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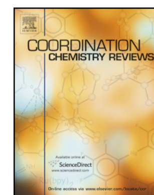

Review

Vanadium–phosphatase complexes: Phosphatase inhibitors favor the trigonal bipyramidal transition state geometries

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Contents

1. Introduction 164
2. Fundamentals of phosphate ester hydrolysis; reaction, transition state and categorization 165
   2.1. Enzyme-catalyzed hydrolysis of phosphate esters 165
   2.2. Enzyme categorization of phosphatases 166
   2.3. Five-coordinate transition-state geometry – ideal and alternative possibilities 166
   2.4. Speciation of vanadate, vanadyl cation and vanadium complexes 167
   2.5. Methods of inhibition of phosphatase 168
3. X-ray structural characterization of protein–inhibitor complexes: resolution and experimentally imposed limitations 168
4. PDB structures of phosphatases containing a bound vanadium 170
   4.1. Search parameters 170
   4.2. Descriptors of structurally characterized species 173
      4.2.1. Nitrogen-containing active sites 173
      4.2.2. All-oxygen-containing active sites 173
      4.2.3. Sulfur-containing active sites 176
5. Inhibition of phosphatase by vanadium compounds 178
   5.1. Measuring inhibition of vanadium compounds 178
   5.2. Oxoanions (phosphate, arsenate, vanadate, chromate, molybdate and tungstate) 178
   5.3. Vanadium complexes 193
6. Discussion and future 194
7. Summary 195
   Acknowledgements 196
   References 196

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ABSTRACT

Over the past two decades increasing information about the function and structural detail of phosphatases has become available detailing the interaction with vanadate or other vanadium compounds. Considering the importance of the phosphorylation reaction in signal transductions the structural details of the interaction of vanadate or other vanadium species with many phosphatases are used to provide information on the nature of successful inhibitors of these enzymes. Analysis shows that most of the available X-ray

Abbreviations: acac, acetylacetonate; ALP, alkaline phosphatase; AcP, acid phosphatase; AttoPhos, 2′-[2-benzothiazoyl]-6′-hydroxybenzothiazole phosphate; CCSD, Cambridge Crystallographic Structural Database; Cys, cysteine; DEA, diethanolamine; DiFMUP, 8-difluoro-4-methylumbelliferyl phosphate; DNM, dinuclear metal; EC, Enzyme Commission; EDTA, ethylenediaminetetraacetic acid; FDP, fluorescein diphosphate; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HEPPS, 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid; HPP, hexose phosphate phosphatase; K_i, dissociation constant of enzyme–inhibitor complex; MES, 2-(*N*-morpholino)ethanesulfonic acid; MOPS, 3-(*N*-morpholino)propanesulfonic acid; MUP, 4-methylumbellifery phosphate; NPP, nucleotide pyrophosphatase/phosphodiesterase; NG, not given; PDB, Protein Data Bank; PEG, polyethyleneglycol; PEP, phosphoenolpyruvic acid; *p*NPP, *para*-nitrophenylphosphate; PTP, protein tyrosine phosphatase; RNA, ribonucleic acid; RPTP, receptor-like protein tyrosine phosphatase; SP, square pyramidal; TAPS, (2-hydroxy-1,1-bis(hydroxymethyl)ethyl)-amino-1-propanesulfonic acid; TBP, trigonal bipyramidal; Tes, (2-{[2-hydroxy-,1-bis(hydroxymethyl)ethyl]amino}ethane-sulphonic acid); Tris, 2-amino-2-hydroxomethyl-propane-1,3-diol.

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structures of vanadium–phosphatase complexes contain vanadium with five coordinating atoms in trigonal bipyramidal coordination geometries even though corresponding small molecule analog compounds may have square pyramidal geometries. This finding for the static structures in their solid state documents the fact that the variety of phosphatases all stabilize a vanadium geometry that is closer to the trigonal bipyramidal geometry than square pyramidal geometry. We also review the efficacy of vanadium-based inhibitors and examine both oxometalates and vanadium coordination complexes. The evaluation of the inhibitory efficacies of the oxometalates provides the opportunity to identify product-based inhibitors and transition-state-based inhibitors. Whether initial coordination geometry is important to inhibitor design geometry was examined. For vanadium–phosphatase complexes, regardless of what form was added to the protein crystal in all but one case vanadate was found bound in the phosphatase. Because of speciation considerations and prior hydrolysis of potential vanadium complexes, this result may be a consequence of the experimental conditions. With regard to inhibition we find that the coordination geometry of the starting complex does not need to be trigonal bipyramidal to result in a effective phosphatase inhibitor and that all reported phosphatase inhibitors span a range of only three orders of magnitude in K_i across all phosphatases examined.

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1. Introduction

Removing a phosphate group from a biomolecule is a central reaction in biology and catalyzed by a range of enzymes, collectively named phosphatases [1–5]. Phosphorylation/dephosphorylation is currently recognized as a major metabolic control system that activates or inhibits metabolic reactions by affecting the phosphorylation state of metabolites and enzymes [1,6–8]. A number of chemical signaling systems have been used throughout molecular evolution. Examples include ribosylation, adenylation, isoprenylation and methylation [9]. Because phosphorylation introduces a charge and sometimes even a double charge, often a dramatic change of a protein properties result, which will impact how the different parts of protein folds associate with each other and the protein surface. Specifically, in some cases phosphorylations change a hydrophobic surface or neutral surface into a hydrophilic surface, thus destroying an interaction that may have been favorable prior to the phosphorylation [5,10]. Therefore, phosphorylation is a well suited process to alter properties of peptides and thus modulate the activity of enzymes in crucial metabolic pathways. For phosphorylation of proteins, several different types of amino acid side chains are typically phosphorylated inducing various regulatory responses in the cell; serine, threonine, tyrosine, and aspartate result in an O-phosphate group, histidine, arginine, and lysine result in an N-phosphate group, and cysteine results in a S-phosphate group, each of which result in a different response. Phosphatases are enzymes that remove these phosphate group by dephosphorylation [1,11], and thus important contributors in signal transduction pathways. This process supports a simple switch system, which is easily adopted to “turn on” and “turn off” important processes by phosphorylation/dephosphorylation of the enzymes in question. Alternatively, understanding the inhibition of these enzymes is important, and this manuscript concerns how vanadate and related vanadium compounds inhibit phosphatases [12–15].

The introduction of the charged phosphate group is also important for the small molecules of intermediary metabolism. For example, the intracellular phosphorylation of glucose by hexokinase is well known to trap glucose inside the cell as the charged glucose-6-phosphate, which is not recognized by the GLUT facilitated diffusion transporters located in the plasma membranes whether or not their presence in the plasma membrane is strongly insulin sensitive [16,17]. Whether the phosphorylated form of the metabolite or protein is active or inactive, it is critical to recognize that the dephosphorylated form will have the opposite action. Nature chose well because multiple chemical moieties (OH, NH, SH) can be phosphorylated making phosphorylation a widely applicable system with several levels of control. Indeed, the specificity of phosphatases is an important part of metabolic regulation and changing concentrations of substrates and inhibitors of phosphatases can have a large effect. Specificity of the phosphatases for a particular phosphatase inhibitor leading to an effect in some metabolic pathways, but not others is critical for this regulation. This process can occur if the inhibitor contains some recognition feature on the organic part of the substrate or a specific part of the enzyme as an allosteric regulator.

Of the alternative mechanisms for signaling processes, methylation is the system of choice for fine tuning metabolic signaling via epigenetic (or post-translational) modification [9,18]. Methylation is increasingly found to be important in other biological processes such as translation [19] and protein degradation of other cellular proteins [9]. Because methylation generally changes the hydrophobicity, the changes in peptide structure by methylation, although significant, will not be as large as the introduction of a charge. The change in hydrophobicity by a methyl group is however sufficient to affect the conformation and shape of the peptide fragment in a protein. Specifically, DNA is not likely to bind to hydrophobic regions in the histones. Although there are no charge changes in these modifications and interactions, increased hydrophobicity could modulate the affinity of the DNA for the histone protein and thus fine-tune the associations between hydrophobic surface in the histone and DNA. Therefore, from a chemical and biophysical perspective the choice of chemical modification distribution on major and minor signal transduction control pathways makes sense. The methylation of amines or thiols are changes that will affect the conformation choice of a peptide in contrast to the phosphorylation which dramatically affects the peptide properties; as a result methylation is used for fine-tuning the histone binding to DNA and phosphorylation is used as the major regulatory control in biological systems on a wide range of systems.

Because of the key role of phosphatases in signal transduction, it is not surprising that these enzymes have become a key target for studying metabolism [10], for modifying cell signaling [20,21], and for treatment of diseases [10,22]. Specifically, phosphatases have been targeted as an entry for treatment of diabetes [23–29] and trypanosomal diseases such as Chagas disease and leishmaniasis [30–34], often with vanadium species. Orthovanadate, the simple vanadium oxoanion often called just vanadate (VO_4^{3-}), is a well-known inhibitor of phosphatases [12–15], and because of its potency has been studied with many different enzymes [35,36]. The effects of vanadate have stimulated the development and testing of many other vanadium compounds as phosphatase inhibitors [37–40]. This review will investigate the reported X-ray structures of phosphatases with a vanadium bound in the active site as illustrated in Fig. 1 [41]. We chose to use X-ray crystallographic data, because they provide the opportunity to observe molecular details,

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