New Features in Pentacoordinate Phosphorus Chemistry

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ABSTRACT

In reactions centered at phosphorus, whether chemical or biochemical, a pentacoordinate transition state species or an intermediate or a stable molecule is very often encountered. In this Account, recent developments in this important area are discussed and compared with the earlier literature. Particular reference, with results from our laboratory, will be made to the apicophilicity, fluxional behavior, bond parameters, and tetra- vs pentacoordination. It is shown that the familiar apicophilicity rules give an oversimplified picture as demonstrated by several exceptions. Extremities of the P−O or P−N bond distances in PX_4N and PO_4N systems as revealed by a database search and possible future directions in this area are also discussed.

Introduction

Nucleophilic displacement reactions at a tetracoordinate phosphorus(V) center are involved virtually in every aspect of cellular energetics and many aspects of biosynthesis.[1,2] Both enzymatic and nonenzymatic hydrolyses of RNA are shown to take place via cyclic pentacoordinate trigonal bipyramidal transition state species.[2] It is assumed that the phosphoryl transfer reactions such as energy transfer and DNA formation via ATP also go through the pentacoordinate phosphorus intermediate, which is formed by the nucleophilic attack at the tetracoordinate phosphorus center.[1c] The phospho-enzyme intermediate (E−P) in the action of protein tyrosine phosphatases (signaling enzymes that control a diverse array of cellular processes) is assumed to be pentacoordinate (species **I** in Figure 1).[1d]

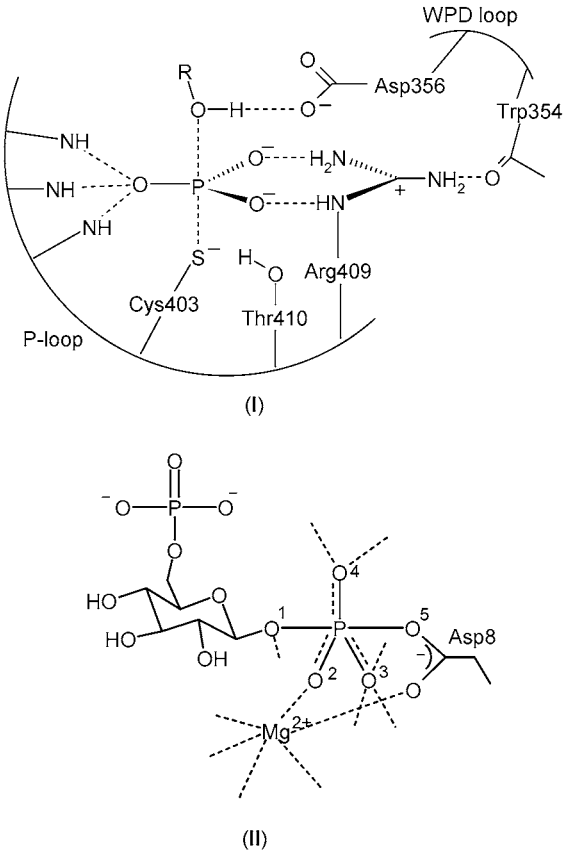

FIGURE 1. Transition state (**I**) for the phospho-enzyme intermediate formation in *Yersinia* protein tyrosine phosphatases (PTPs) and a simplified drawing of the β-glucose-1,6-(bis)phosphate intermediate (**II**) structure in the active site of β-phosphoglucomutase. The extra hatched-line bonds from O(1), O(3), and O(4) are hydrogen bonds. Selected bond parameters are as follows: P−O(1) 2.0 Å; P−O(2), P−O(3), and P−O(4) 1.7 Å; P−O(5) 2.1 Å; O(1)−P−O(5) 174°.

Recent structural characterization of the stabilized pentacovalent phosphorane (**II**) in the biochemical phosphoryl group transfer reaction is significant in this context.[3] Latest studies have also shown that the inhibition of human α-thrombin by a phosphonate tripeptide proceeds via a pentacoordinate phosphorus intermediate.[4] Thus the central role of phosphates in the living world has given rise to extensive kinetic and mechanistic investigations on solvolytic reactions of simple phosphoric acid esters with emphasis on the formation, isomerization, and breakdown of the pentacoordinate intermediate.[1d,5,6] Theoretical calculations are also useful in characterizing the structure of transition states/intermediates, but the mechanistic speculations based on such calculations need to be tested experimentally.[7,8] The behavior of hydroxyphosphoranes and their salts should be interesting in this context, but there are only a few well-authenticated examples.[9]

Two other exciting developments related to enzyme action also call for attention:[10] (i) The X-ray crystal structure of phospholipase D (that catalyzes the hydrolysis of phospholipids) soaked with dibutyrylphosphatidylcholine (a substrate) demonstrates that the reaction proceeds

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via a phosphohistidine intermediate and provides unambiguous identification of a catalytic water molecule, ideally positioned for apical attack on the phosphorus (**III**; Figure 2a) and consistent with an associative in-line phosphoryl

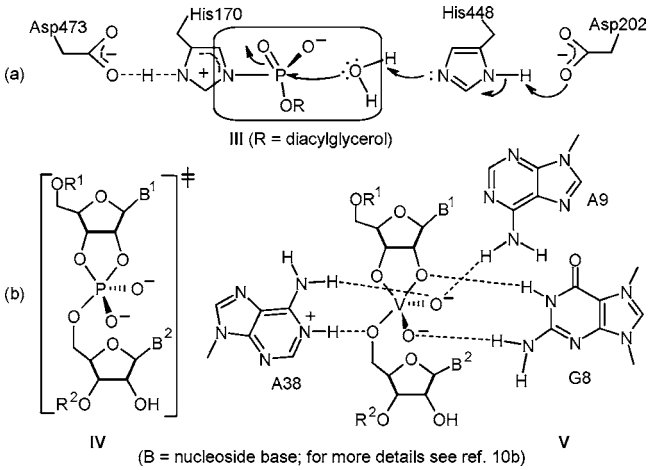
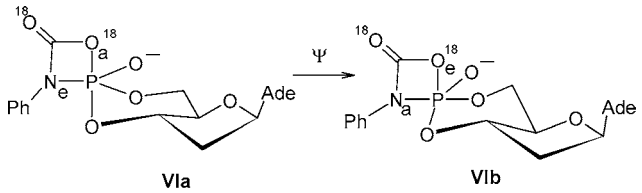


FIGURE 2. (a) A drawing of the active site in phospholipase D (PLD_{pmf}) (**III**) soaked with dibutyrylphosphatidylcholine for 8 h showing the location of water poised for attack at the apical site as revealed by X-ray crystallography and (b) the pentacoordinate trigonal bipyramidal phosphorus transition state proposed in the reversible transesterification reaction catalyzed by the hairpin ribozyme (**IV**) and the vanadate transition state mimic complex (**V**) stabilized by five hydrogen bonds (X-ray).

transfer reaction.[10a] In one of the structures, an apparent five-coordinate phosphorus transition state is observed. (ii) The hairpin ribozyme catalyzes reversible, site-specific cleavage of the phosphodiester backbone of RNA through transesterification. A vanadate complex (**V**) of the enzyme that mimics the pentacoordinate trigonal bipyramidal phosphorus transition state (**IV**) has been characterized crystallographically and vindicates the proposed mechanism of action (Figure 2b).[10b]

Pentacoordinate phosphorus is also encountered in the important Wittig, Aza−Wittig, Horner−Wadsworth−Emmons, Seyferth−Gilbert (homologation), Stec (cf. structures **VIa,b**), and Mitsunobu esterification reactions.[11,12]



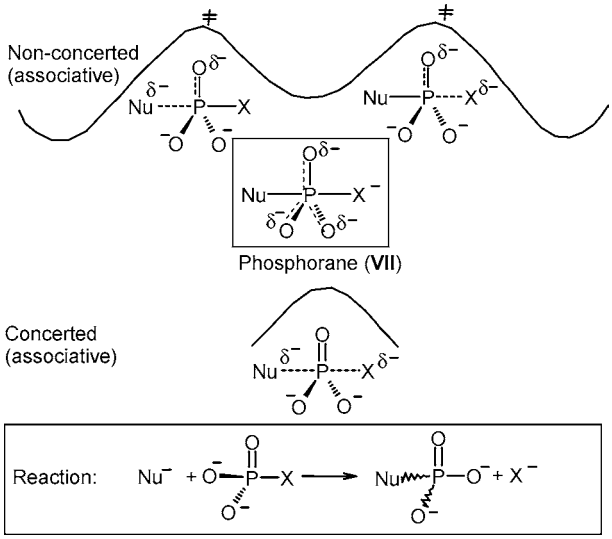
Pseudorotation proposed for pentacoordinate phosphorus species in the synthesis of deoxyadenosine cyclic [^{18}O]phosphate by Stec reaction

Numerous other reactions involving P^{III} or tetracoordinate P^{V} compounds also lead to pentacoordinate phosphoranes.[13] The propensity of pentacoordinate phosphorus to further expand its coordination number also warrants attention with regard to the mechanistic aspects of phosphoryl transfer enzymes.[14] The purpose of this Account is to highlight recent developments particularly on the current knowledge of apicophilicity, fluxionality, and bond parameters. The discussion could serve to understand the stability (lifetime) and stereochemistry of transient species involved in chemical and biological processes.

Bent's Rule, Apicophilicity, and Ring Strain

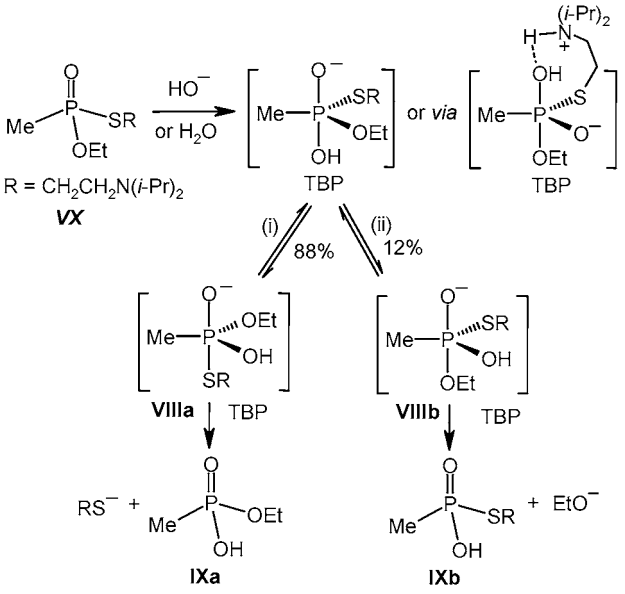
In the general case of nucleophilic substitution, if the pentacoordinate phosphorus species (**VII**; cf. Scheme 1)

Scheme 1



has sufficient lifetime (nonconcerted pathway), it can undergo intramolecular ligand exchange processes that in turn will have a significant bearing on the stereochemistry of products. For example, hydrolysis of the exceedingly toxic nerve gas agent VX [*O*-ethyl-*S*-(2-diisopropylamino)ethyl methylphosphonothiolate] with an alkali can lead to different products depending upon whether the −SR or the −OEt group is apical (Scheme 2).[15] Thus the

Scheme 2

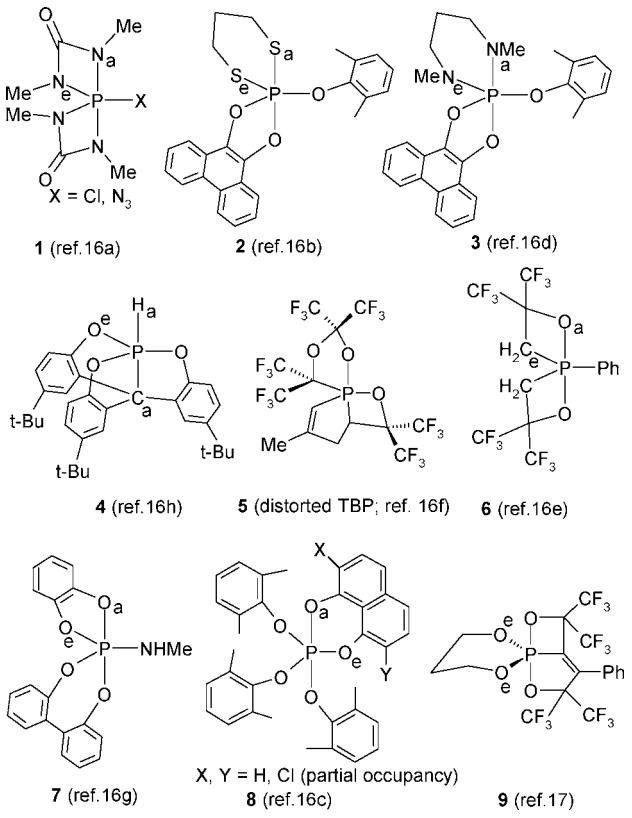


Hydrolysis of ***VX*** (a chemical warfare agent)

relative preference of a substituent to occupy the apical or equatorial site in the more commonly observed trigonal bipyramidal (TBP) geometry has been a subject of intense studies in the past.[16−22]

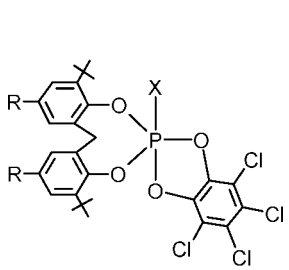
According to Bent's rule or in terms of the 3c−4e bonding picture for the apical bonds in trigonal bipyramidal phosphorus, more electronegative substituents prefer apical sites (i.e., more apicophilic).[23] This is perhaps too simplistic a picture. In cyclic/fused ring phosphoranes with a trigonal bipyramidal phosphorus, ring constraints dominate over the electronegativity effects in apical site occupancy even for highly electronegative substituents (cf. Chart 1, compounds **1**−**5**).[16] In general, four- to seven-membered rings at phosphorus prefer apical−equatorial disposition (e.g., **1**−**8**), unless constrained by fused rings (e.g., **9**).[17] Hydrogen bonding can affect ring conformations but, unlike ring strain, is not strong enough to change the apicophilicity of the substituents.[16g,18] High apicophilicity is supposedly favored by high electronegativity, small size, and stronger π-acceptor properties; π-donating and bulkier groups are supposed to occupy the equatorial site.[6d,19] Based primarily on variable temperature NMR or activation enthalpy different scales of apicophilicity are available: (a) F > H > CF_3 > OPh > Cl > SMe > OMe > NMe_2 > Me > Ph;[6d] (b) OMe ≈ H > COMe ≈ SMe > NMe_2 > Me > *n*-Bu;[20a] (c) Ph > CH_2OMe > Me > CH_2Ph > Et > *n*-Pr ≈ *n*-Bu (in $CDCl_3$) or Ph > CH_2OMe > CH_2Ph > Me > Et > *n*-Pr > *n*-Bu (in CD_3CN).[20b] Theoretical calculations predict the gas-phase apicophilicities in the order F > OH > H > Me > NH_2 for the neutral oxyphosphoranes.[20c]

Chart 1

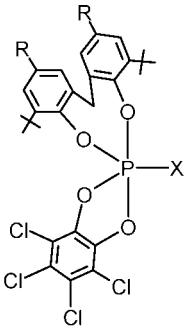


In contrast to the compounds shown in Chart 1, the eight-membered 1,3,2-dioxaphosphocin ring shown in Chart 2 can readily occupy either diequatorial or apical−equatorial disposition in a TBP geometry. This feature is dictated by the preference of the fifth ligand to go apical or equatorial thus allowing us to determine its relative apicophilicity. Holmes[21] reported compounds **10** and **11**, and we reported compounds **12**−**28**.[16g,18b,22] Note that without the *tert*-butyl group *ortho* to the phenolic oxygen, the eight-membered ring prefers only the apical−equatorial disposition.[16d]

Chart 2



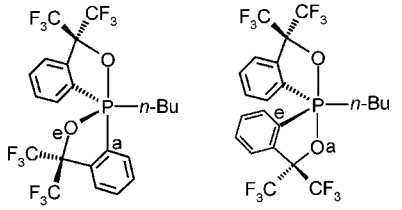
R	X
t-Bu	Ph (**10**)
t-Bu	Et (**11**)
t-Bu	OC_9H_6N (oxinate) (**12**)
Me	Ph (**13**)
Me	Et (**14**)
Me	*t*-Bu (**15**)
Me	Cl (**16**)
Me	N_3 (**17**)
Me	NCS (**18**)
Me	NMe_2 (**19**)
Me	NMePh (**20**)
Me	$N(i\text{-}Pr)_2$ (**21**)
Me	SC_6H_4-4-Cl (**22**)



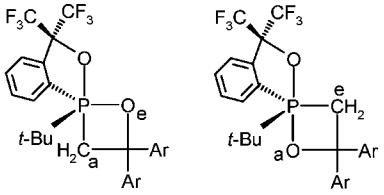
R	X
t-Bu	NHC_6H_{11} (**23**)
Me	Me (**24**)
Me	NH_2 (**25**)
Me	NHMe (**26**)
Me	NHPh (**27**)
Me	$N{=}PPh_3$ (**28**)

The high apicophilicity of an −SR group agrees with the hydrolysis of the chemical warfare agent VX mentioned above. The greater apicophilicity of the phenyl group compared to methyl is *opposite* to that given by Corbridge[6d] but consistent with that of Akiba;[20b] however, the *apical* occupancy of the ethyl group (compound **14**) compared to the *equatorial* occupancy of methyl (compound **24**) is different from that observed by Akiba.[20b] Perhaps more dramatic are the (i) *apical* placement of the bulky *tert*-butyl group in **15** compared to *equatorial* placement of the much smaller methyl group in **24** and, similarly, (ii) *apical* placement of $-N(i\text{-}Pr)_2$ in **21** compared to *equatorial* placement of the *more electronegative* and *much smaller* $-NH_2$ in **25**.[24] These are clear cases of "reversed apicophilicty" or "antiapicophilicity".

The significant apicophilic character of carbon over oxygen is also exhibited in compounds **29** and **30** for which both C-apical and O-apical isomers are isolated (note, compounds **30a,b** are also important as Wittig reaction intermediates).[25] The C-apical isomer is the kinetically controlled product. Steric effect is likely to be the major cause for stabilization against pseudorotation



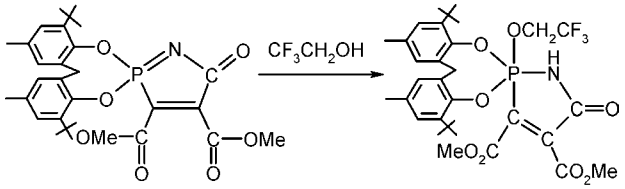
29a (C-apical) **29b** (O-apical)



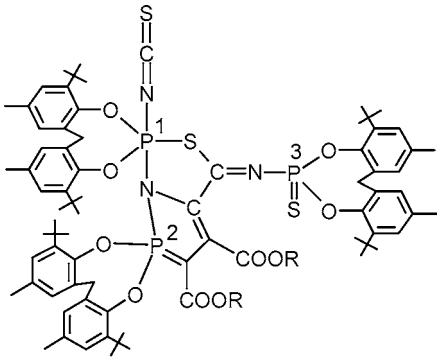
30a (C-apical) **30b** (O-apical)

in the isomers that exhibit reversed apicophilicity. In the spirophosphorane **32** (Scheme 3) also, "reversed apicophilicity" is observed in the five-membered ring (carbon vs nitrogen) despite the greater steric requirement at the (=)$C(CO_2R)$ center relative to NH center.[26] The fused ring between P(1) and P(2) in the structure of **33** is likely to be

Scheme 3



31 [δ(P) 56.7] **32** [δ(P) -65.0, -72.5; X-ray]

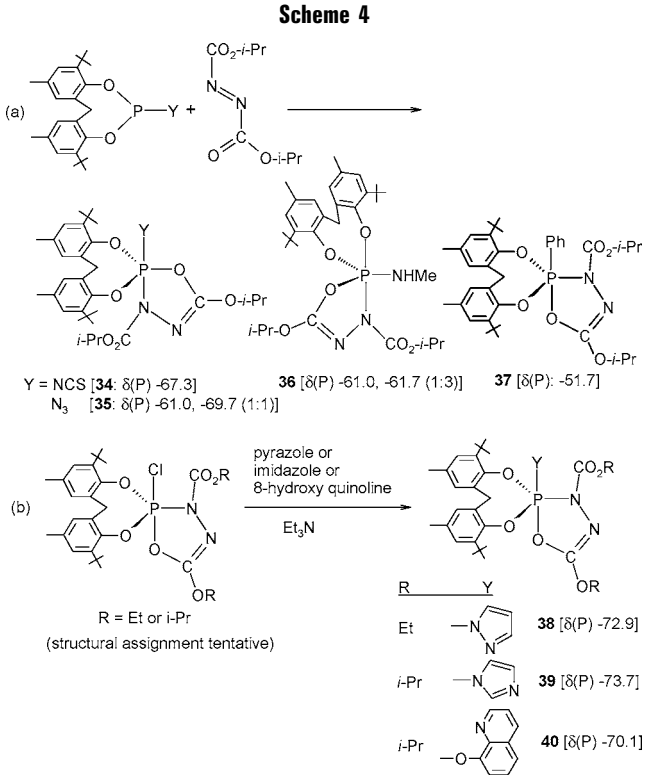


33 [δ(P) -51.1(d), 40.0(d), 60.6(s)]

the reason for nitrogen (rather than oxygen) to occupy the apical position of a trigonal bipyramid.[27]

In our efforts to isolate possible intermediates in the early stages of the Mitsunobu reaction, we have uncovered a rich variety of pentacoordinate phosphoranes, many with reversed apicophilicity (Scheme 4).[28,29] The N(apical)−O(equatorial) disposition for the five-membered ring in compounds **34**−**36** and **41** should have been unfavorable according to apicophilicity rules. Whether we are isolating the kinetic or thermodynamic products needs further verification, but it can be noted that compound **41** can be prepared by both routes a and b shown in

Scheme 4

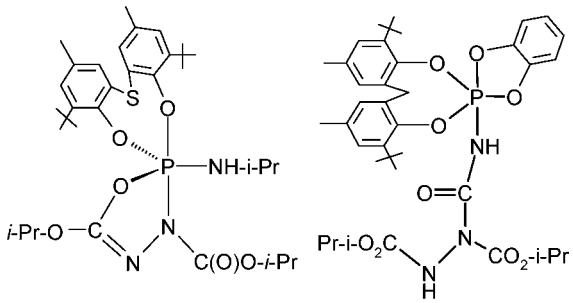


Y = NCS [**34**: δ(P) -67.3] **36** [δ(P) -61.0, -61.7 (1:3)] **37** [δ(P): -51.7]
N_3 [**35**: δ(P) -61.0, -69.7 (1:1)]

R = Et or i-Pr
(structural assignment tentative)

R	Y	
Et		**38** [δ(P) -72.9]
i-Pr		**39** [δ(P) -73.7]
i-Pr		**40** [δ(P) -70.1]

Scheme 4. Finally, compound **42** with an apical amide type NHC(O)R illustrates that the apicophilicity or Bent's rule cannot be taken for granted.



41 [δ(P) -54.5, -63.4, -63.7] toluene-d_8 at 243K] **42** [δ(P) -59.3]

A criterion that can be used to show the involvement of the lone pair of electrons on nitrogen in π-bonding with phosphorus is the sum of bond angles at nitrogen. In compounds **21**, **38**, and **39**, this sum at the *apical* nitrogen is essentially 360° (planar) but the P−N distances are still long [1.672(2), 1.763(2), and 1.752 Å, respectively]. Current thinking involves 3c−4e apical bonds and does not favor significant phosphorus d-orbital involvement.[30] Hence a rationalization is yet to come for a critical assessment of this observation.

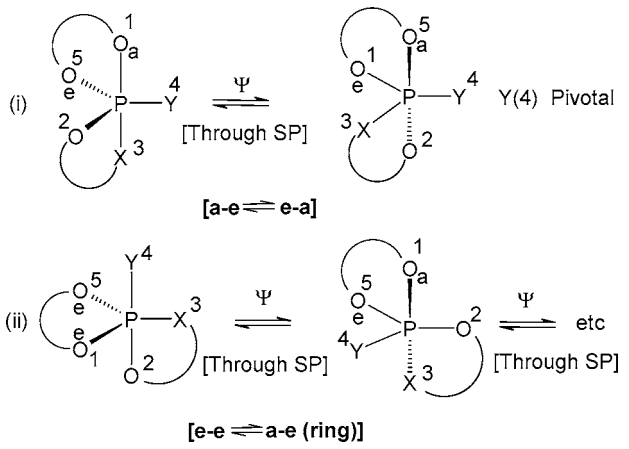
In practically significant systems, the actual pentacoordinate structure could vary between TBP and square/rectangular pyramidal (SP/RP) geometry. In most cases, TBP geometry, generally with some distortion, is favored, and SP/RP geometry is mostly limited to spirobicyclic derivatives with two unsaturated five-membered rings with like atoms in any one ring attached directly to

phosphorus or when more strained three/four membered rings are present (with only one exception).[6c] A *less* apicophilic group in TBP geometry is expected to be *more* apicophilic in SP/RP geometry.[30b]

Berry Pseudorotation and Fluxional Behavior

Intramolecular exchange processes in acyclic pentacoordinate phosphoranes appear to occur mostly through Berry pseudorotation.[6a] Even for monocyclic and spirocyclic phosphorane, this is a good option, although in principle a turnstile mechanism could also be operating. Barriers to pseudorotation are influenced by charge state, apicophilicity of ligands, intramolecular hydrogen bonding, cyclic structure, and solvation.[8b] In the case of monocyclic/spirocyclic phosphoranes with a TBP geometry, both apical−equatorial ⇔ equatorial−apical [a−e ⇔ e−a, process i] and e−e ⇔ a−e [process ii] exchanges for the rings can be envisaged. Scheme 5 depicts this for a set of

Scheme 5



spirocyclics; the square pyramidal (SP) transition state is not shown. Cessation of process i for the *o*-chloranil system (cf. Chart 2) would lead to a single ^{31}P NMR resonance or very closely spaced signals due to different conformations of the eight-membered ring (boat−chair and tub). For the same *o*-chloranil system, in process ii, the local environment at phosphorus changes significantly and at least two well-separated signals are expected if this is occurring. As an example, compound **19** exhibits the following peaks in the ^{31}P NMR:[22b] 233 K, δ −42.2 and −43.1 (1:1, conformational isomers), −47.1; 253 K, δ −42.8, −47.1 (e−e and a−e isomers for the eight-membered ring, process ii); 328 K, δ −42.8.

Thus it appears that only one isomer is preferred at higher temperature, suggesting the presence of an "unsymmetrical potential well". To our knowledge, such an unsymmetrical coalescence behavior has not been discussed in detail in the earlier work.

Multiple choices including tetracoordinate forms (see later) for isomer formation are available for the dialkyl azodicarboxylate system (cf. Scheme 4) since the five-membered ring can have two energetically favorable dispositions, N(apical)−O(equatorial) and N(equatorial)−O(apical). This feature is illustrated by the ^{31}P NMR spectra shown in Figure 3 for compound **41**. It exhibits three

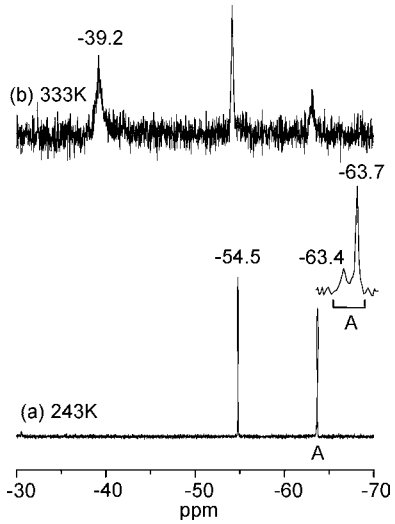
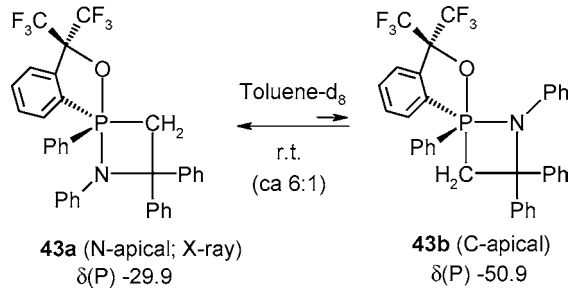


FIGURE 3. The ^{31}P NMR spectra of **41** in toluene-d_8 at (a) 243 and (b) 333 K. The spectra are reversible in this temperature range.

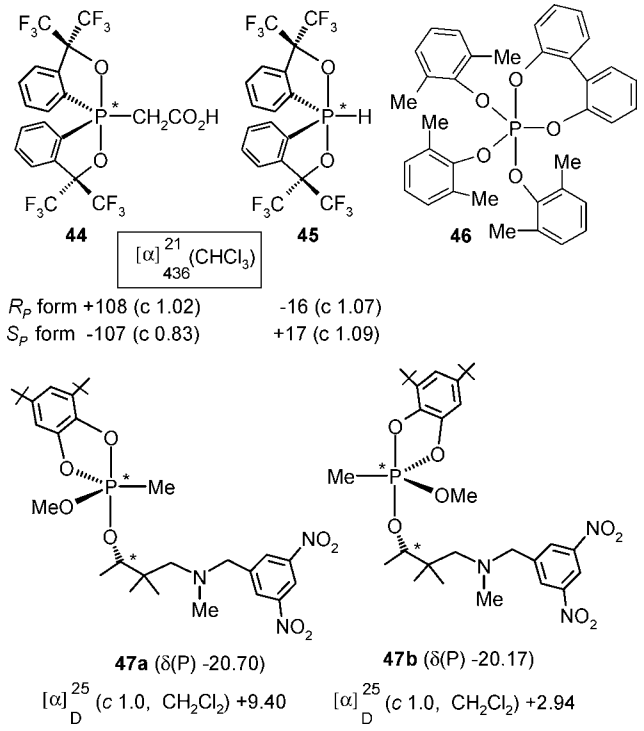
signals at 243 K [δ −63.7, −63.4, −54.5] but a fourth one [δ −39.2 (br)] is also seen at 333 K.[29] Normal spectral behavior with a symmetrical coalescence is again not observed.

The pentacoordinate 1,2-λ^5-azaphosphetidine, **43a**,, which is the N-apical isomer [X-ray; δ(P) = −29.9], upon



dissolution in toluene-d_8 at room temperature gives an additional ^{31}P NMR signal [δ(P) = −50.9] ascribed to the C(apical) isomer **43b**.[31] In such a situation, since the five-membered ring at phosphorus has retained its disposition, it is likely that an a−e ⇔ e−e exchange (process ii) similar to that shown in Scheme 5 is involved here.

If the activation energy for the intramolecular exchange becomes high enough, it should be possible in favorable cases to isolate enantiomerically pure pentacoordinate phosphoranes *with chirality only at phosphorus*. Compounds **44** and **45** represent two such rare examples.[32] In sterically congested systems, bond rotation can also be frozen at low temperatures. This is elegantly shown in compound **46**, which shows *six separate methyl* signals in the ^{1}H NMR at less than −20 °C.[16c] Such a phenomenon is perhaps responsible for the *polymorphism* shown by compound **2** (cf. Chart 1), which can be crystallized in at least two modifications: one triclinic and the other monoclinic. The difference between the two is mainly in



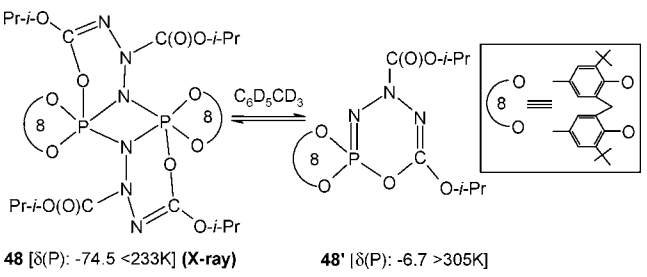
the orientation of the xylyloxy group with respect to the rest of the molecule.[16b] Configurationally stable pure diastereomers with five different substituents (e.g., **47a,b**) on phosphorus can also be isolated in favorable cases, if Berry pseudorotation is sufficiently slow.[33] The two diastereomers are interconvertible by heating, but at room temperature, they are configurationally stable.

To Pentacoordinate or not?

It is now well-established that Ph_3PI_2 and Ph_3PBr_2 crystallized from diethyl ether have a molecular charge-transfer "spoke" structure $Ph_3P{-}I{-}I$ or $Ph_3P{-}Br{-}Br$ and not the pentacoordinate structure originally assumed.[34] The phosphorus in Ph_3PF_2, however, has a trigonal bipyramidal geometry.[35] Finally, Ph_3PCl_2 when crystallized from a less polar solvent like diethyl ether is pentacoordinate at phosphorus, while that obtained from the more polar solvent dichloromethane had an ionic structure $[Ph_3PCl\cdots Cl\cdots ClPPh_3]Cl{\cdot}2CH_2Cl_2$ in which phosphorus can be considered as tetracoordinate. Thus the reactivity of "Ph_3PCl_2" (which is quite widely used) could vary depending on solvent polarity.

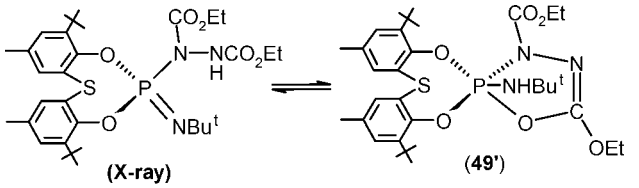
The equilibria of the types (a) phosphite−phosphorane [e.g., 1,2-$(HO)C_6H_4OP(1,2\text{-}O_2C_6H_4) \leftrightarrow HP(1,2\text{-}O_2C_6H_4)_2$], (b) phosphonium salt−phosphorane (e.g., $PCl_5 \leftrightarrow PCl_4^+PCl_6^-$), and (c) pentacoordinate ⇔ hexacoordinate phosphorus are well-known.[36] Here we restrict ourselves to two other examples from our studies. The first one involves pentacoordinate ⇔ tetracoordinate equilibrium (Scheme 6). Steric factors appear to be responsible for the observation of the monomeric form **48′** at higher temperatures.[28b] In the range 243−295 K, ^{31}P NMR signals for both the monomer and the dimer are observed. The second

Scheme 6



example involving **49** shows a more intriguing behavior (Scheme 7). At 255 K, four distinct signals are observed

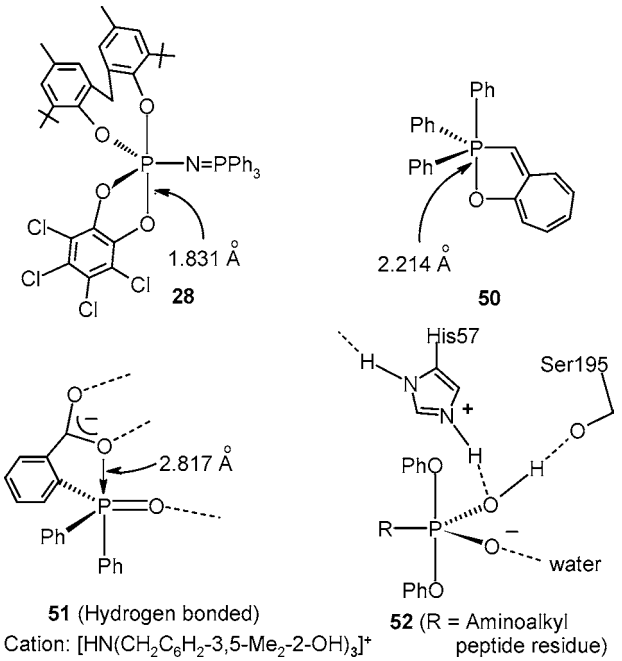
Scheme 7



in the ^{31}P NMR in the range −50 to −57 ppm. These are in the region close to that for the pentacoordinate −NH−*i*-Pr compound **41** (vide infra). Thus multiple signals for **49** are consistent with the presence of isomeric pentacoordinate species.[28b]

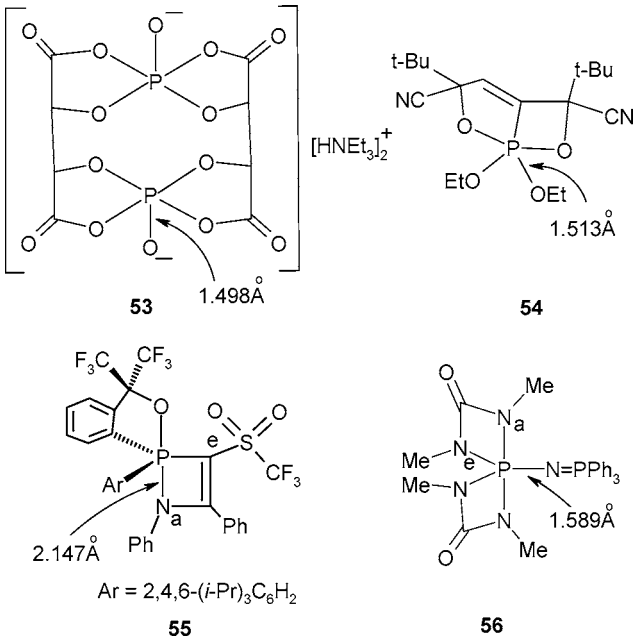
Bond Distances—What Are the Limits?

One of the questions regarding pentacoordinate species **II** reported by Lahiri et al.[3] relates to the long apical P−O bond distances of 2.0−2.1 Å. In known structures of *penta*oxyphosphoranes, the P−O distances generally fall in the range 1.57−1.77 Å [Cambridge database search, November 2004]. However, pentacovalent phosphoranes with longer apical P−O distances do exist [e.g., **28**, **50**].[22a,37]



As shown for **51**, this distance could still be longer, depending on the extent of contribution from coordinate covalent character.[38] If the P═O (equatorial) oxygen is involved in hydrogen bonding or if it abstracts a proton, the apical O→P bond could shorten and approach the covalent bond distance. The hydrogen bonding interaction could also affect the reverse phenomenon. The structure of **II** is *anionic* around phosphorus with apical carboxylate oxygen, and with significant hydrogen bonding. Thus the observed apical P−O bond lengths appear reasonable. Stabilization of pentacoordinate phosphorus intermediate through hydrogen bonding has also been demonstrated recently in the X-ray structure of the complex (**52**) of human α-thrombin with the inhibitor (α-aminoalkyl)-phosphonate.[4]

Compounds **53** and **54** are two examples in which the P−O bond distance falls below the normal range [Figure 4a].[9,39] Thus the variation in P−O single bond distances is of the order of 0.6 Å. The P−N bond distances also span a large range (generally 1.60−1.80 Å), but examples of extremes (**55** and **56**) are also known [Figure 4b].[40] Relatively speaking, the range of P−C bond distances is narrow (1.70−1.95 Å), and the extremes are 1.688 and 1.987 Å. This range is less than that for P−O or P−N distances and is expected since carbon does not have a lone pair of electrons to interact further with phosphorus.



Summary and Outlook

The previous notion on the site preferences in pentacoordinate phosphorus needs modifications in the light of what is discussed above. Earlier experimental scales of apicophilicity have been built mostly by activation barrier (NMR) to pseudorotation, a kinetic feature. However, an ideal scale should be based on stabilities of different isomers, a thermodynamic feature.[20b] This aspect needs to be evaluated more thoroughly. The 3c−4e bond concept for the apical bonds in TBP geometry, rather than

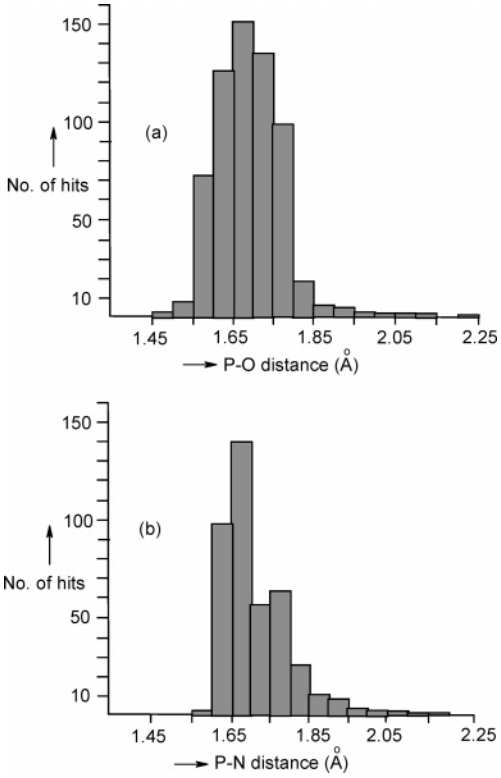
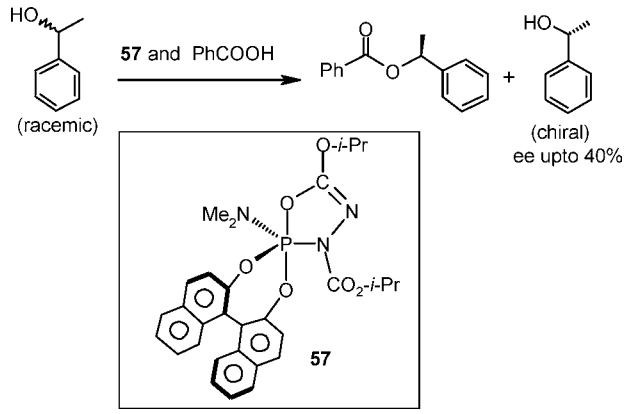


FIGURE 4. Variation in the P−O and P−N bond distances in pentacooordinate phosphorus compounds with connectivities PX_4O and PX_4N [X = any atom, $R \leq 0.075$, nonpolymeric structures, P connected to five atoms only; Cambridge Database, November 2004]: (a) P−O distances; (b) P−N distances.

any significant involvement of phosphorus d-orbitals, seems to be the model of choice.[41] This theory also rationalizes the longer P−X apical distances in TBP geometry, sometimes going much beyond the Shoemaker−Stevenson equation (e.g., **50** and **55**). The π-bonding effects involving the lone pair of electrons on nitrogen and phosphorus d-orbital do not seem to be valid, and if so, more theoretical investigations of orbitals involved in such interactions is to be undertaken. Two areas that could catch up in the future are (i) the isolation/understanding of phosphoranes of biological relevance/interest and (ii) use of pentacoordinate compounds as precursors for organic synthesis. Recent structural characterization of thymidine and substituted inositol-based phosphoranes are in this direction.[42] However, systematic stabilization of anionic phosphoranes (perhaps through hydrogen bonding) of relevance to enzyme action and RNA cleavage (such as **52**) would require more planning.

As regards utility, the chiral pentacoordinate phosphorane $(Me_2N)P[2,2'\text{-}O_2\text{-}(C_{10}H_6)_2][N(CO_2\text{-}i\text{-}Pr)NC(O\text{-}i\text{-}Pr)O]$ (**57**; δ(P) −36.7) that is analogous to some of those discussed above (**34**−**40**) could be utilized for the kinetic resolution of secondary alcohols (with ee up to 40%) in an asymmetric Mitsunobu reaction (Scheme 8).[12] Studies such as extrusion of an olefin directly from pentacoordinate phosphetane, the second step in the Wittig reaction, will be useful in furthering our knowledge of the mechanism.[13b,43] Enhanced reactivity of pentacoordinate siliconates relative to their tetracoordinate counterparts, in

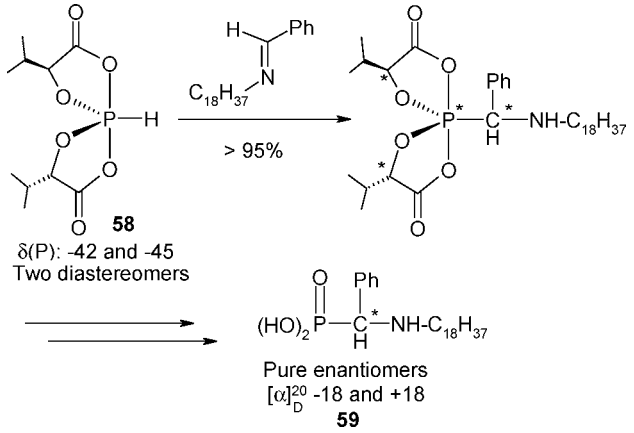
Scheme 8



say, allylation reactions is well-known;[6c] corresponding studies on the use of pentacoordinate phosphorus is a relevant area.

Chiral P−H spirophosphoranes **58** undergo asymmetric addition with prochiral aldimines and, after selective hydrolysis, afford α-(amino)phosphonic acid amphiphiles **59** in both enantiopure forms (Scheme 9).[44a] Hydrido-

Scheme 9



phosphorane, $HP[OCH_2CH\{CH(Me)(Et)\}NH]_2$, derived from *iso*-leucinol, forms chelate complexes with $PdCl_2(RCN)_2$ in its tautomeric open P^{III} form. These palladium complexes catalyze enantioselective alkylations.[44b] Thus chiral and catalytic phosphorane-based systems are likely to be an attractive area for further exploration.

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