JOC Article

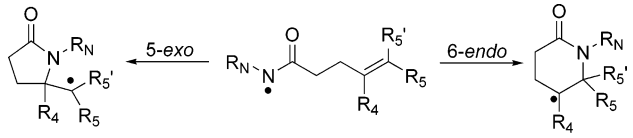
Controlling Regioselectivity in Cyclization of Unsaturated Amidyl Radicals: 5-*Exo* Versus 6-*Endo*

Yi-Yun Yu,[†] Yao Fu,*[,†] Miao Xie, Lei Liu,*[,‡] and Qing-Xiang Guo[†]

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China, and Department of Chemistry, Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology, Tsinghua University, Beijing 100084, China

fuyao@ustc.edu.cn; lliu@mail.tsinghua.edu.cn

Received January 24, 2007



R_N = H, Me, i-Pr, t-Bu, Ph

R_4 = H, Me, i-Pr, t-Bu, Ph, CN, COOEt, Cl, OMe

$R_5 = R_5'$ = H, Me, Ph, CN, COOEt, Cl

Intramolecular cyclization of an amidyl radical onto an olefin provides an appealing method for the synthesis of lactams and other nitrogen-containing heterocycles. Here we conducted the first, systematic theoretical study on the regioselectivity in the cyclization of various types of pent-4-enamidyl radicals that carried synthetically relevant substituents. It was found that the cyclization of most of the substituted pent-4-enamidyl radicals produced the 5-*exo* products (γ-lactams) almost exclusively. Marcus theory analysis showed the involvement of both the thermodynamic (stabilization of the starting double bond or the resulting radical center) and intrinsic (mainly steric effects) contributions in determining the 5-*exo* selectivity. Nonetheless, in two types of systems we found that the δ-lactams became the favored products through the 6-*endo* cyclization. In one of the systems an aromatic substituent was placed at the C4-position, whereas in the other system an electron-rich aromatic ring was incorporated into the pent-4-enamidyl radical backbone at the C2- and C3-positions. This unprecedented 6-*endo* mode of amidyl radical cyclization provided an interesting route for the preparation of mono- and bicyclic δ-lactams (pyridinones).

1. Introduction

Recently the radical-based cyclization methods have become important components of the organic synthesis repertoire.[1] The utility of this methodology is mainly due to the fast rates of radical reactions in general, the ease of five- and six-membered-ring production, and the stability of unprotected polar functional groups to the radical reaction conditions. Up to now most of the radical cyclization reactions involve carbon-centered radicals, whereas heteroatom-centered radicals have received considerably less attention.[2] This is, in part, because the precursors for the heteroatom-centered radicals are either relatively unstable or difficult to prepare. Furthermore, the factors that determine the kinetics and regioselectivity in the cyclization of heteroatom-centered radicals have not been well established.

A case for example is the intramolecular cyclization of an amidyl radical onto an olefin. This cyclization reaction was proposed many years ago to have high potential for the synthesis of lactams and other nitrogen-containing heterocycles.[3] Besides,

[†] University of Science and Technology of China.
[‡] Tsinghua University.

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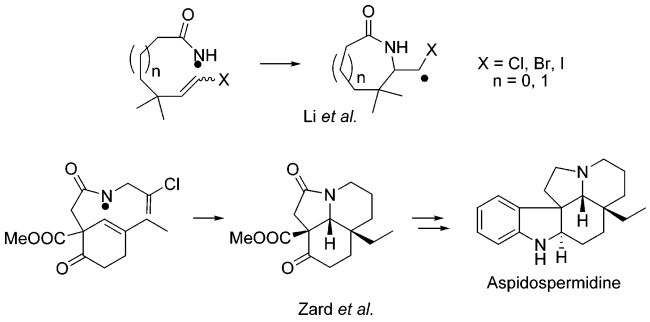
10.1021/jo070146h CCC: $37.00
Published on Web 09/21/2007

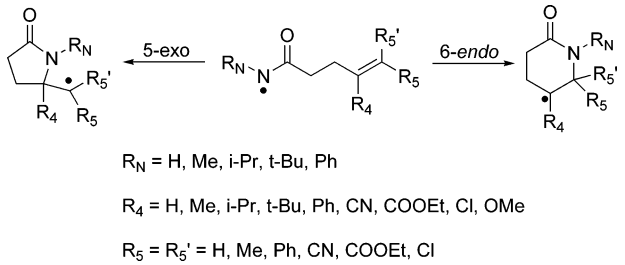
SCHEME 1



because amidyl radicals are electrophilic in character, they can provide an Umpolung reactivity that complements the nucleophilic character of nitrogen in polar reactions. Despite these attractive features, synthetic applications of the amidyl radical cyclization have remained very rare in organic chemistry. The major reason for this is that the available precursors for amidyl radicals have been limited, for many years, to some notoriously reactive species such as *N*-halo- and *N*-nitrosoamides, whose preparation precludes many functional groups in the substrate.

To solve the above problem a number of groups have attempted to develop new methods to generate the amidyl radicals under milder conditions. For example, Newcomb et al. utilized *N*-hydroxypyridine-2-thione imidate esters and *N*-acyl PTOC carbamates to produce amidyl radicals.[4] Weinreb et al. found that β-tosylethylhydroxylamine could be used as a hydroxylamine equivalent in amidyl radical-olefin cyclizations.[5] Zard et al. discovered that *N*-allylsulfonimides and *N*-(*O*-ethylthiocarbonylsulfanyl)amides could also serve as effective amidyl radical precursors.[6] More recently, Li and co-workers reported a highly important and interesting finding that *N*-acyltriazenes could be used as a tin-free and initiator-free source for amidyl radicals.[7] With these improved methods in hand, Clark et al.[8] and Li et al.[9] recently developed convenient routes to the synthesis of cyclic iminoketones or lactams via amidyl radical cyclization (Scheme 1). Zard et al. accomplished an elegant total synthesis of (±)-Aspidospermidine through a cascade radical cyclization starting from an amidyl radical.[10] Furthermore, in 2006 Newcomb et al. successfully produced

SCHEME 2



N-aryl-5,5-diphenyl-4-pentenamidyl radicals by 266 nm laser-flash photolysis of the corresponding *N*-(phenylthio) derivatives.[11]

The capability of producing amidyl radicals under mild conditions evidently will boost their importance in the field of organic synthesis. It is expected that an increasing amount of research will be directed, in the future, to the exploration of plausible cyclization reactions of diverse amidyl radicals under various chemical environments. An important subject encountered in these studies will be the regioselectivity problem, which is obviously crucial to the success of implementing the amidyl radical cyclization reactions in any target-oriented organic syntheses.[12] Unfortunately the previous experiments have not provided adequate information concerning the regioselectivity in the cyclization of amidyl radicals. In this regard we have carried out the first systematic theoretical study about the 5-*exo* versus 6-*endo* selectivity in the cyclization of pent-4-enamidyl radicals carrying various substituents (Scheme 2). Through the study we hope to gain a rational understanding about the regioselectivity in amidyl radical cyclizations. Additionally, we hope to provide systematic regioselectivity data that may help synthetic chemists design the experiments in a rational fashion.

2. Unsubstituted Pent-4-enamidyl Radical

Before discussing more complex systems, we first examine the cyclization of an unsubstituted pent-4-enamidyl radical. Four different transition state structures are successfully found for the cyclization of this compound by using the standard UB3LYP/6-31+G(d,p) method (Figure 1). Two of them correspond to the 5-*exo* cyclization mode, which are different from each other for exhibiting either a boat-like envelope conformation or a chair-like envelope conformation. Meanwhile, there are two transition state structures that can lead to the 6-*endo* cyclization product. These two transition state structures differ from each other because one of them exhibits the chair conformation, whereas the other shows the boat conformation.

The energies for all the transition state structures are calculated by using both the UCCSD(T)/6-311+G(d,p) and UB3LYP/6-31+G(d,p) methods (Figure 2). It is found that the energy level for the 5-*exo*-chair transition state is +6.9 (+5.3) kcal/mol relative to the starting material, whereas the energy level for the 5-*exo*-boat transition is +6.7 (+5.6) kcal/mol

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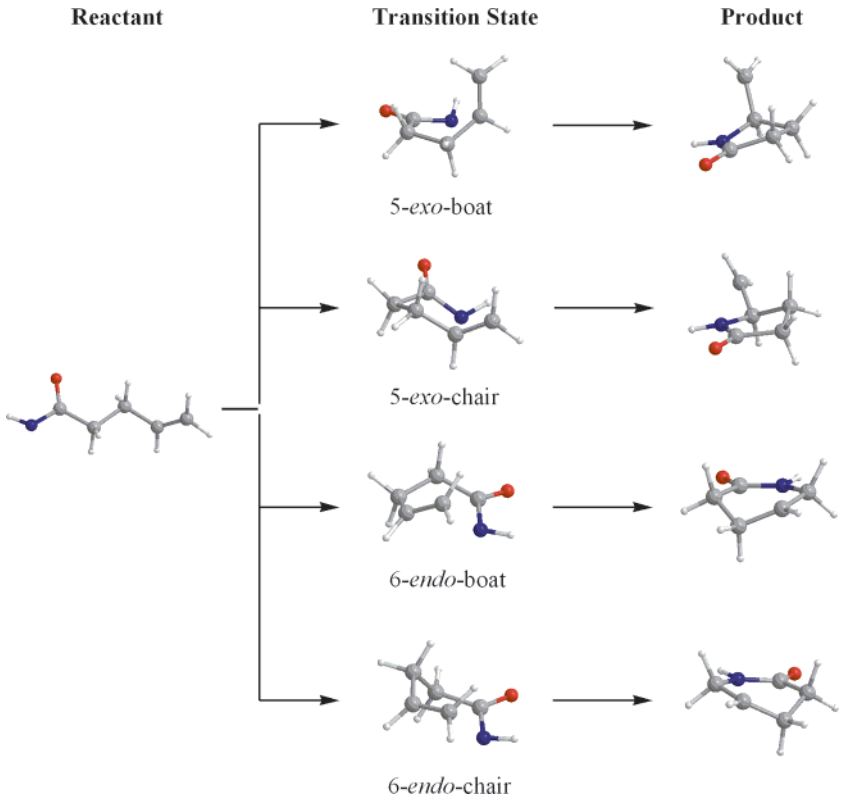


FIGURE 1. Optimized structures for the transition state in the cyclization of the pent-4-enamidyl radical.

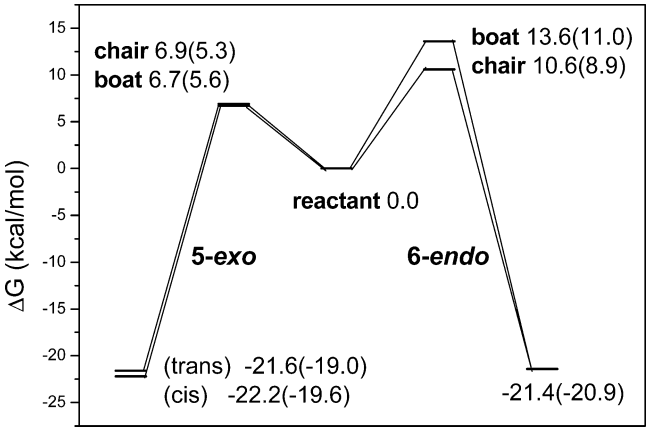
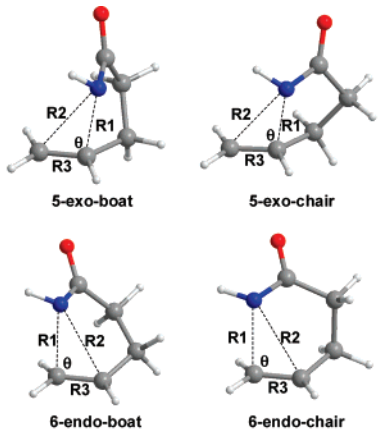


FIGURE 2. Energy profiles in different modes of cyclization of the pent-4-enamidyl radical calculated by the UCCSD(T)/6-311+G(d,p) method (UB3LYP/6-31+G(d,p) results are shown in parentheses).



Radicals	R1 (Å)	R2 (Å)	R3 (Å)	θ(deg)
5-*exo*-boat	2.277	2.861	1.361	100.7
5-*exo*-chair	2.206	2.833	1.366	102.4
6-*endo*-boat	2.196	2.602	1.370	90.7
6-*endo*-chair	2.235	2.678	1.366	92.9

FIGURE 3. Structural parameters in the transition states for the cyclization of the pent-4-enamidyl radical.

(values in parentheses are UB3LYP results). On the other hand, the energy level for the 6-*endo*-chair transition state is +10.6 (+8.9) kcal/mol relative to the starting material, and the energy level for the 6-*endo*-boat transition is +13.6 (+11.0) kcal/mol. Evidently the 5-*exo* mode of cyclization is more favorable than the 6-*endo* mode by over 3 kcal/mol, which corresponds to a regioselectivity of 5-*exo*:6-*endo* > 99:1. Furthermore, the reaction energies for both the 5-*exo* and 6-*endo* cyclization products are about −21 to −22 (or −19 to −20) kcal/mol, which indicates a highly exothermic transformation and, therefore, a kinetic control in the regioselectivity.

A closer inspection of the four transition-state structures reveals some structural features that may explain the energy difference (Figure 3). It is found that the R1, R2, and R3 (symbols shown in Figure 3) parameters are fairly close to each other in all the four transition states. This means that the bond length is not a determining factor for the energy. On the other hand, when we measure the θ angle between the attacking nitrogen atom and the C=C double bond, we find that the 5-*exo* transition state has a significantly larger θ angle than the 6-*endo* mode by over 10°. According to the "Burgi−Dunitz"-like trajectory[13] for the trig-mode cyclization reactions, we expect that the best overlap between the incoming reactive center and

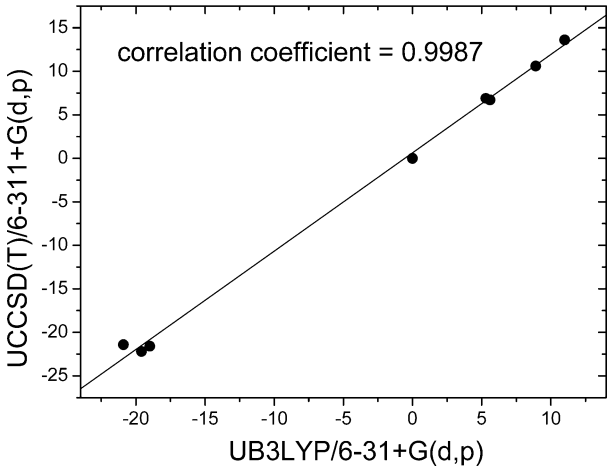


FIGURE 4. Correlation between the UCCSD(T)/6-311+G(d,p) and UB3LYP/6-31+G(d,p) results.

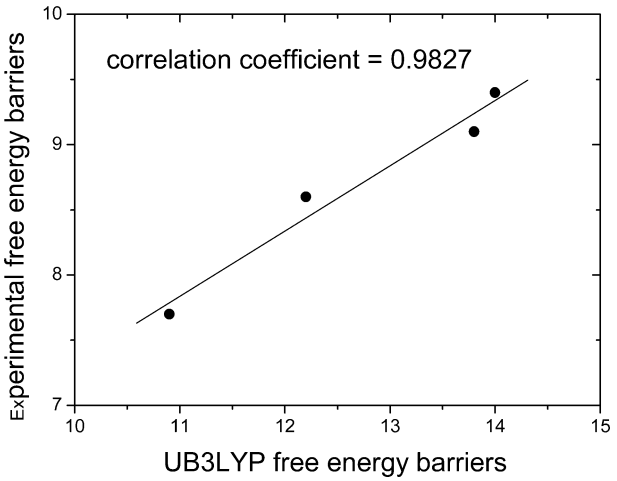


FIGURE 5. Correlation between the experimental and UB3LYP/6-31+G(d,p) free energy barriers (kcal/mol).

the π-system should be close to 109°. Thus, the 5-*exo* mode is more favorable than the 6-*endo* mode because the former allows for a more desirable attacking trajectory in the cyclization.

Note that the free energy barriers calculated by the UCCSD-(T)/6-311+G(d,p) method are systematically higher than the values predicted by the UB3LYP/6-31+G(d,p) method by ca. 1−2 kcal/mol. Nonetheless, when the UCCSD(T) results are plotted against the UB3LYP data, we obtain an excellent regression line with a very high correlation coefficient of 0.9987 (Figure 4). Thus, although the UB3LYP method cannot accurately predict the absolute free energy barriers, it can reliably predict the relative free energies in the cyclization of pent-4-enamidyl radicals. The same conclusion can also be made by comparing the experimental[11] and theoretical free energy barriers for the cyclization of *N*-aryl-5,5-diphenyl-4-pentenamidyl radicals. As shown in Figure 5, although the UB3LYP free energy barriers are systematically lower than Newcomb's experimental values by ca. 3 kcal/mol, the correlation coefficient between the theoretical and experimental barriers is as high as 0.9827, indicating the reliability of using the UB3LYP method to calculate the relative free energy barriers. Furthermore, it is also evident from Table 1 that the other popular DFT methods such as BHandHLYP and MPW1K do not provide better predictions than the B3LYP functional.

3. C5-Substituted Pent-4-enamidyl Radicals

According to the Baldwin−Beckwith rules,[14] substitution on an olefinic bond disfavors radical addition at the substituted position. Thus, we expect that pent-4-enamidyl radicals carrying substituents at the C5-position will enhance the regioselectivity for the 5-*exo* cyclization mode. To examine whether this hypothesis is correct, we have studied the cyclization of several 5-substituted pent-4-enamidyl radicals that possess typical substituents including Me (to represent alkyl groups), Ph (to represent aryl groups), CN, COOEt, and Cl (to represent halogens). For each radical, we have considered both the 5-*exo* and 6-*endo* cyclization modes. In each mode, we have considered both the boat and chair conformations for the transition state. Note that from now on all the calculations are performed by using the UB3LYP/6-31+G(d,p) method. As demonstrated in the previous section, although the UB3LYP method cannot accurately predict the absolute free energy barriers, it can reliably predict the relative free energy barriers and, therefore, the regioselectivities.

The detailed activation free energies are shown in Table 2. It is found that all the substituents at the C5-position decrease the activation free energies for the 5-*exo* mode cyclization, but increase the activation free energies for the 6-*endo* cyclization. This observation appears to be consistent with the Baldwin−Beckwith prediction. However, it is important to note that the 5-*exo* cyclization is actually accelerated by the substituents. This indicates that the steric hindrance cannot be the only driving force for the enhanced regioselectivity. To further elucidate the mechanism for the substituent effects, we decided to use the Marcus theory[15] to separate the intrinsic and thermodynamic contributions to the observed activation free energies.

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

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + \frac{1}{2}\Delta G_R + \frac{(\Delta G_R)^2}{16\Delta G_0^{\ddagger}} = \Delta G_0^{\ddagger} + \Delta G_{thermo}^{\ddagger} \quad (1)$$

where the activation free energy ($\Delta G^{\ddagger}$) of a nondegenerate reaction is the sum of the intrinsic barrier ($\Delta G_0^{\ddagger}$) and the thermodynamic contribution ($\Delta G_{thermo}^{\ddagger}$). The intrinsic barrier corresponds to a hypothetical thermoneutral process (i.e., a degenerate transformation). 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 the Marcus theory was developed for the electron-transfer reactions. More recently the Marcus theory has

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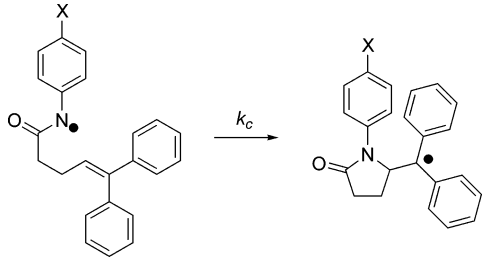
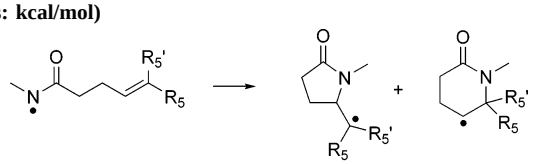
TABLE 1. Experimental and Theoretical Free Energy Barriers in the Cyclization of *N*-Aryl-5,5-diphenyl-4-pentenamidyl Radicals



substituent (X)	k_c (s^{-1})[a] exptl	free energy barrier (kcal/mol)[b] exptl	B3LYP	BHandHLYP	MPW1K
H	$(7.8 \pm 0.3) \times 10^5$	9.4 ± 0.0	14.0	17.8	14.0
F	$(1.3 \pm 0.1) \times 10^6$	9.1 ± 0.1	13.8	17.4	13.7
$COCH_3$	$(3.0 \pm 0.1) \times 10^6$	8.6 ± 0.0	12.2	16.1	12.4
CN	$(1.4 \pm 0.1) \times 10^7$	7.7 ± 0.0	10.9	15.2	11.2

[a] Experimental values taken from ref 11. [b] Basis set = 6-31+G(d,p).

TABLE 2. Activation Free Energies ($\Delta G^{\ddagger}$) and Their Intrinsic ($\Delta G_0^{\ddagger}$) and Thermodynamic Contributions ($\Delta G_{thermo}^{\ddagger}$) in the Cyclization of C5-Substituted Pent-4-enamidyl Radicals (units: kcal/mol)



	5-*exo*			6-*endo*		
$R_5 = R_5'$	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$
H	9.1	15.4	−6.4	14.0	20.0	−6.8
Me	6.4	13.6	−7.2	16.4	20.8	−3.7
Ph	5.4	14.4	−9.1	21.7	22.0	−0.4
CN	6.4	16.3	−9.9	23.1	22.7	−0.5
COOEt	8.4	16.6	−8.2	22.6	24.5	−1.9
Cl	7.1	15.3	−8.3	20.3	28.0	−7.7

also been successfully applied to a wide array of organic reactions including the radical cyclization.[16]

By using the Marcus theory it is straightforward to calculate the intrinsic barrier ($\Delta G_0^{\ddagger}$):

$$\Delta G_0^{\ddagger} = \frac{1}{2}\left[\Delta G^{\ddagger} - \frac{1}{2}\Delta G_R + \sqrt{(\Delta G^{\ddagger})^2 - \Delta G^{\ddagger}\cdot\Delta G_R}\right] \quad (2)$$

With the intrinsic barrier in hand, we are then able to calculate the thermodynamic contribution to the overall activation energy using the following equation.

$$\Delta G_{thermo}^{\ddagger} = \Delta G^{\ddagger} - \Delta G_0^{\ddagger} \quad (3)$$

An important advantage of using Marcus theory is that we can now quantitatively analyze the mechanism of substituent effects. The 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 change because the reaction is more exothermic or endothermic).

The intrinsic and thermodynamic contributions to the energy barriers in the cyclization of 5-substituted pent-4-enamidyl radicals are shown in Table 2. The results indicate that the intrinsic contributions in the 5-*exo* cyclization are all around 15 kcal/mol. They are not dramatically changed by the substitution at the C5-position presumably because the C5-substituents cannot produce significant steric hindrance in the 5-*exo* cyclization reaction. On the other hand, the thermodynamic contributions in the 5-*exo* cyclization vary in a range from about −6 to −10 kcal/mol. All the substituents bring about a more negative thermodynamic contribution than the unsubstituted case. This behavior may be attributed to spin delocalization effect produced by these substituents, which stabilizes the final 5-*exo* cyclization product. Thus, the 5-*exo* cyclization is accelerated by the C5-substituent due to thermodynamic reasons, but not due to the intrinsic contributions.

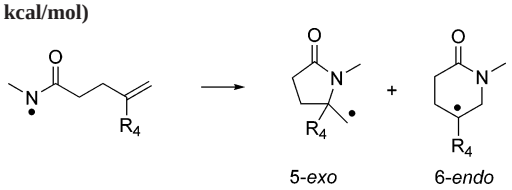
In comparison to the 5-*exo* case, the intrinsic contributions in the 6-*endo* cyclization increase significantly from +20.0 for the unsubstituted radical to +28.0 kcal/mol for the chlorinated radical. This increase is obviously due to the steric hindrance produced by the C5-substituents, which can retard any attack at the C5-position. Meanwhile, it is interesting to find that the thermodynamic contributions in the 6-*endo* cyclizations also change dramatically in a range from about 0 to −8 kcal/mol. Because there cannot be any strong interactions between the substituents and the radical center in the 6-*endo* cyclization product, we hypothesize that the variation of the thermodynamic contributions may originate from the hyperconjugation between the substituent and the C=C double bond in the starting material. Anyhow, it is now clear that the C5-substituent decelerates the 6-*endo* cyclization due to both intrinsic and thermodynamic reasons.

4. C4-Substituted Pent-4-enamidyl Radicals

The above results indicate that we can only see the 5-*exo* products (i.e., γ-lactams) in the C5-substituted pent-4-enamidyl radicals. To synthesize δ-lactams (i.e., 6-*endo* products) using the same type of chemistry, we hypothesize that it is necessary

(16) (a) Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 12583. (b) Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 9534. (c) Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 9329. (d) Wu, C. W.; Ho, J. J. *J. Org. Chem.* **2006**, *71*, 9595.

TABLE 3. Activation Free Energies ($\Delta G^{\ddagger}$) and Their Intrinsic ($\Delta G_0^{\ddagger}$) and Thermodynamic Contributions ($\Delta G_{thermo}^{\ddagger}$) in the Cyclization of C4-Substituted Pent-4-enamidyl Radicals (units: kcal/mol)



	5-*exo*			6-*endo*		
R_4	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$
H	9.1	15.4	−6.3	14.0	20.8	−6.8
Me	8.6	14.1	−5.4	11.3	18.8	−7.4
i-Pr	8.7	13.5	−3.8	11.0	18.5	−7.5
t-Bu	8.7	13.0	−4.2	9.1	17.4	−8.4
Ph	**12.1**	**16.1**	**−4.0**	**10.6**	**20.8**	**−10.2**
CN	12.8	16.4	−3.6	13.0	22.8	−9.8
COOEt	11.1	15.1	−4.0	12.6	22.0	−9.4
Cl	11.8	18.0	−6.2	13.0	19.5	−7.5
OMe	10.6	14.3	−3.7	11.1	15.6	−8.4

to introduce a substitution group at the C4-position. This substituent may retard the 5-*exo* attack at the C4-position due to the steric hindrance. Simultaneously, the same substituent may also stabilize the 6-*endo* product through the spin delocalization effect. The remaining question is: Which type of C4-substituent is strong enough to completely alter the 5-*exo* versus 6-*endo* regioselectivity?

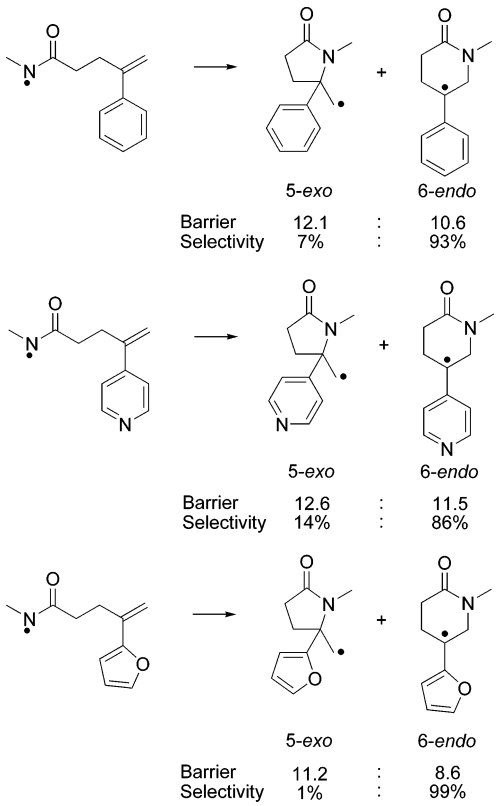
To answer the above question, we have examined a number of C4-substituted pent-4-enamidyl radicals (Table 3). It is found that an alkyl C4-substituent cannot change the 5-*exo* versus 6-*endo* selectivity because the former cyclization always exhibits a lower activation free energy. Interestingly, from the least sterically demanding group (H) to the most bulky one (*t*-Bu), the activation free energy actually decreases for both the 5-*exo* (by 0.4 kcal/mol) and 6-*endo* (by 4.9 kcal/mol) cyclizations. Presumably, these decreases of activation energy are due to the enhanced hyperconjugation ability of the *t*-Bu group as compared to H. Thus, compared to the electronic factors, the steric hindrance only plays a minor role in determining the regioselectivity in the amidyl radical cyclization.

As to the electronic factors, we next consider several synthetically relevant radical-stabilizing substituents including Ph, CN, COOEt, Cl, and OMe at the C4-position. It is found that the activation free energy for the 5-*exo* cyclization increases in all these C4-substituted compounds by 1.5−3.0 kcal/mol. This observation can be explained by the fact that the hyperconjugation between the C4-substituent and the C═C double bond is lost after the cyclization. Indeed, as shown in Table 2 the thermodynamic contribution to the activation barrier of 5-*exo* cyclization is always lower in the C4-substituted case than the C4-H one.

On the other hand, it is also found that the activation barrier for the 6-*endo* cyclization is reduced by about 1−3 kcal/mol in the presence of these radical-stabilizing C4-substituents. This observation can be attributed to the enhanced hyperconjugation between the C4-substituent and the radical center in the product. In agreement with this explanation, the thermodynamic contributions to the 6-*endo* cyclization are calculated to be higher in the presence of these C4-substituents.

The above results indicate that a radical-stabilizing group at the C4-position can retard the 5-*exo* cyclization but accelerate the 6-*endo* cyclization. The major reason for this behavior is the thermodynamic factor instead of any steric hindrance. Due to this phenomenon, the dominant 5-*exo* regioselectivity in the amidyl radical cyclization can be greatly affected by these C4-substituents. As shown in Table 3, in the cases with the CN, COOEt, Cl, and OMe substituents, the energy barrier for the 5-*exo* cyclization is only about 1 kcal/mol lower than that for the 6-*endo* cyclization. More significantly, in the case of Ph substitution, the energy barrier for the 5-*exo* cyclization is 1.5 kcal/mol higher than that for the 6-*endo* cyclization. This means a *complete* change of regioselectivity where *δ*-lactams become the major product![17]

SCHEME 3



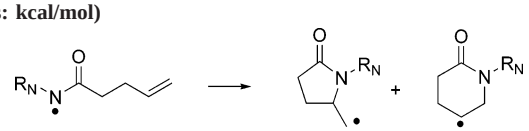
To confirm the above finding, we have also examined the 4-substituted pent-4-enamidyl radicals carrying other aromatic groups including pyridine (to represent electron-poor arenes) and furan (to represent electron-rich arenes). As shown in Scheme 3, the pyridyl case exhibits a regioselectivity of 14:86 for 5-*exo* versus 6-*endo*, whereas the regioselectivity is 1:99 for the furanyl case. These results are compared to 7:93 for the phenyl case. Thus, we conclude that all the aromatic groups at the C4-position should lead to the 6-*endo* regioselectivity to give *δ*-lactams as the major products. Furthermore, electron-rich aromatic substituents tend to produce a higher 6-*endo* regioselectivity than electron-poor ones.

5. *N*-Substituted Pent-4-enamidyl Radicals

Besides the C4- and C5-substituents, an additional position where the substitution may strongly affect the 5-*exo* versus

(17) Recent examples for 6-*exo*-*trig* radical cyclizations: (a) Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619. (b) Zhang, X. Q.; Guzi, T.; Pettus, L.; Schultz, A. G. *Tetrahedron Lett.* **2002**, *43*, 7605. (c) Joshi, S. N.; Puranik, V. G.; Deshmukh, A.; Bhawal, B. M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3073. (d) Pedrosa, R.; Andres, C.; Duque-Soladana, J. P.; Roson, C. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2809.

TABLE 4. Activation Free Energies ($\Delta G^{\ddagger}$) and Their Intrinsic ($\Delta G_0^{\ddagger}$) and Thermodynamic Contributions ($\Delta G_{thermo}^{\ddagger}$) in the Cyclization of *N*-Substituted Pent-4-enamidyl Radicals (units: kcal/mol)



	5-*exo*			6-*endo*		
R_N	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G_0^{\ddagger}$	$\Delta G_{thermo}^{\ddagger}$
H	5.3	13.3	−8.0	8.9	17.8	−8.9
Me	9.1	15.4	−6.4	14.0	20.8	−6.8
i-Pr	11.2	16.5	−5.3	17.0	22.1	−5.1
t-Bu	10.5	14.9	−4.4	16.9	20.5	−3.6
Ph	15.6	16.5	−1.0	21.3	22.4	−1.0

6-*endo* regioselectivity is at the amidyl nitrogen. To test this type of substitution, we have studied several synthetically accessible amidyl radicals carrying an *N*-H, *N*-Me, *N*-*i*-Pr, *N*-*t*-Bu, or *N*-Ph group (Table 4).

As seen in Table 4, it is interesting to find that the activation free energy is dramatically increased in both 5-*exo* and 6-*endo* cyclization due to *N*-substitution by about 4−12 kcal/mol. Examination of the intrinsic contributions to the energy barrier indicates that the *N*-substitution leads to a more positive intrinsic barrier by 2−5 kcal/mol, presumably because it causes some steric hindrance at the nitrogen radical. Furthermore, it is evident from Table 3 that the thermodynamic contribution to the energy barrier becomes less negative by 2−8 kcal/mol in the presence of an *N*-substituent. This observation may be attributed to the hyperconjugation (or conjugation) interaction between the *N*-substituent and the amidyl radical in the starting material, which is completely lost after the cyclization. Thus, both the intrinsic and thermodynamic factors increase the overall energy barrier in the cyclization of *N*-substituted amidyl radicals.

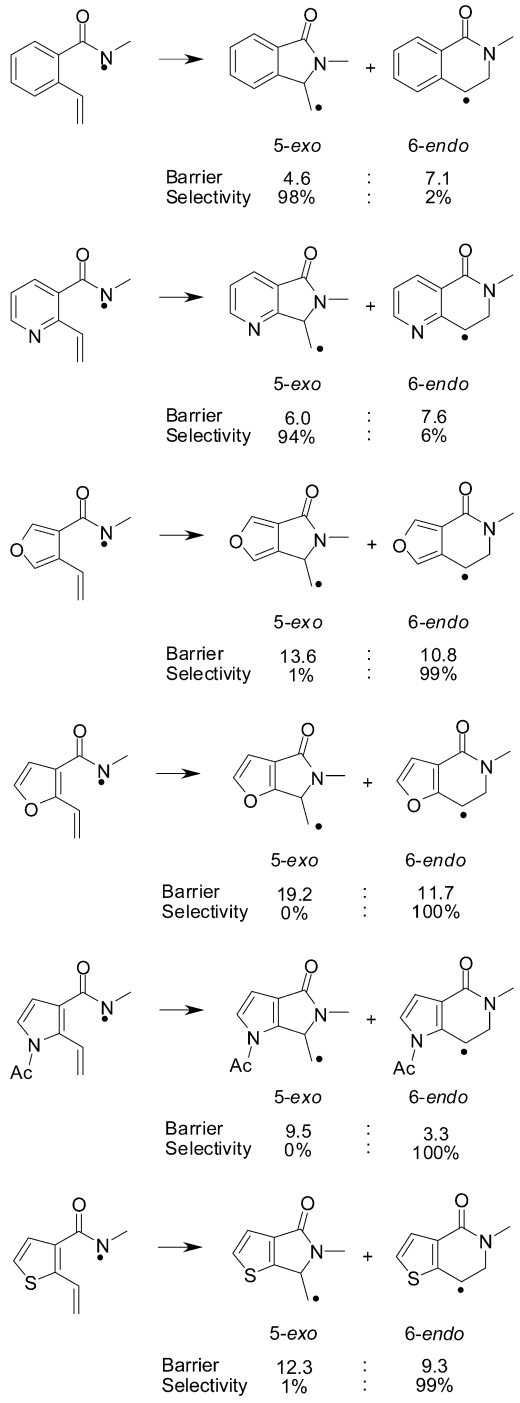
Comparing the 5-*exo* versus 6-*endo* cyclizations, we find that the *N*-substitution does not change the selectivity. In fact, as shown in Table 4 all the energy barriers for all the 6-*endo* cyclization reactions are about 5−6 kcal/mol higher than the energy barriers for the 5-*exo* cyclization. This means an overwhelming selectivity for the 5-*exo* products in all these *N*-substituted amidyl radicals.

6. Bicyclic Systems

The above results strongly suggest that γ-lactams (or, pyrrolidinones) should be the predominant products in the cyclization of almost all the pent-4-enamidyl radicals via the 5-*exo* mode. The only chance to prepare δ-lactams (or, piperidinones) through this type of chemistry requires one to introduce an aryl group at the C4-position. Here we have examined an additional type of substitution, where the aryl group is incorporated in the backbone of the pent-4-enamidyl radical. This system is highly interesting from the synthetic point of view, because it allows for the construction of bicyclic isoquinolinones and their analogues from monocyclic starting materials.

Our results are shown in Scheme 4. It is found that the incorporation of a benzene ring at the C2- and C3-positions gives a resgioselectivity of 5-*exo*:6-*endo* = 98:2. Changing the benzene ring to pyridine gives a similar regioselectivity of 5-*exo*:6-*endo* = 94:6. Thus, both the benzene and pyridine substitutions are not sufficient to cause the 6-*endo* selectivity. At this point it becomes highly interesting to find that the incorporation of a furan ring (where the vinyl group is at furan's 3-position) gives a regioselectivity of 5-*exo*:6-*endo* = 1:99. Furthermore, when we move the vinyl group from furan's 3-position to its 2-position, an even larger difference (i.e., 7.5 kcal/mol) between the 5-*exo* and 6-*endo* barriers is obtained so that the 5-*exo*:6-*endo* selectivity technically becomes 0:100.

SCHEME 4



To confirm the above findings, we also have examined the pyrrole and thiophene systems. For the pyrrole system, the 6-*endo* barrier is about 6.2 kcal/mol lower than the 5-*exo* barrier, which means that the 5-*exo*:6-*endo* selectivity is technically 0:100. For the thiophene system, the 6-*endo* barrier is about

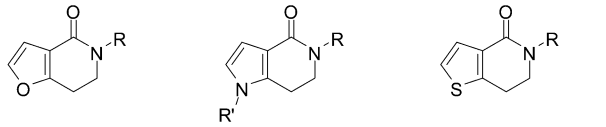


FIGURE 6. The structures for dihydrofuropyridinone, dihydropyrrolpyridinone, and dihydrothienopyridinone.

3.0 kcal/mol lower than the 5-*exo* barrier, which means that the 5-*exo*:6-*endo* selectivity is around 1:99. Thus, the incorporation of a five-membered aromatic ring at the C2- and C3-positions of the pent-4-enamidyl radicals can lead to a high regioselectivity toward the 6-*endo* products, whereas six-membered aromatic substitutions can only provide the 5-*exo* products. These observations may be attributed to the strain generated in trying to make two fused flat 5-membered rings. Thus, our results suggest an interesting route for the synthesis of dihydrofuropyridinone, dihydropyrrolpyridinone, and dihydrothienopyridinone derivatives (Figure 6).

7. Conclusions

Intramolecular cyclization of an amidyl radical onto an olefin represents an appealing method for the synthesis of lactams and other nitrogen-containing heterocycles. In the present research we have performed the first, systematic theoretical study on the regioselectivity in the cyclization reactions of various pent-4-enamidyl radicals. The following conclusions can be made from our results:

1. For an unsubstituted pent-4-enamidyl radical and a majority of its substituted derivatives, the radical cyclization reaction produces a 5-*exo* product (i.e., a γ-lactam) almost exclusively.

2. Substitutions at the C5-position enhance the 5-*exo* selectivity. Marcus theory analysis shows the involvement of both the thermodynamic (stabilization of the starting double bond or the resulting radical center) and intrinsic (mainly steric effects) contributions to the enhanced regioselectivity.

3. Most C4-substituted systems also exhibit the 5-*exo* selectivity. The only chance to see δ-lactams as the major products through 6-*endo* cyclization requires the presence of an aromatic substituent at the C4-position. Such a change to 6-*endo* selectivity is caused by the thermodynamic reasons, but not by any steric reasons.[18]

4. Substitution at the amidyl nitrogen significantly decelerates the cyclization reaction. However, this type of substitution does not cause a change in the regioselectivity.

5. An additional method to cause the 6-*endo* selectivity is the incorporation of an electron-rich aromatic ring into the pent-4-enamidyl radical backbone at the C2- and C3-positions. This method provides an interesting route for the preparation of dihydrofuropyridinone, dihydropyrrolpyridinone, and dihydrothienopyridinone derivatives.

(18) As pointed out by one of the reviewers, "an example of a 6-endo cyclization related to the Ph-substituted case highlighted in Table 3 has been observed in the reviewer's laboratory" (unpublished result).

8. Computational Methodology

Ab initio calculations were performed with the Gaussian 03 suite of programs.[19] Geometry optimizations were performed with the UB3LYP/6-31+G(d,p) method without any constraint. Frequency calculations were carried out at the same UB3LYP/6-31G+(d,p) level of theory for 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 and only one significant imaginary frequency, while no imaginary frequencies were observed for the minimum-energy species.

Single-point energies were calculated with the CCSD(T)/6-311+G(d,p) method for the unsubstituted amidyl radical and the UB3LYP/6-31+G(d,p) method for substituted systems. Corrections of the energy to 298 K were made from the frequency calculations including the zero-point energy corrections. It is worth noting that a number of recent studies have demonstrated the reliability of using the UB3LYP method to predict the geometry, zero-point vibrational energies, and reaction barriers for various types of radical cyclization reactions.[12]

Acknowledgment. This study was supported by the National Natural Science Foundation of China (No. 20602034). We also thank the USTC Supercomputer Center.

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

JO070146H

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