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A DFT study on the competing mechanisms of PPh_3-catalyzed [3 + 3] and [3 + 2] annulations between 5-acetoxypenta-2,3-dienoate and 1C,3O-bisnucleophiles

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ABSTRACT

In this paper, the competing mechanisms of PPh_3-catalyzed [3 + 3] annulation reaction (including possible pathways a, b and c) and [3 + 2] annulation reaction (including possible pathways a′, b′ and c′) between 5-acetoxypenta-2,3-dienoate and 1C,3O-bisnucleophile have been theoretically investigated using density functional theory (DFT). Among the six possible pathways, our computational results indicate that pathway c is the most energy favorable pathway at acid condition, whereas pathway b′ is the most energy favorable pathway at base condition. Thus, the different acid/base condition would be the switch for the two competing reactions, which is in agreement with the experiment results. Moreover, the analysis of global reactivity indexes has been carried out to explore the role of the catalyst PPh_3, which demonstrates that Lewis base catalyst PPh_3 noticeably strengthens the nucleophilicity of the reactant and makes the annulation reactions easier to occur. This work should be helpful for not only understanding the role of PPh_3 catalyst in the [3 + 3] and [3 + 2] annulations, but also the role of the real switch (i.e., the acid/base additives) in the competing [3 + 3] and [3 + 2] annulations, and thus provides valuable insights on the rational design of more efficient catalysts for this kind of reactions.

1. Introduction

Phosphines, which have been recognized as a remarkable Lewis base catalyst [1], have shown great potential for helping facilitate annulation reactions [2–5]. Since Zhang and Lu report the first phosphine-catalyzed [3 + 2] annulation reaction of 2,3-butadienoates and imines (or alkenes) in 1995 [6], organophosphine has been employed as a favorable catalyst for chemists to obtain a wide array of cyclic product from simple building block [2,7–19]. Over the past decades, a series of heterocyclic compounds have been synthesized by this way. And, most of the products of the phosphine-catalyzed annulations can be used in the chemical, pharmaceutical and medical areas [20–24]. Due to the high efficiency of phosphine catalysts, more and more attention has been attracted by this kind of annulations, and a large number of studies have been presented in both experiment and theory.

In experiment, there have been many works on the development of the phosphine-catalyzed annulations. In 2003, Zhu et al. firstly reported the [4 + 2] annulation reaction of allenoates and *N*-tosylbenzaldimines to form functionalized tetrahydropyridines [25], which leads to the large-scale applications of the phosphine-catalysts. Since the pioneer work of Lu and Kwon are reported, many efforts have been devoted to improve and develop various kinds of the phosphine-catalyzed reactions [2,12,26–39]. In 2009, Kwon reported phosphine-catalyzed [3 + 3] annulations of aziridines and allenoates to get azidirines in room temperature [40]. In 2009, Lu reported phosphine-catalyzed [3 + 3] annulation reactions of modified tert–butyl allyliccarbonates and substituted alkylidenemalononitriles under reflux [41]. Both of them obtained good yields and diastereoselectivities. Then, Zhang et al. reported the [4 + *n*] (*n* = 1, 2) annulations of allenolates with 1,*n*-bisnucleophiles with good yield and selectivity in benzene solvent at room temperature [42]. In 2011, Kwon reported the phosphine-catalyzed [4 + 3], [3 + 3] and [3 + 2] annulations of azomethine

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imines with allenoates with good yields at mild condition [29]. Besides, there are various kinds of phosphine-catalyzed annulation reactions, which are contributed to expand the applications in heterocycle synthesis[43–54].

In theory, several theoretical studies on the mechanisms and stereoselectivities of the phosphine-catalyzed annulation reactions have been reported in recent years [55]. In 2006, Kwon and Dudding studied the mechanisms on the phosphine-catalyzed [2 + 2 + 2] annulation reactions of allenoates with acrylates, imines and aldehydes at the B3LYP/6-31G(d) level for the first time, and their calculated results show the regioselectivities are consistent with those in the experiment [56]. In the next year, Yu and co-authors investigated the phosphine-catalyzed [3 + 2] annulation reactions of allenoates and alkenes at the same level, and they firstly found that the protic additive/media can assist the [1,2]-proton transfer [57,58]. Then, Creech et al. studied the phosphine-catalyzed [3 + 2] annulation reaction of acrylates and allenoates at the B3LYP/6-31G(d) level, and they also obtained the similar conclusion that the protic media can mediate the proton transfer process [59]. In 2008, Creech and Kwon found that the alcohol can mediate the [1,*n*]-proton transfer in the phosphine-catalyzed [3 + 2] annulations of 2,3-butadienoates and aldehydes [60]. And in 2012, Chen et al. explored the detailed mechanisms of the phosphine-catalyzed annulations of allenoates and Nazarov reagents at the B3LYP/6-31G(d) level, and found the alcohol can promote the [1,2]-proton transfer [51]. In 2013, Qiao and Han have investigated the mechanisms and stereoselectivities of phosphine-catalyzed [4 + 2] annulations of allenoates and ketones (or aldimines) at the M06-2X/6-31G(d, p) level, and the global reactivity analysis shows that the catalyst phosphine enhanced the nucleophilicity of allenoates [61].

Interestingly, Hu et al. recently found that the acid/base condition can be a switch for the PPh_3-catalyzed [3 + 3] and [3 + 2] annulation reactions of 5-acetoxypenta-2,3-dienoate and 1C,3O-bisnucleophiles in experiment [62], i.e., the two different conditions with the same reactants and catalyst would lead to the different products. To the best of our knowledge, the phosphine-catalyzed [3 + 2] annulation reaction mechanism has been studied in theory, but the possible mechanisms of phosphine-catalyzed [3 + 3] annulations have not been investigated before, thus, the role acid/base conditions (like a switch) remains unclear by now. In addition, there are some questions still need to be explored and solved, for example, the detailed mechanisms of the two competing reactions the roles of catalyst PPh_3 and protic media AcOH, and the determining step of the phosphine-catalyzed [3 + 3] annulation and so on. All the above questions promoted us to perform this theoretical work, which should be useful for understanding the competing reaction mechanisms better, and also provide valuable insights for rational design and development for the phosphine-catalyzed annulation reactions.

In the present study, the reactants **R1** (5-acetoxypenta-2,3-dienoate, depicted in Scheme 1), **R2** (3-oxo-3-phenylpropanenitrile, depicted in Scheme 1), and catalyst **PPh$_3$** (triphenylphosphine, depicted in Scheme 1) were chosen as the objects of investigation. The reaction mechanisms were studied using the density functional theory (DFT), which has been widely used in the study of the organic and enzymatic reaction mechanisms [63–73].

2. Computational details

All theoretical calculations were performed using Gaussian 09 programs [74]. All structures of reactants, transition states, intermediates, and products were optimized at M06-2X/6-31G(d, p) level [75,76] in toluene solvent using the integral equation formalism polarizable continuum model (IEF-PCM) [77,78]. M06-2X can get the more accurate energy barrier than other density functional methods, especially for the hydrogen shift. Considering the key role of the hydrogen-shift transition states in the competing pathways of the title reaction, the calculation was performed by using the Minnesota 06-2X functional [79]. The corresponding vibrational frequencies were calculated at the same level to take account of the zero-point vibrational energy (ZPVE). We confirmed that each transition state has only one imaginary frequency, and all the reactants, intermediates, and products have no imaginary frequencies. Moreover, the intrinsic reaction coordinate (IRC) calculations at the same level were performed to ensure that the transition states led to the expected reactants and products. Furthermore, single-point energies have been refined at the M06-2X/6-311 + G(d, p) level in toluene solvent using IEF-PCM. All discussions in this paper are based on the single-point energies plus ZPVE corrections.

3. Results and discussion

As proposed by the experimental report (Scheme 1), the process associated with the structural transfer from reactants to intermediate **M6** (depicted in Scheme 2) should be the same in the two competing reactions, then we suggested and investigated six possible reaction pathways for the following processes, which lead to the two different products including **P1** (derivatives of 2H-pyran, depicted in Scheme 3) and **P2** (derivatives of furan, depicted in Scheme 4). The detailed reaction mechanisms have been illustrated below.

3.1. The structural transfer from reactants to intermediate M6

As shown in Scheme 2, there are four reaction steps for the structural transformation from the reactants **R1**, **R2** to the intermediate **M6**:

The first step is the catalyst **PPh$_3$** nucleophilic attacks on **R1** to form intermediate **M1**. The distance of P1—C2 is shortened from 2.27 Å in transition state **TS1** to 1.82 Å in intermediate **M1**, and the angle of C3—C2—C4 changes from 178.82° in reactant R1 to 126.97° in intermediate **M1** (Fig. 1). In this step, the addition of catalyst **PPh$_3$** makes reactant **R1** to be a very active zwitterionic intermediate.

Then the second step is the breaking of the bond C5—O6 via transition state **TS2** (Scheme 2). This step includes two processes: firstly, intermediate **M2** is formed by the by weak interaction between intermediate **M1** and reactant **R2** (Scheme 2). As shown in Fig. 1, the distances of C5—O6, C4—C5, and O6—H7 are changed from 2.04 Å, 1.38 Å, and 2.10 Å in transition state **TS2** to 3.10 Å, 1.33 Å, and 1.90 Å in intermediate **M3**, separately, which indicates the C5—O6 bond has been broken in intermediate **M3** and the hydrogen bond of O6···H7 has been strengthened simultaneously.

The third step is the elimination of **AcOH** via transition state **TS3**. As can be seen in Fig. 1, the distances of O6—H7 and H7—C8 change from 1.20 and 1.43 Å in transition state **TS3** to 0.98 and 2.26 Å in intermediate **M4**, respectively, which indicates that the bond H7—C8 is broken and the O6—H7 bond is formed in intermediate **M4** via transition state **TS3**.

The last step is an intermolecular nucleophilic attack process via transition state **TS4**. As presented in Fig. 1, the structure of intermediate **M5** composes of two parts which are combined by weak interaction, and the distance of C3—C8 is 3.17 Å, then C8 atom attacks to the atom C3 to form intermediate **M6**. The distance of C3—C8 is shortened from 3.17 Å in intermediate **M5** and 2.46 Å in transition state **TS4** to 1.58 Å in intermediate **M6**, respectively, which demonstrates the full formation of C3—C8 bond. In addition, the energy barriers of the four steps are 9.93, 15.73, 0.85,