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An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenoates and Alkenes

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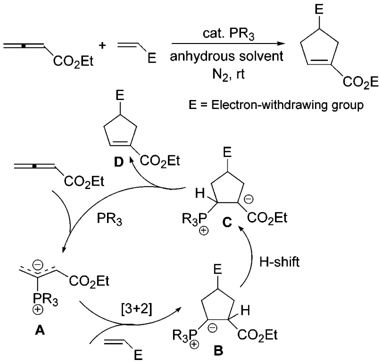
The Lu phosphine catalyzed (3 + 2) cycloaddition between allenoates and activated alkenes,[1,2] as exemplified by the reaction shown in Scheme 1, provides an efficient approach for the synthesis of five-membered carbocycles, which are prevalent in many natural products and compounds of pharmaceutical significance. The proposed mechanism for the Lu reaction (shown in Scheme 1) starts from the formation of a zwitterionic intermediate **A** between allenoate and phosphine.[1,2a] Intermediate **A** acts as a 1,3-dipole and undergoes a (3 + 2) cycloaddition with an electron-deficient olefin to give a phosphrous ylide **B**. Then an intramolecular [1,2] proton transfer is speculated to convert the phosphorus ylide **B** to another zwitterionic intermediate **C**, which, upon loss of the phosphine catalyst, gives rise to the final cycloadduct **D**. The Lu (3 + 2) cycloaddition is also efficient for the synthesis of five-membered heterocycles if imines are used as dipolarophiles.[3] Through elegant work in the groups of Zhang and Fu,[4] asymmetric versions of the Lu (3 + 2) cycloaddition have been developed. Applications of the Lu (3 + 2) cycloaddition to the total synthesis of natural products have also been documented by Lu, Krische, and Pyne, respectively.[5] Further elegant developments and extensions of the chemistry of allene-PR$_3$ have been widely pursued by many other groups as well.[6]

However, to date, the detailed mechanism of the Lu reaction has not been investigated either experimentally or theoretically.[7] In-depth understanding of the potential energy surface, structures of the intermediates and transition states, and regio- and stereochemistry in the Lu reaction would be useful. Mechanistic information concerning the Lu reaction may help to guide future design of new organocatalytic reactions.[8]

Here we wish to communicate our theoretical and experimental study of the Lu (3 + 2) reaction, with emphasis on the details of the [1,2] proton-transfer step. Although the typical Lu reaction condition is supposed to be anhydrous, our study shows that a trace amount of water existing in the reaction system plays a critical role in assisting the process of [1,2] proton shift.

DFT calculations[9] using the B3LYP/6-31+G(d) method have been applied to understand the Lu reaction, and the computed potential-energy surfaces for the model reaction of 2,3-butadienoate **1**, acrylate **2**, and PMe$_3$ are given in Figure 1. Calculations show that the formation of 1,3-dipole **3** from **1** and PMe$_3$ is slightly exothermic by 1.0 kcal/mol in terms of ΔE_0 in the gas phase. The free energies of this complex are +11.5 and +9.7 kcal/mol compared to reactants in the gas phase and benzene solution, respectively. Calculations indicated that the subsequent (3 + 2) cycloaddition process between **3** and **2** is stepwise, starting from a Michael addition to generate a zwitterionic intermediate **IN1**, which then converts to **IN2** via a ring-closure reaction. These two transition structures in the stepwise (3 + 2) cycloaddition process are very close in energy in both the gas phase and solution. The overall process transforming the reactants and the catalyst to **IN2** requires activation free energies of 31.3 and 28.3 kcal/mol in the gas phase and benzene solution, respectively. The formation of **IN2** is exothermic by 13.9 kcal/mol; however, this (3 + 2) process is endergonic by 12.2 and 11.0 kcal/mol in the gas phase and benzene solution, respectively, suggesting that the formation of **IN2** is not favorable thermodynamically. Therefore, the stepwise (3 + 2) steps must be followed by some exergonic reactions to drive the reaction to completion.

Scheme 1. The Lu (3 + 2) Reaction and Its Proposed Mechanism (Only the Major Product Is Given).



The originally proposed [1,2] proton transfer converting **IN2** to **IN3** is exergonic by about 8.0 kcal/mol, implying that formation of **IN3** can drive the above stepwise (3 + 2) cycloaddition to occur. However, the computed activation free energy of the [1,2] proton transfer from **IN2** to **IN3** is 39.3 and 39.6 kcal/mol in the gas phase and in benzene solution,[10] indicating that this step is not possible kinetically, considering the fact that the Lu (3 + 2) cycloadditions are usually conducted at room temperature.

To obtain more information about the Lu reaction, we conducted a PPh$_3$ catalyzed (3 + 2) cycloaddition of deuterium labeled 2,3-butadienoate **8** (2-D incorporation level is about 95%) and fumarate **9** (I, Scheme 2) in anhydrous benzene (refluxed with Na and freshly distilled prior to use) according to Lu's procedure.[1] It was found that 4-D and 4-H substituted products **10** and **11** were both obtained

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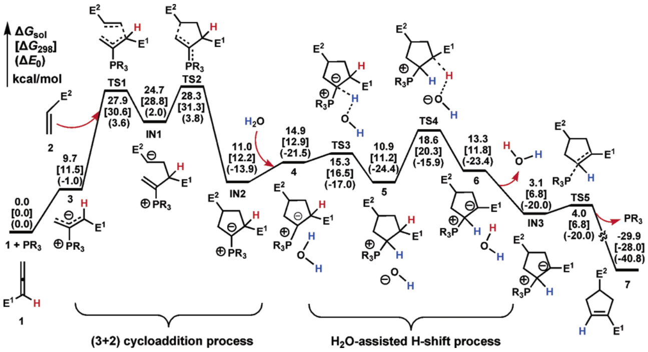
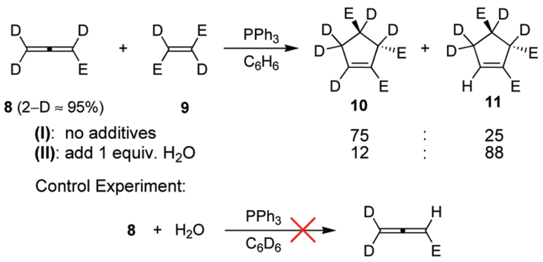


Figure 1. The DFT computed energy surfaces of the Lu (3 + 2) reaction ($E^1 = E^2 = CO_2Me$, $R = CH_3$).[9]

Scheme 2. Isotopic Labeling Experiments ($E = CO_2Me$).[11]



with a ratio of 75:25. This indicates that the [1,2] proton transfer from **IN2** to **IN3** is not a simple intramolecular process. We speculated that the formation of **11** was due to the presence of a trace amount of water in the reaction system. Therefore, we computed a possible H_2O assisted [1,2] proton shift process, which is also given in Figure 1. Calculations showed that **IN2** can form a complex with water, and this complexation step is exothermic by 7.6 kcal/mol and endergonic by 3.9 kcal/mol in benzene. Then a proton transfer from water to the carbon atom connected with the phosphorus atom requires only 0.4 kcal/mol activation free energy in benzene. This step leads to the formation of another complex **5**, in which there is a strong attraction between the hydroxyl anion and the PMe_3 moiety. The subsequent step is the abstraction of proton by hydroxyl anion with an activation free energy of 7.7 kcal/mol in benzene, giving rise to another complex **6**. Loss of water from complex **6** gives **IN3**, which can then easily furnish final (3 + 2) cycloadduct **7** and PMe_3 with an activation free energy of 0.9 kcal/mol in benzene. The water assisted H-shift process converting **IN2** to the final product and PR_3 requires only 7.7 kcal/mol activation free energy and is exergonic by 40.9 kcal/mol.

We also ran the reaction between **8** and **9** in the presence of 1 equiv of H_2O (II, Scheme 2). It was found that the ratio of 4-H substituted product **11** was remarkably increased (from 25% to 88%). To rule out the possibility that the introduction of hydrogen takes place between 1,3-dipole **3** and H_2O, we conducted a control experiment (Scheme 2). ^1H NMR indicated that no deuterium and hydrogen exchange between allenoate and water occurred, proving that the hydrogen exchange happens after the formation of **IN2** (Figure 1).[11] These results further confirm that the intramolecular [1,2] H-shift is impossible and a trace amount of water does play a catalytic role in assisting the [1,2] proton transfer.

In conclusion, the Lu (3 + 2) cycloaddition has been investigated with joint forces of computation and experiment. The formation of a 1,3-dipole is slightly exothermic, and the subsequent (3 + 2) cycloaddition is a stepwise process with an activation free energy of 28.3 kcal/mol. The generally accepted intramolecular [1,2] proton shift in the Lu reaction is not possible owing to the very high activation barrier of 39.6 kcal/mol required for this process.[10] Calculations and experiments revealed that water assists this process with an activation free energy of 7.7 kcal/mol. The discovery of the catalytic role of a trace amount of water in the Lu reaction suggests that a trace amount of water could also act as a catalyst in some other "anhydrous" reactions involving [1,2] or [1,*n*] proton shifts.[12] The present study could have implications for other organocatalytic reactions.[8,13,14] Further mechanistic investigations on allene chemistry and other organocatalytic reactions are in progress.

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Supporting Information Available: Computational and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Computational details and references are given in the Supporting Information. The reported relative energies are free energies in benzene (ΔG_{sol}), and free energies (ΔG_{298}) and the zero-point energies corrected electronic energies (ΔE_0), both in the gas phase, respectively. Even though for a bi- or trimolecular process, the computed ΔG_{sol} values are somehow overestimated (owing to the overestimation of the entropy contributions in solution), the main purpose of such calculations is to appreciate how solvent influences a reaction (such as on its reaction rate, regio- and stereochemistry). A discussion of regiochemistry is given in the Supporting Information.
(10) Calculations showed that tunneling effect for this step is negligible.[9]
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