)$_2$(bpbp)(AsO$_4$H)]$^+$), 801 ([(VO)$_2$(bpbp)(PO$_4$H)]$^+$), 423 (([(VO)$_2$(bpbp)(AsO$_4$H$_2$)]$^{2+}$), and 401 [(VO)$_2$(bpbp)(PO$_4$H$_2$)]$^{2+}$. Reactions were performed by mixing appropriate volumes of 10 mM solutions of complex **1** (in acetonitrile), arsenate (aqueous solution of NaH$_2$AsO$_4$ adjusted to pH 3 using aqueous NH$_3$), or/and phosphate (aqueous solution of H$_3$PO$_4$ adjusted to pH 3 using aqueous NH$_3$) and diluting the mixture with 50 mM ammonium formate buffer pH 3.0 to give a final concentration of 1 mM of each reactant. At prescribed times (0.25 to 30 h), an aliquot of the reaction mixture was removed, diluted 1+199 with 50 mM ammonium formate buffer pH 3.0, and measured by ESIMS (m/z 845, 801, 423, 401). Standard solutions of the oxoanion complexes **2** and **3** were prepared from the dried crystalline samples of **2**·**2**H·(ClO$_4$)$_3$ and **3**·**3**H·(ClO$_4$)$_3$. Quantification of reaction products was performed by external calibration using standard solutions of **2** (m/z 401) and **3** (m/z 423).

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