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Density Functional Theory Study of Ruthenium (II)-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Tricarbonyl Compounds

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Density functional theory has been employed to study the mechanism of the [2+2+2] ruthenium(II)-catalyzed cycloaddition between 1,6-diynes and tricarbonyl compounds, proposing a viable multistep-pathway according with that was previously suggested, but clarifying some aspects. This process is compared with the one-step reaction in absence of catalyst.

Introduction

Cycloadditions play a fundamental role in Organic Synthesis. During the last decades, transition metals are undoubtedly joined to these kind of reactions. Via carbometalation it is possible to form carbon–carbon bonds, opening new ways to synthesize novel compounds. In general, these catalysts allow to perform cycloadditions that in absence of catalyst are forbidden or difficult to achieve.[1,2] In concrete, transition metals are able to catalyze dimerization and trimerization of alkynes and alkenes. Using Csp-heteroatom triple bonds or Csp²-heteroatom double bonds, it is also possible to obtain heterocyclic compounds.[3]

The use of ruthenium complexes in cycloadditions is increasing.[4] Ruthenium complexes show a very interesting reactivity as well as catalytic activity,[5–7] which are quite different from those of palladium or rhodium, due to ruthenium has many coordination sites compared with metals of groups 9 or 10.

The [Cp*Ru(cod)Cl] complex was used as catalyst in the [2+2+2] cycloaddition between 1,6-diynes and tricarbonyl compounds (electron-deficient ketones) in a recent work by Yamamoto et al.[8] After our studies of other transition-metal catalyzed cycloadditions,[9] we focused our attention on the mechanism proposed by Yamamoto et al. for a ruthenium-catalyzed cycloaddition (see Figures 1 and 2). It can proceed through an oxidative cyclization between the less hindered alkyne and the ketone carbonyl group to produce an oxaruthenacyclopentene intermediate,[10] then the insertion of the other alkyne followed by the reductive elimination of the product completes the catalytic cycle. Yamamoto et al.[8] pointed that the final dienone could be obtained via electrocyclic ring opening of the product of the previous cycloaddition. Their mechanistical proposal is mainly based on previous literature of similar compounds, but no experimental evidence is provided by the authors and only the final product is identified by X-ray. The possible main steps are suggested without more details in the experimental work.

Taking into account Yamamoto's work,[8] density functional theory has been employed in the present work to study the

mechanism of this [2+2+2] cycloaddition, which is not trivial due to several complex conformational changes that are needed to achieve the product. The goal of this work is to provide a detailed study of the mechanism, completing and confirming the Yamamoto's hypothesis. The role of the ruthenium catalyst was analyzed comparing the catalyzed-cycloaddition with the same reaction in absence of catalyst.

Computational Details

Calculations were carried out with density functional theory (DFT) employing B3LYP functional. B3LYP 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).[11] 6-31G(d) Pople's basis set were used for C, O, H, and Cl atoms, and the effective core potential LANL2DZ was used for Ru atom.[12] This methodology is an appropriate solution since DFT allows the consideration of electronic correlation providing good results taking into account the system size. The chosen basis set is a habitual election in these kind of transition metal reactions.[13] Intrinsic reaction path (IRC) were obtained at the same level.[14] All the stationary points were characterized as minima or transition states by vibrational frequency analysis, using analytical second derivatives. All calculations were carried out with Gaussian 03 program.[15]

Results and Discussion

We modeled the experimental reaction as Figure 1 shows in order to keep the essence of the studied system, but optimizing the computation time. The ester groups have been substituted by aldehyde groups, and R = H has been chosen for the diyne. As commented above, the basic steps were suggested by Yamamoto et al.[8] In the present work the whole catalytic cycle was studied, adding the necessary steps to complete the mechanism (see Figure 3 and Figure 4).

A complex formed by the ruthenium atom and two ligands, pentamethylcyclopentadienyl (Cp*) and chlorine, is the active species as catalyst.[8] Diformylketone **1** and the catalyst **2** form an initial complex **I3** in which the ruthenium atom bonds with the reactant through two carbonyl groups, adopting a classical tetrahedral geometry. The symmetric 1,6-diyne **4** interacts with

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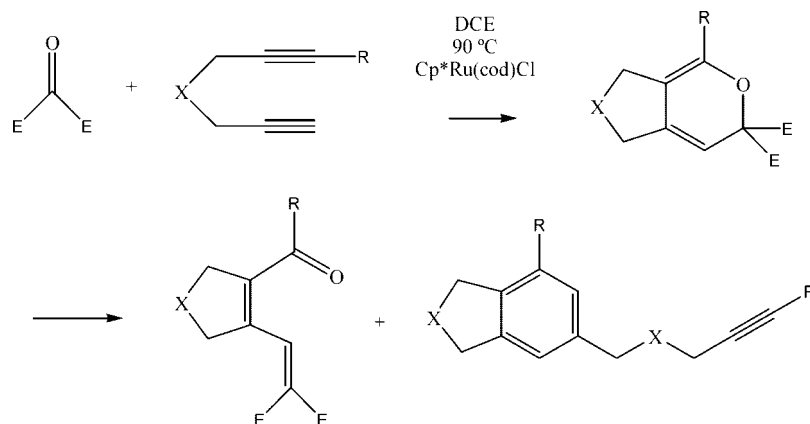
Figure 1. Experimental [2+2+2] ruthenium-catalyzed cycloaddition between 1,6-diynes and tricarbonyl compounds with $E = CO_2Me$.[8] In the present work this reaction has been modeled using $E = COH$, $X = O$ and $R = H$.
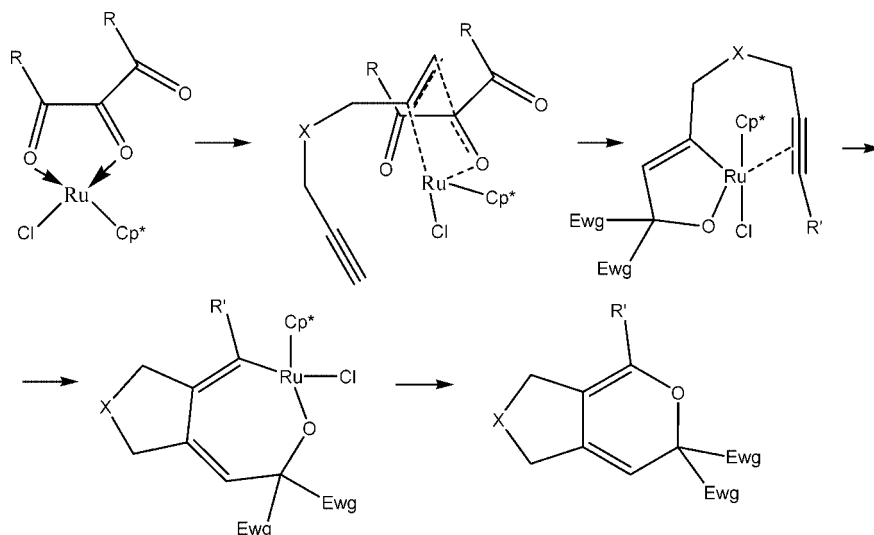
Figure 2. Mechanistic proposal of Yamamoto et al.[8]

TABLE 1: Absolute and Relative Electronic Energies (Zero Point Energy Included) for the [2+2+2] Catalyzed Cycloaddition in Gas Phase at B3LYP/6-31G(d)+LANL2DZ Level
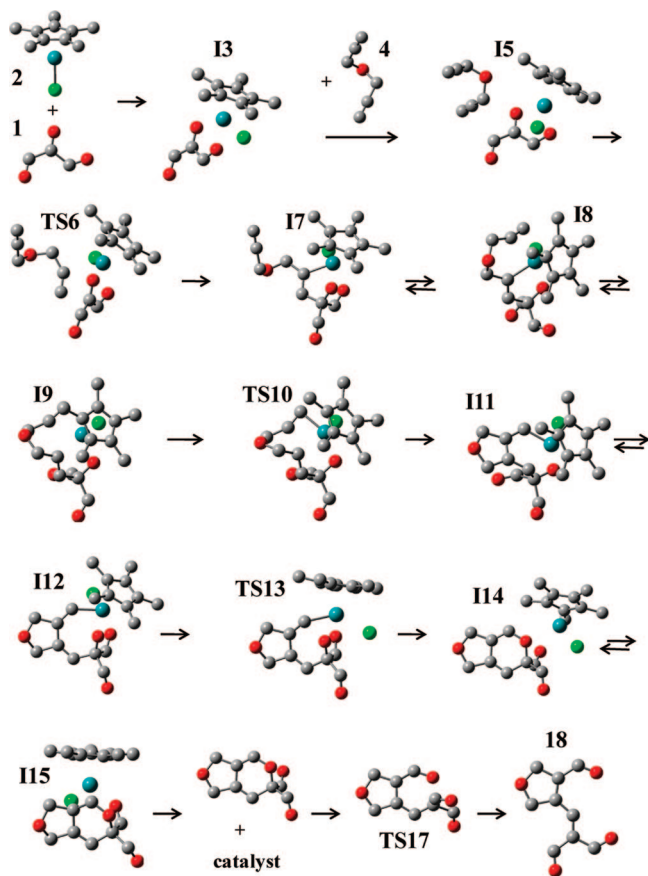
	E (au)		ΔE (kcal/mol)
1	−341.07585		
2	−944.00870		
I3	−1285.13290	**1 + 2 + 4**	0.00
4	−307.19265	**I3 + 4**	−30.34
I5	−1592.33180	**I5**	−34.26
TS6	−1592.28342	**TS6**	−3.90
I7	−1592.33895	**I7**	−38.75
I8	−1592.32321	**I8**	−28.87
I9	−1592.32083	**I9**	−27.38
TS10	−1592.31647	**TS10**	−24.64
I11	−1592.38320	**I11**	−66.52
I12	−1592.39662	**I12**	−74.94
TS13	−1592.35651	**TS13**	−49.77
I14	−1592.42540	**I14**	−93.00
I15	−1592.43558	**I15**	−99.38
I16	−648.39814	**I16 + 2**	−81.34
TS17	−648.37383	**TS17 + 2**	−66.09
18	−648.41205	**18 + 2**	−90.08

complex **I3** forming **I5**. In this structure **I5**, the two reactants and the catalytic species are already present.

Taking **I5** as starting point, the following steps are the consecutive addition of the two alkyne groups of the diyne. First, in transition state **TS6** one of the alkynes is forming two new

bonds with ruthenium and one of the carbonyl groups, being the intermediate **I7** the result of this addition. Structures **I8** and **I9** are conformers of the intermediate **I7**; these two conformational changes are necessary to adopt a position in which the second alkyne can interact with the metal. The second alkyne addition takes place in transition state **TS10**, which connects intermediates **I9** and **I11**. It is worth noting that the hetero five-member ring present in the final product is now formed in **I11**. Intermediate **I12** is a conformer of **I11** obtained by single rotations of C−C bonds. The atom disposition in structure **I12** allows the ruthenium atom to bond with two carbonyl groups. This interaction is crucial in transition state **TS13**, where the reductive elimination of the catalyst takes place and the six-member heterocycle of the product is formed; the reductive elimination is a typical last step in transition metal catalyzed cycloadditions. As result of this step, the bicyclic product is finally formed in intermediate **I14**, therefore, the main transformations to perform the reaction takes place essentially in these **I5**−**I14** steps.

However, this bicyclic structure is not the observed product of the reaction. To achieve the dienone, a new conformational change followed by an electrocyclic reaction is needed. In **I15**, the ruthenium atom is interacting with a carbonyl group and the double bond of the six-member heterocycle. Finally, only a simple pericyclic ring opening from **I16** to product **18** is needed. **18** is the most stable conformation of the observed final product of the [2+2+2] cycloaddition.

Figure 3. B3LYP/6-31G(d)+LANL2DZ transition states and intermediates structures for the catalyzed [2+2+2] cycloaddition in gas phase. Reactants and products are labeled just with numbers; intermediates and transition states are preceded by I and TS, respectively.
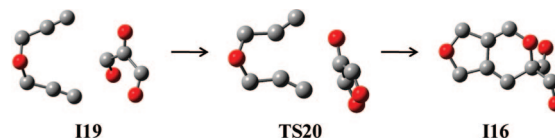
Figure 5. Noncatalyzed [2+2+2] cycloaddition in gas phase. This reaction is followed by the electrocyclic reaction described in Figure 3 (**I16**-**TS17**-**18**) to achieve the final product.

reaction. The first transition step of the cycloaddition is the highest point of the reaction, which corresponds to the addition of the first alkyne of the diyne (**TS6**, almost 28 kcal/mol). After the conformational changes **I7**−**I8**−**I9,** it takes place the second alkyne insertion, which in comparison is notably easier than the first one, so the total difference from intermediate **I7** to transition state **TS10** is less than 15 kcal/mol.

Removing of the ruthenium catalyst from the bicyclic structure is another crucial step, clearly exergonic ($\Delta G^{\ddagger} \sim 26$ kcal/mol, $\Delta G_{\text{I12}-\text{I14}} \sim -21$ kcal/mol). The cost of the electrocyclic ring opening (**I16**-**TS17**-**18**) is also below 15 kcal/mol, being the whole reaction a very exergonic process (~ 74.4 kcal/mol).

It is remarkable the importance of the entropic factor in this cycloaddition, revealed by comparison between electronic and free energy values. However, the energy barriers are of the same order of magnitude in the two cases.

Some pericyclic reactions are not feasible in practice, and many of them are directly forbidden due to symmetry restrictions.[16] In absence of catalyst (see Figure 5) the reaction between **1** and **4** to give **I16** is a concerted process that takes place through a transition state in which the two alkynes of the diyne and the carbonyl group interact at the same time. This reaction followed by the electrocyclic opening described above gives the **18** product. The highest point of the reaction in absence of catalyst is almost 44 kcal/mol (Figure 6). Therefore, ruthenium allows the performance of a cycloaddition that in another way would be very difficult to carry out, transforming a one-step reaction with a high energy barrier into a multistep process with slower barriers.

Table 1 and Figure 4 summarize the energy values obtained for structures **1**−**18**. Table 1 contains electronic energies, and Figure 4 shows the free energy profile of the complete reaction in kcal/mol at 90 °C, the experimental temperature of the
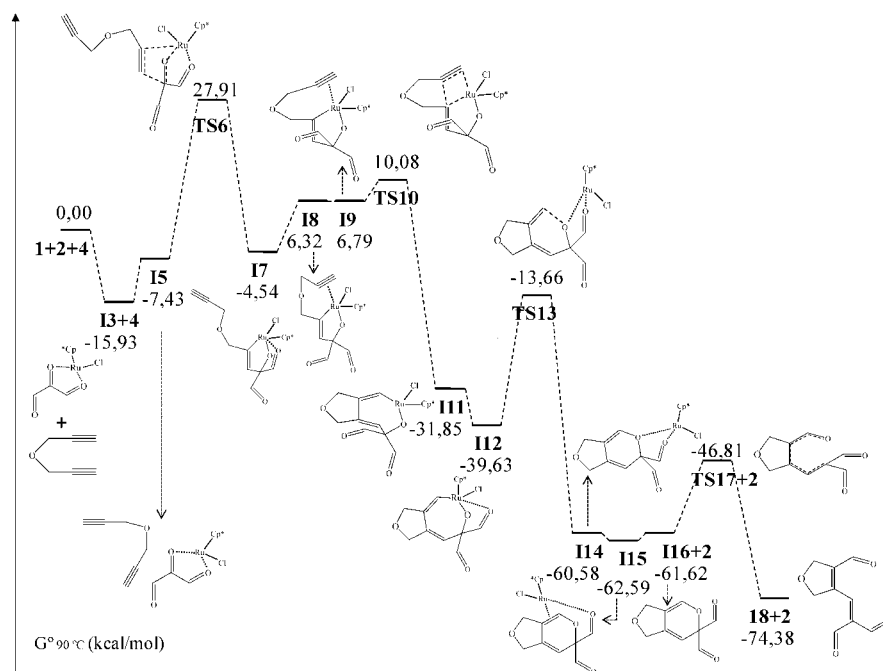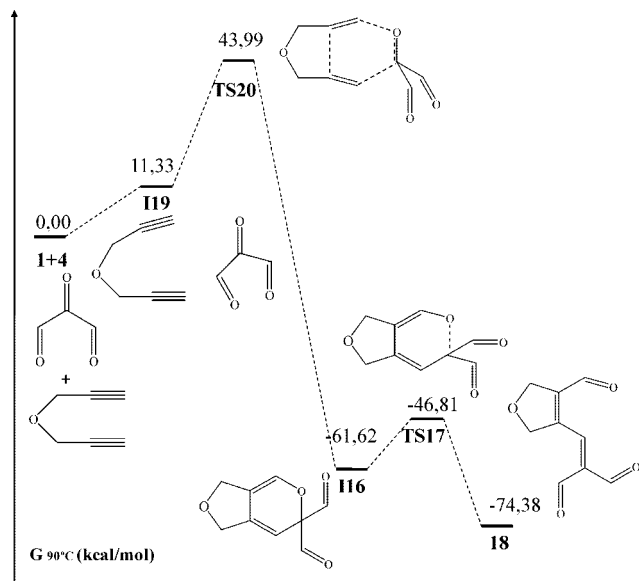

Figure 4. Free energy profile of the catalyzed [2+2+2] cycloaddition in kcal/mol at 90 °C in gas phase.

Figure 6. Free energy profile for the noncatalyzed [2+2+2] cycload-dition in kcal/mol.

It is very interesting to include the mechanism of the studied catalyzed cotrimerization in a more general vision of the cotrimerization of alkynes and double bonds. In a recent paper, Varela et al. reported a ruthenium-catalyzed reaction forming polycyclic cyclohexadienes from 1,6-diynes and alkenes.[17] In their discussion about the possible mechanism of this reaction and following the general trends found in the previous literature (the same we have considered in the present work), they proposed two pathways in function of the type of alkene chosen for the reaction. To explain the experimental results, they performed some DFT calculations of one of the steps of the catalytic cycle. Taking into account that we have calculated all the catalytic cycle and summarizing their ideas and the present study (see Figure 7), we think that it is really useful to compare these diynes reactions. These reactions can be summarized as it follows. After the last multiple bond insertion, when the heptametallacycle is formed, there are three possibilities: (a) if an acyclic alkene is used, the product is obtained through a β-elimination plus a reductive elimination and a posterior electrocyclic reaction;[17] (b) if a cyclic alkene is used, the product is obtained through a simple reductive elimination;[17] (c) if a heterodouble bond like the one used in this work is the reactant, the product is obtained through a reductive elimination and a subsequent electrocyclic reaction. The heptametallacycle is the same for the three showed cases, and its later evolution depends on the nature of the double bond added to the diyne. Varela et al. justified the different products on (a) and (b) by sterical reasons, due to the difficulty of the β-elimination when a cyclic alkene is used. The tricarbonylic compound used in the present work does not have suitable hydrogens for a β-elimination, so only the reductive elimination takes place. It is worth noting
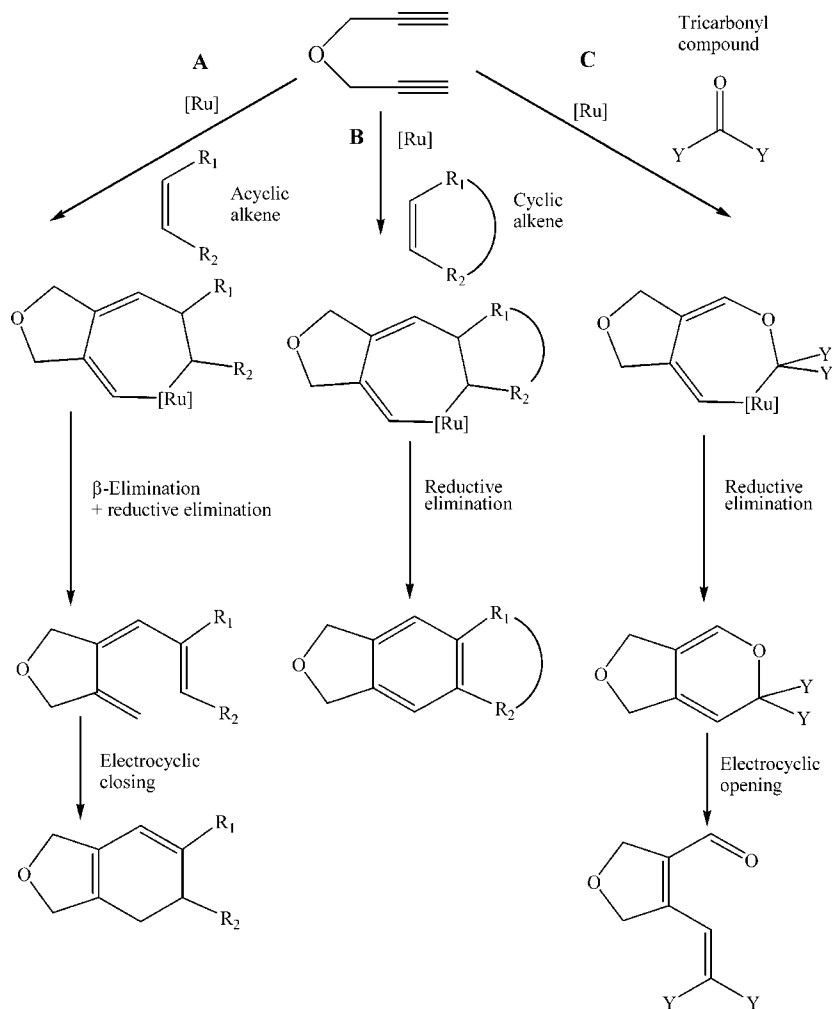
Figure 7. Mechanistical proposals for the [2+2+2] cycloaddition of 1,6-diynes and double bonds.

that the position of the double bonds in the product previous to the electrocyclization is the same. So, this study agrees with their suppositions and complements quite well the general vision of this cycloaddition.

Conclusions

The mechanism of the ruthenium-catalyzed [2+2+2] cycloaddition between 1,6-diynes and tricarbonyl compounds was studied using density functional theory, comparing this multistep process with the noncatalyzed one. The catalyzed mechanism requires several conformational changes. It has four main steps with the addition of the first alkyne group being the key step. This mechanistical proposal seems to fit well with the suggested pathways pointed by other authors in similar reactions.

Supporting Information Available: Supporting Information includes molecular modeling coordinates for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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JP802763M