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Theoretical Study of the [2+2+2+1] Cycloaddition Mechanism of Enediynes and Carbon Monoxide Catalyzed by Rhodium

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The [2+2+2+1] cycloaddition mechanism of enediynes and carbon monoxide catalyzed by the $[Rh(CO)_2Cl]_2$ rhodium dimer has been studied using density functional theory, comparing this multistep process with the two-step reaction in the absence of a catalyst. According to our results, the multistep mechanism agrees with that previously suggested. The great selectivity of this reaction and the influence of the chosen solvent in this selectivity were also analyzed.

Introduction

Cycloadditions play an important role in the continuous search for new reactions in organic synthesis. In some cases, these reactions need the presence of functional groups that enhance the reactivity of a given substrate. In general, olefins, dienes, or acetylenes exhibit poor reactivity and require extreme conditions or special methods for obtaining good yields. Metal catalysts form complexes with olefins, dienes, or acetylenes, increasing their reactivity and enabling highly selective cycloaddition reactions, thus opening interesting pathways for a new synthetic chemistry.

The term "carbocyclization" is used for describing ring-forming processes which involve the formation of new carbon−carbon bonds via carbometallation. This fact distinguishes carbocyclizations from radical cyclizations and photochemical or thermal cycloadditions. Transition metals like cobalt, iron, molybdenum, nickel, palladium, rhodium, ruthenium, titanium, and zirconium are used in carbocyclizations.[1,2]

Rhodium(I) complexes have been employed in the past decade in intra- and intermolecular [*m*+*n*] cycloadditions. Their versatility allowed them to be used in multicomponent [*m*+*n*+*o*+···+*x*] reactions.[3] Examples of these rhodium complexes are the Wilkinson catalyst, $RhCl(PPh_3)_3$; the $[Rh(CO)_2Cl]_2$, $[RhCl(BINAP)_2]_2$, and $[RhCl(dppb)]_2$ dimers; or the [(arene)Rh(COD)] SbF_6 salt cation. The $[Rh(CO)_2Cl]_2$ rhodium dimer is an efficient catalyst for [5+2], [6+2], or [5+2+1] reactions.[4]

A recent paper by Bennacer and co-workers[5a,5b,5c] reported a new [2+2+2+1] cycloaddition between enediynes and CO to form tricyclic 5-7-5 molecules using the $[Rh(COD)Cl]_2$ dimer as catalyst (see Figure 1). This product had been previously synthesized with the same reactants and $PhMe_2SiH$.[5a] They serendipitously discovered that the reaction also proceeds in the absence of silane, forming the same product and a small amount of 5-6-5 product. The use of 1,2-dichloroethane as solvent instead of toluene allowed us to improve the selectivity of the reaction.

It is important to remark that reaction mechanisms with and without silane are completely different.[5b] Bennacer and co-workers proposed the following mechanism for the reaction shown in Figure 1a: (i) the rhodium is coordinated with the two triple bonds, forming a five-member metallacycle; (ii) the olefin coordinates with the rhodium atom and a CO molecule is inserted as ligand, forming a 5-7-5 system; (iii) the CO ligand is inserted in the cycle forming a 5-8-5 system; and (iv) the [2+2+2+1] cycloadduct is obtained by reductive elimination, and the rhodium catalyst begins the cycle again. An early reductive elimination step occurring before the CO insertion results in the [2+2+2] cycloadduct.

The goal of this work is to study the mechanism of the [2+2+2+1] cycloaddition and to analyze the role of the rhodium catalyst in order to make a comparison with the hypothetical reaction pathway in the absence of a catalyst. The role of the dichloroethane as solvent was also studied. To explain the selectivity of the reaction, the formation of another possible product, the 5-6-5 system, and the influence of the solvent were analyzed.

Computational Details

Calculations were done with DFT (density functional theory) employing two different functionals, B3LYP and MPWLYP1M. B3LYP[6] combines the three-coefficient dependent hybrid functional for the exchange energy proposed by Becke (B3) with the correlation functional proposed by Lee, Yang, and Parr (LYP). MPWLYP1M[7] is a hybrid GGA (generalized gradient approximation) correlation functional developed specifically for organometallic chemistry calculations by D. G. Truhlar's group. 6-31G(d,p) Pople's basis set was used for C, O, H, and Cl atoms, and the effective core potential LANL2DZ was used for the Rh atom.[8] IRCs (intrinsic reaction path)[9] were obtained at the same levels. Each of the stationary points was characterized as minimum or transition state by the vibrational frequency analysis, using analytical second derivatives.

For calculations taking into account dichloroethane and toluene solvents, the PCM method[10] (polarized continuum model) developed by Tomasi was used. All calculations were carried out with Gaussian03 program.[11]

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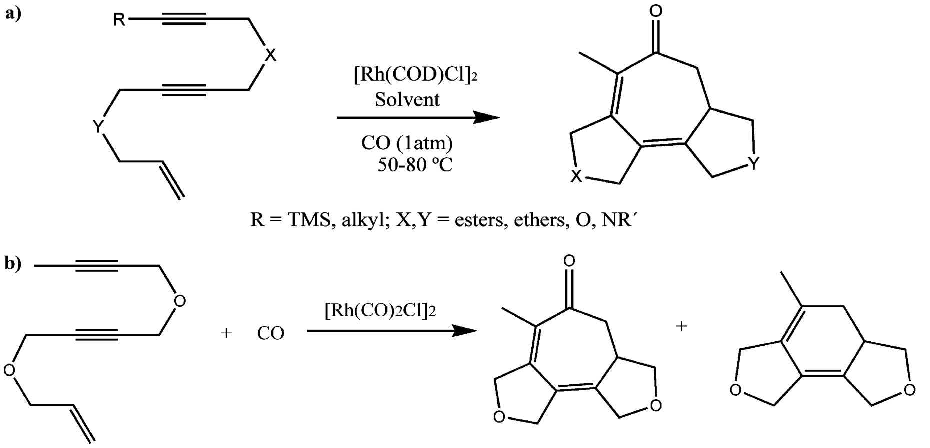

Figure 1. (a) General [2+2+2+1] cycloaddition.[5a] (b) [2+2+2+1] reaction studied in this work. For experimental data, see ref 5b.

Results and Discussion

A. Rhodium-Catalyzed [2+2+2+1] Cycloaddition in the Gas Phase. Although Bennacer and co-workers[5] used the $[Rh(COD)Cl]_2$ dimer as the catalyst in their experimental study, we have chosen the $[Rh(CO)_2Cl]_2$ dimer for our calculations, which is frequently used in experimental studies for this kind of cycloadditions. We have considered this ligand as a reasonable model to study the reaction mechanism. This procedure allowed us to realize a saving of computational cost. The $[Rh(CO)_2Cl]_2$ dimer is found in equilibrium with two monomeric units, and the rhodium atom bonded to two ligands (CO and Cl) is the active species.[12] Figures 2 and 3 show the intermediates and the transition states geometry and the energy profile for the [2+2+2+1] cycloaddition in the gas phase catalyzed by rhodium. **I1**, the starting complex, shows an arrangement in which the transition metal is coordinated to the two enediyne triple bonds. These two bonds are parallel and depicted as a tweezer. Considering those multiple bonds as two different ligands, rhodium adopts a planar-square geometry. From the point of view of the transition metal, **I1** is a $16e^-$ complex. In spite of the known "$18e^-$ electron rule", it is usual in Rh(I) and in other d^8 metals from the 8−11 groups to adopt $16e^-$.[13]

Through the transition state **TS2** we get **I3**, where a five-atom ring and a five-atom metallacycle are formed.[14] The enediyne double bond must interact with the rhodium atom to expand the five-atom metallacycle to an eight-atom metallacycle. The intermediate **I3** is in conformational equilibrium with **I4**. The conformer **I4** will be the one that leads to the ring expansion.

There is an insertion of a CO molecule which coordinates to the rhodium atom in **I5**. This insertion is an exothermic process where the transition metal adopts an octaedric structure with a coordination number equal to six. The rhodium interacts with four carbons in the plane (one of them, the CO ligand), and Cl and the initial CO are above and below the plane.

TS6 corresponds to the metallacycle expansion from five to seven atoms. The rhodium complex in **TS6** has octaedric geometry and $20e^-$. Using the ligand field theory, this means that the first antibonding molecular orbital will be occupied. This unfavorable situation is clearly overcome in **I7**, where the rhodium coordination number decreases to five, adopting a square-base pseudopyramidal geometry. The **I7** complex satisfies the $18e^-$ electron rule.

One of the CO ligands and the carbon which is next to the rhodium atom interact in **TS8**, so the CO insertion in the main ring takes place, forming a new 5-8-5 system in **I9**. Through the transition state **TS10** the two carbon atoms bonded to the rhodium atom form a new bond, and finally, in **I11**, we get the desired 5-7-5 product. The rhodium atom has a coordination number equal to four in **TS10**, but in **I11** is equal to three, adopting a T-shape geometry. Whereas the transition metal is bonded through the carbon atom to the carbonyl group in the transition state, in **I11** the rhodium interacts with the cycloheptanone oxygen atom. A new enediyne molecule will react with the catalyst, beginning the cycle again.

Two different functionals were used for the calculations of the catalyzed cycloaddition in the gas phase: B3LYP and MPWLYP1M with 6-31G(d,p)+LANL2DZ basis set (see Table 1). Looking at the obtained values, we can conclude that using a specific functional for organometallic compounds is not especially relevant in this case. Except for **TS10**, the barriers are quantitatively very similar in both cases, so we will take B3LYP as the reference method in the following sections.

If we take a look at Table 1 and Figure 3, we can observe that **TS6** and **TS10** are very energetically expensive in relation to the **I5** and **I9** intermediates (over 30 kcal/mol in terms of free energy). However, **TS2** is the highest free energy point of the reaction pathway (+21.21 kcal/mol with the B3LYP method). It is remarkable that from **I5** to **I11** there is an energy difference of about 20 kcal/mol between the electronic energy and the free energy. This is due to the CO insertion which influences the entropy factor of the free energy.

B. Noncatalyzed [2+2+2+1] Cycloaddition in the Gas Phase. In practice, the formation of the 5-7-5 product in the absence of a catalyst starting only from the enediyne and CO is not feasible. It is well-known that the double and triple bonds need functional groups to enable their reactivity. However, there is no problem in trying to calculate a hypothetical reaction

TABLE 1: Relative Electronic Energies (Zero-Point Energy Included) and Free Energies for the Catalyzed Reaction in the Gas Phase with B3LYP, and Relative Electronic Energies (Zero-Point Energy Included) with MPWLYP1M (kcal/mol) (Basis Set = 6-31G(d,p)+LANL2DZ)

	E_{rel} B3LYP	ΔG_{rel} B3LYP	E_{rel} MPWLYP1M
I1 + CO	0.00	0.00	0.00
TS2 + CO	21.55	21.21	19.65
I3 + CO	−27.94	−25.47	−28.60
I4 + CO	−27.32	−22.46	−27.57
I5	−38.80	−22.00	−41.00
TS6	−4.64	12.55	−10.13
I7	−51.37	−33.23	−52.23
TS8	−40.81	−22.46	−42.95
I9	−54.85	−34.52	−57.02
TS10	−22.99	−3.31	−43.98
I11	−61.44	−41.30	−57.33

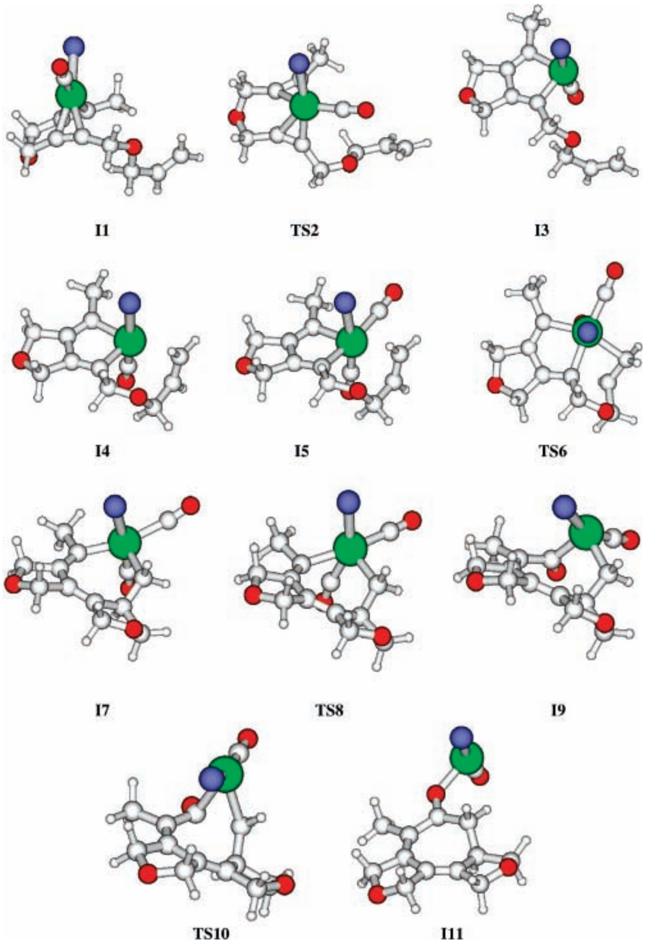

Figure 2. Illustration of the reaction pathway's structures for the [2+2+2+1] cycloaddition in the gas phase at the B3LYP/6-31G(d,p)+LANL2DZ level.

pathway in the absence of a catalyst and see how expensive it would be. That calculation was made at the B3LYP/6-31G(d,p) level.

Figure 4 shows the structures for this noncatalyzed pathway. It was not possible to find any transition state that allows us to start with the enediyne and CO and to get to the 5-7-5 product in one only step. A two-step reaction mechanism was found. In a first transition state, **TS2**, the CO molecule interacts with the two enediyne triple bonds, giving two five-member rings in **I3**. Another conformer of this structure, **I4**, is the one which has a suitable spatial disposition to react. Observing the double bond disposition in **I4**, there are two possibilities: either the terminal olefin carbon interacts with the carbonyl group carbon (**TS5_1**) or with the carbonyl group oxygen (**TS5_2**).

Considering the electronic energies (see Table 2 and Figure 5), the highest point of the reaction without a catalyst is almost 30 kcal/mol, corresponding with the first transition state. That value is 7.72 kcal/mol higher than the analogue value in the catalyzed reaction at the B3LYP/6-31G(d,p) level. Looking at the Gibbs free energy, the difference increases to almost 37 kcal/mol. The main reason is that in the absence of a catalyst the entropy plays a much more important role. In summary, the involvement of the rhodium catalyst allows us to convert a two-step process in a multistep process with lower activation energies. The olefins are activated because they are polarized: the σ-donation from the ligand to the metal decreases the electron density in the bonded atom, but the π-retrodonation from the metal to the olefin increases the electron density in the carbon atom of the other ligand.

C. [2+2+2+1] Cycloaddition in Dichloroethane Solution. The experimental reaction[5b] was carried out in dichloroethane solution at 50 °C during 21 h. The cycloaddition in dichloroethane solution at the B3LYP/6-31G(d,p)+LANL2DZ level was studied by performing single-point calculations with PCM method. Table 3 shows the results of these calculations. The most obvious conclusion is that there are not quantitative important energetic differences in dichloroethane. The reaction key step is still the same in solution, and only a slight decrease in the energy is observed (from 21.55 in the gas phase to 20.07 kcal/mol in solution). However, it is remarkable that the final

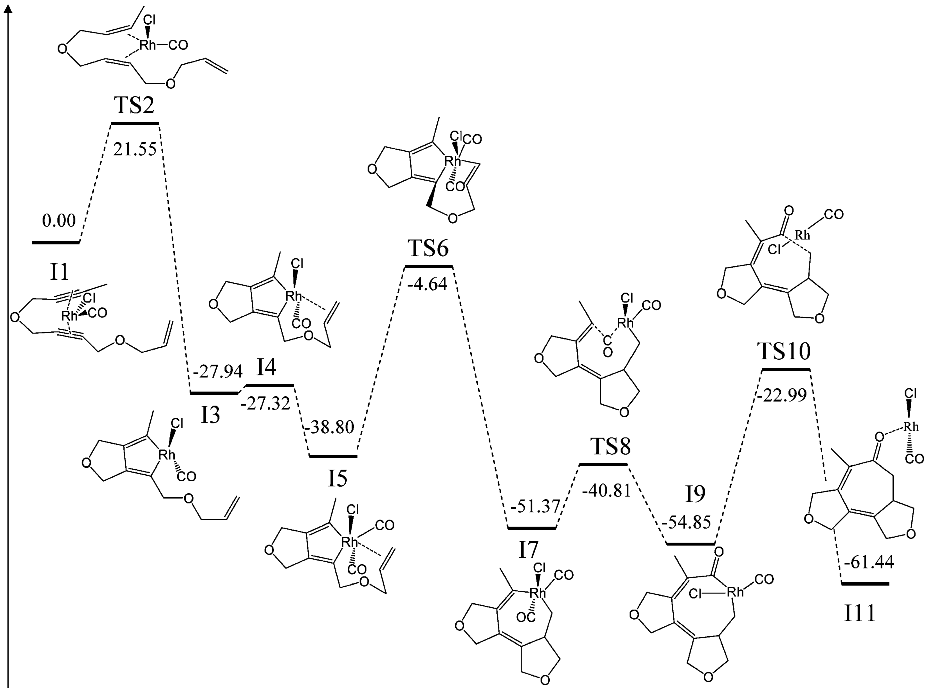

Figure 3. Relative energies with zero-point energy included in kcal/mol for the catalyzed reaction in the gas phase at the B3LYP/6-31G(d,p)+LANL2DZ level.

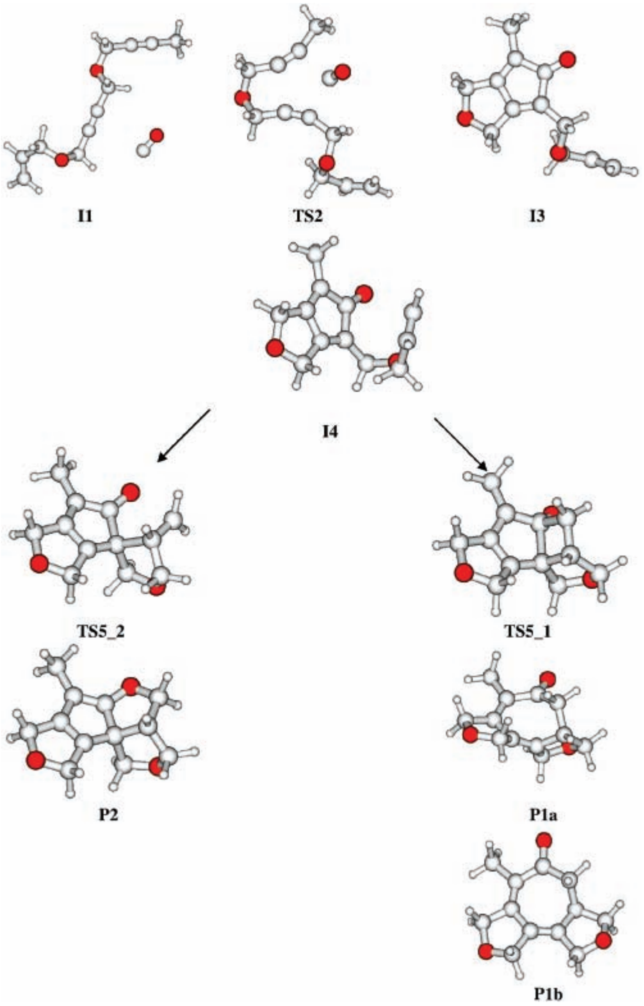

Figure 4. Illustration of the reaction pathway's structures without a catalyst in the gas phase at the B3LYP/6-31G(d,p)+LANL2DZ level.

TABLE 2: Electronic Energies (ZPE Included) and Free Energies for the Reaction without a Catalyst in the Gas Phase at the B3LYP/6-31G(d,p) Level (kcal/mol)

	E_{rel}	ΔG_{rel}
I1	0.00	0.00
TS2	29.27	36.81
I3	−65.43	−52.45
I4	−63.44	−50.03
TS5_1	−17.39	−6.10
TS5_2	−22.70	−3.10
P1_a	−43.46	−25.36
P1_b	−89.32	−71.02
P2	−66.18	−46.51

product, **I11**, is much more stable in solution than in the gas phase, so in dichloroethane solvent the reaction is more exothermic.

D. Formation of the 5-6-5 Product. The solvent influences the selectivity. The reaction of enediynes with CO in the presence of Rh catalyst and $PhMe_2SiH$ affords only the 5-7-5 product. As indicated in the introduction, it was serendipitiously discovered that in the absence of hydrosilanes it was also possible to perform the reaction, but with a small amount of 5-6-5 product. We have done B3LYP/6-31g(d,p)+LANL2DZ gas-phase, dichloroethane and toluene solution calculations for explaining the reaction selectivity.

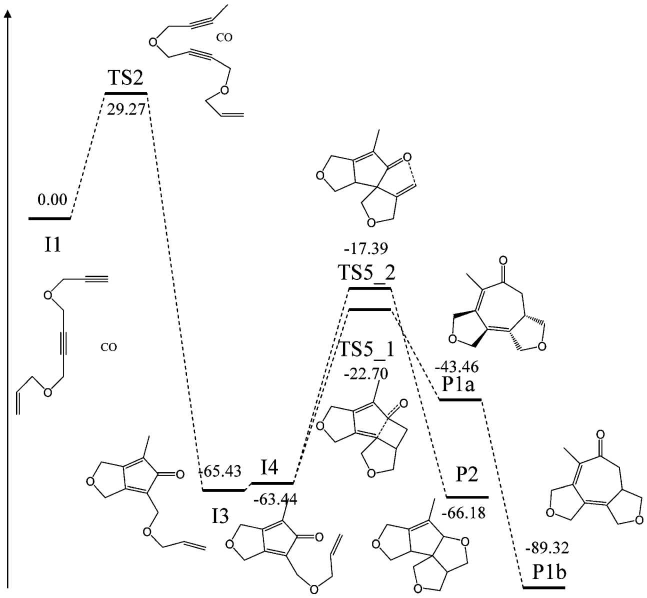

Figure 5. Relative electronic energies with zero-point energy included in kcal/mol for the reaction in the gas phase without a catalyst at the B3LYP/6-31G(d,p) level.

TABLE 3: Single-Point Calculations of Electronic Energies with the PCM Method in Dichloroethane Solution at the B3LYP/6-31G(d,p)+LANL2DZ Level

	E_{rel}(kcal/mol)
I1 + CO	0.00
TS2 + CO	20.07
I3 + CO	−29.51
I4 + CO	−28.70
I5	−41.40
TS6	−7.59
I7	−53.81
TS8	−44.99
I9	−59.45
TS10	−27.83
I11	−73.26

The 5-6-5 product is due to a reductive elimination possibility in the **I7** intermediate. Then, this 5-6-5 product is the result of a [2+2+2] elimination reaction. Instead of CO insertion, we searched for the transition state which allows the elimination, **TS_El** (see Table 4 and Figure 6). In terms of electronic energy, the difference between **TS_El** and **TS8** is almost exactly 15 kcal/mol. So almost all of the molecules will reach **I9** and not the elimination product 5-6-5. This fact explains the high selectivity in this catalyzed reaction.

In general, dichloroethane improves the reaction selectivity with most of the substrates used in the experiments,[5a] but in some cases toluene gave a best result. About the calculated reaction, we also have an experimental reference in dicloroethane.[5b] If transition states **TS_El** and **TS8** in toluene and dichloroethane are analyzed, it can be observed that the barrier for the 5-7-5 product in dichloroethane is slightly lower than in toluene, and the elimination process essentially is not affected by changing the solvent. Then dichloroethane would be, a priori, the most appropriate solvent to perform the reaction with a better selectivity.

The **I7**−**TS8** barrier decreases using dichloroethane instead of toluene. This fact let us think that if a more polar solvent is used, the reaction selectivity could be improved. Some calculations were performed at the B3LYP/6-31G(d,p)+LANL2DZ level with the PCM method to see how the energy difference changes if the solvent polarity is increased. We calculated that difference with two hypothetical solvents of dielectric constant $\epsilon = 30$ and $\epsilon = 60$. Looking at Table 5, it can be seen that

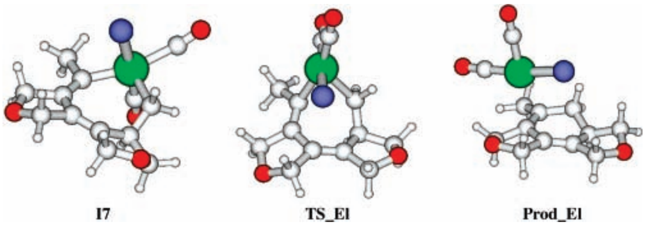

Figure 6. [2+2+2] elimination reaction in the gas phase to obtain the 5-6-5 product.

TABLE 4: Electronic Energies in kcal/mol (ZPE Included) Relative to I7 Intermediate, for Transition State TS8 (5-7-5 Product), Transition State TS_El (5-6-5 Product) in the Gas Phase, Dichloroethane Solution, and Toluene Solution at the B3LYP/6-31G(d,p)+LANL2DZ Level with the PCM Method

	gas phase	in $(CH_2)_2Cl_2$	in toluene
I7	0.00	0.00	0.00
TS8	10.56	8.82	9.46
TS_El	24.24	23.83	23.91
Prod_El[a]	−35.51	−35.60	−35.52

[a] **Prod_El** is the product 5-6-5 of the elimination.

TABLE 5: Relative Energies of TS8 and TS_El with Respect to I7 at Different Values of ϵ (kcal/mol)

ϵ	E_{rel} (**TS8**)	E_{rel} (**TS_El**)	E_{rel} (**TS_El**) − E_{rel} (**TS8**)
2.4 (toluene)	9.46	23.91	14.45
10.4 (dicloroethane)	8.82	23.83	15.01
30	7.78	23.35	15.57
60	8.81	24.41	15.60

using a more polar solvent favors the reaction selectivity, but no significant changes are observed beyond $\epsilon = 30$.

Conclusions

DFT calculations were carried out to study the mechanism of the Rh-catalyzed [2+2+2+1] cycloaddition between enediynes and CO in the gas phase and in dichloroethane solution. We found a possible four-step mechanism in which the rhodium atom forms a complex with the two triple bonds of the enediyne. An initial five-atom metallacycle leads to an eight-atom metallacycle, and the catalyst is eliminated in the last step, giving the 5-7-5 product. The comparison with the noncatalyzed reaction shows that the rhodium catalyst allows the energy barrier to be decreased in the highest energy point of the reaction by more than 7 kcal/mol due to the induced polarization in the olefins. Finally, the formation of the 5-6-5 product was studied to understand the high selectivity of this reaction, and it was found that solvent polarity favors the reaction selectivity.

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Supporting Information Available: Additional tables with absolute energies, and molecular modeling coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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