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# Recent advances in studying the mechanism of phospho-Michael addition of tertiary phosphines to electron-deficient alkenes on the basis of kinetic isotope effects

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## ABSTRACT

The previously proposed mechanism for phospho-Michael addition of tertiary phosphines to electron-deficient alkenes has been amended according to the secondary kinetic isotope effects provided by  $\alpha$ -deuterated activated alkenes. The data obtained have shown that rate-determining protonation of intermediate phosphonium zwitterion proceeds not directly at its carbanionic center but first at a heteroatom of the attached electron-withdrawing group, with subsequent isomerization of the enolic/eniminic intermediate to stable keto-/cyanophosphonium product.

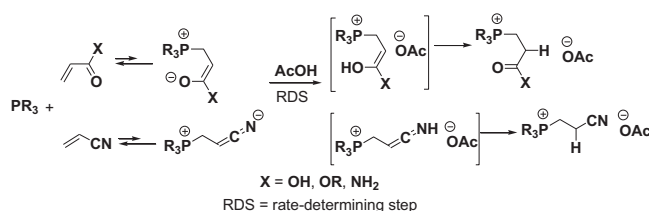
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Kinetics; mechanism; kinetic isotope effects; vibrational-rotational coupling; reactive intermediates

## GRAPHICAL ABSTRACT



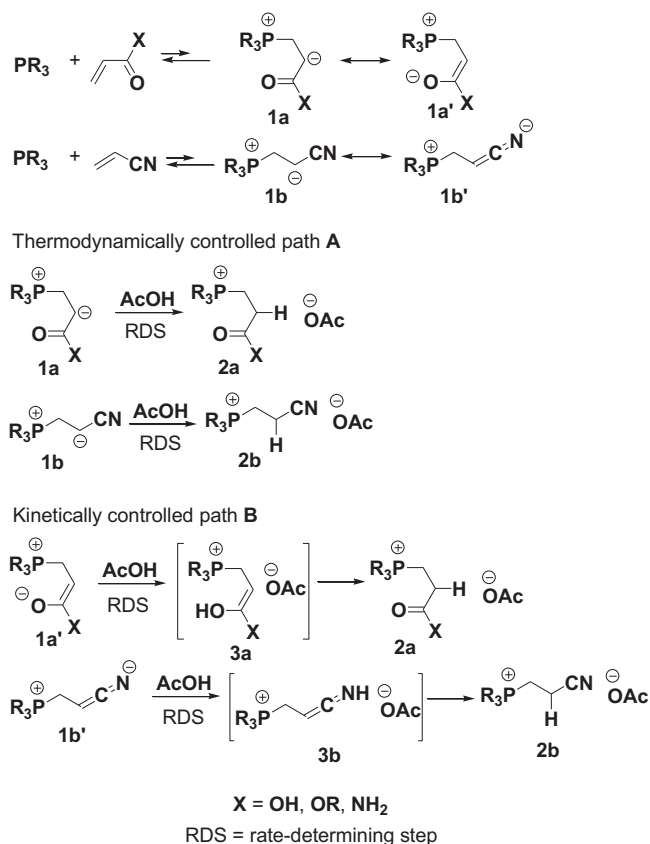
## Introduction

Phosphonium zwitterions generated from conjugate addition of tertiary phosphines to electron-deficient alkenes, alkynes, and allenes are reactive intermediates involved in many synthetically useful phosphine-catalyzed reactions.<sup>[1–5]</sup> However, isolation and structural studies of this type intermediates are challenging tasks due to their high tendency to reconvert to the starting materials or undergo further transformations. Recent investigations by our group showed that the addition of tertiary phosphines to electron-deficient alkenes in the presence of a proton source may serve a convenient model to learn more about stability and reactivity of the phosphonium zwitterions.<sup>[6–16]</sup> The kinetic studies revealed that these reactions show acid dependence, and the rate law depends on proton-donor properties of the solvent. On the basis of kinetic analysis a stepwise reaction mechanism was proposed (Scheme 1), which includes reversible formation of phosphonium zwitterionic intermediate **1**, followed by rate-determining proton transfer from the medium, for example, proton-donor solvent, such as acetic acid. This mechanism is in line with the known instability of the phosphonium zwitterions, and it turns out that their reversion to the reactants proceeds faster than proton transfer from the medium.

Zwitterion **1** is an ambident base which can be protonated on either the carbanionic center under thermodynamic control (path **A**, Scheme 1) or on the heteroatom of the attached electron-withdrawing group under kinetic control (path **B**, Scheme 1), with subsequent isomerization of enolic/eniminic intermediate **3** to thermodynamically stable reaction product **2**. The exact answer to the question whether the reaction follows thermodynamic or kinetic control cannot be obtained from kinetic analysis, but can be provided by secondary kinetic isotope effects produced by  $\alpha$ -deuterated activated alkenes. This paper briefly summarizes recent advances in studying the mechanism of phospho-Michael addition of tertiary phosphines to electron-deficient alkenes on the basis of secondary kinetic isotope effects.

## Results and discussion

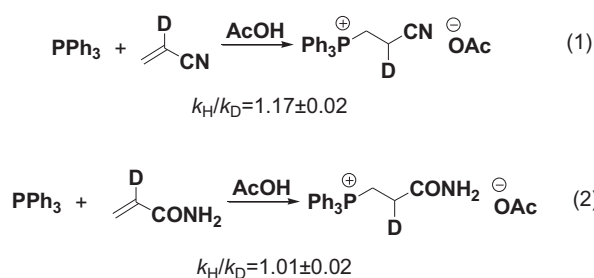
The use of acrylonitrile as a Michael acceptor has proved to be a very useful tool to distinguish between thermodynamically and kinetically controlled pathways of protonation of phosphonium zwitterion generated from addition of a tertiary phosphine to the activated alkene. Acrylonitrile shows unusual vibrational properties in far infrared region due to



**Scheme 1.** Alternative mechanisms for addition of tertiary phosphines to electron-deficient alkenes in acetic acid solvent involving thermodynamically controlled protonation of zwitterionic intermediate **1** at carbanionic center (path A) and the kinetically controlled protonation at heteroatom of electron-withdrawing group (path B).

the presence of vibrational-rotational coupling in this molecule.<sup>[17–20]</sup> Typically, effect of molecular rotation on vibration is negligible, but a very large value of the A rotational constant (49.85 GHz)<sup>[18]</sup> for acrylonitrile allows some rotational energy levels of the ground state to interact with lowest vibrational level related to the in-plane C–C≡N bending mode ( $\nu_{11}=228\text{ cm}^{-1}$ ). This vibrational level interacts with the next nearest vibrational level related to the out-of-plane C–C≡N bending mode ( $\nu_{15}=333\text{ cm}^{-1}$ ) by means of Coriolis effect, the deflection of the moving atoms within rotating plane of the molecule. Interestingly, deuteration of acrylonitrile at the position  $\alpha$  to the nitrile group reduces significantly the A rotational constant (by almost 10 GHz).<sup>[19]</sup> As a result, the interstate perturbations are shifted to very different values of rotational quantum numbers. Such strong effect of the deuteration on the vibrational-rotational coupling allowed to observe a normal secondary kinetic isotope effect ( $k_H/k_D=1.17\pm0.02$ ) for the reaction of  $\alpha$ -deuterated acrylonitrile with triphenylphosphine in acetic acid solvent (Scheme 2, Eq. 1).<sup>[21]</sup> The presence of such effect indicates that the perturbed vibrational level  $\nu_{11}$  changes significantly during the rate-determining step.

According to the theory of kinetic isotope effects,<sup>[22]</sup> the in-plane bending vibration defines the reaction coordinate when  $sp/sp^2$  rehybridization of an atom occurs. This situation corresponds to the mechanism with the path B



**Scheme 2.** Secondary kinetic isotope effects in the reaction of triphenylphosphine with  $\alpha$ -deuterated activated alkenes in acetic acid solvent.

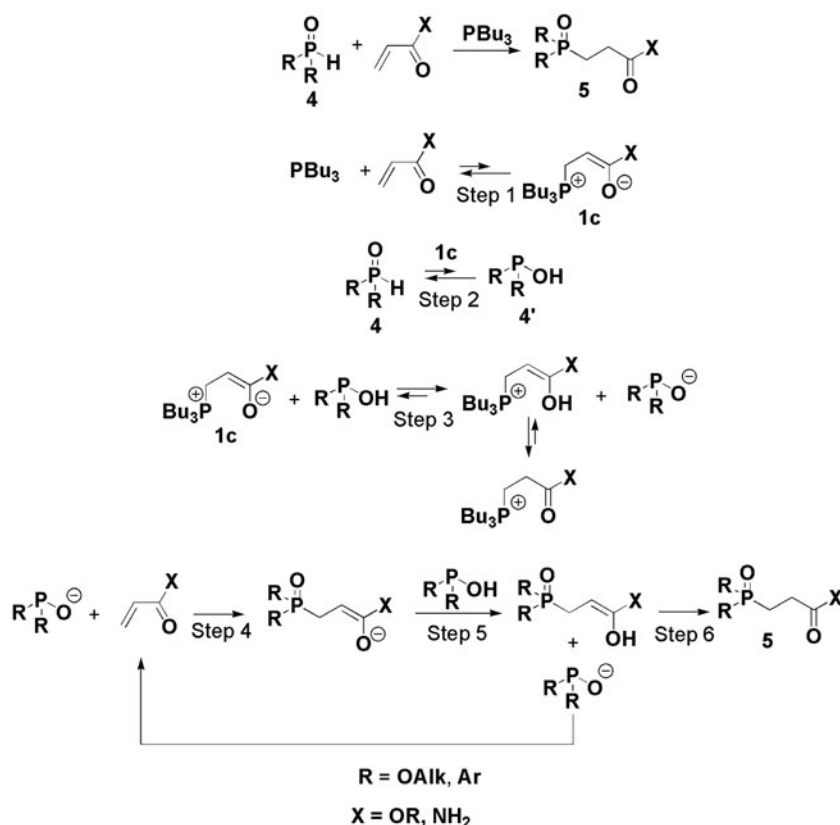
(Scheme 1), in which nitrile group with  $sp$ -hybridized nitrogen transforms to enimine group with  $sp^2$ -hybridized nitrogen during the rate-determining step. The fact that vibrational-rotational coupling in acrylonitrile influences the second reaction step of protonation of zwitterionic intermediate indicates that its lifetime is comparable with the period  $T$  of the in-plane C–C≡N bending:

$$T = \frac{1}{\nu_{11}c} = 138 \text{ fs} \quad (\nu_{11} = 242 \text{ cm}^{-1} \text{ for the condensed phase}).$$

Because of such a short lifetime, typically the fast proton transfer step becomes rate-determining in the studied reaction and proceeds via the kinetically favored path B, which requires a lower activation barrier.

Further evidence for the protonation of phosphonium zwitterion through the path B was provided by secondary kinetic isotope effect produced by  $\alpha$ -deuterated acrylamide (Scheme 2, Eq. 2).<sup>[21]</sup> This isotopologue was obtained by hydration of more the easily available  $\alpha$ -deuterated acrylonitrile in the presence of a copper/vanadium-containing catalyst in high chemical purity (99.9%) and isotopic enrichment ( $>98\%$  D).<sup>[23]</sup> No secondary kinetic isotope effect was found for the reaction of triphenylphosphine with  $\alpha$ -deuterated acrylamide in acetic acid solvent ( $k_H/k_D=1.01\pm0.02$ ). Notably, if protonation occurred at the carbanionic center of phosphonium zwitterion **1** (path A, Scheme 1), the carbon would change hybridization from  $sp^2$  to  $sp^3$ , and an inverse effect ( $k_H/k_D<1$ ) would be expected.<sup>[22]</sup> In the path B, carbonyl oxygen of zwitterion **1a'** acts as a base, and rehybridization of the oxygen is not influenced by the deuteration, because acrylamide shows no vibrational-rotational coupling typical for acrylonitrile.

Given the key role played by phosphonium zwitterions in Michael-type additions catalyzed by tertiary phosphines, this mechanism helps to understand recent experimental findings in chemistry of phosphine-catalyzed Pudovik reaction, the addition of P(O)–H compounds **4** to activated carbon-carbon multiple bonds to form phosphorylated products **5** (Scheme 3).<sup>[24–27]</sup> The very short lifetime of phosphonium zwitterions makes the efficiency of the catalysis strongly dependent not only on the rate of addition of tertiary phosphine to the activated alkene (Scheme 3, Step 1), but also on acid-base equilibria these intermediates are involved in (Steps 2 and 3). For example, in a series of dialkyl phosphites  $(\text{AlkO})_2\text{P(O)H}$ , the reaction rate increases as the acidity of P(O)–H bond increases.<sup>[24]</sup> At the same time, the



**Scheme 3.** Proposed mechanism for  $\text{PBu}_3$ -catalyzed Pudovik reaction.

reaction rate depends considerably on the ease of tautomerization of  $\text{P}(\text{O})\text{-H}$  compound to more acidic but less stable trivalent hydroxy-form  $\text{4'}$ . For this reason, most easily tautomerized  $\text{Ph}_2\text{P}(\text{O})\text{H}$ <sup>[28]</sup> was found to be much more reactive than more acidic dialkyl phosphites in the  $\text{PBu}_3$ -catalyzed Pudovik reaction.<sup>[27]</sup>

## Conclusions

In summary, secondary kinetic isotope effect data allowed to shed more light on the mechanism of phospho-Michael addition of tertiary phosphines to electron-deficient alkenes. Rate-determining protonation of phosphonium zwitterionic intermediate follows kinetic control and proceeds first at heteroatom of electron-withdrawing group, with subsequent isomerization of enolic/eniminic intermediate to thermodynamically stable keto-/cyanophosphonium product. Further mechanistic studies on the phospho-Michael additions are in progress and will be reported in due course.

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