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Influence of Hydrogen Bonding in Competition with Lattice Interactions on Carbonyl Coordination at Phosphorus. Implications for Phosphoryl Transfer Activated States[1]

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A series of phosphorus compounds containing carboxyl groups that serve as mimics for amino acid residues was synthesized. The series was composed of the phosphonium salts **1A**, **1B**, and **2**, the anionic phosphines **3A** and **3B**, and the anionic phosphine oxide **4**. X-ray structural analysis revealed that P–O coordination occurred in the presence of extensive hydrogen bonding and led to pseudo or regular trigonal bipyramidal geometries. ^{31}P chemical shifts indicated retention of the basic coordination geometries in solution. The two forms observed for **1** and **3** revealed the influence of hydrogen bonding on the P–O donor interactions while **2** and **4** showed the influence of molecular packing effects in competition with hydrogen bonding interactions. The results suggest that phosphoryl transfer enzyme mechanisms should benefit by taking into account P–O donor interactions by residues at active sites that can be manipulated by hydrogen bonding and molecular packing effects in enhancing nucleophilic attack at phosphorus centers.

Introduction

On the basis of past work in our laboratory, it is our contention that active site residues, if properly positioned at active sites of phosphoryl transfer enzymes, will enter into donor interaction at the phosphorus atom and hence assist in nucleophilic attack.[2] In continuation of our research to examine factors present at active sites of this class of enzymes that may enhance nucleophilic attack at phosphorus centers, we report the influence of hydrogen bonding in competition with molecular packing effects in effecting P−O donor interactions. For this purpose, a series was prepared that consisted of both anionic and positively charged phosphorus compounds containing carboxyl groups. The series comprised the phosphonium salts **1A**, **1B**, and **2**, the anionic phosphines **3A** and **3B**, and the anionic phosphine oxide **4**, Chart 1. This extends our studies on oxygen atom donor action[3,4] where the oxygen atoms of the carboxyl groups serve as mimics for amino acid residues, in particular, the carboxylate containing amino acids, glutamate (Glu), and aspartate (Asp). Syntheses, X-ray analyses, and ^{1}H and ^{31}P NMR measurements are performed to establish the structural arrangements of **1**−**4** in solution and in the solid state.

In an earlier paper, we examined the competition between hydrogen bonding and P−O donor interaction in a series of phosphorus compounds containing anionic carboxylate groups, Chart 2 (compounds **8**−**10**).[3a] Evaluation of the energies of the donor interactions relative to the energies of the hydrogen bonds that were present showed that the donor energies exceeded the hydrogen bond strengths. In the respective neutral acid forms, Chart 2 (compounds **5**−**7**),[4] the P−O donor interactions were weaker than the hydrogen bonding interactions. In this comparative study, it was concluded that the presence of negative charges in the donor centers improved coordination at phosphorus.

Experimental Section

Diphenylphosphinobenzoic acid (**5**) (Aldrich) and benzyl bromide (Fluka) were used as supplied. Diphenylphosphinoylbenzoic acid (**6**)[4] and tris(2-hydroxy-3,5-dimethylbenzyl)amine[5] were synthesized

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(1) (a) Pentacoordinated Molecules. Part 138. (b) Part 137: Timosheva, N. V.; Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7035−7040.

(2) Holmes, R. R. *Acc. Chem. Res.* **1998**, *31*, 535−542 and references therein.

(3) (a) Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *Inorg. Chem.* **2002**, *41*, 1645−1651. (b) Timosheva, N. V.; Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *Inorg. Chem.* **1998**, *37*, 3862−3867.

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(5) Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 1066−1072.

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Chart 1

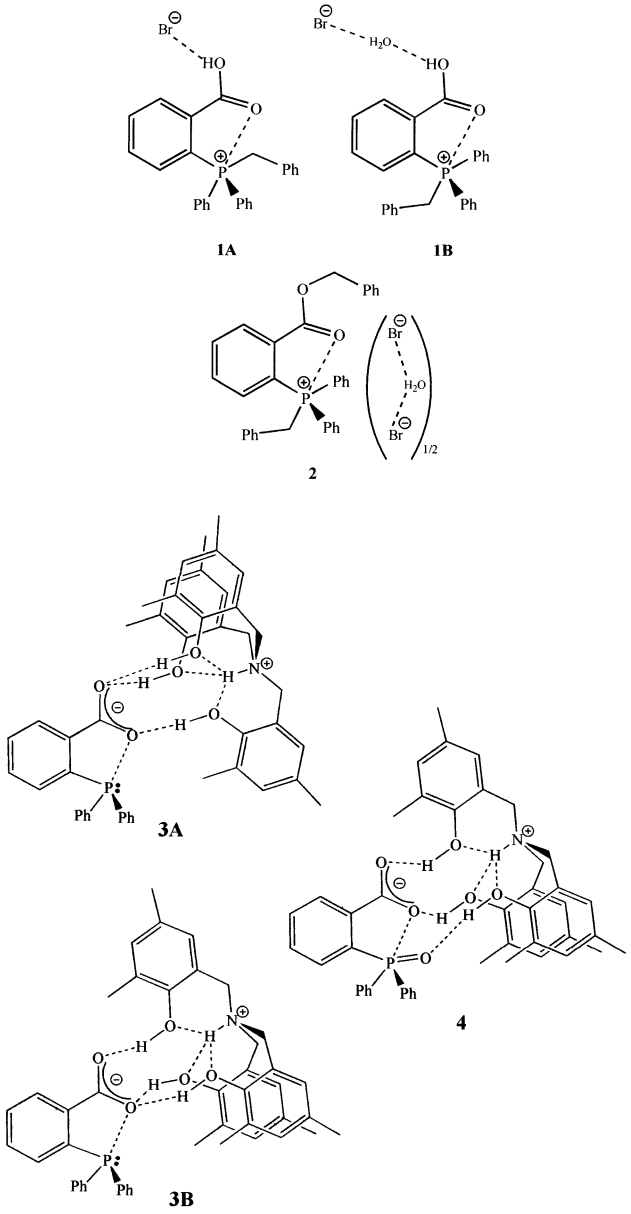
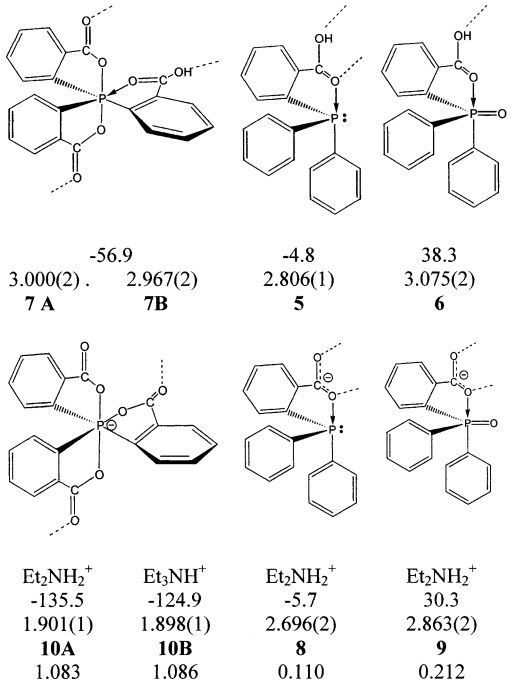


Chart 2



^{31}P, ppm	-56.9		-4.8	38.3
P-O, Å	3.000(2) .	2.967(2)	2.806(1)	3.075(2)
	7 A	**7B**	**5**	**6**

	$Et_2NH_2^+$	Et_3NH^+	$Et_2NH_2^+$	$Et_2NH_2^+$
^{31}P, ppm	-135.5	-124.9	-5.7	30.3
P-O, Å	1.901(1)	1.898(1)	2.696(2)	2.863(2)
	10A	**10B**	**8**	**9**
Δ, Å	1.083	1.086	0.110	0.212

according to our earlier methods. Solvents were purified according to standard procedures.[6] All the reactions and crystallizations were carried out under atmospheric conditions. ^{1}H NMR spectra were recorded on a Bruker AC200 FT-NMR spectrometer. ^{31}P NMR spectra were recorded on a Bruker DPX300 FT-NMR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, and the ^{31}P spectra were recorded in CH_2Cl_2 in the sweep-off mode, unless mentioned otherwise. Chemical shifts are reported in ppm, downfield positive relative to tetramethylsilane or 85% H_3PO_4 and were recorded at 23 °C. Elemental analyses were performed by the University of Massachusetts Microanalysis Laboratory.

Syntheses. [$Ph_2P(2\text{-}C_6H_4CO_2H)(CH_2Ph)$] Br (1). To a solution of diphenylphosphinobenzoic acid (Ph_2P-2-C_6H_4COOH) (**5**) (1.03 g, 3.36 mmol) in dichloromethane (50 mL) was added benzylbromide (0.40 mL, 3.37 mmol). The clear solution was left aside for 24 h to get the crystalline compound (in the form **1A**), which was filtered, washed with dichloromethane (5 mL), and air-dried. Yield 1.60 g (85%, with 1 CH_2Cl_2); mp > 240 °C (d). ^{1}H NMR: 4.90 (d, 14.1 Hz, 2H, PCH_2), 7.10−7.84 (m, 19H, Aryl), 8.55 (m, 1H, Aryl). ^{31}P NMR(MeOH): 27.0. Anal. Calcd for $C_{26}H_{22}O_2PBr\cdot CH_2Cl_2$: C, 57.68; H, 4.30. Found: C, 57.88; H, 4.19.

The hydrated form **1B** was obtained when **1A** was crystallized from a mixture of acetone and ethanol (9:1). Anal. Calcd for $C_{26}H_{22}O_2PBr\cdot H_2O$: C, 63.04; H, 4.88. Found: C, 62.72; H, 4.65.

[$Ph_2P(2\text{-}C_6H_4CO_2CH_2Ph)(CH_2Ph)$] Br (2). To a solution of diphenylphosphinobenzoic acid (Ph_2P-2-C_6H_4COOH) (**5**) (0.500 g, 1.63 mmol) and sodium bicarbonate (0.140 g, 1.67 mmol) in dimethyl sulfoxide (DMSO, 5 mL) was added benzylbromide (0.40 mL, 3.36 mmol). The clear solution was left aside for a week, and water (10 mL) was added. The solution was decanted and the crystalline solid recrystallized from ethanol (10 mL), washed with ethanol (there was some loss during the washing), and air-dried. Yield 0.50 g (54%, with 0.5 water); mp 180−182 °C (d). ^{1}H NMR: 5.06 (s, 2H, OCH_2), 5.24 (d, 14.1 Hz, 2H, PCH_2), 6.94 (m, 2H, Aryl), 7.10−7.35 (m, 9H, Aryl), 7.52−7.70 (m, 10H, Aryl), 7.96 (m, 2H, Aryl), 8.36 (m, 1H, Aryl). ^{31}P NMR(MeOH): 26.8. Anal. Calcd for $C_{33}H_{28}O_2PBr\cdot 1/2H_2O$: C, 68.76; H, 5.07. Found: C, 68.54; H, 5.44.

[$Ph_2P(2\text{-}C_6H_4CO_2)$] [$HN(CH_2C_6H_2Me_2OH)_3$] (3). Diphenylphosphinobenzoic acid (Ph_2P-2-C_6H_4COOH) (**5**) (0.10 g, 0.33 mmol) and tris(2-hydroxy-3,5-dimethylbenzyl)amine (0.14 g, 0.33 mmol) were dissolved in hot acetone (10 mL) and allowed to stand overnight to obtain needlelike crystals. Yield 0.25 g, 93% (with 1.5 acetone). Mp 158−160 °C. ^{1}H NMR: 2.10 (s, 9H, 1.5 acetone), 2.17 (s, 18H, CH_3), 3.99 (s, 6H, NCH_2), 6.67 (s, 3H, Aryl), 6.88 (s, 3H, Aryl), 7.25(m, 12H, Aryl), 7.38 (td, 7.3, 1.3 Hz, 1H, Aryl), 8.24 (ddd, 7.3, 4.8, 1.3 Hz, 1H, Aryl). ^{31}P NMR(CH_2Cl_2): −7.3. Anal. Calcd for $C_{46}H_{48}NO_5P\cdot 1.5C_3H_6O$: C, 76.12; H, 6.67; N, 1.93. Found: C, 75.74; H, 6.55; N, 1.89. The unsolvated form **3B** was obtained as thick plates when **3A** was crystallized from methanol.

[$Ph_2P(O)(2\text{-}C_6H_4CO_2)$] [$HN(CH_2C_6H_2Me_2OH)_3$] (4). Diphenylphosphinoylbenzoic acid $Ph_2P(O)$(2-C_6H_4COOH) (**6**) (45 mg,

(6) (a) Riddick, J. A.; Bunger, W. B. *Organic Solvents: Physical Properties and Methods of Purification*, 3rd ed; Techniques of Chemistry Series; Wiley-Interscience: New York, 1970; Vol. II. (b) Vogel, A. I. *Textbook of Practical Organic Chemistry*; Longman: London, 1978.

Table 1. Crystallographic Data for Compounds **1**−**4**

	1A	1B	2	3A	3B	4A	4B
formula	$C_{26}H_{22}O_2P\cdot Br\cdot CH_2Cl_2$	$C_{26}H_{22}O_2P\cdot Br\cdot H_2O$	$C_{33}H_{28}O_2P\cdot Br\cdot 1/2H_2O$	$C_{19}H_{14}O_2P\cdot C_{27}H_{34}O_3\cdot 1.5C_3H_6O$	$C_{19}H_{14}O_2P\cdot C_{27}H_{34}NO_3$	$C_{19}H_{14}O_3P\cdot C_{27}H_{34}NO_3\cdot 2.5CH_2Cl_2$	$C_{19}H_{14}O_3P\cdot C_{27}H_{34}NO_3\cdot 0.5C_3H_6O$
fw	562.24	495.33	576.44	812.94	725.82	951.11	770.86
cryst syst	triclinic	monoclinic	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P2_1/n$	$Pbca$	$C2/c$	$P2_1$	$P2_1/n$	$P2_1/c$
cryst size, mm^3	0.25 × 0.25 × 0.10	0.90 × 0.75 × 0.75	0.35 × 0.25 × 0.20	0.70 × 0.17 × 0.08	0.70 × 0.50 × 0.30	1.50 × 0.25 × 0.25	0.25 × 0.25 × 0.01
a (Å)	9.9695(3)	10.2857(2)	15.03260(10)	24.2705(2)	11.11280(10)	15.3662(2)	22.6658(8)
b (Å)	11.0013(4)	18.7793(3)	19.08780(10)	13.2047(4)	14.2208(2)	13.22590(10)	16.5115(4)
c (Å)	13.2255(6)	12.5922(2)	59.0383(5)	30.1932(4)	13.1669(2)	25.7310(4)	12.2915(3)
α (deg)	75.8623(12)	90	90	90	90	90	90
β (deg)	80.0830(13)	101.4226(7)	90	107.6908(5)	75.2424(5)	100.2998(5)	104.8739(10)
γ (deg)	72.456(2)	90	90	90	90	90	90
V ($Å^3$)	1333.53(9)	2384.11(7)	16940.4(2)	9218.9(3)	2012.16(5)	5145.09(11)	4445.9(2)
Z	2	4	24	8	2	4	4
D_{calcd} (g/cm^3)	1.400	1.380	1.356	1.171	1.198	1.228	1.152
μ(Mo Kα) (cm^{-1})	18.23	18.16	15.43	1.09	1.14	3.58	1.10
total reflns	4454	4188	14274	8899	8190	8550	7812
reflns with $I > 2\sigma_I$	3652	3366	8153	5503	7082	5642	4004
R^a	0.0552	0.0351	0.0673	0.0783	0.0411	0.0976	0.0927
$R_w{}^b$	0.1492	0.0814	0.1390	0.2000	0.1016	0.2794	0.2191

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

0.14 mmol) and tris(2-hydroxy-3,5-dimethylbenzyl)amine (0.60 mg, 0.14 mmol) were dissolved in hexane−dichloromethane (1:1, 10 mL) and left for slow evaporation. Extremely sensitive needle crystals resulted, which lost the solvent (2.5 CH_2Cl_2) very readily. Yield 95 mg (91%, without solvent); mp 174−178 °C (d). ^{1}H NMR: 2.04 (s, 9H, CH_3), 2.15 (s, 9H, CH_3), 3.96 (s, 6H, NCH_2), 6.62 (s, 3H, Aryl), 6.79 (s, 3H, Aryl), 7.04(m, 1H, Aryl), 7.3−7.7(m, 12H, Aryl), 8.14 (m, 1H, Aryl). ^{31}P NMR(CH_2Cl_2): 31.8. Anal. Calcd for $C_{46}H_{48}NO_6P$: C, 74.48; H, 6.52; N, 1.89. Found: C, 74.32; H, 6.55; N, 1.92. The more stable crystalline form **4B** (with 0.5 acetone) was obtained when **4A** was crystallized from acetone.

X-ray Studies. The X-ray crystallographic studies were performed using an Nonius Kappa CCD diffractometer and graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Data were collected at 23 ± 2 °C for $\theta_{MoK\alpha} \leq 25°$. All 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. Refinements were based on F^2, and computations were performed on a 600 MHz Pentium III computer using SHELXS-86 for solution[7] and SHELXL-97 for refinement.[8] All of the non-hydrogen atoms, except those of disordered solvents, were refined anisotropically. The carboxyl hydrogen atom was included in the calculated position. The hydrogen atoms of the OH groups were located from difference Fourier techniques and refined isotropically, except for the hydrogens of water in **2** which were not included in the calculations. The hydrogens attached to disordered atoms were not included in the calculations. The remaining 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 final agreement factors are based on the reflections with $I \geq 2\sigma_I$. Crystallographic data are summarized in Table 1.

In **1A**, the dichloromethane molecule was disordered with the chlorine atoms having three sets of positions with a 50:30:20 occupancy ratio. The acetone molecules of **3A** were highly disordered, and the carbons and oxygen atoms could not be distinguished due to the disorder. Crystals of **4A** had the most badly behaved dichloromethane molecules which were refined with 5, 7, and 4 positions for chlorines with equal occupancy (four positions for the solvent with half occupancy). Data collection at low temperature (173 K) made these positions more complicated, suggesting a static disorder rather than a dynamic disorder. The half acetone molecule of **4B** was fairly well behaved. However, it was refined at the isotropic level, and no hydrogen atoms were included.

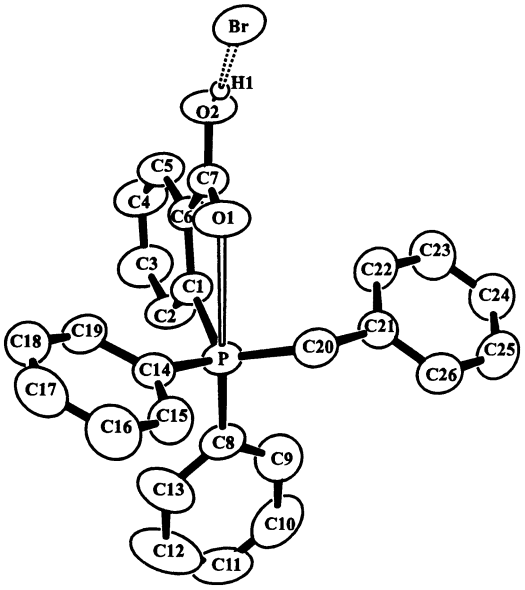


Figure 1. ORTEP diagram of **1A**.

Results and Discussion

The atom-labeling schemes for **1**−**4** are given in the ORTEP[9] plots of Figures 1−6. The thermal ellipsoids are shown at the 50% probability level, and all C−H hydrogen atoms are omitted for clarity. Selected bond parameters are given in Tables 2−5.

(7) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.
(8) Sheldrick, G. M. *SHELXL-97: program for crystal structure refinement*; University of Göttingen: Göttingen, Germany, 1997.
(9) *ORTEP-III for Windows*: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

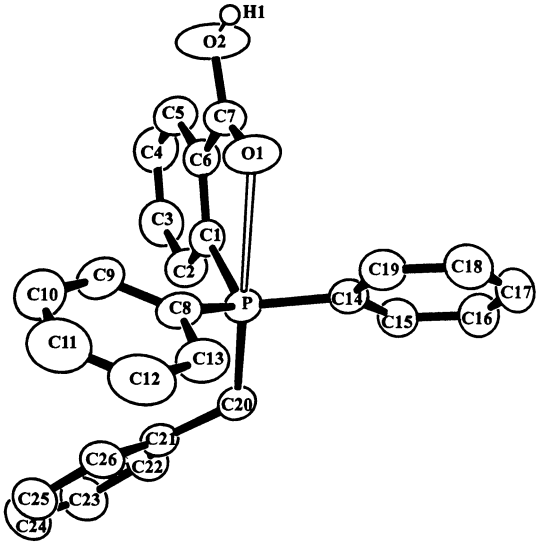


Figure 2. ORTEP diagram of **1B**.

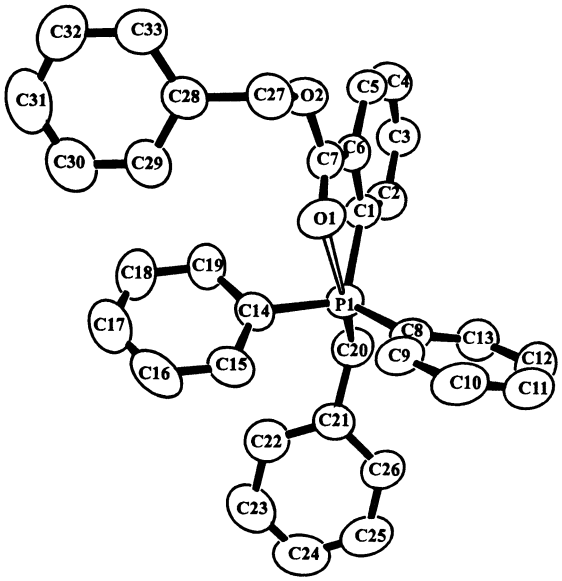


Figure 3. ORTEP diagram of one molecule of **2**. The other two molecules are identical with **A** and **B** used as suffixes in the labeling.

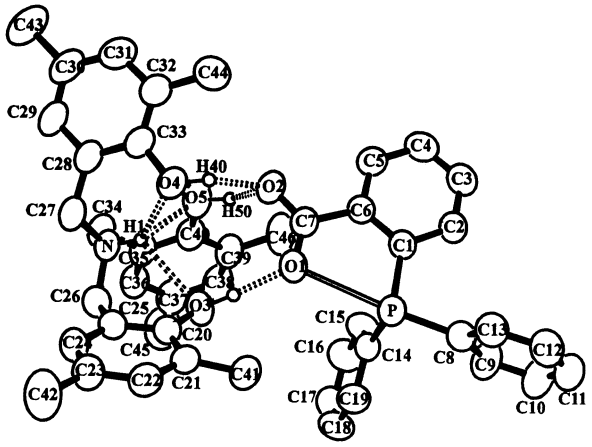


Figure 4. ORTEP diagram of **3A**.

Syntheses. Quaternary phosphonium salt **1** was obtained by reacting phosphine **5** with 1 mol of benzyl bromide. Salt **2** was obtained by reacting phosphine **5** with 2 mol of benzyl bromide in the presence of 1 mol of sodium bicarbonate. The carboxylate salts (**3** and **4**) were prepared by mixing the appropriate acid (**5** or **6**, respectively) with tris(2-hydroxy-3,5-dimethylbenzyl)amine.

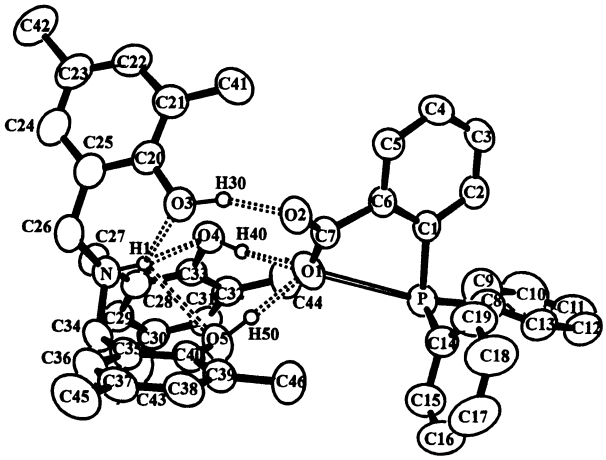


Figure 5. ORTEP diagram of **3B**.

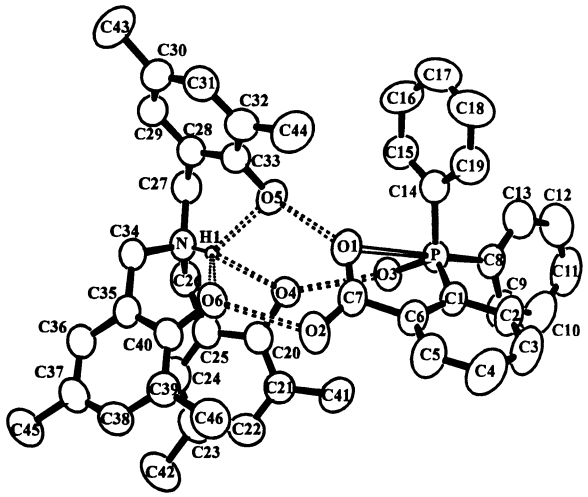


Figure 6. ORTEP diagram of **4A**. The structure of **4B** is identical.

Table 2. Selected Bond Lengths [Å] and Angles [deg] for **1A** and **1B**

param	1A	1B
P−C(1)	1.826(4)	1.808(2)
P−C(8)	1.804(4)	1.791(2)
P−C(14)	1.801(4)	1.801(2)
P−C(20)	1.816(4)	1.826(2)
P−O(1)	2.827(3)	2.757(2)
O(1)−C(7)	1.210(5)	1.195(3)
O(2)−C(7)	1.310(5)	1.300(3)
C(1)−P−C(8)	106.2(2)	112.3(1)
C(1)−P−C(14)	110.5(2)	113.8(1)
C(1)−P−C(20)	117.1(2)	109.2(1)
C(8)−P−C(14)	106.7(2)	114.5(1)
C(8)−P−C(20)	106.8(2)	104.0(1)
C(14)−P−C(20)	109.0(2)	102.0(1)
C(1)−P−O(1)	72.9(2)	73.78(8)
C(8)−P−O(1)	178.9(2)	73.50(8)
C(14)−P−O(1)	74.2(2)	77.53(8)
C(20)−P−O(1)	73.3(2)	176.84(8)
C(7)−O(1)−P	98.6(3)	99.5(2)

Structures. The crystal structures of the phosphonium salts **1** and **2**, phosphine **3**, and phosphine oxide **4** were determined by single-crystal X-ray diffraction. Compound **1** has a carboxylic acid group, and **2** has a carboxyl ester group, with

Table 3. Selected Bond Lengths [Å] and Angles [deg] for **2**

param	molecule 1	molecule A	molecule B
P(1)−C(1)	1.824(5)	1.818(5)	1.819(5)
P(1)−C(8)	1.799(5)	1.790(5)	1.794(5)
P(1)−C(14)	1.794(5)	1.785(5)	1.799(5)
P(1)−C(20)	1.824(5)	1.822(5)	1.817(5)
P(1)−O(1)	2.807(4)	2.970(4)	2.831(4)
O(1)−C(7)	1.203(6)	1.179(6)	1.214(6)
O(2)−C(7)	1.330(6)	1.337(7)	1.334(6)
C(1)−P(1)−C(8)	111.0(2)	107.0(2)	111.1(2)
C(1)−P(1)−C(14)	110.8(2)	112.9(2)	110.4(2)
C(1)−P(1)−C(20)	105.3(2)	106.9(2)	106.3(2)
C(8)−P(1)−C(14)	115.6(2)	116.6(3)	115.6(2)
C(8)−P(1)−C(20)	107.6(2)	109.0(3)	105.3(2)
C(14)−P(1)−C(20)	105.8(2)	104.0(2)	107.6(2)
C(1)−P(1)−O(1)	73.5(2)	71.6(2)	72.8(2)
C(8)−P(1)−O(1)	76.4(2)	81.8(2)	70.5(2)
C(14)−P(1)−O(1)	71.3(2)	67.4(2)	77.7(2)
C(20)−P(1)−O(1)	175.9(2)	168.7(2)	174.5(2)
C(7)−O(1)−P(1)	97.5(3)	92.0(3)	97.4(3)

Table 4. Selected Bond Lengths [Å] and Angles [deg] for **3A** and **3B**

param	**3A**	**3B**
P−C(1)	1.849(4)	1.855(2)
P−C(8)	1.842(3)	1.840(2)
P−C(14)	1.831(3)	1.847(3)
P−O(1)	2.729(3)	2.898(2)
O(1)−C(7)	1.243(4)	1.253(3)
O(2)−C(7)	1.267(4)	1.260(2)
C(1)−P−C(8)	101.12(15)	101.28(10)
C(1)−P−C(14)	102.70(15)	99.25(10)
C(8)−P−C(14)	99.89(15)	101.37(11)
C(1)−P−O(1)	74.42(12)	72.87(7)
C(8)−P−O(1)	175.53(13)	165.45(10)
C(14)−P−O(1)	80.98(12)	92.80(8)
C(7)−O(1)−P	102.2(2)	94.32(12)

Table 5. Selected Bond Lengths [Å] and Angles [deg] for **4A** and **4B**

param	**4A**	**4B**
P−O(3)	1.490(3)	1.487(4)
P−C(1)	1.820(5)	1.819(5)
P−C(8)	1.807(5)	1.821(5)
P−C(14)	1.792(5)	1.786(6)
P−O(1)	2.944(4)	2.817(4)
O(1)−C(7)	1.234(6)	1.201(7)
O(2)−C(7)	1.245(6)	1.238(7)
O(3)−P−C(1)	115.0(2)	115.9(2)
O(3)−P−C(8)	107.9(2)	107.6(2)
O(3)−P−C(14)	114.8(2)	115.2(2)
C(1)−P−C(8)	105.5(2)	105.0(2)
C(1)−P−C(14)	108.4(2)	107.9(3)
C(8)−P−C(14)	104.3(2)	104.2(2)
O(3)−P−O(1)	77.4(2)	75.6(2)
C(1)−P−O(1)	70.4(2)	72.8(2)
C(8)−P−O(1)	174.5(2)	176.8(2)
C(14)−P−O(1)	74.1(2)	74.6(2)
C(7)−O(1)−P	89.1(3)	96.1(3)

the carbonyl oxygen atom in each case interacting with the phosphorus atom, whereas in **3** and **4**, a carboxylate oxygen atom interacts with the phosphorus atom.

More than one form is found for each of the compounds **1**−**4**. Compounds **1**, **3**, and **4** crystallize in different space groups when they are obtained from different solvents.

Suffixes **A** and **B** are used to distinguish one form from the other. Compound **2** shows different behavior. It crystallizes with three independent molecules in each asymmetric unit in the same crystal lattice and does so with considerable variation in P−O distances. This variation that extends from 2.807(4) to 2.970(4) Å must result from crystal lattice effects that have their basis in van der Waals terms which act to alter the packing arrangements of the three molecules.

Table 6. P−O Donor Distances (Å) and ^{31}P Chemical Shifts (ppm)

compd	P−O donor distance	% TBP[a]	^{31}P
1A	2.827(3)	34	24.3
1B	2.757(2)	39	
2	2.807(4)	36	26.8
	2.831(4)	34	
	2.970(4)	25	
3A	2.729(3)	41	−7.3
3B	2.898(2)	30	
4A	2.944(4)	27	31.8
4B	2.817(4)	35	
5[c]	2.806(1)	36	−4.8
6[c]	3.075(2)	18	38.3
7A[c]	3.000(2)	23[b]	−56.9
7B[c]	2.967(2)	25[b]	
8·Et$_2$NH[d]	2.696(2)	43	−5.7
9·Et$_2$NH[d]	2.863(2)	32	30.3
10A·Et$_2$NH[d]	1.901(1)	95[b]	−135.5
10B·Et$_3$N[d]	1.898(3)	96[b]	−124.9

[a] Percent displacement toward a trigonal bipyramid (except for **7** and its salts **10**). [b] Percent displacement toward an octahedron (two forms are known). [c] Ref 4. [d] Ref 3a.

P−O Donor Coordination. In all the molecules studied here, donor coordination by the carbonyl groups exists to varying extents as measured by the degree to which the structures are displaced toward a trigonal bipyramidal (TBP) geometry with the donor oxygen atoms positioned at axial sites, Figures 1−6. These structural displacements are listed as %TBP in Table 6 and cover the range from 25% to 41%. The displacement toward a trigonal bipyramid was determined by the extent to which the P−O donor distance differed from the sum of the van der Waals distance divided by the difference between the sums of the van der Waals distance and the covalent bond length for the P−O bond. The sums of the radii used were 3.35[10] versus 1.83 Å.[11]

In **3**, a lone pair occupies an equatorial site leading to a pseudo TBP geometry. In **1B** and **2**, the benzyl group occupies the axial position trans to the donor atom, whereas in **1A**, one of the phenyl groups is in an axial position, leaving the benzyl group at an equatorial site. The phosphoryl oxygen atom in **4** is at an equatorial position as expected,[12] and one of the phenyl groups is opposite the donor atom.

It is instructive to compare **1**−**4** with studies that were conducted on the series of phosphorus compounds **5**−**7** containing carboxyl groups[4] and their anionic counterparts **8**−**10**.[3a] The latter species were obtained by treatment of the precursor acid forms with amines which also served to introduce hydrogen bonding interactions. The structures shown in Chart 2, hexacoordinated anionic phoshoranate **10A** and **10B**, trigonal bipyramidal anionic phosphine **8**, and trigonal bipyramidal phosphine oxide **9**, revealed the presence

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of P−O donor coordination that was stronger for all anionic members than that which existed in the neutral precursor acid forms **5**−**7**.[3a] The extent of the P−O bond distance shortening is expressed by the Δ values listed at the bottom of Chart 2.

The ^{31}P chemical shifts displayed in Table 6 for phosphonium salts **1** and **2**, phosphine **3**, and phosphine oxide **4** are in the range found for compounds of these types that possess weak donor coordination and are displaced toward TBP geometries.[3,4,13] By contrast, much more upfield ^{31}P shifts are noted for the phosphorane **7** and the anionic phosphoranates **10A** and **10B** which are displaced toward octahedral geometries.

On going from the phosphines to the phosphine oxides, as shown in Table 6 and Chart 2, P−O coordination decreased for the three pairs: from **3A** to **4**, from **3A** to **9**, and from **8** to **4**. Thus, changing the amine cation from $Et_2NH_2^+$ to tris(2-hydroxy-3,5-dimethylbenzyl)amine does not alter the order of donor ability even though there are differences in hydrogen bonding brought about by the substitution of one amine for the other. As observed, the P−O donor ability is expected a priori to be greater in the phosphines than phosphine oxides. This has been amply demonstrated with cyclic phosphorus compounds exhibiting P−S donor coordination.[3a,14−28] In the case of the comparison of phosphine **3B** with phosphine oxide **9**, the reverse is found with **3B** having a slightly longer P−O distance 2.898(2) Å compared to a value of 2.863(2) Å for **9**. As discussed in the following section, hydrogen bonding effects are responsible.

Hydrogen Bonding. Hydrogen bonding is implicated in influencing P−O donor coordination in two examples for the series studied here. This factor reasonably accounts for the difference in donor coordination between **1A** and **1B** and between **3A** and **3B**.

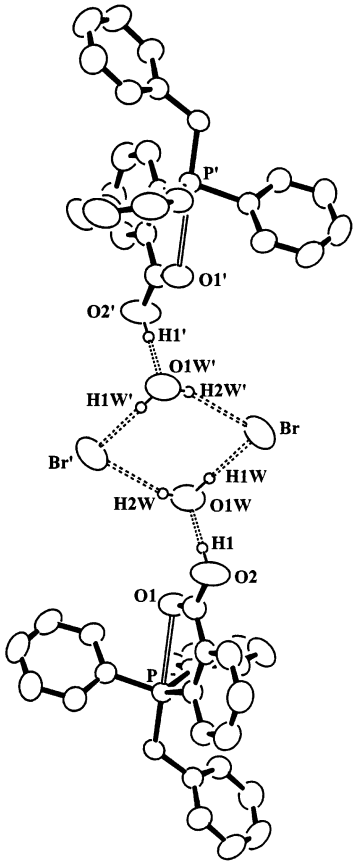

Figure 7. Hydrogen bonded dimer of **1B**.

In the phosphonium salt **1A**, as with **2**, each bromide ion has one hydrogen bond. In **1A**, the hydrogen bond is with the carboxyl hydrogen atom. In **2**, it is with the hydrogen atom of the water molecule (Chart 1). In **1B**, each bromide ion has two hydrogen bonds, both from water molecules, while the oxygen atom of the water molecule is hydrogen bonded to the carboxyl hydrogen. This results in a hydrogen bonded dimer for **1B** (Chart 1 and Figure 7). The shorter distance in **1B** compared to **1A** can be explained on the basis of water being a stronger electron donor than a bromide ion which will increase electron density on the carboxyl group. However, lattice interactions may also be contributory since the three independent molecules of **2** show a considerable variation in the P−O donor bond distance and this variation cannot be ascribed to any other effect. On the basis of the location of a phenyl group in an axial site in **1A** and a benzyl group in an axial site in **1B**, the P−O distance should be shorter in **1A** since phenyl is more electronegative than a benzyl group. Thus, the electronic effects associated with these two groups are not determining.

In the carboxylate salts **3A**, **3B**, and **4**, the carboxylate oxygen atoms are hydrogen bonded to the hydroxyl hydrogen atoms from the cation but in different ways (Chart 1). In all cases, the NH hydrogen atom is hydrogen bonded to all three hydroxyl oxygens as is common for atranes.[29] In **4**, there are three oxygen atoms in the anion (one from P═O and two from the carboxylate group) and three OH hydrogen

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Table 7. Principal Hydrogen Bonding Interactions for **1**−**4**[a]

D−H···A[b]	*d*(D−H), Å	*d*(H···A), Å	*d*(D···A), Å	∠(DHA), deg
1A (Fixed Hydrogen)				
O2−H1···Br	0.82	2.28	3.096(3)	171
1B (H-Bonded Dimer)				
O2−H1···O1w (w = water)	0.87(4)	1.68(4)	2.550(3)	178(4)
O1w−H1w···Br	0.95(5)	2.23(5)	3.177(3)	176(3)
O1w−H2w···Br(2 − *x*, 1 − *y*, −*z*)	0.82(3)	2.50(3)	3.289(4)	160(3)
2 (Hydrogens Not Included)				
O1w···Br1			3.283(4)	
O1w···Br2			3.292(5)	
O2w···Br3			3.14(1)	
O2w···Br3(2 − *x*, −*y*, −*z*)			3.43(1)	
3A (H1 Fixed)				
O3−H30···O1	0.99(2)	1.71(2)	2.694(4)	170(3)
O4−H40···O2	0.99(2)	1.72(2)	2.698(4)	169(4)
O5−H50···O2	0.99(2)	1.75(3)	2.677(4)	154(4)
N−H1···O3	0.91	2.40	2.992(4)	123
N−H1···O4	0.91	2.26	2.898(4)	127
N−H1···O5	0.91	2.24	2.860(4)	125
3B (H1 Fixed)				
O3−H30···O2	0.98(2)	1.67(2)	2.605(2)	159(2)
O4−H40···O1	0.94(2)	1.99(2)	2.912(2)	165(2)
O5−H50···O1	0.97(2)	1.74(2)	2.685(2)	164(2)
N−H1···O3	0.91	2.21	2.834(2)	125
N−H1···O4	0.91	2.18	2.853(2)	130
N−H1···O5	0.91	2.50	3.068(2)	120
4A (H1 Fixed and Other Hydrogens Not Included)				
O5···O1			2.584(5)	
O6···O2			2.694(5)	
O4···O3			2.658(4)	
N−H1···O4	0.91	2.33	2.904(5)	121
N−H1···O5	0.91	2.16	2.806(5)	127
N−H1···O6	0.91	2.21	2.851(5)	127
4B (H1 Fixed and Other Hydrogens Not Included)				
O5···O1			2.592(6)	
O6···O2			2.528(6)	
O4···O3			2.656(5)	
N−H1···O4	0.91	2.37	2.956(5)	122
N−H1···O5	0.91	2.29	2.910(5)	125
N−H1···O6	0.91	2.17	2.806(5)	126

[a] No C−H···O hydrogen bonds are included. [b] D = hydrogen atom donor, and A = hydrogen atom acceptor.

atoms in the cation, and they form a one to one hydrogen bond.

In **3A** and **3B**, only two oxygen atoms are available in the anionic phosphine to hydrogen bond with the three cationic amine hydroxyl groups. In **3A**, the oxygen atom further from phosphorus is hydrogen bonded to two of the amine hydroxyl hydrogens resulting in a fairly stronger P−O interaction (compared to the parent acid **5**, Table 6 and Chart 2). However, in form **3B**, the oxygen atom closer to phosphorus receives the two hydrogen bonds. The hydrogen bonding interactions are summarized in Table 7. As a consequence, the coordinating oxygen atom moves further away from phosphorus than that in the neutral parent acid **5** despite the oxygen atom being part of anionic carboxylate group. This longer P−O distance in **3B** can be explained on the basis that both oxygen lone pairs are partly or fully involved in bonding with the OH hydrogen atoms which leaves less bonding electron density for coordination of the carboxylate oxygen atom with the phosphorus atom. Thus, depending on the location of the hydrogen bonding interactions at the carboxylate group, this example indicates that P−O donor action may be increased or decreased. Noncovalent interactions, such as van der Waals effects, may operate in a similar fashion but are more difficult to quantify as pointed out in the next section.

The latter result confirms that there exists a competition between hydrogen bonding and P−O interactions, which we have described earlier.[3a,4] In addition, this also suggests that even a single hydrogen bond can help manipulate a nucleophile's proximity to phosphorus, which can either promote or block a reaction at a phosphorus center. That is, hydrogen bonding can act as an intermediary in the initial stages of formation or cleavage of P−O bonds. Though similar suggestions have been made earlier,[30] this is the first time concrete structural evidence supporting this postulate has been arrived at independently.

Application to Enzyme Active Sites. The work reported here confirms our earlier studies[3a,4] showing that P−O donor coordination persists in the presence of hydrogen bonding and anionicity in the phosphorus compounds **3** and **4**. Donor action also persists for the cationic phosphorus compounds **1** and **2** in the presence of hydrogen bonding. Thus, active site constraints caused by the presence of hydrogen bonding or substrate charges should not impede coordination by donor atoms that are part of nearby enzyme residues. Only the location and the Lewis base capacity of the donor atoms associated with these residues relative to their distance to the substrate phosphorus center might be a factor governing whether their coordination with the phosphorus atom takes place.

Active sites of phosphoryl transfer enzymes and cAMP have postulated pentaoxyphosphoranes (TBP) as transition states or intermediates, for example, in hydrolysis mechanisms.[24,31−37] These states have highly electrophilic phosphorus atoms capable of forming stronger P−O coordination than that in the present study. This is evident from previous studies[2,14,25,38a] of ours that have been conducted in the absence of hydrogen bonding that show that donor coordination increases in the following order: phosphates < phosphites < pentaoxyphosphoranes. Donor coordination with pentaoxyphosphoranes[2,15−25,27,38,39a] leads to hexacoordinated phosphorus. These studies have included oxygen,[24,27,38] nitrogen,[38b] and sulfur[15−25,27] donor atoms.

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As the present work has shown, the inclusion of enzyme active site constraints, phosphate anionicity, cationicity, and hydrogen bonding interactions, does not serve to diminish the strength of donor interactions relative to analogues of phosphorus compounds lacking these features. In a similar fashion, one would expect that the greater electrophilicity present in pentaoxyphosphoranes to enhance their tendency to transform from a trigonal bipyramidal phosphorane to the hexacoordinated state in the presence of these constaints. In an earlier study of a series of pentaoxyphosphoranes containing a donor group that underwent associative reactions, it was observed that the rate of reaction increased with the degree of octahedral character of the reactant phosphorane.[39b]

A third factor that is important in structuring active site interactions pertains to van der Waals forces that are discussed in terms of conformational distortions in enzyme chemistry.[40] In this study, we observe the influence of this force, termed lattice or packing effects here, in controlling P−O donor interactions in compounds **2** and **4**. The variation in P−O donor distance for **2** extends over a range of 0.163 Å and that for **4** extends over 0.127 Å. This is comparable to the effect of phosphorus anionicity in supporting donor action, cf. **5** with **8** or **6** with **9** in Chart 2. Thus, van der Waals forces are capable of exerting a major influence in determining whether donor coordination will take place at active sites by their ability to position donor atoms of residues close to or further out of the coordination sphere of the substrate phosphorus atom.

Enzyme active sites of phosphoryl transfer enzymes and cAMP invariably are portrayed with nearby residues involved in hydrogen bonding with the substrate but not with donor interactions.[2,31,41] Thus, knowledge of the coordination tendencies of phosphorus which might assist in describing mechanistic action of phosphoryl transfer enzymes and cAMP has not been utilized up to the present. Biochemists have persisted in referring to knowledge of hypervalent phosphorus chemistry as it existed over a quarter of a century ago.

A number of enzymes, whose active sites have been mapped out that contain potential oxygen donor groups include, e.g., alkaline phosphatase, [42,43] orotidine 5′-monophosphate decarboxylase,[44] and tyrosyl-tRNA synthetase.[45] In the latter enzyme operating on ATP, it has been proposed[45] that the carboxylate oxygen atom of tyrosine binds to phosphorus in the transition state giving a pentacoordinate phosphorus atom. Consistent with our work is the likelihood that the carbonyl oxygen atom of the tyrosyl carboxylate group also interacts with phosphorus in promoting a tendency toward hexacoordination.[2,3] Both oxygen atoms of the carboxylate group appear positioned near the substrate phosphorus atom, and one is proposed[45] to enter into in-line attack. The other oxygen atom could easily provide additional coordination on the basis of our work. This would result in a nucleophilic assisted nucleophilic attack in cleaving ATP in an in-line mechanism.

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Supporting Information Available: Additional crystallographic details and X-ray crystallographic files in CIF format for **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) As pointed out in my ACS Monograph (ref 31), although the term transition state refers to a crest in a potential energy surface and intermediate refers to a trough, many authors use these terms somewhat interchangeably, even though in most cases, the activated state is not isolated. Researchers performing a recent X-ray study (D. Dunaway-Mariano and co-workers, personal communication) obtained the first structural evidence of a pentacoordinated phosphorane *intermediate* stabilized by an enzyme catalyzed phosphoryl transfer reaction, the isomerization of β-glucose 1-phosphate to β-glucose 6-phosphate catalyzed by β-phosphoglucomutase from *Lactococcus lactis*. See: Lahiri, S. D.; Zhang, G.; Dunaway-Mariano, D.; Allen, K. N. *Science* **2003**, *299*, 2067−2071, and Yarnell, A. *Chem. Eng. News.*, Mar 31, **2003**, *81*(13), p 5. For a discussion of phosphoryl and acyl transfer reaction mechanisms based on the use of isotope effects, see: Cleland, W. W.; Hengge, A. C. *FASEB J.* **1995**, *9*, 1585−1594.

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