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Phosphonium Phenolate Zwitterion *vs* Phosphonium Ylide: Synthesis, Characterization and Reactivity Study of a Trimethylphosphonium Phenolate Zwitterion

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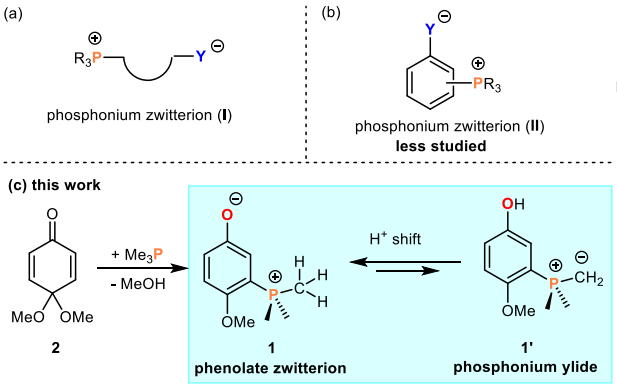
Abstract: 4-Methoxy-3-(trimethylphosphonio)phenolate was obtained from a regioselective addition of PMe_3 to *p*-quinone monoacetal. This compound undergoes hydrogen isotope exchange with D_2O or CD_3CN, and is capable of catalyzing H/D exchange of CD_3CN with substrates bearing weakly acidic hydrogens. It exhibits similar reactivity to phosphorus ylides for olefinations of aldehydes. A possible tautomerization between the phosphonium phenolate zwitterion and phosphonium ylide is proposed for the first time to rationalize the unique reactivity.

Keywords: Phosphonium phenolate zwitterion; H/D exchange; Deuteration; Wittig reagent; Terminal alkenes;

Introduction

Phosphonium zwitterions, an important subclass of phosphonium salts bearing both one positive and one negative charge in the molecule, receive considerable interest in various fields of chemistry ranging from organic synthesis, catalysis, medicinal chemistry and materials.[1,2] For example, lipophilic carboxylate phosphabetaines (**I**, Y = CO_2, Scheme 1a) as analogs of organic amino acids are endowed with a wide range of chemical and biological properties,[3] and have found valuable applications in cellar biology.[4] In organic chemistry, beside as synthetic reagents,[5] phosphonium zwitterions are frequently engaged as reactive intermediates in catalytic reactions, particularly in those involving nucleophilic addition of phosphines to electron-deficient unsaturated systems,[6] and several intermediates have been reported with fair stability for characterization.[7] On contrast, phosphonium zwitterions of type **II** in which the cationic phosphonium and anionic centre are linked by aromatic rings receive limited attentions and have been be sparsely studied (Scheme 1b).[8-10] Specifically, only few examples of triarylphosphonium phenolate zwitterions (Y = O, R = Ph, Scheme 1b) have been reported,[8] and particularly little is known on their alkyl analogs (Y = O, R = alkyl, Scheme 1b).[9]



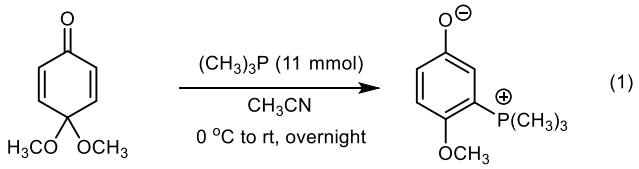
Scheme 1. Phosphonium zwitterions.

Here we report a new trimethylphosphonium phenolate zwitterion **1** (Scheme 1c). This compound was accidently obtained during a mechanistic study on the phosphine-mediated reaction of >P(O)H nucleophiles with *p*-quinone monoacetals we recently developed.[11] Recognizing the little knowledge on this type of products, a subsequent study was conducted to reveal the reactivity. Interestingly, we found that **1** underwent a facile H/D exchange with CD_3CN under mild conditions to give deuterium-labelled trimethylphosphonium phenolate zwitterion **1**-d9 (*vide infra*). Notably, the development of new hydrogen isotope exchange reactions to access

isotopically labeled organic molecules is of current interest in organic chemistry due to the value of deuterated compounds in the study of reaction mechanisms, mass-dependent analysis and biological processes.[12, 13] Thus a new catalytic deuteration process using **1** as the catalyst and CD_3CN as deuterium source was revealed to selectively afford several deuterium-labelled products with high deuteration. In addition, **1** also demonstrated an interesting reactivity similar to a phosphonium ylide and could be used as an olefination reagent to convert aldehydes into terminal alkenes. We proposed a tautomeric equilibrium between the phosphonium phenolate zwitterion and a phosphonium ylide species **1'** to account for the reactivity (Scheme 1c).

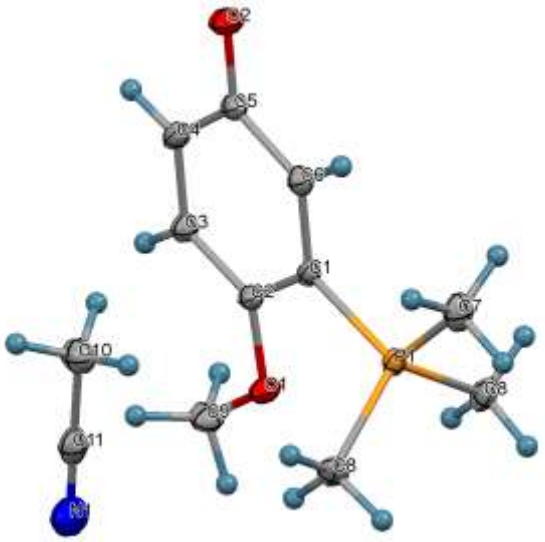
Results and Discussion

When a mixture of *p*-quinone monoacetal **2** (10 mmol), PMe_3 (11 mmol, 1 M in toluene) and CH_3CN (2 mL) was stirred under N_2 overnight, a white solid precipitated. After centrifugation and a simple washing workup, the analytically pure product **1** was obtained in 92% yield (1.820 g) (eq. 1). This selective reaction appears unique for PMe_3. Triphenylphosphine and tricyclohexanylphosphine were unreactive. Tributylphosphine reacted with **2**, but a complex mixture was generated.



2 (10 mmol) **1** (92% yield, 1.82 g) (1)

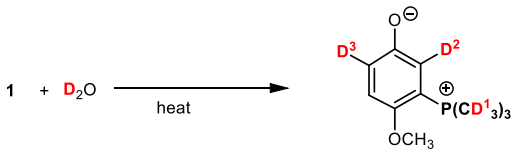
The ^1H, ^{13}C and ^{31}P NMR data of **1** suggested a dipolar structure. Particularly, the ^{31}P NMR spectrum showed a characteristic signal for tetravalent phosphorus at 16.7 ppm in CD_3CN (17.9 ppm in D_2O or DMSO-d6). The structure of **1** was further studied by X-Ray diffraction method.[14] Single crystals were obtained by slow evaporation of a saturated solution of compound **1** in MeCN at room temperature. The crystallographic data reveal that **1** crystallizes in monoclinic space group P $2_1/m$ with one equiv of MeCN (Figure 1). The phosphorus atom exists in a tetrahedral geometry, and is attached to the *ortho*-position of the methoxyl group in the phenyl ring. The C1─P1 bond length is 1.7915(15) Å, similar to previously observed C(sp2)─P(V) bond (1.79 Å).[15] The C5–O2 bond length is 1.3008(18) Å, which is shorter than a C─O single bond (1.33 Å for the C–O bond in sodium phenolate, and 1.36 Å for the C─O bond in phenol)[16] and longer than a C═O bond (1.22 Å for the C═O bonds in benzoquinone).[15] In addition, the C4─C5 and C5─C6 bond lengths are 1.426(2) and 1.428(2) Å, which are slightly longer than common C–C bonds of the phenyl ring. These data may suggest that the negative charge disperses from the O2 atom to the phenyl ring through delocalization, albeit to a small degree only.



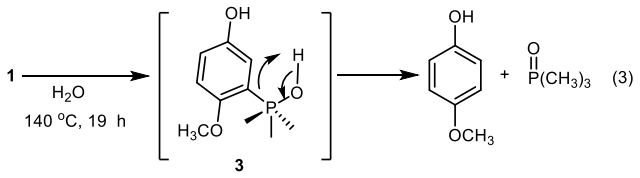
1·CH_3CN (CCDC 1918659)

Figure 1. ORTEP drawing of the molecular structure of **1**•MeCN. Thermal ellipsoids are set at 50% probability. Selected bond lengths (Å): C1–P1 = 1.7915(15), C7–P1 = 1.7896(18), C8–P1 = 1.7879(12), C2–O1 = 1.3783(18), O1–C9 = 1.4285(19), C5–O2 = 1.3008(18), C1–C2 = 1.407(2), C1–C6 = 1.399(2), C2–C3 = 1.391(2), C3–C4 = 1.396(2), C4–C5 = 1.426(2), C5–C6 = 1.428(2).

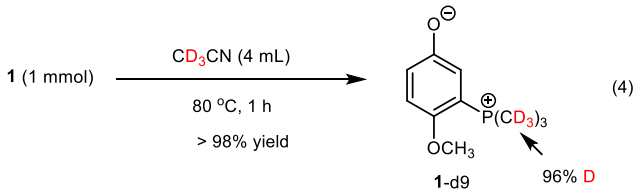
Compound **1** is stable to air and moisture under ambient temperature although it is hydroscopic. However, it decomposed quickly in $CDCl_3$ at room temperature. Upon heating, **1** underwent H/D exchange with D_2O to give partially deuterated product. The deuteration took place both on the methyl groups of the trimethylphosphonium moiety and the phenyl ring. For example, treatment of **1** (6 mg) with D_2O (0.4 mL) at 100 °C for 1 h resulted in 16%, 7%, and 4% of deuteration at the methyl groups and two positions of the phenyl ring (eq. 2). The deuteration rate increased to be 96%, 32%, and 7% after heating for 20 h. Compound **1** appears rather stable in water. No decomposition took place when it was heated in D_2O at 100 °C for 20 h. A significant level of hydrolysis (ca. 64%) was observed until it was heated to 140 °C for 19 h to form 4-methoxyphenol and trimethylphosphine oxide. The hydrolysis probably proceeded via C(sp2)─P bond cleavage of an intermediate **3** (eq. 3).



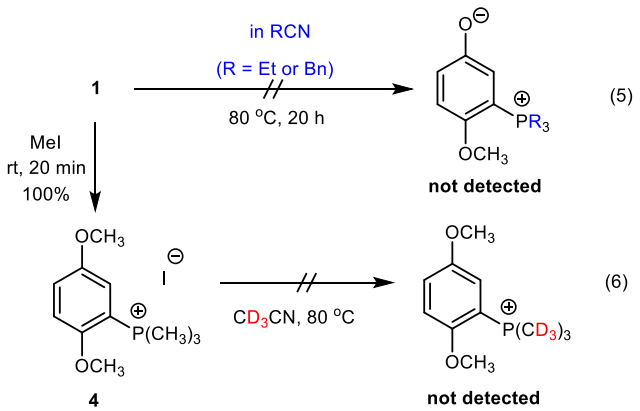
100 °C, 1 h, D^1 = 16%, D^2 = 7%, D^3 = 4%
100 °C, 20 h, D^1 = 96%, D^2 = 32%, D^3 = 7% (2)



Surprisingly, we found that the hydrogen isotope exchange also took place between **1** and CD_3CN upon heating to form **1**-d9, where the CH_3 groups attached to the phosphorus atom were replaced by CD_3. Thus, when **1** (1 mmol) was heated in CD_3CN (4 mL) at 80 °C for 1 h, **1**-d9 was formed in 98% yield with 96% deuteration (eq. 4). Notably, deuterium atoms were not incorporated into the phenyl ring in this reaction as determined by ^1H NMR.

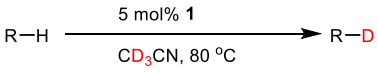


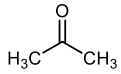
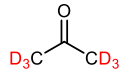
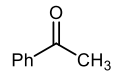
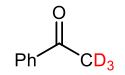
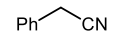
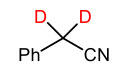
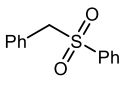
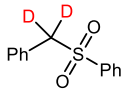
The control experiments showed that no reaction took place when **1** was heated in propionitrile or phenylacetonitrile (eq. 5), indicative of the less possibility of a CD_3-group-transfer process from CD_3CN to **1** to produce **1**-d9. Further, no H/D exchange was observed when the O-methylated product **4** was heated in CD_3CN (eq. 6). According to these results, we suggest that a comparable level of basicity of **1** arising from the oxygen atom with negative charge may account for this interesting H/D exchange process under the reaction conditions (*vide infra*).



In fact, a further study revealed that compound **1** efficiently catalyzed hydrogen isotope exchange of CD_3CN with several substrates bearing weakly acidic hydrogens under mild conditions (Table 1). For example, H_2O was deuterated in CD_3CN in the presence of 5 mol% of **1** with 97% deuteration upon heating for 1 h (entry 1). Under similar conditions, 99% deuterium was incorporated into the hydroxyl group of *t*-BuOH (entry 2). Acetone, acetophenone, phenylacetonitrile and benzylphenyl sulfone also efficiently underwent the H/D exchange reaction, resulting in the formation of deuterated products with high levels of deuterium incorporation at the *α*-carbon atoms (entries 3-6).[17] In the absence of the catalyst, these H/D exchanges hardly happen. The H/D exchanges were also observed using sodium phenolate (PhONa) as the catalyst.[18] For example, PhONa (5 mol%) catalyzed the H/D exchange reactions of CD_3CN with H_2O and *t*-BuOH with similar efficiency, resulting in the formation of D_2O and *t*-BuOD with 94% and 95% deuteration, respectively (entries 1 and 2). However, the reaction of acetophenone took place less effectively to afford the product with only 70% deuteration at the *α*-carbon atom (entry 4). But regardless, these results support the aforementioned assumption.

Table 1. Phosphonium zwitterion **1** catalyzed H/D exchange reactions.[a]



Entry	Substarte	Product	Deuteration (%)	Time (h)
1	H_2O	D_2O	97 (97)[b]	1
2	^{t}BuOH	^{t}BuOD	99 (95)[b]	1
3			96(92)[c]	3(21)[c]
4			96 (70)[b]	3
5			97	2
6			96	7

[a] Unless otherwise noted, a mixture of 0.1 mmol substrate and 0.005 mmol **1** in 0.4 mL CD_3CN was heated at 80 °C for indicated time. Deuteration was determined by ^1H NMR. [b] PhONa (5 mol%) was used as the catalyst. [c]1 mmol scale, 0.5 mol% of **1** used.

Furthermore, compound **1** also showed an interesting reactivity similar to a phosphorus ylide, and thus could react with aldehydes to produce terminal alkenes *in the absence of an extra base* (Table 2). For example, benzaldehyde reacted with 1.0 equiv of **1** at 120 °C in dioxane for 15 h to afford styrene (**6a**) in 82% yield. The reactions of other aryl aldehydes bearing either electron-rich or electron-deficient groups including Et, MeO, Br and CF_3 afforded the corresponding olefins **6b**-**6e** in 64-73% yield. The terminal alkenyl and alkynyl groups were tolerated (**6f** and **6g**). When a cinnamaldehyde was used, 1,3-diene **6h** was obtained in 55% yield. In addition, an aliphatic aldehyde also reacted with **1** to successfully deliver **6i** in 65% yield. More intriguingly, this reaction could be used for the

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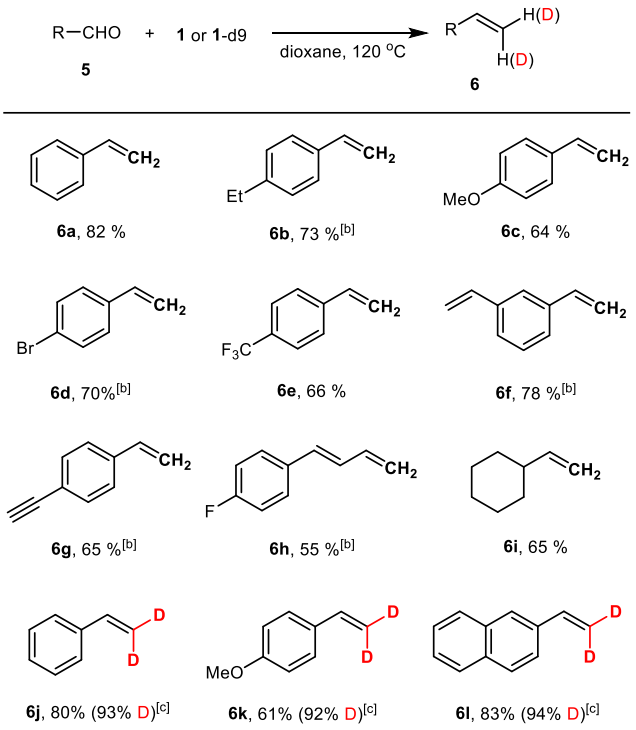
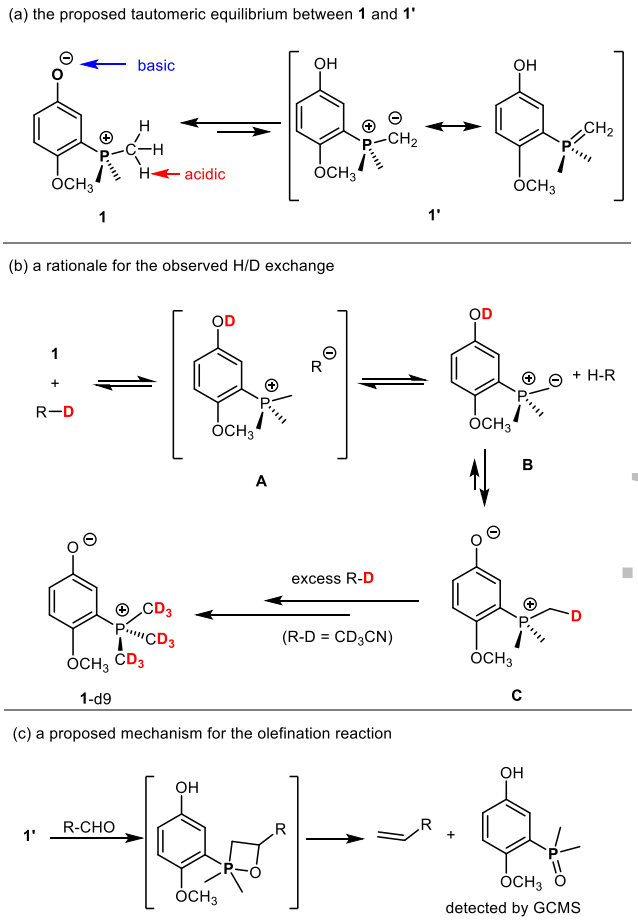
synthesis of 1,1-dideuterio styrenes when **1**-d9 was used, as exemplified by the successful preparation of deuterium-labelled alkenes **6j-6l** in good to high yields with high levels of deuteration at the terminal carbon.

Table 2. Olefination of aldehydes with **1** and **1**-d9.[a]



[a] Unless otherwise noted, 0.1 mmol aldehyde and 1.0 equiv. phosphonium zwitterion in **1** mL dioxane at 120 °C for 15 h. [b] Reaction time: 21 h. [c] 2.0 equiv of **1**-d9 was used.

The obtained results led us to propose that trimethylphosphonium phenolate zwitterion (**1**) may present a tautomeric equilibrium with the corresponding phosphonium ylide **1'** (Scheme 2a). It is reasonable to assume that the phenolic oxygen atom with negative charge may serve as the base functionality to abstract a proton from the weakly acidic methyl groups of the trimethylphosphonium moiety. Thus, **1** may react with CD_3CN to produce a possible phosphonium ylide species **B** via intermediate **A**. Tautomerization of **B** takes place to produce the deuterated intermediate **C**. The presence of excess CD_3CN finally leads to the formation of **1**-d9 (Scheme 2b). Clearly, the reactions of **1** with aldehydes to form terminal alkenes without the need of an extra base support the assumption, although the tautomer **1'** could not be directly observed (Scheme 2c).



Scheme 2. The proposed mechanism: (a) the tautomeric equilibrium between **1** and **1'**; (b) a rationale for the observed H/D exchange; and (c) a proposed mechanism for the olefination reaction.

Conclusion

In summary, we have reported a high-yielding preparation of a new trimethylphosphonium phenolate zwitterion. This compound underwent hydrogen isotope exchange with D_2O and CD_3CN. It catalyzed H/D exchange between CD_3CN and a variety of substrates bearing weakly acidic hydrogens under mild conditions. Particularly, the compound demonstrates a unique reactivity similar to a phosphorus ylide, and can be used as an alternative Wittig reagent for preparation of terminal alkenes including deuterium alkenes, in the absence of extra base. A possible tautomerization from a phosphonium phenolate zwitterion species to a phosphonium ylide to was proposed for the first time to rationalize the obtained results. We believe that this study will be helpful for understanding the properties of similar phosphonium zwitterions and stimulate the practical use of these compounds.

Experimental Section

Synthesis of trimethylphosphonium phenolate zwitterion 1

To a 50 mL dried Schlenk tube equipped with a magnetic stir bar were added *p*-quinone monoacetal **2** (10 mmol, 1.542 g) and CH_3CN (2 mL) under N_2. After the mixture was stirred at 0 °C for 30 min, a solution of PMe_3 (1.0 M in toluene, 11 mmol, 11 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The product precipitated out as white solid. After centrifugation and filtration of the reaction mixture, the white solid product was collected. The obtained solid was washed by a small portion of toluene and CH_3CN, and was dried under high vacuum to give the pure product **1** in 92% yield (1.820 g). white solid, mp. 208.5°C-209.7°C. ^{1}H NMR (400 MHz, CD_3CN): δ 6.77 (t, J = 8.8 Hz, 1H), 6.41 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 6.17 (dd, J_1 = 17.2 Hz, J_2 = 2.8 Hz, 1H), 3.74 (s, 3H), 1.94 (d, J = 14.4 Hz, 9H). ^{13}C NMR (100 MHz, D_2O): δ 160.64 (d, J = 14.5 Hz), 151.33, 126.00 (d, J = 2.7 Hz), 119.79 (d, J = 7.0 Hz), 114.45 (d, J = 9.0 Hz), 108.31 (d, J = 87.2 Hz), 56.39, 8.85 (d, J = 57.9 Hz). ^{31}P NMR (162 MHz, CD_3CN): δ 16.66. Elemental analysis calculated (%) for (**1** · ½ H_2O): C, 57.96; H, 7.78. Found: C, 57.64; H, 7.81. Note: since compound **1** is hydroscopic, water in air might contaminate the sample to give this result during the elemental analysis experiment.

General procedures for 1-catalyzed H/D exchange reactions

A mixture of the substrate (0.1 mmol or 0.2 mmol) and 5 mmol% **1** in 0.4 mL CD_3CN was charged in a heavy-walled NMR tube fitted with a re-sealable Teflon valve (J Young tube) in the glovebox under N_2. Then the mixture was heated at 80 °C for indicated time. After the mixture was cooled to room temperature, the crude mixture was analyzed by ^{1}H NMR to determine the deuteration of the product.

Typical procedure for olefination of aldehydes with 1 or 1-d9 and characterization data of the products

A mixture of an aldehyde (0.1 mmol) and the phosphonium zwitterion **1** (0.1 mmol, 19.8 mg) in dioxane (1.0 mL) was stirred at 120 °C for indicated time. After the mixture was cooled to room temperature, the mixture was passed through a short silica gel column with EtOAc as eluent. The filtrate was concentrated and the residue was further purified by column chromatography on silica gel to give the product **6**.

Acknowledgements

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[18] For experimental details on these results, see the supporting information. For base-mediated H/D exchange reactions, also see refs 12a and 12b.

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UPDATES

Phosphonium Phenolate Zwitterion *vs* Phosphonium Ylide: Synthesis, Characterization and Reactivity Study of a Trimethylphosphonium Phenolate Zwitterion

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