

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 (OCH₂-CRR'CH₂O)PX [X = OPh (1), NMe₂ (2)] in the presence of intentionally added water is effectively inhibited by using simple additives such as KF, K₂CO₃, Et₃N, and molecular sieves. Among these, K₂CO₃ gave the best results. Cyclic H-phosphonates (OCH₂CRR'CH₂O)P(O)H (3), which are the tautomeric forms of the phosphites (OCH₂CRR'CH₂O)P(OH), undergo facile hydrolysis in the presence of aqueous amines to give the acyclic phosphonate salts [H₂NMe₂]⁺[(HOCH₂CRR'CH₂O)P(O)-(H)(O⁻)] (4) that can be reverted back to 3 upon simple heating. Interestingly, competitive reactions of (OCH₂CRR'CH₂O)PX [X = Cl (I–III), NMe₂ (2)] with phenol and water in the presence of K₂CO₃ led only to the phenoxy derivatives and not to the hydrolysis products.

Introduction

Although trivalent 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 (OCH₂CRR'CH₂O)PX [X = OPh (1), NMe₂ (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 (OCH₂-CRR'CH₂O)PCI [(R, R' = Me (I), R, R' = Et (II), R = Me, R' = n-Pr (III)], the hydroxy phosphites (OCH₂CRR'CH₂O)-P(OH), exist essentially in the tautomeric phosphonate form (OCH₂CRR'CH₂O)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 [³¹P NMR]; an analogous reaction with water, when conducted in the presence of K₂CO₃, afforded 1a–c completely unaffected. This inhibition of hydrolysis was also realized when KF, MgSO₄, triethylamine, or molecular sieves was used in place of K₂CO₃, but K₂CO₃ gave the best results. Even with 1:1:3 mole equiv of 1a, K₂CO₃, and H₂O in THF as the solvent, no hydrolysis was observed. The salts NaF and KCl were ineffective in inhibiting the hydrolysis. Both KF and K₂CO₃ 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

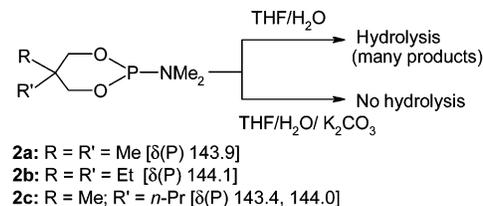
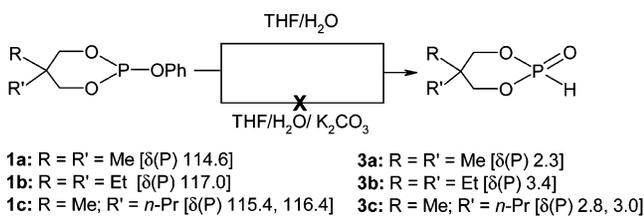


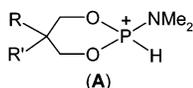
Table 1. Competitive Reaction of Phosphites with Phenol and Water in THF

entry	P(III) compound (1 mmol)	additive:H ₂ O: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 ₆ H ₃ OH)	1d (2%) ^d
9	2a	5:3:1 (2,6-Me ₂ -C ₆ H ₃ OH)	1e (50%) ^d
10	2a	3:1 (2,6-Cl ₂ -C ₆ H ₃ OH)	1d

^a In all cases except entry 10, K₂CO₃ 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; (OCH₂CMe₂CH₂O)-P(OAr) [Ar = 2,6-Cl₂C₆H₃O (**1d**), 2,6-Me₂C₆H₃O (**1e**)].

R' = Et (**b**); R = Me, R' = *n*-Pr (**c**) and (OCH₂CMe₂-CH₂O)P(NH-cycl-C₆H₁₁) is also inhibited by KF and K₂CO₃.

We also conducted competitive reactions of (OCH₂CMe₂-CH₂O)PX [X = Cl (**I**), NMe₂ (**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 K₂CO₃ [Table 1]. Under these conditions, the phenol reacts preferentially to give the phenoxy derivatives **1a–e**. The stoichiometric reaction of **2a** with H₂O/phenol led to **1a** with 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 K₂CO₃ 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.



Compounds **3a–c** undergo facile hydrolysis in the presence of aqueous amines to the acyclic phosphonates [H₂NMe₂]⁺[(HOCH₂CRR'CH₂O)P(H)(O)(O⁻)] (**4a–c**) (90–

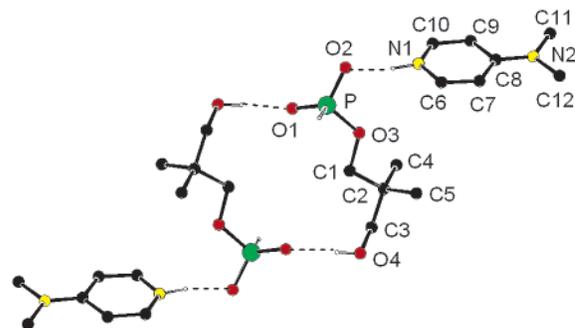
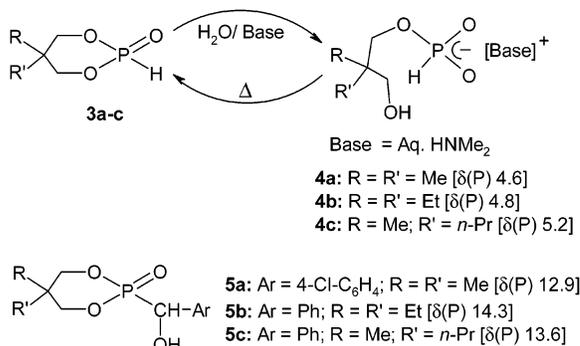


Figure 1. A diagram showing the hydrogen bonded dimeric motif in **4d**; only hydrogen bonded protons are shown. There is a very weak hydrogen bond between HN(1) and O(3) which is not shown in the picture. Selected hydrogen bond parameters (Å, deg): O(4)–HO(4)···O(1) 0.83 (5), 1.82 (5), 2.648 (4), 177(5);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



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 ³¹P NMR as well as derivatization to the Pudovik products (OCH₂-CRR'CH₂O)P(O)CH(OH)Ar [R = R' = Me, Ar = 4-Cl-C₆H₄ (**5a**); R = R' = Et, Ar = Ph (**5b**); R = Me, R' = *n*-Pr, Ar = Ph (**5c**)].¹¹

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 adenylyl cyclase¹² 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.

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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., $(OCH_2CMe_2CH_2O)P(NH-cyc-C_6H_{11})$ (**6**)] could also be prevented. The main limitation, however, is that a phosphite bearing an aromatic diol residue like $(1,2-C_6H_4O_2)P(OPh)$ [**7**; $\delta(P)$ 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 1H (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 (1H , ^{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 (1H , ^{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.

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	<i>a</i>	K_2CO_3	no hydrolysis
3	<i>a</i>	Et_3N	~1% hydrolysis
4	<i>a</i>	$MgSO_4$	~2% hydrolysis
5	<i>a</i>	molecular sieves	~1% hydrolysis
6	<i>a</i>	KCl	complete hydrolysis
7	<i>a</i>	NaF	complete hydrolysis

^a Same as that for entry 1.

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.

4a. Yield: 2.04 g, 96%. 1H NMR: δ 0.69 (s, 6 H, CH_3), 2.43 (s, 6 H, $N(CH_3)_2$), 3.13 (s, 2 H, OCH_2), 3.40 (d, $^3J(HH) = 9.5$ Hz, 2 H, OCH_2), 6.57 (d, $^1J(PH) = 622.2$ Hz, 1 H, $P(O)H$). ^{13}C NMR: δ 21.4 (s, CH_3), 34.5 (s, $N(CH_3)_2$), 36.7 (d, $^3J(PC) = 3.9$ Hz, $C(CH_3)_2$), 67.0, 68.6 (d, $^2J(PC) = 4.0$ Hz, OCH_2). ^{31}P NMR: δ 4.6.

4b. Yield: 2.28 g, 95%. 1H NMR: δ 0.65 (t, $^3J(HH) = 7.4$ Hz, 6 H, CH_2CH_3), 1.05 (m, 4 H, CH_2CH_3), 2.47 (s, 6 H, $N(CH_3)_2$), 3.16 (s, 2 H, OCH_2), 3.45 (d, $^3J(PH) = 8.9$ Hz, 2 H, OCH_2), 6.58 (d, $^1J(PH) = 622.2$ Hz, 1 H, $P(O)H$). ^{13}C NMR: δ 6.8 (s, CH_2CH_3), 21.4 (s, CH_2CH_3), 34.5 (s, $N(CH_3)_2$), 41.5 (br s, CEt_2), 63.1, 65.0 (2 s, OCH_2). ^{31}P NMR: δ 4.8.

4c. Yield: 2.31 g, 96%. 1H NMR: δ 0.78 (s, 3 H, CH_3), 0.85 (t, $^3J(HH) = 6.9$ Hz, 3 H, $CH_2CH_2CH_3$), 1.17–1.23 (m, 4 H, $CH_2CH_2CH_3$), 2.56 (s, 6 H, $N(CH_3)_2$), 3.29 (AB qrt, $^2J(HH) \approx 8.5$ Hz, 2 H, $HOCH_2$), 3.58 (symmetrical m, 2 H, OCH_2), 6.73 (d, $^1J(PH) = 626.1$ Hz, 1H, $P(O)H$). ^{13}C NMR: δ 14.9 (s, CH_3), 16.2, 18.3 (2 s, $CH_2CH_2CH_3$), 34.5 (s, $N(CH_3)_2$), 36.3, 39.4 (s, $C(CH_3)(n-Pr)$), 65.8 (2s, OCH_2), 67.3 (d, $^2J(PC) = 3.5$ Hz, OCH_2). ^{31}P NMR: δ 5.2.

[DMAPH] $^+[(HOCH_2CMe_2CH_2O)P(H)(O)(O^-)]$ (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. 1H NMR ($CDCl_3$): δ 0.78 (s, 6 H, CH_3), 3.13 (s, 6 H, $N(CH_3)_2$), 3.25 (s, 2 H, OCH_2), 3.59 (d, $^3J(PH) = 11.1$ Hz, 2 H, OCH_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, CH_3), 37.1 (br s, $C(CH_3)_2$), 39.9 (s, $N(CH_3)_2$), 67.2, 68.5 (2 s, OCH_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 $K\alpha$ 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, $\alpha = 109.19(7)^\circ$, $\beta = 105.72(3)^\circ$, $\gamma = 99.38(4)^\circ$, $V = 781.4(6)$ Å³, $Z = 2$, $\rho = 1.234$ g cm⁻³, $\mu = 0.187$, $F_{000} = 312$, 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 vacuum. 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. ¹H NMR: δ 0.67, 0.76 (2 t, ³ J (HH) = 7.1 Hz for both, 6 H, CH₂CH₃), 1.05, 1.51 (2 qrt, ³ J (HH) = 7.1 Hz, 4 H, CH₂CH₃), 3.81–4.29 (m, 4 H, OCH₂), 5.04 (d, ² J (PH) = 12.3 Hz, 1 H, P–CH–OH), 5.36 (br. s, 1 H, P–CH–OH), 7.14–7.52 (m, 5 H, Ph–H). ¹³C NMR: δ 6.9, 7.1 (2 s, CH₂CH₃), 22.5, 22.6 (2 s, CH₂CH₃), 37.1 (d, ³ J (PC) \approx 5.5 Hz, C(CH₂CH₃)₂), 71.9 (d, ¹ J (PC) = 157.6 Hz, P–CH(OH)), 75.1, 75.8 (2 d, ² J (PC) = 6.9 Hz for both, OCH₂), 126.9, 127.0, 127.8, 128.1, 137.3 (all C(Ar)). ³¹P NMR: δ 14.3.

5c. Yield: 75%. Mp: 168–170 °C. ¹H NMR: δ 0.71 (s, 3 H, CH₃), 0.91 (t, ³ J (HH) = 7.0 Hz, 3 H, CH₂CH₂CH₃), 1.21–1.45 (m, 4 H, CH₂CH₂CH₃), 3.93–4.07 (m, 4 H, OCH₂), 4.35 (br s, 1 H, P–CH–OH), 5.12 (d, ² J (PH) =

11.8 Hz, 1 H, P–CH–OH), 7.26–7.49 (m, 5 H, Ph–H). ¹³C NMR: δ 14.4, 16.3, 17.7, 34.8 (d, ³ J (PC) \approx 5.5 Hz, C(Me)(*n*-Pr)), 36.1, 71.7 (d, ¹ J (PC) = 160.0 Hz, P–CH(OH)), 75.9, 76.0, 76.4, 126.8, 126.9, 128.0, 128.2, 136.5. ³¹P 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 [(HOCH₂CMe₂CH₂O)P(O)(H)(O⁻)] [H₃NC₆H₁₁]⁺.^{10,16} In the presence of added KF, most of the hydrolysis was inhibited and ³¹P NMR showed >95% of **6**; the slight hydrolysis perhaps occurred during transfer of the CDCl₃ solution to the NMR tube. Similarly, the compound (OCH₂CMe₂CH₂O)P(OCHMe₂) (**8**) did not hydrolyze to any significant extent in THF/H₂O/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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