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Sulfurization of H-Phosphonate Diesters by Elemental Sulfur under Aqueous Conditions

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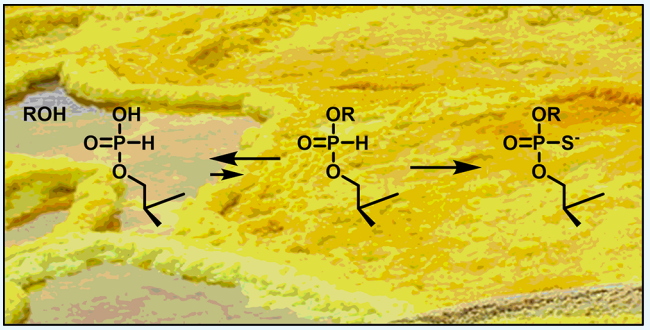
Supporting Information

ABSTRACT: To assess the plausibility of prebiotic nucleic acid polymerization by a sequential phosphitylation−sulfurization mechanism, the rates of hydrolysis and sulfurization of bis(2′,3′-*O*-methyleneadenosin-5′-yl)-H-phosphonate, a dinucleoside H-phosphonate diester, have been determined over a wide pH range (0.52−7.25) and in the presence of varying amounts (0−30 mg) of elemental sulfur. The pH-rate profile of hydrolysis resembled the one previously reported for the H-phosphonate analogue of thymidylyl-3′,5′-thymidine, with a relatively wide pH-independent region flanked by acid- and base-catalyzed regions. Sulfurization to the respective phosphorothioate diester, in turn, was found to be base-catalyzed over the entire pH range studied. Despite the facile hydrolysis of H-phosphonate diesters and the extremely low solubility of elemental sulfur in water, sulfurization and hydrolysis proceeded at comparable rates under neutral and mildly acidic conditions.



INTRODUCTION

The emergence of an information-carrying polymer, possibly RNA, was a defining moment in the origin of life.[1−6] The key step in the prebiotic polymerization of RNA, that is, nonenzymatic esterification of phosphoric acid, is hindered by significant kinetic and thermodynamic barriers, as well as the low solubility of phosphate minerals in water.[7−9] With the notable exception of a recent report on in situ-activated polymerization of nucleoside 5′-monophosphates,[10] the enzyme-free nucleic acid polymerizations described in the literature have employed preactivated monomers.[11−14]

The relatively facile reactions of trivalent phosphorus[15] and high solubility of phosphite minerals[16] make the involvement of phosphorous acid, rather than phosphoric acid, in prebiotic phosphorus chemistry an intriguing alternative.[9,17−20] Trivalent phosphorus could have originated from either terrestrial[21] or extraterrestrial[22−25] sources, and in the Archean ocean, phosphite may have been more abundant than phosphate.[26] Even in contemporary oceans, between 10 and 20% of the dissolved phosphorus bears an oxidation state lower than +5.[27]

In contrast to phosphoric acid, phosphorous acid undergoes rapid esterification under anhydrous conditions.[28,29] The resulting H-phosphonate monoesters are stable in aqueous media, whereas the respective diesters are rapidly hydrolyzed.[30] In the presence of a suitable oxidant, however, H-phosphonates are readily converted to the much more stable pentavalent counterparts, such as phosphates or phosphorothioates. Interestingly, this reaction is faster for diesters than for monoesters[31] or inorganic phosphite[32,33] and could, hence, drive polymerization. Oxidative coupling of H-phosphonate monoesters with alcohols has already been demonstrated in anhydrous media using elemental bromine[34] or sulfur[29] as the primary oxidant. Owing to the reversibility of the hydrolysis and esterification reactions of phosphorous acid derivatives, such a pathway could in principle work even in aqueous solution (Scheme 1). The plausibility of this hypothesis depends on the relative rates of the various hydrolysis, esterification, and oxidation steps.

In the present study, the rates of hydrolysis and sulfurization of bis(2′,3′-*O*-methyleneadenosin-5′-yl)-H-phosphonate (**1h**) were measured over a wide pH range and in the presence of various amounts of elemental sulfur. The symmetric H-phosphonate diester **1h** was chosen as a model compound because of the relative simplicity of the expected product mixture. Fission of either of the P−O bonds yields the same alcohol and H-phosphonate monoester and sulfurization at the phosphorus atom does not give rise to a new chiral center. Finally, the methylene bridge between the 2′- and 3′-oxygens prevents H-phosphonate migration.

RESULTS AND DISCUSSION

Preparation of the H-Phosphonate Diester and Monoester Model Compounds. The model H-phosphonate diester **1h** was synthesized from 2′,3′-*O*-methyleneadenosine (**2**) following a procedure previously reported for various primary and secondary alcohols.[35] Accordingly, the phenoxo

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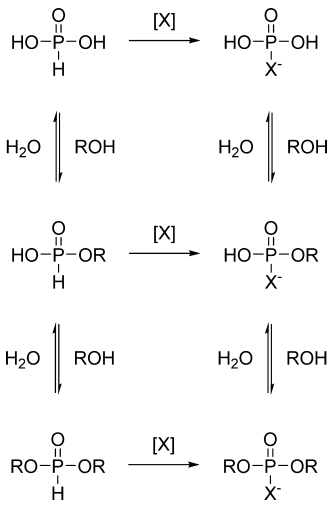
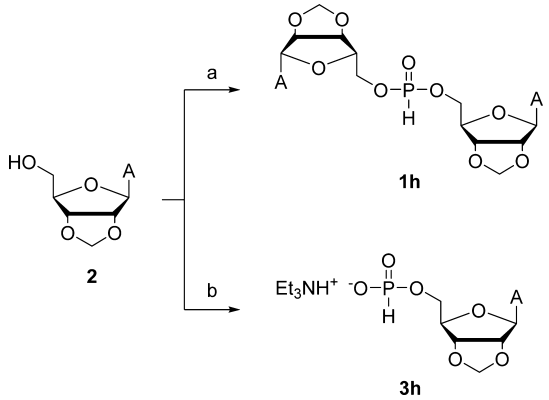
Scheme 1. Oxidation, Esterification, and Hydrolysis Pathways for Phosphorous Acid and Its Mono- and Diesters



ligands of diphenyl phosphite were displaced by 2′,3′-*O*-methyleneadenosine (**2**)[36] in anhydrous pyridine (Scheme 2).

Scheme 2. Preparation of Bis(2′,3′-*O*-methyleneadenosin-5′-yl)-H-phosphonate (1h) and 2′,3′-*O*-Methyleneadenosin-5′-yl-H-phosphonate (3h)[a]



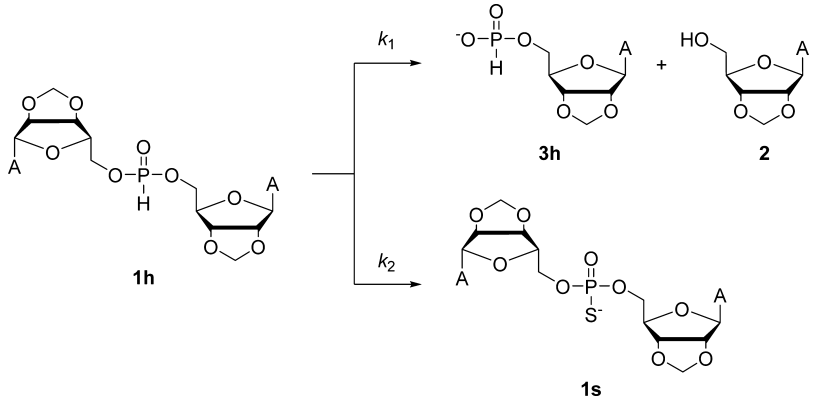
[a]Reagents and conditions: (a) diphenyl phosphite, pyridine, 25 °C; (b) 1. Diphenyl phosphite, pyridine, 25 °C and 2. H_2O, Et_3N, pyridine, 25 °C.

The desired product **1h** precipitated out of the reaction mixture and could be isolated by simple filtration. The respective monoester **3h** was obtained through a similar process except that an excess of diphenyl phosphite was used, and the transesterification step was followed by hydrolytic cleavage of any remaining phenoxo ligands (Scheme 2). The same procedure has previously been used for the preparation of various nucleoside-5′-H-phosphonates.[37]

H-Phosphonate Diester Hydrolysis and Sulfurization. The reactions of the H-phosphonate diester **1h** were first studied in the presence of 0−30 mg of sublimed elemental sulfur to find out whether sulfurization can compete with hydrolysis in aqueous solution. The reaction mixtures were thermostated to 60.0 ± 0.1 °C, and their pH was adjusted to 4.56 with a 100 mM acetic acid buffer and ionic strength to 1.0 M with sodium chloride. The volume of the reaction mixtures was 272 μL, and the starting concentration of **1h** was 10.0 μM. In other words, the amount of sulfur vastly exceeded the amount of **1h** in most of the experiments. However, owing to the extremely low solubility of sulfur in water,[38] the situation was reversed in the solution phase. To obtain a reproducible dispersion of the insoluble sulfur, the reaction mixtures were sonicated before starting the kinetic runs. Samples were withdrawn from the reaction mixtures at appropriate time intervals, and their compositions were determined by reversed-phase high-performance liquid chromatography (RP-HPLC). Only the expected reactions, viz., hydrolysis of **1h** to 2′,3′-*O*-methyleneadenosine (**2**) and its 5′-H-phosphonate (**3h**) (Scheme 3, k_1) and sulfurization of **1h** to the corresponding phosphorothioate (**1s**) (Scheme 3, k_2) were observed during a typical kinetic run. A representative time−concentration profile is depicted in Figure 1. Pseudo-first-order rate constants for the overall disappearance of **1h** were obtained by applying the first-order rate law to the time-dependent concentration of **1h**. The rate constants thus obtained were then broken down to contributions of hydrolysis and sulfurization based on the relative concentrations of **3h** and **1s**, respectively.

The observed pseudo-first-order rate constants for the hydrolysis and sulfurization of **1h** as a function of the amount of sulfur in the reaction mixtures are presented in Figure 2. As expected, the hydrolysis rate was essentially independent on $m(S_8)$. The sulfurization rate, in turn, exhibited a clear dependence on $m(S_8)$ in the presence of small amounts of sulfur, with leveling-off in the presence of larger amounts. The sulfurization rate exceeded the hydrolysis rate when approximately 15 mg of S_8 was added to the reaction mixture.

Scheme 3. Reaction Pathways for the Hydrolysis and Sulfurization of the H-Phosphonate Diester 1h



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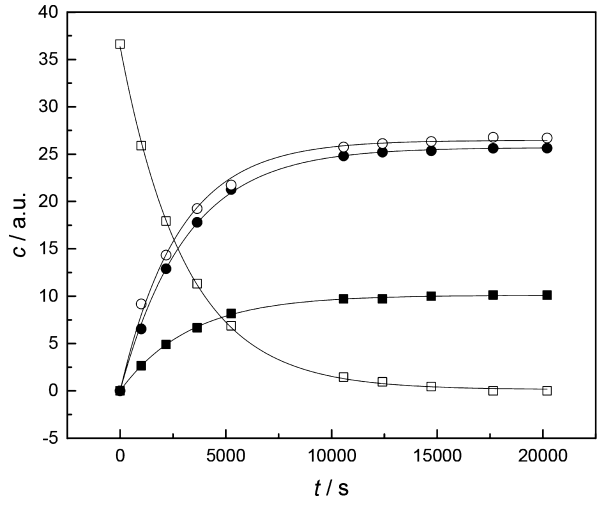

Figure 1. Time-dependent concentration of **1h** (□), its hydrolysis products **3h** (●) and **2** (○), and the sulfurization product **1s** (■) in the presence of 3 mg of sublimed elemental sulfur; T = 60.0 °C, pH = 4.56 (200 mM acetate buffer), and I(NaCl) = 1.0 M.

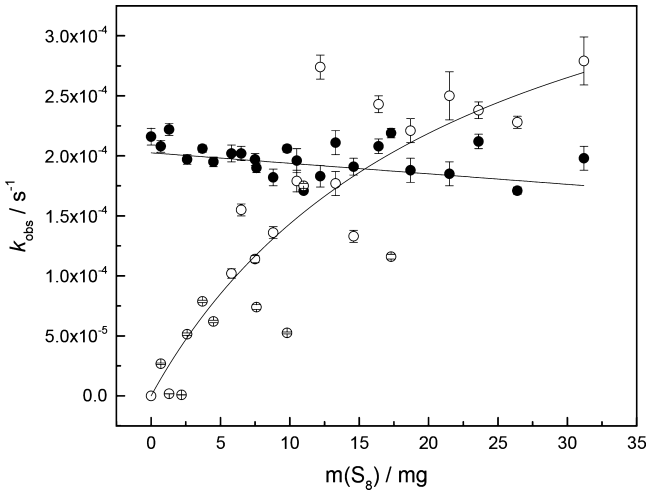

Figure 2. Observed rate constants for the hydrolysis (●) and sulfurization (○) of **1h** as a function of the amount of elemental sulfur; T = 60 °C, pH = 4.56 (100 mM acetate buffer), and I(NaCl) = 1.0 M.

Given the very low (and constant) concentration of elemental sulfur in the solution phase, it appears likely that sulfurization of **1h** takes place at the interface between the solution and the insoluble sulfur particles. This interpretation is further borne out by the observation that the rate of sulfurization was dependent on the particle size of the sulfur used: a single flake of sulfur was approximately an order of magnitude less efficient as a sulfurizing agent than an equal amount of sublimed sulfur (data not shown). Although some of the reaction components, notably the hydrolysis product **3h**, are amphiphilic and could, in principle, solubilize sulfur, such a process is not likely to play a major role at the low concentration of the potential surfactants.[39] The saturation of the sulfurization rate observed at larger amounts of sulfur could stem from aggregation of the particles and the scattering of the data from difficulties in maintaining a uniform particle size distribution throughout the kinetic runs.

Rate constants for the hydrolysis and sulfurization of **1h** were also determined over a wide pH range (0.52−7.25) in the presence of a fixed amount (3.0 mg) of sublimed sulfur (Figure 3). The pH of the reaction solutions was adjusted with

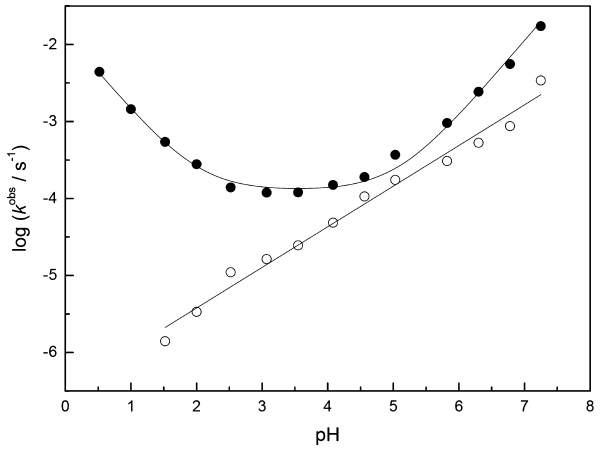

Figure 3. pH-rate profiles for the hydrolysis (●) and sulfurization (○) of **1h** in the presence of 3.0 mg of sublimed elemental sulfur; T = 60 °C and I(NaCl) = 1.0 M.

hydrogen chloride and formic, acetic, and cacodylic acid buffers. Hydrolysis was subject to a very modest buffer catalysis in formic and acetic acid buffers. For the pH-rate profile, rate constants at zero buffer concentration were obtained by linear extrapolation from rate constants measured in 20, 50, 100, and 200 mM buffers. No buffer catalysis was observed with hydrolysis in cacodylate buffer or with sulfurization under any of the conditions used. In these cases, the rate constants presented in Figure 2 are averages of at least three measurements carried out at different buffer concentrations. All of the observed rate constants are summarized in the Supporting Information.

The pH-rate profile for hydrolysis closely resembles the one previously reported for the H-phosphonate analogue of thymidylyl-3′,5′-thymidine.[30] Accordingly, hydrolysis of **1h** was first order in hydronium ion under strongly acidic conditions and first order in hydroxide ion under neutral and mildly acidic conditions. The intervening pH-independent region, however, was considerably wider than with thymidylyl-3′,5′-thymidine. The observed rate constant may be expressed by eq 1

$$k_1^{obs} = k_1^{H}[H^+] + k_1^{W} + k_1^{OH}\frac{K_W}{[H^+]} \quad (1)$$

where k_1^{H} and k_1^{OH} are the second-order rate constants for the hydronium- and hydroxide-ion-catalyzed hydrolysis, respectively, k_1^{W} is the first-order rate constant for the pH-independent hydrolysis, and K_W is the ion product of water under the experimental conditions (1.58×10^{-13} M^2). The values obtained for k_1^{H}, k_1^{W}, and k_1^{OH} by nonlinear least-squares fitting of the experimental data to eq 1 were $(1.4 \pm 0.2) \times 10^{-2}$ M^{-1} s^{-1}, $(1.3 \pm 0.1) \times 10^{-4}$ s^{-1}, and $(7.1 \pm 0.7) \times 10^{3}$ M^{-1} s^{-1}, respectively.

As previously demonstrated for the hydrolysis of simple H-phosphonate diesters,[40,41] all of the partial reactions in all likelihood proceed by a nucleophilic attack on phosphorus (rather than carbon). Accordingly, the most probable explanation for the observed hydronium ion catalysis is facilitation of the nucleophilic attack of a water molecule by preequilibrium protonation of the H-phosphonate. The pH-

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independence, in turn, is open to two kinetically equivalent interpretations, viz., the attack of a water molecule on neutral H-phosphonate or the attack of a hydroxide ion on a protonated monocationic H-phosphonate. Hydroxide ion catalysis becomes the predominant pathway already at pH 5, suggesting that hydroxide ion is a better nucleophile than water by at least 7 orders of magnitude (pK_W under the experimental conditions = 12.8). Similarly, protonation of the H-phosphonate diester makes it more electrophilic, but the magnitude of this activation cannot be estimated as acidity constants of monoprotonated H-phosphonate diesters are not known. Finally, the hydroxide ion catalysis is undoubtedly attributable to the attack of a hydroxide ion on a neutral H-phosphonate.

Sulfurization of **1h** was base-catalyzed over the entire pH range studied, but the dependence on hydroxide ion concentration appears to be less than first order. The observed rate constant may be expressed by eq 2

$$k_2^{obs} = k_2^{OH}\left(\frac{K_W}{[H^+]}\right)^n \quad (2)$$

where k_2^{OH} is the rate constant for the hydroxide-ion-catalyzed sulfurization, K_W is the ion product of water, and n is the reaction order with respect to hydroxide ion. The values obtained for k_2^{OH} and n by nonlinear least-squares fitting of the experimental data to eq 2 were 1.9 ± 0.8 M^{-n} s^{-1} and 0.53 ± 0.02, respectively.

Bases play a dual role in the sulfurization of H-phosphonate diesters.[42] First, a sufficiently strong base is required to abstract the P−H proton, thereby converting the H-phosphonate into a more reactive phosphite anion.[43] Second, bases can activate sulfur by breaking its eight-membered ring structure.[44,45] The fractional order dependence on hydroxide ion concentration probably stems from this dual role as well as the heterogeneity of the sulfurization reaction. It can be speculated that the reaction order n is exactly 1/2, but the data at hand do not allow a firm conclusion to be drawn.

CONCLUSIONS

Sulfurization of H-phosphonate diesters by elemental sulfur is able to compete with hydrolysis despite the extremely low solubility of elemental sulfur in water. The reaction is base-catalyzed over a wide pH range, with the relative rate of sulfurization to hydrolysis reaching a maximum around pH 5. In other words, once formed, H-phosphonate diester linkages could be stabilized by sulfurization to the respective phosphorothioate diester linkages even in aqueous solutions. One could, for example, envision cycles of de- and rehydration driving nucleic acid polymerization in a volcanic environment enriched in phosphite and sulfur.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer, and the chemical shifts are given in ppm. Mass spectra were recorded on a Bruker micrOTOF-Q ESI mass spectrometer. Synthesis of 2′,3′-*O*-methyleneadenosine (**2**) has been described in the literature.[36] The other chemicals were commercial products and were used as received.

Kinetic Measurements. The reactions were carried out in sealed tubes in a dry bath thermostated to 60.0 ± 0.1 °C. The pH of the reaction solutions was adjusted with hydrogen chloride and formic, acetic, and cacodylic acid buffers and the ionic strength (1.0 M) with sodium chloride. Sublimed elemental sulfur was added to the reaction mixtures and dispersed by sonication before the start of each kinetic run. The initial concentration of the starting material **1h** in the kinetic runs was 10.0 μM. The composition of aliquots drawn from the reaction mixtures at appropriate time intervals was determined by RP-HPLC on a Hypersil-Keystone Aquasil C18 column (150 × 4 mm and 5 μm), eluting with a linear gradient (8−55% over 15 min) of acetonitrile in a 60 mM acetic acid buffer (pH = 4.3). The flow rate was 1.0 mL min^{-1}, and the detection wavelength was 260 nm. The observed retention times were as follows: 4.6 min (**3h**), 7.4 min (**2**), 7.7 min (**1s**), and 9.9 min (**1h**). The identity of these components was verified by HPLC-mass spectometry (MS) (with **1s**) or spiking with authentic samples (with **1h**, **2**, and **3h**). Molar absorptivities of the dimeric components (**1h** and **1s**) were assumed to be twice as high as those of the monomeric components (**2** and **3h**).

Bis(2′,3′-*O*-methyleneadenosin-5′-yl)-H-phosphonate (1h). 2′,3′-*O*-Methyleneadenosine (**2**, 0.290 g, and 1.04 mmol) was coevaporated from anhydrous pyridine, and the residue was redissolved in anhydrous pyridine (10 mL). Diphenyl phosphite (95.0 μL and 0.361 mmol) was added, and the resulting mixture was stirred at room temperature for 16 h, during which a solid precipitated. This material was isolated by filtration and found to be the desired product **1h** in sufficient purity for the kinetic experiments. The low yield (18.8 mg and 6%) thus obtained suggests that most of the products remained in the pyridine solution, but no attempts were made to recover it. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.32 (s, 1H, H2), 8.32 (s, 1H, H2), 8.17 (s, 1H, H8), 8.17 (s, 1H, H8), 7.37 (m, 4H, NH_2), 6.73 (d, J = 718.3 Hz, 1H, PH), 6.19 (d, J = 2.3 Hz, 1H, H1′), 6.19 (d, J = 2.3 Hz, 1H, H1′), 5.36 (dd, J_1 = 2.9 Hz, J_2 = 6.6 Hz, 1H, H2′), 5.34 (dd, J_1 = 2.9 Hz, J_2 = 6.5 Hz, 1H, H2′), 5.16 (s, 4H, OCH_2O), 4.96 (m, 2H, H3′), 4.27 (m, 2H, H4′), 4.22 (m, 2H, H5′), 4.12 (m, 2H, H5″). ^{13}C NMR (125 MHz, d_6-DMSO): δ 156.7 (C6), 153.3 (C8), 150.0 (C4), 149.3 (C4), 140.4 (C2), 140.3 (C2), 119.5 (C5), 95.6 (OCH_2O), 88.4 (C1′), 88.3 (C1′), 82.8 (C2′), 82.7 (C4′), 80.4 (C3′), 80.3 (C3′), 65.0 (C5′). ^{31}P NMR (202 MHz, d_6-DMSO): δ 9.7. HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{26}N_{10}O_9P$, 605.1616; found, 605.1610 $[M + H]^+$.

2′,3′-*O*-Methyleneadenosine-5′-H-phosphonate (3h). 2′,3′-*O*-Methyleneadenosine (**2**, 61.3 mg, and 0.220 mmol) was coevaporated from anhydrous pyridine, and the residue was redissolved in anhydrous pyridine (1200 μL). Diphenyl phosphite (100 μL and 0.380 mmol) in anhydrous pyridine (500 μL) was added, and the resulting mixture was stirred at room temperature for 23 h. Et_3N (150 μL) and H_2O (50 μL) were added, and the reaction mixture was stirred for 1 h, after which it was evaporated to dryness. The residue was purified on a silica gel column, eluting with a mixture of Et_3N, MeOH, and CH_2Cl_2 (1:19:80, v/v). The product was obtained as the triethylammonium salt in 69% yield (67.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H, H2), 8.28 (s, 1H, H8), 7.17 (br, 2H, NH_2), 6.84 (d, J = 620.2 Hz, 1H, PH), 6.24 (d, J = 2.7 Hz, 1H, H1′), 5.23 (s, 1H, OCH_2O), 5.16 (dd, J_1 = 2.8 Hz, J_2 = 6.2 Hz, 1H, H2′), 5.10 (s, 1H, OCH_2O), 5.02 (dd, J_1 = 2.5 Hz, J_2 = 6.2 Hz, 1H, H3′), 4.47 (m, 1H, H4′), 4.06 (m, 2H, H5′, H5″), 2.99 (q, J = 7.3 Hz, 6H, NCH_2), 1.21 (t, J = 7.3 Hz, 9H, NCH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0 (C6), 153.3 (C8), 149.4 (C4), 139.3 (C2), 119.2 (C5), 96.3 (OCH_2O), 89.4 (C1′), 84.7 (d, J = 8.2 Hz, C4′), 84.6 (C2′),

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81.6 (C3′), 63.7 (d, J = 4.2 Hz, C5′), 45.5 (NCH_2), 8.6 (NCH_2CH_3). ^{31}P NMR (202 MHz, $CDCl_3$): δ 4.1. HRMS (ESI^+) m/z: calcd for $C_{11}H_{13}N_5O_6P$, 342.0609; found, 342.0597 $[M - H]^-$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00970.

^1H, ^{13}C, and ^{31}P NMR spectra of compounds **1h** and **3h** and the observed rate constants for the hydrolysis and sulfurization of compound **1h** (PDF)

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Notes

The author declares no competing financial interest.

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