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Toward a Stable Hydroxyphosphorane

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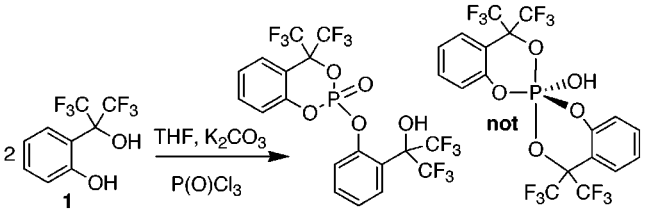
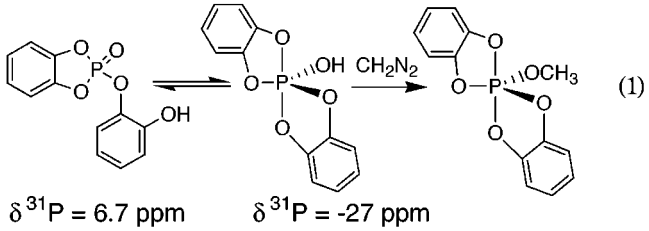
ABSTRACT



Hydroxy-pentaoxy-phosphoranes are transient intermediates formed during the hydrolysis of various phosphoesters. Kinetic analyses support the existence of such compounds, although they are not isolated. In an attempt to create a stable example, 2 equiv of a ligand possessing a very high effective molarity were attached to a central phosphorus. Instead of obtaining a hydroxyphosphorane, analysis by ^{31}P and ^{19}F NMR spectroscopy and X-ray crystallography showed the product to be a phosphotriester. The reason for this is discussed.

Phosphoranes are transient intermediates in the hydrolysis of phosphodi- and phosphotriesters. While the existence of these intermediates is beyond dispute, the nature of the protonation state and/or the lifetime of these compounds remains controversial.[1] Particularly, the stability of a dianionic phosphorane and the pK_a of its conjugate acid are fundamental to determining the role of various functional groups (metal ions, general acid/base catalysts) in the active site of an enzyme during RNA and DNA hydrolysis. While Granoth and Martin determined the pK_a of hydroxyphosphoranes derived from phosphinates,[2] direct measurement of the pK_a of a pentaoxyphosphorane has remained an elusive goal.[3] Ramirez studied the equilibrium between a hydroxyphosphorane and its phosphate triester analogue in acetonitrile-d_3 by NMR spectroscopy and verified the existence of the phosphorane by trapping it with diazomethane (eq 1).[4]



(1)

The choice of ligand is crucial to the stability of oxyphosphoranes.[5] In the case studied by Ramirez, catechol formed a five-membered ring with phosphorus. This study established that the solution concentration of the hydroxyphosphorane increased as the temperature decreased and as the relative solvent basicity increased.

To create a stable hydroxy-pentaoxy-phosphorane, we sought a ligand that would satisfy two criteria: (1) possess an internal nucleophile with a very high effective molarity (EM)[6] and (2) contain groups to minimize competition from S_N1 loss of phosphate.[7] Kirby recently used a high effective molarity structure to stabilize and thereby isolate a tetrahedral intermediate analogous to that formed in amide hydrolysis.[8]

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(1) Perreault, D. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 432−450 and references therein.

(2) Granoth, I.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 4618−4622.

(3) Kluger, R.; Covitz, F.; Dennis, E.; Williams, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1969**, *91*, 6066−6072. Branch, G. E. K.; Calvin, M. *The Theory of Organic Chemistry*; Prentice Hall: New York, 1941, pp 183−270. Guthrie, P. *J. Am. Chem. Soc.* **1977**, *99*, 3391−4001. Granoth, I.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *101*, 5229−5230.

(4) Ramirez, F.; Nowakowski, M.; Marecek, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 4515−4517.

(5) Ramirez, F.; Bigler, A. J.; Smith, C. P. *Tetrahedron* **1968**, *24*, 5041.

(6) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(7) Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 4588.

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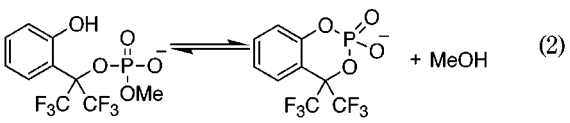
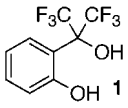
In a similar vein, ligand **1** potentially satisfies our design criteria and was prepared by Dalby and Kirby to study the hydrolysis of phosphate diesters.[9] In their study an EM ≥ 10^{10} mol L^{-1} for **1** was estimated from its rate of cyclization when appended to a phosphate diester (eq 2).[9] In addition,

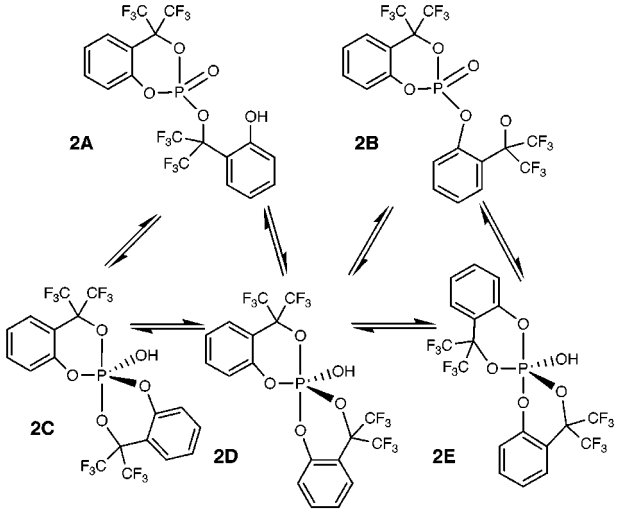


(2)

the two CF_3 groups were included to minimize S_N1 loss of phosphate. Therefore, we set out to determine if **1** would form a stable phosphorane at ambient temperature via preparation of the group of geometrical isomers referred to here as **2** (Scheme 1).



Scheme 1



Synthesis of a phosphorane based upon **1** was envisioned to be achieved through several possible routes. If ligand **1** meets the two design criteria, we envisioned direct access through reaction with $P(O)Cl_3$. In THF with K_2CO_3 as the base, a complex mixture of quartets was observed in the ^{19}F NMR of the crude product from reaction of **1** with $P(O)Cl_3$, and four singlets in the ^{31}P NMR were observed ranging from 4 to −23 ppm. When subjected to Kugelrohr distillation at 135 °C and 1 Torr, a single product was isolated. In the ^{19}F NMR spectrum of the distillate ($CDCl_3$), four quartets were observed with equal integrals (δ −74.08, −77.04 (J = 9.2 Hz); −74.75, −75.08 (J = 8.8 Hz)), while in the ^{31}P NMR spectrum only a singlet at −23 ppm was found. These spectra could either be interpreted as **2A**, **2B**, or **2D** (Scheme 1), since **2C** and **2E** possess C_2-symmetry and therefore should only give two quartets in the ^{19}F NMR spectrum.

Although the ^{31}P NMR chemical shift is similar to that reported by Ramirez for his phosphorane, this is not a completely reliable criterion on which to assign a characterization. Therefore, the solid-state structure was determined by X-ray crystallography. As shown in Figure 1, the product

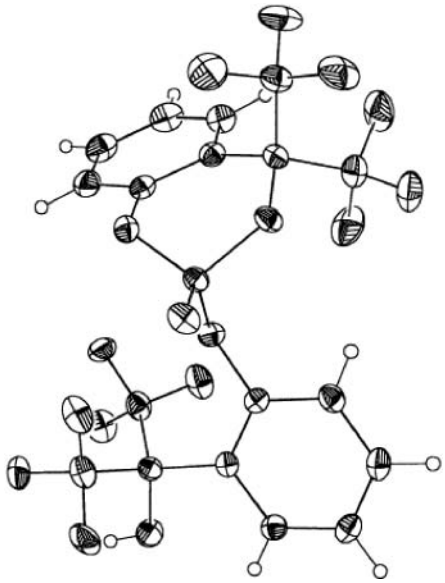


Figure 1. Solid-state structure of **2B**. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms are drawn to an arbitrary size. The minor occupancy F atoms were omitted for clarity.

is phosphotriester **2B**. Apparently the high effective molarity of **1** is not sufficient to create a stable phosphorane. Hence, we next set out to discover conditions that would shift the equilibria given in Scheme 1 toward the phosphoranes.

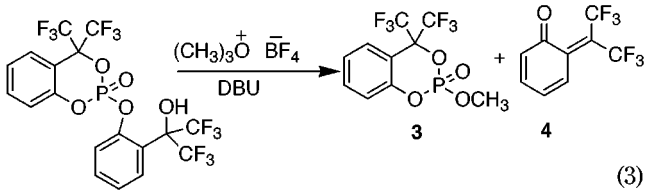
Although Ramirez found a larger population of phosphoranes in more polar and basic solvents and at low temperature, for our study of **2** in CD_3CN, ^{31}P NMR revealed little change in the resonance at 223 or at 300 K. However, in $CDCl_3$ at 223 K the singlet at −23 ppm resolved into two broad peaks (δ −22 and −24 ppm). Since Ramirez found a 34 ppm difference between phosphotriester and phosphorane, we interpret this small separation to be indicative of a dynamic conformational process within **2B** alone. We then attempted to trap the hypothetical phosphoranes.

When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added to **2B** in $CDCl_3$, the ^{31}P NMR chemical shift moved downfield 10 ppm. Addition of Meirwein's salt $(CH_3)_3O^+BF_4^-$) to this solution resulted in a compound whose ^{31}P resonance was a quartet at −15 ppm with J_{PH} = 12 Hz. In the ^{19}F NMR four quartets in the starting material changed to two new quartets (δ = 74.19 and 76.70; J = 9.6 Hz).

(8) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Am. Chem. Soc.* **1998**, *120*, 7101−7102. Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522−529.

(9) Dalby, K. N.; Kirby, A. J.; Hollfelder, F. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1269.

These data suggested the formation of phosphate triester **3** and an elimination product **4** (eq 3). An authentic sample of

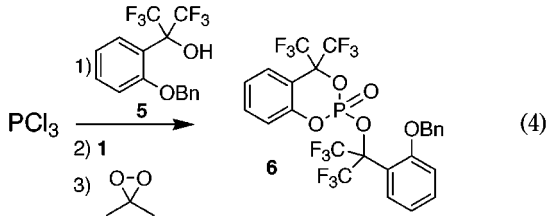


(3)

phosphate triester **3** was prepared from methyl dichlorophosphate, and its NMR spectrum was identical to the compound resulting from the addition of DBU and Meirwein's salt.

Furthermore, on a preparative scale reaction, after allowing **1** and $P(O)Cl_3$ in MeCN to stir with K_2CO_3 as the base at −78 °C, followed by addition of Meirwein's salt, a bright yellow color was observed when the reaction temperature rose above 0 °C, and phosphate triester **3** was isolated as the product. A HRMS of the product mixture confirmed the presence of quinone methide **4** as the elimination product created in the formation of **3**. Although the newly added methyl group is on the phosphoryl oxygen, this does not necessarily indicate that $(CH_3)_3O^+$ underwent a reaction with a phosphorane, since alkylation of the P═O bond of **2B** could lead to **3** and **4**. Therefore, these results again provided no direct evidence for the presence of a phosphorane.

Last, we analyzed a synthetic procedure that would initially form **2A** as a means to check whether **2B** was a thermodynamic sink. Reaction of PCl_3 with **5** and then **1**, followed by oxidation with dimethyldioxirane,[10] resulted in compound **6** (eq 4). The benzyl group could be easily removed in THF at room temperature and 1 atm H_2 with Pd/C in 10 min.



(4)

Analysis of **6** by ^{31}P NMR spectroscopy after deprotection revealed two resonances. The minor one corresponded to **2B**, while the second ($\delta = -26$ ppm) was assigned to **2A**. However, over several days **2A** completely isomerized to **2B**. This isomerization most likely proceeds via the phosphoranes shown in Scheme 1.

One is left wondering why the high effective molarity of **1** did not give a stable phosphorane, let alone why catechol (eq 1) is even more effective than **1** in stabilizing a phosphorane structure. The EM of $\geq 10^{10}$ mol L^{-1} was for the kinetics of a displacement reaction at a phosphorus center (≥14 kcal/mol in rate enhancement, eq 2).[9] Although EM values generally correlate between the kinetics and thermodynamics of reactions, we find here a case where the "kinetic" EM does not impart sufficient thermodynamic stability to increase the concentration of a high energy intermediate enough for its observation or isolation. This is in contrast to catechol, which undoubtedly has a much lower kinetic EM but imparts enough thermodynamic stability to allow observation of the phosphorane at low temperature. The displacement in eq 2 does not involve the intermediacy of a phosphorane but instead a "phosphorane-like" transition state and has entropy assisting the displacement. We postulate that the reason ligand **1** does not act similarly in our study compared to the Ramirez study is the fact that a six-membered ring exists in **2A** and **2B** and a second is formed in phosphoranes **2C**−**2E**. In contrast, five-membered rings are involved when catechol is the ligand. The angle strain in phosphoester five-membered rings is partially relieved in the phosphorane structures.[4,11] We believe that this relief of strain stabilizes the phosphorane depicted in eq 1, whereas there is little difference in strain between the triesters and phosphoranes depicted in Scheme 1. Therefore their relative energies are not significantly perturbed from that of standard triesters and phosphoranes.

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Supporting Information Available: X-ray crystallographic data including experimental parameters and unit cell packing diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016941D

(10) Chappell, M. D.; Halcomb, R. L. *Tetrahedron Lett.* **1999**, *40*, 1.

(11) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. Kluger, R.; Taylor, S. D. *J. Am. Chem. Soc.* **1990**, *112*, 6669. For a solvation viewpoint, see: Dejeagere, A.; Karplus, M. *J. Am. Chem. Soc.* **1993**, *115*, 5316.