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A Computational Investigation of the Reactions of Methylene, Chlorocarbene, and Dichlorocarbene with Cyclopropane

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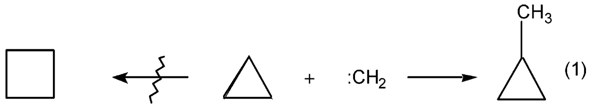
The reactions of CH_2, CHCl, and CCl_2 with cyclopropane, **1**, have been examined computationally. In all cases the lowest energy reaction between the carbene and **1** is predicted to be C−H insertion. In the reaction of CH_2 with **1**, the transition state for C−C insertion leading to cyclobutane is 1.7 kcal/mol higher in enthalpy than the transition state for C−H insertion at the G3B3 level. A pathway higher in energy than C−H insertion in the reactions of CHCl and CCl_2 with **1** involves two-bond cleavages generating ethylene along with chloro and dichloroethylene, respectively.

Introduction

Methylene has been called "the most indiscriminate reagent known in organic chemistry."[1] While there is much experimental[2] and computational[3] evidence to support this claim, it has always been a bit of a puzzle that the great reactivity of methylene does not readily allow insertion into carbon−carbon bonds along with the well-documented insertion into carbon−hydrogen bonds. Although the fact that C−C bonds are some 10−15 kcal weaker than C−H bonds would seem to favor a C−C insertion, it is only in the highly strained central bond of bicyclo[1.1.0]butane that evidence for reaction with a C−C bond is found.[4,5] The reaction of methylene with cyclopropane, **1**, in which there is a 46 kcal/mol difference between the C−C and C−H bond strengths, shows only the C−H insertion product methylcyclopropane, **2**, and products derived from it. No cyclobutane, **3**, from C−C insertion is observed.[6]



3 **1** **2** (1)

Computational studies of the reaction of CH_2 with **1** predict a small barrier to C−C insertion.[3a,b] Although C−H insertion by CH_2 on **1** has not been considered computationally, insertion into the C−H bonds of ethane has also been calculated to be quite facile.[3a,b] Since **1** appears to be a molecule in which C−C insertion could be expected to compete with C−H insertion, we have reinvestigated its reaction with CH_2 computationally in order to determine the barriers to both reactions and the anticipated ratios of C−H to C−C insertion products. In the hope that more stable carbenes will be more discriminating in their reactions and preferentially choose the lower energy C−C bonds for insertion, we have also investigated the reactions of chlorocarbene, **4**, and dichlorocarbene, **5**, with **1**.

Computational Methods

All calculations were made with the Gaussian 98 program system.[7] With an appropriate choice of gradient correction and modest basis set, DFT has been shown to give results of near chemical quality.[8] Becke3LYP, which seems to be a good choice of exchange and correlation functional, has been used with the 6-31G(d) basis set to optimize geometries. Vibrational frequencies have been calculated with the same method and used to determine zero-point and heat capacity corrections.

Absolute energies (hartrees) and zero-point energies (kcal/mol) of various species are presented in Table S1 and relative energies in Table 1. Relative energies are approximated at the QCISD(T)/6-311+G(3df,2p) level through the additivity approximation (eq 2).

$$[\mathrm{QCISD(T)/6\text{-}311{+}G(3df,2p)}] = \mathrm{QCISD(T)/6\text{-}31{+}G(d)} + \mathrm{MP2/6\text{-}311{+}G(3df,2p)} - \mathrm{MP2/6\text{-}31{+}G(d)} \quad (2)$$

Enthalpies are computed by including zero-point and heat capacity corrections from unscaled B3LYP/6-31G(d) frequen-

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TABLE 1. Relative Enthalpies and Free Energies (kcal/mol) at B3LYP/6-31G(d) Geometries[a]

species	B3LYP/a		[QCI/c]		G3B3:	%
	energy	Δ*H*(298K)	Δ*H*(298K)	Δ*G*(298K)	Δ*H*(298K)	C−H insert
CH_2 + **1**	0.0	0.0	0.0	0.0	0.0	
CP1a	−4.9	−2.7	−2.6	4.8	−2.3	
CP1b	−5.3	−2.9	−2.1	5.7	−1.7	
TS1-2	−2.7	−1.5	−1.5	6.7	−1.0	>99.9
TS1-3	−4.0	−1.4	0.3	9.8	0.7	
2	−118.3	−112.5	−108.5	−98.3	−108.8	
3	−119.0	−112.7	−107.9	−96.3	−108.2	
2 $H_2C{=}CH_2$	−95.0	−92.5	−89.8	−90.6	−90.6	
1 + **4**	0.0	0.0	0.0	0.0	0.0	
CP4	−1.5	−0.2	−1.7	4.1	−1.3	
TS4-6	2.6	2.1	2.9	12.9	3.4	>99.9
TS4-10	8.3	9.6	10.0	20.3	10.7	
6	−95.6	−91.2	−89.9	−78.7	−90.1	
$H_2C{=}CH_2$ + **10**	−73.5	−72.6	−71.4	−72.1	−72.2	
1 + **5**	0.0	0.0	0.0	0.0		
CP5	−0.5	0.6	−2.0	0.8		
TS5-7	18.4	17.1	12.5	22.7		96.0
TS5-11	16.2	16.5	14.0	24.1		
7	−74.2	−70.8	−73.8	−62.3		
$H_2C{=}CH_2$ + **11**	−53.0	−53.2	−54.7	−55.0		
TS5-14[c]	23.4	22.5				
14[c]	−23.8	−22.9				
TS14-11[c]	−21.2	−21.2				

[a] The square brackets indicate the use of the additivity approximation (i.e. [QCI/c] = QCI/b+MP2/c-MP2/b). Basis set "a" is 6-31G(d), basis set "b" is 6-31+G(d), and basis set "c" is 6-311+G(3df,2p). Energies are relative to CH_2 + **1**, **1** + **4**, or **1** + **5**.

cies. Free energies at 298 K are computed by including the $T\Delta S$ term with the enthalpy. The G3B3 method[9a] was used to calculate enthalpies (298 K) for the reaction of CH_2 and **4** with **1**. Since enthalpies at the G3B3 and [QCISD(T)/6-311+G(3df,2p)] levels are very similar, the discussion below of the reactions of CH_2, **4**, and **5** with **1** will use enthalpies and free energies at the [QCISD(T)/6-311+G(3df,2p)]//B3LYP/6-31G-(d)+ZPC+Cp(298K) level.

Results and Discussion

The Reaction of Cyclopropane with CH_2. Figure 1 shows structures of various species along the energy surface in the reaction of CH_2 with **1**. The calculations locate two complexes, **CP1a** and **CP1b**, between the reactants lying in rather shallow minima. In agreement with previous calculations,[3a,b] a transition state for the highly exothermic ($\Delta H_{calc.} = -108.2$ kcal/mol; $\Delta H_{expt} = -108.1$ kcal/mol) C−C insertion, **TS1−3**, was located whose energy indicated that this reaction is expected to be quite facile. An examination of the geometry of complex **CP1a** reveals that it is quite similar to that of **TS1−3** and it is reasonable to assume that it is this complex that leads to C−C insertion. A transition state for C−H insertion, **TS1−2**, whose enthalpy was 1.7 kcal/mol lower than that of **TS1−3**, was also identified.

The calculated free energies of **TS1−2** and **TS1−3** and the expected percent C−H insertion products derived from these values are shown in Table 1 along with relative free energies of starting materials, **CP1a**, and **CP1b**. On the free energy surface, the two complexes between CH_2 and **1** lie at higher energy than the starting materials and become less relevant. Even if they were minima, they would not be present in appreciable concentrations. It is interesting that these calculations predict that the yield of the C−C insertion product **3** will be less than 0.1% of that of the C−H insertion product. This is consistent with experimental studies in which a careful analysis of reaction products indicated that there can be no more than 2.3×10^{-3}% of **3** formed in the reaction of CH_2 with **1**.[6] It is thus clear that the introduction of a strained C−C bond is not sufficient to bring about significant C−C insertion by **1**. Similar experimental results are observed in the reaction of CH_2 with cyclobutane,[6] spiropentane,[10] and spiro[3,3]heptane.[10]

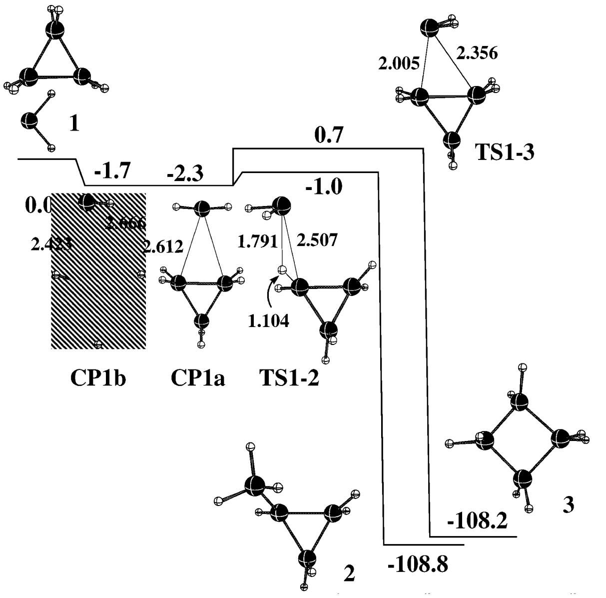

FIGURE 1. Relevant B3LYP/6-31G(d) geometries and G3B3 enthalpies (kcal/mol) along the coordinate for the reaction of CH_2 with **1**.

We calculate a $\Delta\Delta G$ for the difference between C−C and C−H insertion of 3.1 kcal/mol, which is close to the

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(8) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*, Wiley-VCH: New York, 2000.

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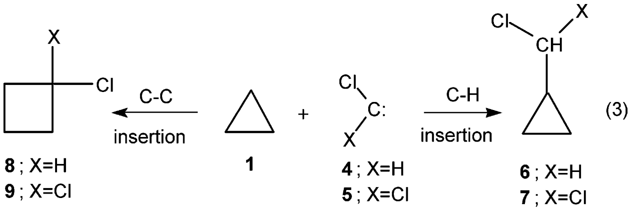
minimum value of $\Delta\Delta G$ (3.2 kcal/mol) from experimental data.[6] There is also the possibility that quantum mechanical tunneling (QMT) may further lower the barrier to C−H insertion relative to C−C insertion. Although QMT has been observed for both hydrogen[11] and carbon[12] in carbene reactions, it is clear that it is more probable for hydrogen and could lower the barrier for C−H insertion in the present case. In any case, these and previous calculations indicate that the barriers to both C−H and C−C insertion are quite low in the reaction of CH_2 with **1** and leave room for the hope that C−C insertion may yet be observed in the reaction of a carbene with a cyclopropane. An obvious modification favoring C−C insertion is the substitution of **1**-d_6 for **1** in this reaction. This would be expected to lower the rate of C−H insertion while leaving the rate of C−C insertion relatively unchanged. Thus, the reaction of CH_2 with **1**-d_6 at low temperature may result in observation of the C−C insertion reaction. Of course, if QMT played a role in the reaction, the **2**:**3** ratio would decrease still further in the presence of deuterated substrate, increasing the likelihood of observing the C−C insertion product.

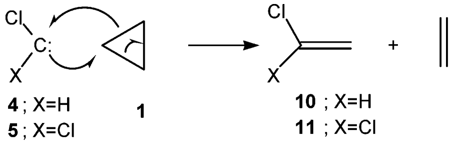
The Reaction of Chloro and Dichlorocarbenes with Cyclopropane. Perhaps the failure of C−C insertion to compete with C−H insertion in the reaction of CH_2 with **1** stems from the fact that methylene is so reactive. Thus, although the C−H bonds in **1** are stronger than those in an unstrained hydrocarbon, the methylene has the energy to insert into these C−H bonds and does so, perhaps before it encounters a C−C bond. A possible way to render C−C insertion competitive with C−H insertion in **1** is to use a less reactive carbene in which insertion into the strong C−H bond in **1** may be less favored. Candidates for carbenes in this approach could be chlorocarbene, **4**, and dichlorocarbene, **5**, in which carbene energy and reactivity is lowered by electron donation by chlorine into the empty p orbital of the singlet carbene. Neither **4** nor **5** has been reported to insert into a cyclopropyl C−H bond.[13]



(3)

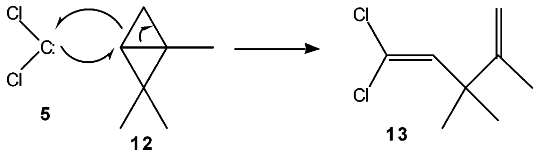
Equation 3 shows products of C−H and C−C insertion in the reaction of **4** and **5** with **1**. In the reaction of both **4** and **5** with **1**, transition states leading to C−H insertion products **6** and **7** were located. The greater stability of carbenes **4** and **5** as compared to CH_2 is reflected in the fact that the barriers to C−H insertions are considerably higher than that for CH_2. The enthalpy of the transition state for C−H insertion by CH_2, while higher than that of **CP1a** and **CP1b** by 0.7 and 1.3 kcal/mol respectively, is actually calculated to be lower in energy than that of CH_2 + **1** by 1.0 kcal/mol. In contrast, the transition state for C−H insertion by **4** (**TS4**−**6**) is 3.4 kcal/mol higher than reactants and 4.7 kcal/mol higher than a complex of **4** + **1** (**CP4**). The enthalpy barriers become even higher in the more stable carbene **5**, in which the transition state for C−H insertion to produce **7** (**TS5**−**7**) is 12.5 kcal/mol higher than reactants and 14.5 kcal/mol higher than an initial complex between **1** and **5** (**CP5**). The fact that carbenes **4** and **5** are less reactive toward C−H insertion on **1** is also indicated by the respective free energies of activation of 12.9 and 22.7 kcal/mol as compared to a free energy of activation of 6.7 kcal/mol for C−H insertion by CH_2. At least in the case of the stabilized carbene **5**, these results indicate that insertion into cyclopropyl C−H bonds would not be expected to be competitive with other carbene reactions, such as dimerization or insertion into weaker C−H bonds. In fact, an investigation of the reaction of **5** with bicyclic hydrocarbons containing a cyclopropyl ring reveals only products of insertion into C−H bonds α to the three-membered ring.[13]

It is interesting that we could not locate transition states leading to **8** and **9** from C−C insertion by **4** and **5**. Instead, both carbenes were found to react by a double C−C insertion, cleaving two cyclopropyl C−C bonds to generate ethylene along with chloroethene, **10**, and 1,1-dichloroethene, **11**, respectively (eq 4).



(4)

Such double C−C insertions have been observed in the reactions of carbenes with bicyclo[1.1.0]butanes.[4,5,14,15] For example Jackson et al. report that the reaction of **5** with 1,2,2-trimethylbicyclo[1.1.0]butane **12** gives a 69% yield of 1,1-dichloro-3,3,4-trimethyl-1,4-pentadiene **13** in a reaction analogous to that in eq 4.[14]



Figures 2 and 3 show relevant geometries and energies on the coordinates for the reactions of **1** with **4** and **5**. In both cases, the double C−C insertion (cleavage) is higher in energy than the C−H insertion. The free energies of activation in Table 1 indicate that formation of ethylene and **10** in the reaction of **4** with **1** would not be competitive with C−H insertion to produce **6**, while reaction of **5** with **1** is predicted to generate cleavage products amounting to approximately 4% of the C−H insertion products. However, since the activation free energies for both C−H insertion (22.7 kcal/mol) and cleavage (24.1

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[10] Wu, G.-X.; Jones, M. Jr.; Doering, W. von E.; Knox, L. H. *Tetrahedron* **1997**, *53*, 9913−9920.

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[12] Zuev, P. S.; Sheridan, R. S.; Albu, T. V.; Truhlar, D. G.; Hrorvat, D. A.; Borden, W. T. *Science* **2003**, *299*, 867−870.

[13] Xu, L.; Smith, W. B.; Brinker, U. H. *J. Am. Chem. Soc.* **1992**, *114*, 783−784.

[14] Jackson, J. E.; Mock, G. B.; Tetef, M. L.; Zheng, G.-X.; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1453−1464.

[15] Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, 3411−3412. These workers react **5** with bicyclobutanes having electron-withdrawing groups at the bridgehead and also observe bicyclo[1.1.1]-pentanes, the C−C insertion procuct.

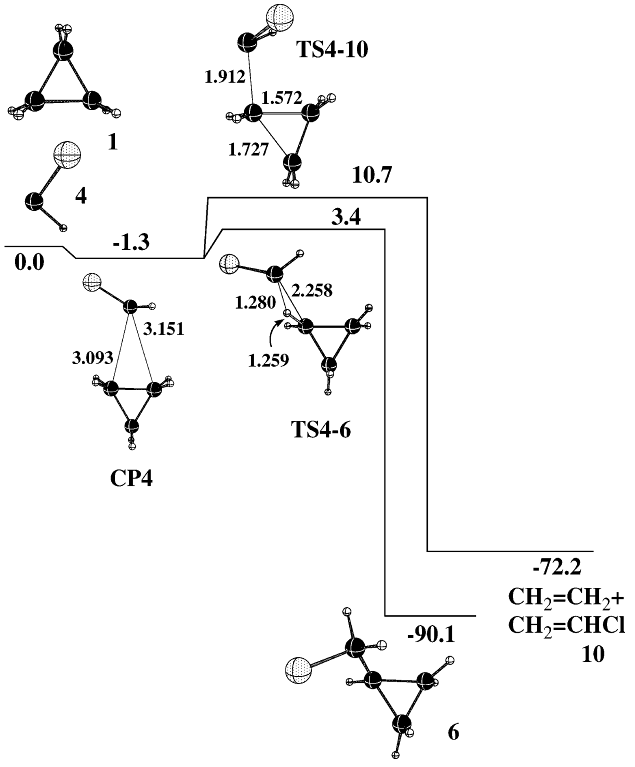


FIGURE 2. Relevant B3LYP/6-31G(d) geometries and G3B3 enthalpies (kcal/mol) along the coordinate for the reaction of **4** with **1**.

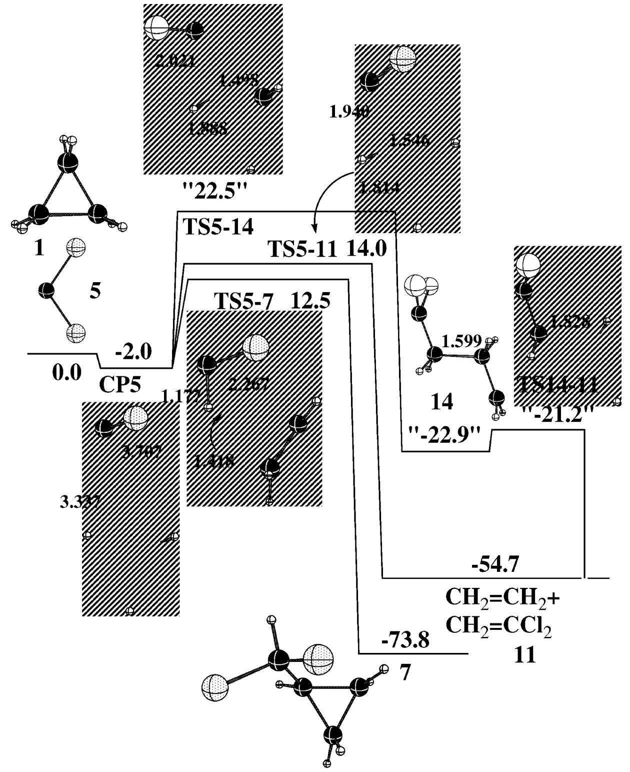
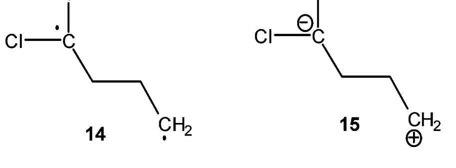


FIGURE 3. Relevant B3LYP/6-31G(d) geometries and [QCI/c] enthalpies (kcal/mol) along the coordinate for the reaction of **5** with **1**. Enthalpies in quotes are at theUB3LYP/6-31G9d) level.

kcal/mol) are rather high in the reaction of **5** with **1**, it would not be surprising if neither of these reactions could compete with carbene dimerization.

Although the double C−C insertion was originally postulated to involve a biradical,[4,5] Jackson et al. report both experimental and computational evidence that the reaction is actually concerted.[14] To reflect the concertedness of the process, they have called it a “two bond pluck” mechanism. While our calculations also support a concerted mechanism for the cleavage, an examination of the geometry of the transition state in Figure 3 (**TS5−11**) reveals that of the two C−C bonds that are cleaved in the reaction, the one at 1.82 Å is largely broken while the other remains essentially intact at 1.55 Å. The C−C bond to the incoming carbene is largely unformed at 1.94 Å. Although **TS5−11**, with minimal bonding between two cyclopropyl carbons, resembles a biradical, we have found that the transition state leading to the actual 1,4-biradical **14** (**TS5−14**, Figure 3) is higher in energy than **TS5−11** by 8.5 kcal/mol. Since **5** is an electrophilic carbene, it is expected to accept electrons from a filled Walsh orbital in **1** in the manner in which other electrophiles interact with cyclopropyl rings. An examination of the electron distribution in **TS5−11**, which shows an excess of electron density on the carbene carbon and a corresponding electron deficiency on the displaced cyclopropyl carbon, supports this conclusion and indicates that resonance structure **15** contributes to the stability of the transition state.



These calculations indicate that all of the carbenes investigated will prefer to react with **1** by C−H insertion rather than by mechanisms involving breaking of C−C bonds. However, the strain of the C−C bonds in **1** renders activation barriers for these mechanisms close in energy to that of C−H insertion. Clearly the additional strain in the bicyclo[1.1.0] skeleton brings about the observed C−C insertion.[4,5,15] When considering C−C insertion, the fact that CH_2 undergoes reaction with **1** by a single C−C insertion while **4** and **5** prefer to react by double C−C insertion, leading to cleavage, probably is a reflection of the electrophilicity of the carbenes. The more electrophilic **4** and **5** drain electron density from a C−C bond, bringing about cleavage of that bond. It is possible that increasing the electrophilicity of the carbene and adding electron-donating groups to the cyclopropyl ring will facilitate the two-bond C−C insertion leading to cleavage in the carbene + cyclopropane reaction. These investigations rationalize the failure to observe C−C insertions by carbenes except in extreme cases in which ring strain plays a crucial role.

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Supporting Information Available: Table S1 contains the absolute energies, zero-point energies, heat capacity corrections, and entropies of relevant species. Table S2 contains Cartesian coordinates of the species listed in Tables 1 and S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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