Evaluating transition state structures of vanadium–phosphatase protein complexes using shape analysis

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ABSTRACT

Shape analysis of coordination complexes is well-suited to evaluate the subtle distortions in the trigonal bipyramidal (TBPY-5) geometry of vanadium coordinated in the active site of phosphatases and characterized by X-ray crystallography. Recent studies using the tau (τ) analysis support the assertion that vanadium is best described as a trigonal bipyramid, because this geometry is the ideal transition state geometry of the phosphate ester substrate hydrolysis (C.C. McLauchlan, B.J. Peters, G.R. Willsky, D.C. Crans, Coord. Chem. Rev. http://dx.doi.org/10.1016/j.ccr.2014.12.012 ; D.C. Crans, M.L. Tarlton, C.C. McLauchlan, *Eur. J. Inorg. Chem.* 2014, 4450–4468). Here we use continuous shape measures (CShM) analysis to investigate the structural space of the five-coordinate vanadium–phosphatase complexes associated with mechanistic transformations between the tetrahedral geometry and the five-coordinate high energy TBPY-5 geometry was discussed focusing on the protein tyrosine phosphatase 1B (PTP1B) enzyme. No evidence for square pyramidal geometries was observed in any vanadium–protein complexes. The shape analysis positioned the metal ion and the ligands in the active site reflecting the mechanism of the cleavage of the organic phosphate in a phosphatase. We identified the umbrella distortions to be directly on the reaction path between tetrahedral phosphate and the TBPY-5-types of high-energy species. The umbrella distortions of the trigonal bipyramid are therefore identified as being the most relevant types of transition state structures for the phosphoryl group transfer reactions for phosphatases and this may be related to the possibility that vanadium is an inhibitor for enzymes that support both exploded and five-coordinate transition states.

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1. Introduction

The hydrolysis of phosphate esters is established to go through five-coordinate phosphorus species and is recognized and referred to as the transition state geometry [1–5]. Because phosphorylation [6] is one of the key signal transduction messages [7], this reaction has an essential place in life-processes [8–11] on top of being an interesting reaction interconverting fundamentally different geometries. Although the ideal geometry of such transition states has the phosphorus or the metal replacement in a perfect trigonal bipyramidal (abbreviation recommended by IUPAC as TBPY-5) geometry, studies more often demonstrate that the TBPY-5 structures are distorted from the ideal geometry [12,13]. Many experimental [14–22] and theoretical experiments [3, 23–29] have been conducted to understand the reaction mechanism for phosphate ester hydrolysis [30–33], with some divergent conclusions, due to the multiple plausible mechanisms and subtle differences in experimental systems as protonation state and leaving group for phosphate ester hydrolysis varies [3]. Recent studies have used data

mining procedures to describe the vanadium–phosphatase complexes [12,34,35]. Because five-coordinate geometries are either TBPY-5 or square pyramid (abbreviated by IUPAC as SPY-5), both geometries should be possible for vanadium to adopt in the protein active sites [12], although distortions in-between are also possible and, in fact, most frequently observed [34]. In small molecule (model) systems, geometric restrictions are generally attributed to coordinating ligands that distort the metal ion coordination environment, however, in a protein-complex such coordinating ligands are typically the protein. In the case of the phosphatases, the protein is generally coordinated in a monodentate manner, and such distortion would be expected to be minimal. However, as recently reported, the vanadium bound to phosphatases so far have been found to be in a TBPY-5 or distorted TBPY-5 geometry [12], even though the corresponding small molecules are overwhelmingly observed to have the square pyramidal geometry (SPY-5) [34]. In the present manuscript we examine the distortions observed in the vanadium bound in phosphatase complexes using the continuous shape measures (CShM) approach and examine how these distortions fall along the reaction pathway from a tetrahedral (unbound) to trigonal bipyramidal geometry (bound).

Describing the geometry of five-coordinate complexes can be nontrivial because the geometries are often distorted from the ideal TBPY-5 and

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SPY-5 geometries. A well-known class of distortions includes those along the Berry interconversion path between TBPY-5 and SPY-5 geometries (Scheme 1a) [36,37]. The simple index angular parameter, tau (τ), was introduced by Addison et al. to calculate any potential distortion, where $\tau = (\beta - \alpha) / 60$ [38], although there are some limitations to τ. At one extreme as shown in Fig. 1a, $\tau = 0$ for a simple ideal SPY-5 geometry: where B, C, D, E, and M are co-planar, and the two basal angles α and β (Fig. 1a) are each 180° [38]. For the ideal TBPY-5 geometry, $\tau = 1$ because the α and β angles (as shown in Fig. 1c) lead to $\tau = (180 - 120) / 60 = 60 / 60$. The more common distorted structures which fall "in between" these extremes, then, will have a τ value between 0 and 1. The choice of co-planar B, C, D, E, and M is one area of contention of the definition of this structure for the SPY geometry (Fig. 1b) and can perhaps be argued to be less defined, so other methods such as the CShM method can be used to better describe these systems (Scheme 1b, c and d) [39,40]. However, because of the simplicity of the τ analysis, distortions other than those on the Berry pathway are not properly identified in the simple τ analysis.

The CShM is a quantitative measure that investigates distortions in a material and provides an output deviation value, S [41–44]. The material can be composed of simple or more complex molecules. A molecule can be subjected to a range of distortions including those found on the Berry pathway between the TBPY-5 and SPY-5 of a vanadium compound [41–44]. Depending on the molecule the distortion can be minor or more extensive and the S value small or large. Specifically, this analysis is based on the application of shape measures to determine how far or how close the geometries are from an ideal polyhedral shape, e.g. the D_{3h} TBPY-5 for a compound with five identical ligands. This analysis therefore calculates the distance to this ideal reference shape, independent of size and orientation [45]. That is, the analysis simply calculates the distances between observed positions such as M–X and M–Y and compares them to the ideal location of a particular shape M–X_0 and M–Y_0. The CShM analysis allows us to compare (on the same scale) the distortion of different molecules from the same ideal shape, or of the same molecule to different shapes [43]. The calculation, then, provides a deviation to the particular shape investigated as output, S. For example, if the geometry is at the ideal 5-coordinate TBPY-5 geometry then the shape measure relative to the trigonal bipyramid is S(TBPY-5) = 0. Because the shape analysis is based on the use of atom positioning, when examining the positioning such as that in the bond lengths involved in bond breaking and bond forming processes (e.g. those in phosphate ester hydrolysis) the analysis is now directly examining the reaction coordinate of a reaction. The reaction progress can therefore easily be addressed by a shape analysis.

In this work we obtain numerical values using CShM analysis [42] for the pentacoordinate vanadium molecules that are phosphate ester hydrolysis transition state analogs. The CShM approach provides a means for handling the cases where, for example, a metal ion is placed in an environment that is ill-defined with regard to the coordination geometry. Such cases often contain several secondary interactions to Lewis bases at distances significantly longer than those expected for a chemical bond, i.e. larger than the sum of the atomic covalent radii by 0.2 Å or more [43]. Within such a framework, CShM allows one to compare in a quantitative way the distance between a set of atoms from that given in an ideal shape (i.e., a polyhedron). One of the advantages of such an approach is that one can in many instances accurately describe structures that are along the path of interconverting two polyhedra with the same number of vertices (e.g., trigonal bipyramidal, TBPY-5, to square pyramidal, SPY-5) [43]. Although this method is generally used for the evaluation of inorganic materials, this approach could be used to examine the metal ion geometry in the active sites of proteins.

The comprehensive exploration of the different distortions of the trigonal bipyramid of vanadium placed in the active sites of the vanadate–phosphatase complexes was exemplified by the reaction pathway of the protein tyrosine phosphatase 1B abbreviated PTP1B [46–49]. The PTP1B is the key protein tyrosine phosphatase that is implicated in the insulin enhancing properties of vanadate and vanadium complexes [50–55]. We therefore propose to use shape measures analysis S(TBPY-5) to provide insights on the distortion of the systems along the reaction pathway, which unlike the τ analysis will also involve distortions other than those defined by the Berry pathway. That is, whereas τ analysis could not differentiate between the two SPY-5 forms shown in Fig. 1a and b, CShM would conclude that only Fig. 1b is SPY-5 (S(SPY-5) = 1.74 vs. S(SPY-5) = 0). Furthermore, the CShM analysis defines an alternative ideal square pyramid to that of Fig. 1a, referred to as a vacant octahedron (vOC-5), and also to explore all intermediate square pyramids
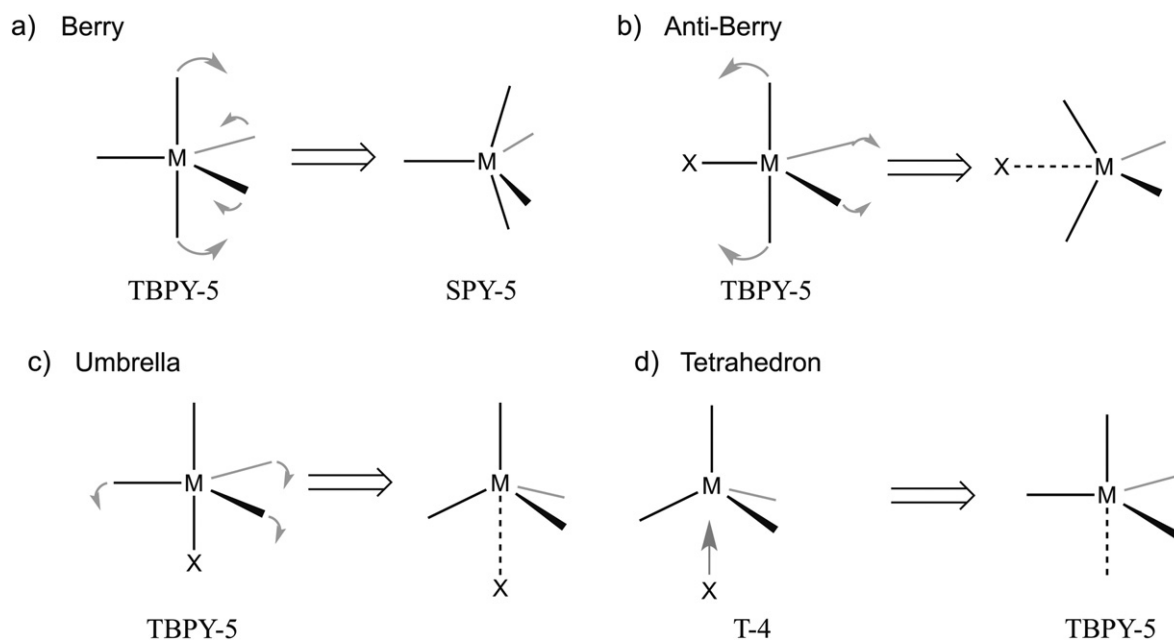
Scheme 1. Distortions to the TBPY-5 geometry are illustrated. (a) the Berry distortion; (b) the anti-Berry distortion; (c) the umbrella distortion and (d) the conversion pathway describing the tetrahedron to TBPY-5.