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Ring Opening versus Ring Expansion in Rearrangement of Bicyclic Cyclobutylcarbinyl Radicals

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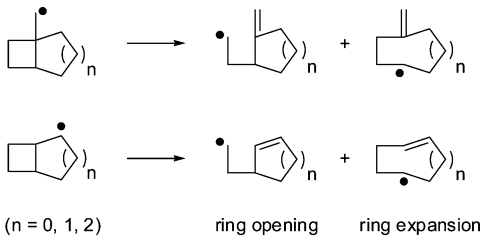

Ring opening and expansion of multicyclic cyclobutylcarbinyl radicals provides an appealing method for the construction of heavily substituted ring systems in a stereocontrollable fashion. Here we conducted the first, systematic study on the regioselectivity in the rearrangement of various synthetically relevant cyclobutylcarbinyl radicals. It was found that a two-layer ONIOM method, namely ONIOM(QCISD-(T)/6-311+G(2d,2p):B3LYP/6-311+G(2df,2p)), could accurately predict the free energy barriers of the ring openings of cyclobutylcarbinyl radicals with a precision of 0.3 kcal/mol. By using this powerful tool we found that the regiochemistry for the ring opening of monocyclic cyclobutylcarbinyl radicals could be easily predicted by the relative stability of the two possible carbon radical products. A linear correlation was found between the activation and reaction free energies. This observation indicated that the ring opening of cyclobutylcarbinyl radicals was strongly affected by the thermodynamic factors. On the basis of the above results we extended our study to the rearrangement of bicyclic cyclobutylcarbinyl radicals that could undergo both ring opening and expansion. It was found that for bicyclic cyclobutylcarbinyl radicals whose radical center was located at the bridge methyl group, ring expansion was the favored rearrangement pathway unless a strongly radical-stabilizing substituent was placed in the cyclobutyl ring adjacent to the bridge methyl group. On the other hand, for bicyclic cyclobutylcarbinyl radicals whose radical center was located at the 2-position, ring opening was the favored rearrangement pathway unless a strongly radical-stabilizing substituent was placed in the cyclobutyl ring at the bridge position.

1. Introduction

Ring opening of cyclic free radicals has long been a subject of broad interest to organic chemists because it has wide potential for both mechanistic (e.g., radical clocks[1]) and synthetic applications. Up to now the free radical ring opening that has attracted the most attention is the ring opening of cyclopropylcarbinyl radicals to 3-butenyl radicals.[2] Considerable efforts have been made to study the rates and regioselectivity of the cyclopropylcarbinyl radical ring-opening reactions. A number of synthetic applications of this type of ring-opening reactions (in particular, applications to ring expansions) have also been developed for the synthesis of naturally occurring as well as pharmaceutically active compounds.[3] Furthermore, in some recent studies attention has been paid to the ring opening of systems other than all-carbon atoms, e.g., 2-aziridinylcarbinyl and 2-oxiranylcarbinyl radicals.[4]

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[‡] University of Science and Technology of China.
(1) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Martin, N. *Tetrahedron* **1993**, *49*, 1151.

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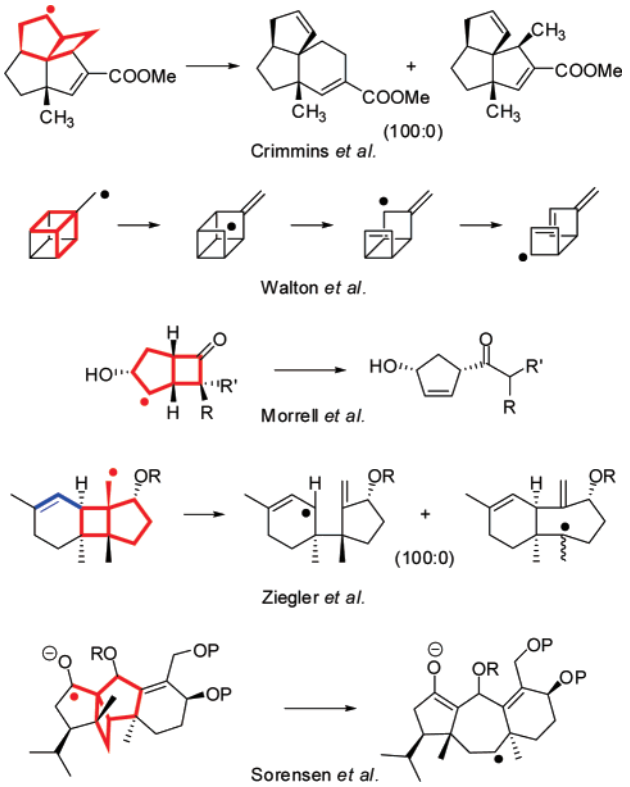
In contrast to the extensive literature related to cyclopropylcarbinyl radicals, the ring opening of cyclobutylcarbinyl radicals has received much less attention although the earliest observations of the this type of ring opening can be dated as far back as 1950s.[5] The reasons for the lack of studies on cyclobutylcarbinyl radicals are probably 2-fold: (1) the cyclobutylcarbinyl radical ring opening is often less efficient than that of the cyclopropylcarbinyl radical and (2) the regiochemistry in the cyclobutylcarbinyl radical ring opening has not been well understood. Despite these limitations, some synthetically useful cyclobutylcarbinyl radical ring-opening reactions occasionally have been reported over the past few years. For example, in 1992 Crimmins et al. reported a tandem fragmentation−expansion sequence that began with a cyclobutylcarbinyl radical (Scheme 1).[6] In 1994 Walton et al. reported fascinating rearrangement of the 9-Basketyl radical by multiple cyclobutylcarbinyl radical ring openings.[7] In 1995 Morrell et al. reported an interesting synthesis of cis-disubstituted cyclopentenes from substituted bicyclo[3.2.0]heptenone radicals.[8] In 2000 Ziegler et al. reported a highly selective cyclobutylcarbinyl radical ring opening in their study toward the synthesis of sesquiterpene FS-2.[9] Finally, in 2006 Sorensen et al. reported convergent syntheses of Guanacastepenes A and E featuring a selective cyclobutylcarbinyl radical ring-opening fragmentation.[10,11]

The above interesting synthetic applications indicate that detailed kinetic and mechanistic studies on the ring opening of cyclobutylcarbinyl radicals are warranted. However, over the past 20 years only several sporadic studies have been conducted concerning this subject.[12−14] In one of these important studies Newcomb et al. accurately measured the rates of ring openings

SCHEME 1



for a few 2-phenyl-substituted cyclobutylcarbinyl radicals by using the laser flash photolysis methods.[13] Furthermore, in 2001 Dolbier et al. demonstrated the utility of the density functional theory (specifically, the UB3LYP/6-311+G(2df,2p)//UB3LYP/6-31G(d) method) in the study of the ring openings of some fluorine-substituted cyclobutylcarbinyl radicals.[14] Despite these pioneering studies, very little mechanistic work has been reported on the regiochemistry in the ring openings of cyclobutylcarbinyl radicals.

In the present study we benchmarked a high-level theoretical procedure that could accurately predict the free energy barriers of cyclobutylcarbinyl radical ring openings with a precision of 0.3 kcal/mol. Equipped with this dependable theoretical tool, we systematically studied the regioselectivity in the ring openings of monocyclic and, more importantly, bicyclic cyclobutylcarbinyl radicals that carried synthetically relevant substituents. Note that all the examples in Scheme 1 show the ring openings of cyclobutylcarbinyl radicals that are fused in multicyclic ring systems. Under these conditions the rearrangement can take place either through simple ring opening or, more interestingly, ring expansion (Scheme 2). If the reaction regioselectivity can be strategically controlled, ring opening of cyclobutylcarbinyl radicals fused in bicyclo[2.2.0]hexanes, bicyclo[3.2.0]heptanes, and bicyclo[4.2.0]octanes provides a highly interesting and creative route toward the construction of

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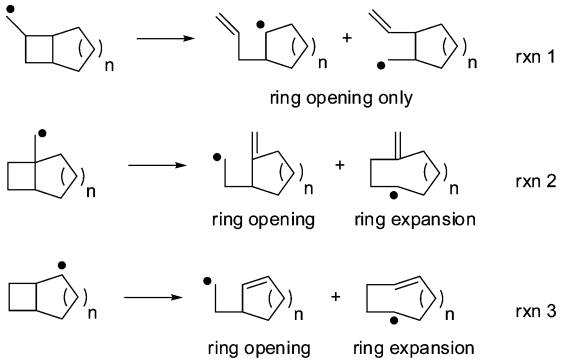
(14) Baker, J. M.; Dolbier, W. R., Jr. *J. Org. Chem.* **2001**, *66*, 2662.

SCHEME 2



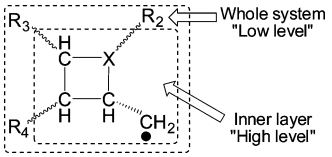
six-, seven-, and eight-membered ring systems via ring expansion (for instance in Sorensen's synthesis of Guanacastepenes A and E[10]).

2. Method

Ab initio calculations were performed with the Gaussian 03 suite of programs.[15] Geometry optimizations were conducted using the B3LYP/6-31G(d) method without any constraint.[16] Frequency calculations were carried out at the B3LYP/6-31G(d) level of theory and performed on all of the species to confirm convergence to appropriate local minima or saddle points on the energy surface. All the zero-point vibrational energies (ZPVE) and thermochemical corrections were calculated using the unscaled B3LYP/6-31G(d) frequencies. In all instances, transition-state structures gave one and only one imaginary frequency, while no imaginary frequencies were observed for the minimum-energy species.

Single-point energies were determined using the ONIOM method,[17] because pure QCISD(T) calculations for the substituted cyclobutylcarbinyl radicals were impractical with the current computational resource.[18] A two-layer ONIOM method was utilized, that is, ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(2df,2p)). The inner layer treated at the "high" level (i.e., QCISD(T)/6-311+G(2d,2p))[19] was comprised of five heavy atoms and their hydrogens, while the whole system was treated at the "low" level (i.e., B3LYP/6-311+G(2df,2p)) (see Chart 1). The gas-phase free energy change was calculated for an ideal gas model under the rigid rotor/harmonic oscillator approximation. It was corrected with ZPVE, thermal corrections (0→298 K), and the entropy terms. All the calculated gas-phase free energies corresponded to the reference state of 1 atm and 298 K.

CHART 1



3. Results and Discussion

3.1. Systems with Known Experimental Data. Many years ago the ring opening of unsubstituted cyclobutylcarbinyl radical was found to be a relatively "slow" reaction with $k = 4.7 \times 10^4$ s^{-1} at 333 K.[12] In 2000 Newcomb et al. further measured the rate constants for the ring openings of several 2-phenyl-substituted cyclobutylcarbinyl radicals by using the laser flash photolysis methods.[13] From these rate constants we have calculated the corresponding free energy barriers ($\Delta G_{exp}^{\ddagger}$) using the transition-state theory (eq 1) with transmission coefficient equated to unity (Table 1). These free energies are then compared with the theoretical values predicted for the corresponding gas-phase transformations at the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(2df,2p)) level. Furthermore, we have also used the B3LYP/6-311+G(2df,2p) method to calculate the energy barriers directly.

$$k = \frac{k_B T}{h} \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \quad (1)$$

From Table 1 it can be seen that the theoretical activation free energies predicted by the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(2df,2p)) method are in excellent agreement with the experimental values. The mean error is +0.2 kcal/mol and the root-mean-square (rms) error is 0.3 kcal/mol (Figure 1a). On the other hand, the theoretical activation free

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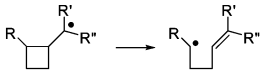
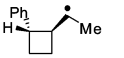
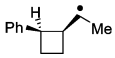
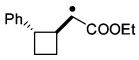
TABLE 1. Experimental (298 K) and Theoretical Activation Free Energies for the Ring Openings of Substituted Cyclobutylcarbinyl Radicals (kcal/mol)



Compound	k_{exp} (s^{-1})	$\Delta G_{exp}^{\neq}$	$\Delta G_{theor}^{\neq}$ (gas-phase)[a]	$\Delta G_{theor}^{\neq}$ (gas-phase)[b]
	5.0×10^2	13.7	14.5	11.9
	4.7×10^4	11.1	11.2	8.6
	1.3×10^7 (THF) 1.3×10^7 (MeCN)	7.7 (THF) 7.7 (MeCN)	7.6	5.3
	3.2×10^7 (THF)	7.2 (THF)	7.3	4.3
	1.0×10^7 (THF) 1.0×10^7 (MeCN)	7.9 (THF) 7.9 (MeCN)	7.8	5.5
	3.9×10^7 (THF)	7.1 (THF)	7.2	4.5
	0.8×10^7 (THF) 0.9×10^7 (MeCN)	8.0 (THF) 8.0 (MeCN)	8.2	5.9
	5×10^6 (THF) 8×10^6 (MeCN)	8.1 (THF) 7.8 (MeCN)	8.8	6.3

[a] Values calculated by the ONIOM(QCISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method. [b] Values calculated by the B3LYP/6-311+G(2df,2p) method.

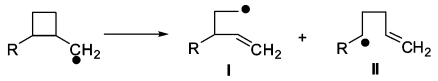
energies predicted by the B3LYP/6-311+G(2df,2p) method are systematically lower than the experimental values by 2.3 kcal/mol (Figure 1b). The rms error of the B3LYP/6-311+G(2df,-2p) predictions is also as high as 2.7 kcal/mol. These results demonstrate that the ONIOM method, put forward in this work, is an appropriate and yet feasible technique to calculate the energy barrier for the ring opening of cyclobutylcarbinyl radicals.

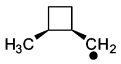
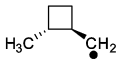
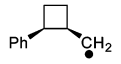
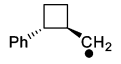
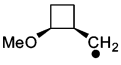
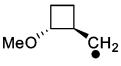
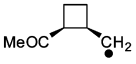
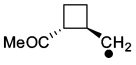
Additionally, it is also evident from Table 1 that the theoretical activation free energies calculated for the gas-phase ring-opening reactions are in good agreement with the experimental values measured in both THF and MeCN. This observation indicates that the energy barriers for the ring opening of cyclobutylcarbinyl radicals are not sensitive to the solvation effect. The absence of a kinetic effect due to changes in solvent polarity is consistent with the expectation that the transition states will not be polarized for radical reactions. On the basis of this observation, we will only study the gas-phase kinetics in the following studies on the ring opening of cyclobutylcarbinyl radicals.

3.2. Monocyclic Cyclobutylcarbinyl Radicals. With a reliable theoretical method in hand, we next study the substituent effects on the regiochemistry in the ring opening of monocyclic cyclobutylcarbinyl radical. Four types of synthetically relevant substituents are considered, which include CH_3 (to represent alkyl groups), Ph (to represent aryl groups), OMe (to represent electron donors), and COMe (to represent electron acceptors). Both the cis and trans isomers of the reactants have been studied (Table 2).

From Table 2, it can be seen that the substituents have a strong control on the regiochemistry of cyclobutylcarbinyl radical ring opening. For Me-substituted cyclobutylcarbinyl radicals (entries 2 and 3, Table 2) the free energy barriers of

TABLE 2. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Monocyclic Cyclobutylcarbinyl Radicals[a]



Entry	R	Structure	I		II	
			$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG
1	H		+14.5	–4.8	+14.5	–4.8
2	*cis*-CH_3		+14.7	–5.5	**+11.2**	–9.5
3	*trans*-CH_3		+14.9	–2.7	**+12.9**	–6.7
4	*cis*-Ph		+15.9	–4.1	**+7.3**	–19.7
5	*trans*-Ph		+15.4	–1.1	**+7.6**	–16.8
6	*cis*-OCH_3		+15.1	–4.4	**+9.2**	–10.5
7	*trans*-OCH_3		+15.0	–2.1	**+10.0**	–8.2
8	*cis*-$COCH_3$		+16.0	–4.0	**+6.4**	–16.7
9	*trans*-$COCH_3$		+15.3	–1.5	**+7.3**	–14.1

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(QCISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method. *cis*-R or *trans*-R depicts the orientation of the R group relative to the $-CH_2^{\bullet}$ group.

the two possible rearrangement modes differ by ca. 2−3 kcal/mol, which means that the ring opening should predominantly produce a Me-substituted carbon radical. Furthermore, once the substituent is changed to Ph, OMe, and $COCH_3$ (entries 4−9, Table 2), the difference of the free energy barriers between the two opening modes increases to ca. 5−10 kcal/mol so that the rearrangement exclusively gives the substituted radical as the product. All the above observations can be readily explained in terms of the radical spin-delocalization stabilization effect[20] of both the electron-donating and -withdrawing groups.[21] Thus, the ring opening of monocyclic cyclobutylcarbinyl radicals can be easily predicted by the relative stability of the two possible carbon radical products.

Interestingly, through simple correlation analysis it is found that the activation free energies of the ring-opening reactions have a linear dependence on the reaction free energies. As shown in Figure 2, when the relative activation free energy between the substituted and unsubstituted cases (i.e., $\Delta\Delta G^{\ddagger} = \Delta G_R^{\ddagger} - \Delta G_H^{\ddagger}$) is plotted against the relative reaction free energy (i.e., $\Delta\Delta G = \Delta G_R - \Delta G_H$), a straight line is obtained with a good correlation coefficient ($r = 0.9476$) and a low standard deviation (sd = 1.1 kcal/mol). The positive slope (0.58) of the correlation

(20) Jiang, X.-K. *Acc. Chem. Res.* **1997**, *30*, 283.
(21) (a) Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 6750. (b) Liu, L.; Cheng, Y.-H.; Fu, Y.; Chen, R.; Guo, Q.-X. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 1164.

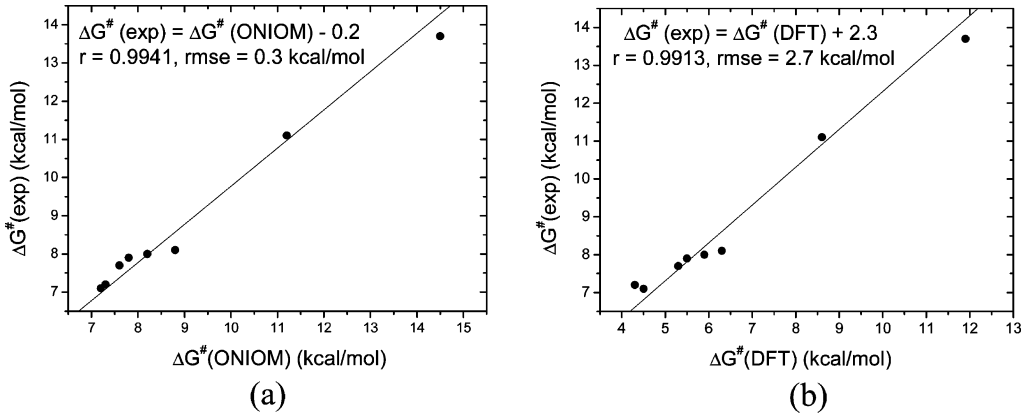


FIGURE 1. Comparing the experimental activation free energies with the theoretical values predicted by (a) ONIOM(QCISD(T)/6-311+G(2df,-2p):B3LYP/6-311+G (2df,2p)) and (b) B3LYP/6-311+G(2df,2p) methods.

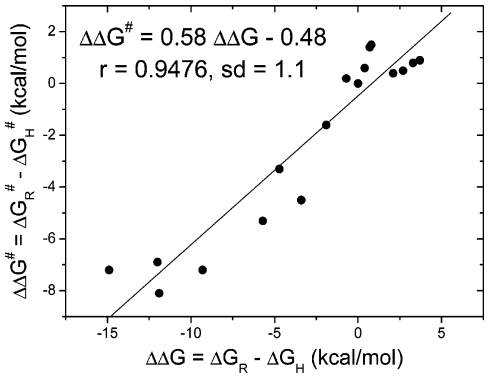


FIGURE 2. Correlation between the relative activation and reaction free energies for monocyclic cyclobutylcarbinyl radicals.

means that a more negative reaction free energy causes a lower activation free energy. This correlation strongly indicates that the substituents influence the cyclobutylcarbinyl radical ring-opening reactions mainly through the thermodynamic factors. (Note: the correlation between reaction thermodynamics and barriers is only an empirical observation without any straightforward physicochemical interpretations. It cannot be perfectly linear because this would imply negative barriers for very exoergic reactions.)

3.3. Bicyclic Cyclobutylcarbinyl Radicals. Compared to the reactions of monocyclic cyclobutylcarbinyl radicals, the ring opening of bicyclic cyclobutylcarbinyl radicals is much more interesting from the synthetic point of view. As shown in the examples in Scheme 1, this type of ring-opening reactions may undergo ring expansion to produce six-, seven-, or eight-membered rings in an elegant fashion. To successfully accomplish such ring expansion reactions it is important to have a sound knowledge of the regiochemistry in the ring opening of bicyclic cyclobutylcarbinyl radicals. However, it is evident from Scheme 2 that such a regiochemistry problem cannot be easily solved by using chemical intuition. Thus, experimental and theoretical studies need to be conducted on these interesting systems to illustrate what the regioselectivities are and how to control them.

In the following sections we will study the regioselectivity in the ring opening of cyclobutylcarbinyl radicals fused with a four-, five-, or six-membered rings, respectively. These bicyclic compounds represent synthetically important systems with possible applications to the construction of cyclohexanyl, cycloheptanyl, and cyclooctanyl rings. Note that although three groups of substrates can be considered for this type of ring-opening reactions (Scheme 2), only two of them (i.e., reactions 2 and 3) may give ring-expansion products. Furthermore, because of the nontrivial difficulty of synthesizing cyclobutanes trans-fused to four-, five-, and six-membered rings, we only consider the cis-fused bicyclic reactants in the present study.

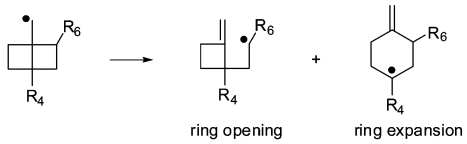
3.3.1. Bicyclo[2.2.0]hexane System. Type I: As mentioned before, two types of synthetically relevant ring openings are considered here. In the first type, the starting material has its radical center located at the bridge methyl group (Table 3). It is found that in the absence of any substituent the ring-opening pathway has a relatively high free energy barrier of +17.3 kcal/mol, whereas the ring-expansion pathway has a very low barrier of +2.8 kcal/mol (entry 1, Table 3). Such a dramatic difference between the energy barriers can be attributed to the high strain of the bicycle[2.2.0]hexane system. As indicated by the reaction free energy, the ring opening only lowers the free energy by −3.9 kcal/mol, whereas the ring expansion dramatically lowers the free energy by −28.1 kcal/mol. The transition structures obtained for ring-opening and ring-expansion reactions of bicyclo[2.2.0]hexan-1-ylmethyl radical are shown in Figure 3.

As to the substituent effects on the regioselectivity, we only consider the substituents at two positions (i.e., R_4 and R_6) that are directly connected to the radical centers of the products. These substituents apparently can exert strong effects on the thermodynamics and, therefore, the kinetics of the ring-opening or -expansion reaction (Note: the reason is provided in Section 3.2). Two representative and synthetically accessible substituents (i.e., Ph to represent strong electron donor and COMe to represent strong electron acceptor) are selected because they can produce significant radical stabilization effects.

It is found that when the Ph or COMe groups are placed at the R_4 position, the activation and reaction free energies of the ring-opening pathway are not significantly affected (entries 2 and 3, Table 3). On the other hand, the reaction free energies of the ring-expansion pathway are lowered by ca. 10 kcal/mol. Correspondingly the activation free energies for the ring expansion should also be significantly lowered. However, after many attempts we cannot obtain the transition state for the ring-expansion pathway (Note: all the TS-optimization directly produces the six-membered-ring product), presumably because this pathway has an extremely low energy barrier.

When the Ph and COMe groups are placed at the R_6 position, it is found that both the activation and reaction free energies

TABLE 3. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[2.2.0]hexan-1-ylmethyl Radicals[a]



Entry	R_4	R_6	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\neq}$	ΔG	$\Delta G^{\neq}$	ΔG
1	H	H	(±) H	+17.3	−3.9	**+2.8**	−28.1
2	Ph	H	(±) Ph	+17.7	−1.8	−[b]	−39.2
3	COMe	H	(±) MeOC	+17.8	−0.9	−[b]	−38.5
4	H	Ph	(±) Ph	+8.5	−21.4	**+3.6**	−28.4
5	H	Ph	(±) Ph	+9.8	−20.2	**+3.4**	−27.3
6	H	COMe	(±) COMe	+8.4	−16.4	**+3.5**	−27.2
7	H	COMe	(±) COMe	+9.3	−15.5	**+3.3**	−26.3

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method. [b] The transition state cannot be found because the energy barrier is too low.

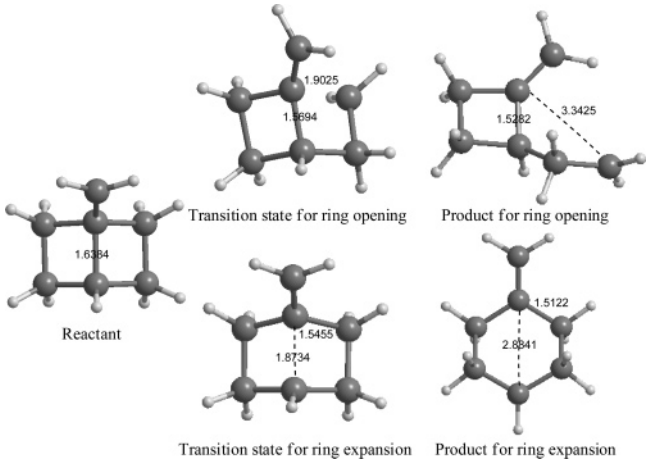
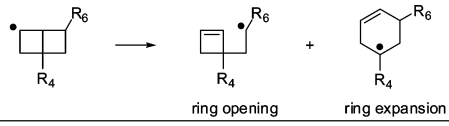


FIGURE 3. B3LYP/6-31G(d) optimized geometries for bicyclo[2.2.0]-hexan-1-ylmethyl radical, its transition states for ring opening and ring expansion reactions, and the corresponding ring opening and ring expansion products.

for the ring-opening pathway are dramatically lowered by ca. 8−9 and 12−17 kcal/mol, respectively (entries 4−7, Table 3). This observation can be easily attributed to the radical stabilization effect at the R_6 position. On the other hand, it is found that the substituents at R_6 do not produce any significant effect on the activation or reaction free energies for the ring-expansion pathways. Despite these changes, it is evident from Table 3 that

TABLE 4. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[2.2.0]hexan-2-yl Radicals[a]



Entry	R_4	R_6	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\neq}$	ΔG	$\Delta G^{\neq}$	ΔG
1	H	H	(±) H	**+15.2**	−4.4	+15.4	−32.2
2	Ph	H	(±) Ph	+16.1	−0.1	**+10.9**	−41.1
3	COMe	H	(±) MeOC	+16.7	−0.1	**+9.4**	−40.9
4	H	Ph	(±) Ph	**+8.1**	−17.3	+16.0	−31.2
5	H	Ph	(±) Ph	**+9.9**	−17.7	+16.3	−31.5
6	H	COMe	(±) COMe	**+7.8**	−13.6	+16.8	−29.1
7	H	COMe	(±) COMe	**+8.6**	−14.0	+16.2	−29.5

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method.

the activation free energy of the ring-expansion pathway is still lower than that of ring opening by ca. 5−6 kcal/mol. Thus ring expansion is strongly favored in the rearrangement of bicyclo-[2.2.0]hexan-1-ylmethyl radicals regardless of the substituents's nature.

Noteworthily it is found that the activation and reaction free energies for the rearrangement of all the bicyclo[2.2.0]hexan-1-ylmethyl radicals also obey the linear correlation illustrated in Section 3.2 (Figure 4a). The slope of the correlation (0.54) is remarkably close to the corresponding value (i.e., 0.58) in Figure 2. Thus, thermodynamic factors also play an important role in determining the kinetics and, consequently, regiochemistry of the rearrangement of bicyclic cyclobutylcarbinyl radicals.

Type II: In the second type of bicyclic cyclobutylcarbinyl radicals, the starting material has its radical center located at the 2-position (Table 4). In the absence of any substituent the ring-opening pathway has a free energy barrier of +15.2 kcal/mol, whereas the ring-expansion pathway has a slightly higher barrier of +15.4 kcal/mol (entry 1, Table 4). Thus, the ring-opening pathway is slightly favored over the ring -expansion pathway, despite the fact that the reaction free energy of ring opening (−4.4 kcal/mol) is considerably less negative than that of ring expansion (−32.2 kcal/mol). This observation can be readily explained by the stereoelectronic effect:[22] the ring opening releases a radical from the rear of a double bond (∠C2−C1−C6 = 115.6° for reactant and 111.1° for TS), whereas the ring expansion has to release a radical from the side of a double bond (∠C2−C1−C4 = 87.6° for reactant and 78.9° for TS).

When the Ph or COMe group is placed at the R_4 position, the activation and reaction free energies of ring opening are not significantly affected (entries 2 and 3, Table 4). On the other hand, the activation free energy of ring expansion is lowed by

(22) Kirby, A. J. *Stereoelectronic effects*; Oxford Science Publications: Oxford, UK, 1996.

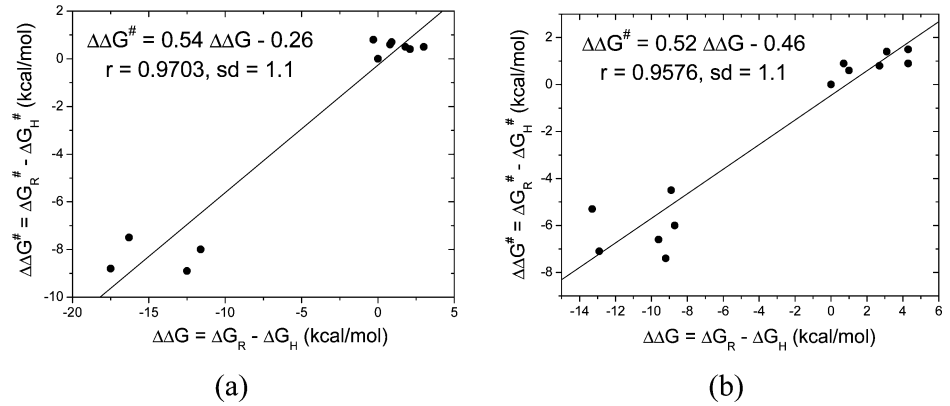


FIGURE 4. Correlation between the relative activation and reaction free energies for (a) bicyclo[2.2.0]hexan-1-ylmethyl and (b) bicyclo[2.2.0]-hexan-2-yl radicals.

ca. 5−6 kcal/mol. The reaction free energy of ring expansion also becomes more negative by ca. 8−9 kcal/mol. The overall outcome is that ring expansion becomes the favored pathway in the rearrangement of 4-Ph- or 4-COMe-substituted bicyclo-[2.2.0]hexan-2-yl radical.

Oppositely, when the Ph or COMe group is placed at the R_6 position, the activation and reaction free energies of ring expansion are not significantly affected (entries 4−7, Table 4). What are affected are the activation and reaction free energies of ring opening, which dramatically decrease by ca. 5−8 and 10−13 kcal/mol, respectively. The overall outcome is that ring opening is strongly favored over ring expansion in the rearrangement of 6-Ph- or 6-COMe-substituted bicyclo[2.2.0]hexan-2-yl radical.

Interestingly the activation and reaction free energies for the rearrangement of all the bicyclo[2.2.0]hexan-2-yl radicals again exhibit a linear correlation (Figure 4b). The slope of the correlation (0.52) is close to the corresponding values (i.e., 0.58 and 0.54) in Figures 2 and 3a. As a result, the thermodynamic factors again play an important role in determining the kinetics and, consequently, regiochemistry of the rearrangement of bicyclic cyclobutylcarbinyl radicals.

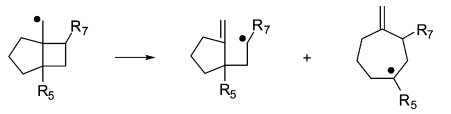
3.3.2. Bicyclo[2.2.0]heptane System. Type I: The bicyclo-[2.2.0]heptane system also has two types of reactants that can undergo radical rearrangement. In the first type, the starting material has its radical center located at the bridge methyl group (Table 5). It is found that in the absence of any substituent the ring-opening pathway has a free energy barrier of +16.5 kcal/mol, whereas the ring-expansion pathway has a barrier of +10.1 kcal/mol (entry 1, Table 5). Thus, ring expansion is the favored pathway in the rearrangement of unsubstituted bicyclo[3.2.0]-heptan-1-ylmethyl radical. Note that the reaction free energies of the two pathways are not significantly different (i.e., −5.2 versus −6.7 kcal/mol).

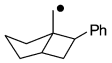
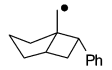
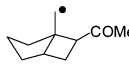
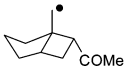
Similar to the observations for the bicyclo[2.2.0]hexan-1-ylmethyl radicals, the Ph and COMe substituents at the R_5 position can dramatically lower the activation and reaction free energies of ring expansion of the bicyclo[3.2.0]heptan-1-ylmethyl radicals by ca. 6−7 and 11−13 kcal/mol, respectively (entries 2 and 3, Table 5). At the same time, they do not significantly affect the activation and reaction free energies of ring opening. The overall outcome is that ring expansion is strongly favored over ring opening in 5-Ph- or 5-COMe-substituted bicyclo[3.2.0]heptan-1-ylmethyl radicals.

Oppositely, when the Ph or COMe group is placed at the R_7 position, the activation and reaction free energies of ring expansion are not significantly affected (entries 4−7, Table 5). What are affected are the activation and reaction free energies of ring opening, which dramatically decrease by ca. 8−9 and 10−15 kcal/mol, respectively. The overall outcome is that ring opening is strongly favored over ring expansion in the rearrangement of 7-Ph- or 7-COMe-substituted bicyclo[3.2.0]heptan-1-ylmethyl radicals. Note that the activation and reaction free energies for the rearrangement of all the bicyclo[3.2.0]heptan-1-ylmethyl radicals exhibit a linear correlation (Supporting information).

Type II: In the second type the starting material has its radical center located at the 2-position (Table 6). In the absence of any substituent the ring-opening pathway has a free energy barrier of +15.8 kcal/mol, whereas the ring expansion pathway has a

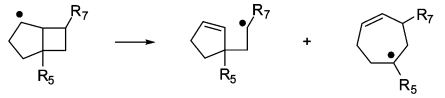
TABLE 5. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[3.2.0]heptan-1-ylmethyl Radicals[a]

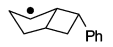
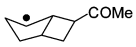
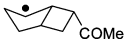


Entry	R_5	R_7	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG
1	H	H	(±) 	+16.5	−5.2	**+10.1**	−6.7
2	Ph	H	(±) 	+17.1	−1.6	**+4.6**	−19.7
3	COMe	H	(±) 	+17.3	−0.9	**+3.2**	−17.9
4	H	Ph	(±) 	**+8.4**	−20.5	+11.4	−6.0
5	H	Ph	(±) 	**+8.6**	−20.0	+11.2	−5.1
6	H	COMe	(±) 	**+8.3**	−16.1	+10.8	−3.6
7	H	COMe	(±) 	**+7.7**	−15.9	+10.3	−3.4

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method.

TABLE 6. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[2.2.0]heptan-2-yl Radicals[a]



Entry	R_5	R_7	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\neq}$	ΔG	$\Delta G^{\neq}$	ΔG
1	H	H	(±) 	**+15.8**	−3.9	+20.2	−5.4
2	Ph	H	(±) 	+15.4	−0.1	**+14.5**	−15.8
3	COMe	H	(±) 	+16.2	−0.3	**+13.0**	−15.6
4	H	Ph	(±) 	**+7.2**	−16.7	+20.1	−4.7
5	H	Ph	(±) 	**+10.2**	−15.1	+23.4	−3.1
6	H	COMe	(±) 	**+7.7**	−12.3	+20.9	−2.0
7	H	COMe	(±) 	**+8.8**	−12.3	+24.2	−2.2

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method.

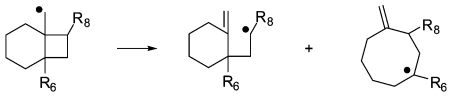
higher barrier of +20.2 kcal/mol (entry 1, Table 6). Thus, the ring-opening pathway is favored over the ring-expansion pathway for the rearrangement of the unsubstituted bicyclo-[2.2.0]heptan-2-yl radical.

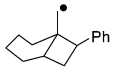
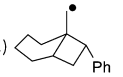
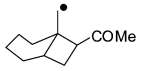
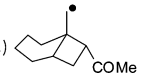
The effects of substitution are similar to the situations observed for the bicyclo[2.2.0]hexan-2-yl radicals. 5-Ph or 5-COMe substitution completely changes the regioselectivity so that the ring expansion pathway becomes dominant. On the other hand, 7-Ph or 7-COMe substitution retains the regioselectivity favoring the ring-opening pathway. Furthermore, the activation and reaction free energies for the rearrangement of all the bicyclo[2.2.0]heptan-2-yl radicals exhibit a linear correlation (Supporting information).

3.3.3. Bicyclo[2.2.0]octane System. Type I: For the first type where the radical center is located at the bridge methyl group (Table 7), it is found that in the absence of any substituent the ring opening and expansion pathways have free energy barriers of +14.5 and +13.4 kcal/mol, respectively. Thus, ring expansion is the favored pathway in the rearrangement of unsubstituted bicyclo[4.2.0]octan-1-ylmethanyl radical. 6-Ph or 6-COMe substitution retains the regioselectivity favoring the ring-expansion pathway. On the other hand, 8-Ph or 8-COMe substitution completely changes the regioselectivity so that the ring-opening pathway becomes dominant. Furthermore, the activation and reaction free energies for the rearrangement of all the bicyclo[4.2.0]octan-1-ylmethanyl radicals exhibit a linear correlation (Supporting information).

Type II: In the second type the starting material has its radical center located at the 2-position (Table 8). In the absence of any substituent the ring-opening pathway has a free energy barrier of +14.1 kcal/mol, whereas the ring-expansion pathway has a higher barrier of +18.2 kcal/mol (entry 1, Table 8). Thus, the ring-opening pathway is favored over the ring-expansion pathway for the rearrangement of unsubstituted bicyclo[2.2.0]-octan-2-yl radical. 6-Ph or 6-COMe substitution completely changes the regioselectivity so that the ring-expansion pathway becomes dominant. On the other hand, 8-Ph or 8-COMe substitution retains the regioselectivity favoring the ring-opening pathway. Finally, the activation and reaction free energies for

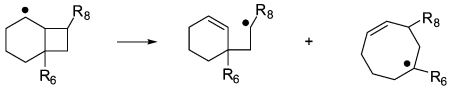
TABLE 7. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[4.2.0]octan-1-ylmethanyl Radicals[a]

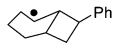
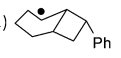
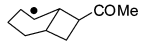
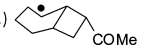


	R_6	R_8	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\neq}$	ΔG	$\Delta G^{\neq}$	ΔG
	H	H	(±) 	+14.5	−7.2	**+13.4**	−3.9
	Ph	H	(±) 	+15.6	−5.7	**+6.1**	−20.2
	COMe	H	(±) 	+15.6	−5.7	**+6.1**	−20.2
	H	Ph	(±) 	**+6.3**	−22.3	+14.8	+2.4
	H	Ph	(±) 	**+7.0**	−19.4	+14.4	+0.6
	H	COMe	(±) 	**+6.7**	−18.1	+15.0	−1.5
	H	COMe	(±) 	**+6.2**	−16.6	+14.0	+3.0

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method.

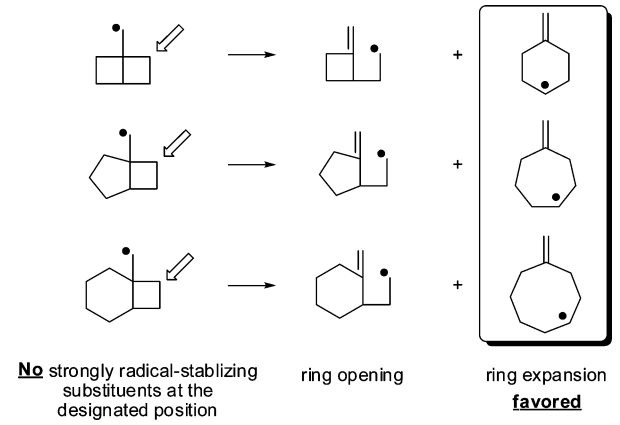
TABLE 8. Activation ($\Delta G^{\ddagger}$, kcal/mol) and Reaction Free Energies (ΔG, kcal/mol) at 298 K for the Ring Opening of Bicyclo[2.2.0]octan-2-yl Radicals[a]



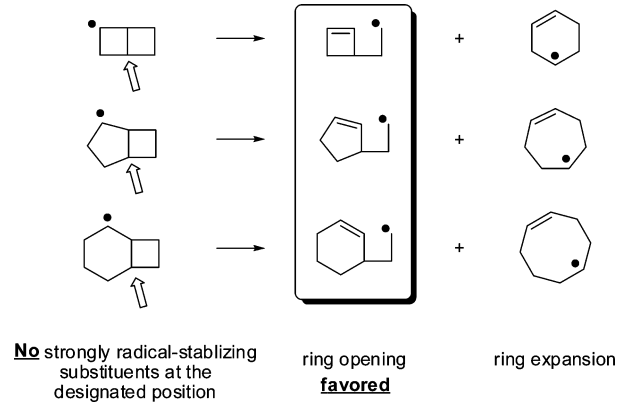
Entry	R_6	R_8	Conformation	Ring opening		Ring expansion	
				$\Delta G^{\neq}$	ΔG	$\Delta G^{\neq}$	ΔG
1	H	H	(±) 	**+14.1**	−5.2	+18.2	−2.7
2	Ph	H	(±) 	+14.8	−0.3	**+13.3**	−4.9
3	COMe	H	(±) 	+15.3	−1.4	**+10.4**	−6.7
4	H	Ph	(±) 	**+7.4**	−15.9	+19.6	+5.0
5	H	Ph	(±) 	**+6.9**	−20.5	+21.9	+0.4
6	H	COMe	(±) 	**+6.6**	−13.0	+19.3	+2.4
7	H	COMe	(±) 	**+6.1**	−15.9	+19.6	−0.6

[a] $\Delta G^{\ddagger}$ values and ΔG values are calculated by using the ONIOM(Q-CISD(T)/6-311+G(2df,2p):B3LYP/6-311+G(2df,2p)) method.

SCHEME 3



SCHEME 4



the rearrangement of all the bicyclo[2.2.0]octan-2-yl radicals again exhibit a linear correlation (Supporting information).

3.4. Synthetic Implications. The above results provide interesting information about how to apply the rearrangement of bicyclic cyclobutylcarbinyl radicals to target-oriented organic synthesis. First, as to the bicyclic cyclobutylcarbinyl radicals whose radical center is located at the bridge methyl group, ring expansion is the favored rearrangement pathway under the conditions where no strongly radical-stabilizing groups are placed at the designated positions shown in Scheme 3. This reaction provides an interesting strategy for constructing six-, seven-, and eight-membered rings carrying multiple substituents. An elegant application of this strategy has already been shown in Sorensen's synthesis of Guanacastepenes A and E (the last example in Scheme 1), where the rearrangement of a cyclobutylcarbinyl radical provided a densely substituted cycloheptanol through selective ring expansion.[10]

Nonetheless, our calculations also indicate that the above ring-expansion pathway can be efficiently switched off by the presence of a radical-stabilizing substituent in the cyclobutyl ring (except for the highly strained bicyclo[2.2.0]hexan-1-ylmethyl radicals). A good example in this context was provide by Ziegler et al. in their synthesis of sesquiterpene FS-2,[9] where the rearrangement of a 7-alkenylbicyclo[3.2.0]heptan-1-ylmethyl radical only produced the ring- opening product without any ring-expansion product (the second to last example in Scheme 1). Evidently the 7-alkenyl group played an important role in determining the observed regiochemistry.

As to the bicyclic cyclobutylcarbinyl radicals whose radical center is located at the 2-position, ring opening is the favored rearrangement pathway under the conditions where no strongly radical-stabilizing groups are placed at the designated positions shown in Scheme 4. This reaction does not appear very interesting from the synthetic point of view because the ring-opening product looks less complex than the starting material containing a fused bicyclic ring. Nevertheless, by using this reaction Morrell et al. once reported a stereoselective synthesis of cis-disubstituted cyclopentenes from substituted bicyclo[3.2.0]-heptenone radicals (the third example in Scheme 1).[8]

4. Conclusions

Ring opening and expansion of multicyclic cyclobutylcarbinyl radicals provides an appealing method for the construction of heavily substituted ring systems in a stereocontrollable fashion. In the present study we carry out the first, systematic study on the regioselectivity in the rearrangement of cyclobutylcarbinyl radicals that carry synthetically relevant substituents. It is found that a two-layer ONIOM method, namely ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(2df,2p)), can accurately predict the free energy barriers of the ring openings of cyclobutylcarbinyl radicals with a precision of 0.3 kcal/mol. By using this powerful tool we find that the regiochemistry for the ring opening of monocyclic cyclobutylcarbinyl radicals can be easily predicted by the relative stability of the two possible carbon radical products. A linear correlation is found between the activation and reaction free energies. This observation indicates that the ring opening of cyclobutylcarbinyl radicals is strongly affected by thermodynamic factors.

On the basis of the above results we next extend our study to the rearrangement of bicyclic cyclobutylcarbinyl radicals that can undergo both ring opening and expansion. It is found that for bicyclic cyclobutylcarbinyl radicals whose radical center is located at the bridge methyl group, ring expansion is the favored rearrangement pathway unless a strongly radical-stabilizing substituent is placed in the cyclobutyl ring adjacent to the bridge methyl group. On the other hand, for bicyclic cyclobutylcarbinyl radicals whose radical center is located at the 2-position, ring opening is the favored rearrangement pathway unless a strongly radical-stabilizing substituent is placed in the cyclobutyl ring at the bridge position. It is remarkable that all these theoretical predictions are in excellent agreement with the available experimental observations. Furthermore, discussions have been made on the involvement of ring strain, stereoelectronic effect, and substituent radical stabilization in determining the observed regiochemistry.

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Supporting Information Available: Detailed optimized geometries and free energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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