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Computational Assessment of Non-Heteroatom-Stabilized Carbene Complexes Reactivity: Formation of Oxazine Derivatives

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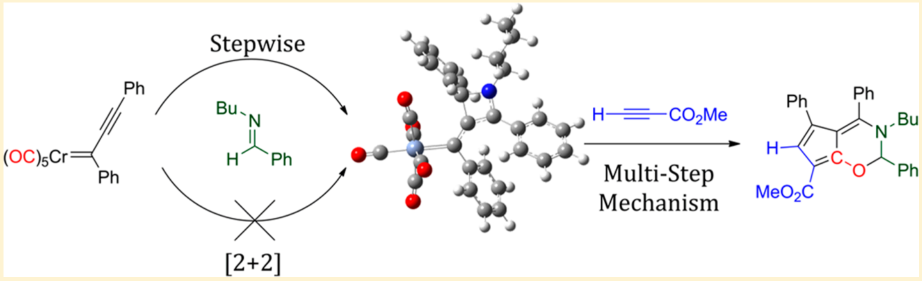
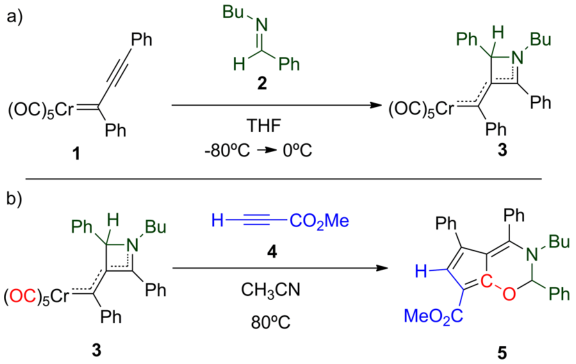
Ⓢ *Supporting Information*



ABSTRACT: A complete DFT-level mechanism elucidation of the two-step reaction of non-heteroatom-stabilized carbenes with imines, followed by addition of alkynes to yield oxazine derivatives, is presented. These compounds show different reactivity than the equivalent Fischer carbene complexes. A rationale of the experimental outcome is presented together with some suggestion for increasing the scope of the reaction, with special attention to the solvent effects in the regioselectivity.

Different studies have consistently shown that group 6 Fischer carbene complexes have an impressive synthetic potential.[1−3] In these compounds, a formal double bond arises from the carbene-to-metal σ donation and simultaneous metal−carbene π back-donation. Fischer carbene complexes are usually electrophilic and susceptible to attack at the carbenic carbon atom. More recently, the non-heteroatom-stabilized carbene complexes have appeared as a new family of compounds that are formally related to Fischer carbene complexes but feature a different reactivity. Similarly to the case of the Schrock-type carbene complexes,[4] these compounds do not present any stabilizing heteroatom. However, they are usually electrophilic at the carbenic atom as the Fischer-type carbene complexes. Thus, these complexes are considered to be a borderline case between both types of carbene complexes, as they partially fit in both categories. The different properties found[5−9] for related Fischer and non-heteroatom-stabilized carbene complexes cause the latter to feature a very different, although rich, reactivity. The generalization of the use of this type of compounds would require not only the exploration of its chemistry toward different reagents but also the study of the mechanistic issues with a special focus on the similarities and differences between these complexes and the well-known Fischer carbene complexes. Following our interest in the mechanism elucidation of Fischer carbene complexes reactions through theoretical calculations,[9−14] we have recently expanded this methodology to explore reaction mechanisms of non-heteroatom-stabilized carbenes.[15] Previous studies have reported a related reaction in which cyclopenta[*e*]-[1,3]oxazines are formed through a sequential (formal) [2 + 2] cycloaddition and the subsequent treatment of the azetine complexes formed with alkynes.[8] This transformation consists of a three-component reaction that allows for the formation of three different carbon−carbon bonds together with one carbon−oxygen bond (see Scheme 1). Beyond the general need of accumulating mechanistic information on non-heteroatom-stabilized carbene complexes reactivity, we focused on this specific reaction due to the good experimental results, the complexity of the products formed, and the presence of intriguing regiochemical issues not fully understood yet. In

Scheme 1. (a) Synthesis of Azetine Complex from Non-Heteroatom-Stabilized Chromium Carbene Complex. (b) Synthesis of Cyclopenta[*e*]-[1,3]oxazine from Azetine Carbene Complex[8]



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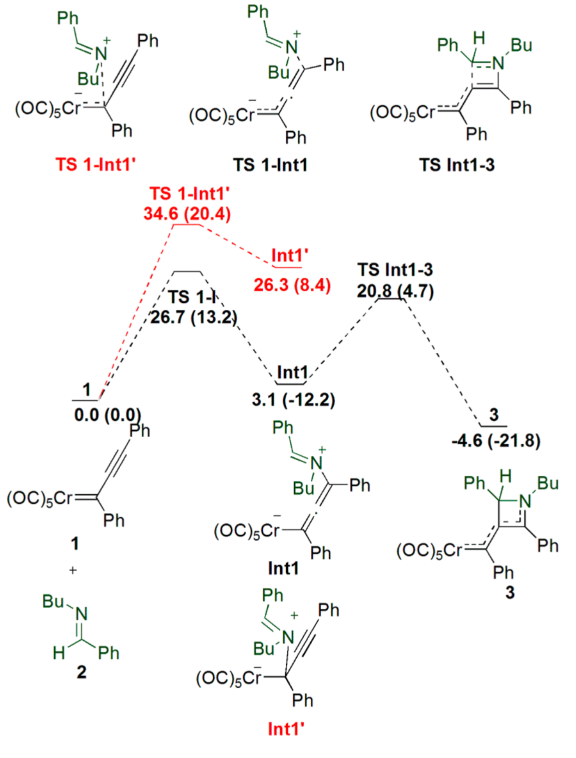
addition, an electrocyclic ring-opening of an azetinium intermediate was postulated for this reaction for the first time, and a computational study could clarify this proposal.

We report herein our results on the theoretical study of the previously reported[8] reaction of non-heteroatom-stabilized carbene **1** to yield cyclopenta[*e*]-[1,3]oxazines **5** in two steps (see Scheme 1). First, the carbene complex reacts with an imine to form 2-azetine carbene complexes **3** (Scheme 1a). Usually, the synthesis of 2-azetines is not simple because they rapidly produce the azadiene derived system. However, the carbene moiety seems to stabilize this structure and allows the formation of bicyclic oxazines through a three-component reaction (Scheme 1b). The complexity of this transformation and the unusual electronic structure of this type of carbene prompted us to carry out a computational study of these two reactions in order to clarify the mechanism. Also, due to the scarce theoretical information on the behavior of this type of compound,[16] these results could help to modulate the reaction for future experimental modifications. The selected methodology (density functional theory (DFT) with the BP86 functional) has proven to give good results with Fischer carbene complexes (see the Computational Details for more information).[13,15,17,18]

We started by computing the first reaction as shown in Scheme 1a. The reaction began with the nucleophilic attack of the imine **2** to the β-carbon of the alkyne in the carbene complex **1** with a barrier of 26.7 kcal/mol (**TS 1-I**), which is the rate-determining step of the process (Scheme 2). While this type of reaction is usual in Fischer carbene complexes, the lack of any heteroratom in the non-heteroatom-stabilized carbene complex **1** could induce a different reaction path. In this case, this lack of heteroatom causes that both the transition structures and the intermediates formed upon the nucleophilic attack are less stable than related Fischer-type compounds.[18] This is reflected in the shorter Cr−C distances and the higher energies in the transition structures and the intermediates. Thus, this reaction step, although qualitatively similar to other examples of Fischer carbene complexes, features some differences that should be taken into account.

Scheme 2. Free Energy Profile of the 2-Azetine Carbene Complex Formation[a]



[a]Enthalpies in brackets. All energies in kcal/mol referred to **1** + **2**.

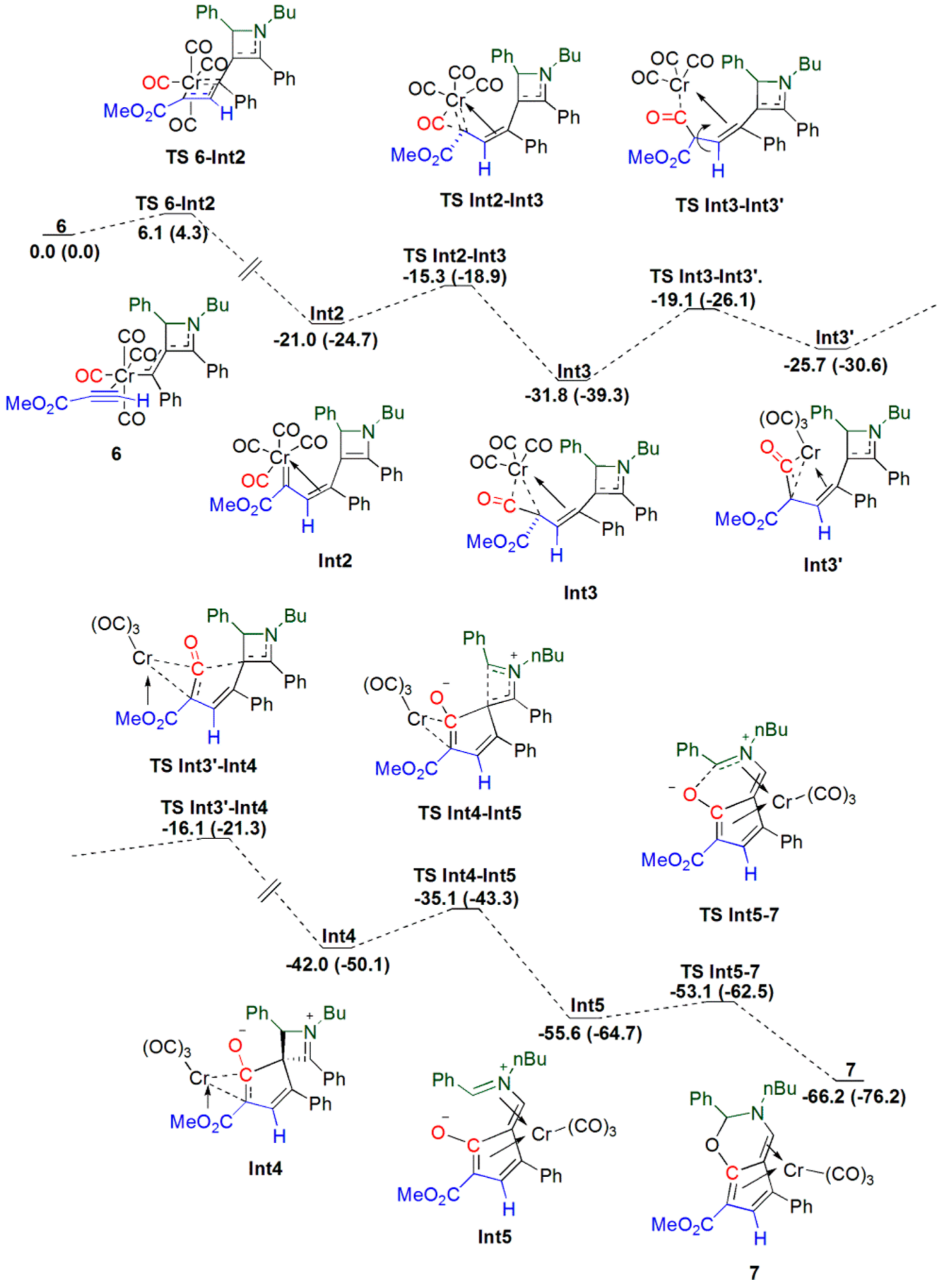
In the next reaction step, the intermediate **Int1** progresses to the 2-azetine product **3** via a ring-closing transition state with a lower barrier (20.8 kcal/mol). The overall reaction is exothermic by 4.6 kcal/mol due to the extended conjugation with the carbene moiety in the azetine carbene complex (see the Supporting Information for the detailed structures).

The search for different reaction mechanisms as the concerted [2 + 2] cycloaddition transition state was not successful. In any case, this mechanism should be much higher in energy due to the Woodward−Hoffmann rules, where the thermal concerted [2 + 2] reaction is forbidden. In contrast, the nucleophilic attack of the imine to the carbenic carbon was also found, but the transition state leading to this addition (**TS 1-Int1′**; see Scheme 1) shows a high energy value of 34.6 kcal/mol. In order to rationalize the position of the nucleophilic attack, we analyzed the structures of both transition states. The relative stability between them can be explained due to the extended conjugation in **TS 1-Int1** in contrast to **TS 1-Int′** (detailed in Figure S1, Supporting Information).

Then, we explored the reaction between the 2-azetine carbene complex **3** with an alkyne. For analyzing this selectivity, we selected an asymmetric alkyne **4** (methylpropiolate) and the azetine carbene complex **3**. A tentative mechanism has been proposed.[8] However, the origin of the regioselectivity remains unclear. Also, an electrocyclic ring-opening of a 1-azetinium intermediate (which had not been reported previously) was postulated, but no direct evidence was provided.

The complete energy profile for the mechanism was characterized by DFT calculations (Scheme 3). First, starting from the 2-azetine carbene complex **3**, the coordinated alkyne is in a *cis*-position with respect to the Cr═C bond, **6**. In this step, two different possibilities for the coordination arise that would ultimately lead to different regioisomers (vide infra). An alkyne migratory insertion (**TS 6-Int2**) with a small energy barrier of 6.1 kcal/mol leads to the formation of a very stable intermediate **Int2** in which another carbene moiety is produced. The interaction between the newly formed alkene and the metal contributes to stabilize this intermediate. It should be noted that this step is irreversible (the inverse process has a barrier of 27.1 kcal/mol), and hence, this is the transition state that determines the regioselectivity as the disposition of the alkyne remains fixed for the rest of the reaction path. After that, a CO insertion step occurs easily via a concerted transition state (**TS Int2-Int3**) with a barrier of 5.7 kcal/mol. Then, a rotation of a C−C single bond is necessary in order to have the right disposition for the ring-closing step. The required energy for this step (12.7 kcal/mol) is mainly due to the loss of coordination between the ketene moiety and Cr in **TS Int3-Int3′**. From the energetic intermediate **Int3′**, the cyclization is very favored and proceeds almost without any free energy barrier, leading to the zwitterionic spirocycle **Int4**. At this point, the electrocyclic ring-opening proposed[8] has a small barrier of 6.9 kcal/mol due to the intrinsic instability of the spirocycle framework. Interestingly, this implies that the previously unknown electrocyclic ring-opening of an azetinium intermediate can effectively take place. Finally, the azadiene

Scheme 3. Free Energy Profile of the Reaction between 3 and Methylpropiolate[a]

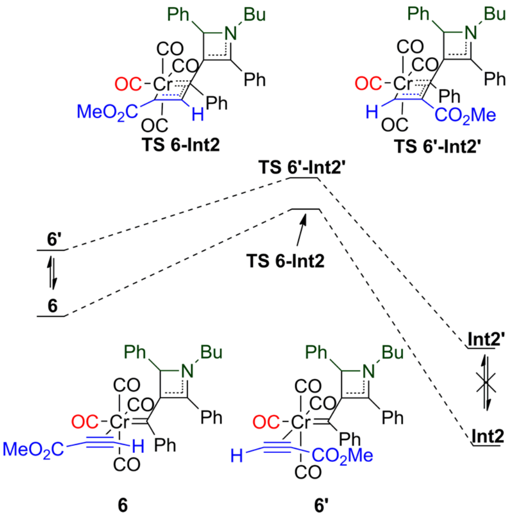


[a] Enthalpies in brackets. All energies are in kcal/mol referred to **6**.

Int5 collapses with the oxygen anion, producing the final product with a barrier of 2.5 kcal/mol. The formation of the very stable compound **7** is the driving force of the reaction.

According to the computed mechanism, the first step is the key for understanding the regioselectivity of the process. From the available experimental data,[8] only one regioisomer was formed. However, the formation of a different regiosiomer could be obtained if this step could be controlled. Thus, to clarify the reaction selectivity and the possibility to tune it, we carried out a detailed study of the migratory insertion step for understanding the reported regioselectivity (Scheme 4, Table S1, Supporting Information). Noteworthy, using the BP86 functional, in the gas phase, the reactants' stability is inversed (**6** is 1.4 kcal/mol more stable than **6′**, Table S1) and the TS has a small difference of 0.6 kcal/mol, with should lead to a mixture of products. We found that the effect of the solvent is critical, due to the different dipole moments of the relevant structures as the charge distribution in the intermediates can be affected by the solvent polarity (see the Supporting Information). Thus, it is required to include the solvent in the calculations in order to achieve a product distribution in agreement with the experimental evidence. In acetonitrile (Table S1 and Scheme 4), the energy difference between the intermediates **6** and **6′** (1.5 kcal/mol) and also between both transition states **TS 6-Int2** and **TS 6′-Int2′** (4.1 kcal/mol) is in agreement with the experimental outcome. It should be noted that, in toluene, the relative stability of the two intermediates (**6** and **6′**) is also reversed, as it happens in the gas phase. Thus, the product distribution could be modified only by changing the solvent polarity. If confirmed experimentally, this could

Scheme 4. Free Energy Profile of the Migratory Insertion Step in Acetonitrile



increase the scope and interest of the reaction as a new set of oxazines could be obtained. This hypothesis should be tested by using a low polarity solvent, which could lead to the synthesis of the opposite regioisomer.

To sum up, we have described the complete mechanism of the reaction between non-heteroatom-stabilized chromium carbene complexes and imines. These compounds feature a borderline behavior between the Fischer-type and the Schrock-type carbene complexes. This implies that the expected reactivity for these species cannot be anticipated with ease. This has been already proven by the different results obtained for structurally related Fischer carbene complexes and non-heteroatom-stabilized carbene complexes under similar conditions.[5−9] Due to this, detailed mechanistic information should be obtained in order to determine, understand, and predict the experimental outcome for these compounds. In this case, the conjugated character of the β-carbon of the alkyne in the initial carbene complex has been shown to control the nucleophilic addition. The complete mechanism of the subsequent reaction between the 2-azetine carbene complexes formed with alkynes was explored. The hypothesis of the electrocyclic azetine ring-opening as a key intermediate in the reaction could be demonstrated. In addition, a strong effect of the solvent polarity on the regioselectivity was found. This could imply that an opposite regiochemistry could be found when using different experimental conditions, potentially extending the scope of the reaction to the synthesis of different products. With the use of non-heteroatom-stabilized carbene complexes, new reaction possibilities arise. While some features of these compounds could mimic the behavior of the well-known Fischer carbene complexes, the chances of new mechanistic alternatives may turn this new class of complexes into a very useful synthetic tool.

■ COMPUTATIONAL DETAILS

All calculations were carried out with the Gaussian 09 program package[19] using the density functional theory with the BP86 functional within the nonlocal density approximation (NLDA) including Becke's[20] nonlocal exchange corrections as well as Perdew's[21] inhomogeneous gradient corrections for correlation. All geometry optimizations were computed without symmetry restrictions. In order to establish the stationary points as minima (without imaginary frequencies) or as transition states (with one imaginary frequency), we did vibrational frequency calculations for all structures. Moreover, connectivity of transition states was confirmed by relaxing to reactants and products or making IRC calculations where the connectivity was not clear. Free energy corrections were calculated at 298.15 K and 10^5 Pa pressure, including zero-point energy corrections (ZPE).

The Hay−Wadt effective core potential with the valence double-ζ split to [341/2111/41][22] was used for the chromium atom and the standard 6-311+G*for the remaining atoms.[23]

All calculations were carried out in solution, using the SMD method[24] as implicit solvent with the experimental solvent (acetonitrile ε = 35.688). In addition, we computed the selectivity-determining step using toluene (ε = 2.3741) as solvent and in the gas phase, reoptimizing the structure with the new conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figure S1, Table S1, computational details, and Cartesian coordinates for computed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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