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The Mechanism of Semibullvalene Bromination

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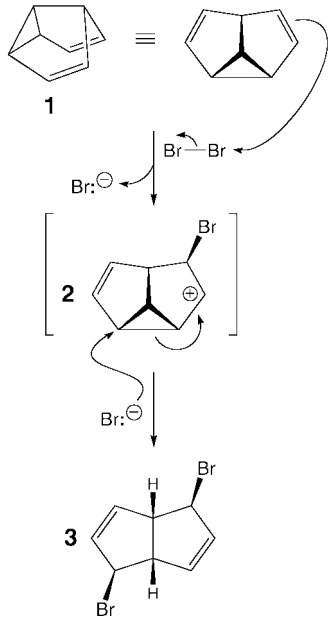
A mechanism for semibullvalene bromination is proposed based on quantum chemical calculations. This mechanism involves concerted bromine addition and cyclopropane ring-opening to form an allylic cation, without the intermediacy of a bromonium or a cyclopropylcarbinyl cation.

Introduction

Semibullvalene (**1**, Scheme 1) has long intrigued organic chemists, primarily due to its low barrier for degenerate Cope rearrangement and the possibility that derivatives might have delocalized ground-state structures displaying neutral homoaromaticity.[1] While various syntheses of semibullvalene have been published,[2] the potential of this molecule as a building block for the synthesis of other interesting structures has been underexploited. However, the regio- and stereoselective dibromination of semibullvalene has been reported.[3] This reaction converts C_s symmetric **1** (C_{2v} on average due to the rapid degenerate Cope rearrangement) into the C_2 symmetric dibromide **3**, thus converting enantiotopic alkenes into homotopic allyl bromide substructures. This sort of interconversion could prove extremely useful in constructing chiral frameworks adorned with functional groups displayed in well-defined orientations, especially if it could be accomplished enantioselectively. Efforts in this direction are ongoing in our laboratories, as are attempts to use semibullvalene derivatization reactions in the construction of complex molecular architectures.



Scheme 1.

How does the bromination of semibullvalene relate to typical alkene bromination reactions? Electrophilic addition of halogens to alkenes is a classic organic reaction (Scheme 2).[4] Since Roberts and Kimball noted that the selectivity for *anti* addition could result from a bridged bromonium ion intermediate, the mechanism of this reaction has generated substantial interest.[4–6] Despite being a standard "textbook" reaction, however, the mechanism of alkene bromination is still being explored today.[6] This is, in part, a reflection of the fact that halogenation mechanisms-are sensitive to substituent effects, geometric constraints, and environmental influences, making it dangerous to assume mechanistic details in many cases.

The bromination of semibullvalene provides an example of how the "standard" mechanism can be perturbed by such influences. The conditions reported in the literature for this reaction involve addition of bromine to a solution of semibullvalene in dichloromethane at –78 °C.[3] These conditions produced a 67% yield of the dibrominated product **3**, and the regio- and stereochemistry of this product was confirmed by X-ray crystallography. It was suggested at the time that this reaction likely proceeds through the cyclopropylcarbinyl cation **2**, which is then attacked by a bromide ion to open the cyclopropane ring and quench the

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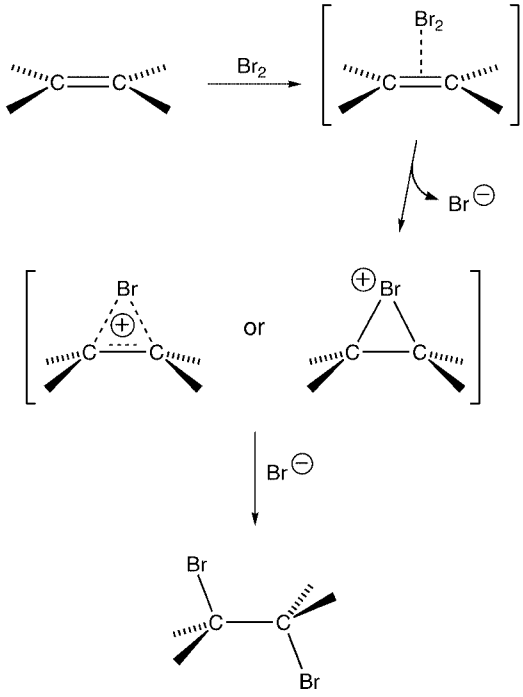


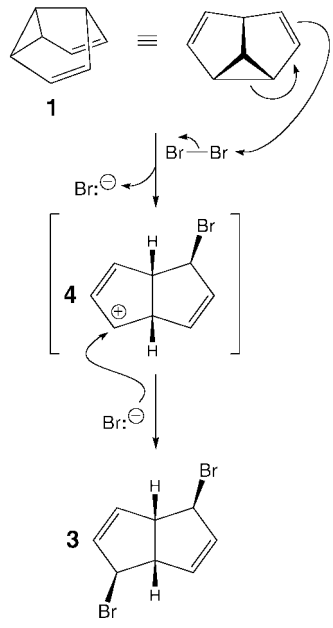
Scheme 2.

positive charge through alkene formation (Scheme 1).[3] The rapidity with which other cyclopropylcarbinyl systems ring-open,[7] however, led us to question whether or not **2** could actually be a stable minimum. Thus, we decided to examine the mechanism of this reaction in detail using hybrid Hartree–Fock/density functional theory calculations [CPCM-B3LYP/6-31G(d); see Computational Methods section for details]. The mechanistic information obtained from these investigations, besides being of fundamental importance to the field of reactive intermediate chemistry, should also facilitate the design of catalysts that can control the enantioselectivity of this and related $C_s \rightarrow C_2$ desymmetrization reactions.

Results and Discussion

Initial Attack of Bromine

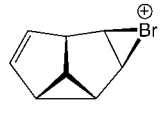
Our attempts to optimize a structure corresponding to **2** in dichloromethane consistently led to structure **4** (Scheme 3).[8] This suggests that bromine addition and cyclopropane ring-opening might be concerted. A constrained optimization, in which the length of the doubly allylic C–C bond (i.e. the C–C bond that breaks as Br_2 is added) was fixed at ca. 1.6 Å while the rest of the structure was allowed to relax, produced a structure resembling **2**, but this structure was approximately 18 kcal/mol higher in energy than **4**.[8,9] The formation of an allylic cation[10] and the relief of strain associated with opening of the cyclopropane ring of **2** both favor formation of **4**.



Scheme 3.

These results suggest that bromine addition and cyclopropane cleavage are concerted. Thus, we would expect to be able to find a single transition structure connecting **1**+Br_2 and **4**+Br^-. Such a transition structure was located and is shown in Figure 1, along with the **1**+Br_2 complex preceding it and the **4**+Br^- complex following it. In addition, an intrinsic reaction coordinate (IRC) plot for the reaction is shown in Figure 2.[11,12] While this reaction occurs on a relatively flat potential surface, our results clearly show that the addition of bromine is both concerted and synchronous with the opening of the cyclopropane ring;[13] note, for example, that the Br–Br and cyclopropyl C–C bonds are both lengthened in the transition structure. Thus, it appears that the mechanism shown in Scheme 3 is preferred to that shown in Scheme 1.

It is worth noting that neither mechanism (Scheme 1 or Scheme 3) involves a bridged bromonium cation. To assess the likelihood of bromine bridging,[3] constrained calculations were performed on a model structure resembling **5** in which the cyclopropane C–C bond was prevented from opening by fixing its distance at ca. 1.6 Å, the C–C bond of the bromonium substructure was fixed at ca. 1.5 Å, and the two C–Br bonds were fixed at ca. 2.1 Å. The structure that results from optimization with these constraints is less stable than **4** by 24 kcal/mol in dichloromethane.[8,14] Thus, initial attack bypasses formation of structures such as **5** (although **1**–Br_2 complexes are observed) and **2**, leading directly to **4** through concerted, synchronous bromine addition/cyclopropane cleavage.



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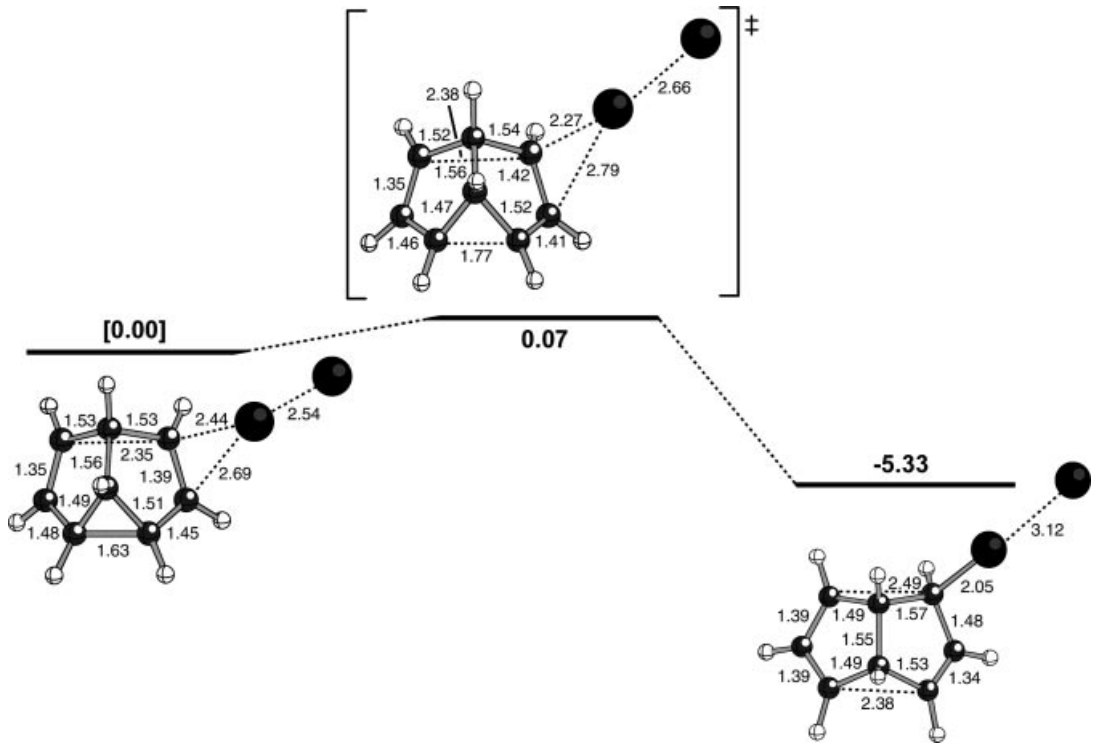


Figure 1. Geometries and relative energies [CPCM-B3LYP/6-31G(d); distances in Å, energies in kcal/mol] for structures involved in the initial addition of bromine to **1** in dichloromethane.

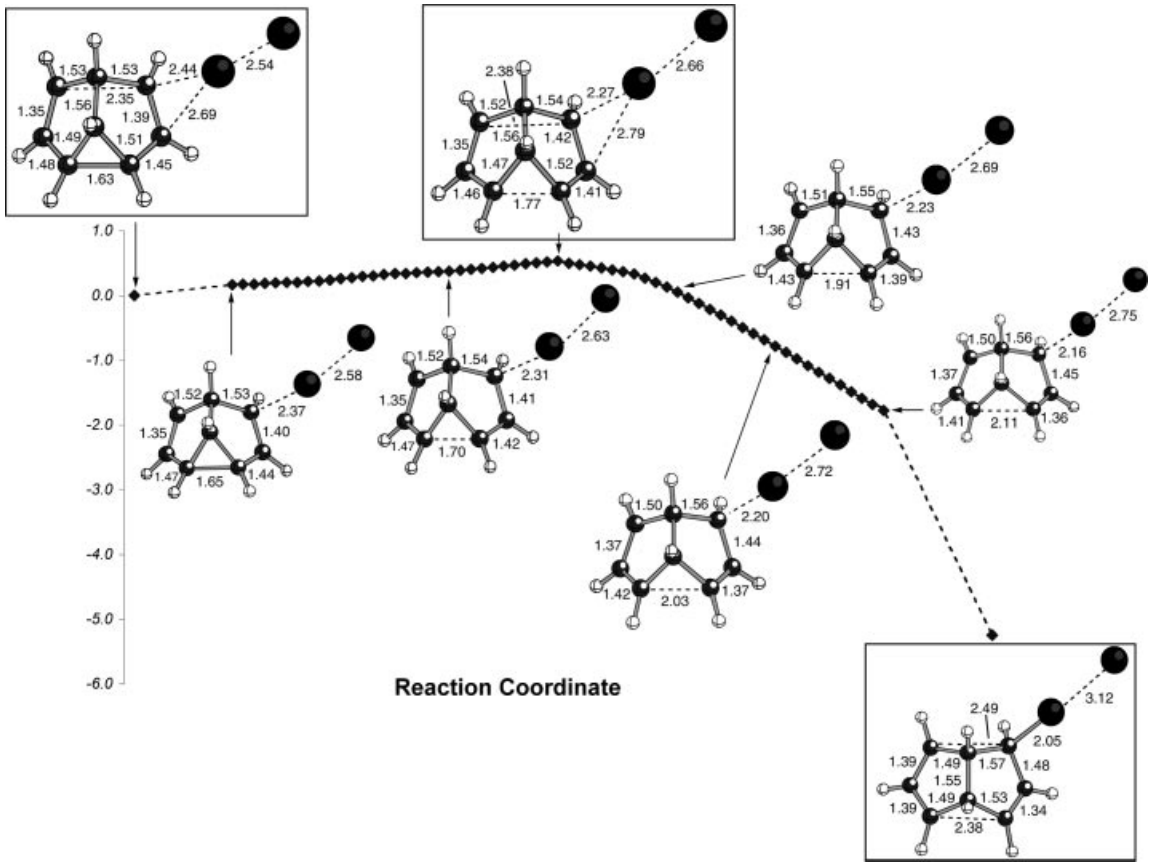


Figure 2. Portion of the reaction coordinate for addition of bromine to the convex face of **1** in dichloromethane [CPCM-B3LYP/6-31G(d), distances in Å]. The reactant minimum (complex of **1** with Br_2), the product minimum (complex of **4** with Br^-), and the transition structure connecting them are shown in boxes.

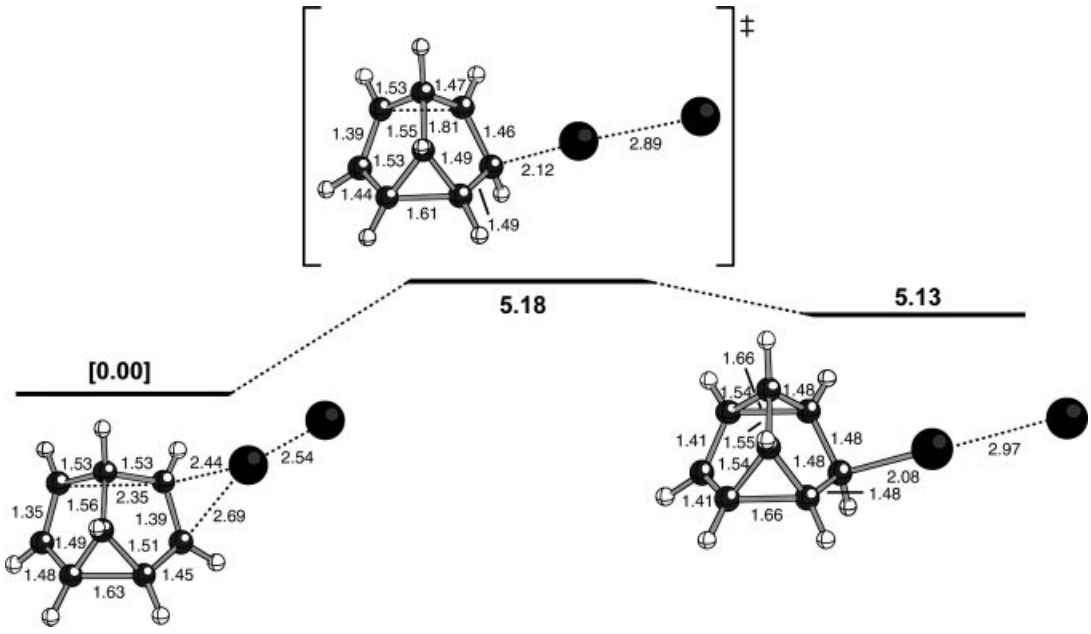
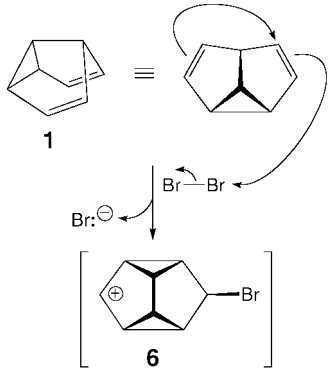


Figure 3. The **1**+Br_2 to **6**+Br^- reaction in dichloromethane [CPCM-B3LYP/6-31G(d), distances in Å, relative energies in kcal/mol].

In addition to the **1** → **3** reaction shown in Figure 1, another reaction involving **1** – formation of cation **6** – was also examined (Scheme 4 and Figure 3).[15] The transition structure for formation of **6** is approximately 5 kcal/mol higher in energy than that for formation of **3** in dichloromethane.[16] In addition, the **6**+Br^- complex is >10 kcal/mol higher in energy than the **3**+Br^- complex in dichloromethane. Overall, formation of **3** should be the dominant pathway (both thermodynamically and kinetically) in dichloromethane, the solvent used in the experiments.[3]



Scheme 4.

Regio- and Stereoselectivity

Bromination of semibullvalene is stereoselective, the incorporation of both bromine atoms of Br_2 occurring on the convex (*exo*) face of **1** to form **3**; no products with either bromine atom incorporated on the concave (*endo*) face have been reported.[3] Our calculations on transition structures for *exo* and *endo* attack (Figure 1 and Figure 4, respectively) are consistent with this result, predicting that initial Br_2 attack from the convex face is favored over attack from the concave face by more than 5 kcal/mol in dichloromethane.[17] This is most likely a steric effect; note that the Br_2 more closely approaches the alkene of **1** that it will attack in the **1**-Br_2 complex and in the corresponding early transition structure for addition to the convex face.

When the bromide ion recombines with the cation **4** there are two possible sites for addition, and attack could occur from either the convex or concave face. The four possible isomeric products (**3** and **7**–**9**) are shown in Figure 5. All of our attempts to locate transition structures for the recombination of **4** and Br^- were unsuccessful. Almost certainly this is a result of the strong impetus for the anionic bromide and the cationic **4** to combine and annihilate their charges. To verify this, we performed a series of optimizations in which the distance of the forming C···Br bond was constrained to particular values between 6 and 2 Å as the reaction proceeds to produce **3**. As shown in Figure 6, a monotonic decrease in energy is observed as the two species approach each other.[18] Although a barrier could, in principle, be observed in the presence of explicit solvent molecules, this would require further simulations of a different sort and is beyond the current study. In any case, our calculations do predict that compound **3** is more stable than **7**, **8** and **9** by 2.0, 1.5, and 2.0 kcal/mol, respectively, in dichloromethane.[19] **3** is likely the most stable product primarily due to steric problems in **7**–**9**.[20] Overall, **3** is 29.4 kcal/mol more stable than the **4**+Br^- complex.

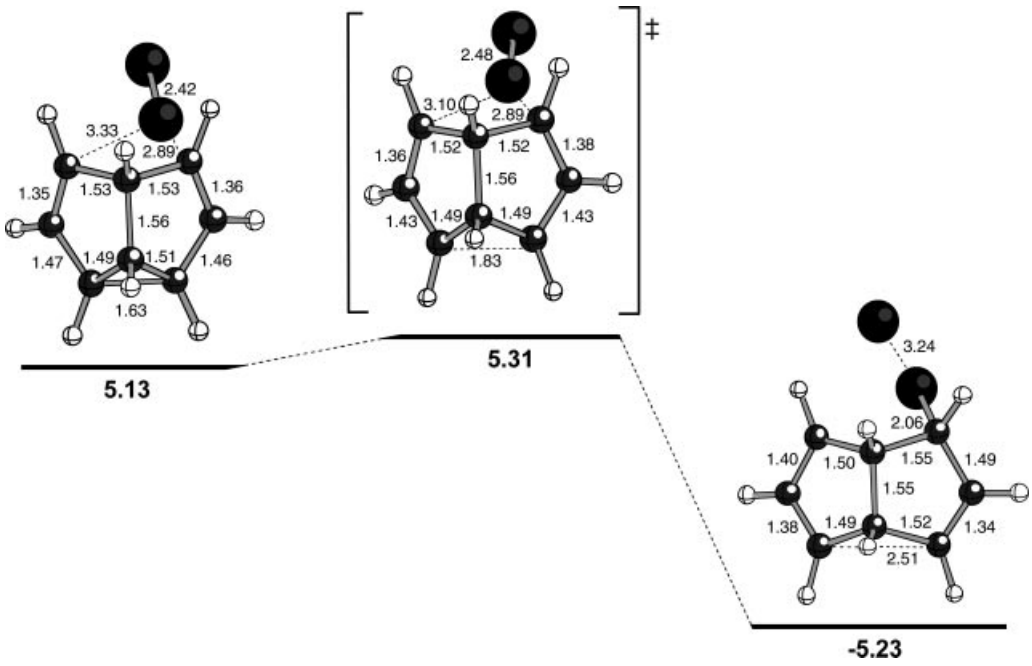


Figure 4. Geometries and relative energies [CPCM-B3LYP/6-31G(d), distances in Å, energies in kcal/mol relative to the **1**-Br_2 complex shown in Figure 1] for structures involved in the initial addition of bromine to the concave face of **1** in dichloromethane. Note that the C···Br distance in the reactant is actually slightly longer than that in the transition structure (2.894 vs. 2.886 Å).

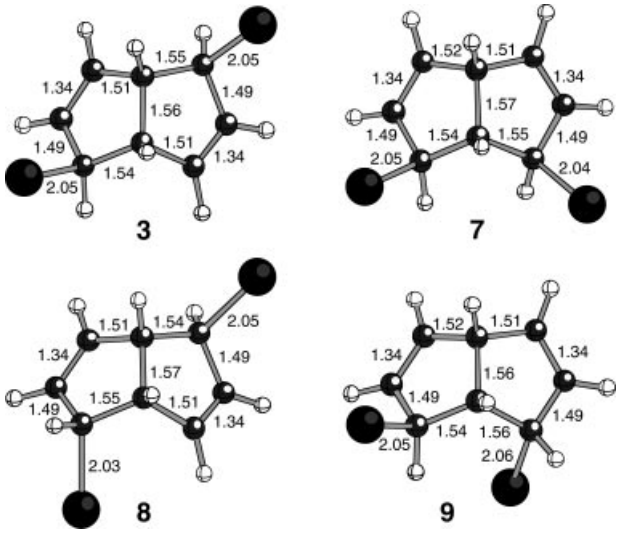


Figure 5. Geometries of the product **3** and its regio- and stereoisomers [CPCM-B3LYP/6-31G(d), dichloromethane, distances in Å].[19]

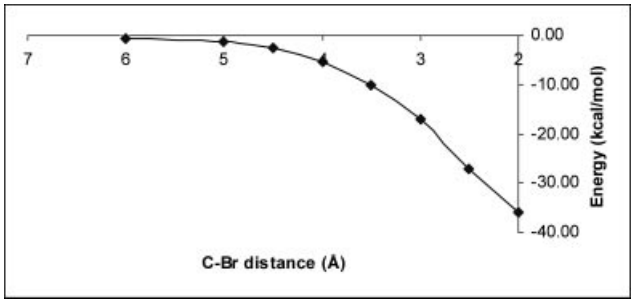


Figure 6. Results of constrained calculations for the addition of bromide ion to compound **4** in dichloromethane (energies are relative to the **1**+Br_2 complex).

Involvement of a Second Br_2?

Various studies have suggested that two molecules of Br_2 can be involved simultaneously in (at least some) alkene bromination reactions,[6h–6j] so we performed additional computations including a second Br_2. In dichloromethane, complexes of Br_2 with **3** and **7**–**9** could be located and had relative energies (0.0, +2.5, +2.1 and +3.1 kcal/mol, respec-

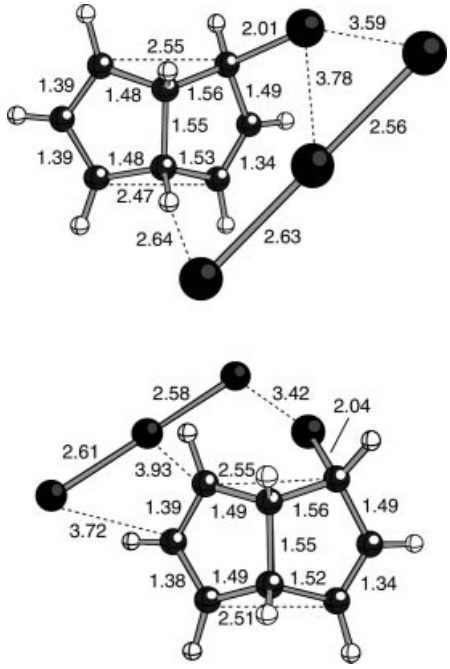


Figure 7. Geometries of **4**·Br_3^- complexes [CPCM-B3LYP/6-31G(d), dichloromethane, distances in Å].

tively) that were similar to those without a complexed Br_2.[21] The only other stationary points that we could locate in dichloromethane were *exo* and *endo* complexes of Br_3^- with **4** (Figure 7). As for the analogous system without a second Br_2, no structures resembling **2** were found, consistent with a concerted bromine addition and ring-opening.[22] Constrained calculations in which the Br···C distances in the **4**·Br_3^- complexes were systematically lengthened showed that departure of the two Br_2 molecules is accompanied by a monotonic increase in energy (for both *exo* and *endo*). This is consistent with our inability to locate transition structures for bromine addition, which is not surprising in that the barriers for this process when only a single Br_2 is involved are very small (see Figure 1, Figure 2, and Figure 4). In addition, similar constrained calculations for the recombination of **4** with Br_3^- showed that this process is again barrierless, although the overall exothermicity of this process is not as great as that with only Br^-, since the larger size of Br_3^- allows for more delocalization of charge.

Conclusions

Our quantum chemical calculations are consistent with a mechanism for the bromination of semibullvalene in which the opening of its cyclopropane ring is concerted and synchronous with the initial attack of bromine, thus constituting a vinylogous attack of a C–C single bond on Br_2 (or Br_2 dimer). This results in the formation of an allyl rather than a cyclopropylcarbinyl or bridged bromonium cation and releases ring strain. Our calculations are also consistent with the experimentally observed regio- and stereochemical course of this reaction. If the enantioselectivity of reactions such as this could be controlled, semibullvalene could find utility as a platform on which to build new chiral architectures that display functional groups in specific spatial orientations.

Computational Methods

GAUSSIAN03[23] was employed for all calculations. All geometries were optimized without symmetry constraints using B3LYP/6-31G(d)[24] unless mentioned otherwise in the text. All stationary points were characterized as minima or transition structures by analyzing their vibrational frequencies. All reported energies for stationary points include zero-point energy corrections from frequency calculations, scaled by 0.9806.[25] Intrinsic reaction coordinate (IRC) calculations[26] were used to further characterize the nature of transition-state structures by mapping out the portions of the reaction coordinate near to them. In order to address solvation effects, CPCM (with UA0 radii),[27] a self-consistent reaction field (SCRF) method, was used to optimize selected structures in dichloromethane (ε = 8.93) and water (ε = 78.39). These computations were also carried out using B3LYP/6-31G(d). Results in dichloromethane (the solvent used in the reported experiments)[3] are discussed explicitly in the text; details on gas phase and aqueous calculations can be found in the Supporting Information. Structural drawings were produced using *Ball & Stick* (N. Müller and A. Falk, *Ball & Stick V.3.7.6*, molecular graphics application for MacOS computers, Johannes Kepler University Linz, 2000).

Supporting Information (for details see the footnote on the first page of this article): Coordinates and energies for all structures, along with IRC plots.

Acknowledgments

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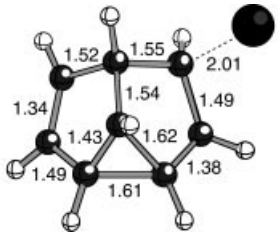
[4] For a detailed review of the electrophilic bromination of alkenes, see: M.-F. Ruasse, *Adv. Phys. Org. Chem.* **1993**, *28*, 207–290.

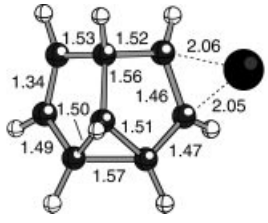
[5] I. Roberts, G. E. Kimball, *J. Am. Chem. Soc.* **1937**, *59*, 947–948.

[6] See, for example: a) M.-F. Ruasse, B.-L. Zhang, *J. Org. Chem.* **1984**, *49*, 3207–3210; b) R. S. Brown, H. Slebocka-Tilk, A. J. Bennet, G. Bellucci, R. Bianchini, R. Ambrosetti, *J. Am. Chem. Soc.* **1990**, *112*, 6310–6316; c) R. Herges, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 51; d) M. Cossi, M. Persico, J. Tomasi, *J. Am. Chem. Soc.* **1994**, *116*, 5373–5378; e) G. D. Allen, M. C. Buzzeo, I. G. Davies, C. Villagrán, C. Hardacre, R. G. Compton, *J. Phys. Chem. B* **2004**, *108*, 16322–16327; f) C. Chiappe, H. Detert, D. Lenoir, C. S. Pomelli, M. F. Ruasse, *J. Am. Chem. Soc.* **2003**, *125*, 2864–2865; g) S. Kozhushkov, T. Spaith, T. Fliebig, B. Galland, M.-F. Ruasse, P. Xavier, Y. Apeloig, A. de Meijere, *J. Org. Chem.* **2002**, *67*, 4100–4114; h) R. Bianchini, C. Chiappe, D. Lenoir, P. Lemmen, R. Herges, J. Grunenberg, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1284–1287; i) R. Herges, A. Papafilippopoulos, K. Hess, C. Chiappe, D. Lenoir, H. Detert, *Angew. Chem. Int. Ed.* **2005**, *44*, 1412–1416; j) H. Slebocka-Tilk, R. G. Ball, R. S. Brown, *J. Am. Chem. Soc.* **1985**, *107*, 4504–4508; k) Biological alkene brominations (using more exotic sources of electrophilic bromine) have also been discussed. See, for example: J. N. Carter-Franklin, J. D. Parrish, R. A. Tschirret-Guth, R. D. Little, A. Butler, *J. Am. Chem. Soc.* **2003**, *125*, 3688–3689.

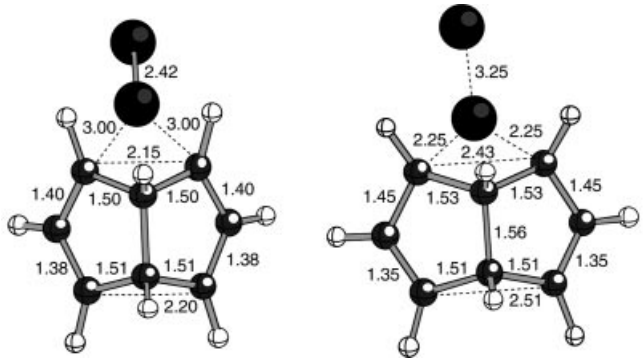
[7] For a thorough review on cyclopropylcarbinyl cations, see: G. A. Olah, V. P. Reddy, G. K. S. Prakash, *Chem. Rev.* **1992**, *92*, 69–95.
[8] Similar results were obtained in the gas phase and water. See Supporting Information for details.
[9] The constrained structure (in dichloromethane; selected distances in Å):



Similar structures were found in the gas phase and water. See Supporting Information for details.
[10] Previous literature suggesting that allylic resonance is stronger than the interaction of a cation with a cyclopropane ring includes: a) L. Radom, P. C. Hariharan, J. A. Pople, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1973**, *95*, 6531–6544; b) D. H. Aue, W. R. Davidson, M. T. Bowers, *J. Am. Chem. Soc.* **1976**, *98*, 6700–6702.
[11] A similar IRC plot was obtained for the reaction in water. This is available in the Supporting Information.
[12] a) While we were not successful in locating the reactant complex in water (even when following the IRC back towards the reactants) due to the flatness of the potential energy surface in this region, a single-point calculation in water was performed on the corresponding complex found in dichloromethane. Using the resulting energy as a reference point for the other structures leads to relative energies (not zero-point energy corrected) of 0.00, +2.14, and –11.48 kcal/mol for the **1**+Br_2 complex, the transition state for ring opening, and the **4**+Br^- complex, respectively, in water; b) No reactant complex or corresponding transition structure was located in the gas phase. Extensive exploration of the energy surface surrounding the **4**+Br^- complex indicated that both increasing and decreasing the C···Br distance produced increases in energy; the former would produce two non-interacting molecules, while the latter would lead to a significant separation of charge that would be extremely unfavorable in the absence of solvent.
[13] This mode of reactivity is related to the reactivity of allylsilanes and, in a reverse sense, the reactivity of some homoallylic alcohols. See, for example: C. M. Lincoln, J. D. White, A. F. T. Yokochi, *Chem. Commun.* **2004**, 2846–2847.
[14] The constrained structure (in dichloromethane; selected distances in Å):



Similar structures were found in the gas phase and water. See Supporting Information for details.
[15] Structure **6**+Br^- is a minimum, but it can be thought of as an *exo* σ complex of Br^+ with the transition structure for Cope rearrangement of **1** (along with a Br^- counterion). For studies on related complexes of the Cope transition structure with Li^+, see: H. Jiao, P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1760–1763. The following two structures were also located. The left-hand structure was found in the gas phase and is a minimum; it appears to be an *endo* complex of Br_2 with the transition structure for Cope rearrangement of **1**. Interestingly, complexation with Br_2 seems to remove the barrier and make the delocalized structure a minimum.[1] The right-hand structure was found in dichloromethane and appears to be a transition structure for intramolecular transfer of the lower bromine (along with its Br^- counterion) from one carbon to another (i.e. the transition structure for the interconversion of the allylic cation/Br^- complex from Figure 4 and its enantiomer). Note that the hydrocarbon framework in the right-hand structure is more open/extended than that in the left-hand structure and both are more open/extended than that in **6**+Br^-.



[16] In water, however, the two transition structures are approximately equienergetic, since the greater separation of charge in the transition structure leading to **6** is better stabilized in more polar environments. As noted above,[12] we were not able to locate the reactant complex in water. Using the energy from the single-point calculation described in ref.[12] as a reference point for the other structures leads to relative energies (not zero point energy corrected) of 0.00, +2.54, and +0.48 kcal/mol for the **1**+Br_2 complex, the transition state for Br_2 attack, and the **6**+Br^- complex, respectively, in water. See Supporting Information for further details.
[17] Using the energy from the single-point calculation described in ref.[12] as a reference point for the other structures leads to relative energies (not zero-point energy corrected) of +5.95, +6.37, and –11.25 kcal/mol for the *endo* **1**+Br_2 complex, the transition state for Br_2 attack, and the *endo* **4**+Br^- complex, respectively, in water.
[18] The decrease in C···Br distance is accompanied by a reduction of negative charge on the attacking Br. For example, the Mulliken charge on this Br is –1.00 at 6.0 Å, –0.98 at 5.0 Å, –0.47 at 2.5 Å, and –0.23 at 2.0 Å.
[19] Our calculations indicate that compound **3** is more stable than compound **7**, **8** and **9** by 2.1, 1.1, and 2.1 kcal/mol in the gas phase and by 1.9, 1.6, and 1.9 kcal/mol in water. Thus, the relative stability of the products is not sensitive to the dielectric constant. The geometries of these structures can be found in the Supporting Information.
[20] Dipole effects may also contribute, at least slightly. Note that the second most stable product, **8**, has its C–Br bond dipoles oriented such that they largely cancel each other.
[21] See Supporting Information for geometries.
[22] Structures with a second Br_2 analogous to the transition structures and minima that precede them in Figure 1 and Figure 4 were located in the gas phase, but single-point calculations on these structures in dichloromethane indicate that the transition structure benefits more from solvation than does the reactant (since charge is separating) to the extent that it becomes lower in energy than the preceding minimum. See Supporting Information for the gas phase structures.
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