solute or ligand. In case of ester derivatives the energy difference between closed and open conformation is less and is probably of the same order of magnitude as the amount of stabilization caused by interactions with solutes, such as methanol or weak acids, or with strong electrophiles, such as osmium tetraoxide. In case of the methoxy derivatives the energy difference between closed conformation 2 and open conformation 3 has vanished. In noncoordinating solvents like CD_2Cl_2, the methoxy derivatives are still predominantly found in the closed conformation 2, but in the presence of any electrophile the equilibrium shift in favor of the open conformation 3. Quinine and quinidine (and other hydroxy derivatives) by themselves already possess a distinct preference for the open conformation 3 and thus do not depend on extra stabilization caused by interactions with solute.

Experimental Section

The NOESY and COSY spectra were measured as 0.05–0.1 M solutions in a 5-mm NMR tube. In the case of the NOESY spectra the oxygen was removed by freeze–pump–thaw cycles and the NMR tubes were sealed under reduced pressure. All spectra (^1H NMR, COSY, NOE-difference, and NOESY) were recorded using a Varian VXR-300 and VXR-500 spectrometer at 20 °C. For each NOESY spectrum between 512 and 1024 FID's of between 1024 and 2048 data points each were collected. The spectral width was chosen as narrow as possible (about 3000 Hz). Corrections with weighting functions (mostly shifted sine bells[15]) were used before Fourier transformations in the t_2 and t_1 dimensions. All NOESY spectra were recorded in phase sensitive mode.[16] Energy calculations were performed on a Convex c210 computer with VAMP version 4.10, a vectorized molecular orbital package based on AMPAC 1.0 and MOPAC 4.10. All optimizations were performed either over all internal coordinates or the Cartesian coordinate system was used, until the root-mean-square of the gradient of the energy was less than 0.1 kcal/Å. All alkaloid derivatives were synthesized by literature procedures.

Acknowledgment. We express thanks for the use of the services of the Dutch CAOS-CAMM center under Grants SON-11-20-700 and STW-NCH-440703. Modeling and computer facilities were provided by Royal Dutch Shell.

Registry No. A, 491-35-0; B, 6281-32-9; C, 64218-83-3; D, 35982-82-2; E, 5632-17-7; dihydroquinine, 522-66-7; dihydroquinidine, 1435-55-8; dihydrocinchonine, 485-65-4; dihydrocinchonidine, 485-64-3; dihydromethoxyquinidine, 122898-88-8; benzoylquinine, 69758-70-9; dihydro-*p*-chlorobenzoylquinine, 113216-88-9; dihydro-*p*-chlorobenzoylquinidine, 113162-02-0; dihydroacetylquinidine, 72989-10-7; dihydrochloroquinine, 50412-62-9; dihydrochloroquinidine, 50412-64-1; deoxycinchonidine, 5808-37-7; epidihydroquinine, 51743-68-1; epidihydroquinidine, 14645-32-0; chloroquinine, 14528-48-4.

(15) Levitt, M. H.; Radloff, C.; Ernst, R. R. *Chem. Phys. Lett.* **1985**, *114*, 435.
(16) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286.

Reversible Oxidation of Phosphylthionates and Phosphylselenonates with Trifluoroacetic Anhydride[1a]

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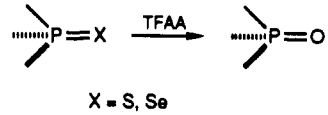
Trifluoroacetic anhydride oxidizes a variety of phosphylthionates and -selenonates into corresponding oxo products at room temperature. In the case of phosphine sulfide **1**, the reaction proceeds with complete racemization, while phosphine selenide **2** is oxidized with a net inversion and a high degree of racemization. The extent of epimerization during the oxidation of diastereomeric phosphoroselenonates is much lower. The variable-temperature ^{31}P NMR spectra show the existence of two intermediates: a phosphonium salt **12** and the pentacoordinated compound **13**, both originating from the acylation of the product at phosphoryl oxygen. Two analogous intermediates containing sulfur or selenium, occurring earlier on the reaction pathway, are also postulated. The entire process is fully reversible as evidenced by the conversion of ethylmethylphenylphosphine oxide into the corresponding sulfide during the desulfurization of methyl-*n*-propylphenylphosphine sulfide. The equilibrium is gradually shifted into the oxidized product by the decomposition processes of trifluorothio- or trifluoroselenoacetic anhydride.

The oxidation of phosphylthioates and phosphylselenoates into their corresponding oxo compounds has been the subject of considerable interest in this and other laboratories. The oxidation reagents applied included potassium permanganate,[2] nitric acid,[3] dinitrogen tetroxide,[4] hydrogen peroxide,[5,6] organic peracids,[7] ozone,[8] dimethyl sulfoxide,[9] and selenoxide.[10] More recently, the

Scheme I



X = S, Se

stereospecific PS → PO conversion of phosphorothioyl analogues of nucleotides by using oxidative bromination[11,12] and [^{18}O]oxygen labeled epoxides[13] have been described. In the course of our earlier studies on the mechanism of the thiono–thiolo rearrangement of phosphylthionates in trifluoroacetic acid medium,[14,15] we have occassionally

(1) (a) Dedicated to Prof. Jan Michalski on his 70th birthday. (b) Current address: Chemistry Department, The Ohio State University, 140 W. 18th Ave., Columbus, OH 43210.
(2) Horner, L. *Pure Appl. Chem.* **1964**, *9*, 225.
(3) Stec, W. J.; Okruszek, A.; Michalski, J. *Angew. Chem.* **1971**, *83*, 491.
(4) Stec, W. J.; Okruszek, A.; Mikolajczyk, M. *Z. Naturforsch. B* **1971**, *26*, 856.
(5) Stec, W. J.; Okruszek, A.; Michalski, J. *J. Org. Chem.* **1976**, *41*, 233.
(6) De'ath, N. J.; Ellis, K.; Smith, D. J. H.; Trippett, S. *J. Chem. Soc., Chem. Commun.* **1971**, 714.
(7) Herriott, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 3304.
(8) Skowronska, A.; Krawczyk. E. *Synthesis* **1983**, 509.
(9) Mikolajczyk, M.; Luczak, J. *Chem. Ind. (London)* **1974**, 701.
(10) Mikolajczyk, M.; Luczak, J. *J. Org. Chem.* **1978**, *43*, 2132.
(11) Conolly, B. A.; Eckstein, F.; Cullis, P. M. *J. Biol. Chem.* **1982**, *257*, 3382.
(12) Sammons, R. D.; Frey, P. A. *J. Biol. Chem.* **1982**, *257*, 1138.
(13) Guga, P.; Okruszek, A. *Tetrahedron Lett.* **1984**, *26*, 2897.

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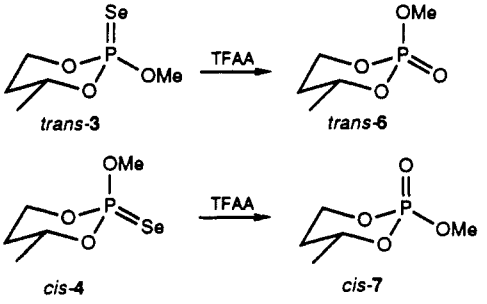
Table I. Yields and Conditions of Desulfurization of Phosphylthionates and Deselenization of Selenoates with TFAA

substrate	conditions[a]	yield, %	$\delta_{^{31}P}$ substrate/product	ref
$Ph_3P{=}S$	benzene, 1.5:1, 1 M, 24 h	80[b]		
$Ph_2P(S)OMe$	CH_2Cl_2, 1:1.1 M, 24 h	85[b]	83.15/36.50	24
$Ph_2P(S)OH$[c]	CH_2Cl_2, 3:1, 1 M, 24 h	75[d]	85.6/32.9	25
$MePrPhP{=}S$	CH_2Cl_2, 1.1:1, 1 M, 48 h	57[b]	36.4/32.5	5, 24
$OCH_2CMe_2CH_2OP(S)OMe$	CH_2Cl_2, 3:1, 0.2 M, 19 h	20[d]	63.3/−7.4	24
	17 days	85[d]		
$MePrPhP{=}Se$	CH_2Cl_2, 1.1:1, 1 M, 48 h	70[b]	25.3/32.5	5
$(MeO)_3P{=}Se$	toluene, 2:1, 0.1 M, 14 days	95	79.0/1.0	26, 27
$Ph_2P(Se)OMe$	CH_2Cl_2, 3:1, 6 days	86[b]	87.5/31.5	24, 26
3	CH_2Cl_2, 1.1:1, 1 M, 48 h	63[b]	70.6/−7.0	5
4	CH_2Cl_2, 1.1:1, 1 M, 48 h	85[b]	66.5/−5.4	5
Ph_3P	CH_2Cl_2–MeCN (1:1), 2:1, 0.2 M	no reaction		

[a] Solvent, molar ratio TFAA/PS substrate, substrate concentration, reaction time, all reactions were performed at room temperature. [b] Yield of the isolated product. [c] Tetraphenylpyrophosphinate was obtained as the product of desulfurization/dehydration. [d] Yield as judged by ^{31}P NMR.

Scheme II



detected trace amounts of desulfurization products. We have found that the loss of sulfur was effected by trifluoroacetic anhydride impurity present in some batches of trifluoroacetic acid. This observation prompted us to investigate the process of the desulfurization of phosphylthionates in more detail. Here, we describe our results on the application of trifluoroacetic anhydride for the PS → PO and PSe → PO conversion of simple organophosphorus compounds.

Results

In a representative experiment triphenylphosphine sulfide was treated in refluxing benzene with 50% molar excess of trifluoroacetic anhydride (TFAA). The reaction was complete within 1 h. The product triphenylphosphine oxide was isolated after crystallization in 80% yield. For most phosphorothionates the reaction can be performed at ambient temperature. The yields and reaction conditions for several substrates are summarized in Table I.

Stereochemistry. Four typical model compounds were used to determine the stereochemistry of the oxidation process: (+)-(*R*)-methyl-*n*-propylphenylphosphine sulfide (**1**), (+)-(*R*)-methyl-*n*-propylphenylphosphine selenide (**2**), *trans*- and *cis*-2-methoxy-4-methyl-2-selenono-1,3,2-dioxaphosphorinane (**3** and **4**, respectively).

Starting from the sulfide (*R*)-**1**, $[\alpha]^{20}_D$ +19.3° (*c* 8.2, methanol, 96.5 ee[16]), and using 10% molar excess of TFAA, methyl-*n*-propylphenylphosphine oxide (**5**), $[\alpha]^{20}_D$ 0.0° (*c* 2.5, methanol) was obtained (57%). The oxidation of the selenide (*R*)-**2**, $[\alpha]^{20}_D$ +9.25° (*c* 8.0, methanol, 45.7% ee[3]) afforded the corresponding oxide (*S*)-**5** with $[\alpha]^{20}_D$ −1.8° (*c* 3.4, methanol, 9% ee[16]) in 70% yield. Small quantities of the substantially racemized selenide were recovered ($[\alpha]^{20}_D$ +0.4°, *c* 1.4, methanol). The stereochemistry of the oxidation of selenoates **3** and **4** (Scheme II) was investigated by means of ^{31}P NMR, based on the known differences of ^{31}P chemical shifts of the diastereomeric products *trans*-**6** and *cis*-**7**.[5,17] *trans*-**3** (100% de) yielded 84% of *trans*-2-methoxy-4-methyl-2-oxo-1,3,2-dioxaphosphorinane (**6**, 86% de, inversion, Scheme II) and *cis*-**4** (69% de) afforded *cis*-**7** (52% de, inversion).[18] Unreacted **4** had undergone substantial epimerization during the oxidation reaction to 34% de, while no epimerization of **3** in the course of the reaction could be detected. In a control experiment a slow epimerization of **7** under the reaction conditions was proven by ^{31}P NMR.

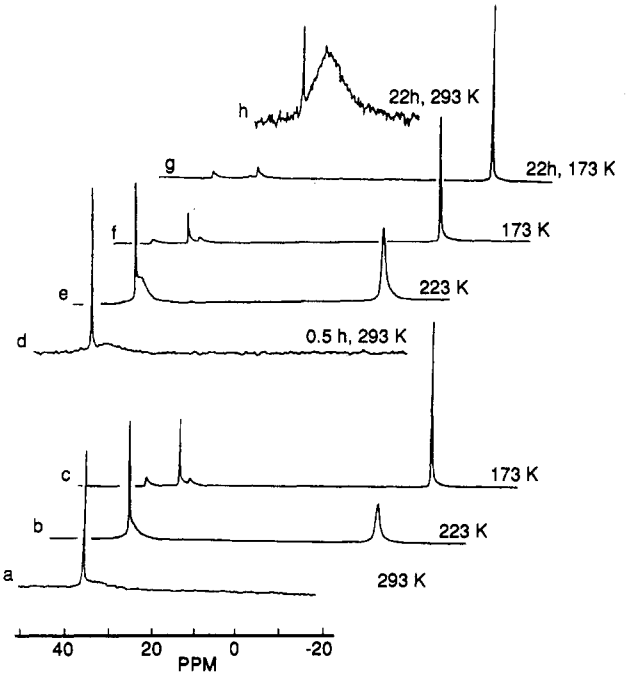


Figure 1. 24.3-MHz ^{31}P NMR spectra of **1** (0.2 M)/TFAA (0.4 M) in toluene-d_8 at indicated temperatures. (a) Sample prepared at low temperature was warmed up to 293 K; (b, c) spectra obtained directly after recording a and b, respectively; (d) sample was warmed up to 293 K within 10 min after recording c and was kept at this temperature for 0.5 h; (e, f) spectra recorded directly after d; (g) spectrum obtained shortly after h; (h) sample was stored at 293 K for 22 h. Each spectrum consists of ca. 1000 transients accumulated within 10 min.

Low-Temperature ^{31}P NMR Studies. ^{31}P NMR spectra of **1** (0.2 M) in TFAA-containing (0.4 M) toluene-d_8

(14) Bruzik, K.; Stec, W. J. *J. Org. Chem.* **1981**, *46*, 1618.
(15) Bruzik, K.; Stec, W. J. *J. Org. Chem.* **1979**, *44*, 4488.
(16) Casey, J. P.; Lewis, R. A.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 2789.
(17) Stec, W. J.; Mikolajczyk, M. *Tetrahedron* **1973**, *29*, 538.
(18) The PSe → PO conversion of **3** and **4** causes the reversal of the relative priority of substituents at phosphorus. Therefore, the reaction proceeding with inversion converts *trans*-**3** into *trans*-**6**.

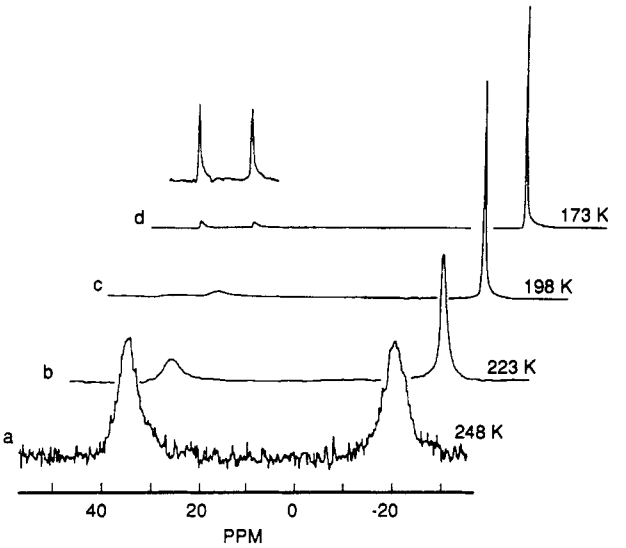


Figure 2. 24.3-MHz ^{31}P NMR spectra of **5** (0.2 M)/TFAA (0.4 M) in toluene-d_8 at temperatures shown.

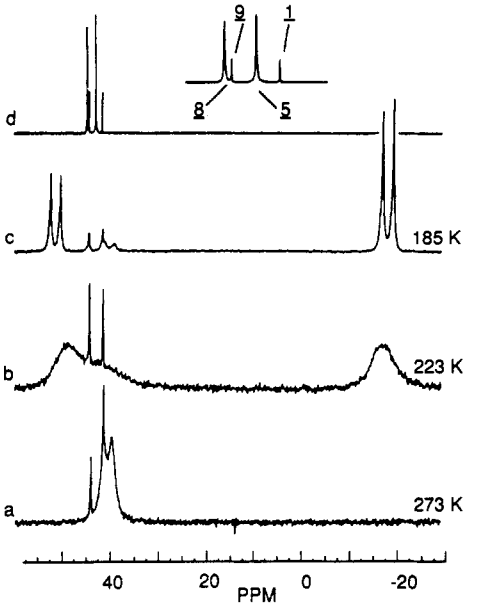


Figure 3. 121.47-MHz ^{31}P NMR spectra of the reaction mixture consisting of **1** (0.08 M), **8** (0.08 M), and TFAA (0.5 M) in methylene chloride at indicated temperatures. The spectrum d was obtained after the reaction was quenched by adding pyridine/water. The differences in the chemical shifts in Figures 1 and 2 as compared to Figure 3 are caused by the aromatic solvent induced shift. Each spectrum consists of 100 scans accumulated within 3 min. About 10 min was allowed to achieve the sample equilibration at the desired temperature. Signals were positively identified as marked in trace d by consecutively adding genuine samples of **1**, **9**, **5**, and **8** to the products of the reaction and recording ^{31}P NMR spectra.

are shown in Figure 1. The experiment was performed on a sample prepared at a low temperature, and NMR measurements were started immediately upon warming the sample to room temperature. The ^{31}P NMR spectrum at 293 K displayed a sharp resonance signal at 36.4 ppm due to the substrate **1** and an unidentified broad peak centered at ca. 33 ppm. Lowering the temperature to 223 K brought about the appearance of the broad line at −21.5 ppm, while the broad signal at 33 ppm remained in the spectrum at lower intensity. The latter peak was split in 173 K spectrum into two lines at 46.1 and 35.1 ppm. At the same time the intensity of the high field signal (at −21.5 ppm) was enhanced. The sample was then warmed up to room temperature, and the recorded spectrum showed only a slight increase in the intensity of the broad line at 33 ppm (as compared to the starting spectrum 1a). The spectra of this sample recorded at 223 and 173 K showed only a small change with respect to spectra 1b and 1c, except for the decreased intensity of the signal from sulfide **1**. Finally, the spectrum acquired after 22 h at room temperature showed an intense broad signal centered about 31 ppm and small quantities of the substrate at 36.4 ppm.

A similar experiment was performed using selenide **2** and TFAA (1:1 mol/mol). In this case the spectrum recorded at 173 K (not shown) consisted also of four distinct signals. The chemical shifts were 46.2 (low intensity), 35.0 (phosphine oxide, **5**), 26.0 (phosphine selenide, **2**), and −21.9 ppm. Only the signal at 26.0 ppm displayed satellite side bands with the splitting of 715 Hz due to ^{31}P–^{77}Se coupling. Therefore, the species giving rise to other signals did not contain selenium bound to phosphorus.

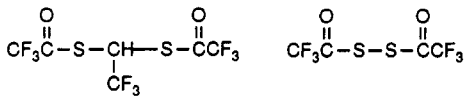
Analogous ^{31}P NMR measurements have been carried out using phosphine oxide **5** in order to determine further the structure of the intermediates giving rise to signals at 46, 35, and −21.5 ppm. The spectra obtained are shown in Figure 2. Clearly, the chemical shifts of signals apparent in the 173 K spectrum coincide with those from Figure 1 (traces c and f). It is therefore reasonable to assume that intermediates giving rise to signals at 46 and −21.5 ppm observed in Figure 1 are identical with those in Figure 2, i.e. they contain no sulfur or selenium.

So far described experiments suggest that the intermediate at −21.5 ppm is capable of undergoing a reverse conversion to phosphine sulfide (or selenide, consult traces 1c and 1d). To examine this hypothesis the following experiment was set up: Phosphine sulfide **1** (0.08 M) and ethylmethylphenylphosphine oxide (**8**, 0.08 M) in methylene chloride were treated with TFAA (0.5 M) at room temperature. The sample was quickly cooled down to 198 K and stored for 1 h. The ^{31}P NMR spectra of this mixture at various temperatures are shown in Figure 3. In all spectra two narrow lines at 42.4 and 39.65 ppm were visible in addition to other broad signals. The 185 K spectrum shows double set of signals analogous to those in Figure 1c as a result of the equilibration between two sets of species[19] related to oxides **5** and **8**. The ^{31}P NMR analysis of the reaction mixture after hydrolyzing TFAA (Figure 3d, see also the figure caption) proved that the two sharp lines in Figure 3(a,b), arose from methylpropylphenylphosphine sulfide (**1**, 39.65 ppm) and ethylmethylphenylphosphine sulfide (**9**, 42.4 ppm).

Product Analysis. The structures of phosphorus-containing products derived from each substrate were proven by ^{31}P and ^{1}H NMR and MS analyses. The GC analysis of the phosphorous products shown in Figure 3d showed four chromatographic peaks, due to the presence of **1**, **5**, **8**, and **9**. The identity of **9** was verified by its mass spectrum, in which the molecular ion at m/z 184 (55%) and the proper fragmentation pattern were observed (see the Experimental Section). Thus, the occurrence of the reverse conversion of phosphine oxide into the corresponding sulfide under the condition of our reaction was evidenced.

(19) In order to obtain time-averaged signal at 24.3 MHz, the exchange rate should exceed 10^3 s^{-1} and 5×1^{-3} s^{-1} for **5** ⇌ **12** and **12** ⇌ **13** exchange, respectively. Signals originating from **12** and **13** can be resolved at a higher temperature than those from **5** and **12**, due to a smaller chemical shift difference in the latter case (Figure 1e and 1f). Note however, that the chemical shift of time-averaged signal from **5** and **12** in Figure 1e is not a mean of the chemical shifts of resolved signals in Figure 1f. This results from a temperature dependence of K_1.

The determination of the structure of non-phosphorous products containing sulfur or selenium proved more difficult. The volatile fraction of the sample obtained from the desulfurization of *O*-methyl diphenylphosphinothionate was analyzed by GC–MS and by ^1H, ^{13}C, and ^{19}F NMR. Two major products, **10** and **11**, giving rise to separate chromatographic peaks were initially identified. The m/z ratios of their molecular ions indicated that these substances were products of a decomposition of trifluorothioacetic anhydride. The mass spectrum of **10** showed fragmentation with ions at m/z 340 (MI), 320 (MI – HF), 243 (MI – CF_3CO), 211 (MI – CF_3COS), 113 (CF_3CS^+), 97 (CF_3CO^+), and 69 (CF_3^+). ^1H NMR spectrum of the mixture comprised only one quartet at 5.98 ppm (8.1 Hz). The proton-coupled ^{19}F NMR spectrum consisted of a doublet at –67.4 ppm (8.0 Hz) in addition to other signals of fluorine atoms not coupled to protons. Our data are consistent with the structure of 1,1-bis(trifluorothioacetyl)-2,2,2-trifluoroethane (**10**). The origin of the proton in this molecule, and the mechanism by which **10** is formed is not clear at present. The MS spectrum of another peak in the GC indicated that it arose from bis(trifluorothioacetyl) disulfide (**11**; m/z 260 (MI + 2, 0.6), 258 (8, MI), 230 (4, –CO), 202 (–CO, –CO, 1), 189 (4, $-CF_3$), 161 (3, $-CF_3CO$), 113, 114 (1, 4, CF_3CS^+), 97 (32, CF_3CO^+), 69 (CF_3^+, BP)). More detailed structural studies were hampered by the high instability of these products. The above analyzed sample after several days at room temperature displayed a complex ^{13}C NMR spectrum and gas chromatogram. The high reactivity of these products made their isolation impossible.



10 **11**

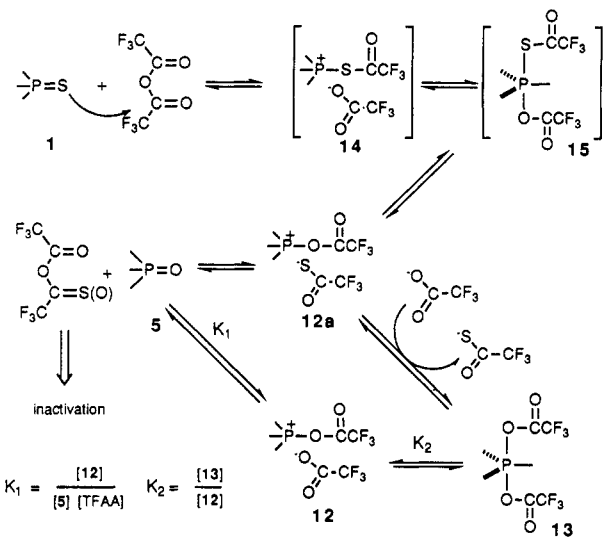
The structure of selenium-containing non-phosphorous products was not investigated due to the deposition of elemental selenium during the reaction.

Discussion

The analysis of spectra shown in Figures 1–3 is of key importance for the understanding of the mechanism of the studied reaction. After recording the spectrum 1c showing the low content of sulfide **1**, and warming up the sample to room temperature, the starting sulfide is regenerated and its concentration (as judged by the integrated signal intensity) reaches almost the starting one (Figure 1d). Hence, the compound giving rise to signal at –21.5 ppm and not containing sulfur is converted back to sulfide **1**. The evidence for the reverse process is further strengthened by the spectra presented in Figure 3 and GC–MS analysis. The comparison of Figures 1 and 2 suggests structures **12** and **13** as the intermediates which give rise to the observed low-temperature signals. Based on the above described evidence we propose the desulfurization mechanism as presented in Scheme III.

The sulfide **1** is first acylated at sulfur into phosphonium-type salt **14** which collapses into the pentacovalent intermediate **15**. The departure of the leaving trifluorothioacetate group produces a new phosphonium intermediate **12a**, and the reaction of **12a** with the trifluoroacetate leads to the second pentacoordinated compound **13**. The cleavage of **12** and **12a** by trifluoroacetate or trifluorothioacetate attack on the carbonyl carbon in **12** or **12a** brings about the formation of the oxidized product and regenerates TFAA or produces trifluorothioacetic anhydride. Both **12a** (and **12** formed by the counterion exchange) and **13** are detectable in the low-temperature spectrum of the reaction mixture (Figure 1), and of **5** + TFAA mixture (Figure 2). At room temperature the acyl group exchange processes are fast enough to produce a time-averaged broad NMR signal arising from **5**, **12**, and **13** (e.g. Figure 1, parts a, d, h). Consequently, the rates of exchange processes **5** ⇔ **12**, **12** ⇔ **13** at room temperature exceed 10^3 Hz.[19] The integrated intensities of signals in Figure 2d allow to determine equilibrium constants K_1 and K_2 (Scheme III) at 173 K as 5.0 L/mol and 13.3, respectively. Phosphine sulfide participate in the equilibrium at such rate that the complete equilibrium is achieved within several minutes at room temperature. The rate of the reverse reactions leading from **13** to **1** are also fast (as suggested by the equal intensity of the lines arising from sulfides **1** and **9** in Figure 3d). The overall rate of the desulfurization process is controlled by the rate of the decomposition of trifluorothioacetic anhydride (or trifluorothioacetate) by its conversion into species such as **10** and **11**. To the best of our knowledge the synthesis of trifluorothioacetic anhydride (which should be an in situ formed reaction product) has not been accomplished to date. We postulate that the analogous mechanism operates in the case of the deselenization reaction.

Scheme III



Sulfur-containing carboxylic anhydrides have been shown to be unstable and undergo condensation or polymerization reactions. The formation of the adamantane-like structures, 1,3-dithietane- and 2,4,6,8,9-pentathiabicyclo[5.1.1]nonane derivatives from trithioacetic anhydride upon storage has been reported.[20] Disproportionation,[21,22] thiono–thiolo isomerization,[22] dimerization,[20,23] and condensation[20] reactions are characteristic of these compounds. Such reactions may be particularly rapid in the case of more reactive trifluorothioacetic anhydride.

(20) Mikolajczyk, M.; Kielbasinski, P.; Barlow, J. H.; Russell, D. R. *J. Org. Chem.* **1977**, *42*, 2345.
(21) Martin, A. A.; Barnikov, G. *Z. Chem.* **1987**, *27*, 90.
(22) Mikolajczyk, M.; Kielbasinski, P.; Shiebel, H. M. *J. Chem. Soc. Perkin Trans. 1* **1976**, 564.
(23) Middleton, W. J.; Howard, E. G.; Sharkey, W. H. *J. Org. Chem.* **1965**, *30*, 5375.
(24) Bruzik, K. S.; Stec, W. J. *Phosphorus Sulfur* **1988**, *35*, 229.
(25) Crutchfield, M. M.; Dungan, C. H.; Letcher, L. H.; Mark, V.; Van Wazer, J. R. *Top. Phosph. Chem.* **1967**, *5*, 1.
(26) Stec, W. J.; Okruszek, A.; Uznanski, B.; Michalski, J. *Phosphorus* **1972**, 97.
(27) Glidewell, E.; Leslie, E. *J. Chem. Soc., Dalton Trans.* **1977**, 527.

The occurrence of the reverse PO → PS reaction is of interest in view of its potential utility for the conversion of phosphoryl compounds into corresponding phosphorothioyl analogues. Although such a synthetic aspect was not evaluated in the current study, the optimization of the reaction conditions and carboxylic thioanhydride or thiocarboxylate/anhydride sytem might produce a new mild reagent for the PO → PS transformation.

The stereochemical results of oxidation of 1 and 2 are explained by the racemization of the sulfide, selenide, or oxide due to the multiple occurrence of the reversible processes shown in Scheme III (each occurring with inversion at phosphorus) before the inactivation of the trifluorothioacetate can take place. The relatively higher degree of inversion observed in oxidations of triesters 3 and 4 can be explained by a much lower nucleophilicity of selenium atom in these cases as compared to phosphine selenide 2 (due to electronic effect of oxygen substituents at phosphorus), slowing down the rates of formation of 12 and 13 and lowering the probability of a return to phosphoroselenonates. In fact, the low-temperature ^{31}P NMR spectra of *O,O,O*-trimethyl phosphoroselenoate/TFAA did not indicate the formation of such intermediates at concentrations above the detection limit.

Experimental Section

All substrates were obtained according to known procedures and were characterized by their ^{31}P NMR spectra (Table I) and other physical data prior to use. ^{31}P Chemical shifts were referenced indirectly to 85% phosphoric acid. Organic solvents were reagent grade and were dried before use by routine methods and were stored in Teflon stopcock sealed ampoules over appropriate dessicants. Trifluoroacetic anhydride was from Merck and was stored in sealed ampoules over P_2O_5. NMR samples and reaction mixtures were prepared using vacuum-line technique to avoid TFAA hydrolysis upon contact with moisture and to protect samples against TFA-catalyzed thiono-thiolo rearrangement in cases when phosphylthioic and -selenoic esters were used a substrates.

General Procedure. Phosphylthionate or -selenonate (10 mmol) was dissolved in methylene chloride (10 mL) and TFAA (15 mmol) was added. The progress of the reaction was monitored by TLC. After the reaction was complete, the solution was treated with methanol (1 mL) and neutralized by washing with aqueous sodium bicarbonate. Methanol (10 mL) was added, and the precipitate of sulfur or selenium was removed by filtration. The solution was concentrated, and the residue was chromatographed on a silica gel column. Esters 6 and 7 were distilled under vacuum.

8: *m/z* 168 (MI, 5), 139 (BP), 125 (18), 91 (7), 77 (21), 47 (15).

9: *m/z* 184 (MI, 55), 156 (BP), 141 (30), 123 (15), 107 (8), 78 (21), 77 (14), 63 (27).

5: *m/z* 182 (MI, 23), 154 (BP), 139 (95), 125 (55), 109 (6), 91 (65), 77 (35), 51 (18).

1: *m/z* 198 (MI 31), 156 (BP), 141 (25), 123 (12), 109 (7), 107 (4), 91 (10), 78 (20), 63 (18).

Registry No. 1, 13153-92-9; 2, 33995-97-0; 3, 33996-01-9; 4, 33996-02-0; 5, 2328-23-6; (*S*)-5, 1515-99-7; 6, 33996-03-1; 7, 33996-04-2; 8, 7309-49-1; 9, 13639-73-1; 10, 129848-65-3; 11, 21690-87-9; 12, 129848-67-5; 13, 129834-42-0; TFAA, 407-25-0.

Structures of Three New Cyclic Heptapeptide Hepatotoxins Produced by the Cyanobacterium (Blue-Green Alga) *Nostoc* sp. Strain 152[1]

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Three new hepatotoxic cyclic heptapeptides in the microcystin class were isolated from the cyanobacterium (blue-green alga) *Nostoc* sp. strain 152 and assigned structures based on their high-resolution FABMS, FABMS/MS, ^1H and ^{13}C NMR spectra, amino acid analysis, and GC on a chiral capillary column. All three toxins (1-3) have 9-acetoxy-3-amino-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid as an unusual structural component (Scheme I) instead of the corresponding 9-methoxyl derivative (Adda) found in the microcystins.

Some genera of fresh and brackish cyanobacteria (blue-green algae) produce potent hepatotoxic cyclic peptides.[2,3] Microcystins,[4] cyclic heptapeptides illustrated by microcystin-LR (4),[3] are the most common of these cyanobacterial hepatotoxins, and nine chemically defined microcystins have been reported (4 and 6-13, Scheme II).[5] Nodularin, whose structure we recently reported,[3] is thus far the only cyclic pentapeptide in this class of hepatotoxins. These compounds all have a unique C_{20} amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), a remarkable structural feature.[6] Adda seems to be important for their

(1) Previous report: Sivonen, K.; Carmichael, W. W.; Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Niemelä, S. I. *Appl. Environ. Microbiol.*, in press.

(2) Carmichael, W. W. In *Handbook of Natural Toxins*; Tu, A. T., Ed.; Marcel Dekker: New York, 1988; Vol. 3, pp 121-147.

(3) Rinehart, K. L.; Harada, K.-I.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557-8558.

(4) Carmichael, W. W.; Beasley, V. R.; Bunner, D. L.; Eloff, J. N.; Falconer, I.; Gorham, P. R.; Harada, K.-I.; Yu, M.-J.; Krishnamurthy, T.; Moore, R. E.; Rinehart, K. L.; Runnegar, M.; Skulberg, O. M.; Watanabe, M. *Toxicon* **1988**, *26*, 971-973.

(5) Carmichael, W. W. In *Natural Toxins: Characterization, Pharmacology and Therapeutics*; Ownby, C. L., Odell, G. V., Eds.; Pergamon: London, 1988; pp 3-16.

(6) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349-4352.

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