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STRUCTURAL STUDIES OF PHOSPHORAMIDATES. CONFORMATIONAL PREFERENCES AND HYDROGEN BONDING

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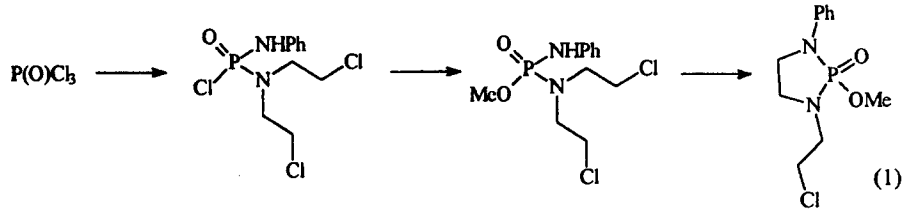
The x-ray molecular structures of five chiral phosphoramidates derived from *N*-phosphorylated nitrogen mustard were determined and the molecular parameters are discussed. The value of the torsion angle of the O=P—N—H function which determines the packing of the molecules was found to determine also the ability of a substrate to form diastereomeric hydrogen-bonded complexes with optically active acids.

INTRODUCTION

The preparation, structure and applications of phosphoric amides are attracting considerable attention. The absolute configuration of alcohols and amines can be determined by converting them into the corresponding phosphoramidates derived from optically active reagents and examining the NMR spectra of the products.[1] *P*-Chiral phosphoramidates show interesting spectroscopic (NMR) and solvating properties.[2] The classical approach involving separation of (+)-camphor-10-sulphonates of basic, optically active phosphinamidates was used as early as in 1960,[3] and the same methodology was recently applied to the determination of the enantiomeric excess (*ee*) of the phosphonic analogues of amino acids.[4] Asymmetric Michael addition was induced by using chiral phosphonic amido esters as nucleophilic precursors.[5] Our own interest in that class of compounds included such topics as solid-state comparison with carboxyamides,[6] hydrogen bonding,[7] cyclization reactions[8] and fragmentation of *N*-phosphorylated nitrogen mustard derivatives.[9]

Recently, we have been developing syntheses of a series of *N*-bis(2-chloroethyl)phosphoric triamides and diamido esters from phosphoryl chloride.[10] In the course of that work, we have prepared some products which seemed interesting as models for structural studies and for application as hydrogen bonding reagents. Three products (**1**, **2**, and **3**) are related to each other via the synthetic sequence [equation (1)], while two other (**4a** and **4b**) represent phosphortriamidates of the 1,3,2-diazaphospholidine series (Scheme 1). Compounds **1**–**4** are highly crystalline solids, hence we decided to determine their crystal and molecular structures in order to evaluate the effect of structural changes on the observed molecular parameters and to correlate the



(1)

1 **2** **3**

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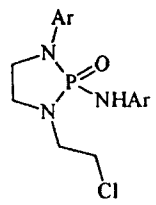


4a, Ar = C_6H_5
4b, Ar = 4-$MeOC_6H_4$

Scheme 1

latter with the hydrogen bonding behaviour of some of the substrates.

RESULTS AND DISCUSSION

Selected molecular parameters for compounds **1**–**4** are given in Table 1. The bond lengths of the P=O moiety range from 1·453(2) to 1·477(2) Å. The shortest is that for **3**, which is as expected, because it is the only compound not involved in hydrogen bonding. The identical values of the P=O bond length for **1** and **2** confirm our earlier observation on similar effects of the Cl and OMe substituents on the phosphoryl centre.[10] The identical distances found in **4a** and **4b** are also informative. As in triamidates, the phosphoryl bond in those compounds is longer than in the preceding diamidates because of the net elecron-releasing effect of three (as opposed to two) nitrogen atoms. It seems, however, that the nature of the N-substituent has a negligible effect on the degree of the electron release: a substrate containing two electron-rich, *p*-anisyl substituents (**4b**) shows the P=O bond distance to be identical with that of its unsubstituted analogue **4a**. The result suggests a low degree of resonance interactions within the phosphoramidate functionality (as opposed to the carboxyamide function), adding some information to the controversial topic of the bonding in the *N*-phosphorylated derivatives.[11] The P—N bond lengths range from 1·624(2) to 1·665(2) Å and are within expected limits.[12] Nevertheless, the observed similarity of the P—N bond lengths for the *N*-alkyl (average 1·638 ± 0·009 Å) and *N*-aryl (average 1·645 ± 0·.015 Å) substituents can be taken again as an indication of poor involvement of the phosphoryl group in the resonance interactions with the NHR amide function. The geometry around the phosphorus atom gives rise to an irregular tetrahedron with the deviations typical for phosphate derivatives, that is with the angles involving the 'electron rich' phosphoryl bond being greater than the ideal value of 109·5° [with the exception of the O(1)—P—Cl bond in **1**, where electronic repulsion seems to be counterbalanced by the steric effects of the two remaining substituents].[13] The N—P—N bond angle shows, however, a strong dependence on the substrate's structure, with all endocyclic values sharply decreased (average 94·1 ± 0·40°). This can be clearly seen in the cyclization of **2** to **3**, where the N—P—N bond angle for the noncyclic substrate (107·2°) is drastically reduced to 94·4° in the cyclic derivative.

The important torsion angles are those which describe the conformation about the amido P—N bond. Thus, in the acyclic substrates **1** and **2** the angles O(1)—P—N(2)—H(2) are large, with values of 118(1) and 130(3)°, respectively. However, in both 1,3,2-diazaphospholidine derivatives **4a** and **4b** the O(1)—P—N(3)—H(3) angles are 7(1)° and 0(2)°, respectively, placing the N—H in an eclipsed position with respect to P=O. This has a significant effect on the packing of the structures. Both **1** and **2** pack with the molecules arranged in infinite chains and stabilized by the intermolecular —N—H···O=P—N—H···O=P— hydrogen bonds, and may be described as a $C^1_1(4)$ pattern,[14] as shown in Figure 1, while **4a** and **4b** form hydrogen—bonded dimers

Table 1. Molecular geometry of phosphoramidates[a]

Bond	1	2	3	4a	4b
P=O(1)	1·466(2)	1·466(3)	1·453(2)	1·477(2)	1·477(2)
P—N(1)	1·636(3)	1·637(3)	1·624(2)	1·646(2)	1·645(2)
P—N(2)	1·629(3)	1·640(3)	1·665(2)	1·656(2)	1·660(2)
P—N(3)				1·637(2)	1·627(2)
P—Cl	2·034(1)				
P—O(2)		1·577(3)	1·577(2)		
O(1)—P—N(1)	111·0(1)	111·3(2)	118·3(1)	117·3(1)	116·9(1)
O(1)—P—N(2)	119·2(2)	115·6(2)	118·2(1)	116·5(1)	117·1(1)
O(1)—P—Cl	109·5(1)				
O(1)—P—O(2)	114·7(2)	106·9(1)			
O(1)—P—N(3)				106·3(1)	107·3(1)
N(1)—P—N(2)	108·0(1)	107·2(2)	94·4(1)	94·3(1)	93·6(1)
O(1)—P—N(2)—H(2)	118·0(1)	130·0(3)			
O(1)—P—N(3)—H(3)				7(1)	0(2)

[a] Bond lengths in Å, angles in degrees.

with an $R^2_2(8)$ pattern,[14] as shown in Figure 2. In contrast, for **3**, which is not capable of hydrogen bonding, the packing of the molecules is governed by the usual van der Waals forces, as shown in Figure 3.

The observed difference in the packing patterns prompted the following question: if the conformational preferences about the P—N bonding in the P(O)—NH moiety can determine the arrangement of the molecules in the crystal lattice owing to the difference in hydrogen bonding (linear vs dimeric), can those effects be preserved in solution to a degree that would force different hydrogen bonding properties upon individual compounds?

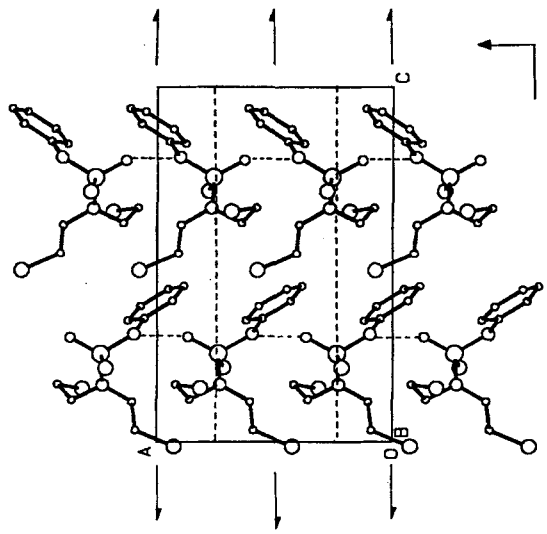


Figure 1. Packing of structure **1**, viewed along [010]. The N—H···O=P hydrogen bonding ribbons run parallel to *A*

Solution studies

The phosphoramidate P(O)NH function consists of both the hydrogen bonding donor and the acceptor centres.[15] The ability to form a 1 : 1 hydrogen—bonded complex with a species also capable of the donor–acceptor interactions should, however, depend on the value of the O=P—N—H torsion angle. ^{31}P NMR spectra of the solutions of racemic substrates **2**, **4a** and **4b** give rise to a single signal indicating that no stable (on the NMR time-scale) hydrogen—bonded self-associates are formed. When, however, an equimolar amount of an optically active acid [(+)-mandelic acid (**5**) or (+)-camphor-10-sulphonic acid (**6**)] was added to the solution, the resulting ^{31}P NMR spectra depended on the type of the phosphoramidate and on the solvent. The results of that study are summarized in Table 2 and lead

Table 2. Chemical shift differences between the ^{31}P NMR signals of the diastereomeric complexes of phosphoramidates **2**, **4a** and **4b** with optically active acids

		$\Delta\delta_P$ (Hz)	
Compound	Solvent	Acid **5**	Acid **6**
2	$(CD_3)_2CO$	0·0	0·0
	C_6D_6	0·0	0·0
4a	$(CD_3)_2CO$	0·0	0·0
	CD_3CN	0·0	3·8
	$CDCl_3$	3·0	7·8
	C_6D_6	9·2	37·5
4b	$(CD_3)_2CO$	0·0	0·0
	CD_3CN	0·0	0·0
	$CDCl_3$	3·1	4·6
	C_6D_6	11·7	11·3

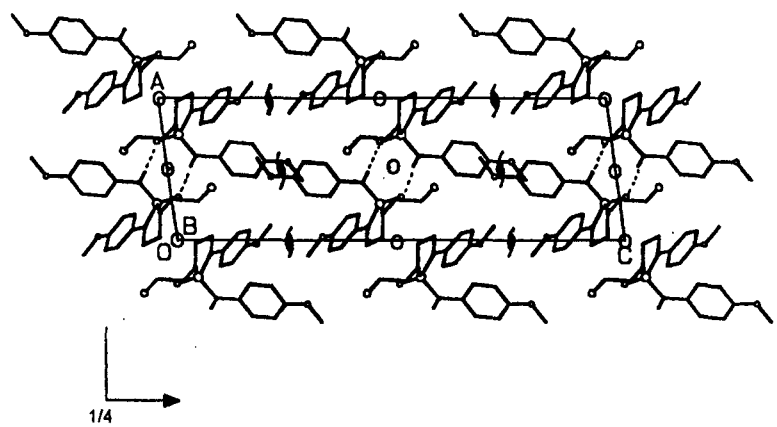


Figure 2. Packing of structure **4b**, viewed along [010]. The molecules form hydrogen-bonded dimers across a centre of inversion

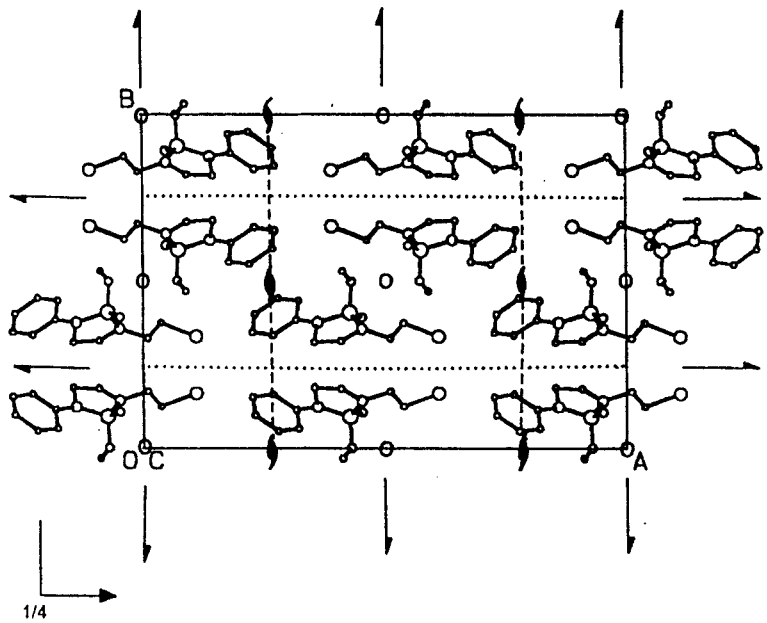
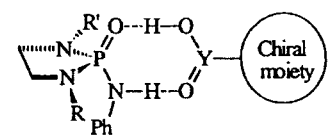


Figure 3. Packing of structure **3**, viewed along [001]

to the following conclusions. Substrate **2**, in both the most (acetone-d_6), and in the least (C_6D_6) polar solvents, yields a single ^{31}P NMR signal, indicating that any interactions that may develop between **2** and the optically active acid are not strong enough to lead to stable diastereomeric species. For both substrates **4** the situation depended on the solvent. In acetone-d_6 (and, to a lesser degree, in acetonitrile-d_3), no formation of diastereomeric complexes was observed. It seems that those solvents are sufficiently strong hydrogen bonding acceptors themselves[16] to break any donor–acceptor complexation involving chiral solutes. In chloroform-*d* and in benzene-d_6, on the other hand, both cyclic amidates **4** give rise to two signals (in a 1 : 1 ratio) in the ^{31}P NMR spectra with the chemical shift difference in the range 3–38 Hz.

We interpret this result as an indication of the formation of a relatively stable, diastereomeric species via mutual hydrogen bonding interactions between the P(O)NH function of **4**, and the acidic group of the chiral acid (Figure 4). Formation of the complex requires the *syn*-periplanar (or nearly *syn*-periplanar) orientation of the O=P—N—H functionality, and that is, in turn, determined by the conformational preferences of the substrate. It was gratifying to find the conclusions based on the molecular orientations observed in the solid state to be confirmed by the solution behaviour of the compounds studied. Both substrates **4** show in the crystalline state the orientation of the O=P—N—H fragment to be almost ideally



5, Y = C
6, Y = S(O)

Figure 4. Proposed diastereomeric hydrogen-bonded complex between **4** and an optically active acid

syn-periplanar, and both are capable of forming stable diastereomeric complexes with the optically active acids. Amidate **2**, on the other hand, showing in the crystal the orientation between *gauche* and *anti*-periplanar, displayed no tendency towards forming observable diastereomeric complexes.

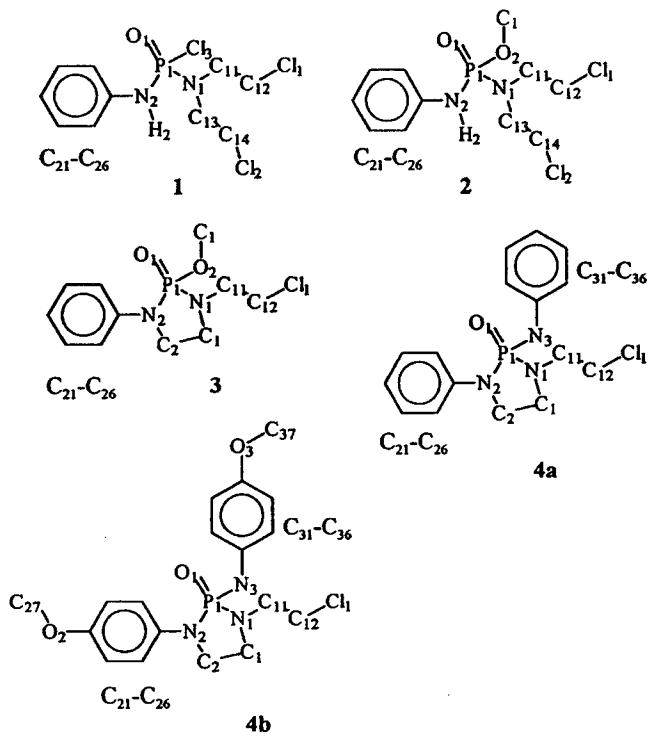
Solubility

The propensity of the substrates of type **4** to interact strongly with the acidic species because of the favourable orientation of their P(O)—NH function was also confirmed by solubility measurements. The solubility of **4a** in benzene (25 °C) is 0·0024 g ml^{-1}. The solubility of **6** in the same solvent (25 °C) is so low that no reliable value could be determined using a standard analytical balance. When, however, **4a** and **6** were

Table 3. Crystal data and experimental and refinement parameters

Parameter	1	2	3	4a	4b
Molecular formula	$C_{10}H_{14}Cl_3N_2OP$	$C_{11}H_{17}Cl_2N_2O_2P$	$C_{11}H_{16}Cl_2N_2O_2P$	$C_{16}H_{15}ClN_3OP$	$C_{18}H_{23}ClN_3O_3P$
Molar mass/g mol^{-1}	315.55	311.15	274.69	335.77	395.81
Space group	$Pca2_1$	$P2_1/c$	$Pbca$	$P2_1/c$	$P2_1/c$
a/Å	9.817(2)	9.702(1)	23.766(2)	8.859(1)	8.527(2)
b/Å	9.394(1)	9.871(2)	16.663(3)	15.630(2)	8.813(1)
c/Å	14.977(3)	15.356(2)	6.541(2)	12.821(3)	26.137(3)
β/°	—	91.65(1)	—	109.72(2)	97.22(1)
V/Å^3	1381.2(4)	1470.0(2)	2590.3(9)	1668.3(5)	1948.6(6)
Z	4	4	8	4	4
D_c/g cm^{-3}	1.517	1.406	1.409	1.337	1.349
μ/Mo K_α/mm^{-1}	0.76	0.55	0.41	0.33	0.30
F(000)	648	648	1152	704	832
Crystal dimensions/mm	0.19 × 0.22 × 0.25	0.22 × 0.22 × 0.25	0.19 × 0.28 × 0.38	0.25 × 0.28 × 0.38	0.28 × 0.31 × 0.31
Θ range scanned/°	2–25	2–25	2–25	2–25	2–25
Range of indices hkl	11,11,17	±11,11,18	28,19,7	±10,18,15	±10,10,31
Intensity variation (%)	2.0	0.2	1.2	0.2	0.1
Scan width (x: + 1.05 tan Θ)/°	0.85	0.85	0.80	0.85	0.80
No. of unique reflections	1262	2584	2276	2932	3425
No. of reflections $I_{rel} > 2\sigma I_{rel}$	1178	1894	1341	2202	2147
R_1[a]	0.024	0.063	0.043	0.047	0.041
wR_2[b]	0.062	0.205	0.119	0.145	0.105
Max. min heights in difference map/e Å^3	0.14, −0.19	1.09, −0.64	0.21, −0.22	0.60, −0.61	0.17, −0.25

[a] $R_1 = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$.
[b] $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$



Scheme 2

mixed in an equimolar ratio, the solubility of the mixture was 0·0110 g ml^{-1}. The interactions between both components therefore increased the solubility of **4a** in C_6H_6 *ca* fivefold, while the solubility of **6** was increased by a very large factor. The ^{31}P NMR spectrum of the new solution showed two signals (ratio 1 : 1) with a separation of $\Delta\delta_P = 37{\cdot}5$ Hz. We take that result as strong support for the postulated diastereomeric complex formed in benzene solution (Figure 4). The complexation engages the most polar fragments of both molecules in mutual hydrogen bonding, leaving the more lipophilic parts exposed to solvation, thus increasing the solubility of the whole species in a non-polar solvent.

In conclusion, we expect that structural modifications of chiral phosphoramidates of the general type XYP(O)NHR, and examination of their conformational preferences in the solid state can lead to a design of useful reagents capable of chiral recognition via hydrogen bonding interactions.

EXPERIMENTAL

The preparation of substrates **1**–**4b** was described previously.[10] (+)-Mandelic acid and (+)-10-camphorsulfonic acid (Aldrich) were used as supplied. ^{31}P NMR—spectra were-recorded on a Bruker AC300 spectrometer at a probe temperature 30 °C. Acetone-d_6 (Aldrich, 99·5 atom% D), acetonitrile-d_3 (Aldrich, 99·5 atom% D), chloroform-*d* (Uvasol, Merck) and benzene-d_6 (Uvasol, Merck) were dried over molecular sieves. The concentration of substrates was 0·20 M. Solubility measurements were carried out as follows. An accurately weighed sample of **4a** (or **6**) was added to dry benzene (5 ml) and the suspension was stirred at 25 °C for 48 h. The insoluble material was filtered, dried and its mass was determined; the filtrate was evaporated to dryness under reduced pressure and the mass of the dissolved material was also determined (total recovery > 99%). In the next experiment, equimolar quantities of **4a** and **6** were mixed and treated in the same way. In addition, after the evaporation of benzene, the soluble material was dissolved in C_6D_6 and the ^{31}P NMR spectrum of the solution was recorded.

Suitable crystals of all five phosphoramidates were obtained by slow evaporation from benzene (**1**, **4a** and **4b**), benzene–hexane (1 : 1) (**3**) or benzene–hexane (1 : 5) (**2**). Preliminary cell dimensions and space group symmetry were determined photographically and subsequently refined by standard procedures on a CAD4 diffractometer. The intensities were collected with the $\omega - 2\Theta$ scan mode and crystal stabilities were moni-

tored by periodic reference reflections. The intensities were corrected for Lorentz, polarization and absorption effects, and the important crystal data and final refinement parameters are given in Table 3. All structures were solved by direct methods using SHELX-S86 and refined by full-matrix least-squares using SHELX–93,[17] refining on F^2. The atomic numbering is shown in Scheme 2. In the final models, the non-hydrogen atoms were refined anisotropically and the aromatic, methylene and methyl hydrogens were geometrically constrained [d(C—H = 0·98 Å] and assigned common temperature factors. Special care was taken with the amido hydrogens. These were located in difference electron density maps and either refined independently or with a simple bond length constraint.

Crystallographic data have been deposited under the Cambridge-Crystallographic Data Deposition Scheme. For details of the scheme, see Instructions for Authors (1996), *J. Chem. Soc., Perkin Trans. 2*, 1996, issue 1.

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