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Research paper

Mechanisms and stereoselectivities of NHC-catalyzed [4+2] cycloaddition reaction between phenylacetic acid and o-quinone methide: A computational investigation

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ABSTRACT

The mechanisms and stereoselectivities in N-heterocyclic carbene-catalyzed [4+2] cycloadditions of phenylacetic acid and o-quinone methide have been studied by the use of density functional theory (DFT) calculations. Various possible reaction pathways were located and compared. The most energy favorable pathway can be characterized by four stages: the formation of intermediate **IM2** via the nucleophilic attack of catalyst to phenylacetic acid (*stage I*); deprotonation of **IM2** to generate the NHC-bounded enolate intermediate **IM4** (*stage II*); addition of **IM4** to **R2** to form the six-membered ring intermediate **IM5** (*stage III*) and elimination of catalyst leading to the *RS*-configuration product **P(RS)** (*stage IV*). For stage II, both direct deprotonation and base-mediated deprotonation were examined, DFT calculations indicate that traces of base are essential for the deprotonation process. The [4+2] cycloaddition step (*stage III*) is found to be the rate- and stereoselectivity-determining step with an overall free energy barrier of 16.6 kcal/mol. The predicted high *cis*-diastereoselectivities and enantioselectivities for the [4+2] annulation reaction are in good agreement with the experimental observations. The present study should be useful to the development of this kind reactions in the future.

1. Introduction

Coumarins as structural motif are often found in a large number of natural products and pharmaceuticals [1]. Among them, 3,4-dihydrocoumarin derivatives exhibit a variety of biological activities and have been used as antihypertensive, antitumor, antioxidation, and antiplatelet aggregation agents [2]. Consequently, the design and development of efficient methods for the synthesis of 3,4-dihydrocoumarin derivatives are of great value and have received considerable attentions [3,4]. Metal-based catalytsis has been widely pursued to construct dihydrocoumarins over the years [4]. However, most of these reactions require harsh conditions or expensive catalysts, which limits the application of these approaches.

In recent years, *ortho*-quinone methides (o-QMs) as important intermediates in both organic synthesis [5] and biological processes [6] have emerged as a versatile synthon for the construction of 3,4-dihydrocoumarins [7]. For example, Lectka et al. [8] reported the [4+2] cycloaddition of o-QMs with silyl ketene acetals to form dihydrocoumarin skeletons, which utilized a chiral phase-transfer catalyst (PTC). Zhou and coworkers [9] demonstrated that the asymmetric addition of deconjugated butenolides with o-QMs afforded a series of functionalized 3,4-dihydrocoumarins, and they rationalized the observed regioselectivity by DFT calculations. With the use of a chiral amidine derivative, Deng and coworkers [10] realized the coupling of carboxylic acids and o-QMs in good yield and excellent stereoselectivities.

The N-heterocyclic carbenes (NHCs) have attracted increasing interest in organic chemistry due to their wide application as ligands in the organometallic catalysts [11] and as Lewis bases catalysts [12]. As important organocatalysts, NHCs have been successfully used in a variety of carbon–carbon and carbon–heteroatom bond formation reactions, such as benzoin, Stetter, Mannich, Michael, Claisen rearrangements, C—H bond activation, C—C bond activation, and cycloaddition [13]. Moreover, the NHC-catalyzed cycloadditions of o-QMs to form dihydrocoumarins have also been reported [14]. In 2009, Ye et al. [14b] have developed a NHC-catalyzed [4+2] cycloaddition of ketenes and o-QMs to obtain dihydrocoumarins. In 2015, Scheidt et al. [14a] reported a highly enantioselective [4+2] annulation for the synthesis of dihydrocoumarin derivatives via NHC catalysis, which utilized a dual activation strategy. Very recently, the Yao group [15] developed the

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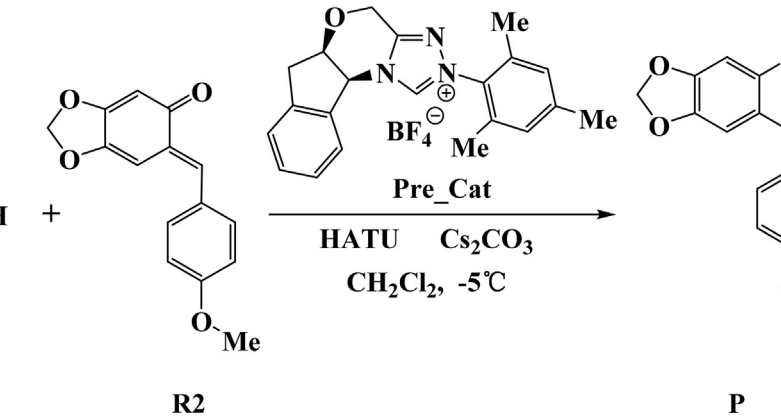

Scheme 1. NHC-catalyzed [4 + 2] cycloaddition reaction.

NHC-catalyzed [4 + 2] cyclization of saturated carboxylic acid with o-QMs for synthesis of dihydrocoumarins. The reaction offered high yields and *enantio*- and diastereoselectivities. More experimental details are illustrated in Scheme 1.

Over the past few years, a number of theoretical studies on different NHC-catalyzed cycloaddition reactions have been reported [16], and these studies have greatly enhanced people's understanding of the mechanistic features of NHC-catalyzed annulations. However, to the best of our knowledge, no theoretical study on the NHC-catalyzed [4 + 2] cycloaddition reaction between saturated carboxylic acid and o-QMs has ever been reported. There remain considerable uncertainties about the mechanism, we are particularly interested in the following questions: (1) How does the catalytic reaction happen? (2) Which step is the rate-determining step? (3) Which step is the stereoselectivity-determining step? (4) What are the roles of NHC catalyst and the additive HAUT? With these questions in mind, we conducted a DFT study on the mechanism and stereoselectivity of the NHC-catalyzed [4 + 2] cycloaddition reported by Yao et al. (Scheme 1) [15]. We wish to unveil the mechanism of the title reaction as well as to determine the factors responsible for enantioselectivity.

The remainder of this paper is organized as follows: The computational methods are described in Section 2. In Section 3.1 of this paper, the mechanisms of [4 + 2] cycloaddition catalyzed by the NHC catalyst are presented. In Section 3.2, the origins of stereoselectivities in the current [4 + 2] cycloaddition reaction are analyzed in detail. The nature of catalyst is illustrated in Section 3.3. We finish with some concluding remarks in Section 4.

2. Computational methods

All calculations presented herein were performed with the Gaussian 09 software package [17]. Geometry optimizations of all the minima and transition states were prformed in the gas phase using the M06-2X method[18] in conjunction with the 6–31G(d,p) basis set. It has been demonstrated that M06-2X provide a better description of kinetics and thermodynamics [19]. All species were fully geometry optimized. In the case of transition states, the Berny optimization algorithm (TS) [20] and "opt = calcfc" key word were used. Vibrational frequency calculations were performed at the same level of theory, to characterize whether the obtained structure is a minimum (with all real frequencies) or a transition state (with only one imaginary frequency), as well as obtain thermodynamic correction. The intrinsic reaction coordinate (IRC) calculations were performed to confirm the transition states indeed connect two relevant minima [21]. Single-point energies were computed at the M06-2X/6–311++G(d,p) level of theory in the solvent phase using the gas-phase optimized geometries. Many previous studies from our group and others indicated that the Cramer-Truhlar continuum solvation model SMD [22] reasonably accounted for the behavior of solvated condensed phases [23]. This solvent model was thus selected to evaluate the solvation effects of dichloromethane (CH_2Cl_2) without defining partial atomic charges. The dielectric constant of CH_2Cl_2 was taken as 8.93. Free energies in solution were calculated by adding the thermal correction at M06-2X/6-31G(d,p) level to the corresponding single-point energy at the SMD(CH_2Cl_2)/M06-2X/6–311++G(d,p) level. All discussions in this paper are based on the Gibbs free energies.

To examine the influence of functionals, other methods (such as B3LYP, M06-2X-D3) were employed with 6–31G(d,p) basis set to optimize the transition states involved in the [4 + 2] cycloaddition step, followed by single-point energy calculations. In addition, to check the influence of basis sets, we also performed geometry optimization at M06-2X/6–31+G(d,p) level. The calculated results are given in Table S1. As can be seen from Table S1, although these results exhibit some quantitative spread, they all predict similar relative energies.

Furthermore, natural bond orbital (NBO) analyses were performed at the M06-2X/6–311++G(d,p) level of theory to assign the atomic charges and Wiberg bond indexes [24]. Moreover, the global reactivity index (GRI) analysis was carried out to reveal the role of the NHC catalyst. The molecular global electrophilicity character is described using the electrophilicity index ω, which is given by the following expression, $\omega = (\mu^2/2\eta)$(eV) [25], in which μ and η are the electronic chemical potential and the chemical hardness, respectively. Both μ and η can be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H - \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [26]. According to the HOMO energies obtained within the Kohn–Sham scheme [27], Domingo and coworkers introduced an empirical (relative) nucleophilicity index N [28], defined as $N = \varepsilon_{H(Nu)} - \varepsilon_{H(TCE)}$. This nucleophilicity scale takes tetracyanoethylene (TCE) as a reference.

3. Results and discussion

3.1. Reaction mechanism

In this part, we will discuss the detailed mechanism of the NHC-catalyzed [4 + 2] cycloaddition shown in Scheme 1. On the basis of our calculation results, the possible reaction mechanism is outlined in Scheme 2. As shown in Scheme 2, the precatalyst **Pre-Cat** is deprotonated with the aid of CO_3^{2-} (derivative from the base Cs_2CO_3) to produce the actual catalyst **Cat** and bicarbonate anion (HCO_3^-) [29]. Note that in the experiment, the catalytic system employs phenylacetic acid as one substrate (o-quinone methide as the other substrate) and HAUT as additives. In our calculations the ester **R1** shown in Scheme 2 was used as the starting reactant, since it can be formed when phenylacetic acid ($PhCH_2COOH$) reacts with HAUT.

Our results suggest that the catalytic cycle includes four stages (as shown in Scheme 2), *i.e.* additon of the actual catalyst **Cat** to **R1**, affording intermediate **IM2** (Stage I), deprotonation of **IM2** to form intermediate **IM4** (Stage II), [4 + 2] cycloaddition of o-quinone methide **R2** with **IM4** to generate intermediate **IM5** (Stage III) and catalyst releases from **IM5** producing the final product **P** (Stage IV). The corresponding free energy profiles are shown in Fig. 1 (Stages 1–2) and 2 (Stages 3–4). As shown in Figs. 1 and 2, we set the free energy of **Cat**+ **R1** + **R2** as 0.0 kcal/mol as reference in the energy profile. In the following section, we discuss the reaction mechanism in terms of the four stages.