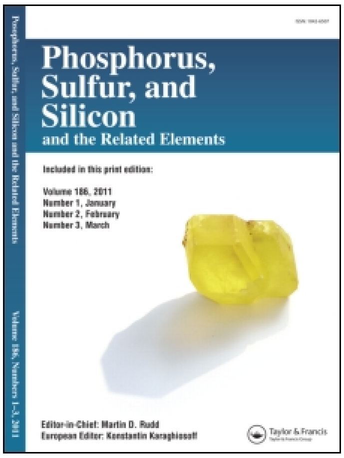

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On the Sulfurization of *H*-Phosphonate Diesters and Phosphite Triesters Using Elemental Sulfur

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On the Sulfurization of *H*-Phosphonate Diesters and Phosphite Triesters Using Elemental Sulfur

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Sulfurization of tetracoordinate and tricoordinate P(III) derivatives, namely, H-phosphonate diesters, H-phosphonothioate diesters, and phosphite triesters with elemental sulfur under various experimental conditions, was investigated.

Keywords Elemental sulfur; phosphite triesters; *H*-phosphonate diesters; *H*-phosphonothioate diesters; sulfurization

INTRODUCTION

Although a variety of sulfurizing reagents, e.g., 3*H*-1,2-benzodithiol-3-one 1,1-dioxide,[1] 3*H*-1,2-benzodithiol-3-one,[2] tetraethylthiuram disulfide,[3] dibenzoyl tetrasulfide,[4] bis(*O*,*O*-diisopropoxyphosphinothioyl) disulfide,[5] 1,2,4-dithiazolidine-3,5-dione,[6] bis (3-(triethoxysilyl)propyl)tetrasulfide,[7] etc., have been proposed for the conversion of P(III) derivatives into the corresponding phosphorothioates or phosphorodithioates, it is elemental sulfur[8] that still remains the reagent of choice for the majority of applications during solution syntheses.

Sulfurization of *H*-phosphonate diesters is mechanistically more complex than that of tervalent phosphorus compounds since it involves

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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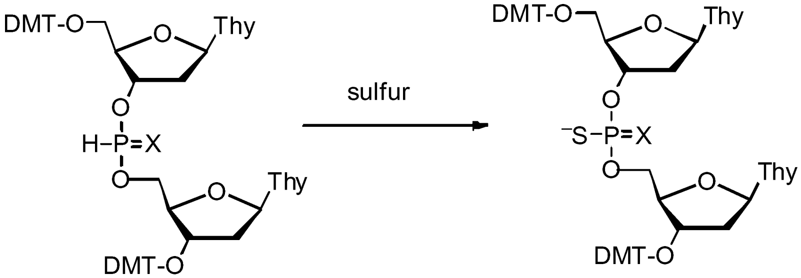
generation of the corresponding phosphite form as the first step of the reaction. For this reason, both polarity of the solvent and the base used for the generation of a phosphite form might influence significantly the rates of sulfurization. In this article, we address these and related problems connected with sulfurization of tetra- and tricoordinate P(III) derivatives.

RESULTS AND DISCUSSION

As model compounds for this study, separate diastereomers of dinucleoside *H*-phosphonate **1a** and dinucleoside *H*-phosphonothioate **1b** were chosen (Scheme 1).



1

2

1a, X=O
1b, X=S

2a, X=O
2b, X=S

Abrreviations: Thy = thymin-1-yl; DMT = 4,4'-dimethoxytrityl

SCHEME 1

The sulfurization was carried out under homogenous reaction conditions as described in the Experimental section. The results for the conversion of *H*-phosphonates **1a** into the corresponding phosphorothioates **2a** are summarized in Tables I and II. (For solubility of sulfur in various organic solvents, see the Experimental section and Table V). The data indicate that the solvent and the base used for the reaction had a profound effect on the rate of sulfurization of *H*-phosphonates **1a**, as was expected for reactions involving the generation of anionic species.

The sulfurization was very fast in highly polar solvents (Table I, entries 1, 2, and 6), and its dependence on the amount of the sulfur

TABLE I Sulfurization of Dinucleoside *H*-Phosphonate 1a with Elemental Sulfur in Different Solvents in the Presence of 2 Equiv. of Triethylamine

Entry	Solvent	Amount of sulfur	Time for completion
1	DMF	2 equiv.	$<$1 min
2	CH_3OH	2 equiv.	$<$1 min
3	Dioxane	2 equiv. 5 equiv. 10 equiv.	40 min 30 min 15 min
4	CH_2Cl_2	2 equiv. 5 equiv. 10 equiv.	60 min 10 min 7 min
5	Toluene	2 equiv. 5 equiv. 10 equiv.	40 min 15 min 6 min
6	Pyridine	2 equiv.	10 min
7	Carbon disulfide	2 equiv.	90 min

used is consistent with a bimolecular rate determining step (Table I, entries 3, 4, anf 5).

The data in Table II indicate also that the efficiency of sulfurization of *H*-phosphonate diesters strongly depends on the basicity of the amine used for the reaction. Weakly basic heteroaromatic amines (entries 2 and 9) or *N*-methylimidazole did not promote sulfurization of *H*-phosphonates **1a** within 2 h (Table II, entries 2, 7, and 9), in contrast to stronger amines (e.g., TEA or DBU) that furnished fast formation of phosphorothioate diesters **2a**.

For sulfurization in the presence of DBU (Table II), remarkable color changes were observed during the course of the reaction in all solvents

TABLE II Sulfurization of Dinucleoside *H*-Phosphonate 1a with 2 Equiv. of Elemental Sulfur and 2 Equiv. of a Base in Different Solvents

Entry	Base	Dioxane	CH_2Cl_2	Toluene
1	TEA	40 min	60 min	40 min
2	Pyridine	nd	nd	nd
3	*n*-Butylamine	20 min	20 h	10 min
4	Diisopropylamine	20 min	2 h	20 min
5	Diisopropylethylamine	50 min	50 min	50 min
6	DBU	$<$ 1 min	$<$ 1 min	$<$ 1 min
7	*N*-Methylimidazole	nd	nd	nd
8	DABCO	30 min	5 h	50 min
9	2,4,6-Collidine	nd	nd	nd
10	Gramine	50 min	3 h	50 min
11	DMAP	60 min	2 h	20 min

Abbreviations: TEA = Triethylamine; DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene; DABCO = 1,4-diazabicyclo[2.2.2]octane; Gramine = 3-(dimethylaminomethyl)indole; DMAP = 4-dimethylaminopyridine.

nd = no sulfurization (or less than 5%) after 2 h.

investigated. The solutions became blue after the addition of DBU to the reaction mixture, then turned green, yellow, and became colorless when the sulfurization was over. Although this may point to a free radical[9] rather than an ionic mechanism for the sulfurization under these reaction conditions, further studies are needed to clarify this issue.

The stereochemical course of the sulfurization[10] under all conditions investigated was checked by ^{31}P NMR spectroscopy using separate diastereomers of **1a**.[11,12] In all cases, the sulfurization was completely stereospecific as evidenced by the transformation of R_P **1a** ("fast", $\delta_P = 6.8$ ppm) into S_P **2a** ($\delta_P = 57.3$ ppm) and S_P **1a** ("slow", $\delta_P = 9.7$ ppm) into R_P **2a** ($\delta_P = 55.8$ ppm) (chemical shifts for the reaction in toluene in the presence of DBU).

Some experiments were also performed on *H*-phosphonothioates **1b** to find out if there were any differences in the rate of sulfurization compared to *H*-phosphonates **1a**. In toluene, using 2 equiv. of sulfur and 2 equiv. of TEA or *n*-butylamine, the reactions were 4 and 3 times faster than those for *H*-phosphonates **1a**, respectively. In neat pyridine, the sulfurization of **1b** was 4 times faster than that of **1a**. These data pointed to higher acidity of the P—H bond in *H*-phosphonothioate versus *H*-phosphonate diesters.

Since it was reported that the rate-limiting step in sulfurization of phosphines was the cleavage of the cyclic structure of S_8,[13–15] we checked if a "preactivation" of sulfur could speed up sulfurization of *H*-phosphonate derivatives. Sulfur in toluene was left standing for 15 min with 2 equiv. of TEA or diisopropylamine, and then **1a** was added. No difference in the rate of sulfurization was noticed compared to the standard sulfurization procedure (however, *vide infra*). Also no effect on the rate of sulfurization was found when the reactions were carried out in the presence of TEA and hydrogen sulfide, or TEA and thiophenol (2 equiv.), as potential nucleophile catalysts for cleavage of the ring structure of sulfur.[13,14]

Finally, the reactivity of S_6 in the sulfurization reaction was evaluated. This form of sulfur was prepared according to the literature procedure,[13,14] but it did not show noticeable differences when it was used instead of commercially available S_8 for the sulfurization of *H*-phosphonates **1a**.

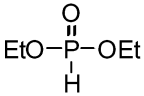
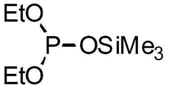
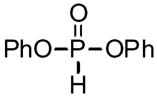
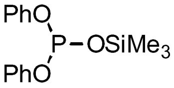
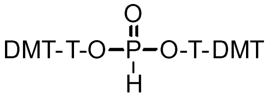
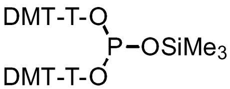
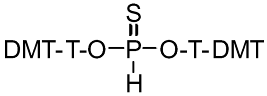
Sulfurization *H*-Phosphonate Diester Derivatives with Presilylation

Since transformation of tetracoordinate *H*-phosphonates into tervalent silyl derivatives is known to facilitate oxidation of these compounds,[16–18] we investigated the effect of silylation on sulfurization of typical *H*-phosphonate diesters (Table III).

The conversion of diethyl *H*-phosphonate diester into its trimethylsilyl ether indeed shortened significantly the time of sulfurization (16 h vs. 2 min); however, for diphenyl and dinucleoside *H*-phosphonates, the silylation had an opposite effect, namely, it slowed down the sulfurization reaction. The most dramatic effect was observed for diphenyl *H*-phosphonate, which, without presilylation, was sulfurized in less than 2 min, while upon conversion into the corresponding trimethylsilyl ether, it took 21 h to bring the sulfurization to completion (Table III).

These somewhat unexpected results can be rationalized in light of reactivity of the generated tervalent species and their concentrations under the reaction conditions.[19] It is reasonable to assume that anionic species generated by abstraction of the proton from *H*-phosphonate diesters should be more reactive toward elemental sulfur than electrically neutral, less basic, tervalent silyl ethers, and their concentration under the reaction condition should be inversely proportional to their basicity. Thus, for diethyl *H*-phosphonate, effective nucleophilicity (product of

TABLE III Comparison of the Sulfurization Times of Various *H*-Phosphonate Derivatives and Their Trimethylsilyl Ethers

Compound	Time	Compound	Time
 $\mathrm{EtO{-}\overset{O}{\underset{H}{P}}{-}OEt}$	16 h		< 2 min
 $\mathrm{PhO{-}\overset{O}{\underset{H}{P}}{-}OPh}$	< 2 min*		21 h
 $\mathrm{DMT\text{-}T\text{-}O{-}\overset{O}{\underset{H}{P}}{-}O\text{-}T\text{-}DMT}$ **1a**	10 min		40 min
 $\mathrm{DMT\text{-}T\text{-}O{-}\overset{S}{\underset{H}{P}}{-}O\text{-}T\text{-}DMT}$ **1b**	< 2 min	with TMS-Cl	< 2 min

Reaction conditions: 4 mM substrate, 2 equiv. sulfur, 2 equiv. Et_3N in pyridine. The silylation was performed in situ using 1.5 equiv. of TMS-Cl, and 1 more equiv. of Et_3N was added. The progress of the reactions was followed by ^{31}P NMR spectroscopy.

*Due to the high susceptibility of $(PhO)_2P(O)H$ to hydrolysis by adventitious water, the reaction mixture was 10 times more concentrated.

reactivity and concentration) of the corresponding phosphonate anion was expected to be low (high reactivity but exceedingly low concentration), and thus the conversion into tervalent species (lower reactivity but high concentration) should speed up sulfurization of this compound. For diphenyl *H*-phosphonate, however, due to its higher acidity compared to the diethyl derivatives, effective nucleophilicity of the diphenyl phosphonate anion was expected to be high (high reactivity and high concentration[20]), and thus the conversion into the less reactive silyl ether should slow down sulfurization of this compound. This was indeed observed. From the fact that dinucleoside *H*-phosphonates **1a**, in contrast to diethyl *H*-phosphonate, underwent sulfurization faster without presilylation (Table III), one can infer that the P—H bond in this compound is more acidic than that in the diethyl derivative.

As expected, the presence of TMS-Cl in the reaction mixture did not affect the rate of sulfurization of *H*-phosphonothioate **1b**, since this compound cannot be converted into the corresponding silyl ethers under the reaction conditions.[21,22]

Sulfurization of Triethyl and Triphenyl Phosphites

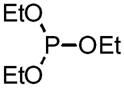
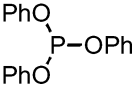
As a final step of these studies, we wanted to clarify the issue of a possible activation of sulfur[13,14] by bases. Since during sulfurization of *H*-phosphonate diesters a base is an indispensable component of the reaction mixture, we investigated the sulfurization of triethyl and triphenyl phosphites, which mechanistically do not require presence of a base.[23]

We found that sulfurization of triethyl phosphite with elemental sulfur in toluene was very sluggish (Table IV), but it was significantly accelerated by the addition of triethylamine. The use of trimethylsilyl chloride in combination with triethylamine had a minor decelerating effect on the rate of sulfurization, probably due to partial hydrolysis of the silylating agent and consumption of the base for neutralization of the acidic products formed.

Triphenyl phosphite turned out to be very resistant to sulfurization in toluene, and did not produce any detectable amounts of triphenyl phosphorothioate neither with nor without triethylamine (Table IV). This is probably due to inductive effect of the phenoxy groups, but also in part, it reflects lower nucleophilicity of tervalent species compared to phosphonate anions.

In pyridine, triethyl phosphite underwent sulfurization rapidly, without a noticeable effect of the triethylamine added. In contrast to these, sulfurization of triphenyl phosphite in pyridine required the presence of triethylamine (Table IV), and even so it was rather slow.[23]

TABLE IV Sulfurization of Triethyl and Triphenyl Phosphite Under Different Experimental Conditions

				
Reactants	Toluene	Pyridine	Toluene	Pyridine
2 equiv. S	nd	<2 min	nd	nd
2 equiv. S + 10 equiv. Et$_3$N	3 h	<2 min	nd	3 h
2 equiv. S + 10 equiv. Et$_3$N + 1.5 equiv. TMS-Cl	5 h	<2 min	nd	5 h

Reaction conditions: 4 mM solution of triethyl or triphenyl phosphite in an appropriate solvent and the reactants as specified in the table. Due to the possible presence of acidic contaminations in the reaction mixtures, an excess of triethylamine (10 equiv.) was used to ensure that enough base was available for a putative activation of sulfur. Progress of the reactions was followed by ^{31}P NMR spectroscopy.

nd = no sulfurization (or less than 5 %) after 3 h.

These preliminary results suggest that triethylamine and pyridine (and most likely other amines and nucleophiles) apparently activate sulfur by breaking its eight-member rings as it was postulated previously.[13,14] By comparing the reactivity of triethyl and triphenyl phosphites towards sulfur in pyridine in the presence and in the absence of triethylamine, it seems that tertiary aliphatic amines are more potent activators of sulfur (formation of more reactive polysulfide species) than pyridine. As expected, such activation appeared to be more important for sulfurization of the less reactive triphenyl phosphite than that of triethyl phosphite.

In conclusion, sulfurization of tetravalent and tervalent P(III) derivatives with elemental sulfur strongly depends on the polarity of the solvent and on the base used. In the case of *H*-phosphonates, polar solvents (Table V) stabilize the generated phosphonate anions and polar species formed from the opening of the eight-membered ring structure of sulfur. Bases that are used for sulfurization of *H*-phosphonate diesters seem to play a double role: generation of phosphonate anions and activation of the elemental sulfur. As to the presilylation step, it may increase or decrease rates of sulfurization, depending on acidity of the P-H bond of *H*-phosphonate diesters. For tervalent P(III) compounds, sulfurization occurs faster in polar solvents (stabilization of polar transition states) and in the presence of amines, which apparently activate sulfur. The importance of the latter phenomenon in the sulfurization of *H*-phosphonate diesters remains to be established.

TABLE V Approximate Solubility of Elemental Sulfur (S_8) in Different Solvents

Entry	Solvent	Solubility (mg/mL)
1	Carbon disulfide	300
2	Toluene	18
3	Pyridine	15
4	THF	11
5	Dioxane	4
6	DMF	1.5
7	Methanol	0.2
8	Acetonitrile	0.1

EXPERIMENTAL

Dinucleoside *H*-phosphonates **1a**[24] and *H*-phosphonothioates **1b**[12] were prepared as described previously. The sulfurization experiments were carried out in the following way: Stock solutions of sulfur and the base were prepared in the same solvent as that for the intended reaction. The solutions were combined in an appropriate ratio, a P(III) substrate was added, and the volume adjusted to 3 mL (the concentration of the P(III) compound, 4.0 mM). The reactions were followed either chromatographically by TLC (for **1a** and **1b**, silica gel plates, $CHCl_3 : CH_3OH$, 9:1, v/v) or by ^{31}P NMR, to ca. 95% completion.

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[19] Since all the reactions were carried out in the presence of triethylamine, a possible activation of sulfur by this base (See refs. [13–15]) cannot be responsible for the differences observed.

[20] Albeit the concentration of diphenyl phosphonate anion was still below the detection level of ^{31}P NMR spectroscopy.

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