The air-dried yellow solid weighed 0.073 g (44%): mp 195 °C; ^{1}H NMR 2.60 (s, 6, $^+$N(CH$_3$)$_2$), 3.32 (s, H$_2$O, exchanges with D$_2$O), 4.87 (s, 4, 2 (CH$_2$)), 7.39 (pseudo t, i.e., overlapping dd, 2, $J_{6,5}$ = $J_{6,7}$ = 8.4 Hz), 7.98 (2 d, coincident, 4, $J_{5,6}$ = 8.4 Hz, $J_{7,6}$ = 8.4 Hz, 5-H, 7-H), 8.20 (s, 2, 2-H), 12.56 (br s, 2, NH, exchanges with D$_2$O); field-desorption mass spectrum (15 mA), m/e 394 (M$^+$ − I).

Anal. Calcd for $C_{20}H_{20}IN_5O_4$: C, 46.08; H, 3.87. Found: C, 46.04; H, 3.72.

Product Mixtures. Each reaction was repeated several times. Increasing the scale of the reaction 200-fold or increasing or decreasing the amount of methyl iodide used or the time of reaction by 50% had no effect on the observed product mixture. For large-scale versions of these reactions, solid starting material was added slowly in portions to neat methyl iodide or to a solution of methyl iodide in absolute ethanol.

(A) Reaction in Neat Methyl Iodide. To 0.015 g of gramine (**1a**) or 4-, 5-, or 6-nitrogramine (**1b–d**) in a 5-mL vial was added 0.5 mL of methyl iodide. The vial was capped, and the suspension was stirred at room temperature for 2 h, by which time a colorless oil, in the case of gramine (**1a**), or a yellow precipitate, in the case of the nitrogramines (**1b–d**), had formed. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, and a ^{1}H NMR spectrum of the residue was obtained in (CD$_3$)$_2$SO.

(B) Reaction in a Large Excess of Methyl Iodide in Absolute Ethanol. In a 5-mL vial, 0.015 g of gramine (**1a**) or 4-, 5-, or 6-nitrogramine (**1b-d**) was dissolved in 1.25-mL of absolute ethanol. To this was added 0.075 mL of methyl iodide. The vial was capped, and the solution was stirred at room temperature for 4 h, by which time a precipitate had formed. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, and a ^{1}H NMR spectrum of the residue was obtained in (CD$_3$)$_2$SO.

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Registry No. **1a**, 87-52-5; **1b**, 7150-46-1; **1c**, 3414-64-0; **1d**, 6954-87-6; **2a**, 5457-31-8; **2b**, 23099-33-4; **2c**, 76599-76-3; **2d**, 22979-90-4; **3a**, 76599-77-4; **3b**, 76599-78-5; **3c**, 76599-79-6; **3d**, 76599-80-9; **5**, 75-58-1; CH$_3$I, 74-88-4.

Phosphoric Amides. 3.[1] Acidic Cleavage of the Phosphorus–Nitrogen Bond in Acyclic and Cyclic Phosphoramidates

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The acidic hydrolysis of carboxylic amides proceeds according to the A$_O$T2 mechanism, involving the rate-determining formation of the oxonium-type intermediate from the O-protonated form of substrate conjugate acid.[2] On the other hand, the generally accepted mechanism for the acid-catalyzed solvolysis of phosphoramidates involves the protonation at the nitrogen atom followed by the bimolecular, direct displacement at phosphorus (A-S$_N$2-P mechanism).[3] Such a mechanism accounts well for the facile cleavage of the P–N bond under acidic conditions,[3] as well as for the predominant inversion of configuration observed in solvolysis of chiral phosphoramidates.[4] However, some examples of the solvolysis resulting in a considerable retention of configuration have been reported. Chiral *O,S*-dialkyl phosphoroamidothioates solvolyze in alcohols at high acid concentrations with up to 86% of retention,[5] and a low stereospecificity was observed for the BF$_3$-catalysed solvolysis of cyclic and optically active phosphoramidates.[6] Although it has been demonstrated that the first case involves, in fact, the double inversion process,[7] in the second case the formation of a pentacoordinated intermediate followed by pseudorotation has been postulated.[4] Such a mechanism requires the addition of a nucleophile to the O-protonated substrate to form the trigonal-bipyrimidal intermediate with the nitrogen substituent initially in the equatorial position. The internal proton (or Lewis acid) transfer from oxygen to nitrogen would be followed by pseudorotation and amine departure, resulting in the retention of configuration at phosphorus.

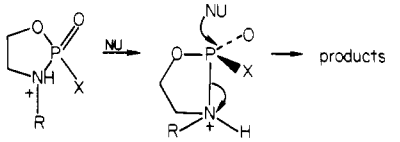
We tested the possibility of the solvolysis pathway following the O-protonated, pentacoordinated, intermediate mechanism by a kinetic approach. Although the oxygen-protonated form (A) of the substrate's conjugate acid is certainly a thermodynamically favored one,[8] the A-S$_N$2-P mechanism requires that the N-protonated tautomeric structure (B) represents the reactive form, attacked by a nucleophile in a rate-determining step (Scheme I). If the P–N bond is cleaved in a rate-determining step,

Scheme I

$$\underset{\text{A}}{X_2P^+(OH)NR_2} \overset{H^+}{\rightleftharpoons} X_2P(O)NR_2 \overset{H^+}{\rightleftharpoons} \underset{\text{B}}{X_2P(O)NHR_2^+} \xrightarrow{NU} TS$$

or if the P^V intermediate is formed from the N-protonated substrate, the application of Westheimer's theory on the nucleophilic displacement in cyclic phosphoryl systems[9] leads to the conclusion that the P–N bond cleavage in B should be subject to steric acceleration in compounds with the nitrogen and phosphorus atoms incorporated into a five-membered ring (Scheme II). Strongly electronegative ammonium nitrogen should preferentially occupy the apical position, suitable for the P–N cleavage step.[10] On the other hand, if the rate-determining step involves the nucleophilc attack at the O-protonated substrate, cyclic

Scheme II



TS or tbp intermediate

(1) Part 2: B. Davidowitz and T. A. Modro, *S. Afr. J. Chem.*, **33**, 74 (1980).
(2) T. A. Modro, K. Yates, and F. Beaufays, *Can. J. Chem.*, **55**, 3050 (1977).
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(10) The participation of the trigonal-bipyramidal intermediate with the protonated nitrogen at the apical position has been postulated by Hudson and co-workers[11] even for the base-catalysed hydrolysis of cyclic phosphoramidates.
(11) C. Brown, J. A. Bourdreau, B. Hewitson, and R. F. Hudson, *J. Chem. Soc., Perkin Trans. 2*, 888 (1976).

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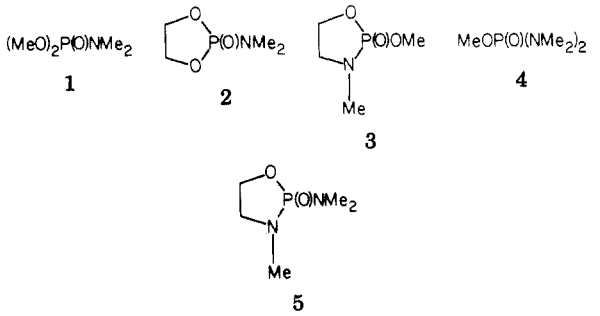
Table I. Phosphorus-Nitrogen Bond Cleavage with TCAA (1 Equiv) in $CDCl_3$ at 34 ± 1 °C

substrate[a]	1	2	3	4	5
10^5k_2, M^{-1} s^{-1} [b]	2.4	1.5	6000	3[c]	35[d]

[a] [Substrate] = [TCAA] = 0.30 M. [b] ±15%. [c] Per single P-N bond. [d] Total P-N cleavage.

phosphoramidates should solvolyze with rates comparable to those of the acyclic systems.

We have studied the acidic P–N bond cleavage in the phosphoramidates and phosphordiamidates **1–5**. Since in

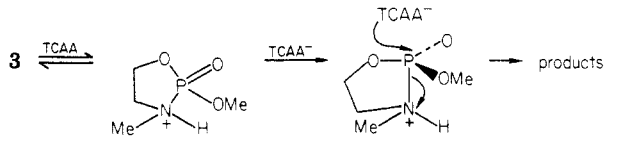


the aqueous acid the fission of the P-N bond is very fast, the reaction was studied in media of much lower solvolyzing power. One reaction system was the solution of the equimolar proportions of a substrate and trichloroacetic acid (TCAA) in chloroform; the other involved solvolysis in the rigorously anhydrous trifluoromethanesulfonic acid (TFMSA). In the first case solvolysis was expected to be slow because of the low concentration of substrate's conjugate acid, and low nucleophilicity of the TCAA anion. In TFMSA, although the protonation of a substrate is complete, it has been demonstrated[12] that the P-N bond in simple amidates is virtually stable due to the very weak nucleophilicity of the TFMSA and its anion.

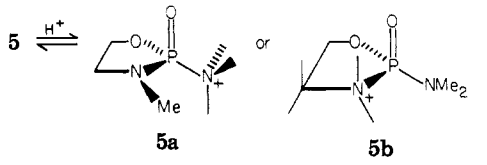
Results and Discussion

The cleavage of the P–N bond in compounds (**1–5**) could be easily observed by ^1H NMR spectroscopy. In substrates, the signals of the *N*-methyl substituents appear as high-field doublets (δ 2.64–2.74; J_{HP} = 10 Hz); upon solvolysis they change to the characteristic triplet of the dimethylammonium (or alkylmethylammonium) ion (J_{HH} = 5.8 Hz) shifted ca. 8 Hz downfield in $CDCl_3$ and ca. 24 Hz upfield in TFMSA. As expected, the reaction of amidates **1–5** with TCAA was sufficiently slow to allow the determination of the second-order rate constants for the P–N bond cleavage. Rate data are listed in Table I. The reactivities of **1** and **2** can be compared with that of the corresponding *N-tert*-butyl derivatives studied previously[13] in anhydrous trifluoroacetic acid (TFAA). Rates of the P–N bond fission in these two media are similar; e.g., for $(MeO)_2P(O)NH$-*t*-Bu in TFAA, $k_2 = 1.9 \times 10^{-5}$ M^{-1} s^{-1}.[13] This result remains in agreement with the general mechanism of the reaction. The weaker acidity of TCAA (relative to TFAA) is compensated for by its higher nucleophilicity, both effects approximately cancelling each other. Diamidate **4** reacts only slightly faster than the monoamide **1**. This can be explained in terms of the compensating effects of the increased basicity of **4** and the decreased electrophilicity of its conjugate acid resulting from the electron-donating effect of the second dimethylamino group. The most obvious result in Table I is the reactivity of the endocyclic P–N bond in **3** relative

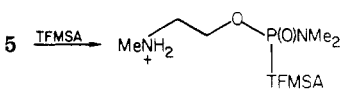
Scheme III



Scheme IV



Scheme V



to that of the exocyclic bond in the isomeric amide **2**. The observed rate acceleration ($k_2(3)/k_2(2) = 4 \times 10^3$) cannot be rationalized without accepting for **3** the direct, rate-determining attack of the nucleophile at the N-protonated substrate (Scheme III). We believe that the observed rate ratio represents in fact the minimum value of rate acceleration. The endocyclic nitrogen atom in **3** is probably less basic than the exocyclic nitrogen in **2** so the relative rate should be corrected to the difference in the concentrations of the corresponding conjugate acids. The difference in the basicity of the endo- and exocyclic nitrogen atoms is demonstrated by the behavior of the cyclic diamidate **5**. The total rate of the P–N bond cleavage in this compound is not significantly greater than in the acyclic substrates **1**, **2**, and **4**; moreover, the cleavage of both the amidate functions proceeds with comparable rates. At 48% conversion the relative intensity of the exo- to endocyclic *N*-methyl signals in the unreacted substrate is changed from the initial value of 2:1 to 2.2:1. This result can only be interpreted in terms of the higher basicity of the exocyclic NMe_2 group so the ring-opening P–N cleavage is inhibited because of the low concentration of the N (endo)-protonated form. Although the difference in basicity can partly be due to some differences in the hybridization of the two nitrogen atoms, the conjugate acid with the exocyclic ammonium ion (**5a**) should be sterically more favored than **5b** because the P–N rotation in **5a** can minimize the torsional strain at the tetrahedral ammonium nitrogen (Scheme IV).[14]

In the TFMSA solution any differences in nitrogen basicities in compounds **1–5** are of no significance and reaction products reflect directly the susceptibility of a given (protonated) nitrogen atom to the nucleophilic displacement. Following our earlier observation,[12] we have found that in TFMSA the phosphorus–nitrogen bond in all substrates with no endocyclic amidate function (**1**, **2**, **4**) remains perfectly stable over a period of at least 72 h.[16] On the other hand, the P–N bond in **3** undergoes solvolysis too fast for the determination of a rate constant (the ^1H NMR spectrum taken 2 min after **3** was dissolved in TFMSA shows 100% of the P–N fission). The most cau-

(12) T. A. Modro, *J. Chem. Soc., Chem. Commun.*, 201 (1980).
(13) T. A. Modro, M. A. Lawry, and E. Murphy, *J. Org. Chem.*, **43**, 5000 (1978).
(14) Similar interpretation involving the relief of the "bond opposition forces" was proposed by Brown et al.[15] in the discussion of rates of solvolysis of alkyl and cycloalkyl tosylates and chlorides.
(15) H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956); H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *ibid.*, **73**, 212 (1951).
(16) The P–N bond in these compounds is probably under these conditions practically infinitely stable. Small quantities of the dimethylammonium ions observed in some cases almost certainly resulted from traces of moisture introduced during or after preparation of a sample.

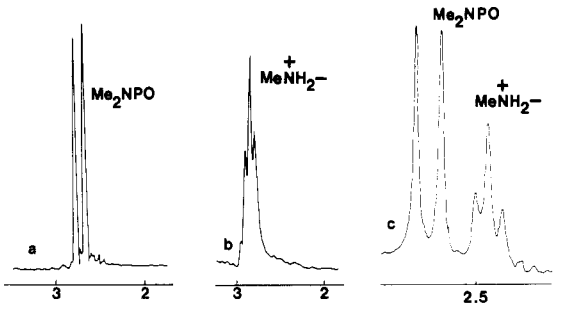


Figure 1. ^{1}H NMR spectra of the *N*-methyl groups, in TFMSA: (a) **2** after 72 h (sweep width 1000 Hz); (b) **3** after 2 min (sweep width 1000 Hz); (c) **5** after 5 min, unchanged after 72 h (sweep width 250 Hz).

tious estimate gives in this case the lower limit of rate acceleration, $k_\Psi(3)/k_\Psi(2) > 10^5$, perfectly in agreement with values observed for solvolysis of other cyclic systems.[9] The behavior of the diamidate **5** in TFMSA conforms well to the pattern observed for other substrates. While the exocyclic dimethylamino group remains unchanged over a long period of time, the cleavage of the endocyclic P–N bond is very fast and quantitative (Scheme V). Figure 1 illustrates the behavior of the acyclic and cyclic phosphoramidates in TFMSA as determined by the ^{1}H NMR of the *N*-methyl substituents.

We believe that our results demonstrate that the acid-catalysed cleavage of the P–N bond in phosphoramidates proceeds via the *N*-protonated species as a reactive form and that the amino group departs directly from the apical position of the trigonal-bipyramidal transition state or intermediate.

Experimental Section

$CDCl_3$ (Aldrich, 99.8 atom % D) was dried with P_4O_{10}, distilled, and stored over molecular sieves. TCAA (May and Baker Ltd.) was distilled under reduced pressure [bp 105 °C (12 mm)] and stored in a desiccator over P_4O_{10}. TFMSA (Aldrich) was distilled from a 10% volume of trifluoromethanesulfonic anhydride with rigorous exclusion of moisture [bp 62 °C (12 mm)] and stored in a desiccator over P_4O_{10}. ^{1}H NMR spectra were recorded at 100 MHz on a Varian XL-100 spectrometer at a probe temperature of 34 ± 1 °C.

Substrates. Amidates **1**, **2**, and **4** were prepared by passing dry dimethylamine through an etheral solution of the corresponding phosphorochloridate at room temperature. Amine hydrochloride was filtered off, the ether removed on a rotary evaporator, and the product purified by distillation.

For **1**: bp 75–76 °C (12 mm) [lit.[17] bp 72–72.5 °C (11 mm)]; ^{1}H NMR δ 2.65 (6 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 3.66 (6 H, d, $J_{H,P}$ = 11 Hz, OMe).

For **2**: bp 95 °C (0.15 mm); mp 50–52 °C [lit.[18] bp 113–114 °C (1 mm); mp 47.5–48.5 °C]. Anal. Calcd for $C_4H_{10}O_3NP$: C, 31.79; H, 6.67; N, 9.27; P, 20.50. Found: C, 31.53; H, 6.64; N, 9.48; P, 20.25; ^{1}H NMR δ 2.74 (6 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 4.20–4.45 (4 H, m, CH_2CH_2).

For **4**: bp 50–51 °C (0.6 mm) [lit.[19] bp 49–50 °C (1 mm)]; ^{1}H NMR δ 2.66 (12 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 3.58 (3 H, d, $J_{H,P}$ = 11 Hz, OMe).

Compound **3** was prepared from methyl phosphorodichloridate, 2-(methylamino)ethanol, and 2 equiv of triethylamine in dry dioxane at 25–30 °C: bp 81–83 °C (0.15 mm); ^{1}H NMR δ 2.71 (3 H, d, $J_{H,P}$ = 10 Hz, NMe), 3.20–3.45 (2 H, m, NCH_2), 3.74 (3 H, d, $J_{H,P}$ = 12 Hz, OMe), 4.10–4.50 (2 H, m, OCH_2). Anal. Found for $C_4H_{10}O_3NP$: C, 31.98; H, 6.89; N, 9.56; P, 20.22.

Compound **5** was prepared as for **3**, with Me_2NPOCl_2, 2-(methylamino)ethanol, and Et_3N as substrates: bp 88–89 °C (0.08 mm). Anal. Calcd for $C_5H_{13}O_2N_2P$: C, 36.59; H, 7.98; N, 17.07; P, 18.87. Found: C, 36.71; H, 7.96; N, 16.94; P, 18.61. ^{1}H NMR δ 2.64 (3 H, d, $J_{H,P}$ = 9.8 Hz, *endo*-NMe), 2.72 (6 H, d, $J_{H,P}$ = 10.3 Hz, *exo*-NMe_2), 3.15–3.50 (2 H, m, NCH_2), 4.00–4.40 (2 H, m, OCH_2).

Kinetics. The substrate (ca. 20 mg) was placed in an NMR tube which was equilibrated in a bath at the temperature of the kinetic run. The solution of an equimolar quantity of TCAA in $CDCl_3$ (0.5 mL) was added from a container also kept in the bath, the tube was placed in the spectrometer probe, and measurements were started. The integration curve was plotted repeatedly in the range of the *N*-methyl group signals (between 2 and 3 ppm) at a sweep width of 250 Hz. Second-order rate constants k_2 were determined from changes in intensity of the signals from N-Me protons in the substrate (or product) molecule. For minimization of the complications resulting from the subsequent interactions between TCAA and the reaction product, rate constants were calculated from the initial part of the reaction (up to 30% of conversion). Satisfactory straight-line plots ($r > 0.99$) were obtained; the reported values are the average of three measurements and are reproducible to within ±15%. For reactions in TFMSA, the acid (0.5 mL) was transferred to the NMR tube containing ca. 25 mg of a substrate in a rigorously moisture-free glovebox, the tube cap was wrapped tightly with Parafilm, and the NMR spectrum was recorded.

Acknowledgment. Financial assistance from the Council of the University of Cape Town is gratefully acknowledged.

Registry No. **1**, 597-07-9; **2**, 7114-66-1; **3**, 30982-84-4; **4**, 7393-11-5; **5**, 51833-54-6; TCAA, 76-03-9; TFMSA, 1493-13-6; methyl phosphorodichloridate, 677-24-7; Me_2NPOCl_2, 677-43-0; 2-(methylamino)ethanol, 109-83-1.

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Theoretical Estimation of pK_a Values of Pyrazinylguanidine Derivatives

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The pivotal role which prototropic equilibria play in the action of numerous therapeutic agents has been thoroughly documented.[2] Therefore, the ability to predict quantitatively one of the thermodynamic parameters connected with these events would be particularly useful in drug design and afford a unique advantage in the selection of analogue members. Herein we contribute a practical solution to the question of how well a chemist can predict, a priori, solution-phase pK_a values and present our initial results on the estimation of pK_a values of amiloride[3] (Figure 1) and its derivatives (Figure 2) based on CNDO/2 calculations of gas-phase proton affinities (PAs).[4]

A more detailed understanding of the factors which influence prototropic equilibria has emerged as one of the

(1) (a) West Point, PA. (b) Rahway, NJ.
(2) Ganellin, C. R. In "Drug Action at the Molecular Level"; Roberts, G. C. K., Ed.; University Park Press: Baltimore, MD, 1977; Chapter 1 and references cited therein.
(3) Amiloride is a potassium-sparing diuretic. For conformational studies of amiloride as well as leading references regarding its synthesis and structure–activity relationships, see: Smith, R. L.; Cochran, D. W.; Gund, P.; Cragoe, E. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 191 and references cited therein.
(4) Proton affinity (PA) is defined for a base B as the heterolytic bond-dissociation energy for removing a proton from the conjugate acid BH^+.

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