Computational Study of C–H Insertion Reactions with Ethyl Bromodiazoacetate

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A computational study of C–H insertion reactions between ethyl bromodiazoacetate and three different substrates is presented. The mechanism of the C–H insertion is shown to

Introduction

Catalytic functionalisation of C-H bonds is an area of immense interest and importance in organic synthesis.^[1] Among the protocols for C-H functionalisation, carbenoid C-H insertions through Rh^{II}-catalysed reactions with diazo compounds represent an attractive combination of selectivity and mild conditions.^[1b,2] Whereas the field of intramolecular carbenoid C-H insertions is well established,^[2d] with a range of diazoesters reacting well, the choice of diazo compounds for use in intermolecular C-H insertions has been limited to aryl- or vinyl-substituted diazoacetates.^[1b,3] We have, however, recently developed a procedure for Rh^{II}catalysed C-H insertion reactions with halodiazoacetates.^[4] Ethyl bromo-, chloro- and iododiazoacetates insert regioselectively into C-H bonds in a variety of substrates with yields up to 82%, and the reaction represents a new method for selective introduction of halogens. Table 1 shows selected examples of C-H insertion reactions with ethyl bromodiazoacetate (1).

The halodiazoacetates^[5] are a novel class of diazo compounds that can be used in C–H insertion reactions, and a deeper understanding of their reactivity is of importance from both a synthetic and a theoretical point of view. As a follow-up to our recent computational study of cyclopropanation reactions with halodiazoacetates,^[6] we will in this paper present a computational study, at the B3LYP level of theory, of C–H insertion reactions with representative halodiazoacetate ethyl bromodiazoacetate (1).

 Rh^{II} -catalysed C–H insertion reactions with diazo compounds are assumed to follow a path in which the carbene moiety of an intermediate metal carbenoid inserts into the C–H bond. The mechanism of the insertion has been de-

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be substrate dependent; the reaction follows either a concerted mechanism or a two-step mechanism in which complete hydride transfer precedes C–C bond formation.

Table 1. Results from C–H insertion reactions with ethyl bromodiazoacetate $(1)^{\left[4\right]}$

Entry	Substrate	Product	Yield [%]
1		Br CO ₂ Et	82
2	\bigcirc	CO ₂ Et	68
3	$\langle \circ \rangle$		63
4	N_		40

bated, but a mechanism involving only the carbenoid and the C–H bond is now preferred.^[2e] Two extremes of this mechanism have been suggested (Scheme 1): a concerted process with C–H and C–C bond formation taking place simultaneously (Path I), or a two-step pathway in which hydride abstraction is followed by C–C bond formation (Path II). It has been argued that because of the high level of enantioselectivity observed in certain C–H insertions, the reaction most likely follows a concerted, albeit asynchronous pathway.^[7] Thus, even though complete hydride transfer has been reported for intramolecular C–H insertions with certain systems, evident by formation of anomalous



Scheme 1. Proposed mechanistic paths for Rh^{II} carbenoid C–H insertions.



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Scheme 2. Formation of carbenoid 2. The energies are zero-point corrected sums of electronic and thermal energies at 25 °C, reported in $kcalmol^{-1}$.

products,^[8] Path I is viewed as the mechanism operating in standard cases,^[2e] a proposal that has been supported by computational studies.^[9]

Results and Discussion

As in our previous computational study of halodiazoacetates,^[6] we chose $Rh_2(O_2CH)_4$ as a model catalyst in the interest of computational facility. $Rh_2(O_2CH)_4$ -catalysed C– H insertion reactions with ethyl bromodiazoacetate are instigated by formation of Rh^{II} carbenoid **2**, through a previously described path^[6] of coordination of **1** to the catalyst followed by nitrogen extrusion (Scheme 2). The carbenoid then goes on to react with a C–H insertion substrate.

We first considered the reaction with the simple substrate methane. Carbenoid C–H insertion reactions involving methane have not been reported in the literature, but methane has been used as a model substrate in a computational study of C–H insertions with diazomethane and methyl diazoacetate.^[9a] Our findings with this rather unreactive substrate mirrors the results from this study in that the insertion follows a concerted pathway (Path I, Scheme 1); the methane C–H bond breaks and new C–H and C–C bonds form in a single event (Scheme 3).^[10]



Scheme 3. Mechanism for C–H insertion reaction with methane. The energies are zero-point corrected sums of electronic and thermal energies at 25 °C, reported in kcalmol⁻¹.

The Wiberg bond orders (BOs) of the forming C–C and C–H bonds in **TS-3** are 0.52 and 0.54, respectively, which implies that C–C and C–H bond formation happen in a quite synchronous manner. The BO of the reacting methane C–H bond is 0.31, and the methane CH₃ moiety has a NBO charge of +0.20, signifying that the methane C–H bond is breaking. The dissociation of the carbene moiety from the catalyst has started; the Rh–C BO has decreased from 0.73

in carbenoid **2** to 0.26 in **TS-3**, and the Rh–Rh BO has increased from 0.46 to 0.60, approaching the value of 0.80 in the free catalyst.

The transition state for this C–H insertion, **TS-3**, represents a predicted energy barrier of 22.9 kcal mol⁻¹. The barrier for insertion of the carbene moiety of carbenoid **2** into a methane C–H bond is thus more than twice as high as the barrier for nitrogen extrusion to form carbenoid **2**, making the C–H insertion step the rate-limiting step of the reaction.^[11] The 22.9 kcal mol⁻¹ barrier is considerably higher than the barriers reported for analogous C–H insertion with diazomethane or methyl diazoacetate,^[9a] a fact that may be explained by a higher stability of carbenoid **2** compared to the analogous non-halogenated carbenoids. Formation of the C–H insertion product (i.e., **4**) is strongly exothermic: the product is 57.7 kcal mol⁻¹ more stable than the starting materials [methane, **1** and Rh₂(O₂CH)₄].

We then turned our attention to 1,4-cyclohexadiene (Scheme 4). This activated^[3a] substrate has been used experimentally in C-H insertion reactions with 1,^[4] giving good yields (Table 1, Entry 2). With 1,4-cyclohexadiene as the substrate, the mechanism for C-H insertion turned out to be quite different from the mechanism found with methane. Instead of concerted C-H and C-C bond formation, the reaction follows a two-step pathway (Path II, Scheme 1); no concerted pathway could be located. The first step is hydride transfer from 1,4-cyclohexadiene to carbenoid 2 to give complex 6. The transition state for hydride transfer, **TS-5**, represents a barrier of 1.5 kcalmol^{-1} and is quite early: the BO of the breaking 1,4-cyclohexadiene C-H bond is 0.72, and that of the forming C-H bond is only 0.16. In complex 6, the broken C–H bond has a BO of a mere 0.03, meaning that complex $\mathbf{6}$ is a zwitterionic complex with the hydride completely transferred from 1,4-cyclohexadiene. This is reflected in the NBO charges. The cyclohexadiene ring in complex 6 has a considerable positive charge of 0.59. An increased BO (1.3) between the carbon atom where the reaction takes place and its neighbouring carbon atoms implies delocalisation of the charge. The Rh-C bond is weakened compared to the Rh-C bond of carbenoid 2, with a BO of 0.40, but no C-C bond formation is detectable (BO 0.09).

The second step of the C–H insertion, leading to product **8** with a relative energy of $-58.8 \text{ kcal mol}^{-1}$, is the C–C bond formation. In the transition state for this step, **TS-7**, the



Scheme 4. Mechanism for C-H insertion reaction with 1,4-cyclohexadiene.^[12] The energies are zero-point corrected sums of electronic and thermal energies at 25 °C, reported in kcalmol⁻¹.

dissociation of the carbene moiety has proceeded rather far, as illustrated by the Rh–C and Rh–Rh BOs of 0.19 and 0.63. The forming C–C bond has a BO of 0.25. The 1.7 kcalmol⁻¹ barrier for C–C bond formation is about the same height as the barrier for hydride transfer, and the rate-determining step for the overall reaction is nitrogen extrusion to form carbenoid **2** (Scheme 2), with a barrier of 8.0 kcalmol⁻¹. Figure 1 shows the energy profile of the reaction; Figure 2 shows the structures of transition states **TS-5** and **TS-7** and zwitterionic intermediate **6**.



Figure 1. Energy profile of $Rh_2(O_2CH)_4$ -catalysed C–H insertion reaction between 1 and 1,4-cyclohexadiene. The energies are zeropoint corrected sums of electronic and thermal energies at 25 °C, reported in kcalmol⁻¹.



Figure 2. Important structures in the C–H insertion reaction between **1** and 1,4-cyclohexadiene.

When Gibbs free energies are considered, zwitterionic complex 6 is more stable than carbenoid 2 by 9.7 kcalmol⁻¹. The barriers for hydride transfer (TS-5) and C–C bond formation (TS-7) remain low, but significant at 1.0 and 2.2 kcalmol⁻¹, respectively.

This reaction is, to the best of our knowledge, the first reported example of an intermolecular Rh^{II}-catalysed C–H insertion reaction in which complete hydride transfer precedes C–C bond formation. The barriers for hydride transfer (**TS-5**) and for C–C formation in the zwitterionic complex (**TS-7**) are both low, but significant.^[13] Davies et al. studied C–H insertions with 1,4-cyclohexadiene with methyl diazoacetate or methyl phenyldiazoacetate as the reacting diazo compounds and report concerted mechanisms for both reactions.^[9c] In the reaction with methyl phenyldiazoacetate, a zwitterionic complex similar to **6** was located, but the authors argue that this complex is merely an artefact of the optimisation algorithm.

THF is another good substrate for C–H insertion reaction with 1 (Table 1, Entry 3). Like 1,4-cyclohexadiene, THF is a compound with a good ability to stabilise a positive charge on carbon atom in a C–H insertion reaction, and once again we found a two-step mechanism for the C– H insertion with carbenoid 2. In this reaction, two diastereomeric products can be formed, each diastereomer with its own path leading to it (Scheme 5).

The transition states for hydride transfer, **TS-9a** and **TS9-b**, are both as early as the analogous transition state for the reaction with 1,4-cyclohexadiene (**TS-5**), and the relevant BOs in **TS-11a** and **TS-11b** are also highly similar to those in **TS-7**. As in the reaction with 1,4-cyclohexadiene, nitrogen extrusion is the rate-determining step of the overall reaction, and C–C bond formation is the rate-determining step of the insertion: **TS-9a** and **TS-9b** represent small energy barriers of 0.2 and 0.9 kcal mol⁻¹, respectively, whereas **TS-11a** and **TS-11b** represent barriers of 3.4 and 1.9 kcal mol⁻¹.

The described C–H insertion reactions and the previously reported cyclopropanation reaction with $1^{[6]}$ are all carbenoid reactions that proceed through intermediate carbenoid **2**. Though there are similarities between the reactions, there are also notable differences. One difference between the studied C–H insertion reactions and the cyclopropanation is the heights of the energy barriers represented by the transition states. Even though the barriers for C–H insertion reaction between carbenoid **2** and 1,4cyclohexadiene or THF are very low, the predicted barriers for cyclopropanation of styrene with carbenoid **2** are even lower. The two diastereomeric transition states represent

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Scheme 5. Mechanism for C-H insertion reaction with THF.^[12] The energies are zero-point corrected sums of electronic and thermal energies at 25 °C, reported in kcalmol⁻¹.

barriers of 0.7 and 1.8 kcalmol⁻¹, respectively. The difference in barrier heights was confirmed by experimental competition experiments (Scheme 6) by using the standard conditions for C-H insertion and cyclopropanation reactions.^[4,5] Ethyl bromodiazoacetate (1) was decomposed by Rh₂(esp)₂^[14] in the presence of an excess amount of both styrene and either 1,4-cyclohexadiene or THF. For THF, the predicted rate-limiting barriers for C-H insertion reaction with 2 are 3.4 (Path a) and 1.9 kcalmol⁻¹ (Path b), in both cases higher than the predicted barriers for cyclopropanation of styrene. This corresponds nicely with the experimental results: the competition experiment with styrene and THF gave only cyclopropanation product; no C-H insertion product was observed. In the case of 1,4-cyclohexadiene, the predicted rate-limiting barrier is lower than with THF; it is 1.7 kcalmol⁻¹. The lower barrier is reflected in the results of the competition experiment with styrene and 1,4-cyclohexadiene. Both C-H insertion and cyclopropanation takes place, but cyclopropanation is the predominant reaction; the cyclopropane and C-H insertion products are formed in a 3:1 ratio.

Another notable difference between the reactions is their mechanisms. The C–H insertion reaction can follow different mechanistic extremes depending on which substrate is used: reaction with methane follows a concerted path with synchronous C–H and C–C bond formation, and reactions with 1,4-cyclohexadiene and THF follow a two-step path with C–H bond formation preceding C–C bond formation. For the cyclopropanation reaction, only one mechanism was observed. This mechanism places in between the two extremes: concerted, but highly asynchronous. The transition states for cyclopropanation are very early; the two forming C–C bonds have BOs of below 0.1 and around 0.1–0.2, respectively. With BOs of 0.15–0.20



Scheme 6. Competition experiments.

and 0.25–0.30 for C–H and C–C bond formation, the transition states for C–H insertion with 1,4-cyclohexadiene and THF are, albeit still quite early, later than those for cyclopropanation. The transition state for reaction with methane, on the other hand, has C–H and C–C BOs of about 0.5, and is thus substantially later than any of the other transition states.

Conclusions

In summary, we have presented a full computational study of C–H insertion reactions between ethyl bromodiazoacetate (1) and three different substrates. The mechanistic path of the C–H insertion has been shown to be dependent on the substrate: reaction with methane follows a concerted mechanism, whereas reactions with 1,4-cyclohexadiene and THF follow a two-step mechanism in which complete hydride transfer precedes C–C bond formation. To the best of our knowledge, this is the first example of an intermolecular C–H insertion reaction shown to follow a two-step mechanism.

Computational Details

Density functional theory (DFT) was employed to investigate the reaction mechanism. The stationary structures of the potential energy surfaces were fully optimised at the B3LYP level of theory^[15] by using the LANL2DZ basis set for Rh, 6-31G* for C, H, N and O and 6-311G* for Br. Natural bond orbital (NBO) analyses^[16] were performed at the same level of theory. Wiberg bond indices^[17] and NBO charges were calculated from NBO theory as implemented in Gaussian 03. Stationary structures were characterised by normal coordinate analysis: No imaginary frequencies for equilibrium structures, and one imaginary frequency for transition structures. Intrinsic reaction coordinate (IRC) calculations were used to confirm that optimised transition structures correctly connect the relevant reactants and products. The reported energies are the zero-point corrected sum of electronic and thermal energies at 25 °C, scaled according to literature (0.9806).^[18] All calculations were carried out using the Gaussian 03 program package.^[19]

Supporting Information (see footnote on the first page of this article): Energies and full geometries for all new structures.

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- [11] Thermal equilibration is assumed.
- [12] The structures shown in Scheme 4are the stationary structures of the most favoured pathway. Other rotamers, of similar energies to the depicted structures, were also identified.
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