Steric Control of Vanadium(V) Coordination Geometry: A Mononuclear Structural Model for Transition-State-Analog RNase Inhibitors

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Introduction:

The role played by vanadium in biochemistry has become widely appreciated in recent years.[1-3] Its involvement ranges from being the active-site metal in a number of enzymes (bromoperoxidase and nitrogenase) to being a potent inhibitor of others.[4-7] Among this latter group are the phosphate-metabolizing enzymes such as RNase, where bound vanadate has been proposed to function as a transition state analog of the pentavalent trigonal bipyramidal intermediate of phosphate hydrolysis.[8] This supposition, first presented by Lindquist *et al.*, was based on the known coordination flexibility of the d^0 V(V) center and has since been borne out by a number of subsequent studies on the inhibitor complex formed between ribonuclease A, vanadate, and uridine. These studies, which include X-ray and neutron diffraction, unequivocally show the presence of trigonal bipyramidal (TBP) vanadium within the enzyme.[9] Despite these studies and the host of solution work using ^{51}V NMR, structurally characterized small-molecule models for trigonal bipyramidal coordination of V(V) remain relatively rare.[10] Several recent examples of TBP V(V) are the bis(μ-pinacolato)dioxovanadium(V) chloride and oxovanadium(V) triethanolaminate reported by Crans *et al.* and the tris(cyclopentanolato)oxovanadium(V) of Rehder and co-workers.[11-13] While all of these complexes adopt a distorted TBP arrangement around the vanadium, it is achieved in two cases by *dimerization* of two tetrahedral V(V) centers. This typically leads to one very long intermolecular bond between the two molecules in the solid state. This phenomenon appears to be quite general, with many four-coordinate V(V) centers dimerizing to produce pseudo-five-coordination and with five-coordinate V(V) dimerizing to give a octahedral species.[14,15]

One of the most successful approaches to stabilizng ususual geometries at a metal center is building into a ligand sufficient steric bulk to eliminate undesirable side reactions such as dimerization.[16,17] We report here the structures of two vanadium(V) complexes which illustrate this approach nicely: (*N*-salicylidene-*N'*-methylethylenediaminato)dioxovanadium(V) (**I**) and its substituted analog (*N*-(3-methyl-6-*tert*-butylsalicylidene)-*N'*-methylethylenediaminato)dioxovanadium(V) (**II**). With the unsubstituted ligand, two five-coordinate monomers dimerize to give a six-coordinate vanadium center, while, with the more sterically bulky ligand, we have blocked this process and have been able to achieve trigonal bipyramidal coordination geometry, similar to that described in the RNase inhibitor complex, in a mononuclear vanadium(V) complex.

Table I. Crystallographic Data for I and II

Complex I	
$C_{10}H_{13}N_2O_3V$	*Pbca*
fw = 260.2	T = 24 °C
a = 9.240(2) Å	λ = 0.7107 Å
b = 13.424(3) Å	ρ_{calcd} = 1.542 g/cm^3
c = 18.066(4) Å	μ = 8.78 cm^{-1}
V = 2240.9(9) Å^3	R^a = 0.0298
Z = 8	$R_w{}^b$ = 0.0412
Complex II	
$C_{15}H_{23}N_2O_3V$	$P2_1/c$
fw = 330.3	T = 24 °C
a = 14.676(3) Å	λ = 0.7107 Å
b = 9.590(2) Å	ρ_{calcd} = 1.293 g/cm^3
c = 13.097(3) Å	μ = 5.95 cm^{-1}
β = 113.00(3)°	R = 0.0497
V = 1696.8(9) Å^3	R_w = 0.0693
Z = 4	

$^a R = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$. $w^{-1} = \sigma^2(|F_o|) + 0.0008|F_o|^2$.

Experimental Section

Preparations. The Schiff base ligand *N*-salicylidene-*N'*-methylethylenediamine was prepared by simple condensation of salicylaldehyde with methylethylenediamine (Aldrich) in dry isopropyl alcohol. After being stirred for 1 h, the deep yellow solution was treated with an equimolar quantity of vanadium triisopropoxide (Johnson-Matthey). The resulting product was removed by vacuum filtration. The yield of pure **I** was approximately 32%. X-ray-quality crystals were obtained by slow cooling of a hot acetonitrile solution of the crude product.

The requisite sterically hindered salicylaldehyde needed for **II** was prepared by direct formylation of the appropriate phenol by a modification of the method of Casiraghi *et al.*[18] The Schiff base and vanadium complex thereof were prepared as described above. The yield of recrystallized product (dichloromethane/ether) was approximately 40%. X-ray-quality crystals of **II** were obtained by slow evaporation from a chloroform/methanol/ether solution over several weeks. Both products were characterized by combination of NMR and IR spectroscopies (supplementary material).

X-ray Crystallography. Data crystals were cleaved from large crystals of **I** and **II** obtained as above and were mounted in Linderman capillaries. The crystals were transferred to a Siemens R3 diffractometer employing graphite-monochromated Mo Kα radiation. Cell constants and an orientation matrix were obtained from 20–25 carefully centered, relatively high angle reflections ($20° \le 2\theta \le 22°$). A total of 1240 independent reflections (R_{int} = 0.0118) were collected over the range of 3.5–43° in 2θ for **I**, with 952 being considered observed ($F > 4.0\sigma(F)$). For **II**, 2123 independent reflections (R_{int} = 0.0323) were collected over a 2θ range of 3.5–45°, with 1887 being considered observed ($F > 4.0\sigma(F)$). Crystal data and data collection parameters are summarized in Table I. Data were reduced and the models refined using the SHELEX program package supplied with the diffractometer. Space groups were unambiguously determined from systematic absences as *Pbca* for **I** and $P2_1/c$ for **II**. The structures were solved by direct methods and refined using full-matrix least-squares procedures. Hydrogen atoms were initially placed at

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Table II. Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Coefficients (Å² × 10³) for I

	x	y	z	U(eq)[a]
V(1)	1473(1)	5247(1)	4558(1)	38(1)
O(3)	700(3)	4181(2)	4806(1)	41(1)
N(1)	1689(4)	6848(2)	4569(2)	44(1)
O(2)	3068(3)	4977(2)	4258(2)	58(1)
C(7)	1455(5)	7447(3)	4032(3)	48(2)
O(1)	396(3)	5480(2)	3670(2)	48(1)
C(1)	324(4)	6217(3)	3185(2)	43(2)
N(2)	2212(3)	5553(3)	5666(2)	44(1)
C(6)	856(5)	7181(3)	3330(2)	45(2)
C(2)	-341(5)	6051(3)	2497(2)	55(2)
C(8)	2171(6)	7268(3)	5281(3)	63(2)
C(9)	3016(5)	6504(4)	5676(3)	65(2)
C(5)	694(5)	7933(4)	2797(3)	65(2)
C(3)	-476(5)	6801(5)	1989(3)	69(2)
C(4)	32(6)	7738(4)	2130(3)	74(2)
C(10)	3078(5)	4764(3)	6033(3)	71(2)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table III. Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Coefficients (Å² × 10³) for II

	x	y	z	U(eq)[a]
V(1)	5369(1)	2291(1)	840(1)	40(1)
O(1)	6661(2)	2948(3)	1167(2)	63(1)
O(2)	4985(2)	3222(3)	1610(2)	57(1)
O(3)	5641(2)	724(3)	1359(2)	56(1)
N(1)	5098(2)	3146(3)	-753(2)	44(1)
C(7)	7164(2)	3712(4)	736(3)	45(1)
N(2)	3945(2)	1536(4)	-208(2)	51(1)
C(5)	8144(2)	4138(4)	1397(3)	46(1)
C(1)	7270(3)	4932(4)	-849(3)	49(2)
C(10)	4091(3)	2983(5)	-1613(3)	54(2)
C(8)	6729(3)	4107(4)	-387(3)	42(1)
C(2)	8207(3)	5360(4)	-230(3)	52(2)
C(9)	5719(3)	3783(4)	-1066(3)	44(1)
C(4)	8622(3)	4945(4)	891(3)	54(2)
C(6)	8629(3)	3688(5)	2620(3)	60(2)
C(11)	3414(3)	2582(4)	-1041(3)	56(2)
C(3)	8778(3)	6288(5)	-713(4)	70(2)
C(12)	3338(3)	972(5)	368(4)	70(2)
C(63)	8679(4)	2102(5)	2681(4)	82(2)
C(62)	8048(3)	4241(6)	3273(3)	82(2)
C(61)	9691(3)	4266(7)	3170(4)	101(2)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

idealized positions and were refined as riding on their respective carbon atoms. Fractional atomic coordinates for I and II are found in Tables II and III.

Results

Description of Structures. Complex I, containing the unsubstituted salicylaldehyde, crystallizes out of the reaction mixture as the nearly insoluble, weakly associated dimer shown in Figure 1. It is only very sparingly soluble in DMF or DMSO. This structure is very similar to that already reported for the analogous $[VO_2(HSHED)]_2$ reported by Pecoraro *et al.*[15] It illustrates the strong propensity of the vanadium center to increase its coordination number via dimerization of two pentacoordinate monomers. This leads to the large asymmetry in the observed V–O bond lengths.

Compound II, prepared using the 3-methyl-6-*tert*-butylsalicylaldehyde, crystallizes from solution as large deep yellow rods. It is soluble in a number of moderate-polarity solvents, including chloroform, acetonitile, and methanol. The structure of II, shown in Figure 2, reveals clearly its mononuclear nature. The geometry about the vanadium is distorted trigonal bipyramidal with the meridionally coordinating Schiff base occupying the two axial positions and one equatorial position. The two oxo groups, as expected from simple VSEPR considerations, occupy the remaining equatorial sites.[19] The bond lengths around the vanadium are unexceptional and are within the ranges seen in previously characterized species. The five-membered ring containing V(1),

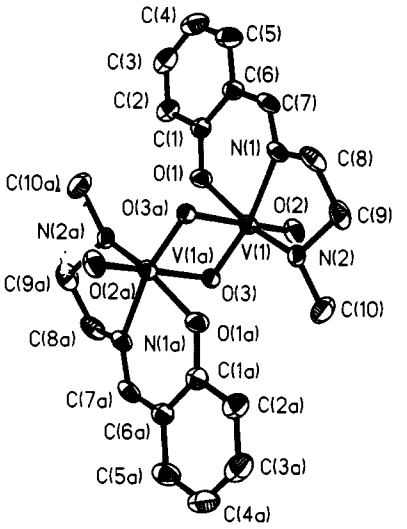
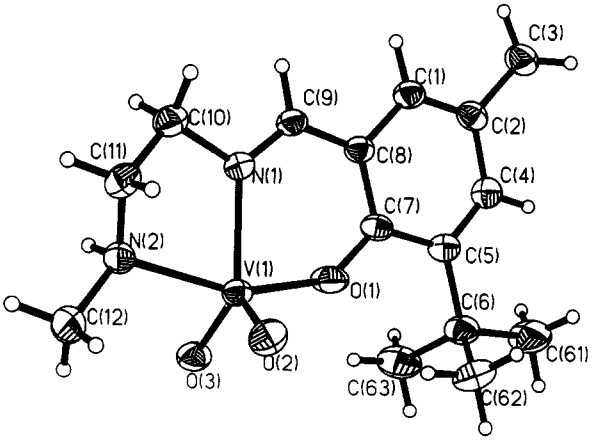


Figure 1. ORTEP diagram for I showing the atom-labeling scheme with 30% probability ellipsoids. Selected bond lengths (Å) and angles (deg): V(1)-O(1), 1.913(3); V(1)-O(2), 1.612(3): V(1)-O(3), 1.661(2); V(1)-N(1), 2.159(3); V(1)-N(2), 2.155(3); V(1)-O(3a), 2.438(3); O(3)-V(1)-N(1), 153.5(1); N(1)-V(1)-O(2), 98.2(1); N(1)-V(1)-O(1), 83.9(1); O(3)-V(1)-N(2), 92.9(1); O(2)-V(1)-N(2), 93.8(1); O(3)-V(1)-O(3a), 77.9(1); O(2)-V(1)-O(3a), 169.3(1); N(2)-V(1)-O(3a), 76.3(1); O(3)-V(1)-O(2), 106.9; O(3)-V(1)-O(1), 98.3(1); O(2)-V(1)-O(1), 103.3(1); N(1)-V(1)-N(2), 76.8(1); O(1)-V(1)-N(2), 155.9(1); N(1)-V(1)-O(3a), 76.0(1); O(1)-V(1)-O(3a), 85.1(1).



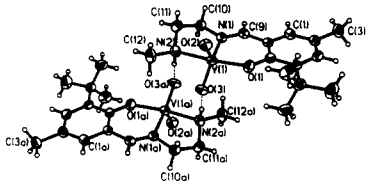


Figure 2. ORTEP diagram for II showing the atom-labeling scheme with 30% probability ellipsoids. Insert shows the hydrogen bonding between symmetry-related molecules. Selected bond lengths (Å) and angles (deg): V(1)-O(1), 1.882(3); V(1)-O(3), 1.634(3); V(1)-N(1), 2.130(3); V(1)-O(2), 1.605(3); V(1)-N(2), 2.130(3); O(3)-V(1)-O(2), 109.8(2); O(2)-V(1)-O(1), 103.9(1); O(2)-V(1)-N(2), 95.6(1); O(3)-V(1)-N(1), 133.1(1); O(1)-V(1)-N(1), 83.1(1); O(3)-V(1)-O(1), 98.8(1); O(3)-V(1)-N(2), 88.5(1); O(1)-V(1)-N(2), 155.3(1); O(2)-V(1)-N(1), 115.1(1); N(2)-V(1)-N(1), 74.9(1).

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N(2), C(11), C(10), and N(1) adopts an envelope configuration with V(1), N(2), N(1), and C(10) roughly in a plane (average deviation 0.059 Å) with C(11) 0.65 Å out of that plane as the "flap" of the envelope.

An interesting feature of the molecule is the strong hydrogen-bonding interaction of the N(1) amino hydrogen on one molecule with oxo group, O(3), on the symmetry-related adjacent molecule in the unit cell, as seen in the insert of Figure 2. The H(20)–O(3) hydrogen bond is a very short, 1.789 Å, with a V–O(3)–H(20) angle of 122°. Additional hydrogen-bonded interactions are also seen in the cell between H(9a) and O(3) (2.45 Å) and H(10a) and O(2) (2.53 Å). The strong hydrogen bond between the amino hydrogen and O(3) leads to a minor asymmetry in the V=O bond lengths with V—O(2) at 1.605 Å and V—O(3) at 1.634 Å.

Discussion

Typically, the two idealized five-coordinate structures, trigonal bipyramidal and square pyramidal, are connected by a relatively shallow potential energy surface. Muetterties and Guggenberger have shown that there is in fact a continuous spectrum of structures along the SP → TBP reaction coordinate path.[20] Thus it is important to couch any discussion of five-coordinate geometries in some semiquantitative way. Muetterties *et al.* characterized the two geometries in terms of three dihedral angles, e_1, e_2, and e_3 (see ref 20). For the idealized TBP geometry, these angles are all 53.1°, while, for SP coordination, they are 75.7, 75.7, and 0.0°, respectively. Alternatively, one could quantitate the deviation from ideal square pyramidal geometry via the deviation from the plane made up of three of the pseudobasal plane atoms by the fourth. On the basis of either criterion, it is clear that the present structure is more nearly TBP than SP (e_1 = 52.5°, e_2 = 68.4°, and e_3 = 23.4°, with O(3) 0.80 Å out of the basal plane formed by O(1), N(1), and N(2), although it is highly distorted.

The structure of the ribonuclease–uridine–vanadate complex has been solved by Petsko, Ringe, and Wlodawer with some details reported as a personal communication in ref 11.[9] It is clear that even though the ligation in the present system is not entirely appropriate, including as it does some nitrogens rather than the all-O environment seen in the uridine vanadate complex, the overall structures are very similar. For example, the angle between the apical substituents is 162° in the uridine vanadate and 155° in II with a similar puckering in the five-membered ring centered on carbon in both. There are even some similarities in the hydrogen-bond arrangements; unfortunately, a lack of reported details prevents a more thorough comparison.

Overall then, we have shown that steric bulk can be used to modify the coordination geometry and/or number of V(V) atoms by preventing dimerization pathways. It is hoped that this will lead to an increased ability to produce systems which model the sterically demanding environments expected to be present in vanadoproteins.

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Supplementary Material Available: Listings of complete bond lengths and angles, anisotropic thermal parameters, and hydrogen atom coordinates and a table of spectral data (IR and NMR) for I and II (5 pages). Ordering information is given on any current masthead page.

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