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Hydrolysis of Cyclic Phosphites/Phosphoramidites and Its Inhibition-Reversible Cyclization of Acyclic Phosphonate Salts to Cyclic Phosphites

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Abstract:

Hydrolysis of cyclic phosphites/phosphoramidites ($OCH_2CRR'CH_2O$)PX [X = OPh (1), NMe_2 (2)] in the presence of *intentionally added water* is effectively inhibited by using simple additives such as KF, K_2CO_3, Et_3N, and molecular sieves. Among these, K_2CO_3 gave the best results. Cyclic H-phosphonates ($OCH_2CRR'CH_2O$)P(O)H (3), which are the tautomeric forms of the phosphites ($OCH_2CRR'CH_2O$)P(OH), undergo facile hydrolysis in the presence of aqueous amines to give the acyclic phosphonate salts $[H_2NMe_2]^+[(HOCH_2CRR'CH_2O)P(O)(H)(O^-)]$ (4) that can be *reverted back to* 3 *upon simple heating*. Interestingly, competitive reactions of ($OCH_2CRR'CH_2O$)PX [X = Cl (I−III), NMe_2 (2)] with phenol and water in the presence of K_2CO_3 led only to the phenoxy derivatives and not to the hydrolysis products.

Introduction

Although tervalent P(III) compounds of the type $(RO)_3P$ or $(RO)_2PNR'R''$ are frequently used in the synthesis of a large number of other phosphorus compounds including nucleosides/glycosides, their high reactivity makes them susceptible to spontaneous oxidation and hydrolysis.[1,2] In other significant applications of P(III) esters as antioxidants[3a−c] and heat stabilizers for synthetic polymers/plastics, hydrolysis in particular is a commonly encountered hurdle during synthesis, storage, and use of pure compounds.[3d,e] Unlike the hydrolysis of phosphate esters,[4] those of phosphites/phosphoramidites are much less investigated,[3,5] although it is known that the P−N bonds in P(III) compounds can be readily cleaved under acid-catalyzed conditions.[6] It is often desirable that hydrolysis of the precursor P(III) derivatives be prevented until reactions with the substrate are conducted.[5] Herein we report the *remarkable inhibition of hydrolysis of cyclic phosphites/phosphoramidites* ($OCH_2CRR'CH_2O$)PX [X = OPh (**1**), NMe_2 (**2**)] *in the presence of added water by several simple salts*.[7] Obviously, such a feature should be common to a large number of other P(III) esters. We believe that these observations can be put to practical use while handling P(III) compounds.[5]

The first-stage hydrolysis products of **1** [(R, R′ = Me (**a**), R, R′ = Et (**b**), R = Me, R′ = *n*-Pr (**c**)] or ($OCH_2CRR'CH_2O$)PCl [(R, R′ = Me (**I**), R, R′ = Et (**II**), R = Me, R′ = *n*-Pr (**III**)], the hydroxy phosphites ($OCH_2CRR'CH_2O$)P(OH), exist essentially in the tautomeric phosphonate form ($OCH_2CRR'CH_2O$)P(O)H (**3a**−**c**).[1] *Reversible hydrolysis of* **3a**−**c**, examples of which are very rare, in the presence of an amine base, is also reported herein.

Results and Discussion

Normal hydrolysis of **1a**−**c** leading to cyclic H-phosphonates **3a**−**c** occurs upon addition of stoichiometric amounts of water under neat conditions (Scheme 1).[8] When **1a**−**c** is stirred with an excess of water (3 mol equiv) in tetrahydrofuran for 12 h, **3a**−**c** as well as further hydrolysis products are observed [^{31}P NMR]; an analogous reaction with water, when conducted in the presence of K_2CO_3, afforded **1a**−**c** *completely unaffected*. This inhibition of hydrolysis was also realized when KF, $MgSO_4$, triethylamine, or molecular sieves was used in place of K_2CO_3, but K_2CO_3 gave the best results. *Even with 1:1:3 mole equiv of* **1a**, K_2CO_3, *and* H_2O in THF as the solvent, *no hydrolysis was observed*. The salts NaF and KCl were ineffective in inhibiting the hydrolysis. Both KF and K_2CO_3 are no doubt hygroscopic, but the effectiveness of the latter in inhibiting hydrolysis is very impressive. Hydrolysis of the phosphoramidites **2** [R, R′ = Me (**a**); R,

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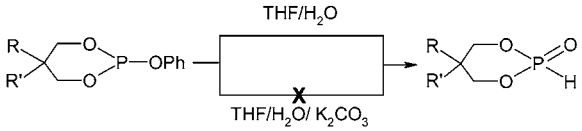
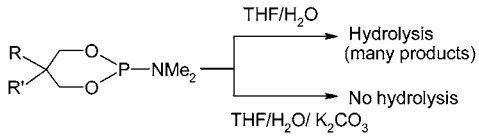
Scheme 1



1a: R = R' = Me [δ(P) 114.6]
1b: R = R' = Et [δ(P) 117.0]
1c: R = Me; R' = *n*-Pr [δ(P) 115.4, 116.4]
3a: R = R' = Me [δ(P) 2.3]
3b: R = R' = Et [δ(P) 3.4]
3c: R = Me; R' = *n*-Pr [δ(P) 2.8, 3.0]



2a: R = R' = Me [δ(P) 143.9]
2b: R = R' = Et [δ(P) 144.1]
2c: R = Me; R' = *n*-Pr [δ(P) 143.4, 144.0]

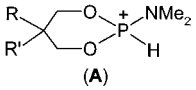
Table 1. **Competitive Reaction of Phosphites with Phenol and Water in THF**

entry	P(III) compound (1 mmol)	additive:H_2O:phenol[a] (mmol)	product[b]
1	**I**	5:1:1	**1a**
2	**II**	5:1:1	**1b**
3	**III**	5:1:1	**1c**
4	**2a**	5:3:1	**1a**
5	**2a**	1:3:1	**1a**
6	**2a**	3:1[c]	**1a**
7	**2c**	5:3:1	**1c**
8	**2a**	5:3:1 (2,6-Cl_2−C_6H_3OH)	**1d** (2%)[d]
9	**2a**	5:3:1 (2,6-Me_2−C_6H_3OH)	**1e** (50%)[d]
10	**2a**	3:1 (2,6-Cl_2−C_6H_3OH)	**1d**

[a] In all cases except entry 10, K_2CO_3 was the additive; in entry 10, molecular sieves (5 times the weight of the phosphite) were used. [b] No hydrolysis except in entries 6 and 10, where 8% and 40% hydrolysis, respectively, occurred. [c] No additive was used. [d] Rest was the starting phosphoramidite; ($OCH_2CMe_2CH_2O$)-P(OAr) [Ar = 2,6-$Cl_2C_6H_3O$ (**1d**), 2,6-$Me_2C_6H_3O$ (**1e**)].

R′ = Et (**b**); R = Me, R′ = *n*-Pr (**c**)] and (OCH_2CMe_2-CH_2O)P(NH-*cyc*l-C_6H_{11}) is also inhibited by KF and K_2CO_3.

We also conducted competitive reactions of (OCH_2CMe_2-CH_2O)PX [X = Cl (**I**), NMe_2 (**2a**)] with a mixture of water and a phenol to ascertain whether any mechanistic contribution is there or not in the inhibition of hydrolysis by K_2CO_3 [Table 1]. Under these conditions, the phenol reacts preferentially to give the phenoxy derivatives **1a**−**e**. The stoichiometric reaction of **2a** with H_2O/phenol led to **1a** w*ith much less hydrolysis* (<10%); the inhibition of hydrolysis is most likely due to the liberated dimethylamine. Use of molecular sieves led to significant hydrolysis. These results suggest that the basic nature of K_2CO_3 does have a role in inhibiting the formation of a transition state species such as (**A**)[6b] by the initial attack of the acidic proton on the phenol at the trivalent phosphorus center, hence, the prevention of hydrolyzed products.



(**A**)

Compounds **3a**−**c** undergo facile hydrolysis in the presence of aqueous amines to the acyclic phosphonates $[H_2NMe_2]^+[(HOCH_2CRR'CH_2O)P(H)(O)(O^-)]$ (**4a**−**c**) (90−95% yield) [Scheme 2]. An X-ray structure of **4d** [base = *N*,*N*-(dimethylamino)pyridine (DMAP)] [Figure 1], which exists as a hydrogen bonded dimer, confirms the identity of these products.[9,10] What is perhaps a lot more interesting is that the *salts* **4a**−**c** *can be thermally converted back to the cyclic phosphites* **3a**−**c**; this is readily confirmed by ^{31}P NMR as well as derivatization to the Pudovik products (OCH_2-$CRR'CH_2O$)P(O)CH(OH)Ar [R = R′ = Me, Ar = 4-Cl−C_6H_4 (**5a**); R = R′ = Et, Ar = Ph (**5b**); R = Me, R′ = *n*-Pr, Ar = Ph (**5c**)].[11]

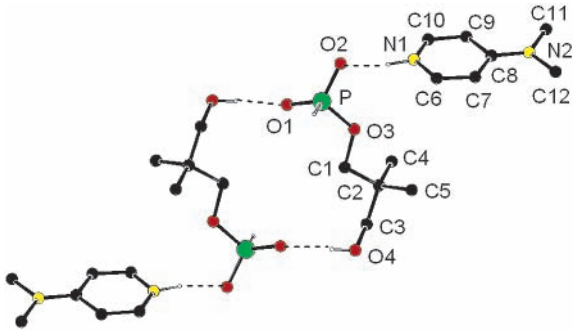
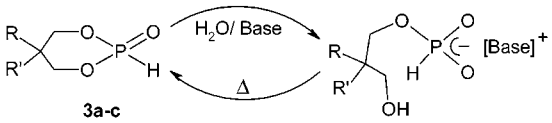


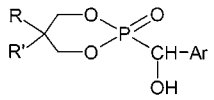
Figure 1. **A diagram showing the hydrogen bonded dimeric motif in 4d; only hydrogen bonded protons are shown. There is a very weak hydrogen bond between HN(1) and O(3) which is not shown in the picture. Selected hydrogen bond parameters (Å, deg): O(4)−HO(4)···O(1) 0.83 (5), 1.82 (5), 2.648 (4), 177-(5); N(1)−HN(1)···O(3) 0.95 (6), 1.73 (6), 2.658 (4), 168(5); N(1)−HN(1)···O(3) 0.95 (6), 2.56 (6), 3.215 (4), 126(4).**

Scheme 2



Base = Aq. $HNMe_2$

4a: R = R' = Me [δ(P) 4.6]
4b: R = R' = Et [δ(P) 4.8]
4c: R = Me; R' = *n*-Pr [δ(P) 5.2]



5a: Ar = 4-Cl-C_6H_4; R = R' = Me [δ(P) 12.9]
5b: Ar = Ph; R = R' = Et [δ(P) 14.3]
5c: Ar = Ph; R = Me; R' = *n*-Pr [δ(P) 13.6]

The cyclization leading to a six-membered dioxaphosphorinane ring from an acyclic phosphate ester, to our knowledge, is observed in two cases before: (a) formation of *cyclic*-AMP from ATP in the presence of adenyl cyclase[12] and (b) formation of 3′,5′-cyclic phosphates from ribonucleoside-5′-phosphates with DCC under the presence of a strong base guanidine.[13] In these cases, cleavage of an O−P or O−C bond from the acyclic precursor is required in the formation of the cyclic phosphate, while, in the formation of **3** from **4**, base elimination and dehydration are involved.

(9) The hydrogen bonds here are only moderately strong. For comparison, see: Kumara Swamy, K. C.; Kumaraswamy, S.; Kommana, P. *J. Am. Chem. Soc.* **2001**, *123*, 12642.
(10) For more details on analogous derivatives, see: Said, M. A.; Kumara Swamy, K. C.; Veith, M.; Huch, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2945.
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(13) Khorana, H. G. *Chemical Biology- Selected Papers of H. G. Khorana*; World Scientific: Singapore, 2000; pp 80−95.

An *immediate application* of the present results is in the preservation of P(III) compounds. We could preserve **1a** (no solvent; 1.5 g, 6.6 mmol)) in the presence of 1 molar equiv of K_2CO_3 and 3 molar equiv of water (stirred) *for 3 days without any apparent hydrolysis*. Hydrolysis of the acyclic phosphites $P(OMe)_3$ and $P(OPh)_3$ was also inhibited by using K_2CO_3. In a similar way, hydrolysis of other aminophosphites [e.g., $(OCH_2CMe_2CH_2O)P(NH\text{-}cyc\text{-}C_6H_{11})$ (**6**)] could also be prevented. The main limitation, however, is that a phosphite bearing an aromatic diol residue like $(1,2\text{-}C_6H_4O_2)P(OPh)$ [**7**; δ(P) 126.6] is still susceptible towards hydrolysis, even in the presence of K_2CO_3.

Conclusions

In summary, we have presented the *remarkable inhibition of hydrolysis of cyclic phosphites/phosphoramidites* **1** and **2** *in the presence of added water by several simple salts*. Competitive phosphorylation of phenols with phosphoramidites in the presence of intentionally added water and metals salts is also presented. We believe that these observations can be put to practical use while handling P(III) compounds in laboratory and as well as in industrial conditions.

Experimental Section

The ^{1}H (200 MHz),^{13}C (50 MHz), and ^{31}P (80.9 MHz) NMR spectra were recorded on a Bruker 200 MHz spectrometer in $CDCl_3$. The chemical shifts reported are relative to that of tetramethylsilane (^{1}H, ^{13}C, $\delta = 0$) and ^{31}P NMR with external standard 85% H_3PO_4 (^{31}P, $\delta = 0$). The chloro precursors **I**−**III** were prepared by the routes reported before;[14] compound **I** is very well-known and is now available from Aldrich. Compounds **1a**−**c**, **2a**−**c**, and **3a**−**c** were prepared by standard routes. Spectroscopic data for **I**−**III** and **1**−**3** are given in the Supporting Information.

Reactions of 1a−c and 2a−c with Water in the Presence of Metal Salts or Et_3N. To freshly distilled **1** or **2** (1 mmol) was added 5 mmol of KF or K_2CO_3 or $MgSO_4$ or Et_3N [or 1.5 g of molecular sieves] followed by dry THF (8 mL) and water (3 mmol). The reaction mixture was stirred continuously for 3 d. THF was removed by vacuum, the residue was dissolved in $CDCl_3$ (1 mL), and after ca. 0.5 h, the solution was syringed out and submitted for spectroscopic analysis (^{1}H, ^{13}C, ^{31}P NMR; primarily ^{31}P NMR was used for analysis). Details are given in Table 2. The spectra in the hydrolysis or its inhibition of **1a** and **2a** were also checked in benzene-d_6/THF or THF without any deuterated solvent. The results were the same as that obtained using $CDCl_3$.

Hydrolysis of acyclic phosphites $P(OMe)_3$ and $P(OPh)_3$ in the absence of K_2CO_3 using similar experimental conditions as those above occurred to an extent of 100% and 40%, respectively. In the presence of K_2CO_3, the hydrolysis was completely inhibited

Reversible Cyclization. (A) Preparation of the Salts 4a−c. To freshly distilled **3** (10 mmol) an excess of aq. dimethylamine solution (ca 20 mL) was added, and the reaction mixture was stirred for 3 h. Compounds **4a**−**c** were obtained by removing excess dimethylamine solution in vacuo at room temperature. The yields were essentially quantitative.

Table 2. **Details on the Hydrolysis Studies of 1a−c and 2a−c**

entry	compound	additive	result
1	**1a**−**c** or **2a**−**c** (1 mmol) + 3 mmol of water)	KF	∼2% hydrolysis
2	*a*	K_2CO_3	no hydrolysis
3	*a*	Et_3N	∼1% hydrolysis
4	*a*	$MgSO_4$	∼2% hydrolysis
5	*a*	molecular sieves	∼1% hydrolysis
6	*a*	KCl	complete hydrolysis
7	*a*	NaF	complete hydrolysis

[a] Same as that for entry 1.

4a. Yield: 2.04 g, 96%. ^{1}H NMR: δ 0.69 (s, 6 H, C*H*$_3$), 2.43 (s, 6 H, N(C*H*$_3$)$_2$, 3.13 (s, 2 H, OC*H*$_2$), 3.40 (d, ^3J(HH) = 9.5 Hz, 2 H, OC*H*$_2$), 6.57 (d, ^1J(PH) = 622.2 Hz, 1 H, P(O)*H*). ^{13}C NMR: δ 21.4 (s, *C*H$_3$), 34.5 (s, N(*C*H$_3$)$_2$), 36.7 (d, ^3J(PC) = 3.9 Hz, *C*(CH$_3$)$_2$), 67.0, 68.6 (d, ^2J(PC) = 4.0 Hz, O*C*H$_2$). ^{31}P NMR: δ 4.6.

4b. Yield: 2.28 g, 95%. ^{1}H NMR: δ 0.65 (t, ^3J(HH) = 7.4 Hz, 6 H, CH$_2$C*H*$_3$), 1.05 (m, 4 H, C*H*$_2$CH$_3$), 2.47 (s, 6 H, N(C*H*$_3$)$_2$), 3.16 (s, 2 H, OC*H*$_2$), 3.45 (d, ^3J(PH) = 8.9 Hz, 2 H, OC*H*$_2$), 6.58 (d, ^1J(PH) = 622.2 Hz, 1 H, P(O)*H*). ^{13}C NMR: δ 6.8 (s, CH$_2$*C*H$_3$), 21.4 (s, *C*H$_2$CH$_3$), 34.5 (s, N(*C*H$_3$)$_2$), 41.5 (br s, *C*Et$_2$), 63.1, 65.0 (2 s, O*C*H$_2$). ^{31}P NMR: δ 4.8.

4c. Yield: 2.31 g, 96%. ^{1}H NMR: δ 0.78 (s, 3 H, C*H*$_3$), 0.85 (t, ^3J(HH) = 6.9 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$), 1.17−1.23 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 2.56 (s, 6 H, N(C*H*$_3$)$_2$), 3.29 (AB qrt, ^2J(HH) ≈ 8.5 Hz, 2 H, HOC*H*$_2$), 3.58 (symmetrical m, 2 H, OC*H*$_2$), 6.73 (d, ^1J(PH) = 626.1 Hz, 1H, P(O)*H*). ^{13}C NMR: δ 14.9 (s, *C*H$_3$), 16.2, 18.3 (2 s, *C*H$_2$*C*H$_2$*C*H$_3$), 34.5 (s, N(*C*H$_3$)$_2$), 36.3, 39.4 (s, *C*(CH$_3$)(*n*-Pr)), 65.8 (2s, O*C*H$_2$), 67.3 (d, ^2J(PC) = 3.5 Hz, O*C*H$_2$). ^{31}P NMR: δ 5.2.

[DMAPH]$^+$[(HOCH$_2$CMe$_2$CH$_2$O)P(H)(O)(O$^-$)] (4d). To a stirred solution of $(OCH_2C(CH_3)_2CH_2O)P(O)H$ (1.50 g, 10.0 mmol) in dichloromethane (10 mL) water (0.18 g, 10.0 mmol) was added followed by DMAP (1.34 g, 11.0 mmol). The mixture was stirred for 3 h, the solution concentrated to 2 mL, toluene (8 mL) added, and the solution preserved at 0 °C. Crystals of **4d** were obtained after 1 d (Yield 2.7 g, 93.1%), mp 88−90 °C. ^{1}H NMR ($CDCl_3$): δ 0.78 (s, 6 H, C*H*$_3$), 3.13 (s, 6 H, N(C*H*$_3$)$_2$), 3.25 (s, 2 H, OC*H*$_2$), 3.59 (d, ^3J(PH) = 11.1 Hz, 2 H, OC*H*$_2$), 6.85 (d, ^1J(PH) = 621.3 Hz, 1 H, P(O)*H*), 6.70, 8.20 (2 d, ^2J(HH) = 15.0 Hz each, 4 H, DMAP−*H*). ^{13}C NMR ($CDCl_3$): δ 21.5 (s, *C*H$_3$), 37.1 (br s, *C*(CH$_3$)$_2$), 39.9 (s, N(*C*H$_3$)$_2$), 67.2, 68.5 (2 s, O*C*H$_2$), 106.7, 139.9, 157.1 (DMAP−*C*). ^{31}P NMR ($CDCl_3$): δ 5.6. The crystals were transferred using a fluorocarbon liquid into a Lindemann capillary, and the data were collected on an Enraf-Nonius MACH3 diffractometer using Mo Kα radiation at 293(2) K. The structure was solved

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and refined using standard methods.[15] Crystal data: a = 8.646(2) Å, b = 8.761(3) Å, c = 11.811(7) Å, α = 109.19(7)°, β = 105.72(3)°, γ = 99.38(4)°, V = 781.4(6) Å^3, Z = 2, ρ = 1.234 g cm^{-3}, = 0.187, F_{000} = 312, data/restraints/parameters 2750/0/189, R1 = 0.0635, wR2 (all data) = 0.1968, S = 1.184, residual electron density 0.564/−0.529 Å^{-3}.

(B) Recyclization of the Salts 4a−c to the Cyclic Phosphites 3a−c and Conversion of 3a−c to the Phosphonates (5a−c). The salts **4a−c** (1.2−1.3 g) were heated at 100 °C for 3 h, and the resulting **3a−c** were distilled under vaccum. The yields of **3a−c** were in the range 60−85%; however, in the conversion of these to the corresponding hydroxyphosphonates by a literature procedure,[11] no difficulties were encountered.

5a. Yield: 60% (from cyclization route). The physical data were identical to those reported by us before.[11]

5b. Yield: 85%. Mp: 130−133 °C. ^{1}H NMR: δ 0.67, 0.76 (2 t, ^3J(HH) = 7.1 Hz for both, 6 H, CH_2CH_3), 1.05, 1.51 (2 qrt, ^3J(HH) = 7.1 Hz, 4 H, CH_2CH_3), 3.81−4.29 (m, 4 H, OCH_2), 5.04 (d, ^2J(PH) = 12.3 Hz, 1 H, P−C*H*−OH), 5.36 (br. s, 1 H, P−CH−O*H*), 7.14−7.52 (m, 5 H, Ph−*H*). ^{13}C NMR: δ 6.9, 7.1 (2 s, CH_2CH_3), 22.5, 22.6 (2 s, CH_2CH_3), 37.1 (d, ^3J(PC) ≈ 5.5 Hz, $C(CH_2CH_3)_2$), 71.9 (d, ^1J(PC) = 157.6 Hz, P−*C*H(OH)), 75.1, 75.8 (2 d, ^2J(P*C*) = 6.9 Hz for both, OCH_2), 126.9, 127.0, 127.8, 128.1, 137.3 (all *C*(Ar)). ^{31}P NMR: δ 14.3.

5c. Yield: 75%. Mp: 168−170 °C. ^{1}H NMR: δ 0.71 (s, 3 H, CH_3), 0.91 (t, ^3J(HH) = 7.0 Hz, 3 H, $CH_2CH_2CH_3$), 1.21−1.45 (m, 4 H, $CH_2CH_2CH_3$), 3.93−4.07 (m, 4 H, OCH_2), 4.35 (br s, 1 H, P−CH−O*H*), 5.12 (d, ^2J(PH) = 11.8 Hz, 1 H, P−C*H*−OH), 7.26−7.49 (m, 5 H, Ph−*H*). ^{13}C NMR: δ 14.4, 16.3, 17.7, 34.8 (d, ^3J(PC) ≈ 5.5 Hz, *C*(Me)(*n*-Pr)), 36.1, 71.7 (d, ^1J(PC) = 160.0 Hz, P-*C*H(OH)), 75.9, 76.0, 76.4, 126.8, 126.9, 128.0, 128.2, 136.5. ^{31}P NMR: δ 13.6.

Hydrolysis of 6 and Its Inhibition. Compound **6** underwent ready hydrolysis in the presence of 3 molar equiv of water in THF leading to $[(HOCH_2CMe_2CH_2O)P(O)(H)(O^-)][H_3NC_6H_{11}]^+$.[10,16] In the presence of added KF, most of the hydrolysis was inhibited and ^{31}P NMR showed >95% of **6**; the slight hydrolysis perhaps occurred during transfer of the $CDCl_3$ solution to the NMR tube. Similarly, the compound $(OCH_2CMe_2CH_2O)P(OCHMe_2)$ (**8**) did not hydrolyze to any significant extent in THF/H_2O/CsF.

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Supporting Information Available

X-ray crystallographic data as CIF file for **4d** (base = 4-(dimethylamino)pyridine), an ORTEP drawing of **4d**, and routine experimental details with spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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