

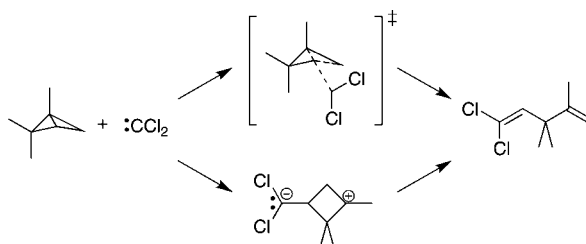
Computational Investigation of the Mechanism of Addition of Singlet Carbenes to Bicyclobutanes

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Singlet carbenes are known to react with bicyclobutanes to yield 1,4-diene products, as in the addition of dichlorocarbene to bicyclobutane to yield 1,1-dichloro-1,4-pentadiene. At least two mechanisms have been proposed to explain this unusual reaction: (1) a concerted process and (2) a stepwise process involving a zwitterionic intermediate. Ab initio electronic structure calculations have been performed in order to help distinguish between these two mechanistic possibilities. In the parent system, the concerted pathway and the corresponding transition structure are readily located. On the other hand, the hypothesized zwitterionic intermediate does not correspond to a minimum at most levels of theory, even in the presence of a polar medium representing the solvent. Instead, this structure corresponds to a transition state or, at best, an extremely shallow minimum. The two pathways—one unambiguously concerted, the other possibly leading through an extremely shallow minimum (intermediate)—have very similar barriers and are expected to be competitive. In the substituted 1,2,2-trimethylbicyclobutane system, five regioisomeric concerted pathways exist and lead to four different diene products. Two of these pathways lie well below the others in energy, and they alone are expected to play a significant role at ordinary temperatures. Of these two pathways, the one calculated to have the slightly lower barrier leads to the only product that is reported experimentally. In addition, a sixth geometry of approach exists, leading over a transition structure of comparable energy to a shallow minimum that corresponds to a zwitterionic intermediate. The calculated potential energy surface suggests that the reaction can proceed through this intermediate both to the observed diene product and to one of the other isomers. It therefore appears that the concerted and stepwise mechanisms are competitive in the substituted system. Taken together, the calculated pathways and barriers do not adequately account for the very pronounced regioselectivity observed experimentally; only modest regioselectivity would be predicted at best. Examination of a calculated potential energy surface defined over two relevant internal coordinates sheds further light on the reaction and suggests that the experimentally observed regioselectivity might derive in considerable part from dynamic effects.

Introduction

Singlet carbenes most commonly react with organic compounds either by addition to π bonds or by insertion into C–H bonds. These forms of reactivity are well-documented and have been extensively studied by computational as well as experi-

mental means.^{1–3} In rare instances, small amounts of insertion into C–C bonds have also been observed, although the only

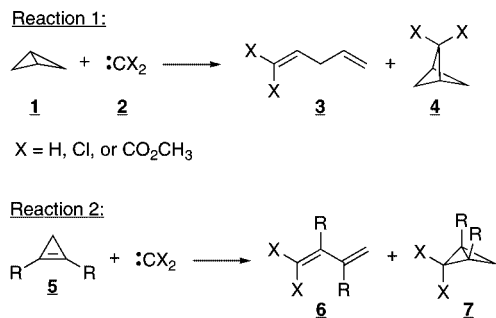
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(2) (a) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 4293–4294. (b) Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933–3938.

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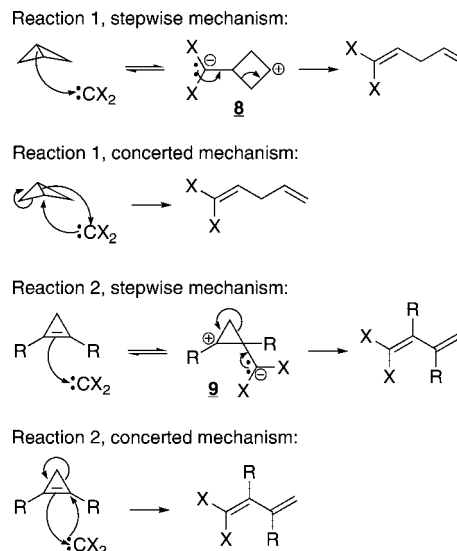
SCHEME 1



known cases occur in intramolecular fashion in strained cyclic systems.⁴ Intermolecular C–C insertion of a carbene, even in a strained system, has never been observed, despite an explicit search for such reactivity. For instance, Becerra and Frey have shown that even cyclopropane and cyclobutane, which would seem to be ideal candidates, yield no observable amounts of the C–C insertion products (cyclobutane and cyclopentane, respectively).⁵ Sevin, McKee, and Shevlin have used electronic structure calculations to explore the reaction of singlet carbenes with cyclopropane and, in agreement with the experimental observations, find a somewhat lower barrier for C–H insertion than for C–C insertion.⁶ Wu, Jones, Doering, and Knox investigated the reactions of carbenes with the still more highly strained spiro[3.3]heptane and [3.3]spiroheptane but, even in these cases, observed no products of C–C insertion.⁷

Bicyclobutane and cyclopropene systems, however, exhibit a third, unique reactivity, shown in Scheme 1.^{8–13} In each case, the carbene reacts in such a way as to generate simultaneously a new σ bond and a new π bond to its reaction partner. These intriguing reactions were initially reported by Doering⁸ and by Wiberg⁹ and have subsequently been studied experimentally by Jackson and Jones,⁴ Brinker,^{12,13} and their co-workers. Such reactions have been observed with dichlorocarbene, methylene, and dicarbomethoxycarbene, generated thermally from chloroform and photochemically from diazomethane and dimethyldiazomalonate, respectively. Reaction partners have included 1,2-diphenylcyclopropene,^{12,13} bicyclo[1.1.0]butane,⁹ 1,3-dimethylbicyclo[1.1.0]butane,⁸ and 1,2,2-trimethylbicyclo[1.1.0]butane,⁴ among others. Given the variety of conditions known to yield singlet carbenes that have been used for this reaction, and the consistency

SCHEME 2



of the results, there appears to be general agreement that the diene products result from singlet, not triplet, reactivity.⁴

However, the mechanism has never been adequately settled. Although several mechanisms have been proposed, debate has focused primarily on two competing possibilities, illustrated in Scheme 2. One mechanism postulates an intermediate, generally supposed to be zwitterionic in character, although sometimes also viewed as a singlet diradical. The other, designated by Jackson and Jones as the “two-bond pluck mechanism,” postulates a concerted process, although not a synchronous one.⁴

Brinker has addressed the mechanistic question for reaction 2 in Scheme 2 through an ingenious use of substituent effects.¹³ He and his co-workers prepared a series of 1,2-diphenylcyclopropene derivatives in which one of the aromatic groups has a para-substituent and determined the regiochemical preferences in reactions with dichlorocarbene. In each case, two zwitterionic intermediates are possible, yielding two different products. The para-substituent, because of its electron-withdrawing or electron-donating character, favors one or the other zwitterion, and thus one ultimate product or the other. The observed regiochemistry of the reactions in fact matches the predictions for the stepwise mechanism. However, the findings do not settle the mechanistic debate since, as Brinker notes, the results are equally consistent with a concerted mechanism featuring a polar transition structure—one with a charge distribution resembling that of the postulated zwitterion.¹³

Recently, Merrer and Rablen used a computational approach to study the mechanism of the reaction of singlet carbenes with cyclopropene derivatives.¹⁴ They found no evidence for the postulated intermediate; no such stationary point could be located on the potential energy surface. On the other hand, they did locate concerted pathways yielding both the predominant 1,3-butadiene products and the minor bicyclo[1.1.0]butane products. At least in the case of cyclopropenes, then, a concerted mechanism featuring a polar transition structure seems more consistent with the available experimental and computational evidence than does a stepwise mechanism.

Jackson et al., on the other hand, have studied the reaction of bicyclo[1.1.0]butane systems in some detail.⁴ Like Brinker, Jackson and Jones used an asymmetrically substituted derivative

(3) Some examples: (a) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770–1776. (b) Houk, K. N.; Rondan, N. G.; Mareda, J. *J. Am. Chem. Soc.* **1984**, *106*, 4291–4293. (c) Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 1919–1920. (d) Bernardi, F.; Bottoni, A.; Canepa, C.; Olivucci, M.; Robb, M. A.; Tonachini, G. *J. Org. Chem.* **1997**, *62*, 2018–2025. (e) Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 10805–10809.

(4) Jackson, J. E.; Mock, G. B.; Tetef, M. L.; Zheng, G.-X.; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1453–1464.

(5) Becerra, R.; Frey, H. M. *Chem. Phys. Lett.* **1987**, *138*, 330–332.

(6) Sevin, F.; McKee, M. L.; Shevlin, P. B. *J. Org. Chem.* **2004**, *69*, 382–386.

(7) Wu, G.-X.; Jones, M. J., Jr.; von Doering, W. E.; Knox, L. H. *Tetrahedron* **1997**, *53*, 9913–9920.

(8) Von Doering, W.; Coburn, J. F., Jr. *Tetrahedron Lett.* **1965**, 991–995.

(9) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749–2769.

(10) Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, 3411–3412.

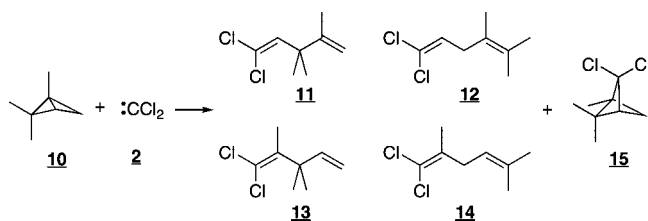
(11) (a) Koptelov, Yu. V.; Kostikov, R. R.; Molchanov, A. P. *Zh. Org. Khim.* **1991**, *27*, 1902–1907. (b) Koptelov, Yu. V.; Kostikov, R. R.; Molchanov, A. P. *Zh. Org. Khim.* **1991**, *27*, 1907–1910.

(12) Weber, J.; Xu, L.; Brinker, U. H. *Tetrahedron Lett.* **1992**, *33*, 4537–4540.

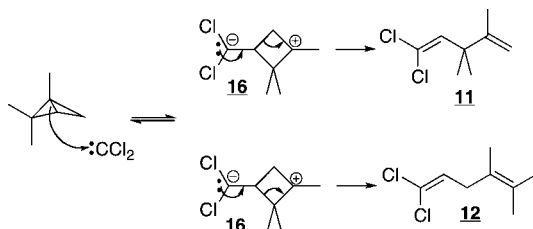
(13) Weber, J.; Brinker, U. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1623–1626.

(14) Merrer, D. C.; Rablen, P. R. *J. Org. Chem.* **2005**, *70*, 1630–1635.

SCHEME 3



SCHEME 4



to investigate the matter. In principle, 1,2,2-trimethylbicyclo[1.1.0]butane, **10**, might yield up to four isomeric pentadiene products **11–14**, as shown in Scheme 3, in addition perhaps to some, probably small, amount of the bicyclo[1.1.1]pentane product **15**.

Jackson et al. reasoned that the postulated zwitterionic intermediate **16** (Scheme 4) would yield a mixture of **11** and **12**, with some preference, perhaps even a strong one, for the more highly substituted alkene **12** (Saitsev's rule).¹⁵ Experimentally, however, dichlorocarbene reacts with **10** to yield measurable amounts of only one isomer, namely, **11**. This result would seem to rule out the stepwise mechanism. Furthermore, Jackson and Jones argued that in the concerted mechanism, the expected transition structure leading to **11** is less sterically congested than that leading to **12**. Consequently, they concluded that the experimental findings supported the concerted (two-bond pluck) mechanism, in addition to refuting the stepwise mechanism. Semiempirical calculations on a simplified model system supported the existence of a transition state with the expected structural characteristics.⁴

The evidence at this point is thus somewhat mixed, although it leans in the direction of concerted pathways. For reaction 2, experimental evidence suggests a stepwise mechanism, or else a highly polar transition structure, while the computational evidence clearly favors the latter. For reaction 1, experimental evidence favors the concerted mechanism, but calculational work has only been carried out at a semiempirical level and on a highly simplified model system—the addition of methylene to the parent bicyclobutane. In order to move the mechanistic debate further forward, we present here the results of an ab initio computational approach similar to that of Merrer and Rablen, but now applied to the reaction of singlet dichlorocarbene with bicyclo[1.1.0]butane (BCB) and 1,2,2-trimethylbicyclo[1.1.0]butane (TM122BCB).

(15) Products **13** and **14** are derived from a second intermediate, obtained by addition of dichlorocarbene to the more sterically hindered side of **10**. Experimentally, products **13** and **14** are not observed. Calculations confirm that the pathways for addition of dichlorocarbene to the more sterically hindered side of 1,2,2-trimethylbicyclo[1.1.0]butane lie several kcal/mol higher in energy than those for addition to the less sterically hindered side (leading to products **11** and **12**). In addition, the intermediate on the pathway to **13** and **14** would presumably be less stable (positive charge of a zwitterion, or unpaired electron of a diradical, at a secondary carbon) than the one on the pathway to **11** and **12** (positive charge or unpaired electron at a tertiary carbon).

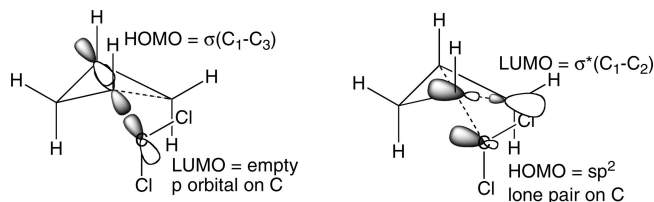


FIGURE 1. Orbital interactions as dichlorocarbene approaches bicyclobutane.

Results and Discussion

Initial investigation focused on the reaction of singlet dichlorocarbene with the parent system bicyclo[1.1.0]butane **1**.¹⁶ Qualitative MO arguments⁴ suggest that the approach pathway should have the geometry indicated in Figure 1. Two orbital interactions are expected to dominate the reaction, as shown in Figure 1. First, and probably most important for the earliest stages of approach, the empty p orbital of the carbene (a LUMO) overlaps with the σ orbital of the highly strained and rather weak central C–C bond of bicyclobutane (a HOMO).¹⁷ This interaction enforces a geometry in which the empty p orbital of the carbene is collinear with the central C–C bond of bicyclobutane. Simultaneously, the lone pair orbital of the carbene donates into the C–C σ^* orbital of an adjacent “edge” C–C bond of bicyclobutane, as shown on the right in Figure 1. Within the geometric constraints dictated by these HOMO–LUMO interactions, several orientations of the dichlorocarbene are conceivable with regard to rotation about the incipient C–C bond, as shown in Scheme 5. Pathway A represents one possibility, the symmetrical geometry of pathway B represents a second, and a third “rotamer” A' exists as well that is enantiomeric with respect to A. In addition, a fundamentally different geometry, approach from the “top” (pathway C in Scheme 5), might be expected to lead directly to 1,1-dichlorobicyclo[1.1.1]pentane **4**, in a manner analogous to the addition of carbenes to alkenes.

Following the semiempirical calculations of Jones,⁴ transition structures were sought for the concerted pathways A and B. Transition structure **17**, corresponding to the concerted pathway A in Scheme 5, was located without difficulty at HF/3-21G*, HF/6-31G*, QCISD/6-31G*, and CCSD/6-31G*. The geometry closely resembles that calculated by Jackson and Jones at a semiempirical level of theory in 1985,⁴ with an incipient C–C bond length of about 2.2 Å. IRC reaction path following at all four levels of theory verified that this transition structure leads

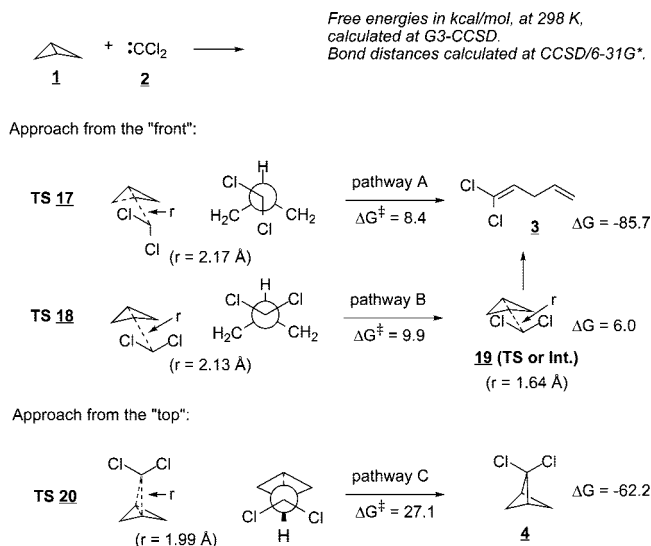
(16) One might ask, why not use methylene or difluorocarbene as computationally less expensive alternatives to dichlorocarbene? In fact, both approaches were explored extensively during the early stages of the investigation. However, methylene is far too reactive; it reacts without barrier along most available pathways and does not provide a useful model of the behavior of dichlorocarbene. Difluorocarbene, on the other hand, while it gave reaction barriers, exhibited significantly different behavior from dichlorocarbene and was also deemed in the end an inadequate model for the experimental system. Furthermore, steric considerations are expected to play an important role in governing the regioselectivity of reaction in the substituted TM122BCB system, and for such purposes one cannot expect fluorine to serve as an adequate model for chlorine. In the interest of brevity and clarity, the calculations carried out on methylene and difluorocarbene reacting with BCB and TM122BCB are not reported here.

(17) It is often argued that this single bond is actually more a π bond than a σ bond, the strain of the bicyclic ring system forcing the p-like atomic orbitals on the two carbons to overlap in a largely parallel, rather than end-on, fashion. However, the electronic structure calculations reported herein show that the approach of the carbene has the geometry shown in Figure 1, in which the empty p orbital on the carbene is almost perfectly collinear with the central C–C bond of bicyclobutane. On the basis of this geometry of approach, it seems more reasonable to depict the C–C bond more or less as a conventional σ bond, as is done in Figure 1.

TABLE 1. Calculated Bond Distances in Transition Structures in Scheme 5 (Å)

reaction of 1 and 2	gas phase				PCM	
	HF/3-21G*	HF/6-31G*	QCISD/6-31G*	CCSD/6-31G*	HF/3-21G*	HF/6-31G*
TS 17 (A)	2.21	2.05	2.17	2.17	2.35	2.22
TS 18 (B)	2.23	2.07	2.12	2.13	2.35	2.24
TS 20 (C)	2.06	2.01	1.95	1.99	2.21	2.11
TS/Int 19	1.60	1.57	N/A	1.64	1.58	1.56

SCHEME 5



to separated reactants in one direction and to the 1,1-dichloro-1,4-pentadiene product in the other. The existence of a concerted pathway leading from dichlorocarbene and bicyclo[1.1.0]butane to 1,1-dichloro-1,4-pentadiene therefore seems well-supported.

The other transition structures from Scheme 5, as well as the reactant and product structures, were readily calculated, as well. Bond distances for the incipient C–C bond are provided in Table 1 for the transition structures, while the CCSD/6-31G* optimized geometries are shown in Figure 2. Calculated free energies for the transition structures and products relative to reactants are shown in Scheme 5; a more extensive tabulation of enthalpies and free energies at a variety of theoretical levels appears in Tables S1–S5 in the Supporting Information.

Before delving more fully into the different reaction pathways and barriers, a word about the levels of theory is in order. Normally, hybrid density functional theory would be considered a valuable and economical means to study a reaction such as this. Indeed, extensive B3LYP/6-31G* optimizations were carried out on this system, particularly during the earlier stages of investigation. However, these B3LYP/6-31G* calculations in almost all cases gave reaction pathways that were monotonically downward in energy and therefore lacked both barriers and transition structures. Therefore, the B3LYP/6-31G* approach was abandoned as a useful means to study these reactions.¹⁸ MP2/6-31G* optimizations, on the other hand, exhibited somewhat erratic behavior and yielded results somewhat at odds with the HF, QCISD, and CCSD calculations, and so the MP2 method was likewise abandoned.

(18) Reaction pathways were nonetheless computed at B3LYP/6-31G* by carrying out partial optimizations with the bond distance constrained to a series of values along the reaction pathway (3.0–1.5 Å in 0.1 Å increments). Single-point calculations at higher levels of theory were additionally carried out at these geometries. The results obtained by using this latter approach (e.g., QCISD/6-31G*/B3LYP/6-31G*) were not substantially different from those obtained using true optimizations at levels of theory that directly yielded barriers. In the interest of brevity, the B3LYP/6-31G* reaction pathway data are therefore omitted.

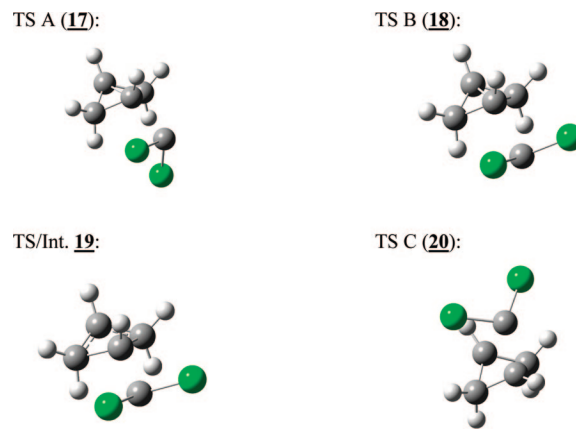


FIGURE 2. CCSD/6-31G* optimized structures of the transition structures and intermediate in Scheme 5.

Single-point calculations were carried out at the optimized geometries in order to obtain somewhat more reliable barrier heights. The single-point methods include the CBS-4 procedure of Petersson and co-workers¹⁹ (defined in terms of HF/3-21G* optimized geometries); CCSD(T)/6-31G* and CCSD(T)/6-311+G** calculations at the CCSD/6-31G* geometries; and CCSD(T)/6-31G* and QCISD(T)/6-31G* calculations at the HF/6-31G* geometries. The CBS-4, CCSD(T)/6-31G*, and CCSD(T)/6-311+G** barriers appear in Table S3 in the Supporting Information, while the results of the single-point calculations at the HF/6-31G* geometries appear in Tables S4 and S5.²⁰

The G3 procedure of Curtiss and co-workers²¹ represents a well-tested and generally reliable means of obtaining fairly accurate relative energies for small organic systems. The sometimes erratic behavior of MP2/6-31G* optimizations in this system precluded use of the G3 method per se since it depends on MP2/6-31G* geometries (or, in the G3B3 variant, B3LYP/6-31G* geometries, also unavailable for this system). However, in Scheme 5 and in Table S3, we report energies labeled “G3-CCSD” that correspond to the G3 method, except that CCSD/6-31G* geometry optimization replaces MP2/6-31G* optimization.

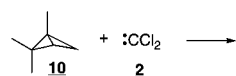
Although the absolute barriers differ somewhat between the various levels of theory listed in the paragraphs above (and tabulated in Tables S1–S5), the variations between the highest levels are small, suggesting that reasonable convergence has been obtained. Furthermore, the differences between the barriers associated with the various pathways (A, B, and C) are still more consistent from one level of theory to the next, even for the more modest computational levels. The CCSD/6-31G*

(19) (a) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104*, 2598–2619. (b) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, *112*, 6532–6542.

(20) In fact, the relative energies derived from the CCSD/6-31G*/HF/6-31G* and QCISD/6-31G*/HF/6-31G* single-point calculations are almost identical to those obtained from the corresponding CCSD/6-31G* and QCISD/6-31G* optimizations, as the data in Table S1 demonstrate.

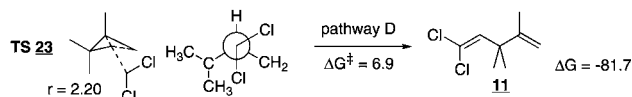
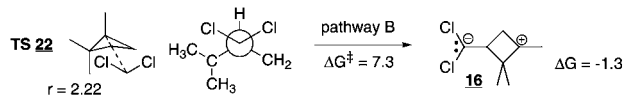
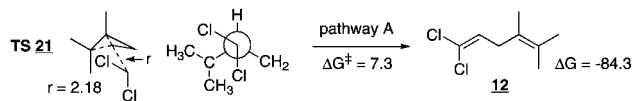
(21) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764–7776.

SCHEME 6

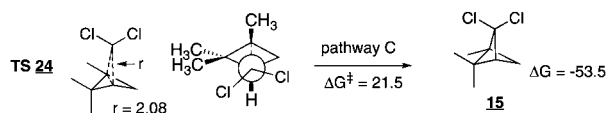


Free energies in kcal/mol, at 298 K, calculated at G3-CCSD. Bond distances r in Å, calculated at CCSD/6-31G*.

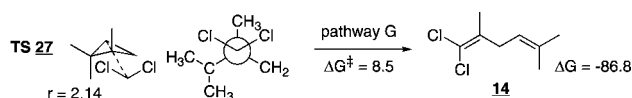
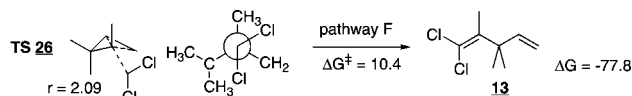
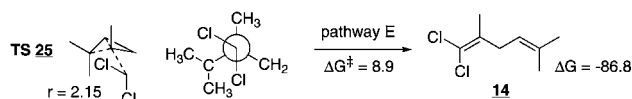
Approach from the "front" (the less hindered side):



Approach from the "top":



Approach from the "back" (the more hindered side):



geometries and the G3-CCSD free energies at 298 K have been singled out as the basis for the discussion that follows, and they are tabulated in Schemes 5 and 6. However, the choice of this particular theory level, as opposed to one of the others, does not affect the qualitative conclusions in any significant manner.

Returning now to discussion of the reaction of dichlorocarbene with bicyclobutane, the higher levels of theory generally agree that a barrier exists along concerted pathway A, but of very low energy. In fact, in most cases, the transition structure is calculated to lie slightly below reactants in energy or enthalpy at 0 K. On the other hand, the transition structure lies ~ 8 kcal/mol above reactants in free energy at 298 K, which is perhaps more relevant to the experimental conditions.

Calculations also readily located transition structure **18** along pathway B, the CCSD/6-31G* geometry of which is shown in Figure 2. The C_s symmetry of this approach pathway has an interesting consequence. As the reaction continues past the transition structure, and the C–C bond contracts further, the energy begins to decrease. Eventually, however, assuming the symmetry is maintained, the energy must arrive at a minimum and then start to rise again. Symmetry demands that this minimum in the energy along the bond contraction coordinate is a stationary point on the potential energy hypersurface. That is, transition structure **18** of necessity leads to another stationary point of like symmetry but with a shorter

bond length (**19** in Scheme 5). This stationary point can in principle be a minimum (intermediate) or a saddle point (transition structure). While one normally expects a transition structure to link two energy minima, it is well-documented that a transition structure can also lead to a second transition structure, and in fact, this situation is not as rare as once believed.^{22–28}

What relation does this second stationary point have to the actual reaction pathway along trajectory B? Both the initial approach geometry and the transition structure have C_s symmetry. However, that symmetry clearly cannot be maintained all the way to product.²⁹ At the transition structure **18**, the energy is at a minimum with respect to rotation of the carbene counterclockwise or clockwise (leading eventually to TS **17** or its enantiomer, respectively), although of course at a maximum with respect to the distance between the carbene and the bicyclobutane. If, as the newly forming C–C bond further contracts, the energy remains at a minimum with respect to rotation around this bond, then the next stationary point (still of C_s symmetry) is a minimum. Presumably, this minimum would correspond to the postulated intermediate **8**. From this intermediate would emanate two enantiomeric pathways, probably over rather low barriers, leading to 1,1-dichloro-1,4-pentadiene. If **19** is a minimum, then it would represent an intermediate on the reaction pathway from transition structure **18** to product **3**.

Alternatively, as the newly forming C–C bond contracts past the initial transition structure **18**, and the energy decreases, there might come a point where the energy is at a maximum with respect to rotation about the newly forming bond. At that point, two enantiomeric pathways of equal energy would necessarily diverge from the trajectory of symmetric contraction. Presumably, these two pathways would lead to two enantiomeric nonplanar conformations of the product diene **3**. This point of divergence on the potential energy hypersurface, where what was previously a "valley" becomes a "ridge", is known as a valley–ridge inflection. While uncommon, such valley–ridge inflection points are now recognized to be not as rare as once thought.^{24–27} They correspond to the relatively infrequent, but certainly feasible, situation in which one transition structure leads to a second transition structure with no intervening minimum (intermediate). In this scenario, the second stationary point of C_s symmetry, arrived at by further contraction of the C–C bond in transition structure **18**, is itself a transition structure (saddle point). This second transition structure is **19**, as shown in Scheme 5. However, the pathway from transition structure **18** to the enantiomeric conformations of 1,1-dichloro-1,4-pentadiene **3** would not normally pass through this second transition structure **19**; instead, the reaction would be expected to follow the minimum energy pathways, which diverge from the pathway of symmetric contraction at the valley–ridge inflection point and do not reach **19**.

What do the calculations reveal about the nature of **19**? If **19** is a minimum, then it would likely correspond to the postulated intermediate **8** of the stepwise reaction mechanism. However, at HF/3-21G*, HF/6-31G*, and QCISD/6-31G*, stationary point **19** is in fact a transition structure (saddle point) indicated by IRC following to connect two enantiomeric conformations of 1,1-dichloro-1,4-pentadiene. At these levels of theory, then, pathway B provides an alternative route to product **3** but still represents a concerted reaction mechanism; that is, the pathway contains no intermediate (minimum). While pathway A is

asynchronous, pathway B is in some sense even more asynchronous, but nonetheless neither pathway passes through a minimum. However, at CCSD/6-31G*, it turns out that **19** is indeed a minimum, although seemingly a very shallow one. At CCSD/6-31G*, then, a stepwise pathway arguably exists that is only slightly higher in energy than the concerted pathways A and its enantiomer A'. Even in this case, though, the potential energy well is probably so shallow that the barriers to exit lie below the zero-point energy for the vibrational coordinate corresponding to rotation about the new C–C bond—in which case, there is arguably no intermediate, even in the presence of a minimum on the potential energy surface.

Dichlorocarbene can also approach bicyclobutane from a third, completely different geometry, as illustrated by pathway C in Scheme 5. Pathway C (TS **20**) corresponds to approach from above and consequent addition to the central, highly strained C–C bond of bicyclo[1.1.0]butane. Calculations readily locate this pathway and the corresponding transition structure. IRC reaction path following confirms that this pathway, in many ways analogous to the conventional addition of a singlet carbene to an alkene to yield a cyclopropane, leads to the bicyclopentane product **4**. However, Tables S1, S2, and S3, as well as the free energies in Scheme 5, show that the barrier lies much higher in energy than the other pathways that lead to the pentadiene product **3**. This finding agrees to some degree with the experimental observation that, in most cases, pentadiene products are obtained in far greater yield than bicyclopentane products.^{4,8} In fact, given the barrier heights, it is hard to understand why bicyclopentane **4** appears among the products at all. It is conceivable that an alternative route exists for the formation of this product via pathway B and transition structure **18**. All that is required for **18** to become **4** is for the dichlorocarbene fragment to tuck itself further under the bicyclobutane, while the bicyclobutane moiety simultaneously flattens and then puckers in the opposite direction.

Numerous additional attempts were made to locate a structure corresponding to the postulated intermediate **8**, other than the shallow minimum **19** identified at CCSD/6-31G* along pathway B. These attempts included HF/3-21G*, HF/6-31G*, and B3LYP/6-31G* optimizations both in the gas phase and in the presence of a simulated solvent (PCM) and relied on a wide variety of bond distance and angle constraints, approach geometries, etc. However, consistent with the semiempirical findings reported by Jackson and Jones for the addition of methylene to **1**,⁴ all of these attempts failed. Either the reactants flew apart or the structure collapsed to a reaction product, or if certain symmetry constraints were used, the final structure had one or more imaginary frequencies and so did not correspond

TABLE 2. Calculated Changes in HF/6-31G* Mulliken Atomic Charges on Going from Reactants to Transition Structures

HF/6-31G* Mulliken charges	BCB system		TM122BCB system			
	TS A	TS B	TS A	TS B	TS D	Int
C(+),change	0.058	0.054	0.045	0.032	0.045	0.141
C(-),change	-0.034	-0.046	-0.038	-0.032	-0.039	-0.191

to a minimum. We conclude from these failed efforts that structure **8** does not correspond to a minimum on the potential energy surface, except at CCSD/6-31G*, at which level it corresponds to a very shallow minimum (**19**).³⁰

Brinker's experiments on carbene addition to cyclopropenes indicated that, if the reaction were concerted, at least the transition structure had to be rather polar in the sense expected for a zwitterionic intermediate.¹³ It is therefore of interest, in the closely related system under examination here, to determine how polar the calculated transition structures are. Table 2 lists the change in HF/6-31G* Mulliken atomic charges on going from reactants to each of the two transition structures A (**17**) and B (**18**). In fact, a small but significant separation of charge (0.05 electrons) does take place in the expected direction.

In summary, then, calculations provide the following description of the parent system. The lowest energy pathways correspond to A in Scheme 5, plus the enantiomeric pathway A'. These two pathways lead in concerted fashion to 1,1-dichloro-1,4-pentadiene product, over a low barrier that is estimated at G3-CCSD to lie 3 kcal/mol below reactants in enthalpy at 0 K but ~8 kcal/mol above reactants in free energy at 298 K. A third pathway, B, lies about 1.7 kcal/mol higher and also leads to 1,1-dichloro-1,4-pentadiene. At most levels of theory, the second stationary point that lies along this trajectory is a transition structure; the actual reaction pathway avoids this second transition structure by diverging from the trajectory of symmetrical contraction in the vicinity of the valley–ridge inflection point. At CCSD/6-31G*, on the other hand, pathway B in fact leads to a minimum corresponding to the postulated intermediate **8**. However, the minimum is shallow, likely with an exit barrier lower than the zero-point energy for the molecular vibration associated with rotation to enantiomeric conformations of diene **3**. Therefore, it is probably most accurate to view pathway B as a rather asynchronous but nonetheless concerted alternative pathway. Finally, some 18 kcal/mol higher than the optimal pathway A lies concerted pathway C leading to 2,2-dichlorobicyclo[1.1.1]pentane.

We sought to clarify matters further by exploring computationally the substituted 1,2,2-trimethylbicyclo[1.1.0]butane (TM122BCB) system that Jackson, Jones, and co-workers studied experimentally.⁴ This experimental work relied for its interpretation on the assumption that one could predict the behavior of the stepwise and concerted mechanisms. Specifically, as explained in the Introduction, it was assumed that the intermediate **16** would lead either to a mixture of the products **11** and **12** or preferentially to **12**. On the other hand, an explanation was provided that rationalized the strong observed preference for **11** over **12** in terms of the isomeric transition structures expected for the concerted mechanism. We hoped that careful computational work could place the interpretation

(30) Using the PCM (polarizable continuum model) solvation model in Gaussian to simulate the presence of a solvent did not change this conclusion—even in the presence of a polar medium, the intermediate **8** is not a minimum. On the other hand, placement of an electron-donating substituent such as methyl or amino on the positively charged carbon does stabilize the structure sufficiently to make it a minimum on the potential energy surface.

(22) If **19** is a saddle point, the minimum energy reaction pathways avoid passing through this stationary point.

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(29) The product can also adopt C_s symmetry, of course. However, there is no way to get from the transition structure **18** to product **3** while maintaining symmetry because the product and reactant planes of symmetry are different. As it turns out, the reaction pathways passing through **17** and **18** lead to a nonplanar conformation of **3**.

of these experiments on firmer ground by providing a more rigorous basis for the assumptions about how the two mechanisms would behave. First, we sought to obtain relative barrier heights for the two regioisomeric transition states leading to the products **11** and **12** in order to support or refute the claim that the concerted mechanism is consistent with the observed preference for **11**. Second, we sought to determine whether an intermediate and a stepwise pathway exist for this system and, if so, whether the intermediate would rearrange preferentially to **12**. It is worth noting that even if the zwitterionic intermediate **8** does not exist in the parent system, it might well exist in the substituted system since the 1-methyl group of TM122BCB would stabilize the carbocationic center of **16**.

TM122BCB presents a rather more complex set of alternatives for reaction than does BCB, and Scheme 6 depicts the seven possible geometries of approach. The carbene is still expected to approach the bicyclobutane in such a way that the empty p orbital is collinear with the central C–C bond. However, due to the unsymmetrical substitution of the bicyclobutane, it is now possible for the carbene to approach from two distinct sides: one approach to the unsubstituted bridgehead carbon (the “front”), and the other approach to the more sterically hindered methyl-substituted bridgehead carbon (the “back”). Furthermore, for either approach, three distinct “rotamers” about the incipient C–C bond exist. Whereas for the unsubstituted system two of the possibilities were enantiomeric and, therefore, isoenergetic, in the case of TM122BCB, all three rotamers are diastereomeric with respect to each other. In Scheme 6, pathways A, B, and D depict approach from the front, while E, F, and G depict approach from the back. Finally, a seventh possibility C exists as well, corresponding to approach from “the top”, equivalent to pathway C in the unsubstituted system and presumably leading to the bicyclopentane product.

All seven transition structures depicted in Scheme 6 were located at HF/3-21G*, HF/6-31G*, QCISD/6-31G*, and CCSD/6-31G*. IRC following proved impractical at the correlated levels of theory, but at HF/6-31G*, it verified that each transition structure connected a separated pair of reactants with the product shown in Scheme 6.^{31,32} Scheme 6 lists bond distances in the transition structures calculated at CCSD/6-31G*, along with free energy differences calculated at G3-CCSD. A more extensive tabulation of bond lengths, enthalpies, and free energies calculated at a variety of theoretical levels appears in Tables S6, S7, S8, and S9 in the Supporting Information.³³ The geometries of the CCSD/6-31G* optimized transition structures are shown in Figure 3.

The calculations clearly show that the concerted pathway remains viable in the TM122BCB system. As expected, the three approach paths E, F, and G to the sterically more hindered side of the bicyclobutane lie significantly higher in free energy than the three approach paths A, B, and D to the less hindered side.

(31) There were two anomalies in this regard. At HF/3-21G*, the intermediate **16** does not exist, and so TS **22** leads to **11** instead. At HF/6-31G*, however, TS **22** indeed leads to the intermediate **16**. Also, at HF/6-31G*, IRC following indicates that TS **24** leads to **12** instead of **15**. However, at HF/3-21G*, IRC following indeed leads to the expected product **15**. This latter deviation from what is shown in Scheme 6 is more serious, but we still believe it is best to regard **24** as leading to **15**, as shown in Scheme 6.

(32) In analogy to what is observed in the unsubstituted system, it is possible that at some levels of theory, such as CCSD/6-31G*, pathway G might lead over TS **27** not directly to **14** (or **13**), but rather to a shallow minimum, and that this intermediate would then partition between products **13** and **14**.

(33) As with BCB, qualitatively similar results were obtained for the addition of difluorocarbene, but the data are omitted in the interest of brevity. In the case of difluorocarbene addition, however, the zwitterionic intermediate was not found to exist, and transition state B led directly to product.

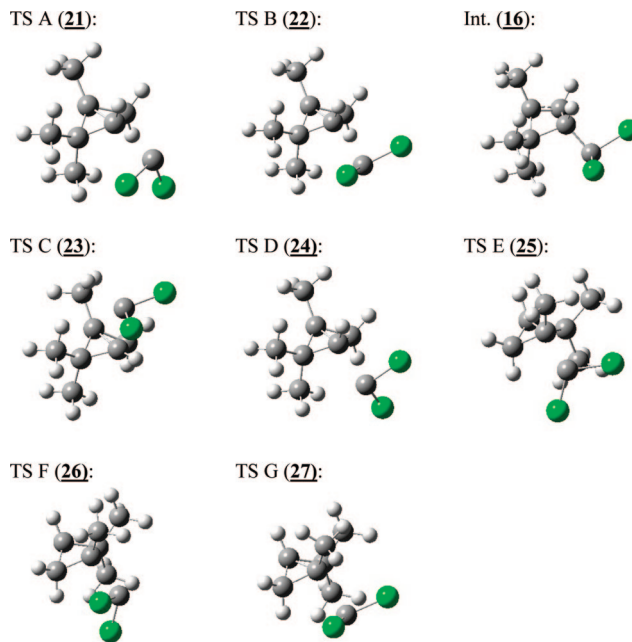


FIGURE 3. CCSD/6-31G* optimized structures of the transition structures and intermediate in Scheme 6.

The difference is about 2 kcal/mol at CCSD(T)/6-311+G**//CCSD/6-31G* and G3-CCSD and is sufficient (although only just barely) to rationalize the fact that **13** and **14** are not observed as significant products. Also, the approach from above, pathway C, lies some 15–18 kcal/mol above the others, enough presumably to shut down this pathway entirely. In fact, this pathway lies sufficiently high in energy that it cannot account for the small amount of bicyclopentane product observed experimentally; perhaps the bicyclopentane product results from a different process instead.³⁴

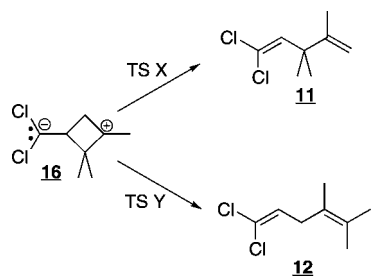
The calculations provide little support for the claim that the concerted mechanism should strongly favor product **11** over product **12**. The relative barriers for pathways A, B, and D suggest that indeed pathway D, leading over TS **23** to **11**, is the most favored, consistent with experimental findings. However, the preference amounts only to a small fraction of a kcal/mol; in fact, all three transition structures **21**, **22**, and **23** lie within 0.5 kcal/mol of each other at CBS-4, CCSD(T)/6-31G**//CCSD/6-31G*, CCSD(T)/6-311+G**//CCSD/6-31G*, and G3-CCSD. Under these circumstances, the predicted preference for **11** over **12** would be modest at best. The calculated barrier cannot adequately account for the exclusive production of **11** reported experimentally.

In the parent system, no intermediate was found at most levels of theory. In the substituted system, however, the 1-methyl group might be expected to provide considerable stabilization for development of a positive charge. Indeed, pathway B via transition structure **22** is calculated to lead to a minimum corresponding to the intermediate **16** at HF/6-31G* and CCSD/6-31G*, although not at HF/3-21G*.³⁵ Figure 3 shows the CCSD/6-31G* optimized geometry of this intermediate. As expected for the zwitterionic depiction, the intermediate has a nearly planar geometry at the carbon bearing a positive charge and a pyramidal geometry at the carbene carbon, which formally bears a negative charge. The intermediate lies rather high in

(34) It is conceivable that pathway B leads to **15** as an alternate product.

(35) The intermediate **16** also exists at B3LYP/6-31G*.

SCHEME 7



energy, only ~ 10 kcal/mol below the transition structure **22**, and some 80 kcal/mol above products.

What of the expected behavior of this intermediate? Presumably, two transition structures exist, as shown in Scheme 7, leading from **16** to the two diene products **11** and **12**. Attempts to locate these transition structures did not fare as well as hoped. Since **16** is not a minimum at HF/3-21G*, and optimizations using QCISD/6-31G* for this structure had convergence problems, it is only at HF/6-31G* and CCSD/6-31G* that the searches could be conducted.³⁶ After extensive searching on the very flat potential energy surface in the vicinity of **16**, one transition structure was indeed located at HF/6-31G*, although not at CCSD/6-31G*. This transition structure looks qualitatively as if on its way to diene product **11**. However, IRC following indicates that it connects **11** and **12** rather than **11** and **16**.

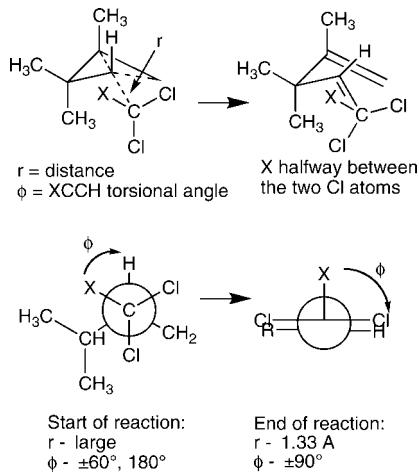


FIGURE 4. Definition of the two coordinates used for potential energy surfaces.

The anomalous IRC results probably reflect at least to some degree the fact that the potential energy hypersurface is very flat in the region of the intermediate **16**. It is useful at this point to consider an actual potential energy surface, defined for the two coordinates shown in Figure 4. One coordinate corresponds to the length of the newly forming C–C bond, while the other corresponds to torsion about that bond. Figure 5 shows how this potential energy surface, calculated at B3LYP/6-31G*, looks in the immediate vicinity of the intermediate **16**. The intermediate exists on a shallow and flat plateau, the exit barriers to which are only a few kcal/mol.³⁷

Despite our best efforts, we reluctantly conclude that we are unable to calculate how the intermediate would partition to products—to dienes **11** and **12** and, possibly, to bicyclopentane **15**, as well. It is worth noting that, given the barrier heights, intermediate **16** actually represents a more plausible route to **15** than does pathway C and the associated transition structure

B3LYP/6-31G*

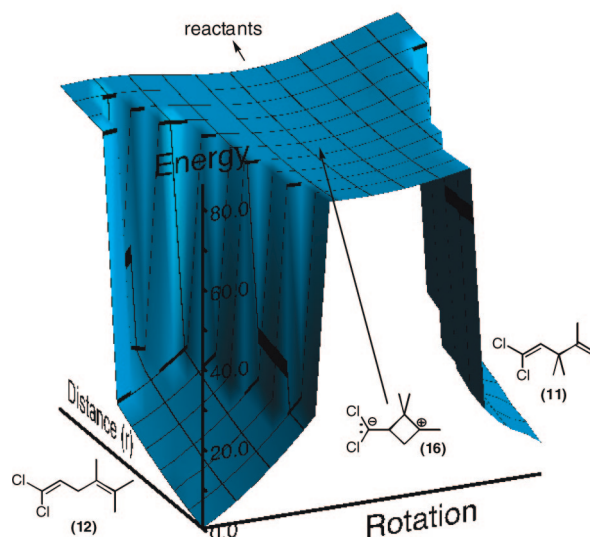


FIGURE 5. B3LYP/6-31G* potential energy surface in the vicinity of the intermediate **16**. The two horizontal axes correspond to the bond rotation coordinate and the bond distance coordinate defined in Figure 4. Energies in kcal/mol.

24. In fact, even if the exit barriers could be computed reliably, this information probably still would not yield a reliable prediction of the behavior of the intermediate. When an intermediate occupies a very flat region of a potential energy surface, the behavior often is not statistical and can only be predicted using direct dynamics simulations.³⁸

On the topic of dynamic effects, it is also of interest to consider the nature of the potential energy surface at the beginning stages of the reaction, during the approach to the various transition structures in Scheme 6. Figure 6 depicts such a potential energy surface. It shows what happens as dichlorocarbene approaches the “front” of TM122BCB, in a manner leading to transition structures **21**, **22**, and **23** (pathways A, B, and D in Scheme 6). The potential energy surface offers three distinct channels, leading to the three transition structures. The bond rotation barrier separating the channels for pathways B and D is considerably lower than the barriers separating the A channel from the other two. As a result, a considerably wider swath of initial approach geometries probably leads into channels B and D than into channel A. Thus, there might be an entropic factor, not fully captured in the thermodynamic correction factors computed from harmonic frequencies at the transition structures, that favors entry into channels B and D instead of A. Such a factor might help explain the strong preference for the product of channel D (**11**) over the product of channel A (**12**).

The predicted reactivity of the substituted TM122BCB system can thus be summarized as follows. The seven approach pathways depicted in Scheme 6 all exist, and a corresponding transition structure exists for each pathway. The most favored pathways, A, B, and D, all lie within 0.5 kcal/mol of each other

(36) The intermediate also exists at B3LYP/6-31G*, and searches for the transition structures leading from the intermediate to diene products were therefore also conducted at B3LYP/6-31G*. One of the transition structures was eventually located, with considerable difficulty; the other was never located.

(37) Inspection of the calculated potential energy surface in Figure 5 yields these estimates for the barriers from the intermediate **16** to products **11** and **12**: barrier from **16** to **11**, 3.6 kcal/mol; barrier from **16** to **12**, 1.0 kcal/mol.

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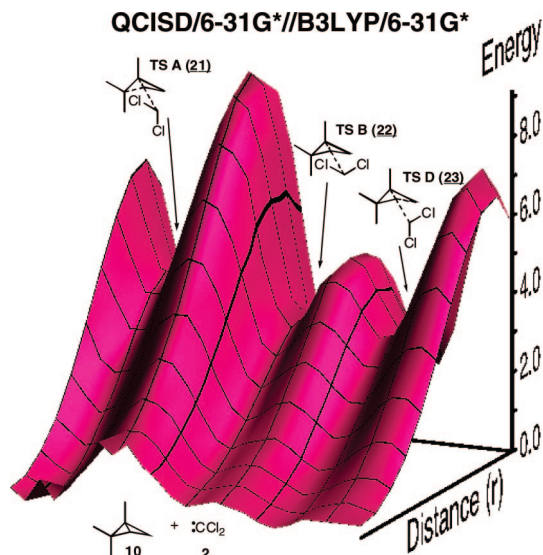


FIGURE 6. QCISD/6-31G*/B3LYP/6-31G* potential energy surface for approach of dichlorocarbene to TM122BCB. The two horizontal axes correspond to the bond rotation coordinate and the bond distance coordinate defined in Figure 4. Energies in kcal/mol.

and lead both to the observed product **11** as well as to the unobserved isomer **12**. Pathway A leads to **12**, and pathway D leads to **11**, in both cases in concerted fashion. On the other hand, pathway B leads over a transition structure of comparable energy to a zwitterionic intermediate which then is presumed to partition itself between the diene products **11** and **12**. Although pathway D leading to **11** is calculated to lie the lowest in energy, the energy differences between pathways A, B, and D are nowhere near sufficient to account for observation of **11** as the exclusive experimental product. The calculations suggest that in this system the stepwise and concerted mechanisms are competitive and operate simultaneously. The more sterically hindered approach paths E, F, and G, as well as the approach from above, C, are all computed to lie sufficiently higher in energy that they probably play little role in the reactivity of the system. Pathway C in particular is computed to lie prohibitively high in energy compared to the other pathways that are available.

Conclusion

Broadly speaking, electronic structure calculations of the reaction of singlet dichlorocarbene with bicyclo[1.1.0]butane yield a zwitterion corresponding to the postulated intermediate in the stepwise mechanism and the transition structures proposed for the concerted “two-bond pluck” mechanism. A delicate balance exists between the concerted and stepwise pathways, which seem to be of comparable energy. For the unsubstituted system, the balance of evidence points to a concerted mechanism. Two distinct geometries of approach are energetically accessible, over transition structures having charge distributions qualitatively similar to that for the postulated zwitterionic intermediate. One of the pathways leads to product in a rather direct fashion, while the other pathway is more asynchronous in nature and either passes a valley–ridge inflection point and then skirts a second transition structure or passes through a very shallow minimum (intermediate) on the way to product. For the substituted system, on the other hand, it appears that two isomeric concerted pathways compete with a stepwise pathway that has a comparable barrier. The intermediate on this pathway

lies in a rather shallow minimum, and its behavior might well not be statistical.

It is worth pointing out that both of the major experimental investigations must be regarded as inconclusive. Brinker’s study¹³ provides convincing evidence about the nature of the charge distribution in the transition structure but does not directly speak to the question of whether or not an intermediate lies on the pathway that follows this transition structure. The Jackson and Jones study,⁴ on the other hand, relies on an assumption about the behavior of the postulated intermediate. However, that assumption might well not be warranted for an intermediate such as this that lies in a very shallow minimum at the bottom of a steep drop on the potential energy surface. In the end, the calculations presented here cannot account for the regiochemical preference observed in the reaction of dichlorocarbene with TM122BCB.

Calculations

Both ab initio and density functional calculations were carried out using the Gaussian 03 package,³⁹ using standard Pople basis sets.⁴⁰ The density functional theory (DFT) calculations employed the B3LYP functional.⁴¹ Tight SCF convergence criteria were used for all DFT calculations (scf=tight). Geometry optimizations were carried out at HF/3-21G*, HF/6-31G*, QCISD/6-31G*, and CCSD/6-31G* and, where possible, at B3LYP/6-31G*. In addition, QCISD/6-31G*, QCISD(T)/6-31G*, CCSD/6-31G*, and CCSD(T)/6-31G* single-point calculations were carried out at the HF/6-31G* optimized geometries. Also, CCSD(T)/6-31G* and CCSD(T)/6-311+G** single-point calculations were performed on the CCSD/6-31G* optimized geometries. Two composite procedures were used to obtain more precise energies: the CBS-4 M procedure of Petersson and co-workers⁴² and G3-CCSD. The latter refers to the G3 procedure of Curtiss et al.,⁴³ but using the CCSD/6-31G* geometry in place of the MP2/6-31G* geometry.

For the parent (unsubstituted) system, all transition structures were verified as first-order saddle points via calculation of vibrational frequencies at the level of theory used for geometry optimization. Thermodynamic corrections were applied without scaling of the vibrational frequencies, using the thermochemistry output from Gaussian. For the substituted TM122BCB system, the same approach was used for the HF/3-21G and HF/6-31G* optimizations. For the QCISD/6-31G* and CCSD/6-31G* optimizations, however, frequency calculations proved impractical since the numerical calculation of second derivatives is necessary. Consequently, in these cases, zero-point energies and thermodynamic corrections were obtained only at the HF/6-31G* level (from the

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HF/6-31G* optimization and frequency calculations). However, formal confirmation of the nature of the stationary points (as minima or transition structures) was obtained via CCSD/6-31G* frequency calculations in the following key cases: the intermediate **16** was verified as having no imaginary frequencies, and the transition structures **21**, **22**, **23**, and **24** were verified as each having a single imaginary frequency.

The IRC procedure of Gonzalez and Schlegel was used to verify which reactant and product structures were connected by each transition structure, at HF/3-21G*, HF/6-31G*, and, in the case of the unsubstituted system, CCSD/6-31G*.⁴⁴ The IRC procedure was used to follow the reaction coordinate in both the forward and the reverse direction starting from the transition structure, and the two final structures thus obtained were subsequently subjected to unconstrained geometry optimization. The end points of these optimizations defined the reactant and product structures linked by the transition structure.

Transition structure geometry optimizations were in some cases carried out using Schlegel's synchronous transit-guided quasi-Newton method (QST2 and QST3 procedure).⁴⁵ In other cases, partial optimization with a constrained distance for the newly forming C–C bond (typically 2.1 Å) yielded a suitable starting geometry for complete (unconstrained) optimization to the true transition structure. Although results are not reported here, for the sake of brevity, entire reaction pathways were explored in many cases through a series of constrained B3LYP/6-31G* optimizations in which the newly forming bond was frozen at a series of fixed distances: 3.0, 2.9, 2.8, 2.7, 2.6, 2.5, 2.4, 2.3, 2.2, 2.1, 2.0, 1.9,

1.8, 1.7, and 1.6 Å. All other geometric variables were unconstrained. This approach was used to obtain the potential energy surface in Figure 5; this approach, coupled with QCISD/6-31G* single-point calculations, was used to obtain the potential energy surface in Figure 6.

The effect of bulk solvent was simulated in some calculations using the PCM continuum reaction field model.⁴⁶ The solvent was set to cyclohexane, which from among the solvent parameter sets available in Gaussian is the most similar to pentane, the solvent used experimentally.

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Supporting Information Available: Bond distances for the transition structures in Scheme 6 (Table S6); relative enthalpies at 0 K and free energies at 298 K (in kcal/mol) for all the species represented in Schemes 5 (Tables S1–S5) and 6 (Tables S7–S10) at a variety of levels of theory; energies in Hartrees (Table S11) and optimized geometries for all the species represented in Schemes 5 and 6; tabulation of G3-CCSD calculations (Table S12); HF/6-31G* geometries of transition structures in Scheme 6 (Figure S1). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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