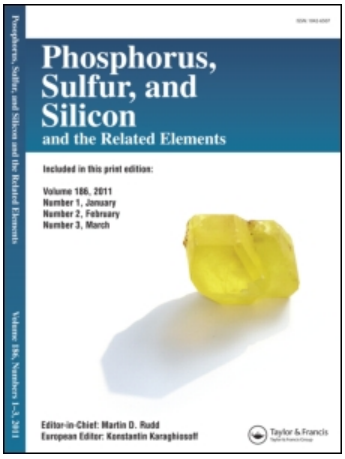

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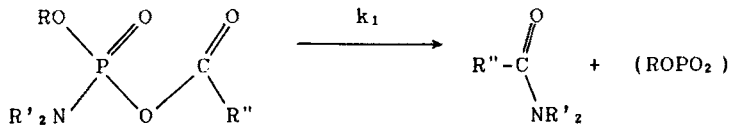
Cyclic mixed anhydride, *N*-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane (**1a**) has been synthesised and the rate of its fragmentation involving nitrogen migration from phosphorus to carbonyl carbon has been measured. (**1a**) was found to be *ca.* 60 times less reactive than the non-cyclic, O-methyl-*N*,*N*-dimethyl analogue. The crystal and molecular structure of (**1a**) has been determined using x-ray diffraction. $Pna2_1$, $a = 22.229(6)$, $b = 7.597(2)$, $c = 7.210(2)$ Å; $V = 1217.6(6)$ Å^3. Final $R = 3.08\%$ for 1037 reflections with $I(rel) > 2\sigma I(rel)$ and 157 parameters. The observed conformation of the molecule of (**1a**) is very different from that required for the fragmentation to occur; in order to achieve the geometry postulated for the transition state significant rotations about the P—O and O—C bonds would be necessary and steric hindrance by the 4,6-axial hydrogens would be expected.

We have recently reported[1] that mixed anhydrides (**1**) derived from carboxylic acids and amidoesters of phosphoric acid undergo fragmentation involving transfer of the amino group from the phosphoryl to the carbonyl centre (Equation 1).



(1)

(**1**)

Investigation of the substituent effects on the rate of reaction (1) reveals that the polarity of neither the carbonyl substituent (R″)[1] nor the N-group (R′)[2] has much effect on the magnitude of the rate constant k_1. These results imply that the reaction does not involve significant charge development in the transition state. An MNDO-SCF MO study[3] supports the hypothesis of a concerted mechanism for the fragmentation, and indicates a planar, four-membered transition state (Figure 1) with all four interatomic distances within the POCN system being of the bonding order (1.53–1.89 Å). In order to obtain additional support for the

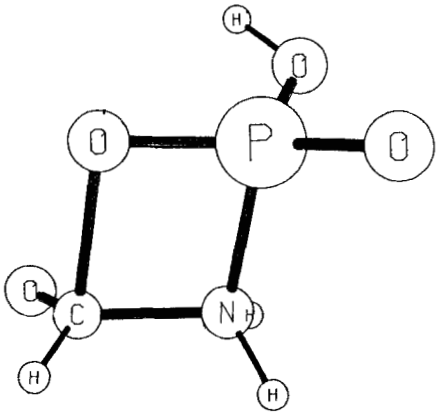
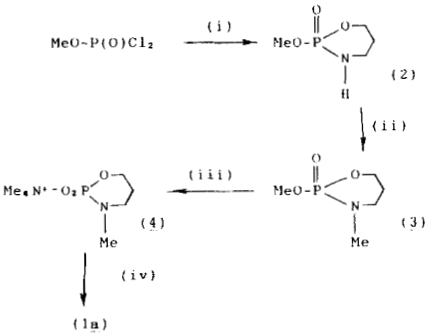


FIGURE 1 Transition state for the [1, 3] amino group migration in (**1**).[3]

postulated cyclic mechanism, we decided to investigate the effect of conformational constraint in system (1) on its fragmentation.

RESULTS AND DISCUSSION

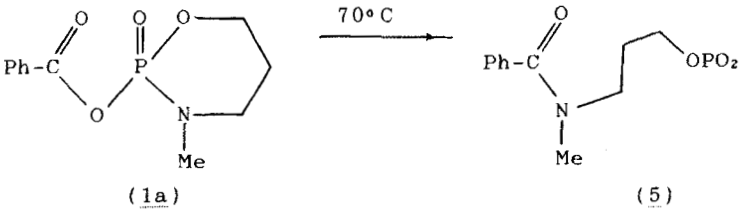
We have synthesised the cyclic anhydride, *N*-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane (**1a**) (Scheme 1) in which the phosphate ester and amide functions are incorporated into a six-membered ring.



(i) $H_2N(CH_2)_3OH$, Et_3N;
(ii) NaH, Me_2SO_4;
(iii) Me_3N; (iv) PhC(O)Cl

SCHEME 1

We have compared the rate of fragmentation of (**1a**) (Equation 2) in $CDCl_3$ with that previously determined[1] for the non-cyclic substrate, $(MeO)(Me_2N)P(O)OC(O)Ph$, (**1b**).



(1a) (5) (2)

Although the benzamide product (**5**) could not be isolated because of the subsequent polymerisation of the metaphosphate function,[4] its formation was easily monitored by ^{1}H n.m.r. spectroscopy due to the appearance of a new signal, corresponding to the *N*-methyl and *N*-methylene groups in (**5**), *ca.* 0.1 ppm lowfield relative to the *N*-methyl group signal in (**1a**) (Figure 2). Rate measurements showed that fragmentation of (**1a**) occurs much more slowly than the analogous reaction of (**1b**); the relative rate in $CDCl_3$ being k_1(**1a**)/k_1(**1b**) = $k_{rel} = 1.7 \times 10^{-2}$. Since the electronic effects of the substituents at phosphorus on the anhydride function in (**1a**) and (**1b**) are approximately the same, the observed difference in reactivity must stem from the conformational differences between these two substrates. A concerted mechanism of fragmentation (Figure 1) requires close approach of the phosphoramidate nitrogen to the carbonyl carbon in a geometry similar to that involved in Wittig or other reactions promoted by phosphorus-stabilised anions.[5] In the case of substrate (**1a**) this would require

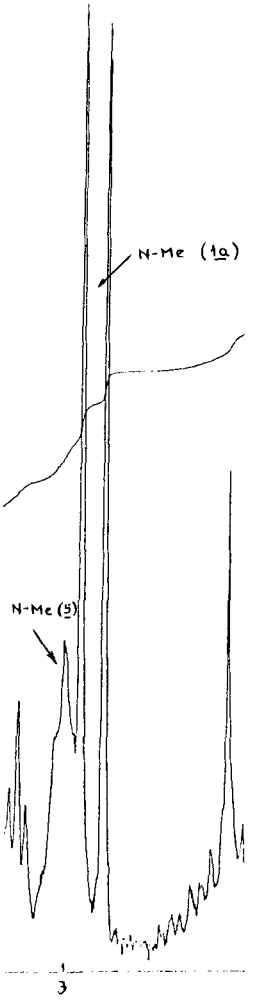


FIGURE 2 ^{1}H n.m.r. spectrum (200 MHz) in $CDCl_3$ of (**1a**) after 281 h at 70°C; 28.7% conversion.

formation of a bicyclic structure of the bicyclo[0,2,4]octane type and would depend on the conformational preference of the 2-benzoyloxy substituent in the molecule of (**1a**). Since pure (**1a**) proved to be a crystalline (albeit hydrolytically unstable) compound, we decided to determine its structure and to analyse the molecular parameters obtained from the point of view of their relation to the postulated transition state for the fragmentation. The perspective view of (**1a**), together with atomic nomenclature, is given in Figure 3, while selected molecular parameters are listed in Table I. In order to compare our data with the molecular parameters available in the literature for a related structure we include in Table I results reported[6] for *N*-methyl-2-phenoxy-2-thio-1,3,2-oxazaphosphorinane, $PhOP(S)OCH_2CH_2CH_2NMe$ (**6**). The first obvious conclusion is the close similarity between the two 1,3,2-oxazaphosphorinane systems, (**1a**) and (**6**). Except for the difference in the exocyclic P—OR bond distance (resulting from the difference in the electronegativity of the phenoxy and benzoyloxy groups), the corresponding bond distances and angles in (**1a**) and (**6**) are very similar. The OC(O)Ph substituent in (**1a**) occupies the axial position in the chair conformation

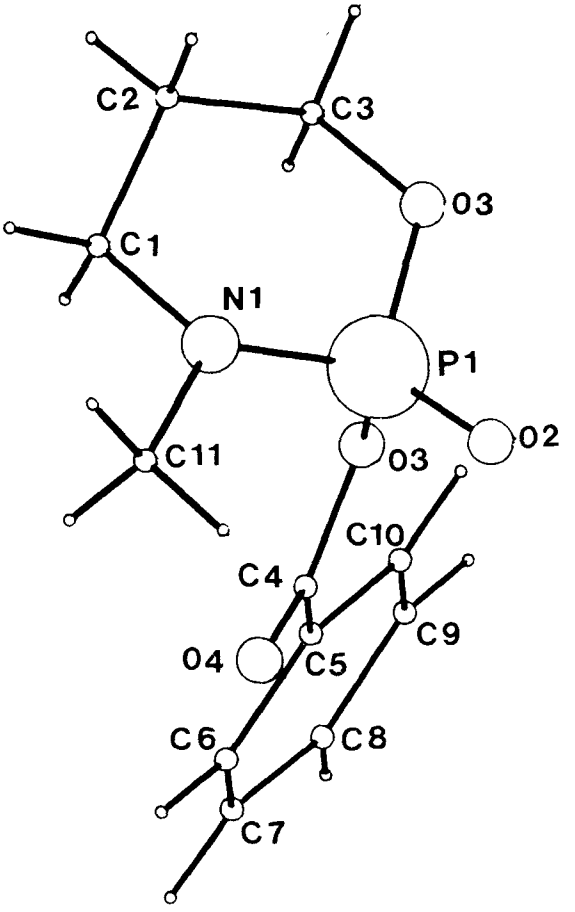


FIGURE 3 A perspective view of (**1a**) with atomic numbering.

TABLE I

Selected Intramolecular Parameters for (**1a**) and (**6**)

	1a	**6**
Bond lengths, Å		
P(1)–O(2)	1.445(3)	
P(1)–O(1)	1.636(2)	1.605(2)
P(1)–O(3)	1.573(2)	1.576(2)
P(1)–N(1)	1.628(3)	1.638(2)
O(1)–C(4)	1.373(3)	1.404(2)
N(1)–C(11)	1.454(5)	1.453(4)
Bond angles, deg.		
N(1)–P(1)–O(1)	109.5(1)	103.8(1)
N(1)–P(1)–O(3)	104.3(1)	104.3(1)
O(1)–P(1)–O(3)	97.1(1)	104.2(1)
P(1)–O(1)–C(4)	122.9(2)	122.5(1)
P(1)–N(1)–C(1)	119.0(3)	117.7(2)
P(1)–N(1)–C(11)	120.5(3)	119.7(2)
C(1)–N(1)–C(11)	115.1(3)	113.9(2)
Torsion angles, deg.		
N(1)–P(1)–O(1)–C(4)	−64.1(3)	
P(1)–O(1)–C(4)–C(5)	−176.5(2)	
Interatomic non-bonded contacts, Å		
N(1) . . . C(4)	3.270(4)	
Nitrogen planarity		
Deviation of N(1) from the P(1)–C(1)–C(11) plane, Å	0.205(3)	0.26

of the oxazaphosphorinane ring, as does the OPh group in (**6**), in agreement with the general trend[7] of electronegative groups to locate themselves in the axial position of this cyclic system. In both compounds the hybridisation of the nitrogen atom is very close to sp^2, with the deviation of the N atom from the PCC plane being only 0.205(3) Å for (**1a**) and 0.26 Å for (**6**), and the sum of the angles at N being 354.6(3)° and 350°, respectively. The molecular parameters that are most relevant to the reactivity of (**1a**) discussed in this paper, are the intramolecular nitrogen–carbonyl carbon distance and the torsion angles formed by the N(1)–P(1)–O(1)–C(4) and P(1)–O(1)–C(4)–C(5) backbone of the anhydride system. The N . . . C(carbonyl) distance in (**1a**) is 3.270(4) Å, much greater than those (2.0–2.6 Å) found in molecules containing interacting amino and carbonyl groups.[8] The geometry of the postulated transition state (Figure 1) requires syn-periplanar orientation of the nitrogen and carbonyl carbon (NPOC torsional angle = 0°) and orthogonal orientation of the carbonyl centre with respect to the four-membered ring system of the transition state (POCC torsional angle = 90°). The molecular conformation observed for (**1a**) in the solid state is very far from that expected for the fragmentation to occur. In order to achieve the "ideal" geometry for the P - - - C nitrogen transfer, rotation by 64.1(3)° about the P(1)–O(1) and by 86.5(2)° about the O(1)–C(4) bonds is necessary. As

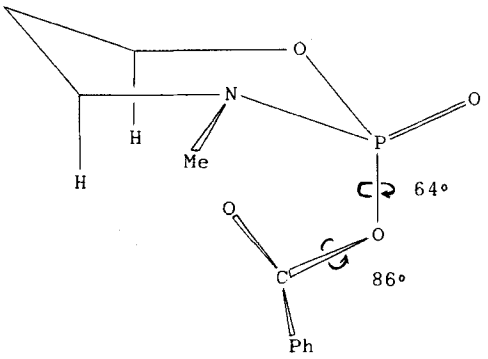


FIGURE 4 Schematic representation of steric hindrance in the fragmentation of (**1a**).

illustrated schematically in Figure 4, such conformational changes would be unfavourable because of the steric hindrance caused by the two axial hydrogens at positions 4 and 6 of the oxazaphosphorinane ring. In a non-cyclic anhydride (**1b**) the four-center transition state can be achieved without so much steric interference, as no conformational constraints are imposed on the phosphoric amide and ester groups. We conclude therefore that the rate of amino group transfer from P to C in system (**1**) (Equation 1) is sensitive to the steric environment at the phosphoryl center, in agreement with the opinion[9] that "... steric effects should be important for concerted, highly organised transition states."

EXPERIMENTAL

General. ^{1}H n.m.r. spectra were recorded on a 200 MHz Varian XL200 spectrometer using TMS as an internal standard. Analyses for C, H and N were carried out at the University of Cape Town. All solvents and reagents were purified by conventional means before use. Triethylamine was distilled from KOH pellets. Methyl phosphorodichloridate was prepared from methanol and $POCl_3$;[10] bp 62–66°C (15 mm), (lit.[10] bp 62–64°C (15 mm)).

Preparation of 2-methoxy-2-oxo-1,3,2-oxazaphosphorinane (**2**). $MeOP(O)Cl_2$ (56 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a cooled, stirred solution of 3-aminopropanol (56 mmol) and Et_3N (112 mmol) in CH_2Cl_2 (100 ml) at 5°C. Stirring and cooling were continued for 6 h, the mixture was left overnight at 0°C and filtered. The filtrate was washed twice with ice-cold water (2 × 15 ml) and the combined aqueous layers were re-extracted with CH_2Cl_2 (10 ml). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure yielding 3.03 g of the crude product which still contained some Et_3NHCl. CCl_4 (2 ml) was added, the precipitate was filtered off and the filtrate was evaporated under reduced pressure yielding 2.0 g of crude (**2**) (24%). ^{1}H n.m.r. ($CDCl_3$): δ 1.55–2.15 (2H, m, CCH_2C); 3.10–3.50 (2H, m, NCH_2); 3.70 (3H, d, J 12.5Hz, OMe); 3.93 (1H, bs, NH); 4.20–4.50 (2H, m, OCH_2). (Found: C, 33.40; H, 7.05; N, 9.05. $C_4H_{10}NO_3P$ requires C, 31.80; H, 6.67; N, 9.27%). ^{1}H n.m.r. showed that the product still contained *ca.* 10% of Et_3NHCl. No attempts were made to remove the salt, and crude (**2**) was used in the next step.

Preparation of N-methyl-2-methoxy-2-oxo-1,3,2-oxazaphosphorinane (**3**). 2.0 g of (**2**) was dissolved in THF (20 ml) and added to a suspension of NaH (0.68 g, 14 mmol) in THF (20 ml) and the mixture was stirred at room temperature until the evolution of hydrogen was complete (1 h). Me_2SO_4 (13 mmol) in THF (10 ml) was then added slowly with stirring and the mixture was stirred for further three hours and left at room temperature for 1 h. After filtration and removal of the solvent under reduced pressure the product was purified by column chromatography (Kieselgel 40; $CHCl_3/Et_3N$, 4:1) yielding 0.61 g (*ca.* 31% based on **2**; 7% based on $MeOPOCl_2$) of (**3**). ^{1}H n.m.r. ($CDCl_3$): δ 1.60–2.30 (2H, m, CCH_2C); 2.68 (3H, d, J 12.5Hz, NMe); 2.90–3.20 (2H, m, NCH_2); 3.68 (3H, d,

J 12.5Hz, OMe); 4.10–4.40 (2H, m, OCH_2). (Found: C, 36.60; H, 7.35; N, 8.40. $C_5H_{12}NO_3P$ requires C, 36.37; H, 7.32; N, 8.48%).

Preparation of tetramethylammonium salt of N-methyl-2-hydroxy-2-oxo-1,3,2-oxazaphosphorinane (**4**). 10 mL of 3.0 M solution of Me_3N in MeCN were added to a solution of (**3**) (3.7 mmol) in MeCN, the solution was sealed in a glass tube and incubated in a water bath at 80°C for 21 h. After removal of the solvent under reduced pressure and washing the residue with MeCN, 0.57 g (2.5 mmol, 69% based on **3**) of (**4**) was obtained as colorless solid. ^{1}H n.m.r. (D_2O): δ 1.70–1.90 (2H, m, CCH_2C); 2.47 (3H, d, J 12.6Hz, NMe); 2.85–3.05 (2H, m, NCH_2); 3.20 (12H, s, NMe_4^+); 4.15 (2H, d of t, J 12.7, 6.2Hz, OCH_2).

Preparation of N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane (**1a**). A solution of PhCOCl (1.8 mmol) in MeCN (2 ml) was added to a suspension of (**4**) (2.5 mmol) in MeCN (10 ml) and the mixture was stirred at room temperature for 2.5 h. After filtration and evaporation of the solvent the residue was redissolved in CCl_4 (2 ml) and filtered through cotton wool. Evaporation of the solvent gave 0.37 g (81% based on **4**) of (**1a**) as a crystalline, moisture-sensitive compound. ^{1}H n.m.r. ($CDCl_3$): δ 1.70–2.40 (2H, m, CCH_2C); 2.90 (3H, d, J 12.5Hz, NMe); 2.95–3.45 (2H, m, NCH_2); 4.10–4.60 (2H, m, OCH_2); 7.50 (2H, t, J 5Hz, 2xm-H); 7.65 (1H, t, J 5Hz, p-H); 8.12 (2H, d, J 5Hz, 2xo-H). (Found: C, 50.80; H, 5.50; N, 5.75. $C_{10}H_{14}NO_4P$ requires C, 51.76; H, 5.80; N, 5.76%).

Kinetic measurements. Approximately 0.025 g of (**1a**) was dissolved in 0.4 ml of $CDCl_3$, the solution was transferred to an n.m.r. tube, sealed and incubated in a water bath at 70°C. The ^{1}H n.m.r. spectra of the solution were recorded periodically and the progress of the reaction was followed by comparing the growth of the broad signal at δ 3.0 and the reduction of the doublet at δ 2.9. The first-order rate

TABLE II

Experimental data for the X-ray diffraction study on **1a**

Crystal data	
molecular formula	$C_{11}H_{14}O_4NP$
molecular weight	255.21 g mol^{-1}
space group	$Pna2_1$
a	22.229(6) Å
b	7.597(2) Å
c	7.210(2) Å
V	1217.6(6) Å^3
D_c (for $Z = 4$)	1.39 g cm^{-3}
μ	2.21 cm^{-1}
$F(000)$	536
Radiatiation used	MoKalpha, $\lambda = 0.7107$ Å
Data collection	
crystal dimensions	0.41 × 0.47 × 0.56 mm
scan mode	$\omega - 2\theta$
scan width	$(0.83 + 0.35 \tan\theta)°$
aperture width	$(1.30 + 1.05 \tan\theta)$ mm
aperture length	4 mm
range scanned	1–25° in θ
crystal stability (% decay)	0.2%
no. reflections collected	1113
no. reflections observed, N	1037 with I(rel) > 2σI(rel)
Average transmission for absorption corrections	98.2%
Final refinement	
number of variables, NP	157
$R = \sum \|\|F_0\| - \|F_c\|\| / \sum \|F_0\|$	3.08%
$R_w = \sum w^{1/2} \|\|F_0\| - \|F_c\|\| / \sum w^{1/2} \|F_0\|$	3.05%
weighting scheme	$w = (\sigma^2 F)^{-1}$
U (hydrogens)	0.076(3) Å^2
$S = \{\sum w \|F_0\| - \|F_c\|\}^2 / \{\text{N-NP}\}^{1/2}$	2.28

TABLE III

Fractional atomic coordinates ($\times 10^4$) with e.s.d.'s in parentheses for the non-hydrogen atoms of (**1a**)

	x/a	*y/b*	*z/c*
P(1)	1578	1201(1)	0
O(1)	982(1)	2402(3)	413(4)
O(2)	1606(1)	580(4)	−1892(4)
O(3)	2061(1)	2637(3)	501(4)
N(1)	1650(1)	−279(4)	1618(5)
O(4)	319(1)	198(3)	165(6)
C(1)	1730(2)	297(5)	3551(5)
C(2)	2216(1)	1684(5)	3691(6)
C(3)	2112(2)	3228(5)	2421(6)
C(4)	409(1)	1727(4)	407(6)
C(5)	−50(1)	3097(4)	704(5)
C(6)	−629(1)	2551(5)	1145(6)
C(7)	−1076(1)	3786(5)	1372(6)
C(8)	−951(2)	5556(5)	1161(6)
C(9)	−380(2)	6095(5)	718(6)
C(10)	73(2)	4873(5)	489(5)
C(11)	1385(2)	−2016(4)	1395(7)

constant, k_1 was determined from the relative integrated areas of these signals. The kinetic runs gave linear plots with r values greater than 0.97 and average rate constant $k_1 = (3.11 \pm 0.51) \times 10^{-4}\ h^{-1}$.

Structure determination and refinement. Crystals of (**1a**) suitable for X-ray diffraction measurements were obtained by slow evaporation of the ethereal solution, at room temperature and with exclusion of moisture. The unit cell was determined by least squares refinement on the setting angles of 24 reflections ($16 \leq \Theta \leq 17°$) on an Nonius CAD4 diffractometer. 1113 unique reflections out to $\Theta = 25°$ were collected in the $\omega - 2\Theta$ mode. Crystal orientation and stability were periodically monitored throughout the data collection. The data were corrected for Lorentz-polarization factors and an empirical absorption correction[11] applied. Using the SHELX-76 program system,[12] the structure was solved by first locating the P atom in a Patterson map, and then locating the remaining non-hydrogen atoms by computation of successive difference maps. In the final least-squares refinement cycles all non-hydrogen atoms were treated anisotropically. At this stage methylene and aromatic hydrogen atoms were placed geometrically with all C–H distances fixed at 1.00 Å; the H's on the N-substituted methyl group were treated as a rigid moiety. All H atoms were assigned a single isotropic temperature factor. In the final refinement, a weighting scheme was applied. No attempt was made to determine the absolute structure of the crystal. Further details of the crystal parameters, data collection and structure refinement are given in Table II. Final fractional atomic coordinates are reported in Table III (H-atom coordinates, anisotropic thermal parameters, geometric data and structure factors are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd, Cambridge CB2 1EW, U.K.). The program PARST[13] was used for molecular geometry calculations and PLUTO[14] for Figure 3.

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