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Hexacoordinate Phosphorus via Donor Interaction. Implications Regarding Enzymatic Reaction Intermediates

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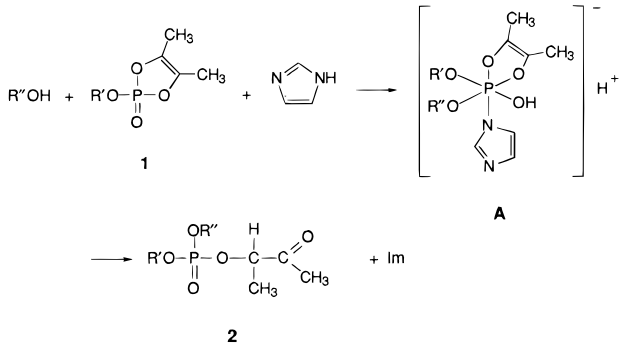
Introduction

This Account shows that donor interactions lead to higher coordinated states of phosphorus during reactions. This increase in coordination has important implications for mechanistic studies of nucleophilic displacement reactions of phosphoryl transfer enzymes. The latter mechanisms invariably depict phosphorus in an activated state intermediate having a trigonal bipyramidal (TBP) geometry.[1−7] For example, the proposed TBP transition-state complex in the activation of tyrosine in the tyrosyl−tRNA synthetase system[8] involves formation of an axial P−O bond from the tyrosyl carboxylate group. This leads to cleavage of the opposite axial P−O linkage. However, recent work[9] provides ample evidence of carbonyl group coordination in the absence of enzyme activity. If this occurs at the enzyme active site portrayed in Figure 1, a hexacoordinate transition-state complex will be formed. The likelihood of donor action existing at active sites of phosphoryl transfer enzymes will be considered in this account as well as the consequent effect on reaction rates.

In discussing mechanisms of nucleophilic displacement reactions of tetracoordinated phosphorus, pentacoordinated compounds have served as models for intermediates and transition states.[1−7] Although at one time pentacoordination for phosphorus was considered a rarity, there are now over 6000 known derivatives,[10] knowledge of which has greatly assisted in understanding the nuances of mechanistic variations for reactions of tetracoordinate phosphorus.

A much less studied area of phosphorus chemistry deals with the hexacoordinate state. Here the number of existing compounds is relatively small. A recent review by Cavell and co-workers[11] covers approximately 200 examples of neutral hexacoordinate derivatives. Associated with this area, a variety of studies have appeared in the literature that have dealt with nucleophilic displacement reactions of pentacoordinated phosphorus where hexacoordinate states have been invoked as controlling features.[3,12−19] Most of these studies have centered on oxyphosphoranes. In addition, there are studies of reactions of tetracoordinate phosphorus which have been considered to involve hexacoordinate states.[3,20−24] For example, nucleophilic catalysis of the phosphorylation of alcohols by the cyclic phosphate **1** in the presence of imidazole was proposed by Ramirez et al.[20] to proceed with ring opening via the hexacoordinate intermediate **A** to give **2**. The imidazole catalyst acts in a nucleophilic assisted attack at phosphorus by the alcohol. Ramirez and co-workers[20] infer that analogous mechanisms may be important to the behavior of some enzymes that are involved with phosphoryl group transfer whereby amino acid residues enter into the catalytic activity. The intervention of both five- and six-coordinate species is suggested.



Hexacoordinate Phosphorus

Nitrogen Donor Action. Such reactions could benefit immeasureably from a more in-depth knowledge of factors important in stabilizing hexacoordinate vs pentacoordinate phosphorus. A beginning in this area has been made where the donor atoms common at enzyme active sites have been employed to induce hexacoordinate formation. Chart 1 shows some examples, **3**−**7**.[25−29] Although nitrogen is illustrated in Chart 1 as the Lewis base atom, oxygen donor groups are also known in this context[3,11] and recently sulfur[3,25,30−38] and the sulfonyl group[38−40] have been studied in producing additional coordination. The latter work has been largely carried out in our laboratory with these two types of donor groups.

As illustrated in Chart 1, most of the previous work[3,11,25−29] has concentrated on restricted cyclic systems such that little flexibility existed in fixing the coordination site. By way of contrast, we have utilized more flexible ring systems containing the donor group which allows for different kinds of geometries and ring conformations. For example, recent work led us to the first pentaoxyphosphorane (**8**)[41] that had a hexacoordinate geometry via nitrogen donor action. The nitrogen atom was part of a

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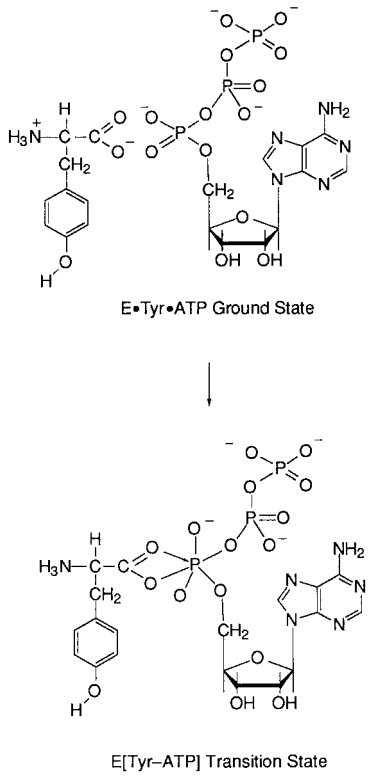
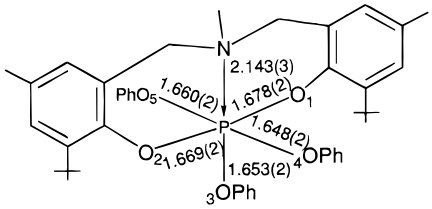


FIGURE 1. Ground-state complex[8] and proposed transition-state complex[9] in the activation of tyrosine by the tyrosyl−tRNA synthetase.

ten-membered cyclic system that coordinated to place the ring in a trans orientation. The P−N distance of 2.143(3) Å compares with 1.85 Å[42] for the sum of the covalent radii and 3.40 for the van der Waals' sum.[43]



N-P-O3 = 178.1(1)°; 73.4% octa

8

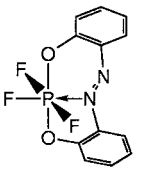
Sulfur and Oxygen Donor Action. With the presence of sulfur[3,30−38] or sulfonyl[38−40] groups as bridging ligands between aryl groups in eight-membered ring systems, we have allowed for non-coordinating conformations so that one could better evaluate the tendency for donor action to occur. For example, studies with oxyphosphoranes have yielded three types of geometries, two of which are non-coordinating trigonal bipyramids (TBP) with the cyclic component occupying either axial−equatorial (a−e) or diequatorial (e−e) sites, and one which is an octahedral geometry as a result of donor action. Representative examples that have been subjected to X-ray analysis are displayed in Chart 2.[30,32,39,40,44] Included are the percent octahedral formation derived from the X-ray parameters as discussed later. Donor coordination takes place in **9**,[32] **11**,[40] and **13**[39] leading to hexacoordinated compounds. Oxyphosphoranes **10**,[30] **12**,[40] and **14**[44] lack donor action and remain as trigonal bipyramids. Whenever donor action occurs in these systems, the ring conformation assumes a *syn*-boat shape. For derivatives lacking donor coordination, the ring usually is in an *anti*-chair conformation. However, **14** is an exception and has the rings in *syn*-boat conformations even though no sulfur coordination takes place. The P−S distances for **14** approach the sum of the van der Waals radii of 3.75 Å.[43] The range over which the phosphorus−donor atom distance varies in the coordinating forms is from 3.04 to 2.36 Å for oxyphosphoranes containing a sulfur donor atom. When the sulfonyl oxygen atom acts as the donor atom, the range of P−O distances extends from 2.65 to 1.94 Å in oxyphosphorane molecules.

The structural data on these molecules were used to evaluate the degree of displacement along a coordinate from an ideal square pyramid (SP) toward a regular octahedron. The ideal SP is the one viewed in the absence of the incoming donor atom where the trans basal O−P−O angles are 150°.[45−47] The phosphorus atom in all of the structures studied is displaced from a mean plane of the four basal oxygen atoms toward the remaining oxygen atom which is trans to the incoming donor atom. An analysis[37] shows that the percent displacement from the SP toward an octahedron (% octa) varies from 24 to 76%[34,37] as the P−S donor distance decreases and from 28 to 82%[39,40] when the sulfonyl oxygen atom acts as the coordinating agent. Figure 2 indicates the degree of conformity of the P−S donor distance with the degree of displacement along the SP−octa trajectory for bicyclic oxyphosphoranes.[31,35,37] Extrapolation to 100% octahedral formation shows that a P−S donor distance of 2.08 Å would occur. This compares closely to the sum of the phosphorus and sulfur covalent radii of 2.12 Å.[42]

Use of this type of flexibility in a ring system that allows the donor atom a range of movement relative to phosphorus from the van der Waals' distance (which is 3.65 Å for sulfur) to the respective covalent bond distance of 2.12 Å allows for meaningful investigations of substituent effects. It is noted that **10** and **14** in Chart 2 have P−S distances for these non-coordinating oxyphosphoranes that are near the van der Waals' sum.

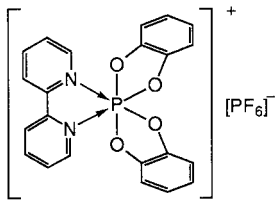
From these studies, it is determined that the sulfur atom is a stronger coordinating agent than the sulfonyl oxygen atom. This is established by noting that sulfur coordinates to give a hexacoordinated derivative when the sulfonyl group does not. For example, with the identical ligand composition other than the presence of a bridging SO_2 group in place of the sulfur atom, Chart 2 shows that **9** is hexacoordinate due to sulfur donor action, whereas **12** is pentacoordinate and lacks any donor coordination.[40] Other comparisons indicate the same result. Electronegativity effects in enhancing the Lewis acidity at the phosphorus center are apparent in increasing the formation of hexacoordination. Thus, **11**[40] in Chart 2 with three pentafluorophenoxy ligands shows much stronger P−O coordination (1.936(7) Å, 82% octa) compared to **15**,[39] which has three phenoxy ligands instead. Here the P−O

Chart 1



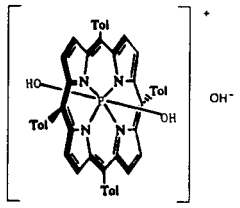
3 [25]

P-N, Å = 1.88(1), 1.95(1)
(Nitrogen positions disordered)



4 [26]

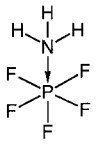
P-N, Å = 1.896(4), 1.898(4)



Ave. P-N = 1.89Å

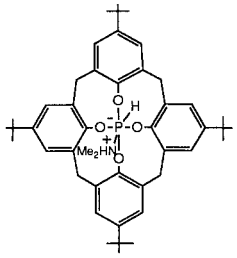
5 [27]

P-O (ave), Å = 1.693(4) ± 0.16



6 [28]

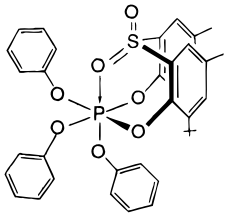
P-N,Å = 1.842(2)



Zwitterionic p-*tert*-butylcalix[4]arene-P(H)NHMe$_2$

7 [29]

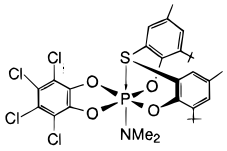
distance is 2.487(3) Å, over 0.55 Å longer, and the geometry is located approximately 44.5% toward an octahedron. The electronegativity effect is clearly evident



P-OSO = 2.487(3)Å; 44.5% octa

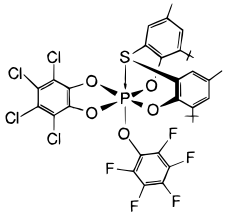
15 [39]

on going from pentaoxyphosphoranes to tetraoxyphosphoranes, where ligands of lower electronegativity replace attached oxygen atoms. This is seen in the tetraoxyphosphorane **16**,[35] which has an NMe_2 group in place of a pentafluorophenyl group in the pentaoxyphosphorane **17**.[48] This results in over a 0.2 Å shortening in the P−S distance in **17** relative to **16**.



P-S = 2.731(2)Å; 37.1% octa

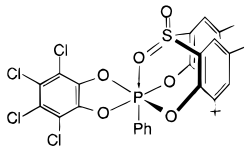
16 [35]



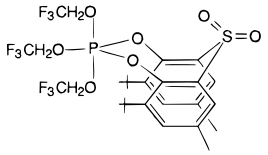
P-S = 2.494(3); 68.2% octa

17 [48]

Isomerism. In this illustration of the variety of factors controlling hexacoordinate formation, one other observation is worthy of consideration and has a bearing on the delicate energy balance between five- and six-coordination in these cyclic systems. Several oxyphosphoranes containing the sulfonyl group[39,40] as part of the cyclic system show evidence of the presence of isomers in solution from the observance of two closely spaced ^{31}P NMR signals in $CDCl_3$ solution. The ^{31}P signals for **18** [40] are −39.4 and −46.4 ppm. For **19**,[39] they are −73.1 and −85.5 ppm.



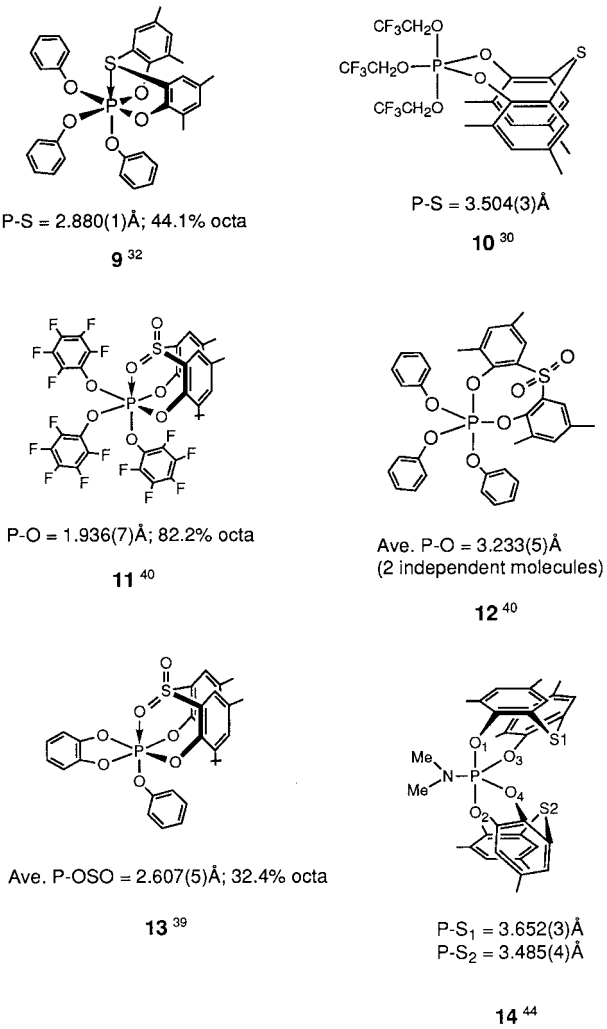
18 [40]



19 [39]

In view of the existence of trigonal bipyramidal geometries in the absence of sulfone donor action and the formation of octahedral geometries as a result of sulfone donor action, it seems most reasonable that the presence of isomers is due to these two representations. Their energies should be close to each other since the alteration of substituents either by way of subtle steric or electronegativity effects may induce the appearance of one form over the other. Cyclic phosphoranes with methylene[30,39] or sulfur[30−36] bridges in place of the sulfone group lack evidence for isomeric representations. Since the sulfur atom acts as a stronger donor in comparison to the sulfone group,[40] perhaps this factor acts to increase the

Chart 2



energy difference between penta- and hexacoordinated structures relative to those with the sulfone group. The lack of appearance of isomers for cyclic phosphoranes with a ring containing methylene bridge is expected since it does not act as a donor group to yield a hexacoordinated isomer.

By studying the VT ^{1}H NMR spectrum of **19**, an activation energy for the exchange between penta- and hexacoordinate isomers of 17 kcal/mol was obtained. The requirement to form the hexacoordinated geometry like **18** from the pentacoordinated geometry like **19** is for a conformational rearrangement of the eight-membered ring to take place such that the *anti*-chairlike form changes to a *syn*-boatlike arrangement. This process followed by sulfone donor action or accompanying it would allow conversion to the octahedral isomeric formulation.[40]

Pentacoordinate Phosphorus via Donor Action

Like that for oxyphosphoranes, recent studies have shown that phosphates (**20** and **21**)[49] and phosphites (**22**-**25**)[48,49] displayed in Chart 3 will coordinate with sulfur donor atoms present in the same flexible eight-membered ring system that was discussed above. The P−S distances span

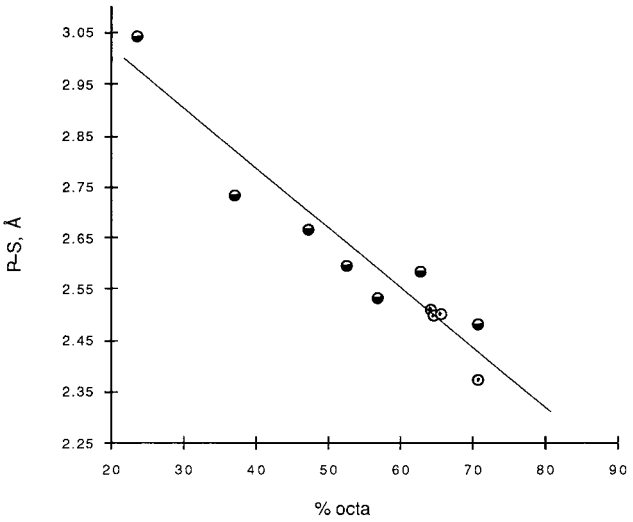


FIGURE 2. Variation of the P−S distance with the percent octahedral character of bicyclic oxyphosphoranes. The open circles refer to bicyclic pentaoxyphosphoranes. The half-filled circles refer to bicyclic tetraoxyphosphoranes. A listing of compounds is given in ref 37, Table 2.

3.177(2) to 2.816(2) Å. These refer to phosphate **20** to phosphite **24**, respectively. With donor atom coordination, the tetrahedral phosphate assumes a TBP geometry while the pyramidal phosphites become pseudo-TBP where a lone electron pair is envisioned to occupy an equatorial site.

As with the oxyphosphoranes, a more quantitative description of the geometrical change due to sulfur coordination is available. For this purpose, a simple linear relation between the van der Waals' sum (3.65 Å) and the sum of the covalent radii (2.12 Å) for phosphorus and sulfur is used relative to that obtained for the P−S distances from the X-ray studies.[48,49] The P−S distance along with the percent displacement toward a TBP or pseudo-TBP geometry is included below each structural representation for **20**−**25**.

The important point that arises from these studies is that phosphates coordinate with sulfur to a lesser degree than phosphites.[48] Figure 3 illustrates this feature.[50] The composition of phosphate **21** is most comparable to phosphite **24**, differing only in the presence of a phosphoryl oxygen atom in place of a lone pair. Associated with these structures, the P−S distance in phosphite **24** is 0.3 Å shorter than that for phosphate **21**, most likely an indication of the phosphoryl back-bonding effect[49] in decreasing the electrophilicity at phosphorus.

Although with the limited series studied, phosphates appear to coordinate with sulfur to a lesser degree than phosphites, oxyphosphoranes coordinate to sulfur more strongly than phosphites. The average P−S bond distance for pentaoxyphosphoranes is 2.525(2) Å,[30−34,37,48] which compares with 2.922(4) Å for phosphites **22**−**25**, a difference of 0.40 Å. The replacement of the lone pair from the phosphorus center of phosphites by additional electronegative ligands increases the ability of phosphorus to undergo stronger coordination in forming hexacoordinated geometries via sulfur donor action. This bond

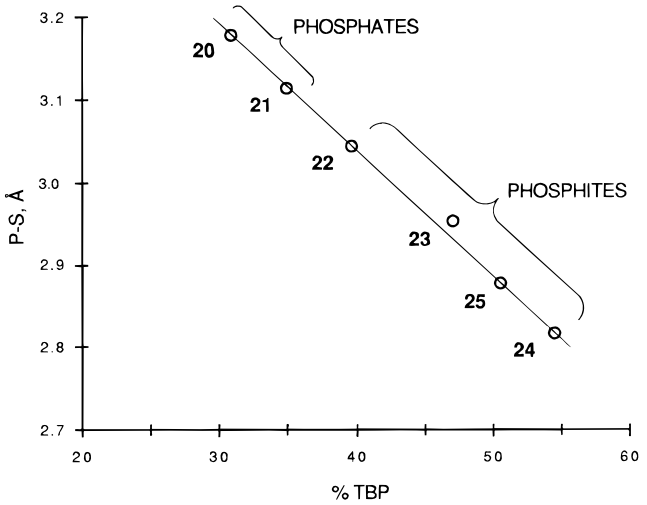


FIGURE 3. Graphical display of the variation of the P−S distance for phosphates and phosphites portrayed in Chart 3. See ref 50.

distance effect is even greater when pentaoxyphosphoranes are compared with phosphates in sulfur donor action. Here an average P−S bond difference of 0.62 Å is involved.

Enzyme Mechanisms

With the evidence now available indicating the ease with which sulfur, oxygen, and nitrogen donor atoms interact with phosphorus and cause an increase in coordination geometry, it is instructive to examine possible interactions at enzyme active sites concerned with phosphorus containing substrates. As pointed out above, such coordinative interactions from nearby residues that may have an available donor group have not been considered previously.[3] In mechanisms of phosphoryl transfer enzymes, it has been traditional to propose pentacoordinate phosphorus intermediates having trigonal bipyramidal geometries.[1−3,5b,51−53] Although speculative at this juncture from the work presented above, a rate enhancement effect may be expected. The presence of donor action in a phosphate acting as a substrate, for example in cAMP,[3] should alter the phosphate structure modestly toward a TBP geometry where it would be better situated for

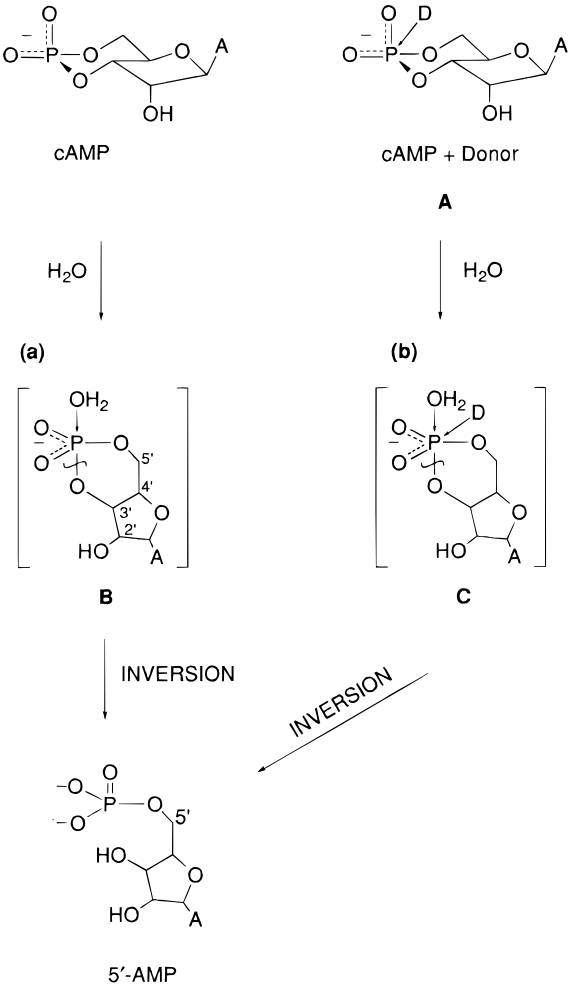
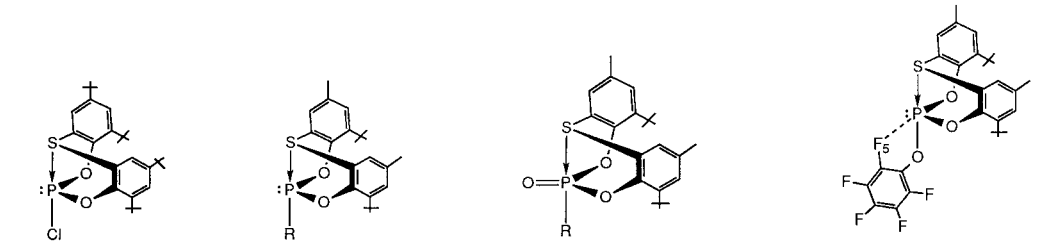


FIGURE 4. (a) Enzymatic hydrolysis of cAMP. Formation of 5′-AMP with inversion favors in-line attack opposite the 3′-oxygen atom with phosphodiesterases.[61] (b) Formation of a possible hexacoordinate intermediate **C**.

nucleophilic attack by a water molecule in enzymatic hydrolysis. It is known that phosphodiesterases cause the hydrolysis of cAMP with inversion of configuration.[54−60] This process is illustrated in Figure 4, path a,[61] which shows the formation of intermediate **B** in the absence of donor action. However, in the presence of donor action,

Chart 3. P−S Distances



3.043(2)Å; 39.7% TBP — **22** [49]

R = NMe_2: 2.952(9)Å; 47.1% TBP — **23** [49]

R = Cl: 2.816(2)Å; 54.5% TBP — **24** [49]

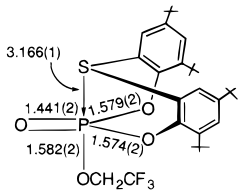
R = Cl: 3.114(2)Å; 35.0% TBP — **21** [49]

R =  3.177(2)Å; 30.9% TBP — **20** [49]

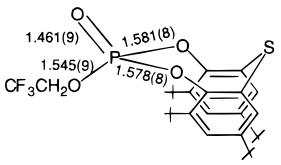
2.876(2)Å; 50.6% TBP — **25** [48]

the formation of activated state **C** is a possibility via path b in Figure 4. Here donor coordination would be greater than that in the enzyme−phosphate substrate **A** and result in a geometry displaced toward an octahedron. The enhanced donor coordination in the activated state **C** relative to that in the enzyme−substrate complex **A** allows for a rate enhancement due to the loosening of the P−O bond undergoing cleavage caused by formation of a higher coordinate geometry.

Evidence already presented in this work that indeed this is a likely possibility is found from the detailed examination of the structures of phosphates undergoing donor coordination compared to related phosphates lacking donor coordination. This information when coupled with comparative structural information on pentaoxyphosphoranes with and without donor action that may serve as models for activated states in phosphoryl transfer enzymes provides an initial approach toward establishing the likelihood of a resultant rate enhancement. For example, X-ray analysis of phosphate **26**[31] reveals the isolation of two crystalline forms which differ in their ring orientation. In one form of **26**, the ring exists in a *syn*-boat conformation and exhibits sulfur donor action (P−S = 3.166(1) Å) while the other form has the ring in an *anti*-chair conformation and lacks donor coordination (P−S = 3.499(5) Å). The average P−O single bond distances are 1.578(2) Å for **26** (syn form) and 1.568(8) Å for **26** (anti form). The difference is not significant, amounting to 0.01 Å.

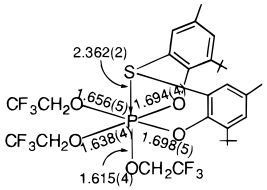


26 [31] (*syn* form)

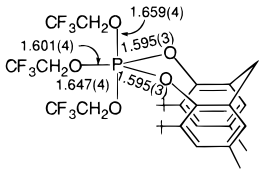


26 [31] (*anti* form)

In a similar manner, on comparing the structures of the cyclic pentaoxyphosphorane **27**,[34] which is hexacoordinate due to the presence of sulfur coordination, with the cyclic pentaoxyphosphorane **28**,[30,62] which lacks any



27 [34] (69.4%)

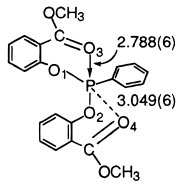


28 [30,62]

donor coordination and has a TBP geometry, the effect of donor coordination in **27** is to cause a significant increase in P−O bond distances relative to **28**. The two compositions are the same other than the presence of a methylene group in **28** in place of a sulfur atom in **27**. The average P−O bond distance in **27** is 1.660(4) Å, which compares with 1.619(4) Å for **28**. Thus, an average increase of 0.041 Å is experienced for the P−O bonds in the hexacoordinate state. This loosening of bonds should facilitate P−O bond cleavage. It is typical for pentaoxyphosphoranes that the P−O bond opposite the donor interaction is the shortest in the formation of a hexacoordinate geometry.

With reference to the hydrolysis of cAMP in Figure 4 (path b) used to illustrate the concept, the phosphate−substrate complex has been positioned somewhat toward a TBP due to modest donor action from an appropriate enzyme residue. In formation of **C**, nucleophilic attack by a water molecule is partially assisted by stronger coordination of the donor group relative to that in the phosphate leading to a more ready rupture of the six-membered ring than in the activated state **B** (path a) due to the greater loosening of the P−O bond undergoing cleavage to give 5′-AMP. Thus, a rate enhancement effect is expected due to tighter binding of the donor group in the enzyme-transition state. As indicated for formulation **C**, the donor interaction **D** is placed cis to the incoming water molecule. In this position, the bond opposite the donor would be the shortest. The resultant geometry may be envisioned as being mildly displaced toward an octahedron where the P−O bond being cleaved largely retains the weak axial character of a TBP that is present in **B**. The incoming donor then acts as an assist in nucleophilic displacement as a result of the combined donor capacity of the two entering entities. This suggests that the effect is to accentuate the weakening of the P−O bond undergoing cleavage.

It is interesting that in our most recent work we find that a carbonyl oxygen atom of tricoordinated phosphorus compound (**29**[9]) containing two appended methylsalicylate ligands weakly coordinates to the phosphorus atom by forming six-membered rings. The crystal structure reveals a pseudo-TBP geometry with the carbonyl oxygen situated at an axial position and a lone electron pair presumed to occupy an equatorial site.



29 [9]

The P−O3 distance of 2.788(6) Å is about 0.55 Å shorter than the van der Waals' sum of 3.35 Å.[43] Its presence causes a geometry that is displaced about 37% toward an ideal TBP. The carbonyl O3−P−O2 axial angle is 172.2(1)°. A weaker carbonyl oxygen interaction from the second axially oriented methylsalicylate ligand, P−O4 = 3.049(6) Å, is not effective in disturbing the local geometry at phosphorus. It might be anticipated that replacement of the phenyl group with an oxygen containing ligand would enhance the carbonyl oxygen donor interaction.

This may well be the case with pentaoxyphosphoranes containing nearby carboxylate groups yet to be investigated.

Summary and Conclusions

A new aspect of active site interactions of phosphoryl tranfer 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 if this effect is present. It is shown that the donor groups, oxygen, sulfur, and nitrogen, typical of enzyme residues at active sites of phosphoryl transfer enzymes, cause higher coordination. Specifically, tetracoordinate phosphate substrates are displaced modestly toward trigonal bipyramid geometries by donor coordination while five-coordinate pentaoxyphosphoranes are displaced more strongly toward octahedral geometries by donor action. The studies suggest that donor interactions at applicable active sites may assist in nucleophilic attack in causing a more ready cleavage of P−O bonds undergoing displacement to form products.

The Future

There are aspects of future research in this area that need to be addressed by phosphorus chemists and by biochemists. It is obvious that hexacoordination for phosphorus depends on the presence of sufficient electrophilicity provided by the attached ligands such as exists in oxyphosphoranes.[37] Thermodynamic data on the stability differences between penta- and hexacoordination would be welcome. As described in the section on isomerism, the energy difference between these two geometries appears small when properly tuned with the strength of a donor group. This feature alludes to the ease of formation of the hexacoordinated state in nucleophilic substitution.

Another aspect which requires attention has to do with the location of entering and departing groups. For pentacoordinate intermediates in nucleophilic displacements, these groups do so from axial positions of a TBP[2] resulting in an inversion stereochemistry,[5b] an in-line process. Pseudorotation of the activated intermediate which is a prominent feature of pentacoordination[5a] is invoked to explain retention stereochemistry in nonenzymatic reactions.[5b] In phosphoryl transfer enzyme mechanisms, however, retention is invariably associated with multiple inversion processes of TBP transition states.[5b] On considering hexacoordinate intermediates, little is known about the stereochemistry of participating groups. As outlined in the discussion accompanying Figure 4, donor action is shown to provide an assist in the hydrolysis of cAMP resulting in inversion stereochemistry. This topic must be greatly expanded before definitive conclusions are reached.

Reactivity studies also provide an unexplored area which should be pursued. It is necessary to learn the relative reaction rates of penta- vs hexacoordination using a variety of ligands for structurally established compounds that model active site formulations.

There is a need to probe active site environments of phosphoryl transfer enzymes to establish the importance or lack thereof of donor action by amino acid residues and to evaluate potential rate enhancement effects that result. It may be that other interactions at active sites take precedence, e.g., salt bridges, metal ion interactions, hydrogen bonding. Perhaps the construction of model systems that play one effect vs another may aid in the evaluation of the influence of donor interactions in inducing increased coordination at phosphorus.

With the combined knowledge from chemists of various disciplines, significant progress should come about in this relatively new area of study. Whether or not hexacoordination at phosphorus is a viable theme for biological mechanisms is a question for the future, there is little doubt that knowledge gained in studying the consequences of hexacoordination will help immensely in interpreting nucleophilic displacement reactions of nonenzymatic processes.

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