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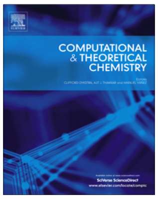

# Construction of six-membered nitrogen-heterocycles *via* intramolecular cyclization of iminyl radical: A theoretical perspective

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## ABSTRACT

In this study, we reported a potential method of constructing six-membered nitrogen-containing heterocycles *via* intramolecular cyclization of $R^2$-substituted 4-penteniminyl radicals ($R^2$ = $-NO_2$, $-SO_2OH$, $-CF_3$, $-SO_2Ph$, $-CN$, $-CONMe_2$, $-p$-$PhNO_2$, and $-COOH$). All of these investigated iminyl radicals exhibit strong preference for 6-*endo* cyclization products over 5-*exo* products. We further explored possible reasons to lead to the predominant 6-*endo* regioselectivity, including electronic density, stereoelectronic effect (intrinsic barrier), and thermodynamic contribution to reaction barrier. The computed results provided a potential synthetic strategy towards constructing six-membered N-heterocycles by intramolecular cyclization of substituted iminyl radicals.

## 1. Introduction

Intramolecular free-radical cyclization reactions in organic synthesis have been achieved during the last three decades [1–6]. The synthesis technology is nowadays routinely considered in the construction of carbo- and heterocyclic compounds [7–13]. A well-known fact is that the intramolecular cyclization reactions of the $sp^2$- and $sp^3$-carbon radicals onto C=C bond *via* 5-*exo* ring closure are kinetically favored and give exclusively five-membered ring products [14–17]. Some few reactions can give a mixture of both 5-*exo* and 6-*endo* products [18–20], in which the latter is less competitive with the former. Similarly, the intramolecular cyclization reactions of the substituted iminyl radicals **1a**–**1o** (Scheme 1) onto C=C bond also provide only 5-*exo* products [21–39]. The construction of six-membered N-containing rings by intramolecular radical addition onto unsaturated C=C bond thus remains a complicated problem [40]. Iminyl radical, generated by many experimental methods [38,39,41–44], is a useful synthetic intermediate in constructing N-heterocycles [21–37]. However, the dominant 5-*exo* reaction mode limits its application in constructing six-membered N-heterocycles.

For the substituted 4-penteniminyl radicals shown in Scheme 1, the nitrogen-centered radical addition onto C=C bond is an electrophilic reaction [45]. Thus, an electron density decreasing and/or a steric resistance increasing at 2-position carbon atom ($C_2$ atom) can perhaps lead to a preferential 6-*endo* intramolecular cyclization reaction [46–49]. Also, it is possible for the 6-*endo* reaction which is more exothermic than the corresponding 5-*exo* process, stemming from the stabilization of electron-withdrawing substituents on the radical center of a six-membered intermediate, to give a thermodynamically controlled 6-*endo* product [45]. Therefore, an electron-withdrawing substituent at 2-position carbon atom seems to be favorable to 6-*endo* cyclization reactions. Based on the assumption, in this study, we designed several $R^2$-substituted 4-penteniminyl radicals **6j**–**6p** (Scheme 2) to evaluate the probability of constructing six-membered nitrogen-heterocycles. The calculated results indicated that these designed radicals can preferably undergo intramolecular 6-*endo* radical cyclization reactions, and they can be considered as potential targets for further experiments.

## 2. Computational details

All calculations were performed at the B3LYP/6-311G(d,p) and B3LYP/LANL2DZ (species including Sn atom) levels of theory [50–58]. By the calculated energies of stationary points through the reactions, we constructed reaction potential energy surfaces (PESs). In all calculations, the effect of solvent was considered by employing the PCM theory [59–61] with $C_6H_5CH_3$ as solvent. Vibrational analysis verified the identity of each stationary point as either a minimum or a transition state (TS). Optimization and frequency calculations using B3LYP and BH*and*HLYP [53,62] methods with the 6-311G(d,p), 6-311++G(2df,2p), and *aug-cc-p*VDZ

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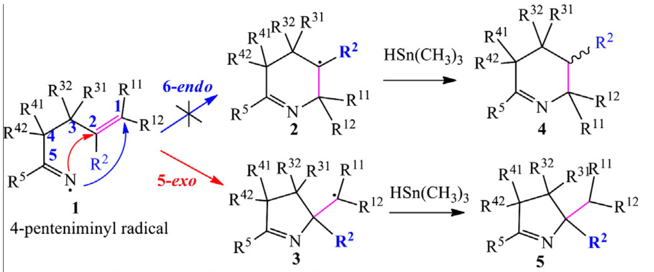


**1a**: $R^5$=-Ph, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1b**: $R^5$=-$OCH_3$, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1c**: $R^5$=-$CH_2CH_2COOCH_3$, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1d**: $R^5$=-Ph, $R^{41}$=$R^{42}$=-$CH_3$, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=H
**1e**: $R^5$=-Ph, $R^2$=-$CH_3$, $R^{11}$=$R^{12}$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1f**: $R^{41}$=$R^{42}$=-$CH_3$, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^5$=H
**1g**: $R^5$=-$CH_3$, $R^{11}$=$R^{12}$=-Ph, $R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1h**: $R^{11}$=-Ph, $R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=$R^5$=H
**1i**: $R^5$=$R^{11}$=-Ph, $R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1j**: $R^{11}$=$R^{12}$=$R^5$=-$CH_3$, $R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=H
**1k**: $R^{41}$=-Ph, $R^{11}$=$R^{12}$=$R^2$=$R^{31}$=$R^{32}$=$R^{42}$=$R^5$=H
**1l**: $R^{31}$=-Ph, $R^{11}$=$R^{12}$=$R^2$=$R^{32}$=$R^{41}$=$R^{42}$=$R^5$=H
**1m**: $R^{31}$=$R^{32}$=-$CH_3$, $R^{11}$=$R^{12}$=$R^2$=$R^{41}$=$R^{42}$=$R^5$=H
**1n**: $R^{11}$=-$CH_3$, $R^{12}$=-$CO_2Et$, $R^{31}$=-$OCH_3$, $R^2$=$R^{32}$=$R^{41}$=$R^{42}$=$R^5$=H
**1o**: $R^{11}$=-$CH_3$, $R^{12}$=-$CO_2Et$, $R^2$=$R^{31}$=$R^{32}$=$R^{41}$=$R^{42}$=$R^5$=H

**Scheme 1.** Examples of intramolecular cyclization reactions of iminyl radicals onto unsaturated carbon-carbon double bond.

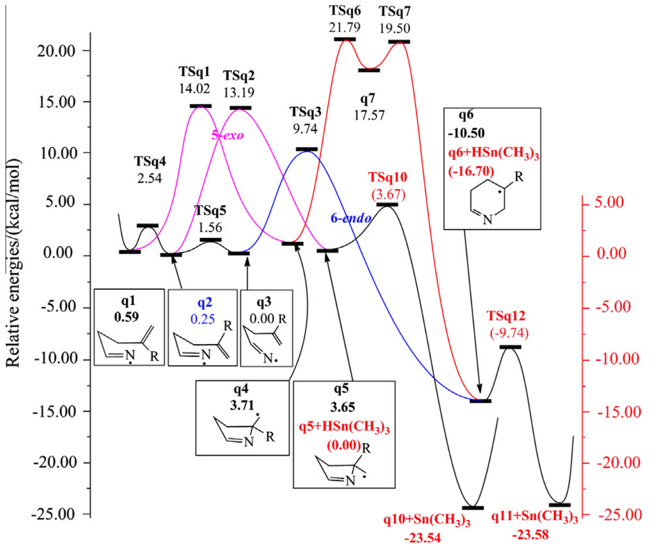


**Fig. 1.** Reaction potential energy profile of system **1q** (R = –COOH). For the radical cyclization reactions, the reference zero is reactant **q3**. For the reduction reactions of 5-*exo* and 6-*endo* cyclic radicals (red part), the energy of **q5**+$HSn(CH_3)_3$ is taken as the energy zero point. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

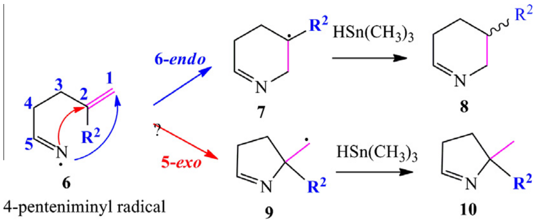
basis sets [63–65] were further performed for obtaining precise energies of several key reaction TSs. All energies and structural data were given in Supporting Information.

## 3. Results and discussion

As a representative example, Fig. 1 gave the reaction PES of **6q**, and other PESs (Figs. S1–S7) were listed in Supporting Information. Fig. 2 described the schematic structures of radical reactants and cyclization reaction TSs. Based on these reaction potential energy profiles (Fig. 1 and Figs. S1–S7), the following several reaction channels of systems **6j**–**6q** can be noted. First, chain N-radical reactants can undergo internal conversion by carbon–carbon bond rotation. Second, iminyl radicals can attack intramolecular C═C double bond to give five- and six-membered cyclic radical intermediates *via* 5-*exo* and 6-*endo* ring closure pathways, respectively. Third, five-membered cyclic radicals can expand into six-membered ring radicals *via* neophyl rearrangement [66,67]. And last, the reduction reactions of ring radicals with tin hydride ($HSn(CH_3)_3$) can give final five- and six-membered nonradical products.

Now, we will analyze the favored reaction pathways by the calculated energies. The internal conversions between chain reactant radicals *via* bond rotation possess lower-lying TSs than cyclization reactions. Therefore, they are fast reactions. The radical stereochemistry seems to be lost. For each system, because two neophyl rearrangement TSs are energetically the highest among all reaction pathways, they cannot make a significant impact on 5-*exo* and 6-*endo* cyclization reactions. Furthermore, the reduction processes of the formed cyclic radical intermediates take precedence over ring-opening reactions by comprising their reaction barrier heights and TS energies. Therefore, as shown on the PESs of eight investigated systems (Fig. 1 and Figs. S1–S7), these reactant radicals should preferentially cyclize in 5-*exo* or 6-*endo* fashion to give cyclic N-heterocyclic radical intermediates, which are followed by reduction in the presence of $HSn(CH_3)_3$ as a proton trap to generate final nonradical heterocyclic products. However, for the two competitive cyclization pathways, can the products prefer 6-*endo* structures?

Table 1 gives the relative energies of 5-*exo* and 6-*endo* cyclization TSs at different levels of computation. Note that five-membered N-heterocyclic radicals can be formed through two different reaction channels, chair-like and boat-like 5-*exo* TSs (Fig. 2). The calculated results indicate that the former is lower in energy than the latter for all systems in addition to **6o**. To evaluate which reaction channel is the most favorable, we compared the reaction barriers and TS heights of 5-*exo* and 6-*endo* cyclization pathways. The results show that the 6-*endo* cyclization TS in each designed system lies lower than the boat-like and chair-like 5-*exo* ring closure TSs at all computation levels. Therefore, the 6-*endo* cyclization pathways are more favorable in energy than the 5-*exo* channels and the resulting 6-*endo* cyclic compounds are dominant products. The reaction regioselectivity is changed dramatically



**6j**: $R^2$=-$NO_2$
**6k**: $R^2$=-$SO_2OH$
**6l**: $R^2$=-$CF_3$
**6m**: $R^2$=-$SO_2Ph$
**6n**: $R^2$=-CN
**1o**: $R^2$=-C(=O)$NMe_2$
**1p**: $R^2$=-*p*-$PhNO_2$
**1q**: $R^2$=-COOH

**Scheme 2.** Schematic reaction systems in this study.

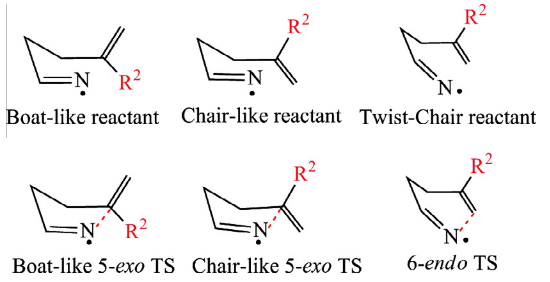


**Fig. 2.** Schematic structures of chain radical reactants and cyclization reaction TSs.