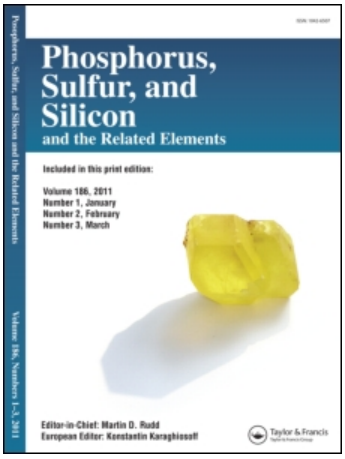

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Donor Interactions at Phosphorus. Implications Regarding Enzymatic Reaction Intermediates

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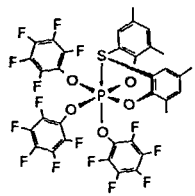
In recent work on the biological relevance of hypervalent phosphorus compounds, a new aspect of active site interactions of phosphoryl transfer enzymes undergoing nucleophilic attack is suggested by structural studies on phosphites, phosphates, and oxyphosphoranes which are shown to interact with donor groups to give higher coordinate geometries. The degree of coordination increases from phosphate to pentaoxyphosphoranes which model substrates and active site transition states, respectively. Thus a rate enhancement effect is anticipated due to stronger enzyme binding in the transition state-enzyme complex. The studies suggest that donor interactions at applicable active sites may assist in nucleophilic attack in causing a general loosening of P-O bonds undergoing cleavage to form products via a hexacoordinate transition state. Previously, only pentacoordinate intermediates have been invoked in nucleophilic displacement reactions of phosphoryl transfer enzymes. The results are illustrated with reference to the tyrosyl-tRNA synthetase system. Earlier, application to the enzymatic hydrolysis of cAMP was made.

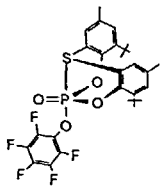
Keywords: phosphoryl transfer enzymes; donor coordination

INTRODUCTION

Nucleophilic displacement reactions of phosphoryl transfer enzymes invariably depict phosphorus in an activated state intermediate having a trigonal bipyramidal (TBP) geometry.[2] Recent studies on related series of phosphates and oxyphosphoranes, which may be regarded as models for enzyme substrates and transition states, respectively, show that coordination by nitrogen, oxygen, and sulfur ligands occurs.[2,3] The degree of coordination is much greater for oxyphosphoranes than that for phosphates[2] as measured by the shortness of the phosphorus-donor atom distance or the degree of structural displacement toward a higher coordination state, e.g., 1 compared to 2.[4]



P-S = 2.389(5); 82% octa
^{31}P, -93.0
1

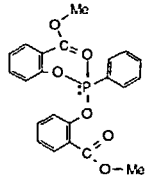


P-S = 3.085(2)Å; 37% TBP
^{31}P, -24.0
2

The implication is that if the nitrogen, oxygen, or sulfur atoms of active site residues of phosphoryl transfer enzymes interact at phosphorus to promote higher coordinate formation, a possible rate enhancement effect will result due to the tighter bonding in the activated transition state relative to that for the substrate.[2] Summaries of additional studies have been reported that support the premise stated above. Application is made here to the tyrosyl t-RNA synthetase system.[5]

CARBONYL OXYGEN ATOM COORDINATION AND THE TYROSYL-tRNA SYNTHETASE SYSTEM

X-ray analyses of bis(methylsalicylate-O)phenylphosphine ($OC_6H_4CO_2Me)_2PPh$ (**3**), revealed a pseudo trigonal bipyramidal structure due to coordination of a carbonyl oxygen atom at an axial site.[6] Comparisons with X-ray structures for carboxylate containing phosphorus compounds exhibiting oxygen coordination show the formation of four- and five-membered cyclic systems. Thus, **3** appears to be the first example of formation of a six-membered ring via carbonyl oxygen coordination. Reference is made to the tyrosyl-tRNA synthetase system where it is proposed that carbonyl oxygen atom coordination is a likely occurrence in the transition state based on the analysis presented in this work.[6]



P-O = 2.788(6)Å; 37% TBP

In the mechanism describing the activation of tyrosine in the tyrosyl-tRNA synthetase system,[5] the proposed transition-state complex involves formation of an axial P-O bond from the tyrosyl carboxylate group. This leads to cleavage of the opposite P-O linkage from a TBP intermediate. Based on the work,[6] it is likely that the carbonyl oxygen atom acts in a donor capacity and forms an additional coordinate bond at phosphorus to give a hexacoordinate formulation as shown in the figure.

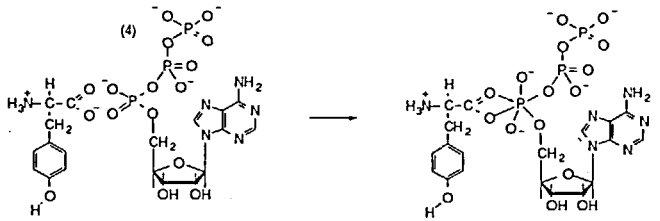
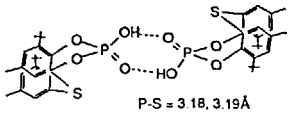


FIGURE. The ground state complex[5] and proposed transition state complex[6] in the activation of tyrosine by tyrosyl-tRNA synthetase.

ANIONIC PHOSPHATE FORMATION

In general, substrates and transition states at active sites of phosphoryl transfer enzymes involve anionic formulations rather than neutral entitites that we have described.[2] It is therefore of interest to determine the structural influence of anionic formation. Toward this end, we have synthesized and carried out the X-ray studies of the phosphate **4** and its anionic counterpart **5**.[7] Each contains the same flexible eight-membered ring system that interacts at the phosphorus atom and causes a structural displacement toward a TBP geometry, 30% TBP for the neutral phosphate **4** and 24% TBP for the anionic analog **5**. The respective P-S donor distances are 3.19Å and 3.28Å, an increase going to the anionic form of only 0.09Å. Thus, the decrease in the phosphorus atom electrophilicity due to anionic formation does not exert a major effect on the donor action. It is anticipated to even less in an oxyphosphorane due to the inherent higher electrophilicity at phosphorus caused by an increase in the number of electronegative ligands.



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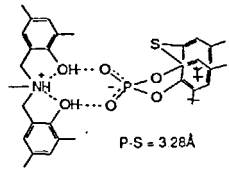

5

SULFUR DONOR ACTION VS HYDROGEN BONDING

It is noted that in the phosphates **4** and **5**, donor action from sulfur takes place in the presence of hydrogen bond formation. Hydrogen bond formation is a prevalent feature taking place at enzyme active sites. In structures like **4** and **5**, the effect of hydrogen bonding at the phosphoryl oxygen atoms is expected to very modestly increase the electrophilicity at phosphorus, thus promoting donor coordination. Hence, if a nearby residue is properly positioned at an active site of a phosphoryl tranfer enzyme, the presence of hydrogen bonding should not act as a strong deterent to donor atom coordination.

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References

[1] This presentation represents the award address of Robert R. Holmes who was the recipient of the 1997 International Council on Main Group Chemistry (ICMGC) Award for Excellence in Research.
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