A Density Functional Theory Study of the 5-Exo Cyclization Reactions of α-Substituted 6,6-Diphenyl-5-hexenyl Radicals

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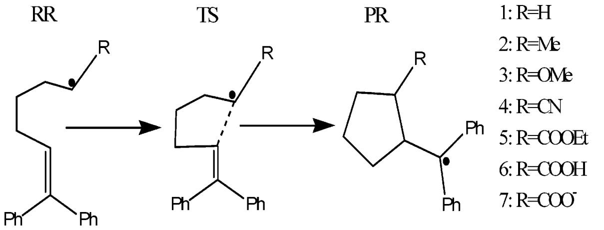

Density functional theory computations were done to study the 5-exo radical cyclization reactions of α-substituted 6,6-diphenyl-5-hexenyl radicals. The methoxy electron donor group substitution reduced the barrier to reaction by about 0.5 kcal/mol. On the other hand, the electron acceptor group substitutions (ethoxycarbonyl, carboxylic acid, carboxylate, and cyano) raised the barrier to reaction by varying amounts (0.5−2.1 kcal /mol). The entropic terms of these cyclization reactions are briefly discussed. Solvent effects on these reactions were explored by calculations that included a polarizable continuum model for the solvent. The density functional theory calculated results were found to be in good agreement with the experimental data available in the literature and help to explain some of the observed variation in these types of cyclization reactions with various substitutions. Our results also provide an explanation for why the rate constant for the carboxylate group substituted radical was found to be an order of magnitude smaller than the rate constant for those radicals with carboxylic acid and ethoxycarbonyl substitutions.

Introduction

Radical reactions have attracted increasing interest for their wide application in organic synthesis and in understanding the reaction mechanisms and kinetics involved in radical chemical reactions.[1] The kinetic effects of different substitutions on radical reactions have remained a topic of interest for a number of years since they are informative for both mechanistic work and for use in organic synthesis. 5-Exo radical cyclization reactions have been widely investigated for many years, and the absolute rate constants have been measured by indirect kinetic methods.[2] Newcomb and co-workers have directly measured the rate constants for a range of these types of cyclization reactions.[3−7] By introducing the use of a diphenyl group or so-called "reporter group", Newcomb and co-workers have precisely measured the rate constants for a number of 5-exo radical cyclization reactions.[3−7] They obtained experimental rate constants in the range of $k = (3.5-50) \times 10^6\ \mathrm{s}^{-1}$ for these kinds of cyclization reactions with different substitutions.

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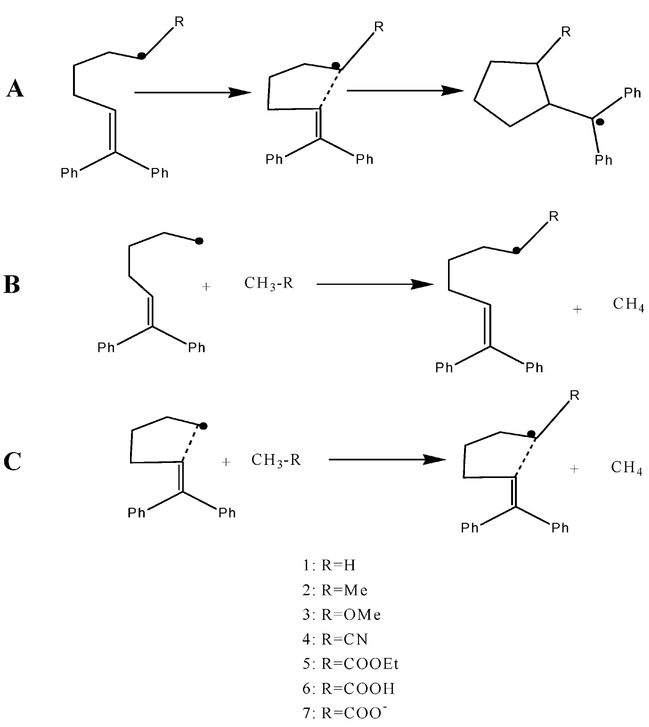
SCHEME 1



The preceding experimental results[3-7] suggest that the barriers for these reactions vary noticeably with different substitutions. In particular, the rate constant for the carboxylate group substituted radical was found to be an order of magnitude smaller than the rate constant for those radicals with carboxylic acid and ethoxycarbonyl substitutions. The density functional theory (DFT) method has been demonstrated to perform well for finding the geometry, zero-point vibrational energies, and reaction barriers for a number of radical reactions.[8-11] In this article, we report DFT calculations for seven different 5-exo radical cyclization reactions of α-substituted 6,6-diphenyl-5-hexenyl radicals at the UB3LYP/6-311+G**//UB3LYP/6-31G* level of theory. The calculated results were found to be in good agreement with the experimental results in the literature. We briefly discuss the effect of different substitution groups and some solvent effects on the 5-exo radical cyclization reactions examined here. We also discuss why the rate constant for the carboxylate group substituted radical cyclization reaction is an order of magnitude smaller than the rate constants for those radicals with carboxylic acid and ethoxycarbonyl substitutions.

Computational Methods

All of the reactant, product, and transition state geometry involved in the radical cyclization reactions (see Scheme 1 for an overview of the cyclization reactions examined) were optimized at the UB3LYP/6-31G* level of theory using the Gaussian 98 program suite.[12] Vibrational frequency calculations were performed for all of the stationary points at the UB3LYP/6-31G* level of theory to obtain corrections for the zero-point energies (ZPEs) and to ascertain that the computed transition states were first-order saddle points. Single-point energy calculations were also carried out at the UB3LYP/6-311+G** level of theory to get more accurate results. The ZPE corrections were scaled by a factor of 0.9806.[13] The Cartesian coordinates, the total energies, and selected output from the calculations for all of the calculated structures are provided in the Supporting Information. Intrinsic reaction coordination (IRC) computations were done to confirm that the transition states connected the appropriate reactants and products for the radical cyclization reactions examined in our study. Solvent effects on the reactions have also been considered by employing UB3LYP/6-31G* optimizations of the gas-phase stationary points and using a relatively simple self-consistent reaction field (SCRF)[14] method based on the polarizable continuum model (PCM) of Tomasi and co-workers.[16]

Results and Discussion

Figure 1 presents the optimized geometry obtained at the UB3LYP/6-31G* level of theory for the unsubstituted reactant radical (RR), transition states (TS), and product radical (PR) for reactions A shown in Scheme 1.

Figure 1 shows that, as the reaction goes from the radical reactant to the transition state, the distance between the C1 and C5 atoms changes substantially from 3.109 to 2.399 Å, and the bond length of C5−C6 changes from 1.351 to 1.380 Å. As the reaction goes from the transition state to the radical product, the C5−C6 double bond completes its change from a double bond to a single bond and the C1−C5 bond becomes completely formed. The reaction process can also be monitored by observation of the changes in the spin densities. In the radical reactant, the spin density mainly concentrates on the C1 atom and has a value of 1.05. In the transition state, the spin density mainly delocalizes to the C1 and C6 atoms and has values of 0.83 for the C1 atom and 0.35 for the C6 atom. In the product radical, the spin density mainly focuses on the C6 atom and has a value of 0.73. Some spin density also delocalizes into the nearby connected diphenyl group.

The optimized geometry, relative energies, and spin densities were also calculated for radical cyclization reactions with different substitutions as indicated in Scheme 1A and Table 1. We only investigated the minimum-energy conformations of the radicals, in which the substitution group and the alkyl diphenyl group are always in trans configuration. The computed optimized geometry and energies for all of the structures are given in the Supporting Information. Table 1 shows the key

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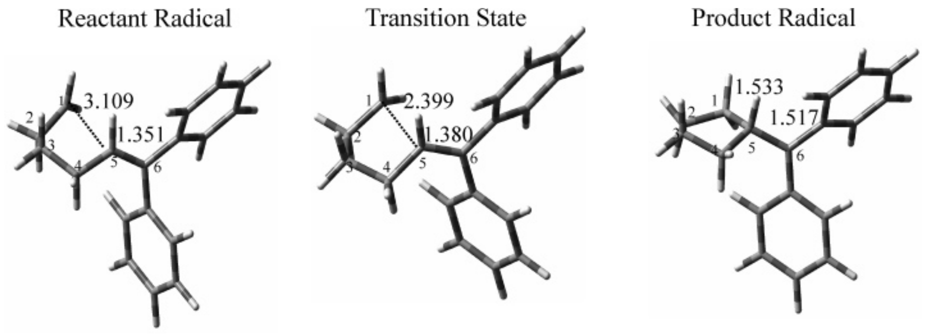
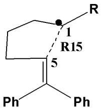


FIGURE 1. Optimized geometry of the unsubstituted reactant radical, transition state, and product radical for type A reactions shown in Scheme 1.

TABLE 1. Comparison of the Distance of the C1 and C5 in the Reactants, Transitions States, and Products for the Cyclization Reactions Investigated Here[a]

	R_{15} (Å) RR	R_{15} (Å) TS	R_{15} (Å) PR	ΔR_{15} (Å) RR	ΔR_{15} (Å) TS	ΔR_{15} (Å) PR
R = H	3.109	2.399	1.533	0	0	0
R = Me	3.107	2.375	1.586	−0.002	−0.024	0.053
R = OMe	3.164	2.367	1.592	0.055	−0.032	0.059
R = CN	3.066	2.280	1.599	−0.043	−0.119	0.066
R = CO_2Et	2.990	2.309	1.598	−0.119	−0.09	0.065
R = CO_2H	3.064	2.312	1.580	−0.045	−0.087	0.047
R = CO_2^-	2.985	2.320	1.580	−0.124	−0.079	0.047

[a] Note: RR = radical reactant, TS = transition state, and PR = product radical.

TABLE 2. Calculated Barrier and Reaction Energies at UB3LYP/6-311+G//UB3LYP/6-31G* with ZPE Corrections**

substitution	barrier (kcal/mol)	reaction energies (kcal/mol)
R = H	4.24	−19.7
R = Me	4.51	−17.4
R = OMe	3.55	−15.2
R = CN	6.33	−9.7
R = CO_2Et	4.79	−11.8
R = CO_2H	4.80	−11.3
R = CO_2^-	5.95	−14.3

TABLE 3. Energetics for the Isodesmic Reactions (with ZPE at UB3LYP/6-311+G//UB3LYP/6-31G*)**

substitutions	reactants (kcal/mol)	transition states (kcal/mol)
Me	−4.93	−4.66
OMe	−12.44	−13.13
CN	−12.45	−10.36
CO_2Et	−10.43	−9.88
CO_2H	−10.92	−10.36
CO_2^-	−17.00	−15.28

structural changes calculated for the distance of the C1 and C5 atoms in the reactant radicals, the cyclization transition states, and their product radicals for the seven reactions examined. In both the RR and TS, the distances between the C1 and C5 atoms (R_{15}) of those substitutions that have strong conjugation with the radical center (namely the cyano, ethoxycarbonyl, carbonyl acid, and carboxylate substitutions) are noticeably smaller than those of methyl or methoxy substitutions. In the PR state, the changes in the distance of the C1 and C5 atoms are relatively insensitive, varying only a small amount with values from 1.580 to 1.599 Å for all of the substitutions.

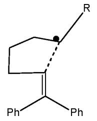
Table 2 lists the calculated data for the activation barrier and the reaction energies of the cyclization reactions studied. Compared with the unsubstituted reaction, the methoxy substitution reduces the barrier by about 0.69 kcal/mol, while the cyano, ethoxycarbonyl, carboxylic acid, and carboxylate substitutions raised the activation barrier by about 0.56, 0.55, 1.71, and 2.09 kcal/mol, respectively. The methyl group substituent slightly increases the activation barrier by about 0.27 kcal/mol. The radical cyclization reactions are expected to be exothermic since a σ-bond is formed at the expense of a π-bond. For reaction 1 without any substitution, the distance between the C1 and C5 atoms is 1.533 Å and the reaction energy is −19.7 kcal/mol. For the reactions with substitutions, the corresponding reactions are less exothermic, with the reaction energies ranging from −17.4 to −9.7 kcal/mol. For these reactions, the distance between the C5 and C6 atoms increases by about 0.047−0.066 Å. The lower values for the reaction energies can be attributed to the interaction of these substitution groups with the diphenyl group in the product radicals that also results in a larger distance between the C5 and C6 atoms.

To better understand the observed substituent effects, we also did calculations for the isodesmic reactions (reactions in which the reactants and products have the same number for each type of bonds and thus many sources of errors cancel) of the reactant radicals and the transition states. These isodesmic reactions are shown as reactions B and C in Scheme 1. Selected results from the isodesmic reaction calculations are collected in Table 3.

For the methyl substitution, the reactant radical is stabilized by 4.93 kcal/mol whereas the transition state is stabilized by 4.66 kcal/mol, resulting in a slight net increase in cyclization barrier to reaction by about 0.27 kcal/mol. The stabilization energies calculated are quite similar to those of the ring-opening reactions with a methyl substitution on the radical center.[15] We can easily attribute these stabilization energies to the hyperconjugation of the methyl group with the radical center. As the reaction goes forward toward the transition state, the electron spin density on the radical center decreases; thus, the hyperconjugation with the radical center in the transition state becomes weaker compared with that in the reactant.

For the electron donor group, methoxyl substitution, the reactant radical is stabilized by 12.44 kcal/mol whereas the transition state is stabilized by 13.13 kcal/mol, resulting in a net decrease in the barrier to reaction by 0.69 kcal/mol. The distance between the radical center (C1) and methoxyl remains unchanged, while the charges on the C1 atom increase from 0.108 to 0.135 as the reaction goes from the radical reactant to the transition state. This indicates that the methoxyl stabilization might be inductive instead of conjugative in nature.

TABLE 4. Comparison of the Calculated and the Experimental Results for the Seven Reactions A of Scheme 1

	theoretical[a] (Eyring equation)					experimental[b] (Arrhenius equation)		
	$\Delta H^{\#}$ (kcal/mol)	$\Delta H^{\#} + RT$ (kcal/mol)	$\Delta S^{\#}$ (cal/mol K)	log A	k (s^{-1})	k_{obs} (s^{-1})	E_a (kcal/mol)	log A
R = H	3.30	3.88	−9.14	10.79	2.3×10^8	3.7×10^7	3.49+/−0.14	10.17+/−0.11
R = Me	3.60	4.18	−10.59	10.48	6.7×10^7	2.2×10^7	3.12+/−0.05	9.67+/−0.04
R = OMe	2.86	3.44	−8.39	10.96	7.2×10^8	4×10^7	2.34+/−0.22	9.30+/−0.16
R = CN	5.54	6.12	−10.14	10.57	3.1×10^6			
R = CO_2Et	4.10	4.68	−9.36	10.74	5.3×10^7	5.4×10^7	2.9+/−0.4	9.9+/−0.3
R = CO_2H	4.10	4.68	−9.03	10.82	6.2×10^7	4×10^7		
R = CO_2^-	5.29	5.87	−6.24	11.43	3.3×10^7	3.5×10^6	6.5+/−0.6	11.4+/−0.4

[a] The theoretical data were calculated at the UB3LYP/6-311+G**//UB3LYP-6-31G* level of theory. [b] The experimental data are from refs 3, 7, and 17.

The electron acceptor group substitutions raise the barrier of the reactions compared with the unsubstituted reaction. The cyano substituted reactant radical is stabilized by 12.45 kcal/mol, whereas the transition state is stabilized by 10.36 kcal/mol, resulting in a net increase 2.09 kcal/mol in the barrier to reaction. The effect of the cyano substituent can be attributed to the strong conjugation of the cyano moiety with the radical center. As the reaction goes toward the transition state, the electron spin density on the radical center decreases from 0.827 to 0.572; thus, the conjugation with the radical center in the transition state becomes weaker compared with that in the reactant radical. The different conjugation can also be observed from the changes in the distance of the C1−cyano bond, which increases from 1.392 to 1.413 Å as the reaction goes from the reactant to the transition state.

It is intriguing to compare the isodesmic reactions for the ethoxycarbonyl, carboxylic acid, and carboxylate substitutions. All three of these substitutions result in a net increase in the barrier to reaction. The ethoxycarbonyl and carboxylic acid substitutions stabilize the reactant radical by 10.43 and 10.92 kcal/mol, respectively, and stabilize the transition state by 9.88 and 10.36 kcal/mol, respectively. This results in a net increase in the barrier to reaction of 0.55 and 0.56 kcal/mol, respectively. As for the carboxylate substitution, the reactant radical is stabilized by 17.0 kcal/mol while the transition state is stabilized by 15.28 kcal/mol, resulting in a net increase in the barrier to reaction of 1.71 kcal/mol. This increase in the barrier to reaction for the carboxylate substitution is noticeably larger than that for the ethoxycarbonyl and carboxylic acid substitutions. The kinetic effects on the cyclization reactions were examined by considering the stabilization energy of the substitution groups with the radical center. It is expected that a more effective delocalization of the reactions will lead to a higher activation barrier. For the ethoxycarbonyl and the carboxylic acid substitutions, the electron density changes in the radical center C1 are 0.261 and 0.262 from reactant radical to transition state, respectively. For the carboxylate substitution, the electron density change in the radical center on C1 is 0.569, and this makes the net increase in the activation barrier somewhat larger than those of the ethoxycarbonyl and carboxylic acid substitutions.

To gain insight into these reactions, we calculated the kinetics data for reaction A in Scheme 1. The theoretical kinetics data were based on the Eyring equation, while the experimental data available were based on the Arrhenius equation. Therefore, for accurate comparison, we need to deduce the relationship of the parameters between two equations.

$$k = k_B T/h \times \exp(\Delta S^{\#}/R) \times \exp(-\Delta H^{\#}/RT) \quad \text{(Eyring equation)}$$

$$k = A \exp(-E_a/RT) \quad \text{(Arrhenius equation)}$$

From the above two equations, we can easily obtain the following expressions:

$$E_a = \Delta H^{\#} + RT \qquad A = kT/h \times e \times e^{\Delta S^{\#}/R}$$

Table 4 lists a comparison of the calculated and experimental data for the cyclization reactions of interest. At first sight, it is somewhat surprising that the rate constants calculated in the gas phase using a modest level of theory match reasonably well with the experimental results. Further investigation of the kinetics data shows the theoretical calculations overestimate the activation barriers by about 0.4−1.7 kcal/mol, while the activation entropy was underestimated by about 2−8 cal/mol K compared with the experimental data in most cases. The underestimation of the entropic term contribution to the activation free energy ($\Delta G^{\#}$) is about −0.6 to −2.4 kcal/mol at room temperature. For the carboxylate substitution, the calculated activation barrier is underestimated by about 0.63 kcal/mol and the activation entropy calculated is in excellent agreement with the experimental data. We will further discuss the reactions of the three carbonyl-containing substitutions in the next section.

Radical cyclization reactions for the carboxylate substitution are thought to be important for studies of molecular rearrangements catalyzed by coenzyme B_{12}-dependent enzymes because the radical anion produced closely resembles the reactive species in nature.[17] Further investigation of the kinetics data for these three reactions shows that the activation entropy for the carboxylate substitution is −6.24 cal/mol K, which contributes 1.83 kcal/mol to the activation free energy at room temperature. For the ethoxycarbonyl and carboxylic acid substitutions, the activation entropies are −9.36 and −9.03 cal/mol K, respectively, which contribute 2.74 and 2.65 kcal/mol, respectively, to the activation free energy at room temperature. The more favorable entropic terms for the reaction of the carboxylate substitution compared with those of the other two reactions are in agreement with the expectation of Newcomb and co-

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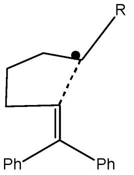
[17] Miranda, N.; Daublain, P.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2003**, *125*, 5260.

TABLE 5. Comparison of the Kinetic Data Calculated for the Gas-Phase and Solution-Phase Reactions to the Corresponding Solution-Phase Experimental Results



	theoretical				experimental[a]	
	$\Delta G^{\#}$ (gas phase)	$\Delta G^{\#}$ (THF)	$\Delta G^{\#}$ (ACN)	k (ACN) (s^{-1})	$\Delta G^{\#}$	k_{obs} (s^{-1})
R = CO_2Et	6.84	6.29	6.26	1.4×10^8	6.78	5.4×10^7
R = CO_2H	6.75	6.43	6.58	8.3×10^7	6.95	4×10^7
R = CO_2^-	7.11	6.69	7.83	9.9×10^6	8.37	3.5×10^6

[a] From ref 17.

workers.[17] Their experimental results also show that even though there is a more favorable entropic term for the reaction of the carboxylate substitution, the activation enthalpy factor contributes much more to the activation free energy, which in turn causes the rate constant for the carboxylate substitution reaction to still be 1 order of magnitude lower than those of the other two reactions. The negative charge in the radical anion was thought to be a critically important feature.[17] Our present theoretical calculations also show that the rate constant of the carboxylate case is slower but not too much more than that of the other two reactions. Considering the sensitivity to polar solvents for a reaction involving the carboxylate substitution that possesses a negative charge, the effects of the solvent were introduced to the cyclization reaction comparison purposes. The solvent effects on these three reactions were investigated using the UB3LYP/6-31G* optimizations of the gas-phase stationary points and then using the SCRF method based on a PCM model developed by Tomasi and co-workers.[16] Because the solvent used in the experimental work was acetonitrile (ACN), we used its dielectric constant of $\epsilon = 36.64$ for the calculations in acetonitrile solvent. We also did calculations for the relatively low polar solvent tetrahydrofuran (THF) with a dielectric constant of $\epsilon = 7.58$ for comparison purposes to estimate the importance of a large change in the solvents dielectric property.

Inspection of Table 5 shows that the activation free energy in both THF and ACN decreases compared with that in the gas phase. However, the difference of the free energy calculated in the THF solvent and the ACN solvent is very small, which means the different extent of the solvent polarity imposes nearly the same influence on the reactivity of the ethoxycarbonyl and carboxylic acid substitutions. In contrast, for the carboxylate substitution, the solvent polarity has a different effect on the reaction: the activation free energy decreases 0.41 kcal/mol in THF while it increases 0.7 kcal/mol in ACN compared with the gas-phase values, and this contributes to a further reduction in the rate constant. This contrasting solvent effect on the reaction of the carboxylate substitution helps confirm the speculation that the radical anionic feature is critically important for the much lower rate constant. In agreement with the experimental results, the calculated rate constant for carboxylate in ACN is 9.9×10^6 s^{-1}, nearly 1 order of magnitude lower than the 1.4×10^8 s^{-1} and 8.3×10^7 s^{-1} rate constants for the reactions of the ethoxycarbonyl and carboxylic acid substitutions.

Conclusions

The 5-exo radical cyclization reactions of α-substituted 6,6-diphenyl-5-hexenyl radicals have been investigated using DFT calculations at the UB3LYP/6-311+G**//UB3LYP/6-31G* level of theory. The methoxy substitution reduced the barrier by 0.5 kcal/mol, and the methyl substitution slightly raised the barrier by 0.3 kcal/mol. For the electron acceptor substitutions, such as ethoxycarbonyl, carboxylic acid, carboxylate, and cyano substitutions, the barriers to reaction were raised by 0.55, 0.56, 1.71, and 2.1 kcal /mol, respectively. The solvent effects on the reaction barriers were considered through the use of the SCRF method based on a PCM model. The calculated kinetics data are in good agreement with the available experimental results. Investigation of the reactions of carbonyl-containing substitutions in THF and ACN solvents shows that the radical anionic feature of the carboxylate group contributes to the further reduction of its reaction rate constant, which is consistent with the experimental results reported by Newcomb and co-workers in ref 17.

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Supporting Information Available: Cartesian coordinates, total energies and vibrational zero-point energies for the reactants, transition states and products for the reactions investigated. This material is available free of charge via the Internet at http://pubs.acs.org.

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