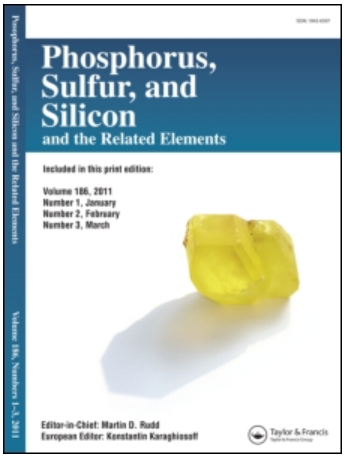

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Studies with Metaphosphoric Acid Derivatives

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STUDIES WITH METAPHOSPHORIC ACID DERIVATIVES[1]

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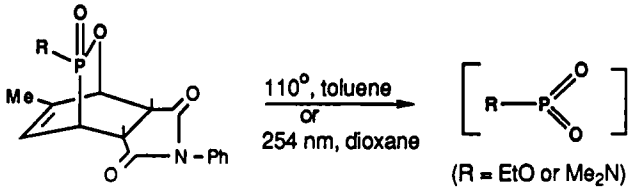
Abstract A variety of O-alkyl, N,N-dialkylamino, and N-alkylamino metaphosphates, as well as O-alkyl metathiophosphates, have been generated by thermal or photochemical fragmentation of 2,3-oxaphosphabicyclo[2.2.2]octene derivatives. The metaphosphoric acid derivatives are detected by trapping reactions, including a new reaction with epoxides to form 1,3,2-dioxaphospholanes, and by direct ^{31}P NMR observation on THF solutions at -78°C. Applications of metaphosphates as novel phosphorylating agents are possible.

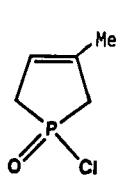
Previous work in this laboratory[2-4] has established the 2,3-oxaphosphabicyclo[2.2.2]octene ring system to be a useful precursor for generation of derivatives of metaphosphoric acid by fragmentation processes.



New results from continued study of this method are reported here.

The heterocycles used as metaphosphate precursors are prepared by a procedure[2-4] which has been found to have considerable generality in the type of substituent to be placed on phosphorus. Phosphinic chloride **1** is reacted with the proper nucleophile, and the product treated with bromine. The dibromophospholane is dehydrobrominated with triethylamine in the presence of N-phenylmaleimide, which intercepts the intermediate phosphole oxide in a

Diels-Alder reaction as **2**. Oxygen-insertion into a bridging C-P bond gives the metaphosphate precursor **3**.



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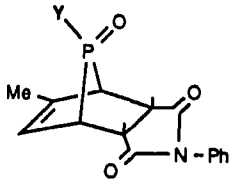

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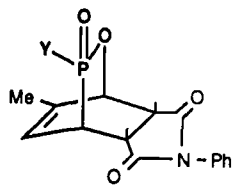
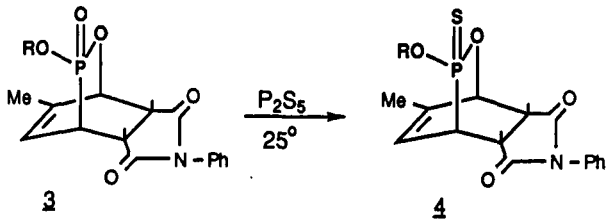


3

Seven new esters and amides having structure **3** have been prepared and fully characterized in our recent studies. The esters were used to generate the following alkyl metaphosphates: **$MeO\text{-}PO_2$**, **$Me_3CCH_2O\text{-}PO_2$**, **$PhCH_2O\text{-}PO_2$**, **(S)-MeEtCHO-PO_2**. From the amides were prepared: **$Et_2N\text{-}PO_2$**, **$Me_3CNH\text{-}PO_2$**, **(Mesityl)-NH-PO_2**. Both the thermal (110°C in toluene for esters; 120°C for the more stable amides) and the photochemical (in dioxane, THF, or MeCN) methods were effective for the fragmentation of **3**. The metaphosphates generated underwent immediate condensation reactions to give polyphosphoric acid derivatives as evidenced by characteristic complex ^{31}P NMR signals in the approximate regions δ -10 and -20. When the alkyl metaphosphates were generated in the presence of alcohols or amines as trapping agents, polyphosphate formation was avoided and mononuclear phosphates [$ROP(O)(OH)OR'$ and $ROP(O)(OH)NR_2$] were formed, frequently as the only phosphorus product. Some of these products were isolated by silica gel chromatography and identified spectroscopically; instability of a few products prompted a methylation by CH_2N_2 to give distillable trialkyl phosphates.

Trapping of the metaphosphoramidates with alcohols was effective only when they were produced by the photochemical method; the more forcing thermal conditions led to extensive or complete replacement of the amino group by alkoxy. The phosphoramidates proved to be unstable in isolation attempts, but methylation gave isolatable derivatives.

The first examples of alkyl metathiophosphates have been prepared, using both the thermal and photochemical fragmentations of bridged thionophosphonates (**4**) prepared from **3** esters.



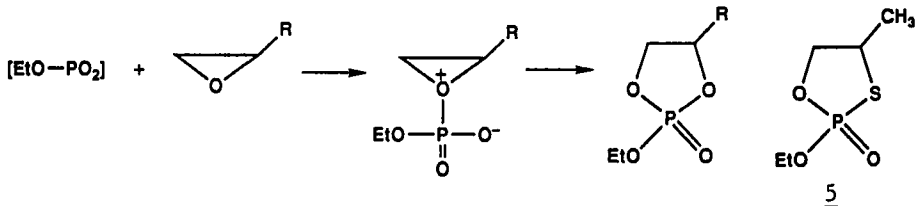
3 4

The following alkyl metathiophosphates have been generated: **EtO-P(S)O, Me_3CCH_2O-P(S)O, (S)-MeEtCHO-P(S)O.** The metathiophosphates reacted with alcohol trapping agents to form exclusively the O,O-dialkyl thionophosphates (RO)(R'O)P(S)OH, easily recognized from their ^{31}P NMR shifts in the range $\underline{\delta}$ 60-65.

It is of special significance that (S)-sec.butyl metathiophosphate, generated by *both* the thermal and photochemical methods, gave a 1:1 mixture of diastereomeric thionophosphates on reaction with ethanol ($\underline{\delta}$ 61.03 and 61.10, 300 MHz spectrometer). This is the expected result for a planar metaphosphate intermediate,[5] and indeed provides a compelling argument for the existence of the metaphosphate as a free species at the time of generation by the fragmentation processes.

Photochemical fragmentation of metaphosphate precursors with bulky P-substituents is being conducted at -78°C. ^{31}P NMR measurements are made at this temperature to determine if a metaphosphate is present. Tetrahydrofuran is the preferred solvent at -78°C but it is likely that a complex would form with the metaphosphate as proposed[6] for other solvents with lone pairs (e.g., dioxane and acetonitrile). When Et_2N-PO_2 was generated from **3**, Y = Et_2N, in THF at -78°C, the major ^{31}P NMR signal had $\underline{\delta}$ +12, which was seen to diminish on warming of the solution to room temperature with formation of polyphosphate products ($\underline{\delta}$ -11 and -22), or to disappear when ethanol was added, whereupon the signal ($\underline{\delta}$ +9) for the expected trapping product $Et_2NPO(OH)(OEt)$ was appeared.

The formation of a complex with THF is consistent with a new reaction observed for alkyl metaphosphates; thermal generation of ethyl metaphosphate in the presence of an epoxide gives complexes that undergo ring opening and closure to form 1,3,2-dioxaphospholanes as the major products.



R = Me, Ph, $ClCH_2$, $BrCH_2$, $MeOCH_2$

Thus, with R = Me, a 1:1 mixture of diastereomeric dioxaphospholanes ($\underline{\delta}$ ^{31}P +16.7 and +16.5) is obtained. Metathiophosphates react similarly to give 1,3,2-oxathiaphospholanes (**5**, $\underline{\delta}$ ^{31}P +40.6).

The high reactivity of the metaphosphoric acid derivatives causes consideration of their use for special applications in the synthesis of phosphates. The OH groups on the surface of solids, especially silica gel, are reactive to metaphosphates, and are converted to phosphate groups. Another application now being explored is the synthesis of sugar and peptide phosphates. The advantage offered to these fields by the metaphosphate method lies in the wide variety of P-functionalities that can be generated in the single step of phosphorylation. We have, for example, performed the phosphorylation at CH_2OH of 1,2,3,4-tetraacetyl-β-D-glucopyranose using photochemically generated N,N-dimethylmetaphosphoramidate. The product had a ^{31}P shift of $\underline{\delta}$ +9.2, as expected for the desired phosphoramidate.

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1. Supported by grants from the Petroleum Research Fund of the American Chemical Society and from the Army Research Office.
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