but also the inhibitory effect of free EtS^- on the formation of $RC(O)COO^-$ are well explained by Scheme I.

Registry No. CO_2, 124-38-9; AcSEt, 625-60-5; $CH_3CH_2C(O)SEt$, 2432-42-0; PhC(O)SEt, 1484-17-9; EtSH·Na, 811-51-8; $(Bu_4N)_3$-$[Mo_2Fe_6S_8(SPh)_9]$, 68197-68-2; $(Et_4N)_3[Mo_2Fe_6S_8(SEt)_9]$, 72895-02-4; $AcCO_2^-$, 57-60-3; $CH_3CH_2C(O)CO_2^-$, 339-71-9; $PhC(O)CO_2^-$, 50572-54-8; HCO_2^-, 71-47-6; AcCl, 75-36-5; AcOAc, 108-24-7; AcSAc, 3232-39-1; AcSPr, 2307-10-0; 1-acetylimidazole, 2466-76-4; acetyl coenzyme A, 72-89-9.

Is the Vanadate Anion an Analogue of the Transition State of RNAse A?[†]

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Abstract: The electronic structures of models of the monoanion phosphorane transition state in ribonuclease A and its putative vanadate transition-state analogue are compared. The electrostatic potential and gross atomic populations agree well for the vanadium and phosphorus trigonal-bipyramidal transition-state structures for both equatorial and axial bonds to hydroxyl ligands but are different for the V–O and P–O bonds. The P–O bond is semiionic but V–O is a multiple bond that is much less polar. A similar difference in the polarity between P–O and V–O is found for the dianion. Ionic hydrogen bonds to the cationic residues will not be comparable between the V–O and P–O bonds. The vanadium compound is not a transition-state analogue for such H-bonds. The pattern of Lys-41 and His-12 residue bonding observed for the vanadate-inhibited RNase A should not be used to analyze the mechanism. Proton transfer between the five-coordinate transition state and the His-119 residue is a step in both the cyclization and hydrolysis phases of the mechanism. The proton transfer curve from the equatorial hydroxyl ligand to a model of His-119 is calculated to be essentially equivalent for the vanadium and phosphorus five-coordinate models of the active site. Residue binding to the vanadate monoanion would be analogous to stabilization of the transition-state intermediate. Stable vanadium dianion intermediates, which are electronic analogues of the dissociative phosphorus dianion, are calculated with both equatorial–equatorial and equatorial–axial deprotonated oxygen sites. The equatorial–axial dianion is lowest in energy and accounts for the binding of the His-119 residue in the vanadium system although the binding is weaker than for the phosphorus analogue.

1. Introduction

Ribonuclease A (RNase A) cleaves RNA by transphosphorylation and subsequent hydrolysis of the 2′,3′-cyclic phosphate intermediate. In both steps a five-coordinate phosphorane transition state is hypothesized. Vanadium can adopt a number of valence states with a variety of conformations and a uridine vanadate was proposed as a stable analogue of the transition-state complex[1] for RNase A. Subsequently, crystallographic, neutron diffraction, and NMR studies[2–4] of a complex of uridine vanadate and RNase A examined a five-coordinate vanadate at the active site and determined the protonation states of the bound residues. The Lys-41 and His-12 residues were not found in H-bonding positions expected from the presumed mechanism[1] and raised doubts on details of that mechanism. Although there is experimental evidence that the Lys-41 is flexible[3,4] in the native enzyme, another explanation for the H-bonding at the active site is possible if the vanadate(V) (designated V) does not have comparable electronic properties to the phosphorane(V) (designated P) transition state leading to different hydrogen binding behavior and orientations. The H-bonding orientation to the His-119 residue also is surprising. The His-119 residue in the uridine vanadate RNase is actually positioned closest to the equatorial oxygen. But the largest hydrogen-bonding density is reported at the axial oxygen,[2] with the distance from His-119 to the axial oxygen about 0.6 Å longer than that to the equatorial. Apparently this residue is interacting with both the axial and equatorial ligands. Analysis of the neutron scattering finds the three residues, His-12, Lys-41, and His-119, protonated in the crystal and presumably bound to the dianion, but the NMR results strongly suggest the vanadate in solution is a monoanion.[4]

Although both the P and V five-coordinate monoanions are structurally related trigonal bipyramids, the electronic differences between the valence p-oribtal in P and the d-orbital in V are substantial. Formally the two complexes can be considered to be comparable as p^0 or d^0 systems, but the calculated populations for p and d are closer to the neutral atoms. The five-coordinate vanadate is a stable molecule and an enzyme inhibitor but the analogue properties are presumed to be manifest in the position of the protons and the H-bonding to the surrounding residues.[5] This paper will examine whether the vanadium five-coordinate complex is a transition-state analogue (TSA) electronically as well as structurally by examining the comparable geometric and electronic characteristics of the five-coordinate monoanion and dianion, H_4XO_5 (X = P or V).

One test compares the electrostatic potential generated by $H_4XO_5^-$ (X = P or V) at equatorial and axial H-bonding sites that are important in binding the three cationic residues implicated in the mechanism. The similarities and differences in the electronic structure of the P and V compound are analyzed. It is well-known that the central phosphorus atom often forms bonds of an ionic or "semipolar" character.[6] The semipolar P–O bond in the phosphorane is a single ionic or dative ionic bond. This type of

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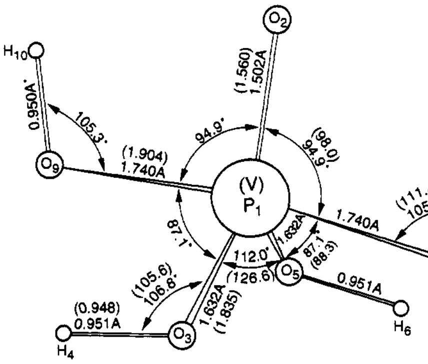

Figure 1. Comparison of the optimized trigonal-bipyramidal geometries between the P and V versions of $H_4XO_5^-$. When P distances and angles are identical from symmetry, the corresponding V values are not repeated.

P–O bond in H_3PO is found to be well-represented by an SCF calculation.[7] The small extent of double-bond character for P–O due to back-bonding has been determined by correlation calculations.[8] If a semipolar bond formed for both the phosphorus and vanadium molecules, the similar electronic structure could result in a comparable electrostatic potential. However, the semipolar bond probably does not exist for vanadium compounds. For example, a covalent V–O bond has been calculated for the vanadyl ion[9] and, we will show below, for H_3VO. The V–O bond in the five-coordinate model system, H_4XO_5 (X = P, V), will also be found below to be more covalent than the P–O bond, but this does not preclude the possibility that the X–OH bonds are electronically similar. The comparative electronic behavior of the V and P bonds will be related to the geometry and the electrostatic potentials in the vicinity of the bond. Electronic differences between the P–O and V–O bonds in both the monoanion and dianion suggest an electronic basis for the unusual hydrogen bonding of the His-12 and Lys-41 residues observed experimentally.

Another test we propose for the electronic TSA is the comparability of the proton transfer curves from the protonated cation hydrogen bound to the five-coordinate P or V complex. A recently proposed mechanism suggests explicit steps requiring proton transfer between the TS or the H-bond-stabilized TS and the protonated His-119 residue.[10] The proton-transfer steps are required because, in an initial step, a proton neutralizes the anion phosphodiester, which results in a monoanion phosphorane transition state.[10] Note that proton transfers either between the His-12 residue and the O2′ or between the His-119 and the O5′ are not relevant here because these steps ultimately break a P–O bond. In order to test the electronic behavior of the five-coordinate TS in the simplest manner, we retain all X–O bonds and study the proton transfer between the His-119 residue and the TSA. This transfer is assumed[10] to occur from an equatorial oxygen in the TSA to the His in the cyclization reaction and from the His to the TSA in the hydration step.

The proton-transfer energy curves for five-coordinate P and V complexes that model the TSA of the enzyme are calculated for the equatorial bond. The model is intended to test the comparability of the electronic structure between the V and P models of the TS for the X–O(H) equatorial bonds. The model is simple and does not consider the mechanistic questions regarding the location and flexibility of the His and Lys residues or the actual mechanism for proton transfer as it may occur in the enzyme. The vanadate dianion may have only a transitory existence during the transfer of a proton between equatorial and axial sites. No stable five-coordinate intermediate dianion has been found for ethylene phosphate,[11] but a weakly bound intermediate is found when a methoxy is substituted for a hydroxyl ligand.[12] Since a proton is being transferred, this test measures the comparability between V and P of the electrostatic potential near the equatorial X–O(H) bond for a fixed X–O geometry. We shall determine how the TSA responds to the tests proposed here and in what sense the vanadate can be considered a transition-state analogue.

Table I. Net Atomic Populations

	charge		
	P	V	
	−1	−1	−2
X	1.57	1.42	0.93
O	−0.86	−0.63	−0.60, −0.63
$O(H)_{eq}$	−0.81	−0.89	−0.87, −0.87
$O(H)_{ax}$	−0.98	−0.93	−0.93
H_{eq}	0.46	0.48	0.33 (av)
H_{ax}	0.48	0.44	0.30 (av)

Table II. Electrostatic Potentials at the H-Bond Distance (kcal/mol)[a]

	P	V
O	−155	−85
$O(H)_{eq}$	−95	−95
$O(H)_{ax}$	−105	−105

[a] 1 kcal = 4.184 kJ.

Table III. Basis Set and Correlation Dependence of Polarity

	dipole moment, D	
	SCF	CISD
	DZ(O)	
H_2POH	3.03	2.96
H_3PO	4.93	4.46
VH_2OH	2.19	2.34
VH_3O	2.37	1.19
	DZP(O)	
H_2POH	2.67	2.65
H_3PO	4.49	4.21
VH_2OH	2.24	2.34
VH_3O	2.10	1.22

2. Method

The $H_4XO_5^-$ monoanions energy-gradient optimized to a trigonal-bipyramidal structure for both X equal to P and V in self-consistent-field (SCF) calculations using the Hondo[13] and Gaussian-82[14] molecular orbital codes. This symmetry was not imposed on the monoanions. As seen in Figure 1 the V and P five-coordinate monoanions are structurally similar. The axial and equatorial X–O(H) bond lengths differ between 0.15 and 0.2 Å for V and P, but the Mulliken populations in Table I and the electrostatic potentials shown in Figure 2 strongly suggest that these bonds have a similar polar electronic structure. The potentials in Table II evaluated at an H-bond distance of 2 Å from O for V and P complexes show very similar values off the hydroxyl ligands. No symmetry was imposed on the dianions and local minima were found for the vanadium compounds.

Compact effective potentials (CEP) were used in place of the chemically unimportant core electrons. The CEP and concomitant basis sets have been generated for all the main-group and transition-metal elements from hydrogen through radon.[15] For vanadium the Ne core is replaced by the CEP leaving the 3S, 3P, 3D, and 4S orbitals in the valence space.

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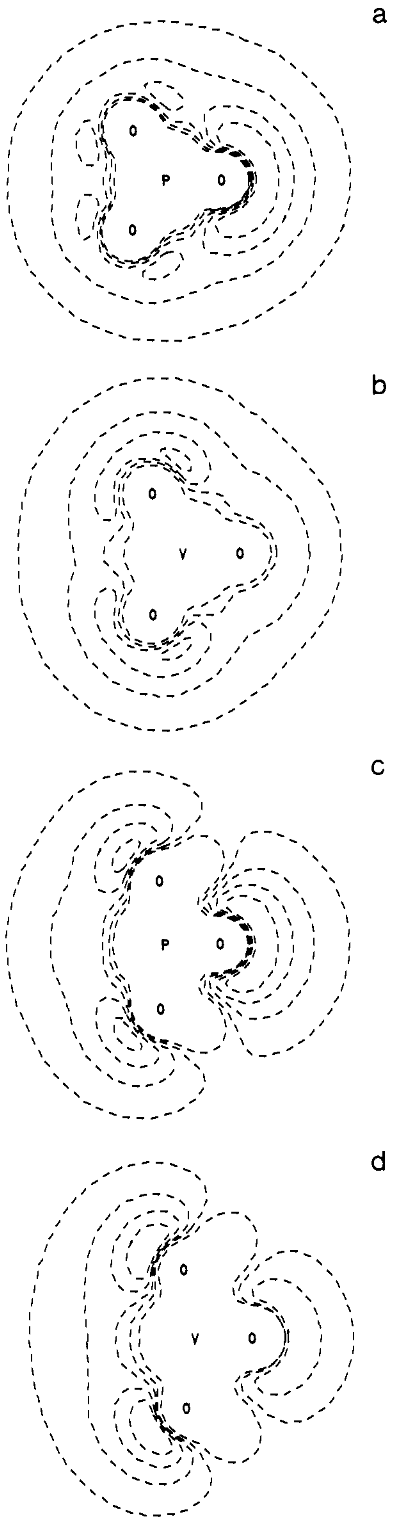

Figure 2. Electrostatic potential for $H_4XO_5^-$: (a, b) equatorial plane P and V respectively; (c, d) plane containing axial and O–(X) oxygens. The outermost contour is −50 kcal/mol and successive contours decrease by 25 kcal/mol.

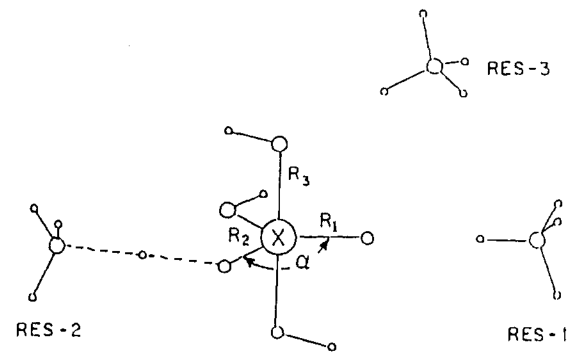

Figure 3. Schematic representation of model for proton transfer. Two ammonium ions are bound to the $H_4XO_5^-$ anion, one to an axial oxygen and the other to an equatorial oxygen. A third ammonia shares a proton with an equatorial oxygen and the potential curve for this proton transfer is calculated. Distances and angle given in Table I. The three residues that are modeled are RES-1 Lys-41, RES-2 His-119, and RES-3 His-12.

The 3D basis set uses the 6d primitive set determined by Rappe et al.[16] with the contraction coefficients obtained in atomic SCF calculations with the CEP. This basis is sufficiently flexible to represent both covalent and ionic bond possibilities. The energy gradient optimization of the monoanion was initially done with the CEP equivalent of a double-ζ basis (CEP-31G), but the addition of first a polarization function to oxygen ($\zeta = 0.75$) and then a diffuse function ($\zeta = 0.057$) was found to alter the distances only slightly and not alter the qualitative relationship between the P and V anion electrostatic potentials. A single polarization function was also used for phosphorus ($\zeta = 0.60$) but again comparison with calculations with two d functions showed little effect on the properties under consideration. The basis with a single polarization function for P and O was used for the calculations of both the proton-transfer curves and, for that reason, the electrostatic potentials reported here.

The effect of correlation on the X–O bond was examined by comparing the dipole moment for $H_4XO_5^-$ (X = P, V) at the SCF and MP2[17] levels of accuracy. The size of the five-coordinate complex precluded a more accurate correlation calculation with the polarization functions on oxygen. This was done by examining, in Table III, the variation of the dipole moment for the H_3XO and H_2XOH systems as a function of oxygen polarization functions between the SCF and an all single and double excitations configuration interaction calculation (CISD). These comparisons provide a simple way of determining the change, if any, of the bond polarity as a function of correlation of the electronic wave function. We expect the dipole moment will not change much for the semiionic bond or single polar bonds for X–O(H) but will alter if the covalent bonding increases for the X–O bond. Correlation only affects the dipole moment in H_3VO.

The interaction of the active-site cation residues with the P or V five-coordinate complex is modeled by a cluster of two ammonium ions and an ammonia bound to a H_4XO_5 monoanion (X = P or V) as seen in Figure 3. As suggested by the RNase A mechanism,[9] two of the cations are bound to equatorial ligands to represent the Lys-41 and His-119 interactions. The ammonium cation representing the Lys-41 interacts in a fixed fashion with an X–O bond, while the other ammonia represents the His-119. The proton is transferred from the oxygen to the ammonia model of His-119 without altering the complex geometry in any other way. This is considered sufficient to compare the relative behavior between the P and V monoanion complexes without examining the actual proton path, which would be affected by relaxation of the five-coordinate complex. A third ammonium is bound to the axial O–H ligand and represents the His-12 residue. The overall charge of the complex is +1 as assumed in the mechanism.[9] The calculated geometries of the monoanion five-coordinate complexes were initially fixed for the model of the interacting complex. The final complex geometry was obtained by setting all the (X)O···H(N) distances to 2 Å. For the hydroxyl ligands the (N)H–O–V angles (RES-2 and -3) were set to 120° and 180° for the P–O and V–O oxygens (RES-1). The proton on the axial ligand bound to an ammonium cation (RES-3) is rotated 180° and relaxed to avoid the repulsive interaction with the cationic proton. The proton is transferred linearly between N and O (RES-2). This leads to a slight discrepancy with the optimized bond angle of about 106° for both V and P monoanions when the proton is on the oxygen.

Ammonia or ammonium cations described by a self-consistent-field (SCF) wave function with a STO-3G basis set have been found to represent binding behavior of imidazole to metal cations.[18] This simple basis will also be used to model lysine since we are more concerned with comparative behavior than the absolute interaction energies. Other important H-bonding and protein environmental interactions are also ignored by assuming that the comparative behavior of the P and V complexes will not be affected.

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3. Results and Discussion

The bond lengths are most similar for the P–O and V–O bonds but the Mulliken populations and examination of the dependence with correlation of the electronic structure of these bonds described below show that the electronic structure of the P–O and V–O bonds are fundamentally different. All the V–O distances are in reasonable agreement with a hypothesized structure[1] and with values recently reported for a comparable trigonal-bipyramidal structure.[19] The calculated V–O bond length of 1.560 Å compares well with a value of 1.576 Å found in a pinacol–vanadium complex. Considering the constrained nature of the remaining V–O bonds, the measured axial distance of 1.960 Å can be compared with the calculated value of 1.904 Å. It is interesting to note that even for oxovanadium(IV) trigonal-bipyramidal structures, the V–O multiple bond distance is 1.59 (ref 20) and 1.60 Å[21] suggesting a similar electronic structure for this bond. An equatorial bond distance is 1.92 Å, but this large bond length is determined, in part, by bidentate ligand binding.

The geometry of the vanadate complex with RNase is uncertain[2,3] because an appropriate model structure was not available to initiate the crystallographic refinement, but protein data bank values are available in one case[4,22] and were communicated to Crans et al.[15] in the other. Since these vanadium–oxygen bond lengths suggest the vanadate in the crystal is the dianion,[4,15] energy gradient optimization determined stable dianion intermediates deprotonated at either two equatorial oxygens (vee) or at one axial and one equatorial oxygen (vae). These intermediates are asymmetrical structures whose internal coordinates are provided in the supplementary material. Internal hydrogen bonding is important for these models. For example, in the vee structure one axial hydrogen atom orients toward the more polar of the two O–V bonds, which also has the larger bond distance. The second axial hydrogen interacts with the more polar equatorial hydroxyl oxygen and the equatorial hydrogen interacts with the most polar axial hydroxyl that has the longest O(H)–V bond distance. Another vee structure is found by rotating and optimizing the axial hydrogen so it points toward O–V. The vae structure that is presumably observed in the crystal is about 1 kcal/mol lower in energy. Mulliken populations in Table I for both vae and vee dianion structures differ from those of the monoanion, with smaller positive values for hydrogen suggestive of more polar hydroxyl ligands and larger negative values for O(–V). The structures are substantially distorted from trigonal bipyramid. The two V–O bond lengths in vae are 1.62 and 1.65 Å and the equatorial V–O(H) lengths are 1.93 and 1.99 Å. Experimental values in the RNA–uridine vanadate complexes differ by about 0.1 Å with the short bonds reported as 1.70 (ref 15) and 1.75 Å,[3] while the long bonds do not exceed 1.89 (ref 15) and 1.91 Å.[3] It is interesting to note that the longest calculated axial V–O(H) bond has a length of 2.03 Å. The angle between the axial oxygens (∠O7–V–O9) is about 148°, which is to be compared to an angle of 149° in the pinacol complex and 162° in the uridine–vanadate complex.[15] Electronically, both calculated dianion structures resemble a distorted $H_2VO_4^-$ interacting with a OH^-. This is the analogue of the phosphorus dianion, which dissociates to phosphate and hydroxyl anions.[10] The dianion structure in the crystal is stabilized by the hydrogen bonds, and the long V–O bond that corresponds to the dissociating OH^- is not found.

The electronic structure of the monoanions can be compared at the SCF level by examining the atomic populations and the closely related electrostatic potentials. Comparison of the V and P populations in Table I shows a substantial difference only at the V–O or P–O bond with V–O substantially less polar. However, the V and P orbital populations for both the equatorial and axial O(–H) atoms are much closer. Electrostatic potential maps in Figure 2 support these conclusions. The electrostatic potentials are similar for both the V and P at the equatorial and axial hydroxyl oxygens and the potential is substantially reduced at the hydrogen-bonding distance of 2 Å off the V–O oxygen as seen in Table II. Mulliken populations are similar for all oxygen sites between the monoanion and dianion. Another indication that the electrostatic potential off O–V is weaker than for O(H)–V is the propensity for internal hydrogen bonds to go to hydroxyl oxygens when feasible. Hydrogen bonding will then be similar between P and V at all the O(H)–V sites but not at O–V in the dianion as well as in the monoanion. But this site is involved in the apparent discrepancy in the positions of His-12 and Lys-41. The weaker H-bonding interaction to equatorial O–V could allow other protein forces to determine the relative positions of His-12 and Lys-41.

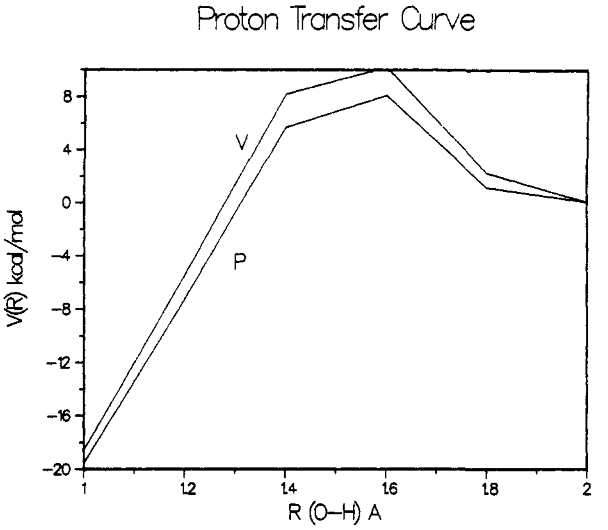

Figure 4. Proton transfer from oxygen on TS to nitrogen on ammonia modeling the His-119 residue.

The difference in the electrostatic potential near the X–O bond for V and P at the SCF level suggests that V–O is not described as a semiionic bond. The extent of covalent bonding was tetsed by calculating the dipole moment for the two ions in the DZP basis at the MP2 level of correlation. For $H_4PO_5^-$ the dipole moment change from SCF to the MP2 is only 0.02 D. The orbital populations support the semiionic model where substantial charge, of the order of two electrons, is transferred from the phosphorus to the OH ligands. The remaining three electrons are hybridized sp^2 and make three single bonds in the equatorial plane to O^- and the two OH ligands. The axial OH ligands are more ionic but donate about half an electron back to the phosphorus, which manifests itself as d population because of the highly polar nature of the phosphorane anion.

The gross atomic population for the central atom is similar for the vanadium and phosphorus monoanions. The valence s electrons are substantially ionized but the three electrons on the vanadium are in d orbitals and the back donation is into p orbitals on the vanadium. The MP2 dipole changes by 0.9 D or nearly 50%, reflecting a covalent V–O bond. A correlated electrostatic potential would be even less polar than the SCF values depict. It is evident that H-bonding to the V–O bond would not be comparable to that for P–O in the phosphorane transition state. The observation of the Lys-41 bound to this position for the vanadate inhibitor is not relevant to H-bonding to the phosphorane transition state.

Concern that the conclusions regarding the electronic structure of the X–O and X–O(H) bonds could be altered by the addition of polarization functions or the level of correlation is allayed by the results in Table III. The dipole moments vary substantially with correlation only for the V–O bond in H_3VO. This is the same conclusion reached with the MP2 calculation on the five-coordinate complex. The correlation calculation reinforces the conclusion from the SCF data that H-bonding preferences to the V–O oxygen

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does not provide any information on the mechanism because this bond is not as polar as the P–O bond. The vanadate is not a TSA in this aspect of its behavior.

To test the interaction with the His-119 residue, five points along the proton transfer curve from oxygen to nitrogen were calculated by using the model shown schematically in Figure 3. As seen in Figure 4 the energy curves for both P and V complexes are very similar. The similarity in the proton-transfer energetics occurs in spite of differences in the X–O(H) bond lengths between the P and V five-coordinate monoanions. The relative energy origin is arbitrarily set for the proton 1 Å from the nitrogen. As the proton is moved to the oxygen, it first passes through a maximum at about half the distance. The attraction of the dianion then takes over rapidly with the equilibrium position of the proton on the oxygen in this model. The binding energy to oxygen is relatively so large that it is evident that either the proton shuttles between equatorial and axial oxygen sites only within the influence of the His or large additional interactions must be considered for the proton to shuttle between the phosphorane TS and the His-119 residue as contemplated in the mechanism. An obvious candidate is the Asp-121 that is H-bonded to His-119.[23,24] The Asp stabilizes the protonated state of the His-119 but is not part of a charge relay.[24] In agreement with Umeyama[24] the present results suggest that the potential of the Asp is an important part of the mechanism if an initial proton transfer is required to neutralize the phosphate anion. Substituting Asn or a less polar group for Asp should inhibit the proton transfer from the TS and therefore the initial cyclization reaction. Stabilizing the vanadate monoanion would produce a structure closer to the TSA. Apparently the vanadate monoanion is the dominant species in solution,[4] suggesting the Asp is shielded from the monoanion. We conclude that the five-coordinate monoanion is both an electronic and a structural TSA with regard to interaction of His-119 with an equatorial oxygen ligand.

4. Conclusion

The five-coordinate vanadate inhibitor is found electronically to have both similarities to and differences from the phosphorane. The observed Lys-41 and His-12 orientations, which generated the initial interest, are not found relevant to the RNase A mechanism. Since the electrostatic potential at H-bonding distances of O–(V) for both monoanion and dianion vanadates are considerably smaller than expected for O–(P) in the transition-state phosphorane, the flexible Lys-41 side chain can search for and, apparently, bind to the more electronegative axial O–(H) site. The position of this residue is, therefore, not probing the electronic properties of the transition state and irrelevant to the mechanism but another indication of the flexibility of this side chain.

On the other hand, H-binding of His-119 to O–(H) probes the transition-state electronic behavior since the electrostatic behavior at all other oxygen sites is similar for the vanadate and phosphorane, and the stabilization of the vanadate dianion provides an electronic view of the dissociating phosphorus dianion. Although the variations in dianion bond distances can be probed as the calculated structure varies from the monoanion, the P dianion rapidly tends to a dissociating $H_2PO_4^-$. Observation of the vanadate dianion in the crystal is supported by the calculation of a stable and energetically favored vae intermediate. The observation of His-119 proximity to both axial and equatorial oxygens is suggestive of the relative flatness of the potential in this region. For static binding the axial oxygen has the larger electrostatic potential, which supports the observed orientation of the H-bond, but the His-119 can readily interact with the equatorial position if the potential alters during reaction. The importance of the observation of the dianion and the vae form of the dianion, though, is dependent on the extent to which the V and P dianions are analogous. An H-bond-stabilized vae P dianion should also be lowest in energy, suggesting the His-119 binding in the crystal structure is probing one of the steps in the hydrolysis of the phosphate. Modification of the protein to stabilize the monoanion vanadate would be of interest since the transition state occurs with this ionicity at an earlier stage in the mechanism.

Supplementary Material Available: Tables of Cartesian and internal coordinates of the equatorial–axial and equatorial–equatorial five-coordinate vanadate anions (2 pages). Ordering information given on any current masthead page.

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Theoretical Determination of Partition Coefficients

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Abstract: The free energy perturbation method, implemented within a molecular dynamics framework, has been used to calculate differences in log *P*s between methanol, ethanol, and propanol partitioned between water and carbon tetrachloride. The calculated results agree with experiment to within 0.45 log P unit or about 3 kJ mol^{-1}. The difference in log P between methanol and ethanol was determined relatively easily. However, difficulties were experienced in extending the calculations to include the more flexible propanol molecule. A systematic variation of parameters was performed which highlighted the reason for the poor results, namely, the failure of the atomic charges to give a good description of the electrostatics in all conformations. This problem was overcome by using charges derived from the molecular electrostatic potential (MEP) for each conformation, weighted according to the appropriate Bolzmann population. It is proposed that these multiple conformation MEP derived charges will be useful in many other applications.

Introduction

Partition coefficients, which describe the partitioning of a solute between an organic and an aqueous phase, find extensive use in medicinal chemistry and drug design. It is often assumed that partition coefficients, and in particular those obtained for the water–octanol system, reflect the hydrophobicity of the solute molecule. The hydrophobicity is often used to describe the free energy changes involved in the movement of a drug from the aqueous phase to a lipid bilayer[1] but may also be important in the binding of the substrate to its macromolecular active site.

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