Base Induced Rearrangement of an α-Bromophosphonamidate: Stereochemistry of Ring Opening of the Azaphosphiridine Oxide Intermediate as revealed by X-Ray Crystallography

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Methoxide-induced rearrangement of the α-bromophosphonamidate **1b** (X = Br) gives two products, **2b** and **3b**, corresponding to breakdown of the intermediate azaphosphiridine oxide **4b** by nucleophilic attack at phosphorus, and cleavage of the P–N bond (major pathway) with inversion of configuration or the P–C bond (minor pathway) with retention; this suggests involvement of a five-coordinate species as an intermediate, not merely as a transition state.

α-Chlorophosphonamidates undergo a base-induced rearrangement that gives rise to two types of product.[1–3] Thus, for example, **1a** (X = Cl) is transformed by methoxide into a mixture of the α-aminophosphonate **2a** and the phosphoramidate **3a**.[3] A reactive azaphosphiridine oxide **4** is probably formed initially; this phosphorus analogue of an α-lactam has not been detected, but the products correspond to nucleophilic attack at phosphorus and opening of the three-membered ring, with P–N or P–C cleavage.[3]

Little is known about azaphosphiridine oxides, but other three-membered rings containing the P=O group have received more attention, and in some cases they have actually been isolated.[4] Even for these, however, there is apparently no information on the stereochemistry of nucleophilic substitution. This, in spite of the fact that studies on four- and five-membered rings[5] have contributed much to the understanding of nucleophilic substitution at phosphoryl centres in general.[6] By taking advantage of the α-chlorophosphonamidate rearrangement, it seemed possible that, with a single substrate, we could determine the stereochemistry of P–N and P–C cleavage in the same azaphosphiridine oxide.

As substrate for a stereochemical study, the menthyl α-bromophosphonamidate **1b** (X = Br) seemed attractive on two counts: the menthyl group, being chiral, should assist analysis of the stereochemistry at phosphorus; and bromine, being a better leaving group than chlorine, should allow the rearrangement to proceed under mild conditions, with less risk of stereoisomerisation of the products once formed. Accordingly, bromomethylphosphonic dibromide[7] was treated first with (−)-menthol–Et_3N, then with Bu^tNH_2, to give the α-bromophosphonamidate **1b** (X = Br) as a mixture of diastereoisomers (*ca.* 1:1 by ^{31}P NMR). Repeated crystallisation [EtOH (aq.), then light petroleum] afforded a single diastereoisomer of **1b** (X = Br), mp 155–155.5 °C, δ_P (CH_2Cl_2) 18.0 (≥99%), δ_H ($CDCl_3$) 4.225 (1 H, m, POCH), 3.278 (2 H, ABP, δ_A 3.341, δ_B 3.211, J_{AB} 13.0, J_{AP} 10.3, J_{BP} 7.1 Hz, PCH_2Br) and 1.355 (9 H, d, J_{PH} 0.6 Hz, $PNBu^t$).† Single crystal X-ray analysis revealed the stereostructure (Fig. 1) and, based on the known configuration of the menthyl group (1*R*, 2*S*, 5*R*),[8] the *S* configuration at phosphorus (Scheme 1).‡

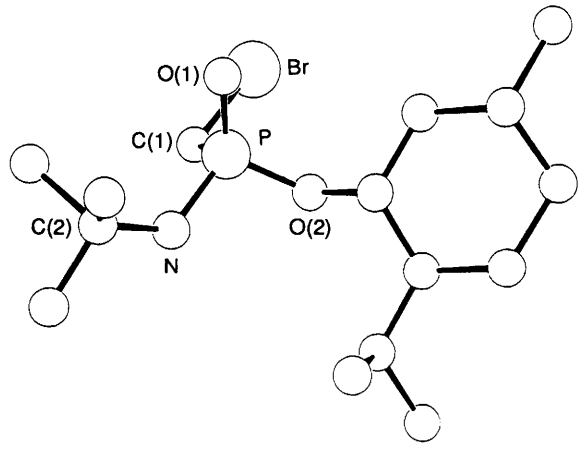


Fig. 1 X-Ray structure of substrate **1b** (X = Br); configuration at phosphorus. Selected bond lengths (Å) and bond angles (°): P–C(1) 1.837(20), P–N 1.618(16) P–O(1) 1.424(14), P–O(2) 1.573(13); C(1)–P–N 105.8(9), C(1)–P–O(1) 112.5(9), C(1)–P–O(2) 98.7(9), N–P–O(1) 115.5(9), N–P–O(2) 104.8(8), O(1)–P–O(2) 117.7(8).

† The new compounds **1b**, **2b** (picric acid salt), **3b**, **5b** and **6b** (dicyclohexylamine salt) were characterised spectroscopically and by elemental analysis or (for **3b**) accurate mass measurement.

‡ *Crystal data*: Data for **1b** and **2b** were measured on a Stoe STADI-2 diffractometer. Data for **6b** were measured on a Siemens P4 diffractometer. All data were collected using graphite monochromated Mo-Kα radiation (λ = 0.7107 Å) at 290 K with an ω scan technique. The data were corrected for Lorentz and polarisation effects.

For **1b**: $C_{15}H_{31}BrNO_2P$, M = 368.3, hexagonal, space group $P6_1$, a = 10.581(2), c = 30.345(25) Å, V = 2942(3) Å^3, Z = 6, D_c = 1.248 g cm^{-3}, $F(000)$ = 1164, μ = 2.18 mm^{-1}. An absorption correction was applied to the data, maximum and minimum transmission factors 0.757 and 0.250 respectively. 1732 Unique reflections were measured with 687 having $I > 3\sigma(I)$ regarded as observed. The structure was solved by direct methods, using SHELXS86, and difference Fourier techniques using the program SHELX76. The bromine and phosphorus atoms were refined as anisotropic, all other non-hydrogen atoms were refined with isotropic thermal parameters. The hydrogen atoms were included in calculated positions. Final R = 0.085 and R_w = 0.065 [where $w = 1/\sigma^2F + 0.00013F^2$] for 90 variables, $(\Delta/\sigma)_{max}$ = 0.001.

For salt of **2b**: $C_{16}H_{35}NO_3P^+C_6H_2N_3O_7^-$, M = 548.5, triclinic, space group $P1$, a = 20.935(20), b = 13.210(13), c = 10.618(3) Å, α = 91.80(6), β = 95.2(1), γ = 94.5(1)°, V = 2913(4) Å^3, Z = 4, D_c = 1.25 g cm^{-3}, $F(000)$ = 1168, μ = 0.15 mm^{-1}. All crystals examined were found to be non-single. A relatively simple twin with the *c* axes of both components aligned and the *a** and *b** axes of one crystal component aligned with $-a^*$ and $-b^*$ of the other component was used for data collection. The relative intensities of the two components were measured and the coincident *hk*0 reflections scaled accordingly. 7415 Unique reflections were measured with 4703 having $I > 2\sigma(I)$ regarded as observed. The non-centric space group $P1$ was assumed since the compound is optically active. The structure was solved with difficulty by direct methods and difference Fourier techniques; several possible solutions were explored before the correct solution was found. The structure consists of four unique formula units, with different conformations. No hydrogen atoms were located and all atoms were refined as isotropic. Final R = 0.132 and R_w = 0.142 for 543 variables, $(\Delta/\sigma)_{max}$ = 0.53. Although the final R factor is high due to problems of possible overlap of reflections and lack of sufficient data for full refinement, the essential details of the structure are unambiguous.

For salt of **6b**: $C_{11}H_{22}O_3PS^-C_{12}H_{24}N^+\cdot\frac{1}{2}C_4H_{10}O$, M = 484.7, monoclinic, space group $C2$, a = 18.218(10), b = 9.892(6), c = 15.851(9) Å, β = 90.27(3)°, V = 2856(3) Å^3, Z = 4, D_c = 1.127 g cm^{-3}, $F(000)$ = 1068, μ = 0.20 mm^{-1}. 1478 Unique data were measured with 1274 data having $I > 2\sigma(I)$ regarded as observed. The structure was solved by direct methods and difference Fourier techniques. All non-hydrogen atoms except those of the solvent molecule were refined as anisotropic. The hydrogen atoms bonded to nitrogen were located from difference Fourier maps and the positional parameters refined; all other hydrogen atoms were included in calculated positions. Final R = 0.0583 and R_w = 0.0629 for 277 variables, $(\Delta/\sigma)_{max}$ = 0.52.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See notice to Authors, Issue No. 1.

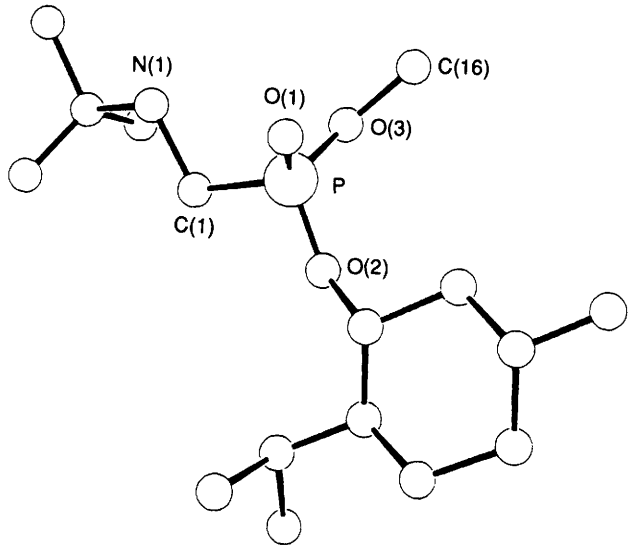


Fig. 2 X-Ray structure of picric acid salt of product **2b** (picrate anion omitted); configuration at phosphorus. One of four unique formula units in the unit cell. Selected bond lengths (Å) and bond angles (°) for this particular formula unit: P-C(1) 1.836(20), P-O(1) 1.500(13), P-O(2) 1.502(13), P-O(3) 1.559(15); C(1)-P-O(1) 119.3(8), C(1)-P-O(2) 100.2(8), C(1)-P-O(3) 100.1(8), O(1)-P-O(2) 116.7(7), O(1)-P-O(3) 110.9(7), O(2)-P-O(3) 107.8(8). The four formula units in the unit cell had different conformations but the same configuration at phosphorus. Average bond lengths (Å) and bond angles (°): P-C(1) 1.823, P-O(1) 1.457, P-O(2) 1.539, P-O(3) 1.552, C(1)-P-O(1) 115.8, C(1)-P-O(2) 100.2, C(1)-P-O(3) 103.1, O(1)-P-O(2) 117.9, O(1)-P-O(3) 111.0, O(2)-P-O(3) 107.4.

The $(S)_P$-α-bromophosphonamidate reacted quite readily with methoxide in tetrahydrofuran–MeOH (9:1) at room temperature (0.2 mol dm^{-3} $PhCH_2\overset{+}{N}Me_3\bar{O}Me$; 1.5 mol equiv.; 4.5 h), giving two products in a 5:1 ratio (^{31}P NMR). The major product, isolated by extraction (from diethyl ether) into aqueous acid, was the α-aminophosphonamidate **2b**, δ_P ($CDCl_3$) 28.4, δ_H ($CDCl_3$) 4.273 (1 H, m, POCH), 3.765 (3H, d, J_{PH} 10.8, POMe), 2.922 (2 H, ABP, δ_A 2.941, δ_B 2.903, J_{AB} 13.9, J_{AP} 14.9, J_{BP} 15.7 Hz, PCH_2N), and 1.076 (9 H, s, NBu^t). Although predominantly one diastereoisomer, minor signals in the ^1H and ^{31}P NMR spectra indicated 4–5% of the other diastereoisomer (δ_P 28.1).

The phosphoramidate minor product **3b** was also *ca.* 95% one diastereoisomer, δ_P ($CDCl_3$) 11.5 (other diastereoisomer, 10.5), δ_H ($CDCl_3$) 4.137 (1H, m, POCH), 3.614 (3 H, d, J_{PH} 11.4 Hz, POMe), 2.663 (3 H, d, J_{PH} 9.6 Hz, PNMe) and 1.314 (9 H, s, NBu^t).

When a similar reaction was interrupted before completion (t = 16 min; 93% complete), the minor product was still obtained as a 95:5 mixture of diastereoisomers, but the major product was now 99% one diastereoisomer. This suggests that cleavage of the P–N bond in the azaphosphiridine oxide intermediate is completely stereospecific, but the product may subsequently suffer some stereoisomerisation, whereas cleavage of the P–C bond is inherently somewhat non-stereospecific.

For the α-aminophosphonate **2b**, a crystalline derivative was readily obtained by treatment with picric acid. The X-ray structure of the resulting salt, mp 118.5–120.5 °C, was solved only with difficulty (crystals non-single) (Fig. 2, picrate not shown; one of four unique formula units in the unit cell) but the configuration at phosphorus (Scheme 1) became clear beyond doubt.

For the phosphoramidate **3b** there is no direct way of obtaining a crystalline derivative. The related secondary amide **5b** was therefore prepared [$\delta_P(CH_2Cl_2)$ 7.2 and 6.7],

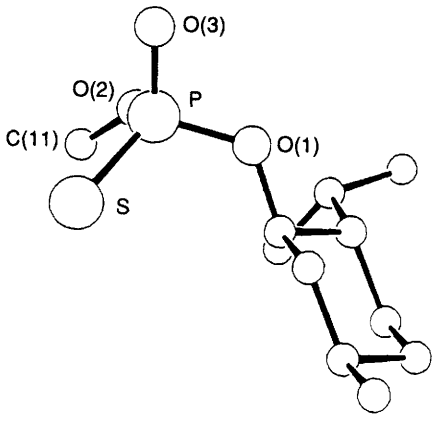
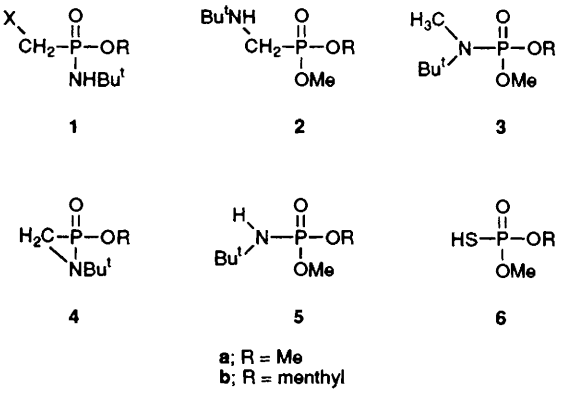
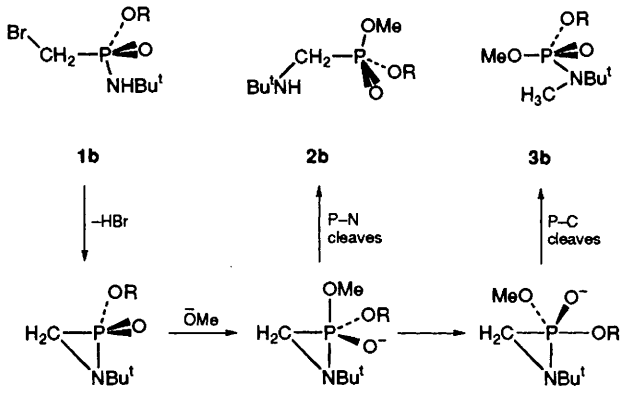


Fig. 3 X-Ray structure of dicyclohexylamine salt of derivative **6b** (dicyclohexylammonium cation and diethyl ether of crystallisation omitted); configuration at phosphorus. Selected bond lengths (Å) and bond angles (°): P-O(1) 1.577(7), P-O(2) 1.543(9), P-O(3) 1.483(8), P-S 1.932(3); O(1)-P-O(2) 99.1(6), O(1)-P-O(3) 105.6(4), O(2)-P-O(3) 109.2(6), O(1)-P-S 113.2(3), O(2)-P-S 111.4(4), O(3)-P-S 116.8(3).



and one of the diastereoisomers was separated chromatographically from the mixture (δ_P 7.2; ≥96%). On alkylation with NaH–MeI, this gave the same diastereoisomer of **3b** as had been dominant in the rearrangement. Since the *N*-methylation reaction does not involve any change at the phosphoryl centre, determination of the configuration of **5b** would lead directly to the configuration of **3b**. Unfortunately, while **5b** was crystalline, it proved impossible to grow a single crystal adequate for X-ray analysis. The secondary amide was therefore treated with NaH–CS_2 to give (after acidification) the thiophosphoric acid **6b**, δ_P ($CDCl_3$) 61.2. This formed a crystalline salt with dicyclohexylamine, δ_P ($CDCl_3$) 55.9, and the X-ray structure [Fig. 3, $(C_6H_{11})_2\overset{+}{N}H_2$ and diethyl ether of crystallisation not shown] revealed the configuration at phosphorus. The transformation *P*-$NHBu^t$ → *P*-SH would not be expected to change the configuration at phosphorus, and for several similar examples there is proof that the configuration is retained.[9] It therefore seems safe to suppose that **5b** has the same configuration as **6b**, and that the rearrangement product **3b** does as well (Scheme 1).

Comparing the stereostructures of the rearrangement products and the substrate (Scheme 1), it can be seen that P–N bond cleavage in the azaphosphiridine oxide gives **2b** with inversion of configuration at phosphorus, but P–C bond cleavage gives **3b** with (predominant) retention. The explanation may be that the attack of methoxide at phosphorus in the azaphosphiridine oxide occurs almost exclusively opposite the more apicophilic nitrogen atom, and that a five-coordinate phosphorane intermediate is formed.[6] This intermediate can break down directly, by cleavage of the (approximately) apical



P–N bond, or after permutational isomerisation, by cleavage of the newly-apical P–C bond. The apparent need to invoke permutational isomerisation is important: it requires the five-coordinate species to be a true intermediate, not merely a transition state. This, notwithstanding the fact that the leaving group (nitrogen or carbon) is part of a three-membered ring and its departure must surely afford much relief of strain.§ Even in this extreme situation, it seems that a concerted S_N2 mechanism is not as energetically favourable as a stepwise $S_N2(P)$ addition–elimination mechanism, with a five-coordinate phosphorane intermediate.

§ Angle strain in the three-membered ring can, of course, be eased considerably simply by forming a five-coordinate species, even without any breaking of the P–N or P–C bond.

We thank Julie Trafford for valuable preliminary experiments, the SERC for a research studentship (to R. S.-M.), and Leicester University Computer Centre who provided support and facilities for X-ray single crystal calculations.

Received, 6th August 1993; Com. 3/04762H

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