

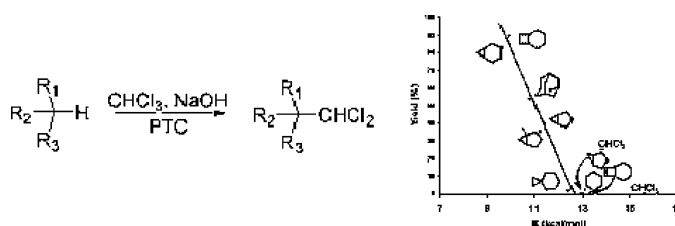
# Toward Selective Reactions with C—H Bonds: A Rationale for the Regio- and Stereochemistry of Dichlorocarbene Insertions into Cyclic Hydrocarbons<sup>†</sup>

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DFT calculations have been performed to study the course of dichlorocarbene insertion reactions into alkanes and to better understand the regio- and stereoselectivities observed. At the B3LYP/6-31G(d) level of theory, the selectivity of dichlorocarbene insertions into a number of hydrocarbons agrees well with the obtained experimental results. The reactivity of a specific C—H bond is determined by the capacity of the remaining alkyl fragment to effectively delocalize the partial positive charge buildup during the reaction. This activity can readily be estimated by calculation of the hydride transfer potential (HTP). A comparison with the structure and the stability of the corresponding cation is useful to emphasize the origins of the selectivity. Dichlorocarbene is also predicted to react efficiently with acidic C—H bonds through a nucleophilic–electrophilic mechanism. In principle, an attack of a carbene on an appropriately substituted three-membered ring may lead to fragmentation of the molecule.

## Introduction

The activation of saturated hydrocarbons<sup>1</sup> has been described as “the search for the Holy Grail”<sup>2</sup> for chemists. In the reaction of a carbene with such compounds a new C—C bond is formed. Dichlorocarbene has proven to be particularly useful for C—H insertion reactions into activated bonds because of its good selectivity and reactivity.<sup>3</sup> Furthermore, the resulting geminal

dihalomethyl group can easily be hydrolyzed to an aldehyde, allowing a further functionalization.

The insertion of carbenes into C—H bonds has already been treated by theory.<sup>4–6</sup> Recently, the reaction path of the insertion

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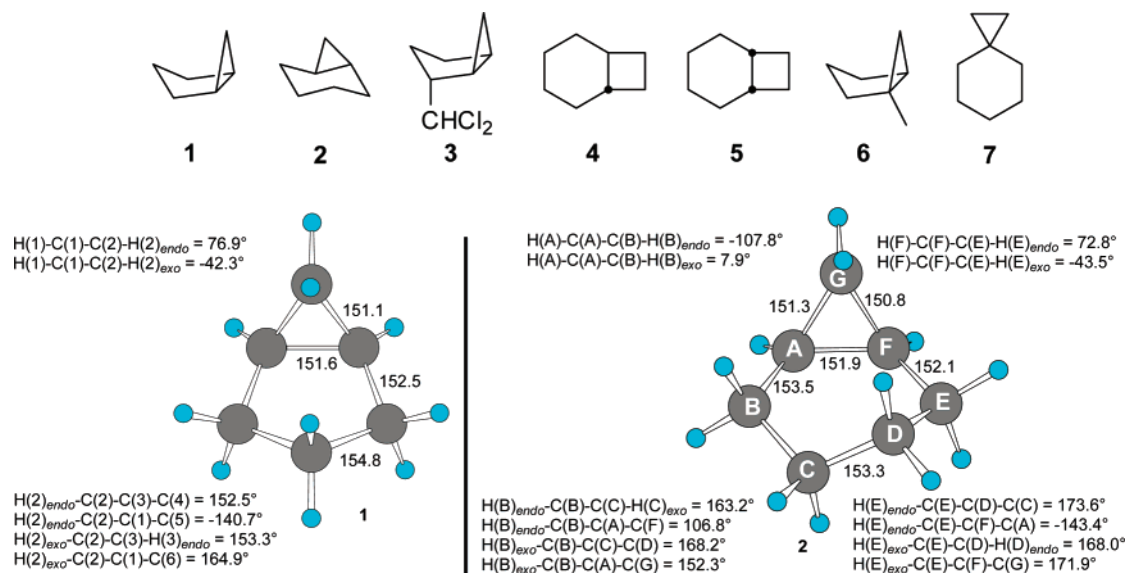


FIGURE 1. Geometries of **1** and **2** as given by B3LYP/6-31G(d) calculations. Bond lengths in picometers and dihedral angles in degrees.

of singlet chlorocarbenes in methane and ethane has been thoroughly investigated at the MP2, CCSD, CCSD(T), and B3LYP levels with the 6-31G(d,p) basis set as well as with the G3MP2 and MP2/G3MP2Large methods.<sup>7</sup> The results were found to coincide satisfactorily; the lowest activation barriers were calculated with MP2/G3MP2Large and the highest with CCSD/6-31G(d,p).<sup>7</sup>

The insertion of dichlorocarbene into C–H bonds occurs initially through an electrophilic phase followed by a nucleophilic phase resulting in a net charge flow from the alkane to the inserting carbene during the first part of the reaction. For dichlorocarbene, the turning point, i.e., a charge minimum on CCl<sub>2</sub>, occurs just before the transition state.<sup>7</sup>

We have recently detailed a successful methodology based on the combination of ultrasonication with phase transfer catalysis (PTC)<sup>8</sup> for the regio- and stereoselective insertion of dichlorocarbene into the  $\alpha$ -C–H bonds of cyclopropanes.<sup>9</sup> Accordingly, we have performed computations to better understand and more correctly predict the observed selectivities.

## Results and Discussion

First of all, we investigated bicyclo[3.1.0]hexane (**1**) at the B3LYP/6-31G(d) level of theory. Two conformers were found: **1a** and **1b**. **1a** possesses a boat form (Figure 1) and is 3.0 kcal/mol more stable than **1b**, which exists in a chair form. The preference for the boat conformation is due to a staggered arrangement of the hydrogen atoms. This is in accordance with experimental results obtained by electron-diffraction, microwave,

TABLE 1. Activation Energies for the Insertion of Dichlorocarbene into Bicyclo[3.1.0]hexane (**1**)

| bond   | orientation | <i>E</i> (kcal/mol) |
|--------|-------------|---------------------|
| 1      | C(1)–C(2)   |                     |
| 1      | C(1)–C(5)   | 16.0                |
| 1      | C(1)–C(6)   | 16.6                |
| endo-2 | C(2)–H      | 12.4                |
| endo-2 | C(2)–C(1)   | <i>a</i>            |
| endo-2 | C(2)–C(3)   | 12.5                |
| exo-2  | C(2)–H      | 11.4                |
| exo-2  | C(2)–C(1)   | 12.4                |
| exo-2  | C(2)–C(3)   |                     |
| endo-3 | C(3)–H      | 13.2                |
| endo-3 | C(3)–C(2)   | <i>b</i>            |
| exo-3  | C(3)–H      | 14.6                |
| exo-3  | C(3)–C(2)   | 15.0                |
| endo-6 | C(6)–H      | 18.5                |
| endo-6 | C(6)–C(1)   | 23.5                |
| exo-6  | C(6)–H      |                     |
| exo-6  | C(6)–C(1)   | 17.3                |

<sup>a</sup> Steric repulsion with the cyclopropane ring. <sup>b</sup> Steric repulsion with endo-6.

and far-infrared spectroscopy.<sup>10,11</sup> However, the ring-puckering potential energy profile determined from far-infrared data provides the boat conformation as the sole minimum.<sup>11</sup> Calculations at the B3LYP/6-31G(d,p) level of theory predict the chair structure to sit only in a shallow minimum.<sup>11,12</sup>

Table 1 summarizes the activation energies obtained for the insertion into the C–H bonds of **1**. For each C–H bond, the

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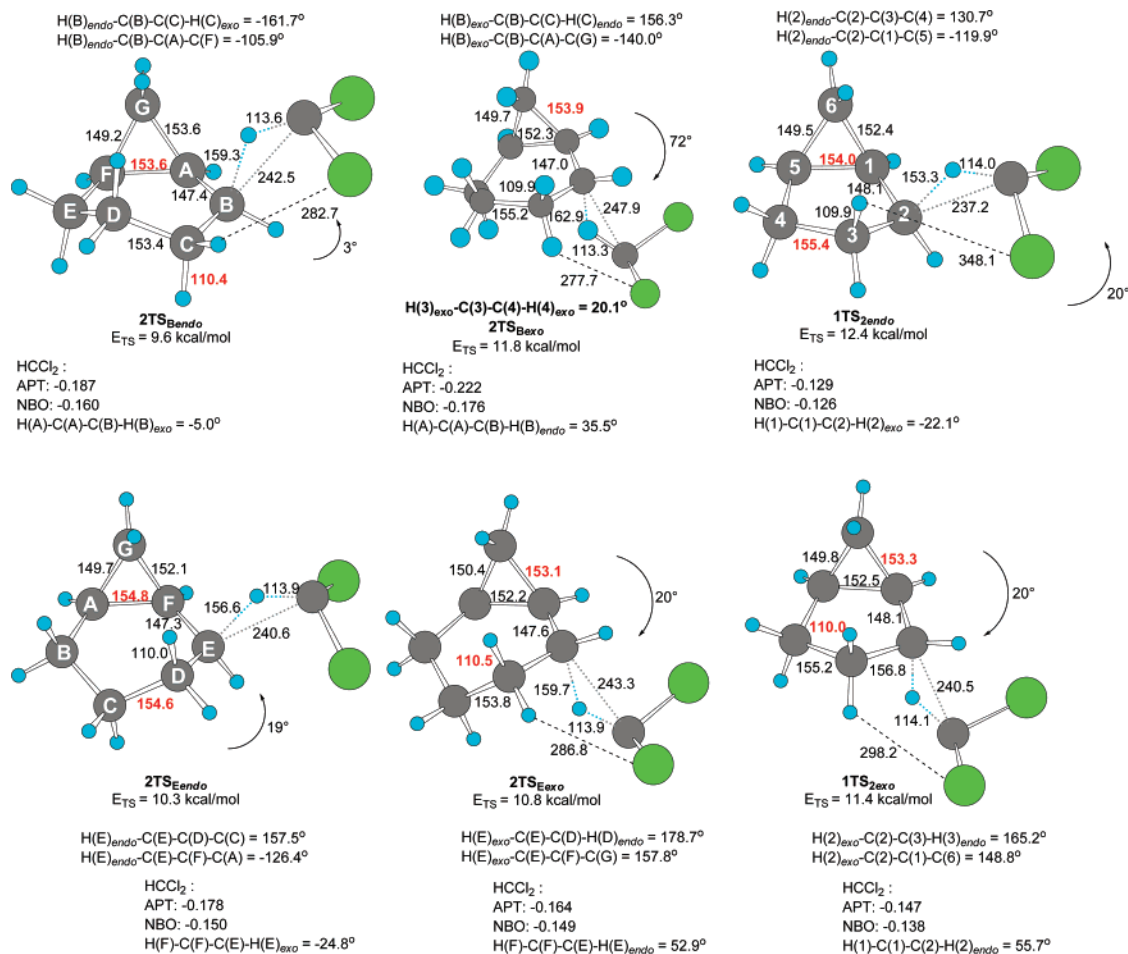
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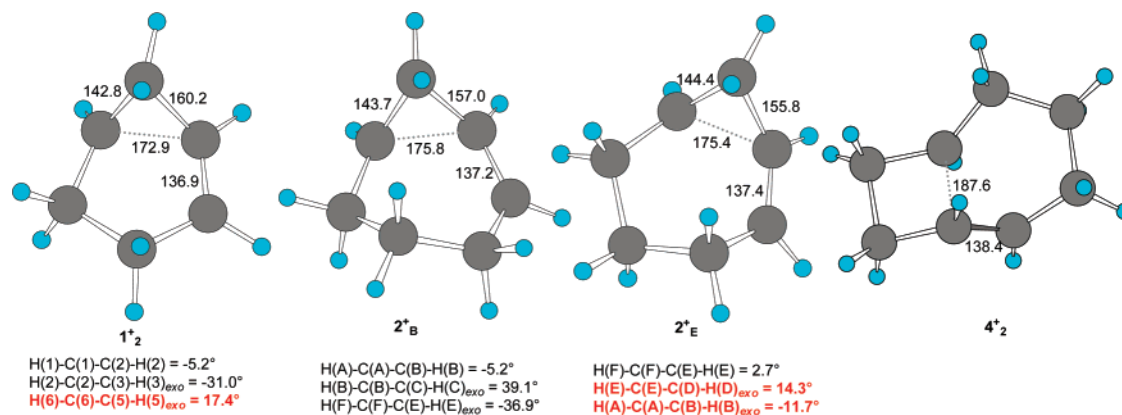
**FIGURE 2.** Geometries of the transition states of the insertion of dichlorocarbene into **1** and **2** as given by B3LYP/6-31G(d) calculations. The lengths of the bonds which are elongated in comparison to the ground state structure are in red. The dihedral angles given are those connecting two bonds with strong interactions according to NBO analyses. The arrows describe the amplitude of the rotation of C(2) from the initial to the transition state. Bond lengths in picometers and dihedral angles in degrees.

dichlorocarbene can approach the alkane through three different orientations; the most efficient pathway remains the one with the approach above the geminal C–H bonds, minimizing steric repulsion. Only in a few cases no transition states were found for the approach above a specific bond due to steric hindrance, e.g., for the approach above the C(2)–C(1) bond during the attack of  $H(2)_{endo}$  and above the C(3)–C(2) bond by the reaction with  $H(3)_{endo}$ . Our attempts to locate the corresponding transition state lead to an approach above the corresponding C–H bond. The experimental results are fully confirmed: with 11.4 kcal/mol, the lowest reaction pathway is insertion at C(2) into the *exo*-C–H bond followed by insertion into the *endo*-C–H bond of C(2) with 12.4 kcal/mol. According to the Boltzmann distribution, these two values correspond to an *endo/exo* ratio of 19/81 (22/78 for  $\Delta G_{298}$ ), quite close to the obtained experimental ratio of 26/74.<sup>13</sup> Since  $CCl_2$  is an electrophilic

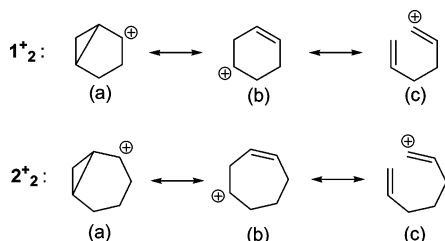
carbene, the C–H insertion starts by interaction of the LUMO of the carbene with the alkane, i.e., the hydrogen moves toward the carbene carbon by following a trajectory perpendicular to the Cl–C–Cl plane. At the transition state (Figure 2), the attacked C–H bond is almost broken ( $d = 156.8$  pm in  $1TS_{2exo}$ , which results in the formation of **3**), whereas with 114.1 pm the distance between the carbene carbon and the hydrogen corresponds almost to a normal C–H bond. Therefore, it is possible to consider a  $HCCl_2$  and a  $C_6H_{11}$  unit in the transition state. A population analysis shows that the  $HCCl_2$  fragment possesses a partial negative charge (APT: -0.147; NBO: -0.138 for  $1TS_{2exo}$ ) and the  $C_6H_{11}$  fragment a partial positive charge (APT: +0.147; NBO: +0.138). Indeed, the results correlate well with the stability of the corresponding bicyclo-[3.1.0]hexanyl cations obtained experimentally. The most stable bicyclo[3.1.0]hexanyl cation is the cyclopropyl carbinyl  $1^+_2$  (Figure 3), because of an efficient delocalization of the positive charge by the three-membered ring.<sup>14</sup> Other carbocations are only poorly stabilized.<sup>14</sup>

(13) A more accurate estimation also would consider the differences in the free energies, the solvent, and all different approaches during the insertion. However, this would imply much more computational effort and would not lead to a significant improvement of the predictive value. In this work, the ratios calculated from the free energy are about the same as the ratios presented in Table 2, because in every case very similar reactions are compared (all of them are insertions into C–H bonds and the reactants are the same). Therefore, the calculated entropies of activation differ only by less than 1 cal·mol<sup>-1</sup>·K<sup>-1</sup>, allowing a direct comparison of the activation enthalpies.

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**FIGURE 3.** Structures of cations  $1^+_2$ ,  $2^+_B$ ,  $2^+_E$ , and  $4^+_2$ . Bond lengths in picometers and dihedral angles in degrees. The torsion angles of hydrogen atoms in a synperiplanar arrangement are given in red.



**FIGURE 4.** Resonance structures contributing to  $1^+_2$  and  $2^+_2$ .

It is worth noticing that the insertion goes along with a partial rotation of C(2): In both cases, the dihedral angle  $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2)$  is reduced by  $20^\circ$  in order to take on a conformation more in accordance with the geometry of the bicyclo[3.1.0]hexan-2-yl cation ( $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2) = -5.2^\circ$ , Figure 3) and in agreement with the “double bond–no bond” resonance structures (b) and (c) contributing to the stabilization of  $1^+_2$  (Figure 4). Indeed, during the reaction, the attacked carbon atom is subjected to planarization. It follows that a C–H bond will be more easily broken if this process requires a minimal amount of reorganization between the ground state and the transition state. The preference for the *exo*-insertion may be enhanced by steric factors, since this side is less hindered. Moreover, electronic factors may play a role since the breaking of  $\text{C}(2)\text{--H}(2)_{\text{endo}}$  is only poorly stabilized by the  $\text{C}(3)\text{--C}(4)$  bond ( $130.7^\circ$  at the transition state, which is in an anticlinal arrangement and cannot be effectively involved in hyperconjugation).

A similar analysis can be made to explain the selectivity observed in bicyclo[4.1.0]heptane (**2**). In this case too, DFT calculations predict the experimental ratios quite accurately (*endo*/*exo* = 87/13 (86/14 for  $\Delta G_{298}$ ) versus 81/19 according to the experiment): the barrier for the transition state leading to the *endo*-product is 9.6 kcal/mol, whereas 10.8 kcal/mol are required for formation of the *exo*-product. Norcarane **2** exists in only one chemically relevant conformation (Figure 1).<sup>12d,15</sup> However, the carbon atoms in the  $\alpha$  position to the three-membered ring are oriented differently. In analogy to the two conformers of bicyclo[3.1.0]hexane (**1**), we define C(B) as the carbon atom placed in a local arrangement similar to that of **1** in its chair form, and C(E) as the carbon atom with a local conformation like the boat form of **1**. Correspondingly, two

different conformations should be considered for the bicycloheptan-2-yl cation:  $2^+_B$  and  $2^+_E$ . DFT calculations predict  $2^+_B$  to be 2.6 kcal/mol more stable than  $2^+_E$ . This is probably due to the presence of two synperiplanar arrangements in  $2^+_E$  causing eclipsing strain. In the same way, the activation energies obtained for the carbene insertion into the C–H bonds are lower for C(B)–H than for C(E)–H (Table 2).

The insertion into C(B)–H( $B_{\text{endo}}$ ) is the one that requires the lowest activation barrier (9.6 kcal/mol). It is also the only insertion in which the attacked carbon atom is not required to rotate during the reaction, since the torsion angle of the remaining alkyl subunit in **2** ( $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2)_{\text{exo}} = -7.9^\circ$ ) is nearly the same as that in the bicycloheptan-2-yl cation  $2^+_B$  ( $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2) = -5.2^\circ$ ) and, therefore, the same as that in the transition state  $2\text{TSS}_{\text{Bendo}}$  ( $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2)_{\text{exo}} = -5.0^\circ$ ). This nearly planar geometry is required for an effective stabilization of the partial positive charge by the contributing structures (b) + (c) of cation  $2^+_2$  (Figure 4). On the contrary, insertion into C(B)–H( $B_{\text{exo}}$ ) goes along with an important rearrangement: C(B) rotates by  $72^\circ$  until the transition state is reached in order to reduce the large dihedral angle of the reactant **2** ( $\text{H}(1)\text{--C}(1)\text{--C}(2)\text{--H}(2)_{\text{endo}} = 107.8^\circ$ ). Because of this torsion, H(3) and H(4) are forced to lose their staggered conformation ( $\text{H}(3)_{\text{exo}}\text{--C}(3)\text{--C}(4)\text{--H}(4)_{\text{exo}} = 20.1^\circ$  in  $2\text{TSS}_{\text{Bexo}}$ ). This unfavorable interaction plus the considerable rearrangement are probably the origin for the increase in barrier height calculated for the insertion into C(B)–H( $B_{\text{exo}}$ ) (11.8 kcal/mol), when compared with the insertion into C(B)–H( $B_{\text{endo}}$ ).

Interestingly, although C(E) is placed in a similar environment in **2** as C(2) in **1**, i.e., a boat structure, insertion into C(E)–H( $E_{\text{endo}}$ ) is preferred over insertion into C(E)<sub>exo</sub> according to the B3LYP calculations. One of the factors controlling this selectivity is probably hyperconjugation of the breaking bond with C(3)–C(4). In  $2\text{TSS}_{\text{Endo}}$ , this bond is antiperiplanar ( $157.5^\circ$ ), whereas it is anticlinal in **1** ( $130.7^\circ$ ).

In summary, the selectivity of the insertion reaction of dichlorocarbene into the  $\alpha$  position to a cyclopropane ring is determined by a combination of electronic and steric criteria. First of all, the C–H bond needs to be activated.<sup>3a</sup> In other words, the partial positive charge buildup should be efficiently stabilized by the neighboring atoms.<sup>16</sup> We choose to determine this capability by means of the determination of the hydride transfer potential (HTP) of the respective alkane (Table 2).

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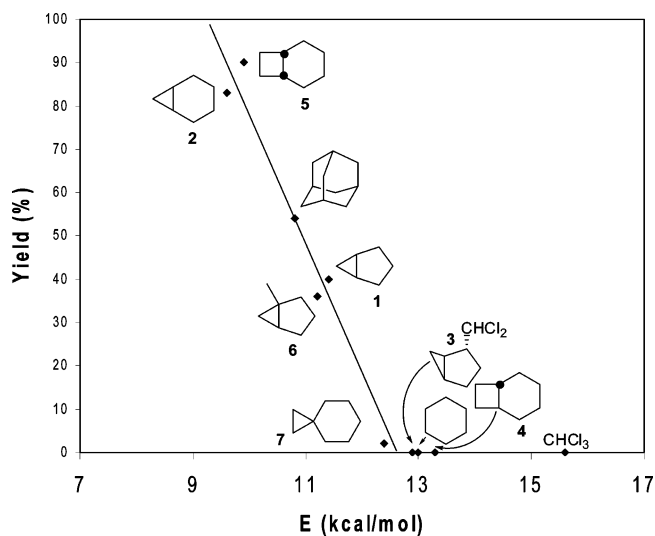
TABLE 2. Activation Energies for Dichlorocarbene Insertions into C–H Bonds

| compd         | bond              | HTP <sup>a</sup><br>(kcal/mol) | E<br>(kcal/mol) | predicted<br>ratio, % | exptl<br>ratio, % | yield,<br>%         |
|---------------|-------------------|--------------------------------|-----------------|-----------------------|-------------------|---------------------|
| 5             | A                 | 87.9                           | 9.9             |                       |                   | 90 <sup>9a,b</sup>  |
|               | F                 | 87.3                           | 10.9            |                       |                   |                     |
| 2             | endo-B            | 85.0                           | 9.6             | 87                    | 81                | 83 <sup>9b</sup>    |
|               | endo-E            | 85.9                           | 10.3            |                       |                   |                     |
|               | exo-E             | 80.2                           | 10.8            | 13                    | 19                |                     |
|               | exo-B             | 76.3                           | 11.8            |                       |                   |                     |
| adamantane    | 1                 | 93.1                           | 10.8            |                       |                   | 54 <sup>b</sup>     |
|               | 2                 | 78.4                           | 13.6            |                       |                   |                     |
| 1             | exo-2             | 76.0                           | 11.4            | 81                    | 74                | 40 <sup>9a,b</sup>  |
|               | endo-2            | 75.0                           | 12.4            | 19                    | 26                |                     |
|               | endo-3            | 68.2                           | 13.2            |                       |                   |                     |
|               | exo-3             | 60.2                           | 14.6            |                       |                   |                     |
|               | 1                 | 62.2                           | 16.0            |                       |                   |                     |
|               | exo-6             | 53.1                           | 17.3            |                       |                   |                     |
|               | endo-6            | 60.0                           | 18.5            |                       |                   |                     |
| 6             | exo-4             | 78.8                           | 11.2            | 66                    | 77                | 36 <sup>9b</sup>    |
|               | endo-4            | 80.2                           | 11.9            | 22                    | 8                 |                     |
|               | exo-2             | 78.6                           | 12.7            | 7                     | other 15          |                     |
|               | endo-2            | 77.7                           | 12.9            | 5                     |                   |                     |
| 7             | axial             | 80.8                           | 12.4            |                       |                   | 2 <sup>9a,b</sup>   |
|               | equatorial        | 73.1                           | 16.4            |                       |                   |                     |
| 3             | exo-4             | 68.9                           | 12.9            |                       |                   | 0 <sup>9b</sup>     |
|               | 2                 | 69.1                           |                 |                       |                   |                     |
|               | CHCl <sub>2</sub> | 61.1                           |                 |                       |                   |                     |
| cyclohexane   | axial             | 66.7                           | 13.3            |                       |                   | trace <sup>9b</sup> |
|               | equatorial        | 72.2                           | 13.4            |                       |                   |                     |
| chloroform    |                   | 39.3                           | 15.6            |                       |                   |                     |
| 4             | equatorial-2      | 81.3                           | 13.0            |                       |                   | 0 <sup>9b</sup>     |
|               | 1                 | 81.5                           | 14.1            |                       |                   |                     |
|               | axial-2           | 68.9                           | 14.8            |                       |                   |                     |
| methane       |                   | 0                              | 22.1            |                       |                   |                     |
| acetonitrile  |                   | 4.5                            | 15.8            |                       |                   |                     |
| malononitrile |                   | 7.2                            | 8.1             |                       |                   |                     |

<sup>a</sup> The hydride transfer potential (HTP) is obtained from the isodesmic equation  $\text{CH}_4 + \text{R}^+ \rightarrow \text{CH}_3^+ + \text{RH}$  by a single point energy calculation for the cation obtained by removal of a hydride ion from the optimized structure of the parent hydrocarbon. <sup>b</sup> In this experiment the Makosza PTC procedure was employed.<sup>17</sup>

Indeed, high yields are obtained by the reaction of  $\text{CCl}_2$  under our reaction conditions<sup>9</sup> for compounds having a high HTP under the condition that they are not sterically hindered. One can recognize a correlation ( $R^2 = 0.74$ ) between the HTP values and the calculated activation barriers. The correlation coefficient is still not very high because only the electronic factors are taken under consideration and not the steric factors. However, a good correlation ( $R^2 = 0.96$  for the linear part of the curve) is obtained between the calculated activation barriers and the experimental yields (Figure 5).

Figure 5 shows that good yields (>80%) are obtained for hydrocarbons in which the calculated barrier toward insertion is lower than 10 kcal/mol. Compounds such as **2** and **5** possess a hydride transfer potential higher than 85 kcal/mol (Table 2). At the other end, compounds with a lower hydride transfer potential (ca. 75 kcal/mol) react with moderate yields (36% for **6** and 40% for **1**) and the DFT calculations predict a barrier toward insertion of 11–12 kcal/mol. For compounds with an even lower hydride transfer potential, still higher barriers are calculated: 13.4 kcal/mol for cyclohexane and 12.9 kcal/mol for **3**. In these cases, no reaction takes place,<sup>18</sup> no matter if the PTC method or our modified PTC method was used. Compound **3** is the insertion product of  $\text{CCl}_2$  into **1**. Its reduced reactivity

FIGURE 5. Correlation between  $E_{\text{TS}}$  and experimental yields.

may be explained by the inductive effect stemming from the chlorine atoms. This absence of reactivity may lead to several competing reactions,<sup>3a</sup> i.e., polymerization of the carbene, an easy process requiring a relatively high carbene concentration, reaction with water, or insertion into the solvent  $\text{CHCl}_3$ . For this reaction, a barrier of 15.6 kcal/mol was calculated.

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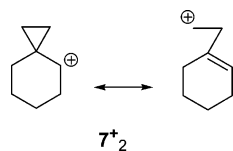


FIGURE 6. Contributing structures to the stabilization of  $7^{+2}$ .

It is worth noticing that insertion into cyclohexane occurs in 32% yield<sup>19</sup> when the Seyferth reagent,  $\text{PhHgCCl}_2\text{Br}$ , is used. Moreover, the newly prepared dichlorodiazirine<sup>20</sup> may prove to be a more powerful source of dichlorocarbene than chloroform.

How to explain these differences in reactivity? It has already been shown by comparison of the selectivities that all of the common dichlorocarbene sources, especially (bromodichloromethyl)phenylmercury<sup>21</sup> and the phase transfer catalysis reaction with chloroform,<sup>22</sup> generate a “free carbene” and not a carbenoid.<sup>3a</sup> The reason for the difference in yields can probably be found in the use of different solvents for the conversion as well as in the kinetics of the carbene’s generation, i.e., the concentration of “free carbene” during the reaction. The fact that the two most efficient methods for insertion into hydrocarbons require elevated temperatures (80 °C for the Seyferth reagent, 60 °C for our combination of PTC with ultrasound) also pinpoints the influence of the reaction temperature. This is also reflected by the high free energies of activation calculated for the insertions into hydrocarbons (20 to 25 kcal/mol).

Spiro[4.2]octane (**7**) presents a borderline case. A yield of only a few percent is expected, since the calculated energy barrier for the insertion into the axial bond is relatively high (12.4 kcal/mol), although this C–H bond is predicted to be better activated (HTP = 80.8 kcal/mol) than the C–H bonds in **1** for example. This discrepancy may be best explained by a steric consideration, due to the proximity of the cyclopropane ring. At the transition state, a short distance of 266.6 pm is found between H(3) and a chlorine atom. Remarkably, the equatorial C(2)–H bond in **7** is not activated owing to an unfavorable orientation of the cyclopropane subunit. This is reflected as well by the low HTP of 73.1 kcal/mol and by the high barrier for insertion (16.4 kcal/mol). A look at the contributing structures to the stabilization of the spiro[2.5]octan-2-yl cation  $7^{+2}$  (Figure 6) suggests that better yields for the insertion into the axial C(2)–H bond may be expected with spiro[2.5]octanes bearing substituents at the cyclopropane moiety.

Another striking result is provided by the bicyclo[4.2.0]octanes **5** and **4** (Figure 7). The *cis*- and the *trans*-isomers, **5** and **4**, respectively, present a totally different reactivity although both compounds should be efficiently attacked at the bridge head, per se a tertiary carbon atom. While compound **5** affords a 90% yield, with **4** no insertion is observed. One of the reasons for this behavior probably is of steric nature, but the difference in bond activation also plays an important role. Indeed, comparison of the HTP of the C–H bonds in **5** and **4** (Table 3) confirms the most activated bonds to be C(A)–H for **5** and C(1)–H for **4**. However, the HTP value is higher in **5** (87.9 kcal/mol) than in **4** (81.5 kcal/mol). This fact can be explained

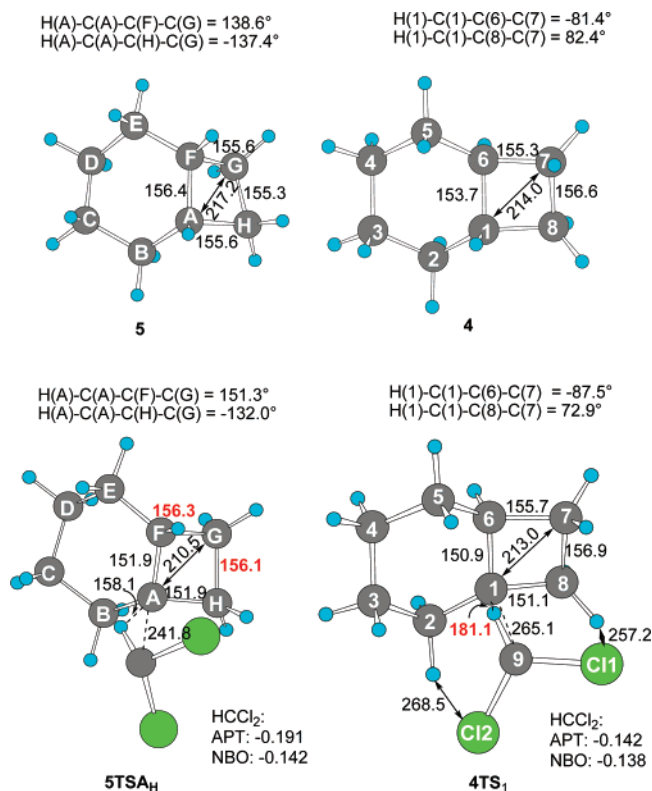


FIGURE 7. Geometries of **5** and **4** and the transition states of the insertion of dichlorocarbene into **5** and **4** as given by B3LYP/6-31G-(d) calculations. Bond lengths in picometers and dihedral angles in degrees.

TABLE 3. Activity of C–H Bonds of Bicyclooctanes **5** and **4**

| compd    | bond         | HTP (kcal/mol) |
|----------|--------------|----------------|
| <b>5</b> | A            | 87.9           |
|          | F            | 87.3           |
|          | equatorial-E | 80.1           |
|          | equatorial-B | 79.5           |
|          | axial-E      | 78.4           |
|          | axial-B      | 75.5           |
|          | endo-H       | 74.5           |
|          | exo-G        | 73.4           |
|          | endo-G       | 69.1           |
|          | exo-H        | 68.5           |
| <b>4</b> | 1            | 81.5           |
|          | equatorial-2 | 81.3           |
|          | cis-8        | 73.7           |
|          | axial-2      | 68.8           |
|          | trans-8      | 63.3           |

by a NBO analysis with  $5^{+}_{\text{Av}}$ . The analysis reveals strong stabilizing interactions arising from the two C–C bonds situated on the opposite side of the cyclobutane ring. These interactions are similar to those found in bicyclobutonium cations and are particularly strong, since both torsion angles are wide ( $\text{H(A)}-\text{C(A)}-\text{C(F)}-\text{C(G)} = 138.6^\circ$  and  $\text{H(A)}-\text{C(A)}-\text{C(H)}-\text{C(G)} = -137.4^\circ$ ).

Indeed, “cyclobutyl cations” have been thoroughly investigated and nonclassical structures were found. For example,  $\text{C}_4\text{H}_7^+$  is best described as an ion in rapid equilibrium with bicyclobutonium cation **9** and the cyclopropylmethyl cation **10** (Scheme 1). Structure **8** is a slightly puckered cyclobutyl cation that is much higher in energy than **9**. It can be computed with B3LYP, but methods including more electron correlation like

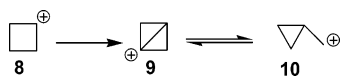
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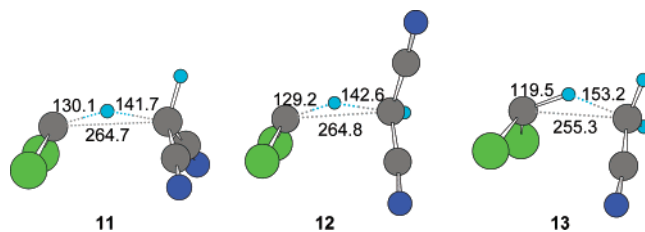
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## SCHEME 1



MP2 lead to a direct collapse to **9**.<sup>23</sup> In accordance with the efficient delocalization of the positive charge at the bridge head of **5**, the attack of dichlorocarbene is predicted to occur preferably at the C(A)–H bond on top of the C(A)–C(H) bond by overcoming a small barrier of only 9.9 kcal/mol. In contrast, the calculated barrier for the insertion into the C(1)–H bond of **4** is high (14.1 kcal/mol) in agreement with its lower HTP value (vide supra) and the poor spatial accessibility of the C(1)–H bond. The geometry calculated for this conversion corresponds to a late transition state: the breaking C–H bond is already 181.1 pm long (see Figure 7) and C(1) is almost planar coordinated. The planarization requires the two rings to fold up during the reaction, thereby increasing steric hindrance even more. This results in an attempt to insert into a C–H bond within a concave environment. At the transition state, this leads to a particularly short distance of 257.2 pm between chlorine atom Cl(1) and H(8). It is the shortest H–Cl distance we found at the transition state for the insertion of dichlorocarbene into the hydrocarbons discussed here and it is less than the sum of the van der Waals radii of chlorine (175 pm) and hydrogen (120 pm). The high barrier calculated for the insertion into the tertiary C–H bond of **4** (higher than that for cyclohexane) led us to the conclusion that insertion into a secondary C–H bond may be more competitive. Indeed, a high HTP value is found for the equatorial bond at C(2). Here, the calculated barrier is only 13.0 kcal/mol. The activation is due to hyperconjugation with the antiperiplanar C(3)–C(4) bond (H(2)–C(2)–C(3)–C(4) = –174.1°) and the strained C(1)–C(6) bond (H(2)–C(2)–C(1)–C(6) = 177.9°). These interactions are also reflected in the geometry of the bicyclo[4.2.0]octan-2-yl cation (**4**<sup>+</sup><sub>2</sub>) with its particularly long central bond (C(1)–C(6)) (see Figure 3).

Concerning the scope of this methodology, we think that the estimation of the activity by use of the HTP determination can be useful for most of the stabilized-electrophilic carbenes reacting by the electrophilic–nucleophilic mechanism<sup>5,7</sup> as in the usual cases. However, the slightly nucleophilic character of dichlorocarbene can be revealed by investigation of an extreme case: the insertion of CCl<sub>2</sub> into the strongly acidic C–H bonds of malononitrile (pK<sub>a</sub> = 11.1).<sup>24</sup> Malononitrile is characterized by an extremely low HTP value (7.2 kcal/mol), but, nevertheless, the calculated barrier for insertion into the C–H bond is particularly low (7.4 kcal/mol). Analysis of the charge repartition at the transition state reveals that the HCCl<sub>2</sub> group is positively charged (APT = +0.303; NBO = +0.310). It means that this reaction is better described by a proton transfer than by a hydride transfer, or in other words, by a nucleophilic phase followed by an electrophilic phase. This result is confirmed by the NBO analysis of the transition state. Electron donation from the lone pair at the carbenic center into the antibonding orbital of the breaking C–H bond is much stronger



**FIGURE 8.** Transition states for the nucleophilic insertion of dichlorocarbene into malononitrile and acetonitrile.

than the electron donation from the C–H bond to the LP\* of the divalent carbon. Astonishingly, in the preferred orientation for the dichlorocarbene attack on malononitrile, an eclipsed conformation is favored (**11**, Figure 8). This means that the  $\pi$ -approach is favored over the  $\sigma$ -approach. To our knowledge, in all previously studied insertion reactions of a carbene into a C–H bond, the  $\sigma$ -approach was preferred with the exception of the insertion of vinylidene into methane.<sup>5,7</sup> This may suggest attracting interactions between the chlorine atoms and the sp carbons. However, the NBO analysis does not reveal any donor–acceptor interactions between them. A second transition state **12** has been found for this insertion, in which only one chlorine is placed in a *syn*-conformation to the cyano group, but this stationary point is 0.7 kcal/mol higher in energy than the previously described transition state **11**.

In contrast, insertion in the C–H bond of acetonitrile (HTP = 4.5 kcal/mol; pK<sub>a</sub> = 31.3<sup>24</sup>) is associated with a prohibitively high-energy barrier (15.8 kcal/mol). The charge repartition at the transition state **13** (HCCl<sub>2</sub>: APT = +0.207 and NBO = +0.169) speaks also for the domination of the nucleophilic mechanism. From a synthetic point of view, a formal CCl<sub>2</sub> insertion into malonic acid derivatives has been obtained several times, but under basic conditions.<sup>25</sup>

Which reactions may compete with the C–H insertion? As already described in the literature, strained cyclopropanes, especially bicyclobutanes, undergo a two-bond insertion cleavage reaction<sup>26</sup> and it is reasonable to think that bicyclo[3.1.0]hexane (**1**) may already be strained enough to undergo ring opening. Indeed, a relatively low activation energy (13.5 kcal/mol) is calculated for the formation of 1,1-dichlorohepta-1,6-diene (**14**) (Figure 9). At the B3LYP/6-31G(d) level of theory, this conversion is described as a concerted process with an asynchronous cleavage of the bonds. This barrier is only 2.1 kcal/mol (1.1 kcal/mol for the *endo* compound) higher than those needed for the obtained C–H insertion products. This result gives hope that the ring opening to a diene may become the main reaction, if a bicyclo[3.1.0]hexane is used as reactant with substituents which can efficiently stabilize the transition state or even favor the formation of a biradical or of a zwitterion as reactive intermediate. However, ring cleavage was never observed during the experimental investigation performed in our group.<sup>9</sup> A second relatively realistic cleavage is obtained by an attack on C(6) leading to the formation of cyclopentene

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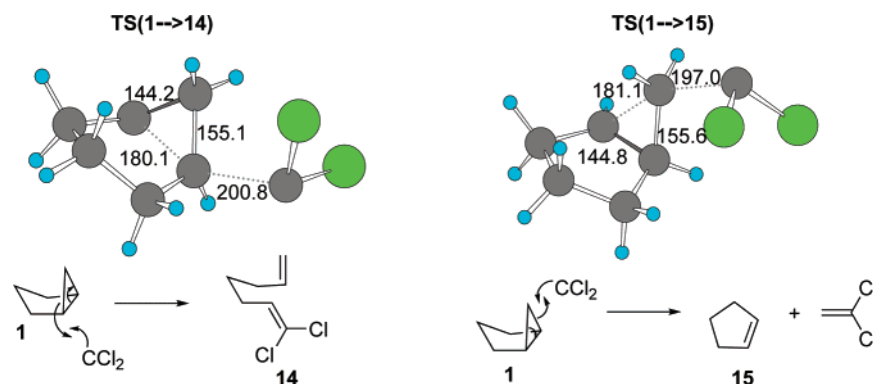


FIGURE 9. Possible side reactions by the addition of dichlorocarbene to bicyclo[3.1.0]hexane.

(15) and 1,1-dichloroethene with an activation energy of 15.6 kcal/mol. The third possibility does not need to be considered, since it would cause the development of a partial positive charge on C(6), which would not be efficiently delocalized, since C(6) bears two hydrogen atoms.

Finally, a potential alternative mechanism should be considered: as carbenes can interact strongly with alkenes and also with three-membered rings,<sup>27</sup> it is interesting to investigate more deeply the possibility that the cyclopropane unit may influence the course of the reaction by an interaction of the Walsh orbitals with the empty orbital of the carbene. Therefore, we have made several attempts to locate complexes between bicyclo[3.1.0]hexane (**1**) and dichlorocarbene (see the Supporting Information, structures **16** and **17**). Indeed, complexes between carbenes and cyclopropane have already been described.<sup>6</sup> However, we were not able to find a minimum with the LUMO of the divalent species pointing toward a C–C bond or a carbon atom of **1**. Instead, extremely weak minima (less than  $-0.6$  kcal/mol for  $\Delta E$ ,  $\Delta G_{298} = +5.2$  kcal/mol) are found, when one of the ubiquitous C–H bonds is oriented toward the LP\* of the carbene. Therefore, it can be concluded that dichlorocarbene does not interact directly with three-membered rings.

## Computational Methods

The Gaussian 03 program<sup>28</sup> was used for density functional theory calculations, employing Becke's<sup>29</sup> three-parameter hybrid method, and the exchange functional of Lee, Yang, and Parr (B3LYP).<sup>30</sup> Geometries were optimized at the B3LYP/6-31G(d) level of theory. The stationary points were characterized by

vibrational analysis. The zero-point vibrational energies (ZPE) were scaled by a factor of 0.9806.<sup>31</sup> All reported energies include zero-point corrections. The hydride transfer potential was obtained from the isodesmic equation  $\text{CH}_4 + \text{R}^+ \rightarrow \text{CH}_3^+ + \text{RH}$  by a single-point energy calculation for the cation obtained by removal of a hydride ion from the optimized structure of the parent hydrocarbon. This permits a rapid estimation of the activity of a specific C–H bond. For this comparison, the structure of the cation is not optimized because the insertion of  $\text{CCl}_2$  into a C–H bond is a concerted process in which only a small partial positive charge is accumulated on the alkyl moiety. Moreover, in strained bicyclic compounds, cations may adopt an equilibrium geometry, which is totally different from the starting geometry, because of the formation of non-classical cations, such as trishomocyclopropyl cations,<sup>14c,e,32</sup> or because of ring opening, i.e., formation of a monocyclic allyl cation from a bicyclic cyclopropyl cation. Since the charge transfer induced by  $\text{CCl}_2$  is small and the concerted reaction does not allow a significant amount of time for a potential rearrangement to proceed, the reactivity of the alkane is better estimated by a comparison with the nonoptimized cation. Moreover, this methodology allows a comparison of the reactivity of both bonds, i.e., the *endo* and the *exo* C–H bonds.

## Conclusion

DFT calculations can be used for prediction of the regio- and stereoselectivity of dichlorocarbene insertions into C–H bonds. For cyclic hydrocarbons, a calculated barrier below 10 kcal/mol leads to excellent yields, whereas a barrier of more than 12.5 kcal/mol is prohibitive for the reaction. The calculated *endo/exo* ratios are in good agreement with the ratios obtained experimentally. Dichlorocarbene insertions proceed in good yields with activated C–H bonds, provided there is no steric hindrance. During the reaction, a partial positive charge accumulates on the alkyl fragment that needs to be efficiently delocalized in order to stabilize the transition state. Therefore, the geometry of the remaining alkyl group has to be similar to that of the corresponding alkyl cation in order to minimize energetically costly rearrangements proceeding from the ground state to the transition state. Thereby, the insertion into this particular C–H bond is favored over other C–H bonds. When three-membered rings are involved, the reaction occurs in the  $\alpha$  position. For electrophilic reactions with an early transition state the reactivity of a specific C–H bond can rapidly be

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estimated by the computation of its hydride transfer potential (HTP), thus facilitating the determination of the potential reaction products. With slightly acidic C–H bonds, the insertion of dichlorocarbene occurs according to a nucleophilic–electrophilic mechanism. In this case, the calculated energy barrier correlates well with the  $pK_a$  of the reactant.

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**Supporting Information Available:** Cartesian coordinates and energies for all relevant stationary points. This material is available free of charge via the Internet at <http://pubs.acs.org>. JO702047B