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The calculated effects of substitution on intramolecular cyclization of 2,5-hexadienyl radicals

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Abstract

The effects of substituents on the rate of intramolecular cyclization of the 2,5-hexadienyl radicals have been investigated computationally with DFT theory, using the UB3LYP functional. Various substituents – CN, NO_2, CH_3, NH_2, and *t*-butyl – at various positions – C_1, C_5 and C_6 – were considered in the calculations. An electron-donating substituent on the C_1 position raises the radical SOMO energies to increase the interaction with the alkene LUMO, whereas an electron-withdrawing counterpart lowers the SOMO and increases the interaction with the alkene HOMO. Both interactions decrease the activation energies, by 0.9–10.2 kcal/mol, and increase the rate of reaction rate, from 3 to 2.7×10^7 times. Similar results were obtained for the substituents at the C_6 position, and the activation energies for the intramolecular cyclization were decreased by 0.2–4.8 kcal/mol and the reaction rate increased from 2 to 2.8×10^3 times. The substituent at the C_5 position favors the formation of a 6-*endo* product because of a steric effect. The effects of disubstituents at both C_1 and C_6 positions were also investigated; the results showed that the electron-withdrawing groups decrease most effectively the activation energies. The so-called captodative effect was also investigated.

Keywords: Density functional theory; Cyclization; Ring closure; Intramolecular

1. Introduction

A synthetic technique to obtain both a high reactivity and a high selectivity in the cyclization of many organic and bioorganic compounds via the formation of *n*-membered rings is still challenging [1–9]. Great interest persists in intramolecular additions of radicals to produce five- or six-membered rings [4,10]. It is well known that, as shown in Scheme 1, the 5-hexenyl radical, **1**, undergoes ring closure in forming the 5-*exo* cyclopentylcarbinyl radical (primary) preferentially (98:2) over the 6-*endo* cyclohexyl radical (secondary).

Nevertheless, to improve the reaction especially for the formation of a six-membered ring, several studies have been devoted to the reactivity of various substituted radicals [11–15]. For instance, the ring closure of 5-methyl-5-hexenyl radical **4**, yields a 2:3 ratio of the 5-*exo*/6-*endo* products **5/6**, a result ascribed to the presence of an unfavorable steric effect in forming the 5-*exo* cyclization. Methyl substituents at other positions, however, reinforce the preference for 5-*exo* cyclization [10d]. For the evaluation of these factors and an effective comprehension of the mechanism of the radical additions, the availability of reliable data from quantum-chemical calculations is essential, but only the intermolecular addition of carbon-centered radicals to multiple bonds has received much attention. Theoretical approaches to intramolecular addition to double bonds seem scarce. Backwith focused attention on the importance of steric and stereoelectronic effects in determining the regio-selectivity and stereo-selectivity of radical reactions [16]. Houk and Spellmeyer reported a transition structure involved in the cyclization of the 5-hexenyl radicals [10d]. Baker and Dolbier applied density-functional theory (DFT) to study the cyclization of fluorinated 4-pentenyl radicals [17]. Della et al. found

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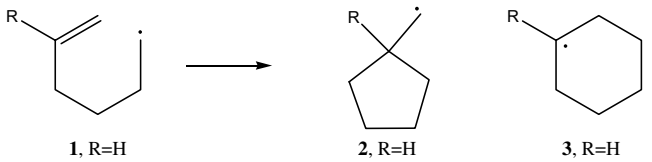

1, R=H **2**, R=H **3**, R=H
4, R=Me **5**, R=Me **6**, R=Me

Scheme 1. Cyclization of the 5-Hexenyl Radical.

that the cyclization of α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-methyl-5-hexenyl radicals revealed a high regioselectivity of the α-sulfonyl-5-methyl-5-hexenyl radical in forming 6-*endo* product [18]. Radicals can be stabilized by substituents that act as either electron donors or acceptors, and when both are present in the same system the so-called mero-stabilization, push–pull stabilization, or capto-dative stabilization is observable [19,20]. A stabilization of this type is believed to result from mutual reinforcement of the two substituent effects [21].

Upon this background, we report an application of density functional theory to investigate the intramolecular cyclization of 2,5-hexadienyl radicals substituted with several functional groups – CN, NH_2 etc. – at the C_1, C_5 and C_6 positions in producing 5-*exo* and 6-*endo* products with various regioselectivities. We employed also the Marcus theory to analyze the weight of contributions from the intrinsic barrier and thermodynamic factors in various substituents and positions in relation to the variation of activation energies of the reaction. By means of disubstitution at the C_1 and C_6 positions, we investigated the capto-dative effect, in which the activation energy of the reaction was expected to be further decreased [22].

2. Computational method

The geometries of all reactants, products and transition structures that involve radical cyclization were optimized using density-functional theory [23–26] with the hybrid UB3LYP [27–29] functional in conjunction with the 6-31G(d) basis set in the Gaussian 03 package [30]. Each stationary point as an energy minimum or a saddle point was verified by calculation of the harmonic vibrational wavenumbers. Zero-point energies were included in the evaluation of activation energies and heats of reactions. Calculations of intrinsic reaction coordinate (IRC) were performed on all transition structures to confirm the connection between the reactants and products [31]. Single-point calculations at two levels – UB3LYP/6-311++G(d,p)//UB3LPY/6-31G(d) and CCSD(T)/cc-pVDZ //UB3LPY/ 6-31G(d) – were performed. To calculate the energies of all structures, we applied the G3-MP2 method with the UB3LYP/6-31G(d) geometries [32]. We investigated substituent effects on the rates of radical cyclization using transition-state theory with Wigner tunneling corrections [33]. With calculations of natural bond orbitals (NBO) (NBO 4.0 implemented in Gaussian software), we analyzed a possible orbital interaction between the substituent and the radical center [34–40].

Murdoch proposed use of the Marcus theory to separate thermodynamic and intrinsic contributions to activation energies [41]. For this separation the Marcus equation is

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + 1/2\Delta E_{\mathrm{rxn}} + (\Delta E_{\mathrm{rxn}})^2/16(\Delta E_0^{\ddagger}) \quad (1)$$

Here the activation energy, $\Delta E^{\ddagger}$, of a nondegenerate reaction is the sum of the intrinsic barrier, $\Delta E_0^{\ddagger}$, and the thermodynamic contribution, no matter whether the reaction, with ΔE_{rxn}, is exothermic or endothermic. The intrinsic barrier is an hypothetical thermoneutral process, e.g., a degenerate transformation. The thermodynamic contribution is an estimate of the variation in activation energy caused by the substituent due to an alteration of the heat of reaction, based on an assumption that the hypersurface of potential energy behaves like two overlapping parabolas representing reactant and product energies, illustrated in Fig. 1. The term $(\Delta E_{\mathrm{rxn}})^2/16(\Delta E_0^{\ddagger})$ is a correction for non-additivity of the intrinsic and thermodynamic effects. The equation is practically equivalent to the assumption that half the reaction energy ΔE_{rxn} contributes to the activation energy $\Delta E^{\ddagger}$. An equivalent expression to solve the resulting quadratic equation for the intrinsic barrier, $\Delta E_0^{\ddagger}$, is

$$\Delta E_0^{\ddagger} = \frac{\Delta E^{\ddagger} - (1/2)\Delta E_{\mathrm{rxn}} + \sqrt{\Delta E^{\ddagger 2} - \Delta E^{\ddagger}\Delta E_{\mathrm{rxn}}}}{2} \quad (2)$$

After obtaining the activation energy and the energy for the reaction, we used this Marcus formula to calculate the intrinsic and thermodynamic contributions.

Employing the transition-state theory (TST), we calculated the rate coefficients at 298 K for radical cyclization of mono- and di-substituents in C_1, and C_6 positions of 2,5-hexadienyl radicals. We take the calculated G3MP2B3 energies and the following equation for the calculation.

$$k_{\mathrm{d}} = k^{\mathrm{W}}\sigma\frac{k_{\mathrm{B}}T}{h}\frac{Q_{\mathrm{TS}}}{Q_{\mathrm{React.}}}\exp\left(-\frac{E_{\mathrm{TS}} - E_{\mathrm{React.}}}{RT}\right) \quad (3)$$

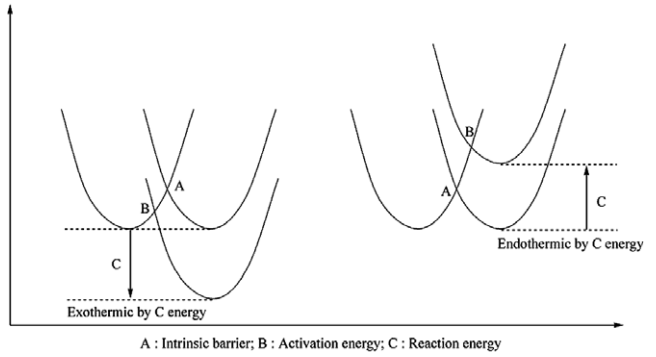

Fig. 1. Diagrams of potential energy to describe the Marcus model for degenerate and exothermic or endothermic reactions: (A) the intrinsic barrier of a thermoneutral reaction; (B) the activation energy of an exothermic (left graph) or endothermic (right graph) reactions; and (C) the reaction energy.