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P–O Donor Action from Carboxylate Anions with Phosphorus in the Presence of Hydrogen Bonding. A Model for Phosphoryl-Transfer Enzymes[1]

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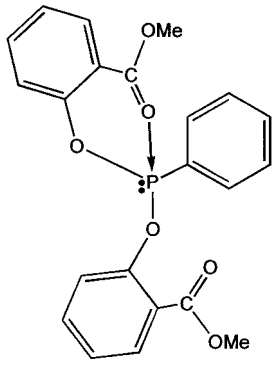
A series of phosphorus compounds (**1**–**3**) containing anionic carboxylate groups were synthesized by treatment of the respective neutral precursor acid forms **B**–**D** with amines, which also served to introduce hydrogen-bonding interactions. The compounds, subjected to X-ray structure analysis, resulted in hexacoordinated anionic phosphoranates **1A** and **1B**, a pseudo-trigonal-bipyramidal anionic phosphine (**2**), and a trigonal-bipyramidal anionic phosphine oxide (**3**). The structures revealed that P–O donor coordination was present in all members of the anionic series **1**–**3** and resulted in stronger interactions than existed in the precursor neutral acid forms **B**–**D** as measured by the presence of shorter P–O distances. Evaluation of the energies of the donor interactions relative to the energies of the hydrogen bonds that were present showed that the donor energies now exceeded the hydrogen bond strengths. ^{31}P chemical shifts indicated that the basic coordination geometries were retained in solution. Both **1A** and **1B** are chiral and exist as racemates. The results suggest that mechanisms of phosphoryl-transfer enzymes should benefit by taking into account donor interactions at phosphorus by residues at active sites in addition to the inclusion of hydrogen bonding. Reference is made to specific phosphoryl-transfer enzymes.

Introduction

In recent work, our interest has focused on exploring the coordination chemistry of phosphorus as it might be perceived to operate at active sites of phosphoryl-transfer enzymes.[2] We have proceeded in a stepwise fashion working with donor groups potentially capable of oxygen atom coordination at phosphorus.[3−8] Thus, we have found that the carbonyl oxygen atom of the salicylate ligand coordinates to phosphorus in bis(methyl salicylate-*O*)phenylphosphine (**A**) to give a pseudo trigonal bipyramid (TBP) as a consequence of axial coordination.[8] The result is a neutral compound.



A

The amino acid residues serine (Ser), threonine (Thr), asparagine (Asn), glutamine (Gln), glutamate (Glu), aspartate (Asp), and tyrosine (Tyr) are potentially oxygen atom donors that might enter into mechanistic considerations at active sites of phosphoryl-transfer enzymes. For example, in phosphatase

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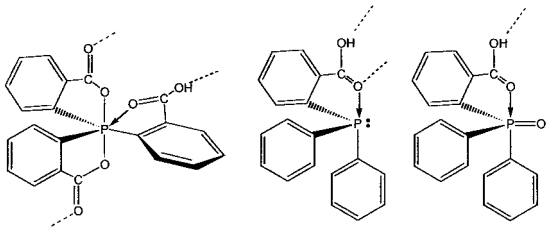
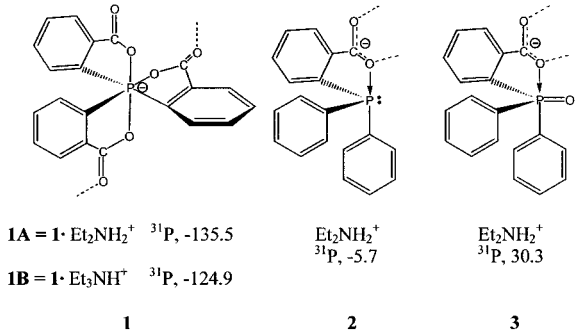
monoester hydrolysis by alkaline phosphatase, a serine residue at the active site is proposed to attack the phosphoryl group, leading to a transitional TBP.[9,10]

In work that followed,[1b] hydrogen bonding, which is a prevalent feature at active sites of enzymes, was introduced in an attempt to learn to what extent oxygen atom coordination would occur in competition with the electronic effects associated with hydrogen bonding. Of interest here, the study[1b] included a phosphorane (**B**), a phosphine (**C**), and a phosphine oxide (**D**), all of which exhibited hydrogen



bonding. In each case, P−O donor coordination persisted. Evaluation of the energies of the two competing bonding types indicated a range for P−O coordination above and below the hydrogen bond energy. These compounds, like **A**, are neutral compounds.

Since anionic carboxylate groups are common at active sites, we have conducted the present study with anionic carboxylate donors in the presence of hydrogen bonding to examine the extent of oxygen atom coordination in systems that may serve more closely as models for phosphoryl-transfer enzymes. The present compounds are the anionic derivatives of the neutral compounds **B**−**D**. They are, respectively, **1**−**3** (only one H-bond is present for **1B**; see eq 1 or Figure 2).



Syntheses and X-ray and NMR measurements are performed to establish the structural arrangements of **1**−**3** and the extent of Lewis acid−base donor interaction that takes place. The relative strengths of the oxygen atom coordination tendencies at phosphorus are estimated and compared with the strengths of hydrogen-bonding interactions to assess their importance in mechanisms of phosphoryl-transfer enzymes.

Experimental Section

Diphenylphosphinobenzoic acid (**C**), diethylamine, and triethylamine (Aldrich) were used as supplied. Phosphorane **B** and diphenylphosphinoylbenzoic acid (**D**) were obtained according to the procedure described in our previous paper.[1b] Commercial acetone was used as a solvent. All reactions and crystallizations were carried out under ambient conditions. Proton NMR spectra were recorded on a Bruker AC200 FT-NMR spectrometer. ^{31}P NMR spectra were recorded on a Bruker DPX300 FT-NMR spectrometer. All ^{1}H NMR spectra were recorded relative to tetramethylsilane in $CDCl_3$, and all ^{31}P NMR spectra were recorded relative to 85% H_3PO_4 in CH_2Cl_2 in the sweep-off mode, unless mentioned otherwise. Chemical shifts are reported in parts per million, downfield positive at 23 °C. Elemental analyses were performed by the University of Massachusetts Microanalysis Laboratory.

Syntheses. 1A. Diethylamine (0.150 mL, 1.45 mmol) was added to a solution of phosphorane acid **B** (0.500 g, 1.27 mmol) in acetone (10 mL) and the solution kept aside for a week. Then the solution was decanted off, and the crystalline solid present was washed with acetone (2 × 5 mL) and air-dried. Yield: 0.50 g (85%). Mp: >240 °C. ^{31}P NMR (DMF): −135.5. Anal. Calcd for $C_{25}H_{24}NO_6P$: C, 64.51; H, 5.20; N, 3.01. Found: C, 64.45; H, 5.22; N, 3.00.

1B. Triethylamine (0.200 mL, 1.43 mmol) was added to a solution of phosphorane acid **B** (0.500 g, 1.27 mmol) in acetone (10 mL) and the solvent removed. The residue that formed was recrystallized from dichloromethane−heptane (1:1, 20 mL). Yield: 0.40 g (64%). Mp: 204−210 °C. ^{1}H NMR: 1.11 (t, 7.4 Hz, 9H, Me), 2.73 (q, 7.4 Hz, 6H, NCH_2), 6.30 (dd, 18.65, 7.4 Hz, 1H, aryl), 7.25−7.98 (m, 11H, aryl). ^{31}P NMR (CH_2Cl_2): −124.9. ^{31}P NMR (DMF): −135.7. Anal. Calcd for $C_{27}H_{28}NO_6P$: C, 65.71; H, 5.72; N, 2.84. Found: C, 65.43; H, 5.80; N, 2.78.

2. A procedure similar to the synthesis of **1A** was used. Quantities used: (diethylamine) 0.200 mL, 1.93 mmol, (phosphine acid **C**) 0.500 g, 1.63 mmol. The solution was decanted off after 4 h and the resulting crystalline solid washed with acetone (2 × 10 mL) and air-dried. Yield: 0.62 g (100%). Mp: 198−202 °C. ^{1}H NMR: 1.08 (t, 7.4 Hz, 6H, Me), 2.57 (q, 7.4 Hz, 4H, NCH_2), 6.73 (ddd, 7.4, 3.4, 1.0 Hz, 1H, aryl), 7.25 (br m, 11H, aryl), 8.06 (ddd, 7.4, 4.0, 1.4 Hz, 1H, aryl). ^{31}P NMR (CH_2Cl_2): −5.7. ^{31}P NMR (DMF): −6.0. Anal. Calcd for $C_{23}H_{26}NO_2P$: C, 72.81; H, 6.91; N, 3.69. Found: C, 72.50; H, 6.99; N, 3.64.

3. A procedure similar to the synthesis of **1A** was used. Quantities used: (diethylamine) 0.200 mL, 1.93 mmol, (phosphine oxide acid **D**) 0.070 g, 0.22 mmol. Yield: 0.070 g (80%). Mp: 163−166 °C. ^{1}H NMR: 0.96 (t, 7.4 Hz, 6H, Me), 2.69 (q, 7.4 Hz, 4H, NCH_2), 7.10−7.65 (m, 11H, aryl), 8.07 (ddd, 7.4, 3.4, 1.0 Hz, 1H, aryl). ^{31}P NMR (CH_2Cl_2): 30.8. ^{31}P NMR (DMF): 30.3. Anal. Calcd for $C_{23}H_{26}NO_3P$: C, 69.86; H, 6.63; N, 3.54. Found: C, 69.70; H, 6.64; N, 3.49.

X-ray Studies. The X-ray crystallographic studies were performed using a Nonius Kappa CCD diffractometer and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Data were collected at 23 ± 2 °C. All of the data were included in the refinement. The structures were solved by direct methods and difference Fourier techniques and were refined by full-matrix least-squares techniques. Refinements were based on F^2, and computations were performed on a 600 MHz Pentium III computer using SHELXS-86 for solution[11] and SHELXL-97 for refinement.[12] All

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(10) Stec, B.; Holtz, K. M.; Kantrowitz, E. R. *J. Mol. Biol.* **2000**, *299*, 1303.
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Table 1. Crystallographic Data for Compounds **1**−**3**

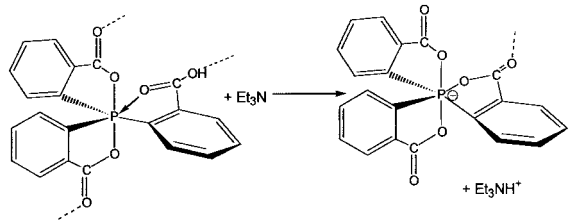
	1A	1B	2	3
empirical formula	$C_{25}H_{24}NO_6P$	$C_{27}H_{28}NO_6P$	$C_{23}H_{26}NO_2P$	$C_{23}H_{26}NO_3P$
fw	465.42	493.47	379.42	395.42
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	Cc	$P2_1/n$	$P2_1/n$
cryst size (mm)	0.50 × 0.30 × 0.20	0.25 × 0.15 × 0.10	0.25 × 0.25 × 0.25	0.50 × 0.25 × 0.08
a (Å)	10.2108(2)	10.2555(4)	9.0370(2)	9.3210(2)
b (Å)	11.9386(2)	28.146(1)	15.8476(5)	14.7405(2)
c (Å)	18.8202(5)	9.4194(5)	14.7986(4)	15.5067(4)
α (deg)	90.00	90.00	90.00	90.00
β (deg)	92.6786(8)	113.106(2)	97.742(2)	100.8712(8)
γ (deg)	90.00	90.00	90.00	90.00
V (Å^3)	2291.73(8)	2500.8(2)	2100.06(10)	2092.33(8)
Z	4	4	4	4
D_{calcd} (g/cm^3)	1.349	1.311	1.200	1.255
$\mu_{Mo\ K\alpha}$ (cm^{-1})	1.62	1.52	1.48	1.54
total no. of reflns	3828	4001	3635	3663
no. of reflns with $I > 2\sigma_I$	3247	3101	2809	2926
R[a]	0.0364	0.0604	0.0462	0.0392
R_w[b]	0.0893	0.1370	0.1168	0.0938

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w(F_o^2) = \{\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4\}^{1/2}$.

of the non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were included in the refinement as isotropic scatterers riding in either ideal positions or with torsional refinement (in the case of methyl hydrogen atoms) on the bonded atoms. The crystals of **1B** belong to a noncentrosymmetric space group, and it was refined as a racemic twin which showed a 60:40 ratio. The final agreement factors are based on the reflections with $I \geq 2\sigma_I$. Crystallographic data are summarized in Table 1.

Results and Discussion

Syntheses. Compounds **1**−**3** were obtained by the addition of either diethylamine or triethylamine to an acetone solution of the appropriate acid **B**−**D**, respectively, and recrystallized directly from the resulting solution. The anionic phosphorane **1B** is highly soluble in polar solvents and hence was crystallized from a heptane−dichloromethane mixture. As representative, eq 1 illustrates the preparation of **1B**.



(1)

^{31}P, -56.9 ^{31}P, -124.9

B **1B**

Structures. The atom labeling schemes for **1**−**3** are given in the ORTEX[13] plots of Figures 1−4 with the thermal ellipsoids at the 40% probability level. Hydrogen atoms are omitted for clarity. Bond parameters are listed in Tables 2−4 for **1**−**3**, respectively.

The crystal structures of the anionic phosphoranes **1A** and **1B**, the phosphine **2**, and the phosphine oxide **3** all have one of the oxygen atoms of the carboxyl group coordinating to the phosphorus atom. Upon removal of the proton from the carboxylic acids **B**−**D**, the phosphorus−oxygen interaction becomes stronger as measured by a comparison of the respective shortening of the P−O distances. These data are summarized in Table 5, where the last column displays the extent to which the shortening took place in each instance. Also listed is the degree to which the increase in coordination caused the structures to be displaced toward a higher coordinate form, an octahedron for **1A** and **1B** and a trigonal bipyramid for **2** and **3**. These values are obtained by assuming a proportional displacement from the sum of the van der Waals radii[14] for phosphorus and oxygen toward that for the sum of the covalent radii,[15] i.e., 3.35 Å vs 1.83 Å.

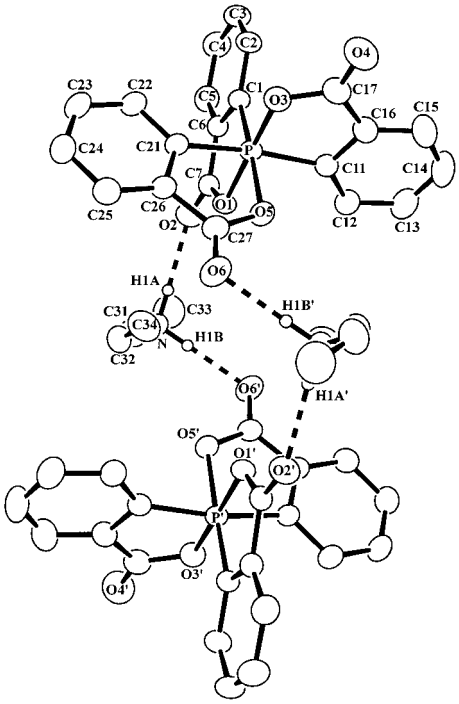


Figure 1. ORTEX diagram of **1A**.

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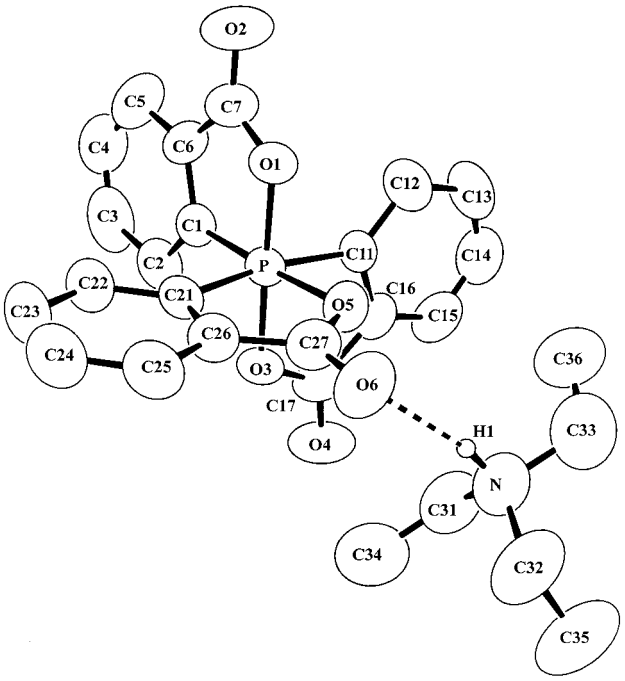


Figure 2. ORTEX diagram of **1B**.

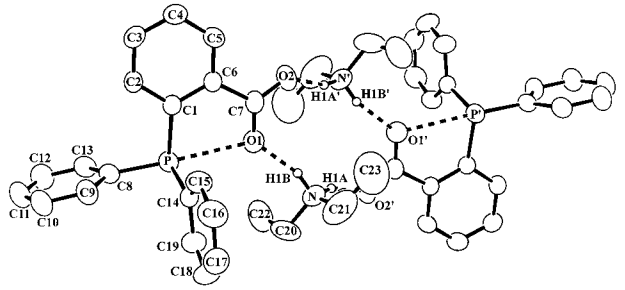


Figure 3. ORTEX diagram of **2**.

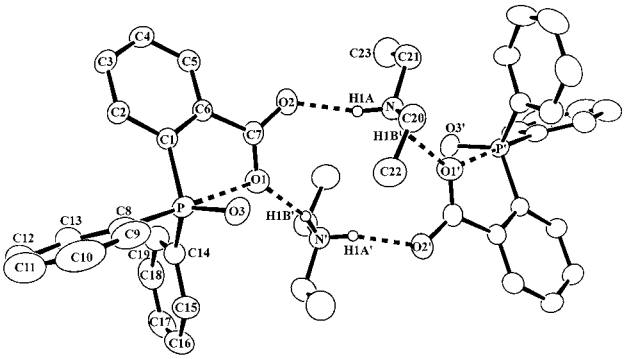


Figure 4. ORTEX diagram of **3**.

The extent of this displacement for **1A** and **1B** is nearly complete, where they are no longer carboxylate anions but are now phosphoranate anions. These are examples of the first hexacoordinate anionic phosphorus compounds containing at least three phosphorus−carbon bonds.

That **1A** and **1B** are now phosphoranates is apparent from the differences in the C−O distances. For **2** and **3**, the C−O distances in the carboxylate groups are very similar, in the range 1.241−1.249 Å as noted in Tables 3 and 4. This is expected for delocalized carboxylate anions. By contrast, the C−O distances for **1A** and **1B** reflect single and double bond values. As seen in Table 2, the oxygen atoms bonded to phosphorus have longer C−O lengths in the range 1.302−1.361 Å. The remaining three C−O bond lengths are shorter, in the range 1.210−1.236 Å.

The donor bond in the anion of **1A** and **1B** is clearly distinguishable since the geometry of the parent acid is retained. In the parent pentacoordinated carboxylic acid, all the phosphorus−carbon bonds are in one plane and the two phosphorus−oxygen bonds are trans to one another.[1b] The same holds true for the hexacoordinate anions also. The sixth coordination in forming the phosphoranate anion occurs opposite to a P−C bond. As expected, due to a poorer trans effect, the resultant P−O bond is weaker as measured by its

Table 2. Selected Bond Lengths (Å) and Angles (deg) for **1A** and **1B**

	1A	**1B**		**1A**	**1B**
P−O(1)	1.796(1)	1.772(3)	O(1)−C(7)	1.322(2)	1.320(7)
P−O(3)	1.746(1)	1.770(3)	O(2)−C(7)	1.223(2)	1.227(7)
P−O(5)	1.901(1)	1.898(3)	O(3)−C(17)	1.339(2)	1.361(6)
P−C(1)	1.849(2)	1.854(5)	O(4)−C(17)	1.210(2)	1.220(6)
P−C(11)	1.854(2)	1.854(5)	O(5)−C(27)	1.302(2)	1.313(6)
P−C(21)	1.857(2)	1.860(4)	O(6)−C(27)	1.229(2)	1.236(6)
O(1)−P−O(3)	176.47(6)	177.7(2)	O(5)−P−C(1)	172.84(7)	176.7(2)
O(1)−P−O(5)	85.54(5)	88.3(2)	O(5)−P−C(11)	83.84(6)	82.8(2)
O(1)−P−C(1)	87.45(6)	88.7(2)	O(5)−P−C(21)	84.34(6)	84.0(2)
O(1)−P−C(11)	92.40(7)	92.0(2)	C(1)−P−C(11)	95.02(7)	95.7(2)
O(1)−P−C(21)	90.20(6)	90.2(2)	C(1)−P−C(21)	97.15(7)	97.6(2)
O(3)−P−O(5)	91.06(6)	89.4(2)	C(11)−P−C(21)	167.65(7)	166.6(2)
O(3)−P−C(1)	95.98(7)	93.5(2)	C(7)−O(1)−P	115.9(1)	115.7(4)
O(3)−P−C(11)	88.16(7)	87.9(2)	C(17)−O(3)−P	116.8(1)	115.0(3)
O(3)−P−C(21)	88.53(7)	89.4(2)	C(27)−O(5)−P	115.7(1)	116.1(3)

Table 3. Selected Bond Lengths (Å) and Angles (deg) for **2**

P−C(1)	1.852(2)	P−O(1)	2.696(2)
P−C(8)	1.848(2)	O(1)−C(7)	1.242(3)
P−C(14)	1.837(2)	O(2)−C(7)	1.246(3)
C(1)−P−C(8)	101.39(9)	C(8)−P−O(1)	174.49(8)
C(1)−P−C(14)	102.87(9)	C(14)−P−O(1)	79.51(8)
C(8)−P−C(14)	97.79(9)	C(7)−O(1)−P	103.07(1)
C(1)−P−O(1)	74.71(7)		

Table 4. Selected Bond Lengths (Å) and Angles (deg) for **3**

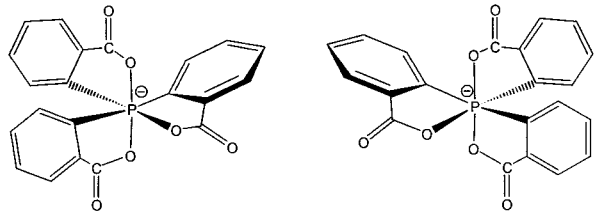
P−O(3)	1.477(1)	P−O(1)	2.863(2)
P−C(1)	1.826(2)	O(1)−C(7)	1.241(2)
P−C(8)	1.821(2)	O(2)−C(7)	1.249(2)
P−C(14)	1.809(2)		
O(3)−P−C(1)	114.45(8)	O(3)−P−O(1)	79.24(8)
O(3)−P−C(8)	109.25(9)	C(1)−P−O(1)	72.44(6)
O(3)−P−C(14)	116.36(8)	C(8)−P−O(1)	170.97(7)
C(1)−P−C(8)	105.69(8)	C(14)−P−O(1)	72.22(6)
C(1)−P−C(14)	109.08(8)	C(7)−O(1)−P	96.1(1)
C(8)−P−C(14)	100.60(8)		

Table 5. Comparison of Oxygen Donor Distances (Å) in the Carboxylate Anions **1**−**3** with Those in the Parent Acids **B**−**D**

neutral compd	P−O distance	% TBP[a]	anionic compd	P−O distance	% TBP[a]	Δ[b]
B	2.984(2)[c]	24	**1A**	1.901(1)	95	1.083
			1B	1.898(1)	96	1.086
C	2.806(1)	36	**2**	2.696(2)	43	0.110
D	3.075(2)	18	**3**	2.863(2)	32	0.212

[a] Percent structural change from a tetrahedron to a TBP except that for **B**, **1A**, and **1B**, which is the percent structural change from a TBP to an octahedron. [b] Δ is the shortening in the P−O donor distance on going to the carboxylate anion from the acid form. [c] Average distance of two structure determinations of crystals of **B** from different solvents. The individual P−O distances are 3.000(2) and 2.967(2) Å.

Chart 1



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longer distance compared to the P−O distances that are trans to each other. As shown in Table 2 for **1A**, the former length is 1.901 Å compared to 1.796 and 1.746 Å for the trans P−O bonds. Similarly for **1B**, the former length is 1.898 Å while the trans P−O bond lengths are 1.772 and 1.770 Å.

The ^{31}P chemical shifts obtained for **1**−**3** and **B**−**D** are indicative of their coordination numbers that are present in the crystal structure determinations. As seen in the schematic representations in the Introduction, there is a strong upfield shift on going from the carboxylic acid form **B** to the anions **1A** and **1B**. This is consistent with the formation of the strong P−O bond, leading to hexacoordination (Table 5). In line with the smaller increase in coordination experienced by the phosphine **2** and the phosphine oxide **3**, the ^{31}P upfield shifts are much less relative to the acid forms.

Chirality.

Since there is no symmetry in the phosphoranates **1A** and **1B**, two possible isomers exist for these asymmetric tricyclic anions. They are shown in Chart 1.

The crystal structure of **1A** in Figure 1 displays isomer I at the top and isomer II at the bottom. For the crystal structure of **1B**, isomer II is presented in Figure 2. Since a chiral selective reagent was not used for **1**, it is expected that both chiral isomers are present in equal amounts. This is apparent from the crystal data, which show that both **1A** and **1B** belong to nonchiral space groups.

Hydrogen Bonding. The crystal structures of **2** and **3** (Figures 3 and 4) reveal dimer formations due to the presence of hydrogen bonding similar to the dimers found for the structures of the acid forms **C** and **D**. However, the hydrogen bonds in the present study are a result of interactions between the carbonyl oxygens and the protons of the cationic amines, giving C═O−H−N interactions, whereas the hydrogen bonds involving the acid forms result in O−H−O interactions. The phosphoranate **1A** also exists in a hydrogen-bonded dimer arrangement (Figure 1), while **1B** is represented as a simple anion−cation hydrogen-bonded structure (Figure 2) by necessity since the cation has only one hydrogen atom. The schematic of Figure 5 perhaps renders the hydrogen bonding more clearly. Table 6 lists the hydrogen bond parameters for **1**−**3**.

It is possible to compare P−O donor coordination and hydrogen bonding in a more quantitative fashion. The hydrogen bond interactions shown in Table 6 are shorter for **2** and **3** and are confined to a narrow range, 2.66−2.73 Å. Examination of the literature on N−H−O hydrogen bonding with regard to the relation between enthalpy and P−O

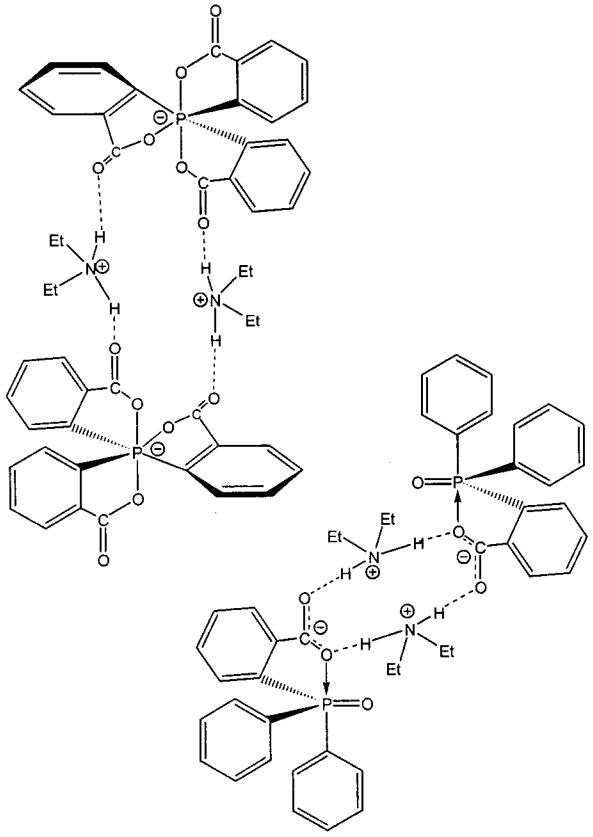

Figure 5. Schematic illustrating the hydrogen-bonded dimer arrangement for **1A** (top) and **3** (bottom). The dimer depiction for **2** is similar to that for **3**.

Table 6. Hydrogen Bond Distances (Å) and Angles (deg) for **1**−**3**[a]

	D−H···A	*d*(D−H)	*d*(H···A)	*d*(D···A)	∠(DHA)
1A	N−H1A···O2	0.90	1.93	2.822(2)	171
1A	N−H1B···O6 (−*x* , 1 − *y*, 1 − *z*)	0.90	1.89	2.777(2)	169
1B	N−H1···O6	0.91	2.02	2.914(8)	169
2	N−H1B···O1	0.90	1.80	2.664(3)	159
2	N−H1A···O2 (−*x* , 1 − *y*, 2 − *z*)	0.90	1.84	2.705(3)	162
3	N−H1A···O2	0.90	1.85	2.732(2)	167
3	N−H1B···O1 (−*x*, 1 − *y*, 1 − *z*)	0.90	1.82	2.692(2)	162

[a] D is the hydrogen atom donor, and A is the hydrogen atom acceptor.

distance[16] suggests that a value of about 4.5 kcal/mol applies here. The phosphoranates **1A** and **1B** that have achieved hexacoordination by forming a covalent P−O bond have longer hydrogen bond distances, presumably because of the reduced electron density at the carbonyl oxygen atom.

To establish a relationship between P−O bond distance and interaction energy, we employed an exponential function governing these quantities. The P−O single bond energy is estimated as 80 kcal/mol, and the sum of the covalent radii of phosphorus and oxygen is 1.83 Å.[17] With the use of the sum of the van der Waals radii of 3.35 Å for these two atoms and setting this distance to correspond to zero P−O bond energy, one may define the exponential relation to connect these limits.

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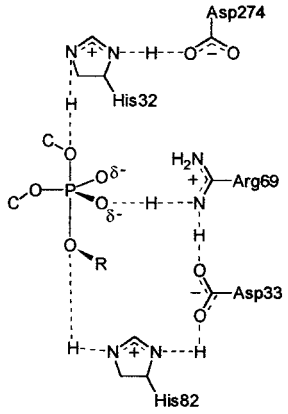
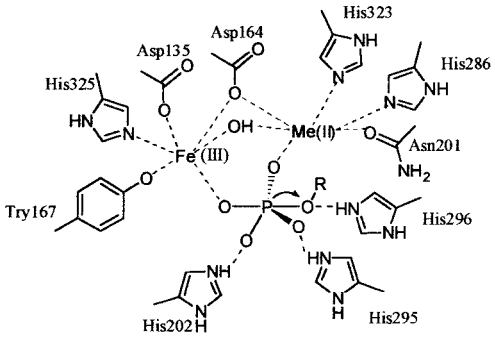
Chart 2



(a) a proposed intermediate in phosphate activation by PI-PLC.



(b) a proposed intermediate for the hydrolysis of phosphomonoesters by PAP.

This procedure allows an estimation of the P−O donor energies for **1**−**3**. These are in kilocalories per mole (**2**) 16 and (**3**) 6.5. The close approach of the P−O bond distance to the covalent value for the phosphoranates **1A** and **1B** suggests that their energy is near 80 kcal/mol. This same procedure for the acid forms gave P−O values in kilocalories per mole (**C**) 10, (**D**) 3.5, and (**B**) 5.0.[1b] For these latter substances, the P−O donor energies were estimated to range from less than to more than the O−H−O hydrogen bond energy, which was assigned a value of 5.5 kcal/mol.[16] In the present series, the anionic forms **1**−**3** have greater P−O donor energies than the acid forms as reflected in the shorter P−O distances (Table 5), and as a consequence, these values all exceed the estimated hydrogen bond energies.

The present anionic series **1**−**3** and their precursor acid forms **B**−**D** all possess three aryl bonds to phosphorus and as such are not the most electrophilic. In our previous studies where we employed more electrophilic compounds, phosphates, phosphites, and pentaoxyphosphoranes, containing flexible eight-membered ring systems, it was found that donor action for these neutral entities lacking hydrogen bonding increased in that order.[4−8,18−32] For example, the P−O donor distances for the pentaoxyphosphoranes spanned the range from 1.94 to 2.65 Å.[6,7] This corresponds to a displacement from a TBP to an octahedron from 28% to 82%, with the upper part of the range approaching that observed in the phosphoranate anions **1A** and **1B**.

Application to Enzyme Active Sites. At present, mechanistic models of nucleophilic diplacement reactions of phosphoryl-transfer enzymes invariably depict a hydrogen-bonded, anionic phosphate undergoing in-line attack, leading to a trigonal-bipyramidal transition state. In the present study, we have demonstrated that P−O coordination is enhanced by the presence of anionic donors which are involved in a hydrogen-bonded network. In previous work, we have shown that P−O donor action is enhanced on going from phosphates to pentaoxyphosphoranes.[2−8] On this basis, it seems reasonable to assume that the initial TBP transition state formed by in-line attack by a nucleophile may undergo rate enhancement from a nearby residue at the active site capable of donor interaction at phosphorus, leading to a hexacoordinated state. We have reported an outline of this type of mechanism.[8]

Recent enzymatic studies continue to focus solely on proposed TBP transition states, e.g., the mechanistic study of the cleavage of the phosphate P−O bond by phosphatidylinositol-specific phospholipase C (PI-PLC)[33] and the hydrolysis of phosphomonoesters by purple acid phosphatase (PAP).[34] Potential donor oxygens from active site residues exist in these enzymes as they do in many other phosphoryl-transfer enzymes.[2,35−39] In the former system, carboxylate goups are present in the form of an Asp residue, Chart 2a. In the latter enzyme, in addition to four Asp residues at the active site, there is a carboxylate-containing Glu, a Tyr, and an Asn residue, Chart 2b. In addition, one may not easily discount the role of water molecules that are prevalent and serve as potential donor molecules as well as their role as

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nucleophiles in initiating attack of a phosphate substrate. Previously, reference was made to the proposed transition state in the activation of tyrosine by the tyrosyl-tRNA synthetase system,[40] where we suggested that donor action by a carboxylate oxygen atom promotes the formation of a hexacoordinate structure.

Summary and Conclusion

Previous work has demonstrated the ease with which phosphorus can increase its coordination geometry. The present study has more closely modeled active sites of phosphoryl-transfer enzymes by the inclusion of anionic groups that allow for oxygen atom donor coordination at phosphorus in the presence of a hydrogen-bonding network. The resulting increase in phosphorus−oxygen donor coordination compared to that in analogous systems containing neutral phosphorus compounds serves as a model applicable to proposed mechanisms at active sites of phosphoryl-transfer enzymes.

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Supporting Information Available: Further crystallographic details and X-ray crystallographic files in CIF format for **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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