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Cyclization or Hydrogen Migration: Theoretical Study and Experimental Evidence on the Reactivities of Unsaturated Amidyl Radicals

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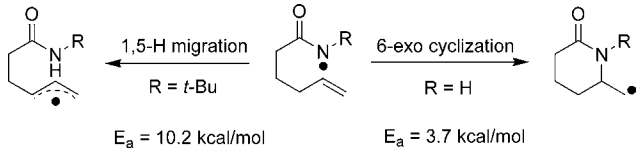
ABSTRACT

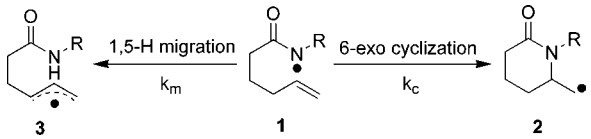


Theoretical calculations (B3LYP/6-31G*) backed up by deuterated experiments reveal that the *N*-substituents (R) play a crucial role in determining the reaction pathways of unsaturated amidyl radicals. With the increase of the bulkiness of *N*-alkyl group, the activation energy for 6-exo cyclization increases steadily, while the activation energy for 1,5-H abstraction remains almost unchanged. Therefore, cyclization occurs exclusively when R is H while 1,5-H migration occurs exclusively when R is *t*-Bu.

Amidyl radicals are highly reactive and electrophilic intermediates. This Umpolung reactivity offers a great potential in organic synthesis via intramolecular cyclization to afford lactams or cyclic amines.[1, 2] However, synthetic methodologies based on amidyl radicals have drawn far less attention than they deserve. This is, in part, because amidyl radicals also undergo intramolecular 1,5-hydrogen abstraction, resulting in the remote functionalization of an unactivated C−H bond.[3] This is particularly the case for 5-hexenamidyl radicals (**1**), as shown in Scheme 1. ESR study by Ingold et al. indicated that, while **1** (R = Me) underwent 6-exo cyclization (to give radical **2**), 1,5-H abstraction leading to the formation of allylic radical **3** was observed in the case of R = Et.[4] However, Newcomb and co-workers demonstrated from LFP experiments that 6-exo cyclization occurred exclusively for **1**, and they measured the rates to be around 1×10^7 s^{-1} at 338 K.[5] This conflict prompted us to look into the reactions in detail. We report here that the *N*-substitution pattern plays a crucial role on the reaction pathways as well as on the reaction rates. Theoretical calculations, backed up by deuterated experiments, provide a general picture of the reactivities of unsaturated amidyl radicals.

We carried out the theoretical calculations on the above reaction model in Scheme 1 using density functional theory, which has been shown to be an increasingly important tool in free radical chemistry.[6,7] All the calculations were performed at the B3LYP/6-31G* level using the Guassian98

Scheme 1



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program,[8] and the activation energies for 6-exo cyclization and for 1,5-H migration are summarized in Table 1 (see the Supporting Information for details).

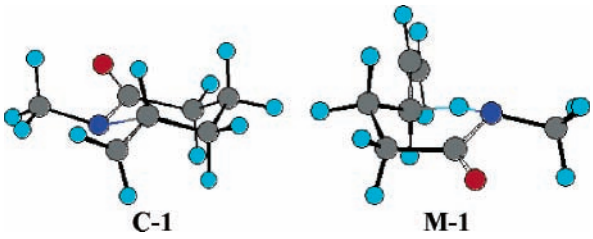
Table 1. Calculated (B3LYP/6-31G*) Activation Energies for **1**

entry	R	$E_a^{1\,a}$ (kcal/mol)	$E_a^{2\,b}$ (kcal/mol)
1	H	3.7	7.4
2	Me	8.5	10.4
3	Et	9.1	10.4
4	Bu	9.3	10.4
5	*i*-Pr	11.0	10.7
6	*t*-Bu	15.0	10.2
7	Ph	17.9	17.1
8	OMe	17.8	22.5

[a] 6-Exo cyclization. [b] 1,5-H migration.

The rate constants (k_c and k_m) in Scheme 1 can thus be estimated from the calculated activation energies (based on transition-state theory). The calculated activation energy (9.1 kcal/mol) for 6-exo cyclization of *N*-ethylhexenamidyl radical (entry 3, Table 1) corresponds to a rate constant of 9.2×10^6 s^{-1} at 338 K, which is in excellent agreement with Newcomb's value (1×10^7 s^{-1}) measured by LFP experiments.[5] For *N*-methylhexenamidyl radical (entry 2, Table 1), the k_c is estimated to be 3.8×10^6 s^{-1} at 300 K, which is also in good agreement with Ingold's value (1×10^6 s^{-1}) measured by ESR experiments.[4] In both cases, the activation energies for cyclization are lower than for the corresponding 1,5-H migration, which coincides with Newcomb's conclusion.[5] For 1,5-H abstraction, the rate constants k_m are estimated to have a magnitude of 10^5 s^{-1} for *N*-alkyl-substituted radicals **1** (entries 2−6, Table 1).

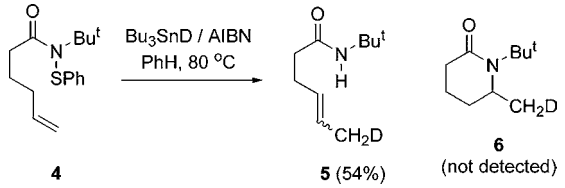
The vast difference in the activation energies for 6-exo amidyl cyclization ranging from 3.7 to ~18 kcal/mol is extremely glaring, which implies that the cyclization rate constants could vary from 10^{10} to 10^{-1} s^{-1} rather than stay around a fixed value. With increasing bulkiness of *N*-alkyl groups, the activation energies for 6-exo amidyl radical cyclization are increased. However, the activation energies for 1,5-H migration remain in the neighborhood of 10.4 kcal/mol (entries 2−6, Table 1). These two different trends can be explained by the computed transition-state structures. The transition state for 6-exo cyclization and for 1,5-H migration of *N*-methylhexenamidyl radical are shown as **C-1** and **M-1**, respectively. **C-1** is in a chair conformation in which the *N*-methyl group is in close contact with the vinyl moiety. **M-1** is in a half-chairlike conformation with the *N*-methyl group away from the core. It is obvious from the two structures that the 6-exo cyclization is more sensitive to the bulkiness of the *N*-substituent than 1,5-H migration. Thus, with the increase of steric hindrance, the reaction pathway is reversed from 6-exo cyclization to 1,5-H migration.



With *N*-phenyl- or *N*-methoxy-substituted radicals **1** (entries 7 and 8, Table 1), the activation energies are significantly increased for both 6-exo cyclization and 1,5-hydrogen abstraction, probably because of their electronic effect in stabilizing the amide radicals (ground-state effect).[9] Moreover, the product radicals are now of comparable energy to the starting amidyl radicals, implying that both pathways become reversible rather than highly exothermic in the N−H-substituted case ($\Delta H \sim -25$ kcal/mol).

To further verify the calculation results, we prepared radical presursor **4** and subjected its benzene solution to the slow addition of Bu_3SnH/AIBN (cat.) at 80 °C according to Newcomb's method.[10] The crude product was checked by ^1H NMR and HPLC and then purified by column chromatography. The deuterated compound **5** was isolated in 54% yield as the mixture of two isomers ($Z/E = 1.4{:}1$), while no cyclization products such as **6** could be detected (Scheme 2). This experiment unambiguously demonstrated that *N-tert-*

Scheme 2



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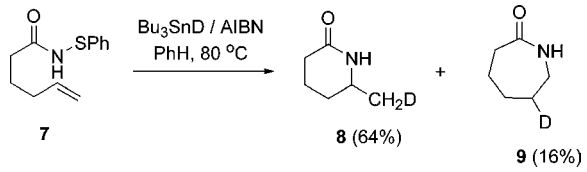
butyl-5-hexenamidyl radical underwent exclusively 1,5-H migration, which was in excellent agreement with the calculation (entry 6, Table 1).

We next synthesized substrate **7** and conducted the same experiment as for **4**. The expected 6-exo cyclization product **8** was isolated in 64% yield along with lactam **9** in 16% yield as the 7-endo cyclization product, while no 1,5-H migration product **10** could be detected by HPLC (Scheme 3). This result was also in excellent agreement with the

Scheme 3



calculation (entry 1, Table 1).

It is worth mentioning that the activation energy for 7-endo cyclization of **1** (R = H) was also calculated at the B3LYP/6-31G* level to be 4.1 kcal/mol, about 0.4 kcal/mol higher than that of 6-exo cyclization. The measured product ratio of **8** to **9** is consistent with this small computed activation energy difference.

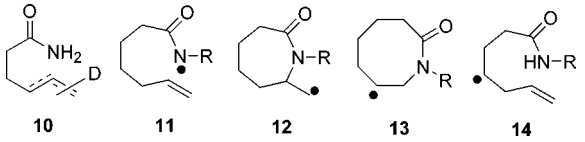
To gain a quantitative view on the above computational results, we carried out the reaction of **7** (0.01 M) with Bu_3SnH (2 equiv)/AIBN added in one portion. The cyclization products were obtained in 73% overall yield while only a trace amount of direct reduction product 5-hexenamide could be detected by HPLC. Since the rate of bimolecular H-abstraction of radical **1** (R = H) with Bu_3SnH is about 1.3×10^9 mol^{-1} s^{-1},[5] the rate constant k_c can thus be estimated to be larger than 2×10^9 s^{-1}, which is consistent with the calculation (entry 1, Table 1).

As an extension of the above investigation, we performed the calculations on the reactions of 6-heptenamidyl radicals **11** (see the Supporting Information for details). The results summarized in Table 2 closely resemble those in Table 1. The computed transition-state stuctures for 1,5-H migration

Table 2. Calculated (B3LYP/6-31G*) Activation Energies for **11**

		E_a (kcal/mol)		
entry	R	7-exo	8-endo	1,5-H
1	H	5.5	6.3	11.6
2	Me	10.5	11.3	14.9
3	*t*-Bu	15.7	16.3	14.7

of **11** (to afford radicals **14**) are almost identical to structure **M-1**, indicating the bulkiness of R has little impact on H-abstraction (entries 2−3, Table 2).[11] On the other hand, cyclization in both exo and endo modes (to afford radical **12** and **13**, respectively) always leads to the close contact of the *N*-alkyl group with the C═C bond, resulting in the significant steric influence on cyclization.



Thus, the above *N*-substituent effect on the reactivities of unsaturated amidyl radicals appears to be general, which should be an important implication in the future development of amidyl radical-based synthetic strategies.

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Supporting Information Available: Preparations and characterizations of **4**, **5**, and **7**−**9**; computational results on cyclization and H-abstraction of radicals **1** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) ,6-H migration is a less common process and rare for amidyl radicals in the literature. We also computed such a process for **11** at B3LYP/6-31G* level, which showed a similar trend in activation energy as 1,5-H migration. See the Supporting Information for details.