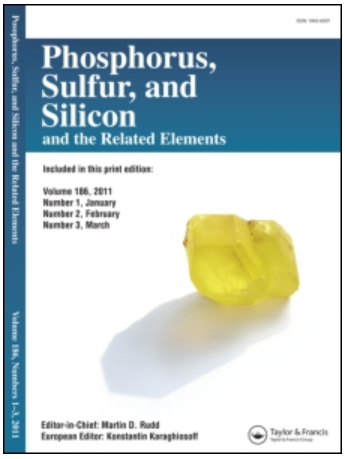

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Modro, Tomasz A. , Roux, Charlotte Le , Wan, Huijie and Modro, Agnes M.(1996) 'Reactivity of N-Phosphorylated Mustards', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 469 — 472
To link to this Article: DOI: 10.1080/10426509608545192
URL: http://dx.doi.org/10.1080/10426509608545192

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 469–472
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REACTIVITY OF N-PHOSPHORYLATED MUSTARDS

TOMASZ A. MODRO, CHARLOTTE LE ROUX, HUIJIE WAN,
AGNES M. MODRO
Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria,
Pretoria 0002, South Africa

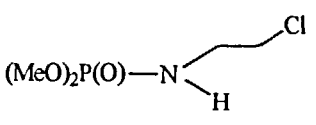
Abstract Products and mechanisms of the fragmentation of ionic phosphoramidates containing the N-(2-chloroethyl) functionality are discussed.

INTRODUCTION

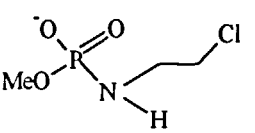
The metabolism of the anticancer prodrug cyclophosphamide is well understood, except of the exact mechanism of the alkylating reactivity of the phosphoramidate mustard, $(HO)(H_2N)P(O)N(CH_2CH_2Cl)_2$ (**1**). Although it is known that **1** is capable of bis-alkylating nucleophilic centres *via* aziridinium ion derived intermediates,[1] whether it reacts as an intact molecule, or the P-N bond cleavage is a prerequisite of the alkylation, remains controversial. In this work, we approached the problem by investigating the fragmentation behavior of some N-phosphorylated nitrogen mustard derivatives (**2**), closely related to **1**, and arrived at the general mechanistic pattern for the reactivity of that system.

RESULTS AND DISCUSSION

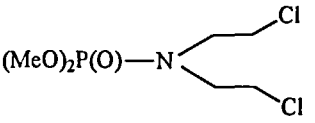
The following compounds **3** were prepared and used as precursors for the ionic substrates **2**, employed in the fragmentation studies.



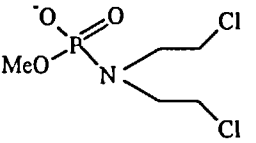
3a



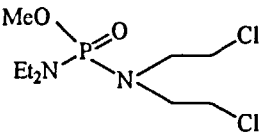
2a



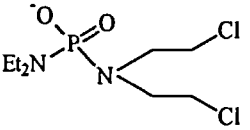
3b



2b

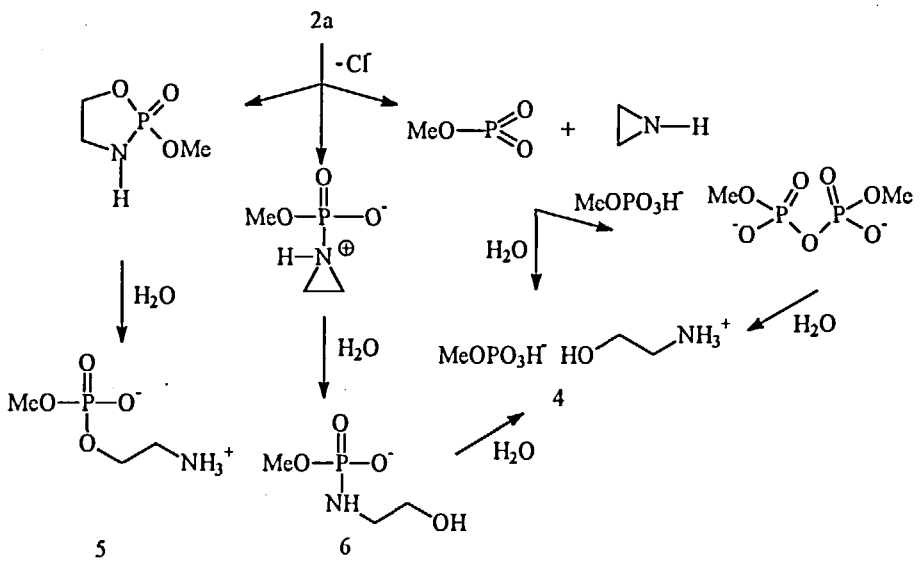


3c



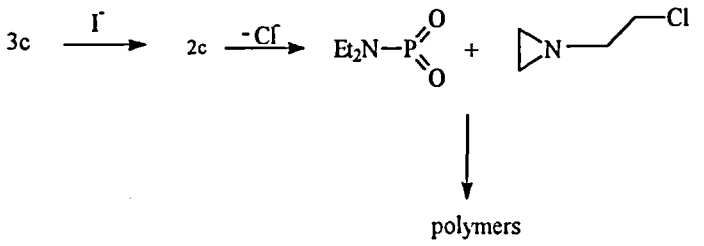
2c

Ions **2a** and 2b could be easily prepared as lithium salts by demetyhylation of the corresponding **3** with LiI. Their fragmentation was then studied in aqueous, or in aqueous - pyridine solutions; the composition of the reaction mixtures as a function of time was determined by NMR spectroscopy, and the individual products were identified by comparison with independently prepared authentic compounds.[2] Fragmentation of **2a** follows three parallel pathways, and the full course of the reaction is presented below.



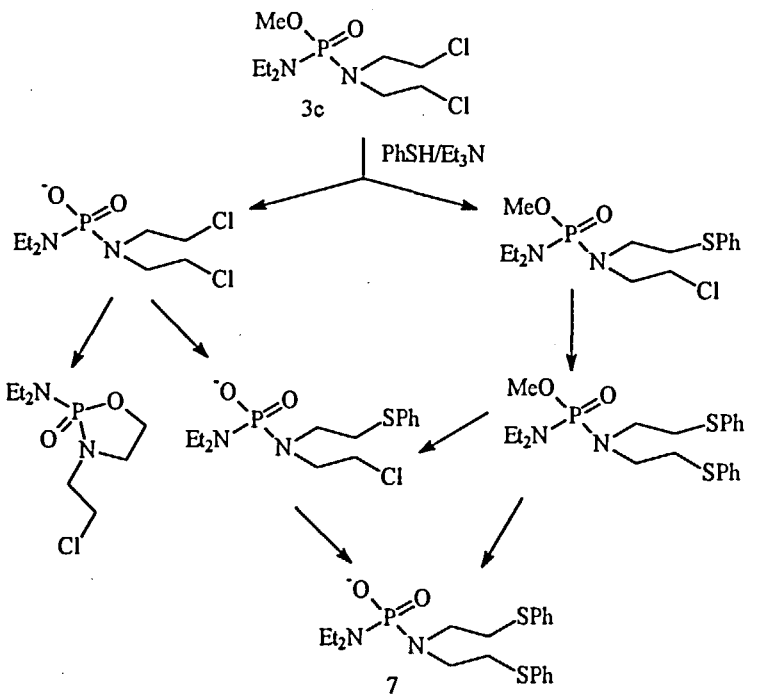
The first pathway is the 1,5-cyclization to a 1,3,2-oxazaphospholidine, which then undergoes slow hydrolysis to a stable diester **5** (*ca* 3%). Second pathway (*ca* 15%) is the 1,3-cyclization to N-phosphorylated aziridinium ion, which reacts fast with water (or any nucleophile present) to give an amidoester **6**, which breakes down slowly to the final product - the salt **4**. The major pathway involves, however, a fragmentation of **2** to methyl metaphosphate and ethylenimine; both reacting fast with water giving directly salt **4**. The metaphosphate can be also trapped by methyl phosphate, yielding transient dimethyl diphosphate, which also hydrolyzes finally to **4**. At the end of the reaction **4** represents *ca* 97% of the product, but it is formed *via* more than one pathway, each involving alkylation of water by an aziridine derivative. Minor product **5** represents the "inactive" direction in a sense that the cyclic intermediate is devoid of any alkylating properties. In the presence of pyridine, the fragmentation followed only the second pathway, with the methyl phosphate salt of N-(2-aminoethyl)pyridinium cation formed as a sole product. The behavior of **2b** paralled that of **2a**, with the "metaphosphate" mechanism representing the major, and the 1,5-cyclization the minor pathways.

The diamidate derivative **2c** demonstrated much higher reactivity than the amidoesters **2a** and **2b**. All attempts to prepare a salt of **2c** by demethylation of **3c** failed, as the demethylation product decomposed spontaneously as soon as it was formed from its precursor. When **3c** was heated with LiI, only a polymeric product was obtained, presumably derived from the monomeric intermediates formed according to the"metaphosphate" mechanism.



The alkylating behavior of **2c** was studied in the decomposition of its precursor **3c**, by incubating **3c** in CD_3CN with an excess of PhSH and Et_3N. All products (transient and stable) were identified by comparison with the standards and the course of the reaction

is shown below.



In the first step two S_N2 reactions take place: the O-demethylation, and the direct displacement of Cl by PhS^-. The demethylated intermediate can undergo 1,5-cyclization or can exchange both Cl atoms for the PhS groups; the other intermediate undergoes further S_N2 reactions. The final **7** is a product of bis-alkylation of thiophenol with **3c**, with the P-N bond retained. It decomposes slowly, yielding the product with $\delta_P \approx -20$, typical for the polyphosphate species observed in other reactions involving release of a metaphosphate intermediate.[3]

In conclusion, we found that the nitrogen mustards of the type **2c** are much more reactive than the ester analogues **2a**, **2b**, and that the alkylation by those systems can involve different mechanisms, including the release of a metaphosphate fragment.

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