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Reactivity of N-Phosphorylated Mustards

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REACTIVITY OF N-PHOSPHORYLATED MUSTARDS

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<u>Abstract</u> 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 bisalkylating 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.





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 CD₃CN with an excess of PhSH and Et₃N. 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_N^2 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_N^2 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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