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Regiochemistry in radical cyclization of allenes

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Abstract—The cyclization of allenic radicals was systematically studied for the first time by computational methods. It was found that the theoretical results at the ONIOM(QCISD(T)/6-311+G(2df,2p):UB3LYP/6-311+G(2df,2p)) level were in good agreement with all the available experimental data. For the cyclization of penta-3,4-dien-1-yl radicals the major product was penta-1,2-diene from direct reduction whereas a small amount of vinylcyclopropane may also be produced. For the cyclization of hexa-4,5-dien-1-yl radicals the major product is 1-methyl-cyclopentene. Furthermore, for the cyclization of hepta-5,6-dien-1-yl radicals both vinylcyclopentane and 1-methyl-cyclohexene are produced. Marcus theory analysis indicated that the formation of an olefinic radical product always had a lower intrinsic energy barrier than the formation of an allylic radical product. On the other hand, the formation of an olefinic radical product was always much less favorable than the formation of an allylic radical product in the thermodynamic term. For the cyclization of substituted hexa-4,5-dien-1-yl radicals, substitution at the allene moiety does not affect the regioselectivity where the allylic radical product is always favored. For the cyclization of hepta-5,6-dien-1-yl radicals, substitution at the allene moiety dramatically affects the regioselectivity, where some radical-stabilizing groups such as –CN and –COMe may even completely reserve the regioselectivity.

1. Introduction

Recently, the use of free radical cyclization reaction for C–C and C–heteroatom bond formation has become widespread in the synthesis of carbocyclic and heterocyclic compounds.[1] Of particular interest are intramolecular processes of olefinic and acetylenic radicals, which have been extensively utilized in the construction of five- and six-membered rings.[2] By contrast, relatively little attention has been directed to the ring closure reactions of allenic radicals, although radical cyclizations of allenes are expected to provide a variety of interesting unsaturated carbocycles or heterocycles that can be further functionalized at the double bond to yield more complex structures.[3]

Among the synthetic studies on radical cyclization of allenes, Hart et al. reported in 1984 the use of intramolecular addition of α-acylamino radicals to allenes in the synthesis of pyrrolizidinone and indolizidinone.[4] Balasubramanian and Balasubramanian reported in 1994 the use of radical cyclization of *o*-haloaryl allenylmethyl ethers and amines in the synthesis of 2,3-dihydrobenzofurans and indoles.[5] More recently, Hatem et al. reported cyclization of β-allenylbenzoyloximes to afford 3*H*-pyrroles and alkylidene-pyrrolines via an iminyl radical.[6] Kang et al. fashioned the use of toluene-*p*-sulfonyl-mediated radical cyclization of bis(allenes) in the synthesis of *trans*-fused five-membered rings.[7] Sha et al. reported photoinduced atom-transfer cyclization of α-iodocycloalkanones bearing an allenyl side chain.[8] Molander and Cormier reported SmI_2-mediated radical cyclization of the allenes with ketones and aldehydes.[9] Moreover, Hsung and Shen reported the radical cyclization of allenamides in the synthesis of isoquinoline, indane, and naphthalene derivatives.[10] It is worth noting that radical cyclization of allenes has also been utilized in the total synthesis of natural products. Chen et al. used radical cyclization of α-allenic ketone to synthesize (±)-α-chamigrene (see Scheme 1).[11] Ley et al. used radical cyclization of allenic xanthate to construct the Azadirachtin skeleton.[12]

An important, yet poorly understood, aspect of the radical cyclization of allenes is the regiochemistry of the reaction. Importantly, Baldwin's rules[13] cannot be readily applied to the prediction of radical cyclization of allenes because instead of two, there are three carbon atoms in the allene group that can be the site of ring closure. Crandall et al. have systematically studied the ring closure of some simple allenic radicals.[14] They found that two types of products, i.e., an olefinic radical product and an allylic radical product, could be generated by cyclization of the allenic radical shown in Scheme 2 with n=1–3. The olefinic radical product was seen with n=1. Alternate cyclization to the allylic radical product was observed exclusively when n=2. On the other

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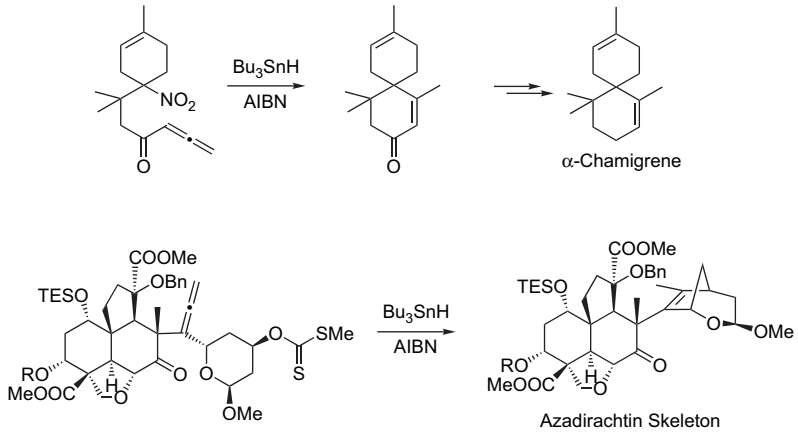
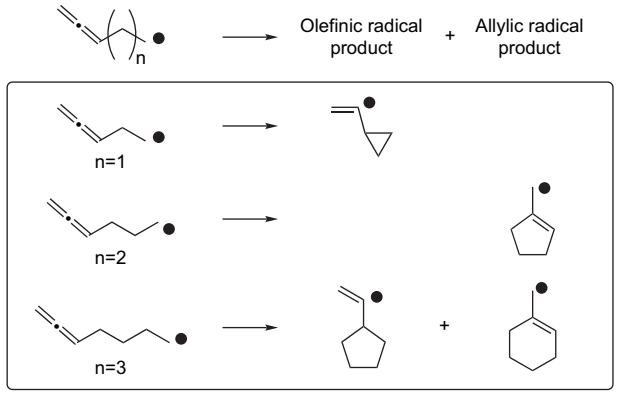


Scheme 1.

hand, both cyclization modes operated for the n=3 case. To make the situation even more complicated, Crandall et al. further found that some radical-stabilizing substituents on the allene moiety could markedly affect the regiochemistry of the cyclization.



Scheme 2.

The intriguing regiochemistry problems of the allenic radical cyclizations have not been examined by any theoretical method.[15] In an effort to bridge this gap, we recently performed systematic high-level theoretical calculations to investigate the regiochemistry of radical cyclization of a variety of allenes. The following questions were asked: (1) can the theoretical calculations reproduce the experimental observations reported by Crandall et al.? (2) What driving forces bring about the observed regioselectivity? (3) How will the substituents affect the regiochemistry of radical cyclization of allenes? (4) What is the regioselectivity in the cyclization of an oxygen- or nitrogen-centered radical to an allene? The answers to these interesting questions are of significant value to the rational design of synthetic routes involving allenic radical cyclizations.

2. Computational methodology

Ab initio calculations were performed with the Gaussian 03 suite of programs.[16] Geometry optimizations were performed using the UB3LYP/6-31G(d) method without any constraint. Frequency calculations were carried out at the UB3LYP/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. In all instances, transition-state structures gave one significant imaginary frequency, while no imaginary frequencies were observed for the minimum-energy species.

Single-point energies were calculated using a two-layer ONIOM method,[17] namely, ONIOM(QCISD(T)/6-311+G(2df,2p):UB3LYP/6-311+G(2df,2p)). The inner layer treated at the 'high' level (i.e., QCISD(T)/6-311+G(2df,2p) comprises five heavy atoms and their hydrogens, while the whole system was treated at the 'low' level (i.e., UB3LYP/6-311+G(2df,2p)) (Chart 1). Corrections of the energy to 298 K were made from the frequency calculations, including zero point energy corrections. It is worth noting that the reliability of using the ONIOM method to handle radical cyclization reactions has been demonstrated in our previous studies.[18]

3. Results and discussion

3.1. Unsubstituted allenic radicals

3.1.1. Penta-3,4-dien-1-yl radical. Radical cyclization of an unsubstituted penta-3,4-dien-1-yl radical can produce three possible products (Fig. 1). The activation free energies for the three-, four-, and five-membered ring products are +15.0, +17.9, and +19.5 kcal/mol, whereas the reaction free energies for the same three products are +4.3, −16.6, and −11.3 kcal/mol, respectively. It is evident that the five-membered ring product is neither kinetically nor thermodynamically favored as compared to the four-membered ring product. On the other hand, the comparison between the three- and the four-membered ring products is less obvious. The three-membered ring product has a lower activation free energy than the four-membered one.

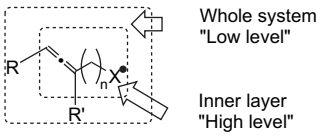


Chart 1.

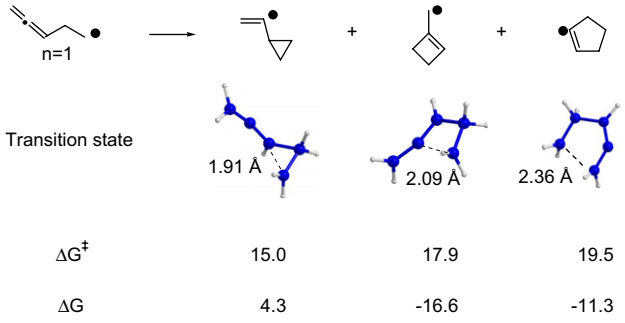


Figure 1. Radical cyclization of an unsubstituted penta-3,4-dien-1-yl radical (unit: kcal/mol).

To further elucidate the regioselectivity for the three- versus four-membered ring products, we consider it to be necessary to calculate the rate of hydrogen abstraction between the radical intermediates and the tin hydride (which constitutes the last step in the radical cyclization reaction). To simplify the calculation, we use trimethylstannane to represent tributylstannane in the realistic experiments. As shown in Figure 2, the hydrogen abstraction reaction between the starting material (i.e., the penta-3,4-dien-1-yl radical) and the trimethylstannane has a free energy barrier of +13.8 kcal/mol. In comparison, the hydrogen abstraction reaction between the three-membered ring radical intermediate and the trimethylstannane has a free energy barrier of +11.6 kcal/mol. The fact that the latter has a lower hydrogen abstraction barrier can be readily explained as the difference between a vinyl radical (which is more reactive) and an alkyl radical.

It should be noted that the activation free energy for the cyclization from the starting material to the four-membered ring intermediate is +17.9 kcal/mol. Evidently, this value is higher than both +13.8 (the reduction of the starting material) and +15.0 kcal/mol (the activation free energy for the cyclization to the three-membered ring intermediate) by over +2.9 kcal/mol. Meanwhile, the same value is also higher than the sum of +4.3 (the free energy difference between the starting material and the three-membered ring intermediate) and +11.6 kcal/mol (the free energy barrier for the hydrogen abstraction of the three-membered ring intermediate) by 2.0 kcal/mol. Thus, the formation of the four-membered ring product should be negligible as compared to the formation of the three-membered ring product.

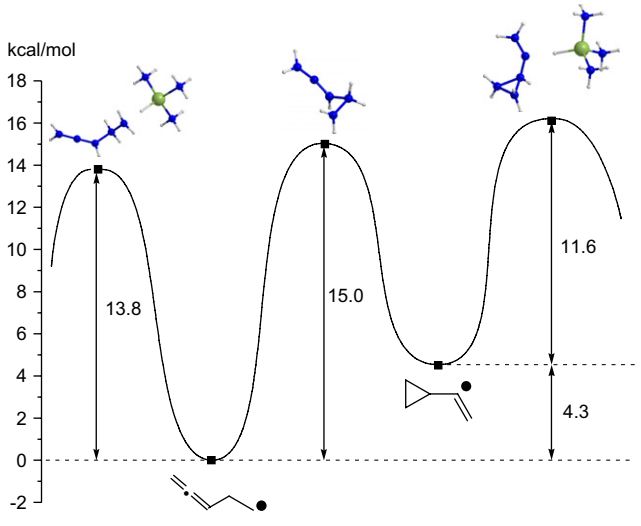
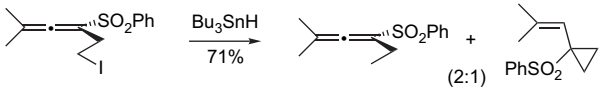


Figure 2. Free energy profiles in the hydrogen abstraction reactions.

Noteworthy, for the radical cyclization of the allene shown in Scheme 3, Crandall et al. reported a ratio of 2:1 for the reduction product versus the cyclized product.[14] This observation indicates that the major product of this reaction should be diene from direct reduction. The cyclization of a penta-3,4-dien-1-yl radical should be able to provide some vinylcyclopropane via the 3-*exo* cyclization mode.



Scheme 3.

3.1.2. Hexa-4,5-dien-1-yl radical. Radical cyclization of an unsubstituted hexa-4,5-dien-1-yl radical can also produce three possible products (Fig. 3). The activation free energies for the four-, five-, and six-membered ring products are +19.6, +8.8, and +14.0 kcal/mol, whereas the reaction free energies for the same three products are+3.7, −39.8, and −19.4 kcal/mol, respectively. Noteworthy, two transition-state structures have been found for the formation of four-membered ring product, which display either a boat-like or chair-like conformation. The energies of these two transition states are differed by 1.6 kcal/mol. Comparing the activation and reaction free energies, we can easily conclude that the formation of the five-membered ring product is much more favorable than the other two possibilities both kinetically and thermodynamically. This result is in excellent agreement with Crandall's experimental finding (see Scheme 2).[14]

3.1.3. Hepta-5,6-dien-1-yl radical. Finally, radical cyclization of an unsubstituted hepta-5,6-dien-1-yl radical can produce three possible products (Fig. 4). The activation free energies for the five-, six-, and seven-membered ring products are +10.7, +11.6, and +13.2 kcal/mol, whereas the reaction free energies for the same three products are −15.8, −42.7, and −17.6 kcal/mol, respectively. For the formation of five- and six-membered ring products, we have found two different transition states that display either a boat-like or

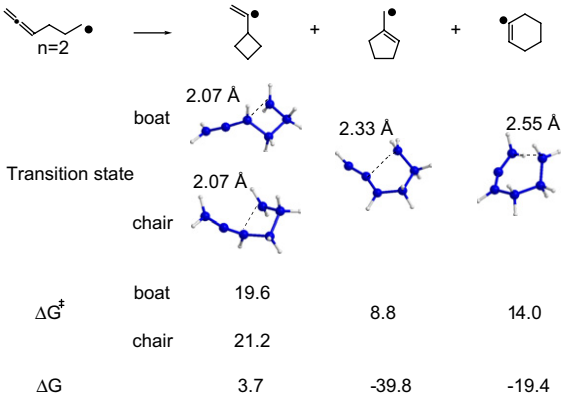


Figure 3. Radical cyclization of an unsubstituted hexa-4,5-dien-1-yl radical (unit: kcal/mol).

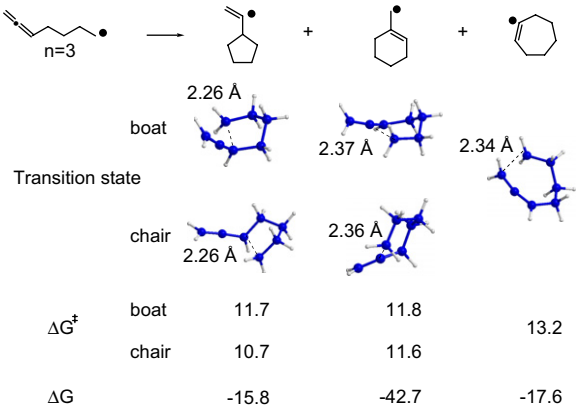


Figure 4. Radical cyclization of an unsubstituted hepta-5,6-dien-1-yl radical (unit: kcal/mol).

a chair-like conformation. The energies of these different conformations are different by less than 1 kcal/mol.

Comparing the activation and reaction free energies, we firstly rule out the formation of the seven-membered ring product, because its activation free energy is 1.6 (or 2.5) kcal/mol higher than the other two possibilities. This magnitude of activation energy difference means a selectivity higher than 10:1. On the other hand, the activation free energy for the six-membered ring product is only 0.9 kcal/mol higher than the five-membered ring case. Mathematically this means a selectivity of 82:18 in the cyclization reaction or in other words, both the five- and the six-membered ring products should be detectable in the experiment. Compared to the results shown in Scheme 2, it is evident that our calculation is again in excellent agreement with Crandall's experimental observation.[14]

3.2. Driving forces for the regioselectivity

Evidently, the regioselectivity observed for the ring closure reactions of allenic radicals cannot be interpreted using Baldwin's rules. For instance, the formation of both five- and six-membered ring products in the cyclization of hepta-5,6-dien-1-yl radical is not consistent with the usual 5-*exo* versus 6-*endo* principle. It appears that a balance between the stereoelectronic factors in the transition state and the thermodynamic contributions (i.e., allylic radical formation) must be considered. Thus, to further elucidate the mechanism for the substituent effects, we decided to use Marcus theory[19] to separate the intrinsic and thermodynamic contributions to the observed activation free energies.

Briefly, Marcus theory can be described using the following equation:

$$\Delta G^{\neq} = \Delta G^{\neq}_{\text{intrin}} + \frac{1}{2}\Delta G_{\text{R}} + \frac{(\Delta G_{\text{R}})^2}{16\Delta G^{\neq}_0} = \Delta G^{\neq}_{\text{intrin}} + \Delta G^{\neq}_{\text{therm}} \quad (1)$$

where the activation free energy ($\Delta G^{\neq}$) of a nondegenerate reaction is the sum of the intrinsic barrier ($\Delta G^{\neq}_{\text{intrin}}$) and the thermodynamic contribution ($\Delta G^{\neq}_{\text{therm}}$). The intrinsic barrier corresponds to a hypothetical thermoneutral process. The thermodynamic contribution is an estimate of the change in the activation energy due to the variation of reaction thermodynamics, which is based on an assumption that the hypersurface of potential energy behaves like two overlapping parabolas representing reactant and product energies. Originally, Marcus theory was developed for the electron-transfer reactions. More recently, Marcus theory has also been successfully applied to a wide array of organic reactions including radical cyclization.[20]

Using Marcus theory it is straightforward to calculate the intrinsic barrier ($\Delta G^{\neq}_{\text{intrin}}$):

$$\Delta G^{\neq}_{\text{intrin}} = \frac{1}{2}\left[\Delta G^{\neq} - \frac{1}{2}\Delta G_{\text{R}} + \sqrt{(\Delta G^{\neq})^2 - \Delta G^{\neq}\Delta G_{\text{R}}}\right] \quad (2)$$

After calculating the intrinsic barrier, the thermodynamic contribution to the overall activation energy can be calculated using the following equation:

$$\Delta G^{\neq}_{\text{therm}} = \Delta G^{\neq} - \Delta G^{\neq}_{\text{intrin}} \quad (3)$$

Marcus theory allows us to separate the intrinsic contributions under a thermoneutral condition (for example, steric hindrance in the transition state) from the thermodynamic reasons (i.e., reactivity changes because the reaction is more exothermic or endothermic).[20]

For the cyclization of allenes, Marcus theory analysis results are shown in Figure 5 (note: from now on, we exclude the possibility for the formation of the largest possible ring product shown in Figs. 1, 3, and 4). Comparing the results for the penta-3,4-dien-1-yl (n=1), hexa-4,5-dien-1-yl (n=2), and hepta-5,6-dien-1-yl (n=3) radicals, we find that the formation of an olefinic radical product always has a lower intrinsic energy barrier ($\Delta G^{\neq}_{\text{intrin}}$) than the formation of an allylic radical product. On the other hand, the formation of an olefinic radical product is always much less favorable than the formation of an allylic radical product in the thermodynamic term ($\Delta G^{\neq}_{\text{therm}}$).

For the penta-3,4-dien-1-yl radical (n=1), the intrinsic term favors the olefinic radical by 12.7 kcal/mol while the thermodynamic term favors the allylic radical by 9.8 kcal/mol. The overall effect is that the olefinic radical product dominates. For the hexa-4,5-dien-1-yl radical (n=2), the intrinsic term favors the olefinic radical by 7.0 kcal/mol while the thermodynamic term favors the allylic radical by 17.8 kcal/mol. The overall effect is that the allylic radical product dominates. Finally, for the hepta-5,6-dien-1-yl radical (n=3), the intrinsic term favors the olefinic radical by 11.3 kcal/mol while the thermodynamic term favors the allylic radical by 10.4 kcal/mol. The overall effect is that both the olefinic and the allylic radical products should be formed to a detectable extent.

3.3. Effects of substituents on regioselectivity

Crandall et al. previously claimed, with limited experimental results, that some radical-stabilizing substituents on the

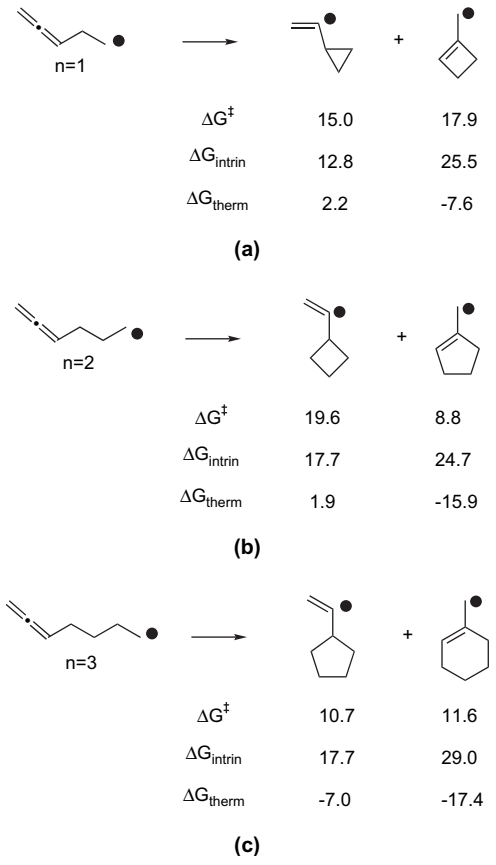


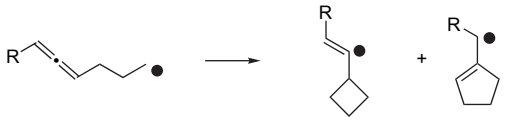
Figure 5. Marcus theory analysis for the cyclization of allenes (unit: kcal/mol).

allene moiety could markedly affect the regiochemistry of the cyclization.[14] Here, we re-examine the effects of substituents on the regioselectivity in allenyl radical cyclization using more systematic data. As shown in the above sections, the cyclization of a penta-3,4-dien-1-yl radical tends to give penta-3,4-diene as the major product through direct reduction. Because this reduction is not a synthetically interesting transformation, we decided to focus on the cyclization of substituted hexa-4,5-dien-1-yl and hepta-5,6-dien-1-yl radicals.

As for substituted hexa-4,5-dien-1-yl radicals, our results show that substitution at C6 changes the free energy barrier for the formation of the olefinic radical by less than 2 kcal/mol (Table 1). Substitution at C6 also slightly reduces the free energy barrier for the formation of the allylic radical by 1.1–3.8 kcal/mol. The overall effect is that the olefinic radical formation is always more difficult than the allylic radical formation by over 10 kcal/mol in the free energy barrier. A similar effect is observed for the substitution at C4 (Table 2). Thus, substituted hexa-4,5-dien-1-yl radicals always cyclize to the allylic radical products.

On the other hand, for substituted hepta-5,6-dien-1-yl radicals our results show that the substituents markedly affect the regiochemistry of the cyclization. In the case of C7-substitution (Table 3), the OCH_3 and Cl groups increase the olefinic/allylic selectivity from 82:18 to 95:5. The Ph group reduces the olefinic/allylic selectivity to 66:34.

Table 1. Cyclization of hexa-4,5-dien-1-yl radicals with a substituent at C6



R	$\Delta G^{\neq}$ (kcal/mol)	
	Olefinic radical	Allylic radical
H	19.6	8.8
Ph	21.4	6.6
OCH_3	18.2	7.7
Cl	20.2	7.4
CN	18.5	5.0
COMe	19.1	6.0

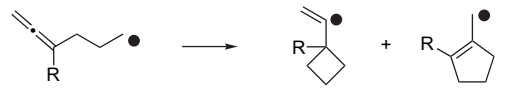
More significantly, the CN and COMe groups reverse the selectivity to 6:94 and 16:84, favoring the allylic radical products. Such a dramatic variation of regioselectivity may be attributed to the hyperconjugation interactions between the allylic radical and the *C*7-substituent. Nonetheless, the OCH_3 and Cl substituents do not favor the allylic radical products although they are radical-stabilizing groups.[21]

For *C*5-substituted hepta-5,6-dien-1-yl radicals, our results indicate that all the substituents reverse the regioselectivity (Table 4). The OCH_3 and Cl groups exhibit olefinic/allylic selectivity of 13:87 and 2:98, whereas in the presence of the Ph, CN, and COMe groups the allylic radicals become the only observable products. Evidently, the favorable hyperconjugation interaction between the *C*5-substituent and the allylic radical is the driving force for the reverse of regioselectivity.

3.4. Cyclization of nitrogen and oxygen radicals onto allenes

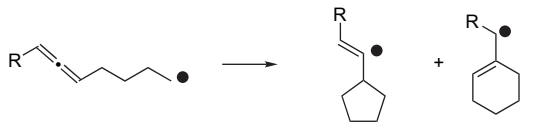
In addition to carbon-centered radicals, nitrogen- and oxygen-centered radicals can also cyclize onto olefins intramolecularly, which provides a highly interesting approach for the synthesis of heterocycles.[22] Efficient cyclization of nitrogen- and oxygen-centered radicals with allenes can be incorporated into effective processes for constructing heterocycles having unsaturated α-substituents. Since the radicals can attack the proximal, central, and terminal carbon atom of the allene, the regiochemistry of the cyclization process is attractive.

Table 2. Cyclization of hexa-4,5-dien-1-yl radicals with a substituent at C4



R	$\Delta G^{\neq}$ (kcal/mol)	
	Olefinic radical	Allylic radical
H	19.6	8.8
Ph	23.2	8.5
OCH_3	25.7	8.7
Cl	22.6	8.6
CN	23.1	8.0
COMe	22.3	9.5

Table 3. Cyclization of hepta-5,6-dien-1-yl radicals with a substituent at C7

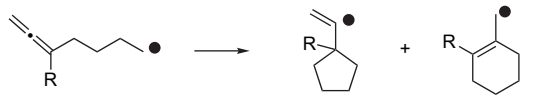


R	$\Delta G^{\neq}$ (kcal/mol)		Selectivity (olefinic/allylic)
	Olefinic radical	Allylic radical	
H	10.7	11.6	82:18
Ph	11.0	11.4	66:34
OCH_3	10.1	11.8	95:5
Cl	9.7	11.4	95:5
CN	9.6	8.0	6:94
COMe	10.1	9.1	16:84

As shown in the above sections, the cyclization of nitrogen- and oxygen-centered radicals can also produce three possible products. Here, we focus on synthetically significant processes for creation of four-, five-, and six-membered heterocycles (Fig. 6). For *N*-methylpenta-3,4-dien-1-aminyl radical (n=2), the activation free energies for the four- and five-membered ring products are +26.1 and +14.5 kcal/mol, whereas the reaction free energies for the same two products are +13.7 and −31.5 kcal/mol, respectively. It is obvious that the formation of the five-membered ring product is much more favorable both kinetically and thermodynamically. Similar results can be concluded by comparing the activation and reaction free energies of the cyclization of penta-3,4-dien-1-oxyl radical (n=2).

For *N*-methylhexa-4,5-dien-1-aminyl radical (n=3), the activation free energies for the five- and six-membered ring products are +15.8 and +17.4 kcal/mol, whereas the reaction free energies for the same two products are −4.1 and −32.3 kcal/mol, respectively. For the formation of five- and six-membered ring products, we have found two different transition states that display either a boat-like or chair-like conformation. The energies of these different conformations are different by less than 1.6 kcal/mol. Comparing the activation and reaction free energies, we noticed that the activation free energy for the six-membered ring product is only 1.6 kcal/mol higher than the five-membered ring case. Mathematically this means a selectivity of 94:6 in the cyclization reaction, both the five- and the six-membered ring products should be detectable in the experiment. Similar results can also be concluded from the cyclization of hexa-4,5-dien-1-oxyl radical (n=3).

Table 4. Cyclization of hepta-5,6-dien-1-yl radicals with a substituent at C5



R	$\Delta G^{\neq}$ (kcal/mol)		Selectivity (olefinic/allylic)
	Olefinic radical	Allylic radical	
H	10.7	11.6	82:18
Ph	15.1	9.5	0:100
OCH_3	13.8	12.7	13:87
Cl	13.3	11.0	2:98
CN	13.4	8.9	0:100
COMe	13.8	9.3	0:100

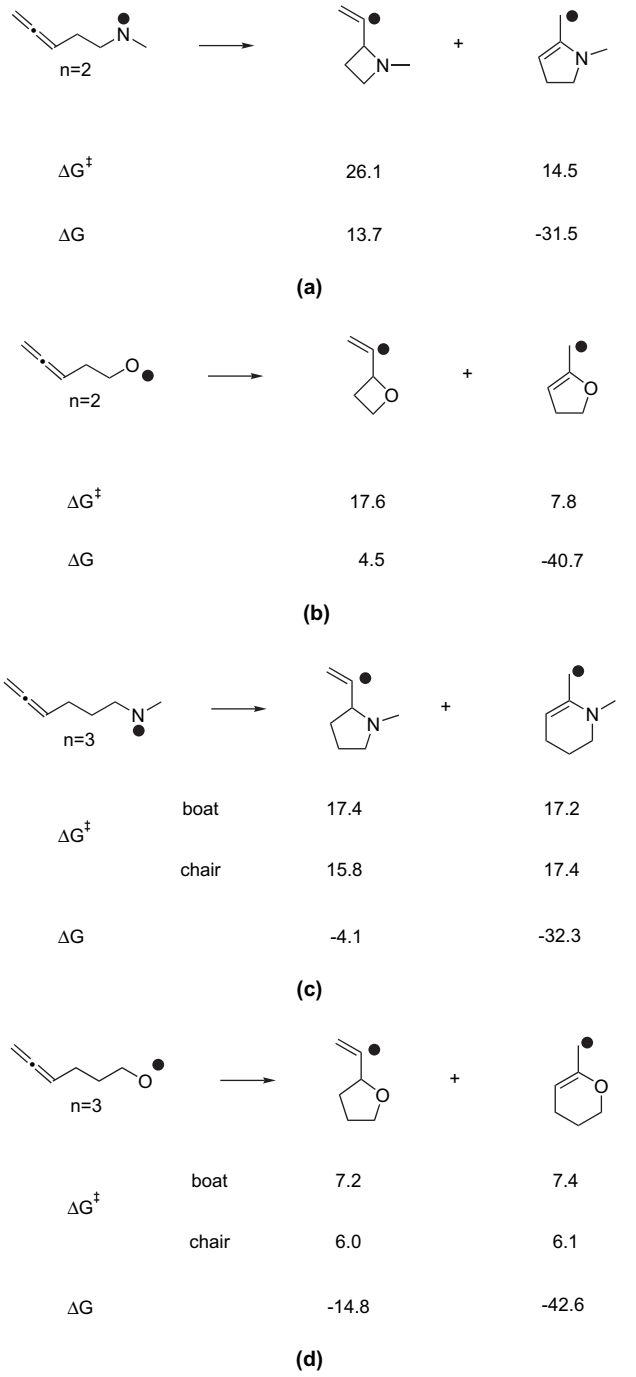


Figure 6. Cyclization of nitrogen and oxygen radicals onto allene (unit: kcal/mol).

4. Conclusions

Radical cyclization of allenes, a scantily studied process, is potentially a powerful method for the synthesis of unsaturated carbocycles and heterocycles. Here, we utilize the ONIOM(QCISD(T)/6-311+G(2df,2p):UB3LYP/6-311+G(2df,2p)) method to systematically study the cyclization of various allenyl radicals. The following results are obtained through the study.

It is found that the theoretical results at the ONIOM level are in good agreement with all the available experimental data,

which suggests the possibility to rationally design the synthetic route involving allenic radical cyclizations. For the cyclization of penta-3,4-dien-1-yl radicals the major product is penta-1,2-diene from direct reduction whereas a small amount of vinylcyclopropane may also be produced. For the cyclization of hexa-4,5-dien-1-yl radicals the major product is 1-methyl-cyclopentene. For the cyclization of hepta-5,6-dien-1-yl radicals both vinylcyclopentane and 1-methyl-cyclohexene are produced.

Marcus theory analysis indicates that the formation of an olefinic radical product always has a lower intrinsic energy barrier than the formation of an allylic radical product. On the other hand, the formation of an olefinic radical product is always much less favorable than the formation of an allylic radical product in the thermodynamic term. The observed regioselectivity is determined by the balance between the intrinsic energy barrier and the thermodynamic term.

For the cyclization of substituted hexa-4,5-dien-1-yl radicals, substitution at the allene moiety does not affect the regioselectivity where the allylic radical product is always favored. For the cyclization of hepta-5,6-dien-1-yl radicals, substitution at the allene moiety dramatically affects the regioselectivity, where some radical-stabilizing groups such as –CN and –COMe may even completely reserve the regioselectivity.

Regioselectivities of nitrogen- and oxygen-centered radical additions to allene range from complete terminal attack to exclusive central carbon addition. For both the cyclization of *N*-methylpenta-3,4-dien-1-aminyl and penta-3,4-dien-1-oxyl radical (n=2),the allylic radical resulting from radical addition to the central carbon is always favored. For the cyclization of *N*-methylhexa-4,5-dien-1-aminyl and hexa-4,5-dien-1-oxyl radicals (n=3), both five- and six-membered ring products should be produced.

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Supplementary data

The Cartesian coordinates of the optimized molecules, the calculated electronic energies, and thermal corrections to Gibbs free energies. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.004.

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