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α-Monodeuterated Benzyl Alcohols and Phosphobetaines from Reactions of Aromatic Aldehydes with a Water/D_2O-Soluble Phosphine

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With the aim of learning more about the bleaching action of pulps by (hydroxymethyl)phosphines, we reacted several benzaldehydes, containing MeO, Me, OH, or halogen substituents, with tris(3-hydroxypropyl)phosphine, $[HO(CH_2)_3]_3P$, in aqueous solution at 90 °C under argon. Effective reduction of the aldehydes to the corresponding benzyl alcohols with concomitant oxidation of the phosphine to the phosphine oxide takes place, the reaction proceeding via an initially formed phosphonium species. When the reactions are carried out in D_2O, the benzyl alcohol product from 3,4-dimethoxybenzaldehyde contains one deuterium atom at the benzyl-carbon atom, consistent with the last step of the mechanism involving a carbanion intermediate. With syringaldehyde (3,5-dimethoxy-4-hydroxy-benzaldehyde), the reduction product (syringyl alcohol) is more reactive toward the phosphine than is the starting aldehyde, and a zwitterionic, phosphobetaine product is formed. In D_2O, the zwitterion benzyl protons and protons of the hydroxypropyl-CH_2 adjacent to the P atom undergo H/D exchange via presumed phosphorus ylide intermediates. Under the same aqueous reaction conditions, tris(3-hydroxypropyl)phosphine, $[HO(CH_2)_3]_3P$ (THPP), does not undergo redox reactions with aliphatic aldehydes but simply promotes a base-catalyzed self-condensation (aldol) reaction. THPP reduction of an aromatic ketone is sluggish, presumably because the carbonyl C-atom is less electrophilic than that present in an aromatic aldehyde.

Introduction

Investigations by our group into aqueous, transition metal-catalyzed hydrogenation of wood lignin and lignin model compounds revealed recently that water-soluble phosphines, particularly, tris(hydroxymethyl)phosphine, $(HOCH_2)_3P$ (abbreviated THP), are themselves excellent bleaching agents for pulps.[1,2] Thus, an understanding of the bleaching mechanism is essential to optimize the bleaching process, which must involve loss of conjugation by interactions of the phosphines with lignin chromophores. Lignin is conventionally described as a complex hydrophobic network of phenylpropanoid units derived mostly from oxidative polymerization of one or more of three types of hydroxycinnamyl alcohol precursors; these are derived by deamination of phenylalanine, followed by hydroxylation of the aromatic ring, methylation, and reduction of terminal acidic groups to aldehyde and then alcohol functionalities.[3] Esters of cinnamic acids, aromatic aldehydes, and quinones are also incorporated into the lignification process.[4]

This paper describes the interaction of aromatic aldehydes in aqueous media mainly with tris(3-hydroxypropyl)phosphine, $[HO(CH_2)_3]_3P$ (THPP); this phosphine is also a bleaching agent for pulps[2] and gives cleaner reactions with

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model compounds than does THP which is prone to loss of formaldehyde.[5] There is substantial literature describing the reactivity of phosphines (and phosphites) toward carbonyl-containing organics. For example, phosphine (PH_3) in the presence of aqueous solutions of a strong acid reacts with aliphatic aldehydes to give quaternary phosphonium salts (eq 1);[6] PH_3 reacts with ketones and aromatic aldehydes with a transfer of the carbon-oxygen to the phosphorus (eqs 2,3);[7] primary and secondary phosphines react with aldehydes to generate tertiary phosphines containing OH-groups in the α-position (eq 4);[8] in the presence of a suitable HX reagent, tertiary phosphines react with aldehydes to give phosphonium salts (eq 5);[9] the secondary phosphine oxides, $R_2P(O)H$, react with aromatic aldehydes to give the tertiary phosphines oxides, $R_2P(O)CH(OH)Ar$ (eq 6);[10] and trimethylphosphite reacts with aliphatic aldehydes to give a cyclic phosphorane intermediate that undergoes rapid hydrolysis to dimethyl-1-hydroxyalkylphosphonates (eq 7).[11]

$$4RCHO + PH_3 + HX \rightarrow [RCH(OH)]_4P^+X^- \quad (1)$$

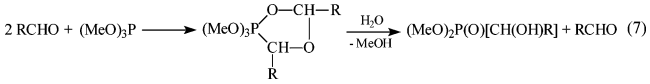
$$3PhCHO + PH_3 \rightarrow [PhCH(OH)]_3P \rightarrow [PhCH(OH)]_2P(O)CH_2Ph \quad (2)$$

$$R'R''C{=}O + PH_3 \rightarrow R'R''CH{-}P(O)(H)_2 \quad (3)$$

$$R'CHO + R''_2PH \rightarrow R''_2P[CH(OH)R'] \quad (4)$$

$$RCHO + PR'_3 + HX \rightarrow R'_3[RCH(OH)]P^+X^- \quad (5)$$

$$ArCHO + R_2P(O)H \rightarrow R_2P(O)[CH(OH)Ar] \quad (6)$$



(7)

Herein, we describe a new redox reaction where an aromatic aldehyde is reduced to the alcohol by the phosphine THPP, which is concomitantly oxidized to the phosphine oxide; the reaction is related to that shown in eq 2, which exemplifies a corresponding intramolecular redox process. The novel chemistry arises because the reactions are carried out in water where OH^- plays a key role. When the aldehyde substrate contains a *p*-OH substituent, the alcohol product undergoes further reaction with the phosphine to generate a zwitterionic phosphobetaine, whose benzyl and CH_2 protons, on C atoms α to the P atom, can undergo H/D exchange in D_2O.

Experimental Section

General. Distilled water and D_2O were stirred for 3 h under Ar; organic solvents were dried over the appropriate agents, and then distilled under N_2. $CDCl_3$ and CD_3OD (Cambridge Isotope Laboratories) were used as received. NMR spectra were recorded at room temperature (~300 K) generally on a Bruker AV300 (300 MHz for ^1H, 121 MHz for $^{31}P\{^1H\}$, and 75 MHz for $^{13}C\{^1H\}$) and, when specified, on a Bruker AV400 spectrometer (400 MHz for ^1H, 61 MHz for ^2D). A residual deuterated solvent proton (relative to external $SiMe_4$) or external 85% aq H_3PO_4 was used as a reference: br = broad, s = singlet, d = doublet, t = triplet, and m = multiplet. *J* values are given in hertz. Elemental analyses were performed by Mr. M. Lakha of the Chemistry department using a Carlo Erba 1108 analyzer. Mass spectrometry was performed on a Bruker Esquire electrospray (ESI) ion-trap instrument using samples dissolved in water or MeOH, with positive-ion polarity, scanning from 60 to 800 *m*/*z*. Gas chromatography was performed on a Hewlett-Packard GC 5890 instrument fitted with an FID detector and two capillary columns (HP OV17), using He as the carrier gas.

The aldehydes and 3,4-dimethoxyacetophenone (all from Aldrich), 3,5-dimethoxy-4-hydroxy-benzyl alcohol (syringyl alcohol, 90%, Lancaster), tris(3-hydroxypropyl)phosphine (THPP, an oil, >80%, Strem Chemicals), and Et_3P (Strem Chemicals) were all used as purchased. THP[12] and $Na[Ph_2(m\text{-}SO_3C_6H_4)P]$[13] were prepared according to the literature. THPP hydrochloride, $[(HOCH_2CH_2CH_2)_3PH]^+Cl^-$, was prepared as an oil by addition of a 37% aq HCl solution (Fisher) to an aqueous solution of THPP (1:1), followed by evaporation of solvent. $^{31}P\{^1H\}$ NMR (D_2O): δ 17.0 ($t, {}^1J_{PD} = 75$). ^1H NMR (D_2O): δ 3.71 ($t, {}^3J_{HH} = 6$, 6H), 2.50−2.33 (m, 6H), 2.01−1.84 (m, 6H).

Purification of the commercial THPP is difficult. A $^{31}P\{^1H\}$ NMR spectrum of a D_2O solution of the phosphine revealed that the impurities (~15%, as judged by peak integrations) were almost certainly two other "closely related" phosphines because (i) their δ_P resonances (singlets at δ −21.4 and −34.5) were close to that of THPP (δ −29.3, see Figure 1A) and because (ii) they react with aldehydes in the same manner as THPP and are converted to phosphine oxides as judged by their δ_P resonances (singlets at δ 60.6 and 63.0), which are in the same region as the resonance for THPPO (δ_P 61.3, see Figure 1C). A patent report on THPP synthesis suggests that the impurities are "telomers of THPP",[14a] while Strem Chemcials have informed us that the major impurity is the THPP isomer $[HO(CH_2)_3]_2P[CH(CH_3)CH_2OH]$.[14b]

Synthetic Scale Redox Reactions of THPP with 3,4-Dimethoxybenzaldehyde (Veratraldehyde, 1) and Related Aldehydes.

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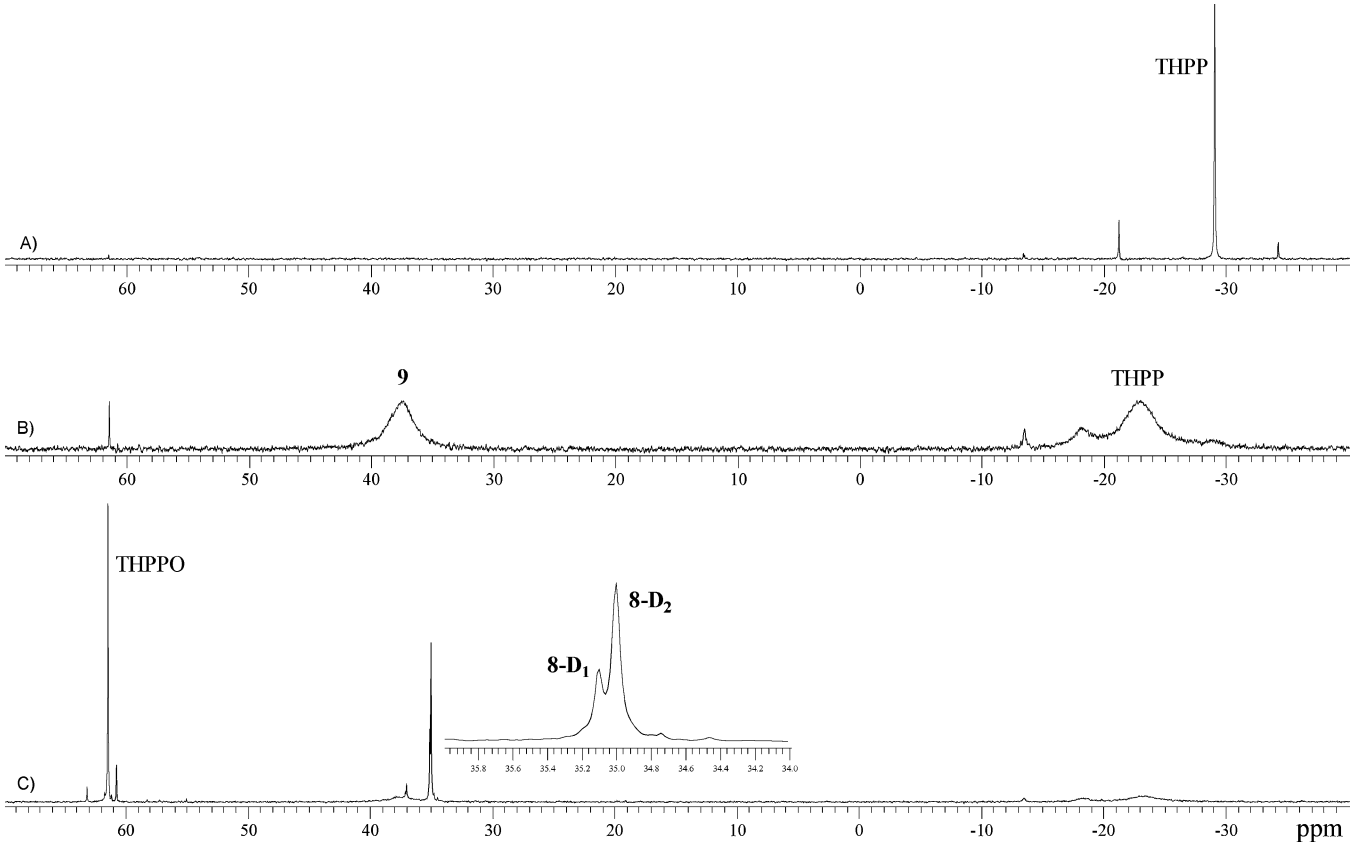

Figure 1. $^{31}P\{^1H\}$ spectrum of (A) THPP in D_2O (unremovable phosphine impurities are seen as singlets at δ −21.4 and −34.5, see text), (B) the initial reaction 1:1 mixture of THPP and syringaldehyde (**7**) in D_2O (the broad signals at δ values of about −18 and −29 result from the impurities present in the THPP, see text and Figure 1A), and (C) the mixture present after 1 day of reaction at 90 °C (the singlets at δ 60.6 and 63.0 are the phosphine oxides formed in the redox reaction of the phosphine impurities with **7**).

Compound **1** (100 mg, 0.60 mmol) was added under Ar to a deoxygenated, aqueous solution (3.5 mL) of THPP (163 mg, 0.78 mmol assuming 100% purity, but see above), and the homogeneous mixture was stirred for 72 h at 90 °C. The product mixture was then extracted with Et_2O (4 × 4 mL), and the ether layers were dried overnight over Na_2SO_4. The veratryl alcohol product (**2**) was separated by column chromatography (silica gel, 230−400 mesh) using a 3:1 Et_2O/petroleum ether mixture as eluant; after removal of solvent under vacuum, **2** was isolated as a colorless liquid (87 mg, 86% yield based on aldehyde). ^1H NMR ($CDCl_3$): δ 6.94−6.80 (m, 3H, C_6H_3), 4.61 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.70 (br s, 1H, O*H*). Removal of water from the aqueous layer yielded a syruplike residue of tris(3-hydroxypropyl)-phosphine oxide (THPPO). $^{31}P\{^1H\}$ NMR (D_2O): δ 61.3 s, which agrees with the literature data.[14] ^1H NMR (D_2O): δ 3.64 (t,$^3J_{HH}$ = 6, 6H, CH_2OH), 1.96−1.70 (m, 12H, PCH_2CH_2). The corresponding reaction of **1** with THPP in D_2O generated veratryl alcohol **2-D$_1$**, monodeuterated in the benzyl position. ^2D NMR ($CHCl_3$, 400 MHz): δ 4.61 (d,$^2J_{HD}$ = 1.8). $^2D\{^1H\}$ NMR: δ 4.61 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.96−6.83 (m, 3H, C_6H_3), 4.61 (t,$^2J_{HD}$ = 1.8, 1H, C*H*D), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

The suggested pathways for formation of **2**/**2-D$_1$** via intermediates **3**−**5** are presented in the Results and Discussion section.

A similar procedure (at corresponding concentrations in water at 90 °C) was used in the redox reaction of THPP with other aromatic aldehydes to give the corresponding alcohol product. Some of the reactions took place in a homogeneous, one-phase solution, but others were seen to involve two-phases (solid/liquid or liquid/liquid); the solubilities of the various organic substrates were not studied quantitatively (see Results and Discussion). The alcohol products and their ^1H NMR data are listed in Supporting Information.

A similar procedure (at corresponding concentrations) was also used in the reaction of THPP with 3-phenyl-propanal; the first intermediate formed was the aldol condensation product that was subsequently dehydrated to give *5-phenyl-2-(benzyl)-2-pentenal* (44 mg, 59%). ^1H NMR: δ 9.45 (s, 1H, C*H*O), 7.34−7.08 (m, 10H, C_6H_5), 6.62 (t,$^3J_{HH}$ = 7, 1H, C=C−*H*), 3.59 (s, 2H, $PhCH_2C{=}C$), 2.81−2.68 (m, 4H, $PhCH_2CH_2$).[15]

A similar procedure was used in the reaction of THPP with 3,4-dimethoxyacetophenone, which was minimally reduced to α-*methylveratryl alcohol* (3 mg, 3%). ^1H NMR: δ 6.96−6.78 (m, 3H, C_6H_3), 4.84 (q,$^3J_{HH}$ = 6, 1H, C*H*), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.47 (d,$^3J_{HH}$ = 6, 3H, CH_3). Approximately 95% unreacted ketone was isolated.

No reactions of veratraldehyde (**1**) were observed with $(HOCH_2)_3P$, Et_3P, or $Na[Ph_2(m\text{-}SO_3C_6H_4)P]$ in the aqueous conditions at 90 °C.

NMR Investigation of the Reaction of THPP with 1. THPP (30 mg, 0.144 mmol) and **1** (23.9 mg, 0.144 mmol) were dissolved in deoxygenated D_2O (1.75 mL), and the mixture was stirred at room temperature for 1 h to completely dissolve the aldehyde. A sample (~0.6 mL) was then placed into a J-Young NMR tube and heated to 90 °C. NMR spectra were subsequently recorded periodically at room temperature. ^1H NMR for THPP: δ 3.60 (t,$^3J_{HH}$ = 6, 6H, CH_2OH), 1.70−1.55 (m, 6H, PCH_2CH_2), 1.51−1.42 (m, 6H, PCH_2CH_2). For **1**: δ 9.52 (s, C*H*O), 7.40 (dd,$^3J_{HH}$ = 8,$^4J_{HH}$ =

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2, 1H, *o-H*), 7.16 (d,$^4J_{HH}$ = 2, 1H, *o-H*), 6.96 (d,$^3J_{HH}$ = 8, 1H, *m-H*), 3.84 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). The ^{31}P{^{1}H} spectrum revealed a broad singlet for THPP at δ −28.5. During the reaction, the NMR signals of **1** and THPP decreased in intensity, while those of THPPO, and the ^{1}H signals of veratryl alcohol **2-D$_1$** [δ 6.99−6.92 (m, 3H, C$_6H_3$), 4.51 (br s, 1H, C*H*D), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3)] became visible and intensified with time.

Reaction of THPP Hydrochloride with 1. The reaction was investigated in D_2O by NMR spectroscopy as above, but using THPP hydrochloride (20 mg, 0.082 mmol) and **1** (13.6 mg, 0.082 mmol). After the mixture had been stirred at room temperature for 1 h, the ^{31}P{^{1}H} spectrum revealed THPP deuterochloride at δ 17.0 (t,$^1J_{PD}$ = 75) and another phosphonium salt (**6**) at δ 37.9 (s) (see eq 8). The ^{1}H spectrum showed resonances of THPP·DCl, **1**, and **6**. [For **6**: 7.18−7.09 (m, 3H, C$_6H_3$), 5.84 (d,$^2J_{PH}$ = 4, 1H, PC*H*), 3.91 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.66 (t,$^3J_{HH}$ = 6, 6H, CH_2OH), 2.37−2.23 (m, 6H, PCH_2), 1.85−1.70 (m, 6H, PCH$_2$CH_2).] No significant changes were observed in the NMR spectra after heating the solution at 90 °C for 24 h. The solvent was then removed, and the residue was submitted for low-resolution ESI MS (MeOH): the cation of the phosphonium salt **6** [*m*/*z* 375.3 (100%, [M]$^+$), calcd 375.4] and the protonated form of THPP [*m*/*z* 209.2 (30% [M + H]$^+$), calcd 209.2], were detected.

Reaction of THPP with 3,5-Dimethoxy-4-hydroxy-benzaldehyde (Syringaldehyde, 7). The synthetic procedure used was similar to that used for the reaction of THPP with **1** in H_2O, but using 110 mg (0.60 mmol) of **7**. After 72 h at 90 °C, extraction of the reaction mixture with Et_2O, followed by drying over Na_2SO_4, yielded some starting aldehyde (10 mg, 9%). From the aqueous layer, a yellow syrupy residue (∼ 250 mg) was obtained, which in D_2O gave a ^{31}P{^{1}H} spectrum showing two equal intensity singlets at δ 61.3 (THPPO) and 34.9 (assigned to the zwitterion **8**, see Scheme 3). The ^{1}H NMR spectrum in D_2O for **8** showed δ 6.50 (d,$^4J_{PH}$ = 2, 2H, C$_6H_2$), 3.79 (s, 6H, OCH_3), 3.65 (t,$^3J_{HH}$ = 6, 6H, CH_2OH, overlapping with the corresponding signal of THPPO), 3.54 (d,$^2J_{PH}$ = 14, 2H, PCH_2Ar), 2.27−2.12 (m, 6H, PCH_2CH$_2$), 1.82−1.66 (m, PCH$_2$CH_2, overlapping with the corresponding signal of THPPO). Reactant aldehyde **7** was also detected in the ^{1}H spectrum (**7**/**8** = 2:3). Low-resolution ESI MS (H_2O) of the residue: *m*/*z* 375.2 [**8** + H]$^+$, calcd 375.4. Further characterization data for **8** (when prepared from syringyl alcohol) are given below.

NMR Investigations of the Reaction of THPP with 7. The procedure follows that given above for the NMR study of the THPP reaction with **1** in D_2O, but using 30 mg of THPP and 26.3 mg of **7**, with ^{1}H and ^{31}P{^{1}H} spectra being recorded periodically at room temperature (see Results and Discussion). After 3 days, the solvent was removed, and the residue was submitted for low-resolution ESI MS (MeOH, *m*/*z* 377.5 [**8-D$_2$** + H]$^+$, calcd 377.4).

Reaction of THPP with Syringyl Alcohol (10) to Give 8. Syringyl alcohol (90%), (98 mg, 0.48 mmol) was added under Ar to a solution of THPP (100 mg, 0.48 mmol) in deoxygenated H_2O (3 mL), and the solution was heated at 90 °C for 16 h with stirring. After removal of the water, the resulting greenish "semisolid" residue of **8** was washed with dry THF and dried overnight under vacuum. Yield: 140 mg, 80%. The ^{31}P{^{1}H} and ^{1}H NMR data and the ESI MS data were the same as given above. ^{13}C{^{1}H} NMR (D_2O): δ 151.1 (d,$^4J_{PC}$ = 3, *m-C*), 146.0 (d,$^5J_{PC}$ = 3, *p-C*), 110.1 (d,$^2J_{PC}$ = 9, C_{ipso}-CH$_2$), 108.6 (d,$^3J_{PC}$ = 5, *o-C*), 61.0 (d,$^3J_{PC}$ = 17, *C*H$_2$OH), 56.6 (s, OCH_3), 25.6 (d,$^1J_{PC}$ = 45, P*C*H$_2$Ar), 23.5 (d,$^2J_{PC}$ = 4, PCH$_2$*C*H$_2$), 14.8 (d,$^1J_{PC}$ = 49, P*C*H$_2$CH$_2$). Anal. Calcd for $C_{18}H_{31}O_6P$: C, 57.74; H, 8.35. Found: C, 57.18; H, 7.62. Attempts to further purify the compound by recrystallization were unsuccessful. Repeating this synthesis in D_2O provided a sample of **8-D$_2$**. ^{2}D NMR (400 MHz, H_2O): δ 3.5 (br s, C_{ipso}−CD_2).

Table 1. Reaction of Aromatic Aldehydes (ArCHO) with THPP[a]

entry	Ar	alcohol yield (%)[b]
1	3,4-(MeO)$_2$C$_6$H$_3$ (**1**)	86
2	Ph	89[c]
3	3-HOC$_6$H$_4$	82
4	2-MeOC$_6$H$_4$	86
5	3-MeOC$_6$H$_4$	81
6	4-MeOC$_6$H$_4$	82
7	2,4,6-(MeO)$_3$C$_6$H$_2$	50
8	4-IC$_6$H$_4$	77
9	4-BrC$_6$H$_4$	83
10	4-ClC$_6$H$_4$	85
11	4-FC$_6$H$_4$	64
12	2,6-Cl$_2$C$_6$H$_3$	85
13	2-MeC$_6$H$_4$	83
14	4-MeC$_6$H$_4$	75
15	3,5-Me$_2$C$_6$H$_3$	65
16	2,4,6-Me$_3$C$_6$H$_2$	10[d]

[a] Reactions performed in water at 90 °C for 72 h, under argon; [aldehyde]/[THPP] = 1:1.3. [b] Isolated yield, unless otherwise stated. [c] Benzyl alcohol yield determined by GC. [d] NMR yield.

Results and Discussion

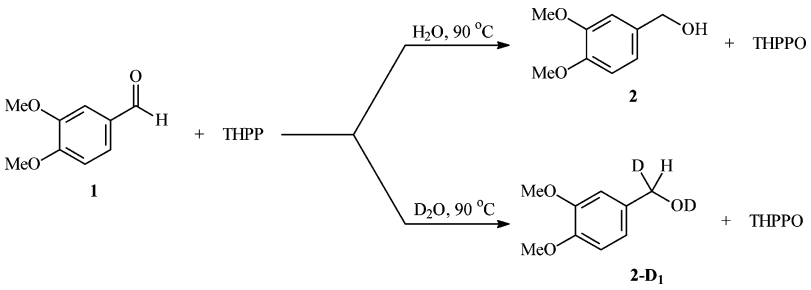
Veratraldehyde (**1**) was considered a simple lignin model compound of good water-solubility, and its reaction with tris-(3-hydroxypropyl)phosphine (THPP) was studied initially. The reaction was not studied in air because of aerial oxidation of THPP to the oxide; under Ar, there is no reaction between **1** and THPP at about a 1:1 ratio in water at room temperature, but after 72 h at 90 °C, veratryl alcohol (**2**) was obtained in an 86% yield (Table 1, entry 1), together with the phosphine oxide, O=P(CH$_2$CH$_2$CH$_2$OH)$_3$ (THPPO), as shown in Scheme 1 (both THPP and **1** are themselves completely stable under the reaction conditions). When the same reaction was carried out in D_2O, veratryl alcohol **2-D$_1$**, monodeuterated in the benzyl position, was formed (Scheme 1). When the reaction in D_2O is monitored by NMR spectroscopy, the THPP is seen as a broad ^{31}P{^{1}H} singlet at δ −28.5, and this is gradually replaced by the sharp singlet at δ 61.3 of THPPO; of note is that THPP itself gives a sharp singlet at δ −29.3. The ^{1}H spectra similarly show disappearance of the signals of THPP and **1**, and generation of THPPO, whose signals are slightly downfield-shifted of those of THPP. The one benzyl proton of **2-D$_1$** is seen as a broad singlet at δ 4.49; the $^2J_{HD}$ coupling (typically ∼1 Hz)[16] was not resolved on the 300 MHz instrument. The ^{2}D and ^{2}D{^{1}H} spectra in $CHCl_3$, and the ^{1}H NMR spectra of **2-D$_1$** in $CDCl_3$, measured on the Bruker 400 MHz, confirm the incorporation of the single deuterium atom, and a measured $^2J_{HD}$ value of 1.8 Hz.

One reasonable mechanism for the reaction, based on that suggested for decomposition of quaternary phosphonium hydroxides,[17] is shown in Scheme 2. Nucleophilic attack of

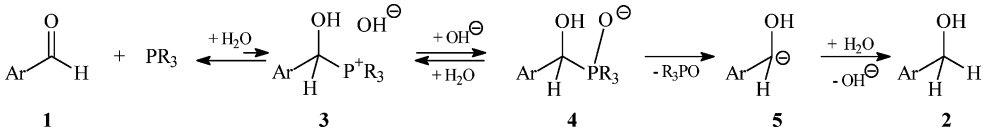
(16) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Weinheim, Germany, 1998; Chapter 3.

(17) (a) McEwen, W. E.; Axelrad, G.; Zanger, M.; VanderWerf. C. A. *J. Am. Chem. Soc.* **1965**, *87*, 3948 and references therein. (b) Hays, H. R.; Laughlin, R. G. *J. Org. Chem.* **1967**, *32*, 1060 and references therein. (c) Pagilagan, R. U.; McEwen, W. E. *Chem. Commun*. **1966**, 652.

Scheme 1



Scheme 2 [a]

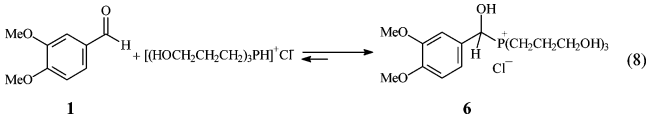


[a] Ar = 3,4-$(MeO)_2C_6H_3$, R= $(CH_2)_3OH$.

the phosphine-P atom on the carbonyl-C atom of **1** could first form the quaternary phosphonium salt **3** (cf. eq 5), which can subsequently react with OH^- to form a pentacovalent phosphorus anionic species (**4**); this then decomposes to the tertiary phosphine oxide and the carbanion (**5**), which rapidly adds a proton/deuteron from H_2O/D_2O to form the alcohol (**2** or **2-D$_1$**). Cleavage of the P−benzyl bond of **4** will be more favored than that of the phosphorus−propyl bond because of formation of the more stable benzyl carbanion. Another mechanism (favored by a reviewer) utilizes the acidity of the OH proton of the phosphonium species (**3** and **4**); loss of phosphine oxide accompanied by a concerted proton/deuteron shift would lead to the alcoholate anion and, subsequently, to **2** or **2-D$_1$**. Of note is that this redox process, when carried out in D_2O, provides a viable new method for synthesizing benzyl alcohols specifically containing one D-atom attached to the benzyl-carbon atom.

Unlike THPP, $(HOCH_2)_3P$ and $Ph_2(m\text{-}NaSO_3C_6H_4)P$ did not react at all with veratraldehyde under corresponding conditions. Presumably these water-soluble phosphines are weaker nucleophiles than THPP, as likely reflected by their $^{31}P\{^1H\}$ shifts in D_2O (δ −23.2 and −5.3, respectively, vs −29.3 for THPP). The more basic Et_3P was also unreactive, but this likely results from its low solubility in aqueous media.

Reaction of **1** with THPP hydrochloride, $[(HOCH_2CH_2CH_2)_3PH]^+Cl^-$, in a 1:1 ratio in D_2O under Ar at room temperature for 1 h, revealed, by NMR spectroscopy, an equilibrium established between the reactants and the phosphonium salt **6** (eq 8). A $^{31}P\{^1H\}$ singlet generated at δ 37.9 is assigned to **6**, the resonance being in the correct range for phosphonium compounds,[18] while the triplet centered at δ 17.0 is that of THPP deuterochloride ($^1J_{PD}$ = 75 Hz) that results from rapid H/D exchange. The ^1H spectrum implies a 3:1 ratio between **6** and the deuterochloride, the benzyl proton signal of **6** appearing as a doublet at δ 5.84 ($^2J_{PH}$ = 4 Hz). The equilibrium mixture was little changed after the solution was heated to 90 °C. The ESI mass spectrum of the residue in MeOH showed a major peak corresponding to the phosphonium ion of **6**, as well as a peak corresponding to protonated THPP (the deuterium of the deuterochloride had undergone D/H exchange with the methanol). Compound **6** contains the same cation as the postulated intermediate **3** in Scheme 2 and provides good evidence for such an intermediate; the conversion through to the phosphine oxide and alcohol clearly requires more basic conditions, and indeed **6** could be converted to **2** by addition of 1 equiv of NaOH. The formation of phosphonium salts by reaction of aldehydes with tertiary phosphines in the presence of acids is well-known (see eq 5).[9]

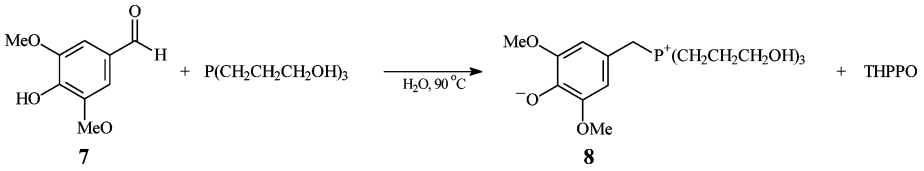


(8)

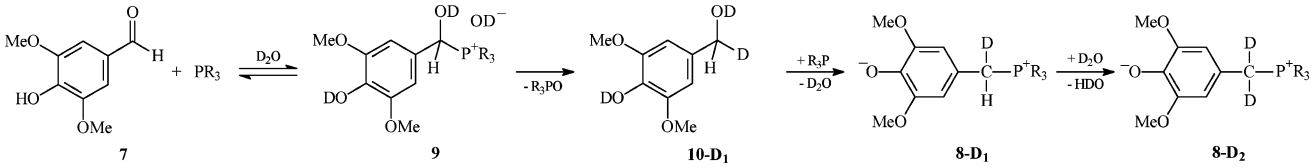
Other aromatic aldehydes also react with THPP under the same aqueous conditions (90 °C, 72 h, under Ar) used for the water-soluble veratraldehyde (**1**) and generate the corresponding alcohols and phosphine oxide (Table 1). The isolated alcohol yields are generally similar to that for **1** (entry 1) and lie in the 80−90% range. The partially soluble benzaldehyde, 3-hydroxybenzylaldehyde, and *o*-, *m*-, and *p*-methoxybenzaldehydes (entries 2−6) give alcohol yields of 81−89%, but the more bulky 2,4,6-trimethoxybenzaldehyde gives only a 50% yield (entry 7). Monomethyl-substituted aldehydes, which appear essentially insoluble, also showed high reactivity, 2-methylbenzyl alcohol and 4-methylbenzyl alcohol being isolated in 83 and 75% yields, respectively (entries 13 and 14), while 3,5-dimethylbenzaldehyde gave 65% yield (entry 15). Mesitylaldehyde showed the lowest conversion to the alcohol (10% yield, entry 16), while the partially soluble aldehydes containing *p*-halogen substituents showed reasonably high reactivities, that of the fluoro aldehyde being lowest at 64% (entries 8−11); 2,6-dichlorobenzaldehyde (entry 12) showed the same reactivity as 4-chlorobenzaldehyde. The electronic and steric effects of the substituents cannot be estimated even semiquantitatively because of the varying degree of heterogeneity in the

(18) Moiseev, D.; James, B. R.; Patrick, B. O.; Hu, T. Q. *Inorg. Chem.* **2006**, *45*, 2917.

Scheme 3



Scheme 4 [a]



[a] R = $(CH_2)_3OH$.

systems that results from varying aqueous solubilities of the aldehydes, some of which are solids and some are liquids. The alcohol products from entries 1−7 are liquids, while the alcohols from the other aldehyde substrates are solids; these also show variable solubilities, but these were always greater than those of their precursor aldehyde.

Of note is that an aromatic aldehyde that contained a *p*-OH group reacted quite differently with THPP; thus, the reaction of 3,5-dimethoxy-4-hydroxy-benzaldehyde (syringaldehyde, **7)** with THPP in a 1:1 ratio (H_2O, 90 °C, 72 h, Ar) did not give syringyl alcohol, at least as the final product. The $^{31}P\{^1H\}$ spectrum of the isolated, syruplike residue in D_2O revealed equal intensity resonances at δ 61.3, corresponding to THPPO, and at δ 34.9, assigned to a zwitterion, **8** (Scheme 3). The benzyl protons of **8** appear as a doublet in the ^1H spectrum at δ 3.54 ($^2J_{PH}$ = 14 Hz), which becomes a singlet in the $^1H\{^{31}P\}$ spectrum. The ESI mass spectrum of the residue dissolved in H_2O showed the main peak at *m*/*z* 375.2, which corresponds to the protonated (hydroxy) form of **8**. Further evidence for the structure of **8** is given below, where the reaction of syringyl alcohol with THPP and other basic phosphines is discussed. When the 1:1 reaction of **7** with THPP in D_2O at 90 °C was followed by NMR spectroscopy, the following features were evident. After the reactants were mixed, the normally sharp $^{31}P\{^1H\}$ resonance of THPP at δ −29.3 (Figure 1A) was seen as a broad downfield-shifted signal at δ −23.1 (Figure 1B). A new broad resonance of similar intensity was seen at δ 37.3, and this is thought to be from a phosphonium intermediate **9** formed during the reversible nucleophilic attack of THPP at the carbonyl-C atom of **7** (see Scheme 4); at the same time, the ^1H resonances of the aldehyde and aromatic protons of **7** appear as broad singlets at δ 9.26 and 6.92, respectively (Figure 2A), shifted upfield from those of just **7** in D_2O (δ 9.64 and 7.20, respectively). The cation of **9**, apparently stabilized by the presence of the *p*-OH/OD group, corresponds to that of **6** (eq 8) and that of **3** in the reaction of THPP with **1** (Scheme 2).

After ∼ 1h, formation of THPPO is seen in the $^{31}P\{^1H\}$ and ^1H NMR spectra, accompanied by loss of **9** and formation of monodeuterated syringyl alcohol **10-D$_1$**; the signal for the two aromatic protons of **10-D$_1$** appears as a sharp singlet at δ 6.66, and that of the single benzyl proton appears as a somewhat broadened singlet at δ 4.47, again because of nonresolution of the $^2J_{HD}$ coupling (Figure 2B). The mechanism suggested for the alcohol production (Scheme 4) corresponds to that of Schemes 1 and 2 for veratraldehyde reduction, where **2-D$_1$** is replaced by **10-D$_1$**. However, after ∼1 day of reaction, **10-D$_1$** shows conversion to **8**, which is first formed as the monodeuterated salt (**8-D$_1$**); this subsequently converts to the bisdeuterated (**8-D$_2$**) salt (Scheme 5). The phosphonium centers of **8-D$_1$** and **8-D$_2$** give rise to $^{31}P\{^1H\}$ singlets at δ_P 35.0 and 34.9, respectively (Figure 1C). The two aromatic protons of both **8-D$_1$** and **8-D$_2$** have the same ^1H NMR chemical shift, which appears as a doublet at δ 6.48 ($^4J_{PH}$ = 2 Hz) (Figure 2B and C). The doublet for the benzyl proton of **8-D$_1$**, expected at $\delta \sim 3.54$ (see above), was not seen, presumably being hidden under the signals of the CH_2 protons of the THPP moieties of **8-D$_1$** and **8-D$_2$**. After 2 days of reaction, the products are essentially THPPO and **8-D$_2$** in a 1:1 mixture, the ^1H resonances of the **10-D$_1$** alcohol almost having disappeared (Figure 2C). Moreover, the ^1H spectrum shows that 50% of the syringaldehyde remains unreacted. This is consistent with the syringyl alcohol **10-D$_1$** having reacted with THPP in a 1:1 ratio to form **8-D$_2$** (Scheme 4) in a somewhat faster reaction than that of the aldehyde, and this is confirmed in a separate study of this reaction (see below and Scheme 4). The mass spectrum, obtained by low-resolution ESI of an aqueous solution of the residue from the reaction of THPP with **7** in D_2O, shows the main peak at *m*/*z* 377.5, which corresponds to the protonated (hydroxy) form of **8-D$_2$**.

The reaction of THPP with syringyl alcohol was studied under the conditions used for the reaction with syringaldehyde (1:1, H_2O, 90 °C, Ar) to confirm the **10-D$_1$** → **8-D$_1$** step of the mechanism shown in Scheme 4. After 16 h, the water was removed, and a greenish solid was obtained. The low-resolution ESI MS of this product dissolved in H_2O showed a main peak at *m*/*z* 375.2, corresponding to the protonated form of **8**, and is the expected two units less than the value observed for the **8-D$_2$** species discussed above. The ^1H, $^{31}P\{^1H\}$, and $^1H\{^{31}P\}$ spectra of a D_2O solution of the residue showed essentially the same set of resonances attributed to **8** formed in the reaction of THPP with **7**. Compound **8** was further characterized by $^{13}C\{^1H\}$ NMR spectroscopy, where the benzyl carbon adjacent to the P-atom

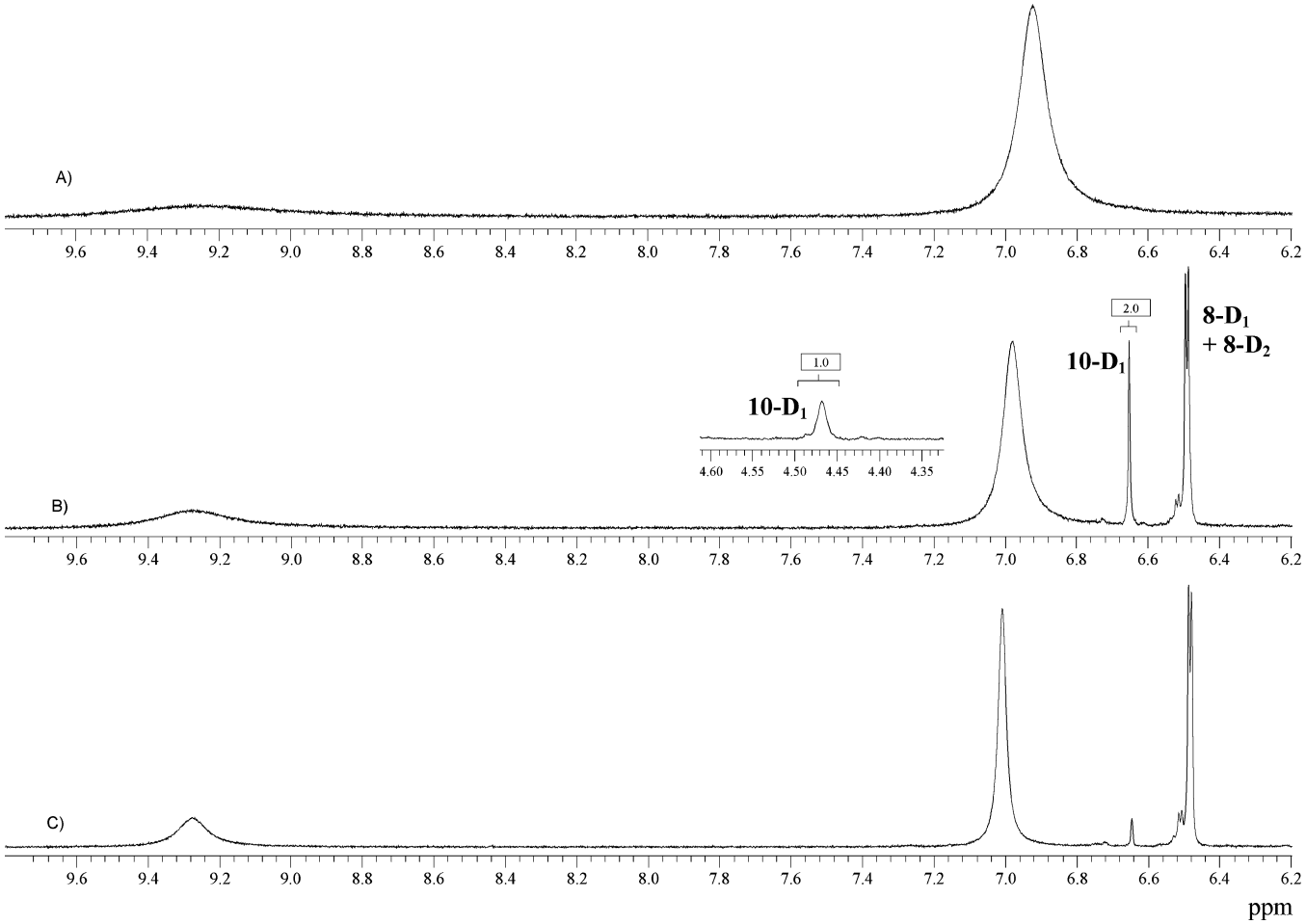
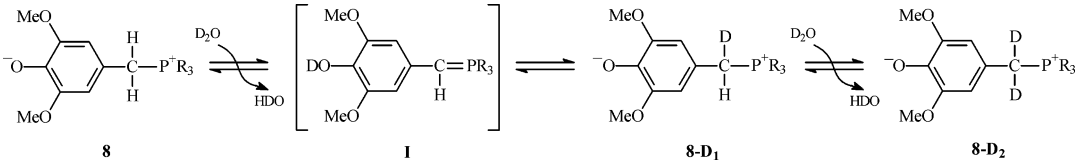


Figure 2. ^{1}H spectrum of the reaction of THPP with **7** (1:1, D_2O): (A) initial reaction mixture, (B) after 1 day of reaction at 90 °C, and (C) after 2 days of reaction at 90 °C. The low-intensity doublet pattern at $\delta \sim 6.5$ in Figure 2B and C is thought to correspond to the two aromatic protons of phosphobetaines akin to **8-D$_1$**/**8-D$_2$** but formed from the impurity phosphines present in the THPP (see Figure 1A−C).

Scheme 5 [a]



[a] R = $(CH_2)_3OH$.

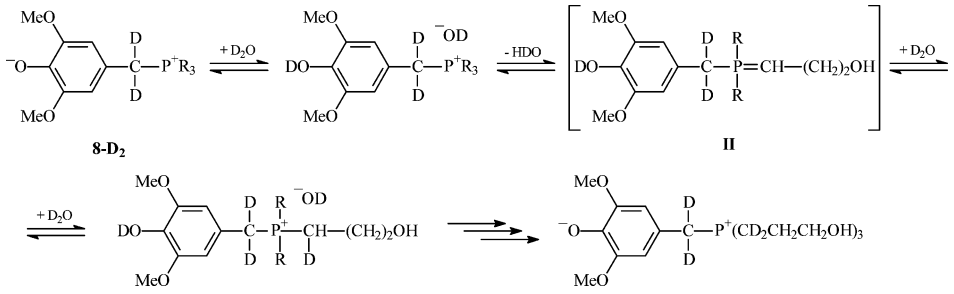
appears as a doublet at δ 25.6 ($^1J_{PC}$ = 45 Hz); indeed, one- to five-bond P−C coupling ($^1J_{PC}$ = 45 Hz to $^5J_{PC}$ = 3 Hz) is observed for all the C-atom resonances except for those of the OMe groups. The elemental analysis of the zwitterionic compound **8** was 0.56% low in carbon and 0.73% low in hydrogen: these discrepancies result from the presence of small amounts of what are believed to be closely related zwitterionic compounds formed by the impurities present in the THPP (see the Experimental Section and Figures 1 and 2). In other ongoing work on a wider range of reactions between basic phosphines (including THP and PEt_3) and hydroxyl-substituted aromatic alcohols, we have isolated a compound exactly analogous to **8** but containing a PEt_3 moiety rather than $[(CH_2)_3OH)]_3P$. This PEt_3-generated phosphobetaine reacts with 1 equiv of HCl to generate the phosphonium chloride $[Et_3P\text{-}CH_2Ar]Cl$, where Ar is the aryl moiety, $C_6H_2[(3,5\text{-}(OMe)_2\text{-}4\text{-}OH]$, and this salt has been structurally characterized by X-ray analysis.[19]

The mechanism of the reaction between THPP and syringyl alcohol likely involves formation of the carbonium ion from the alcohol, followed by nucleophilic attack of the phosphine. The formation of a carbonium ion from benzyl alcohols that contain an *o*- or *p*-OH group, is well-known, the carbonium ion being stabilized by the quinone methide resonance structure.[20] When the benzyl alcohol has a *m*-OH

(19) Moiseev, D.; James, B. R.; Patrick, B. O.; Hu, T. Q. Unpublished work.

(20) (a) Merijan, A.; Gardner, R. D. *J. Org. Chem.* **1965**, *30*, 3965. (b) Becker, H.-D. *J. Org. Chem.* **1969**, *34*, 1203. (c) Volod'kin, A. A.; Ershov, V. V. *Russ. Chem. Rev.* **1988**, *57*, 336. (d) Chiang, Y.; Kresge, A. J.; Zhy, Y. *J. Am. Chem. Soc.* **2002**, *124*, 6349. (e) Toteva, M. M.; Moran, M.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8814.

Scheme 6 [a]



[a] R = $(CH_2)_3OH$.

substituent, such a resonance structure is impossible, and the alcohol is unreactive toward THPP (see Table 1, entry 3).

Formation of a zwitterion, analogous to **8**, has been observed in the reaction of $^nBu_3P$ with the chloromethylphenol 4-OH-3,5-$^tBu_2(C_6H_2)CH_2Cl$ in benzene;[21] the process involves the in situ-formed quinone methide intermediate, where initial loss of chloride occurs instead of loss of hydroxide involved in the formation of **8** from the alcohol. Compound **8** in D_2O solution at room temperature undergoes slow exchange of the benzyl protons with deuterium to generate the bisdeuterated zwitterion **8-D$_2$**, but complete exchange was apparent (loss of the benzyl ^1H resonances) after the solution was heated for 1 h at 90 °C. The ^2D NMR spectrum (400 MHz, H_2O) of a sample of **8-D$_2$** dissolved in H_2O showed a broad singlet at δ 3.5 corresponding to the CD_2 deuterons.

A corresponding H/D exchange (in CD_3OD) has been reported previously within the zwitterion formed from the chloromethylphenol compound noted above, and this was explained in terms of a suggested tautomeric ylide intermediate;[21] a corresponding mechanism for formation of **8-D$_2$** is shown in Scheme 5, where reversible formation of the ylide (**I**) can allow for exchange of both benzyl protons. Maintaining the solution at 90 °C for longer periods led to a slow H/D exchange in **8-D$_2$** of the hydroxypropyl-CH_2 protons adjacent to the P atom; the ^1H multiplet for these six protons at δ 2.30−2.15 slowly disappeared, while the ^2D NMR spectrum (400 MHz) of an isolated residue dissolved in H_2O showed a broad singlet at δ 2.2 corresponding to CD_2 deuterons within a hydroxypropyl side-chain (as well as the broad singlet of the aryl-CD_2 moiety at δ 3.5).

The exchange can be explained as for the benzyl protons, by invoking an ylide intermediate as shown in Scheme 6. A corresponding H/D exchange of the *n*-butyl protons within the chloromethylphenol system mentioned above[21] was not observed, presumably because this system was studied in CD_3OD; the exchange in D_2O results essentially from OD^- accepting a proton from the ylide intermediates, while the alcohol system provides an insufficiently strong basic medium.

Of note is that aliphatic aldehydes, which have a less electrophilic carbonyl-C atom than aromatic aldehydes, are not reduced to the corresponding alcohols by THPP. If α-hydrogen atoms are present, the typical self-condensation (aldol) reaction takes place, this being catalyzed by OH^-, which is presumably generated by the presence of THPP. For example, the reaction of 3-phenyl-propanal (hydrocinnamaldehyde) with THPP in water at the "standard" conditions (1:1 ratio, 90 °C, 72 h, under Ar) generates, in a 59% yield, 5-phenyl-2-benzyl-2-pentenal, the dehydration product of the aldol condensation product (eq 9).

$$2Ph(CH_2)_2CHO \xrightarrow{-H_2O} Ph(CH_2)_2CH{=}C(CHO)(CH_2Ph) \quad (9)$$

The reaction of THPP with 3,4-dimethoxyacetophenone was carried out under the standard conditions to compare reactivity of aromatic aldehydes and ketones. After 3 days of reaction, the corresponding α-methylveratryl alcohol was isolated (cf. Scheme 1), but in only 3% yield, presumably because of the well-known lower electrophilicity of ketones (vs aldehydes).

Conclusions

Substituted benzaldehydes (model compounds for moieties present in wood pulps) can be reduced in water at 90 °C to the corresponding benzyl alcohol by reaction with $[HO(CH_2)_3]_3P$ (THPP), which itself is oxidized to the phosphine oxide. Yields are typically in the 75−90% range for mono- and disubstituted benzaldehydes, although yields are lower with trisubstituted substrates, likely, because of lower solubility in the aqueous medium. Evidence is consistent with a mechanism involving an initially formed phosphonium species and a final protonation of a carbanion intermediate, which in D_2O leads to benzyl alcohols containing one D atom attached to the benzyl-carbon atom. The systems were studied because of their relevance to some water-soluble (hydroxymethyl)phosphines that were recently found to be highly effective bleaching agents for pulps. Less-basic water-soluble phosphines, such as $(HOCH_2)_3P$ and $Ph_2(m\text{-}NaSO_3C_6H_4)P$, are unreactive toward veratraldehyde (3,4-dimethoxybenzaldehyde), presumably because of the lower nucleophilicity of these phosphines compared to that of THPP.

Syringaldehyde (a 3,5-dimethoxybenzaldehyde containing a 4-OH (para) substituent), similarly reacts with THPP to give first syringyl alcohol, but this subsequently reacts with THPP faster than does the aldehyde and affords a stable, water-soluble zwitterion, where the anionic charge is on the phenoxy-oxygen and the positive (phosphonium) charge pertains to a phosphorus center bonded to the three hydroxy-

(21) Starnes, W. H.; Lauff, J. J. *J. Org. Chem.* **1970**, *35*, 1978.

propyl groups and the benzyl C-atom. The benzyl protons and the α-CH_2 protons of the hydroxypropyl groups undergo H/D exchange (the former more rapidly) when the zwitterion is heated in D_2O, the process almost certainly occurring via phosphorus ylide intermediates. Aliphatic aldehydes are not reduced by THPP but undergo the base-promoted self-condensation aldol reaction. 3,4-Dimethoxyacetophenone (the methyl ketone analogue of veratrylaldehyde) is less reactive than the aldehyde toward THPP, and this is attributed to the lower electrophilicity of the ketone carbonyl moiety.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for funding via an Idea to Innovation (I2I) grant and Dr. Maria Ezhova for assistance with the NMR experiments.

Supporting Information Available: ^1H NMR data for the alcohol products formed from substituted bezaldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

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