9-1-2013

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International Journal of Organic Chemistry, 2013, 3, 169-175
http://dx.doi.org/10.4236/ijoc.2013.33021 Published Online September 2013 (http://www.scirp.org/journal/ijoc)

Computational Study of the Cyclization of 5-Hexenyl, 3-Oxa-5-Hexenyl and 4-Oxa-5-Hexenyl Radicals

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Received May 2, 2013; revised June 5, 2013; accepted June 19, 2013

ABSTRACT

The intramolecular cyclization of 5-hexenyl radicals continues to be an important synthetic method for the construction of five-membered rings. The synthetic utility arises from the high degree of regioselectivity to give predominantly cyclopentyl products in high yield under mild conditions. Recently we reported product cyclization studies on 4-oxa perturbed 5-hexenyl radical. In this paper, we report our results from a computational study (UB3LYP and UCCSD (T)) of the cyclization of a series of 5-hexenyl and 3- and 4-oxa-5-hexenyl radicals. Three highly conserved cyclization transitions states (*exo*-chair, *exo*-boat and *endo*-chair) were located for 10 acyclic radicals. Activation energies were calculated for the three modes of cyclization for each radical. Calculated values for the *exo*/*endo* cyclization ratios had a high level of agreement with experiment and predictions were offered for two cases that have not been experimentally tested. The increased percentage of *exo*-cyclization with 3- and 4-oxa substitution is the result of an increase in the energy difference between the *exo*- and *endo*-chair transition states compared to the hydrocarbon systems. The decreased rate of cyclization of the 4-oxa compounds is primarily due to the stabilization of the initial acyclic radical by the vinyl ether linkage. The increase in the rate of cyclization with 3-methyl substitution is due to the increased conformational energy of the starting acyclic radical.

Keywords: Radical Cyclizations; Activation Energies; UB3LYP; UCCSD (T)

1. Introduction

Radical cyclizations continue to be extremely useful reactions for the construction of ring systems via single [1-5] and tandem cyclizations [6-9]. The utility of these reactions stems from the relatively mild reaction conditions (low to moderate temperature and neutral pH), which makes the system compatible with multiple functionalities and the predictable regioselectivity of the cyclization. The cyclization of 5-hexenyl radical based systems has been the most widely employed and studied radical ring-closure reaction. Beckwith established rules to predict the regiochemical outcome for radical cyclizations [10]. In general, these systems cyclize under kinetic control to give *exo* cyclopentyl products. This is in contrast to the intermolecular addition of radicals to alkenes, which in general add *endo* [11,12].

In the mid-1980's, Beckwith and Schiesser [13,14] and Spellmeyer and Houk [15] presented force-field molecular mechanics based models to analyze the intramolecular cyclization of radicals. These studies were quite successful in explaining the regiochemistry of the cyclizations and, in some cases, offered explanations for relative rates of the reactions. Both of these studies concluded that these exothermic cyclizations were characterized by an early transition state and that *exo* versus *endo* selectivity could be attributed to conformational and steric factors in the transition state. More recently, several groups have successfully employed DFT and/or *ab initio* methods to analyze a variety of radical cyclizations [16-19]. A few years ago, we reported a kinetic and product study on the cyclization of a series of 4-oxa-5-hexenyl radicals [20]. We found that 4-oxa substitution increased the preference for *exo* cyclization and decreased the rate of cyclization 3.7-fold compared to the related hydrocarbon 5-hexenyl radicals. In order to better understand these effects we initiated a computational study of the 4-oxa-5-hexenyl intramolecular radical cyclizations. The study was expanded to 5-hexenyl radicals and 3-oxa-5-hexenyl radicals in order to make compari-

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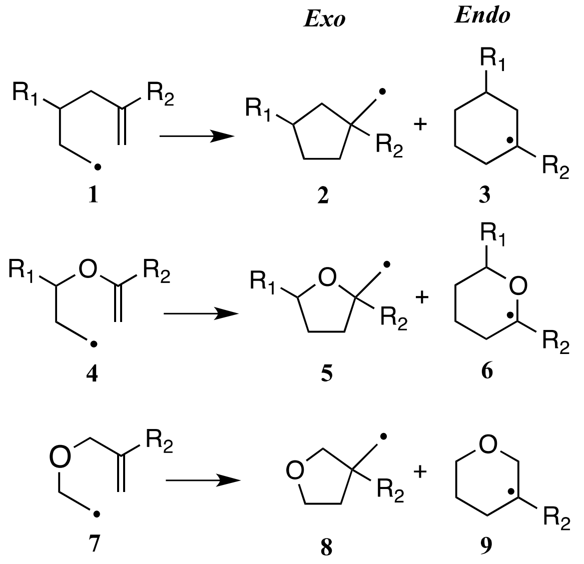
sons using the same computational models. Here we present UB3LYP and UCCSD (T) calculations on ten 5-hexenyl-based radical cyclizations (**Figure 1**).

2. Computational Methods

Global energy minima conformations of the acyclic 5-hexenyl radicals (**1**, **4**, **7**) and the cyclization products (**2**, **3**, **5**, **6**, **8**, **9**) were determined using the Spartan 08 program at UHF-3-21G level of theory [21]. These geometries were further optimized using UB3LYP/6-311+ G (d,p) in the Gaussian 03 program [22]. Transition states (**TS**) were identified at the UB3LYP/6-31G (d) level of theory and then further optimized at UB3LYP/6-311+ G (d,p). All stationary points were analyzed by calculation of their vibrational frequencies. G° values were calculated at 298 K and 1 atm. All transition states had one imaginary frequency that corresponded to the reaction coordinate for cyclization. Single-point energies were determined at the UCCSD (T)/6-31G (d) level of theory using geometries from the UB3LYP/6-31G (d) calculations: (UCCSD (T)/6-31G (d)// UB3LYP/6-31G (d)). All reported UCCSD (T) total electronic energies were not corrected for zero-point energy (ZPE).

The geometries determined at UB3LYP/6-31G (d) and the UB3LYP/6-311+G (d,p) levels of theory were very similar and, in general, differed by no more than 0.025 A in bond lengths, 0.2˚ in bond angles and 0.6˚ in dihedral angles. We found that the energy consequences of the geometries determined using the 6-31G (d) basis set vs. 6-311+G (d,p) to be insignificant when evaluated at a single level of theory: e.g. energies for UCCSD (T)/ 6-31G (d)//B3LYP/6-31G (d) were within 0.15 kcal/mol of the energies calculated using UCCSD (T)/6-31 G(d) //B3LYP/6-311+G (d,p). These small differences canceled out when we determined the activation energies ($E_a = E_{(\text{acyclic radical})} - E_{(\text{transition state})}$).



a: $R_1 = R_2 = H$
b: $R_1 = H$, $R_2 = Me$
c: $R_1 = Me$, $R_2 = H$
d: $R_1 = R_2 = Me$

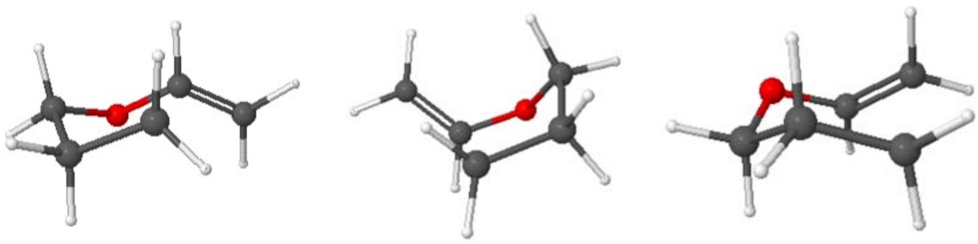
Figure 1. Cyclization of 5-hexenyl radicals.

3. Results and Discussion

3.1. Transition States

We located three transition states for cyclization of the 5-hexenyl radicals that were similar to the structures previously reported by Spellmeyer and Houk (UHF-MP2/ STO-3G) [15] for the parent system: *exo*-chair, *exo*-boat and *endo*-chair (**Figure 2**). In general, we found that transition state bond lengths and bond angles for a particular transition state (e.g. *exo*-chair) were remarkably similar across the three systems that we examined: 5-hexenyl radical **1a**, 3-oxa-5-hexenyl radical **7a** and 4-oxa-5-hexenyl radical **4a**. With the exception of the intrinsic difference of C-O vs. C-C bond lengths, the bond with the largest variation for a particular type of transition state is the partially formed new σ-bond which varies from system to system by a maximum of ~0.1 Å. Corresponding transition state bond angles are all within 3˚ of each other. The largest variations were seen in the dihedral angles (4˚ - 11.5˚) of the three 5-hexenyl transition states (**1a-TS**) compared with the respective 4-oxa-5-hexenyl transition states (**4a-TS)**. The dihedral angles for the 5-hexenyl transition states were much closer to the values found for the 3-oxa-5-hexenyl system (**7a-TS**) varying only 4˚ - 7˚.

The transition state geometries for each pathway (*exo*-chair, *exo*-boat and *endo*-chair) across the 10 radicals examined are consistent with the previously identified early nature of the transition states (**Table 1**). At the transition state, the forming σ-bond (C1-C5 or C1-C6) is long at 2.25 - 2.35 Å while the breaking double bond (C5-C6) is only slightly elongated at 1.36 - 1.38 Å (compared to 1.33 Å in the acyclic radicals). Even strongly polarizing the double bond by 4-oxa substitution has only a small effect on the position of the transition states for all cyclization modes. The *endo* transition states have shorter C5-C6 bond lengths (~1.358 Å) than the *exo* transition states (~1.368 Å) and the forming bond (C1-C6 *endo*; C1-C5 *exo*) is ~0.07 Å longer for *endo* transition states (**Table 1**). These results indicate that the *endo*-cyclization mode has a slightly earlier transition state than the *exo* mode, which is consistent with the higher exothermicity of the *endo* pathway. There are also small differences in the C1-C5 bond distances in the kinetically dominant *exo*-chair transition states: **4a** (2.255 Å) < **1a**



4a *Exo* Chair TS **4a *Exo* Boat TS** **4a *Endo* Chair TS**

Figure 2. Transition states for the cyclization of acyclic radical 4a.

Table 1. Comparison of select transition state bond distances. (Å, UB3LYP/6-31G geometries).

Radical	TS	C1-C5	C5-C6 *exo*	C5-C6 *endo*	C1-C6
1a	*Exo*-Chair	2.276	1.369	-	-
	Exo-Boat	2.276	1.370	-	-
	Endo-Chair	-	-	1.359	2.356
4a	*Exo*-Chair	2.255	1.369	-	-
	Exo-Boat	2.281	1.368	-	-
	Endo-Chair	-	-	1.357	2.334
7a	*Exo*-Chair	2.295	1.365	-	-
	Exo-Boat	2.309	1.369	-	-
	Endo-Chair	-	-	1.358	2.363
Average (StDev)		2.282 (0.018)	1.368 (0.002)	1.358 (0.001)	2.351 (0.015)

(2.276 Å) < **7a** (2.295 Å). These data suggest that *exo*-chair transition state for **7a** is earlier than the *exo*-chair transition state for **1a**, which in turn is earlier than the *exo*-chair transition state for **4a**.

This trend also follows the calculated ΔG_{rxn} (UB3LYP/6-311+G (d,p)//UB3LYP/6-31G (d)) for the *exo* mode of cyclization: **4a** (−8.6 kcal/mol) ≤ **1a** (−8.7 kcal/mol) < **7a** (−14.4 kcal/mol).

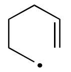
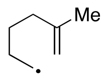
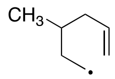
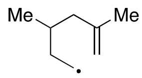
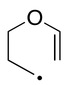
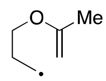
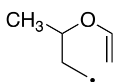
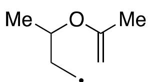
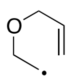
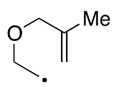
The 3-methyl substituted systems give rise to a doubling of possible transition states as the methyl group can reside in either a pseudo-equatorial or pseudo-axial position. The transition states with the 3-methyl group in the pseudo-equatorial position were found to be lower in energy than the corresponding axial isomers.

3.2. Activation Energies and *Exo*/*Endo* Product Ratios

Table 2 lists the computed activation energies (E_a) calculated as the difference in the energy of the acyclic alkenyl radical in its lowest energy conformation and the energy of the specific transition state. While the trends for the $\Delta G^{\ddagger}$ data derived from the DFT calculations mirrored the E_a's derived from the UCCSD (T) calculations, we found that the UCCSD (T) values more closely reproduced the experimental data for the *endo*/*exo* ratios of the cyclizations (*vide infra*). With this in mind, most of the discussion below will focus on the UCCSD (T) total electronic energies.

In general, we found that the *exo*-chair TS had the lowest E_a for a given cyclization with the notable exception of the 5-methyl substituted hydrocarbon radicals **1b** and **1d** where the *endo*-chair was the lowest energy pathway. In all cases 5-methyl substitution increased the E_a for the *exo*-chair TS's (1.2 - 2.9 kcal/mol) and *exo*-boat TS's (0.9 - 2.6 kcal/mol) while having a smaller effect on the *endo*-chair TS's (± 0.5 kcal/mol). The increase in E_a's of the *exo*-chair TS's are due (in part) to unfavorable 1,3-diaxial interactions with the pseudo-axial methyl group and axial ring hydrogens at C1 and C3 (for **1b** and **4b**). The 5-methyl *endo*-TS's have the pseudo axial methyl group slightly canted away from the forming cyclohexyl ring. This increases the distance of the 1,3-diaxial interactions leading to smaller changes in the *endo* chair E_a's with 5-methyl substitution. Interestingly the difference in E_a for the *exo*-chair and *endo*-chair in the hydrocarbons **1a** (1.9 kcal/mol) and **1c** (2.2 kcal/mol) is significantly smaller than the values for 3-oxa and 4-oxa compounds **4a** (5.0 kcal/mol), **4c** (5.3 kcal/mol) and **7a** (4.0 kcal/mol). In the hydrocarbon radicals, the increase in the energy of the *exo*-chair E_a pathway with 5-methyl substitution is enough to raise the *exo* pathway above the *endo* pathway. In contrast 5-methyl substitution raises the E_a of the *exo*-chair pathway to a greater extent in the 3- and 4-oxa compounds than in the hydrocarbon radicals, but this increase is not enough to overcome the large initial energy difference favoring the *exo*-cyclization pathway for 3- and 4-oxa radicals. The result is that all 3- and 4-oxa radicals are predicted to cyclize to give almost exclusively *exo* products (cyclopentanes), while 5-methyl substituted hexenyl radicals **1b**, and **1d** should cyclize to give *endo* (cyclohexane) dominated product mixtures. Previously Houk's force-field based calculations led him to explain the preference for *exo* closure for the 5-methyl-3-oxa radical **7b** on

Table 2. Calculated activation energies (kcal/mol): $E_a = E_{(acyclic\ radical)} - E_{(transition\ state)}$.

Acyclic Radical	$G^{‡}$ UB3LYP/6-311+G (d,p)			E_a UCCSD (T)/6-31G (d)		
	Exo-Chair TS	*Exo*-Boat TS	*Endo*-Chair TS	*Exo*-Chair TS	*Exo*-Boat TS	*Endo*-Chair TS
 **1a**	10.8	12.2	13.5	8.5	10.1	10.4
 **1b**	14.3	15.3	13.2	10.3	11.7	9.9
 **1c**	9.3/11.2[a]	10.6/12.8[a]	12.4/14.4[a]	8.1/9.4[a]	9.6/10.8[a]	10.3/11.5[a]
 **1d**	12.3/15.8[a]	13.3/16.0[a]	11.5/14.4[a]	9.9/13.1[a]	11.2/12.8[a]	9.8/11.8[a]
 **4a**	11.5	14.3	17.5	10.5	13.2	15.5
 **4b**	16.5	17.0	17.4	13.4	14.1	15.1
 **4c**	8.8/11.5[a]	11.6/14.0[a]	15.3/17.8[a]	8.7/10.9[a]	11.3/13.3[a]	14.0/15.9[a]
 **4d**	13.7/17.7[a]	14.1/17.6[a]	15.2/18.1[a]	11.5/15.1[a]	12.2/14.7[a]	13.6/16.2[a]
 **7a**	6.9	8.7	11.9	6.6	8.9	10.6
 **7b**	10.9	12.9	12.4	8.8	11.5	11.0

a. The first value is with the 3-methyl in the pseudo-equatorial position and the second value is with the 3-methyl in the pseudo-axial position.

decreased steric interactions for the *exo*-boat transition state with oxa versus methylene substitution at the 3-position. In contrast to our results, Houk found the *exo*-boat was the lowest energy transition state for both **7a** and **7b**.

Table 3 shows our calculated *exo*/*endo* product ratios (based on the relative E_a values) and compares these results with the available experimental data. While both the UB3LYP/6-311+G (d,p) and the UCCSD (T)/6-31G (d) calculations give excellent agreement with the experimental data, the UCCSD (T) calculations appear superior. Our calculations show that all 3-oxa and 4-oxa radicals should cyclize to give ≥95% *exo* products. The ratio for radical **4b** stands out as the only entry that does not agree with the experimental data. In this case our calculations predict ~95% *exo* product and the reported value was 62%. Given the excellent agreement in the seven other cases for which we have both calculated and experimental *endo*/*exo* data suggests that there may be an error in the experimental determined value for **4b**. In addition, we predict that the experimentally unobserved radical **1d** will cyclize to produce an almost equal mixture of *endo* and *exo* products whereas the 4-oxa radical **4d** should

Table 3. ***Exo/Endo*** **product ratios.**

Acyclic	Calculated % *Exo* UB3LYP/6-311+G (d,p)	Calculated % *Exo* UCCSD (T)/6-31G(d)	% *Exo* Exp	T (˚C)	Ref
1a	99%	96%	98%	40	[23]
1b	16%	37%	40%	40	[23]
1c	100%	98%	96%	80	[24]
1d	26%	48%	-		-
4a	100%	100%	100%	40	[20]
4b	86%	95%	62%	40	[20]
4c	100%	100%	100%	40	[20]
4d	94%	97%	-	40	-
7a	100%	100%	100%	40	[25]
7b	92%	97%	98%	40	[26]

cyclize with a strong preference for the *exo* pathway. The increased preference for *exo* cyclization with the 3- and 4-oxa substituted radicals make these systems well suited for the synthesis of tetrahydrofurans.

The *exo* cyclization of 3-methyl substituted radicals **1c** and **4c** can give either *cis* or *trans* substituted 1,3-dimethylcyclopentane **2c** and 2,5-dimethyltetrahydrofuran **5c**. The equatorial methyl *exo*-chair and the axial methyl *exo* boat transition states both lead to formation of the *cis* products, whereas the axial methyl *exo*-chair and equatorial methyl *exo* boat transition states lead to *trans* products. We calculated the *cis*/*trans* ratio by using a Boltzman distribution of ΔE_a's over the four *exo* transitions states. Our results give good-excellent agreement with the experimental data showing the strong preference for *cis* products (**Table 4**). The preference for *cis* products is driven by the dominance of the low energy equatorial methyl *exo*-chair pathway.

3.3. Activation Energies and Reaction Rates

The magnitude of the first order rate constant for cyclization is related to the lowest energy E_a. We have previously reported that 4-oxa radical **4a** cyclizes 3.7 times slower than the hydrocarbon radical **1a** [20]. We initially attributed this result to the less favorable nature of the nucleophilic radical adding to the electron rich vinyl ether double. Examination of the data from our calculations shows that the increase in the E_a's for the three cyclization pathways for **4a** compared to **1a** is chiefly due to the lower energy of the conjugated vinyl ether linkage on the reactant acyclic radical. **Table 5** compares the relative energies of isomeric radicals and their transition states. These data show that the vinyl ether linkage lowers the energy of the acyclic 4-oxa radicals **4a** and **4b** by ~6 kcal/mol compared to their isomeric 3-oxa radicals **7a** and **7b**. Radical **7a** has been reported to cyclize ~40 times faster than radical **1a** [25], which is consistent with our finding that **7a** has the lowest E_a value for all the cyclizations we have examined. It is interesting to note that all of the transition states for the cyclization of **7a** are higher in energy than the respective transition states for **4a**, but the large difference in the energy of the acyclic radicals give rise to smaller E_a's and a faster rate of cyclization for **7a**. The comparative rates of cyclization (**7a** > **1a** > **4a**) also correlate with the calculated ΔG_{rxn}'s (the more exergonic cyclizations proceed faster).

Table 4. ***Cis/Trans*** **product ratio for** ***Exo*****-cyclizations.**

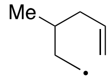
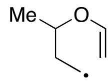
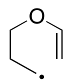
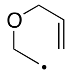
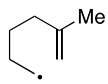
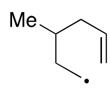
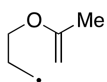
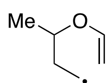
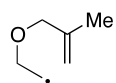
Radical	Calculated UCCSD (T) 6-31G(d) % *Cis*	Calculated UCCSD (T) 6-31G(d) % *Trans*	Experiment % *Cis*	Experiment % *Trans*	Ref
 **1c**	82	18	71	29	[24]
 **4c**	95	5	93	7	[20]

Table 5. Relative energies of hexenyl radical cyclization within isomeric compounds. (UCCSD (T)/6-31G(d), kcal/mol).

Isomers	Acyclic Radical	*Exo*-Chair TS	*Exo*-Boat TS	*Endo*-Chair TS
 **4a**	0	10.5	13.2	15.5
 **7a**	5.8	12.4	14.7	16.4
 **1b**	0	10.3	11.7	9.9
 **1c**	1.4	9.5	11.0	11.7
 **4b**	0	13.4	14.1	15.1
 **4c**	2.0	10.7	13.3	16.0
 **7b**	6.4	15.2	17.9	17.4

An interesting feature of the 3-methyl substituted compounds (**1c**, **1d**, **4c** and **4d**) is that they all have lower *E*a's for all three equatorial methyl transition states (*exo*-chair, *exo*-boat and *endo*-chair) when compared to the corresponding unmethylated compounds (e.g. **1a** vs. **1c** and **1d** vs. **1b**, etc). The equatorial 3-methyl group has little effect on the conformational energy and the geometry of the transition states. Therefore the lower E_a's are principally the result of the increased conformational energy imposed by the methyl group on the acyclic starting radicals. This is analogous to the "gem dialkyl effect" [27], but here we see a substantial effect with only one substituent. The kinetic data is consistent with these findings: **4c** cyclizes six times faster than **4a** [20]; **1c** cyclizes 3.2 times faster than **1a** [24].

4. Conclusion

Our calculations show that the UB3LYP calculated transition state geometries are highly conserved across the three 5-hexenyl radical systems. We studied and the UCCSD (T) calculated E_a's give excellent predictions for the *exo*/*endo* cyclization ratios. The increase in the preference for *exo* cyclization in the 3-oxa and 4-oxa radicals is due to the increased difference between the E_a's for the *exo*-chair and *endo*-chair pathways. The high regioselectivity of these reactions make them well suited for the synthesis of tetrahydrofurans. The observed changes in the rates of cyclization for the 4-oxa and 3-methyl substituted radicals are primarily the result of differences in the relative energies of the starting acyclic radicals. These results highlight the importance of considering the effects of structural changes on both the starting material and the transition state when evaluating changes in activation energies.

5. Acknowledgements

We thank the National Science Foundation (Grant No. 0420717, for Beowulf Computer Cluster) and Oberlin College for financial support. We also thank Matthew Elrod for helpful discussions.

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