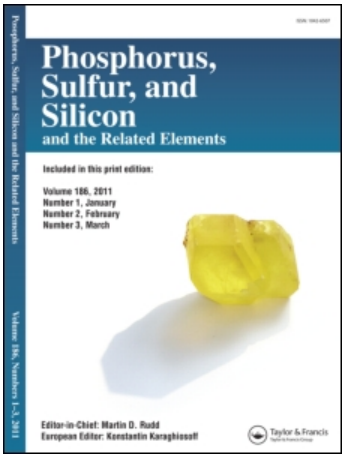

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REACTION OF PROPOSED PHOSPHOROTHIOLATE S-OXIDE INTERMEDIATES WITH ALCOHOLS

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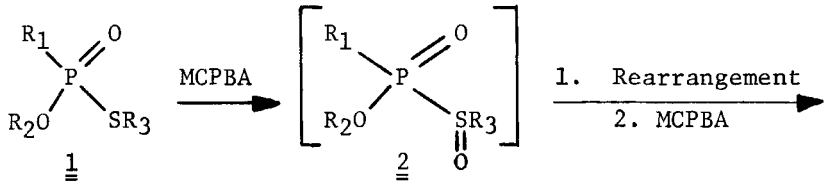
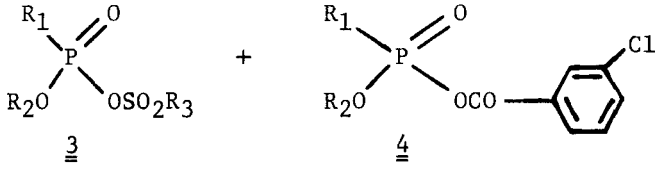
Abstract S-Oxide 2 is an extremely reactive intermediate. Its phosphorylation vs rearrangement rates, strongly depend upon the nature of the nucleophile.

Oxidation of S-alkyl phosphonothiolates, phosphorothiolates and phosphoramidothiolates 1 (equation 1, R_1=alkyl, alkoxy, NH_2, $NHCOCH_3$; R_2=alkyl, aryl; R_3=alkyl, chloroallyl) with m-chloroperoxybenzoic acid (MCPBA) yields a very short-lived intermediate, proposed to be the corresponding phosphorothiolate S-oxide (1,2). S-Propyl phosphorothiolates also undergo oxidative bioactivation in vivo and with microsomal oxidases, probably involving sulfoxidation (3,4). Attempts to directly observe 2 on chemical oxidation have not been successful (1-4). The basis for its instability is not defined.

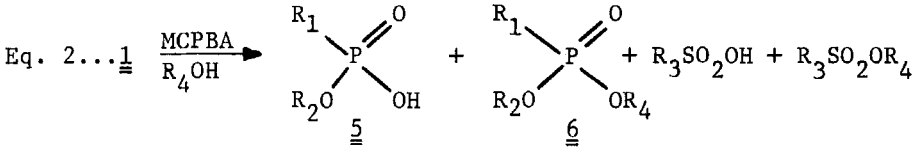


Eq. 1...

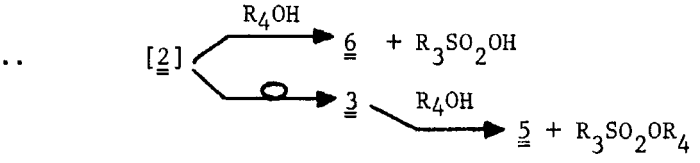


The reaction medium in which 2 is formed determines its ultimate fate. Thus, when formed in the presence of nucleophiles, 2 acts as a strong phosphorylating agent. In the absence of nucleophiles, the rearrangement is favored, leading to 3 which lacks phosphorylation properties. The first products observed and isolated are phosphinyloxysulfonates 3 from phosphorothiolates (1-3)

and m-chlorobenzoyl anhydrides 4 from phosphonothiolates when the reaction solvent is either dry acetone, chloroform or benzene. However, some chemical properties of intermediate 2 can be evaluated on carrying out the MCPBA oxidation reactions in various alcohols. The variety of products obtained on oxidation of 1 in different alcohols are given in equation 2.



The relative percentages of acid 5 and ester 6 in the final oxidation mixture may help to evaluate the relative rates at which intermediate 2 phosphorylates the alcohol (to give 6) as opposed to the rearrangement and further oxidation to sulfonate 3 followed by sulfonylation of the alcohol (to give 5), as indicated in equation 3.



^{31}P nmr monitoring of the oxidation products with excess MCPBA revealed a significant upfield shift, indicating replacement of the original P(O)-S bond with a P(O)-O bond (Table 1). Complete phosphorylation of the solvent is accomplished if the oxidation is carried out in primary aliphatic alcohols giving esters 6, the ultimate products, in 100% yield. Interestingly, these results are independent of the S-alkyl moiety or of any other substituent attached to the phosphorus, i.e. oxidation of alkyl phosphonothiolates, alkyl or aryl phosphorothiolates and alkyl phosphoromidothiolates all give only ester 6. Benzyl alcohol is an exception as a primary alcohol reaction solvent since in this case only 68% of the benzyl ester is formed (Table 1).

MCPBA oxidations in isopropanol and secondary-butanol yield an almost 1:1 mixture of 5 and 6 (Table 1). This indicates that in secondary alcohols both routes shown in equation 3 are almost equally favored. Oxidation in tertiary-butanol, however, leads almost exclusively to acid 5, which is also the only product from initial oxidation of 1 in aprotic solvents followed by reaction with alcohol or water in the presence of triethylamine.

Competitive phosphorylation vs. rearrangement reactions are readily observed when the oxidations are performed in the presence of increasing amounts of ethanol in the reaction mixtures. Thus, at lower concentrations of the nucleophile a considerable amount of the starting material is converted to the pyrophosphorus com-

TABLE 1. Yields of oxidation products 5 and 6 on MCPBA oxidation of 1 in various alcohols and ^{31}P nmr chemical shifts of reactants and products.

Reaction solvent (R_4OH)	Reactants 1			Products, %		$\delta\ ^{31}P$[a]	
	R_1	R_2	R_3	5	6	1[b]	6[c]
CH_3OH	CH_3	i-C_3H_7	C_2H_5	0	100	51.89[d]	30.80
CH_3OH	C_2H_5O	C_2H_5	CH_3	0	100	29.72	5.88
C_2H_5OH	CH_3	C_2H_5	i-C_3H_7	0	100	52.86[e]	30.57
C_2H_5OH	C_2H_5O	C_2H_5	CH_3	0	100	29.72	4.55
C_2H_5OH	C_2H_5O	C_2H_5	i-C_3H_7	0	100	32.79	4.55
C_2H_5OH	C_2H_5O	C_2H_5	$CH_2C(Cl)=CH_2$	0	100	31.35	4.55
C_2H_5OH	C_2H_5O	C_2H_5	$CH_2C(Cl)=CHCl$	0	100	29.78	4.55
C_2H_5OH	NH_2	CH_3	CH_3	0	100	40.41	5.71
C_2H_5OH	NHAc	CH_3	CH_3	0	100	32.43	5.67
C_2H_5OH	C_2H_5O	2-Cl,4-BrC_6H_3	n-C_3H_7	0	100	31.23	-1.16
n-C_3H_7OH	C_2H_5O	C_2H_5	CH_3	0	100	29.72	4.65
$C_6H_5CH_2OH$	CH_3	t-C_4H_9	i-C_3H_7	32	68	47.33[e]	27.51
i-C_3H_7OH	C_2H_5O	C_2H_5	CH_3	41	59	29.72	3.39[f]
s-C_4H_9OH	C_2H_5O	C_2H_5	CH_3	60	40	29.72	3.62[f]
s-C_4H_9OH	C_2H_5O	2-Cl,4-BrC_6H_3	n-C_3H_7	45	55	31.23	-2.09,-2.23[g]
s-C_4H_9OH	NHAc	CH_3	CH_3	52	48	40.41	3.41, 3.29[g]
t-C_4H_9OH	C_2H_5O	C_2H_5	CH_3	96	4	29.72	4.02[f]
t-C_4H_9OH	C_2H_5O	C_2H_5	i-C_3H_7	94	6	32.79	4.00[f]

[a]Phosphorus signals are negative if upfield of 85% H_3PO_4. [b]In $CH_3C(O)CH_3$ or as specified. [c]In the alcohol reaction solvent. [d]In $CHCl_3$. [e]In C_6H_6. [f]Containing traces of the pyrophosphorus compound. [g]A pair of signals due to diastereomers.

pound whereas at higher concentrations phosphorylation is greatly favored indicating involvement of an overall SN_2 mechanism (Table 2).

TABLE 2. Yields of MCPBA oxidation products (%) of $\underline{\underline{1}}$ (R_1=C_2H_5O, R_2=C_2H_5, R_3=i-C_3H_7) in dry acetone in the presence of increasing amounts of ethanol.

$[C_2H_5OH]/[\underline{\underline{1}}]$	$\underline{\underline{3}}$	$\underline{\underline{5}}$	$\underline{\underline{6}}$	Pyrophosphorus compound
0.5	41	11	30	18
1	34	10	38	18
2	19	14	56	11
4	8	12	75	5
10	4	0	94	2
100	0	0	99	traces

We conclude that intermediate $\underline{\underline{2}}$ is extremely reactive, that RS(O)-attached to phosphorus is one of the best known leaving groups, and that its phosphorylation vs rearrangement rates are strongly dependent upon the nature of the nucleophile. The reaction of $\underline{\underline{2}}$ with alcohols is therefore sterically controlled and mainly dependent upon the bulkiness of the alcohol and less upon the phosphorus substituents. Phosphorylation is the exclusive route for reaction of intermediate $\underline{\underline{2}}$ in primary alcohols, as opposed to the rearrangement reaction in a tertiary alcohol, while both routes are expressed in secondary alcohols. These oxidation reactions have synthetic utility in selective removal of the S-alkyl moiety in the presence of other leaving groups attached to phosphorus having even lower pKa values. If an ester is the desired product, it is best to perform the reaction in the presence of the appropriate primary alcohol.

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