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Mechanism and Reactivity of Rh-Catalyzed Intermolecular [5+1] Cycloaddition of 3-Acyloxy-1,4-Enyne (ACE) and CO: A Computational Study

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Abstract

The first theoretical study on the mechanism of $[\text{RhCl}(\text{CO})_2]_2$ -catalyzed [5 + 1] cycloadditions of 3-acyloxy-1,4-enyne (ACE) and CO has been performed using density functional theory (DFT) calculations. The effect of ester on reactivity of this reaction has been investigated. The computational results have revealed that the preferred catalytic cycle involves the sequential steps of 1,2-acyloxy migration, CO insertion, reductive elimination to form ketene intermediate, 6π -electrocyclization, and aromatization to afford the resorcinol product. The 1,2-acyloxy migration is found to be the rate-determining step of the catalytic cycle. The electron-rich *p*-dimethylaminobenzoate substrate promotes 1,2-acyloxy migration and significantly increases the reactivity by stabilizing the positive charge building up in the oxocyclic transition state.

Graphical Abstract

Keywords

(5+1) Cycloaddition; Rhodium catalyst; DFT; Ester effect

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/>

1. Introduction

Six-membered carbocycles are one of the most ubiquitous ring compounds in organic chemistry. Among the various synthetic routes to build six-membered cycles, transition-metal-catalyzed cycloaddition is widely regarded as one of the most efficient approaches to access highly functionalized carbo- and heterocycles.¹ So far, a number of metal-catalyzed [3 + 3],² [4 + 2],³ [5 + 1],⁴⁻⁹ [2 + 2 + 2],¹⁰ [3 + 2 + 1],¹¹ and [4 + 1 + 1]¹² reactions have been developed for the synthesis of six-membered carbocycles. However, the formation of a six-membered ring through [5 + 1] cycloaddition has been much less developed, presumably due to the difficulty of searching the appropriate 5-carbon component. The primary 5-carbon components for transition-metal-mediated [5 + 1] cycloadditions have been focused on vinylcyclopropane (VCP)⁴ and their related derivatives.⁵ Meanwhile, allenylcyclopropanes⁶ and cyclopropenes⁷ have also been adopted as the 5-carbon synthons in some [5 + 1] cycloadditions. Recently, Malacria and co-workers reported a new class of [5 + 1] cycloadditions using 3-acyloxy-1,4-enyne (ACE) in place of VCP as 5-carbon synthon.⁸ This methodology provides an efficient route to the six-membered carbocyclic system of aromatic resorcinols (Scheme 1), a series of valuable compounds with important bioactivity¹³ and antibacterial activities.¹⁴ More recently, Tang et. al. developed a tandem annulation and [5 + 1] cycloaddition of 1,4-enynes to successfully construct substituted carbazoles, dibenzofurans, and tricyclic compounds containing a cyclohexadienone moiety.¹⁵

Compared with the experimental discoveries of several modes of [5 + 1] cycloaddition, theoretical studies on the mechanisms of metal-catalyzed [5 + 1] cycloadditions are even rare. Yu group have reported their density functional theory (DFT) calculations on the mechanism of the [5 + 1] cycloaddition of 1-yne-vinylcyclo-propanes and two CO units.^{5c} To our best knowledge, the mechanism of the [5 + 1] cycloaddition of ACE and CO remains unknown till now. The previous experimental studies by Malacria⁸ suggested several pathways for the formation of the resorcinols through [5 + 1] cycloaddition of ACE and CO (see Scheme S1 in support information). It is not clear which pathway is actually preferred and which step determines the reaction rate. To answer these questions, we performed theoretical computations on these pathways. In addition, the effect of ester on the reactivity of this [5 + 1] cycloaddition is also experimentally found to be interesting¹⁶ as shown in Table 1: significant enhancement of reactivity was observed for benzoate substrate bearing an electron-donating dimethylamino group. For examples, *p*-dimethylaminobenzoate **1c** can react with CO at 50 °C to generate the desired product in good yield in one hour. While pivalate **1b** does not work at the same condition but requires higher CO pressure, higher temperature and longer reaction time (entry 3 vs entries 2 and 2'). Significantly, *p*-dimethylaminobenzoate with methyl substituent at C3 (substrate **1f**) can react with CO at room temperature (entry 6). In contrast, substrate **1e** does not work at room temperature (entry 5). Clearly, the electron-rich *p*-dimethylaminobenzoate dramatically increases the reactivity. In this work, computational investigations on [RhCl(CO)₂]₂-catalyzed intermolecular [5 + 1] cycloadditions between 3-acyloxy-1,4-enynes (ACEs) and CO have disclosed the preferred mechanism and origins of electronic effects of substrates on

reactivities. These results may have broad implications in understanding and design of transition-metal-catalyzed reactions.

2. Computational Details

Geometry optimization and frequency analysis were performed in CH₂Cl₂ solvent with the SMD solvation model using B3LYP and a mixed basis set of SDD for Rh and 6–31G(d) for other atoms. Single point energies were calculated at the M06/6–311+G(d,p) level (SDD for Rh) with the SMD model (CH₂Cl₂ solvent) on B3LYP-optimized geometries. This is the same methodology that we used in our previous theoretical studies of [RhCl(CO)₂]₂-catalyzed [5 + 2] cycloadditions involving 3-acyloxy-1,4-enynes (ACEs).¹⁷ All calculations were carried out with Gaussian 09.¹⁸ All reported free energies involve zero-point vibrational energy corrections and thermal corrections to Gibbs free energy at 298 K. Computed structures are illustrated using CYLVIEW drawings.¹⁹

3. Results and discussion

We employed ACE **1** as the model substrate and computed the mechanism of the [5 + 1] cycloaddition of ACE **1** and CO. The computed Gibbs free energy profiles of several possible reaction pathways are shown in Figure 1. Initially, the rhodium dimer [RhCl(CO)₂]₂ dissociates²⁰ and coordinates to the ACE, leading to the formation of a ACE-Rh(CO)Cl π complex **4**.²¹ This complex enters the catalytic cycle. Among the three possible pathways **a**, **b** and **c**, pathway **a** (in black line) is calculated to be the most favored mechanism. Along pathway **a**, firstly, the stepwise 1,2-acyloxy migration occurs via intermediate **5** to afford **6**. In this step Rh(I) is oxidized to Rh(II). Then coordination of CO to rhodium center generates **7**. Subsequently, CO insertion into the Rh-C(sp²) bond affords the seven-membered metallacycle **9**, which then isomerizes to a more stable species **10** by rupture of Rh-C1 bond followed by rotation of the C2-C3 bond, leading to the styryl group positioned far from the rhodium center in **10**. Then reductive elimination of **10** affords the ketene **11** and the simultaneous release of the active catalyst Rh(CO)Cl, which coordinates to another ACE **1** molecule to start the next catalytic cycle. Isomerization of **11** may afford **12** by rotating the C2–C3 bond. Next, 6 π -electrocyclization of **12** leads to product **2**, which can undergo aromatization to afford the resorcinol product **3**. In pathway **a**, the rate-determining step is 1,2-acyloxy migration, requiring an activation free energy of 17.4 kcal/mol (**TS1**, Figure 1). The energy barrier for CO insertion is 5.4 kcal/mol (from **7** to **TS3**). Reductive elimination of **10** and the subsequent 6 π -electrocyclization of **11** needs to overcome an overall free energy barrier of 12.3 kcal/mol (from **11** to **TS4**). The geometries of the key transition states involved in this favored pathway are shown in Figure 2.

In pathway **b**, the intermediate **6** isomerizes to carbene **13**, in which the C1 atom is positioned far away from the rhodium center. Coordination of CO to rhodium center then forms intermediate **14**. Subsequently, CO insertion into the Rh-C(sp²) bond (**TS5**) generates intermediate **10**. This step requires an activation free energy of 24.5 kcal/mol. The overall activation free energy (from **14** to **TS5**) of pathway **b** is higher than that of the rate-determining step of pathway **a**. The high energy of **TS5** may be attributed to the unstable 12-electron structure of Rh in **TS5**. Therefore, we considered another possible transition state

TS5-1 that possesses two CO ligands. The calculation results showed that the energy of **TS5-1** is also higher than that of **TS3** (see Figure S2 in the Supporting Information). Thus, pathway **b** should be ruled out from the favored pathways.

In pathway **c**, reductive elimination of **9** affords the complex **15**. Aromatization of **15** leads to resorcinol complex **16**, which undergoes ligand exchange to produce resorcinol product **3**. This pathway requires an activation free energy of 27.3 kcal/mol (from **9** to **TS6**), much higher than that of the rate-determining step of pathway **a**. Because the formation of a new bond between two double bonds in **TS4** is easier than that between two single bonds in **TS6**, **TS4** is lower in energy than **TS6**. Therefore, pathway **c** should be ruled out from the favored pathways too. Based on the above data, pathway **a** is proposed as the most preferred mechanism.

We then investigated the effects of substituents on the reactivity of the reaction, which is determined by the barrier of 1,2-acyloxy migration. As shown in Table 1, experimentally, electron-rich esters dramatically increase the reactivity of ACEs in the [5 + 1] cycloaddition¹⁶. This is similar to the Rh-catalyzed intermolecular [5 + 2] cycloadditions of ACEs and alkynes.²² The computed free energy barriers of the 1,2-acyloxy migration steps provide good agreement with the experimental reactivities of different esters (Table 1). This is because that the electron-donating group stabilizes the positive charge building up in the oxocyclic transition state as illustrated in Figure 3. Moreover, computational results show that electronic effects on the rate of the alkyne insertion, the reductive elimination, and 6 π -electrocyclization steps are very small (see Table S1 in the Supporting Information). These results confirm that 1,2-acyloxy migration is the rate-determining step and the different reactivities of ACE substrates are due to the effects on 1,2-acyloxy migration. The activation barriers for acyloxy migration of electron-deficient ester **1g** (R1 = -CF₃, entry 7) increases dramatically compared with those of other esters listed in Table 1. The activation barrier for acyloxy migration of *p*-nitrobenzoate which bears an electron-withdrawing NO₂ group (entry 8) also greatly increases compared with that of the electron-rich *p*-dimethylaminobenzoate (entry 3). These results indicate that electron-deficient esters should be unfavorable for this reaction. The computed barrier of ACE **1i** (R2 = Me, entry 9) is slightly increased compared with that of ACE **1c** (R2 = Ph, entry 3) due to weaker electron-donating ability of methyl group than phenyl group. Significantly, because the substituent at C3 stabilizes the allyl intermediate via hyperconjugation and lowers the barrier of acyloxy migration, the ACE with alkyl substitution at C3 requires relative lower 1,2-migration barrier than ACE without alkyl substitution (Table 1). As a result, the reaction of substrate **1f** occurs at room temperature, while that of **1c** takes place at 50 °C (entries 6 and 3 in Table 1). The pivalate **1e** (entry 5) is predicted to react at 50 °C or at higher temperature according to the calculated 1,2-migration barrier. The computed barrier of ACE **1j** (R3 = Et, entry 10) is slightly decreased compared with that of ACE **1f** (R3 = Me, entry 6) due to stronger hyperconjugation effect of ethyl than methyl group. Moreover, the above computational results implies that the reactivities should be determined by different ester substrates and be irrelevant to CO for the [5+1] cycloaddition or irrelevant to alkynes for the [5+2] cycloaddition, since only ACE is involved in the rate-determining acyloxy migration for

both [5+1] and [5+2]¹⁷ cycloadditions. This is consistent with experiments, for example, both [5+1] and [5+2] reactions with substrate **1f** takes place at room temperature.

4. Conclusion

In summary, we performed DFT calculations to explore the mechanism of [RhCl(CO)₂]₂-catalyzed [5 + 1] cycloaddition of ACE and CO and disclosed the origins of substituent effect on reactivity. The catalytic cycle involves a stepwise 1,2-acyloxy migration to form a rhodium-allyl intermediate, CO insertion into the Rh–C(sp²) bond to generate a seven-membered metallacycle intermediate, reductive elimination to afford ketene, 6 π -electrocyclization and subsequent aromatization to produce the resorcinol product. The 1,2-acyloxy migration is predicted to be the rate-determining step, which is consistent with higher reactivity experimentally observed for ACEs bearing an electron-rich benzoate. Our theoretical studies disclosed here should have broad implications in understanding transition-metal-catalyzed cycloadditions and may facilitate the design of new types of reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Gibbs free energy profile of the [RhCl(CO)₂]₂-catalyzed intermolecular [5 + 1] cycloaddition of ACE 1 and CO. Energies are in kcal/mol and calculated using M06/SDD-6-311+G(d,p)/SMD(CH₂Cl₂)/B3LYP/SDD-6-31G(d)/SMD(CH₂Cl₂).

Figure 2.
Transition states in pathway **a** of the $[\text{RhCl}(\text{CO})_2]_2$ -catalyzed intermolecular $[5 + 1]$ cycloaddition of ACE **1** and CO.

Figure 3.

NPA charges of transition states **entry2-TS1** and **entry3-TS1** in Table 1. In the rate-determining 1,2-acyloxy migration step, the ester carbon (C6) is more positively charged in the transition state (**TS1**) than in the reactant (**4**) and the product (**6**). Thus, the electron-rich *p*-dimethylaminobenzoate substrate stabilizes the positive charge on C6 in the acyloxy migration transition state (**entry3-TS1**) and promotes the reaction. As expected, the C6 atom in **entry3-TS1** is less positively charged than that in the transition state with the acetate substrate (**entry2-TS1**).

Scheme 1.

$[\text{RhCl}(\text{CO})_2]_2$ -Catalyzed [5+1] Cycloaddition of ACE and CO.

Table 1

Experimental results and Computed Activation Free Energies for [5+1] Cycloadditions of ACE Derivatives and CO.

Entry	substrate	R ¹	R ²	R ³	Experimental results ^{a,b}				Computational results	
					p _{CO} (atm)	temp (°C)	time (h)	yield (%)	ref	G (TS1-4) ^c
1	1a	Me	Ph	H	80	80	5h	67	8a	17.4
2	1b	<i>i</i> -Bu	Ph	H	1	50	1h	no reaction	16	15.1
2'	1b	<i>i</i> -Bu	Ph	H	80	80	5h	76	8a	15.1
3	1c	<i>p</i> -Me ₂ NC ₆ H ₄	Ph	H	1	50	1h	66	16	12.7
4	1d	Me	Ph	Me	80	80	15h	68	8a	13.9
5	1e	<i>i</i> -Bu	H	Me	1	r.t.	24h	no reaction	16	12.9
6	1f	<i>p</i> -Me ₂ NC ₆ H ₄	H	Me	1	r.t.	24h	69	16	11.7
7	1g	-CF ₃	Ph	H	-	-	-	-	-	24.8
8	1h	<i>p</i> -O ₂ NC ₆ H ₄	Ph	H	-	-	-	-	-	16.4
9	1i	<i>p</i> -Me ₂ NC ₆ H ₄	Me	H	1	50	1h	35	16	13.4
10	1j	<i>p</i> -Me ₂ NC ₆ H ₄	H	Et	-	-	-	-	-	10.9

^a Conditions for entries 1, 2', and 4: [RhCl(CO)₂]₂ (2.5–5 mol%), dichloromethane (0.05–0.016 M), CO (80 atm).

^b Conditions for entries 2, 3, 5 and 6: [Rh(CO)₂Cl]₂ (5–7 mol%), ClCH₂CH₂Cl (0.4 M), CO (1 atm).

^c Activation free energy (in kcal/mol) of the rate-determining 1,2-acyloxy migration step; energies are calculated using M06/SDD-6-311+G(d,p)/SMD(CH₂Cl₂)/B3LYP/SDD-6-31G(d)/SMD(CH₂Cl₂).