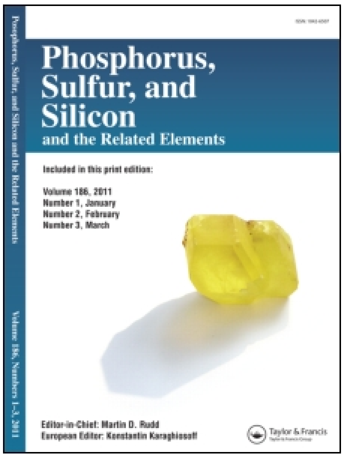

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PHOSPHORIC AMIDES

P-N Bond Reactivity vs ^{15}N NMR Spectroscopic Characteristics

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^{15}N NMR chemical shift values (but not the $^{1}J_{NP}$ values) are a good indication of the relative basicities of nitrogens in phosphoramidates, as demonstrated by the rates of the acid-catalysed cleavage of the exo- and endocyclic P-N bond in selected substrates.

Keywords: ^{15}N NMR spectroscopy[1]; J_{NP} coupling; acidic P-N bond cleavage; basicity of phosphoramidates; exo- and endocyclic P-N bond

Westheimer's theory aimed at the explanation of the hydrolytic reactivity of five-membered cyclic phosphoric esters laid the foundation for the current understanding of the associative mechanism of substitution at the phosphoryl centre.[1] Several years ago we used that theory to explain the dramatic reactivity differences in the acid-catalysed cleavage of the endo- *vs* exocyclic P-N bond in cyclic phosphoramidates **1**, **2**, **3**.[2] (Scheme 1). Relative reactivities of **2** and **1** were found to be k_{rel} (**2/1**) $= 4 \times 10^3$ with respect to CCl_3CO_2H in $CDCl_3$, and $> 10^5$ with respect to CF_3SO_3H (neat). For **3**, the k_{rel} (endo P-N/exo P-N) value was found close to unity in the first medium, while in CF_3SO_3H the P-N (endo) cleavage was virtually instantaneous, but it was not followed by any noticeable fission of the P-N (exo) bond which remained unchanged for a very long time.

The results gave evidence for the "ring effect" operating in the cleavage of the endo P-N bond in **2** and **3**. The additional conclusion was that the exocyclic

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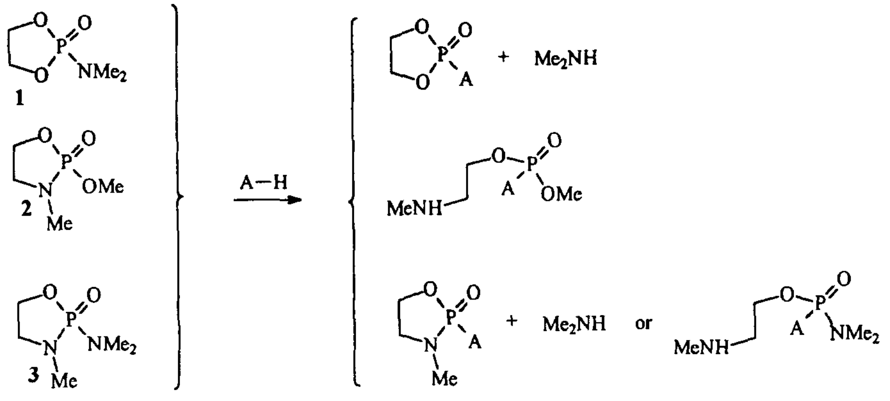
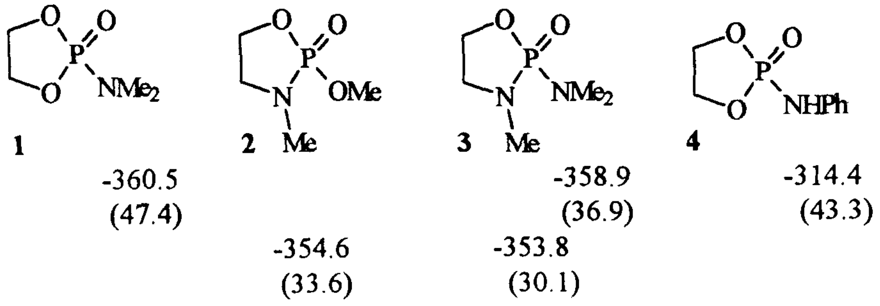
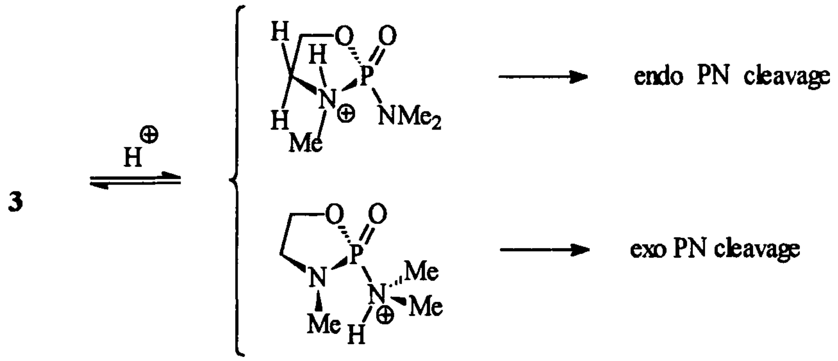


A = CCl_3CO_2, CF_3SO_3

nitrogen is significantly more basic than the endocyclic N, the effect being responsible for the partial reduction of the k_{rel} (**2**/**1**) to a value of only $\cong 10^3$, as well as for the poor selectivity in the cleavage of **3**, observed with respect to a weak acid (CCl_3CO_2H). In CF_3SO_3H, where the basicity differences can be ignored, the "ring effect" on the reactivity could operate to its full extent. Since the protonation equilibria of the individual amido nitrogens in phosphoramidates are not directly available for measurement,[3] we decided to relate the rate data to the relative basicity of the nitrogens probed by the ^{15}N NMR spectroscopy. Spectroscopic parameters of the amidates **1**, **2**, **3** are given in Scheme 2, with δ_N values given relative to $MeNO_2$, and $^1J_{NP}$ values (in brackets) given in Hz. Chemical shift values are rather insensitive to the electronic environment at phosphorus (amidodiesters **1**, **2**, **4** *vs* diamidoester **3**), with both endocyclic ni-





trogens deshielded relative to their exocyclic counterparts. Greater shielding of the exocyclic nitrogens implies, in agreement with the reactivity data, the higher basicity of these centers. For example, the nitrogen atom of the NH_2 group in methylamine is 45 ppm more shielded than that of the NH_2 group in aniline;[4] in the gas phase the proton affinity of the former is 12 kJ mol^{-1} higher than that of the latter.[5] One-bond coupling constants also show a clear trend, with the endocyclic nitrogens characterised by a lower $^1J_{NP}$ value. The interpretation of the nitrogen - phosphorus coupling in terms of the relative basicity of the nitrogens is more difficult. The pioneering work by Gray and Albright,[6] followed by the studies of phosphoramidates by Buchanan and coworkers,[7] indicated high sensitivity of the ^{15}N-^{31}P coupling to nitrogen hybridisation. For a series of heterocyclic phosphoramidates the *decrease* in the $^1J_{NP}$ value was indicative of the *increase* in the pyramidal character of the nitrogen.[7b]

According to this interpretation, the endocyclic amide nitrogens in **2** and **3** should have more pyramidal geometry (increase in the *p* character), hence should be more accessible for the protonation by an acidic catalyst. The kinetic results, on the other hand, indicate that it is the exocyclic nitrogen which represents the most basic centre in the molecule and that the effect is responsible for the partial reduction of the exo/endo selectivity in the P-N bond cleavage. The difference in the basicity of the exo- *vs* endocyclic nitrogens studied may, however stem not from the differences in the hybridisation of the basic atoms, but from the differences in the stability of the corresponding conjugate acids. We interpret the lower protonation equilibrium for the endocyclic N in **3** (or for **2** relative to **1**) as a consequence of the unfavourable torsion angles in the conjugate acid **3a**, involving the eclipsed vicinal bond interactions around the nitrogen, relative to the situation in **3b** (or **1**), where free rotation about the P-N bond can be expected (Scheme 3). The interpretation is in full analogy to the explanation given by Brown and coworkers for the solvolysis rates of alkyl and cycloalkyl derivatives.[8] In a medium such as CF_3SO_3H, a substrate like **3** is not only fully protonated, but also diprotonated to a significant extent.[9] Under those conditions, the solvolysis involves, according to the Westheimer' theory,[11] only the endocyclic P-N bond, in the reaction that follows a trigonal bipyramide transition state (or intermediate and is therefore subject of the usual "ring acceleration" effect). In conclusion, ^{15}N NMR chemical shifts data (but not the $^1J_{NP}$ values) seem a useful indication of the relative basicity of nitrogen atoms in phosphoramidate systems. While the differences in the δ_N values of the individual nitrogens in **1**, **2**, **3** are relatively small (as the centers differ only with respect to the endo *vs* exo location), the N-phenyl derivative **4** (Scheme 2) is characterised by a much more deshielded nitrogen atom. In agreement with this result, it has been found that the basicity of the N atom is so much reduced that the acid-catalysed solvolysis of **4** involves, in fact, the *oxygen - protonated* form of the substrate as the reactive conjugate acid.[10] As far as the coupling constant is concerned, it is interesting to note that the $^1J_{NP}$ value for **4** indicates a more pyramidal nitrogen than that in **1** [$^1J_{NP}$ (**4**) < $^1J_{NP}$ (**1**)],[7a] an obviously erroneous conclusion.

EXPERIMENTAL

Substrates **1**, **2**, **3**, **4** were prepared as described before.[2,10] Their ^{31}P NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ and δ values are given relative to 85% H_3PO_4 as external standard. **1** (mp 47–48°C; from Et_2O), δ_P 27.7; **2** (purified by bulb-to-bulb distillation, oven temp. 120°C/0.15 mmHg), δ_P 23.1; **3** (purified by bulb-to-bulb distillation, oven temp. 110–115°C/ 0.10 mmHg), δ_P 28.8; **4** (mp 111–113°C; from benzene-pet. ether), δ_P 20.7. The ^{15}N NMR measurements were taken on a Bruker AM 500 instrument operating at 50.698 MHz for solutions in $CDCl_3$ at room temperature. For substrates **1**, **2**, **3**, INEPT procedure optimised for long range coupling *ca* 2 Hz with refocusing and broad-band proton decoupling was used. For compound **4** proton-coupled INEPT method was optimised for ^1J coupling *ca* 100 Hz. Typical operating parameters are: spectral width 17000 Hz, acquisition time 1 s, 32K data points with zero-filling up to 64K to get better digital resolution for coupling constants estimation, number of scans between 150 and 1000 to obtain sufficient signal to noise ratio. The chemical shifts are reported relative to external nitromethane as a standard.

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