

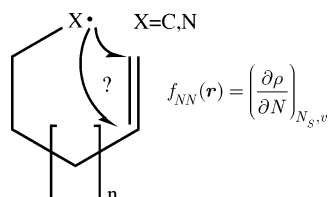
Spin-Polarized Conceptual Density Functional Theory Study of the Regioselectivity in Ring Closures of Radicals

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The regioselectivity of ring-forming radical reactions is investigated within the framework of the so-called spin-polarized conceptual density functional theory. Two different types of cyclizations were studied. First, a series of model reactions of alkyl- and acyl-substituted radicals were investigated. Next, attention was focused on the radical cascade cyclizations of *N*-alkenyl-2-aziridinylmethyl radicals (a three-step mechanism). In both of these reactions, the approaching radical (carbon or nitrogen centered) adds to a carbon–carbon double bond within the same molecule to form a radical ring compound. In this process, the number of electrons is changing from a local point of view (a charge transfer occurs from one part of the molecule to another one) at constant global spin number N_s (both the reactant and the product ring compound are in the doublet state). It is shown that the experimentally observed regioselectivities for these ring-closure steps can be predicted using the spin-polarized Fukui functions for radical attack, $f_{NN}^0(r)$.

Introduction

In 1976, Baldwin introduced a set of simple rules governing the regioselectivity of ring closures.¹ On the basis of the acceptor part of these molecules, containing the carbon atom at which the ring-closure reaction occurs, he divided these reactions into three main groups: the *tetrahedral*² systems, *trigonal* systems, and *diagonal* systems. On the other hand, for the donor part of

the system, one can classify the reactions as nucleophilic, electrophilic, or radicalar intramolecular additions. In the past three decades, these rules have proven to be useful to predict the major outcome of ring-forming reactions.³ However, numerous papers have stressed the limitations of and exceptions to these rules.⁴ For radical cyclization processes, Beckwith at al.⁵

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(2) This is the prevalent nomenclature, describing the geometry of the acceptor atom, sp^3 center as *tet*- (tetrahedral), sp^2 center as *trig*- (trigonal), and sp center as *dig*- (digonal). Another nomenclature indicates where the displaced electrons end up: if the electron pair ends up outside, then this is denoted as *endo*-; if the electron pair ends up within (smaller ring formation), the terminology *exo* is used.

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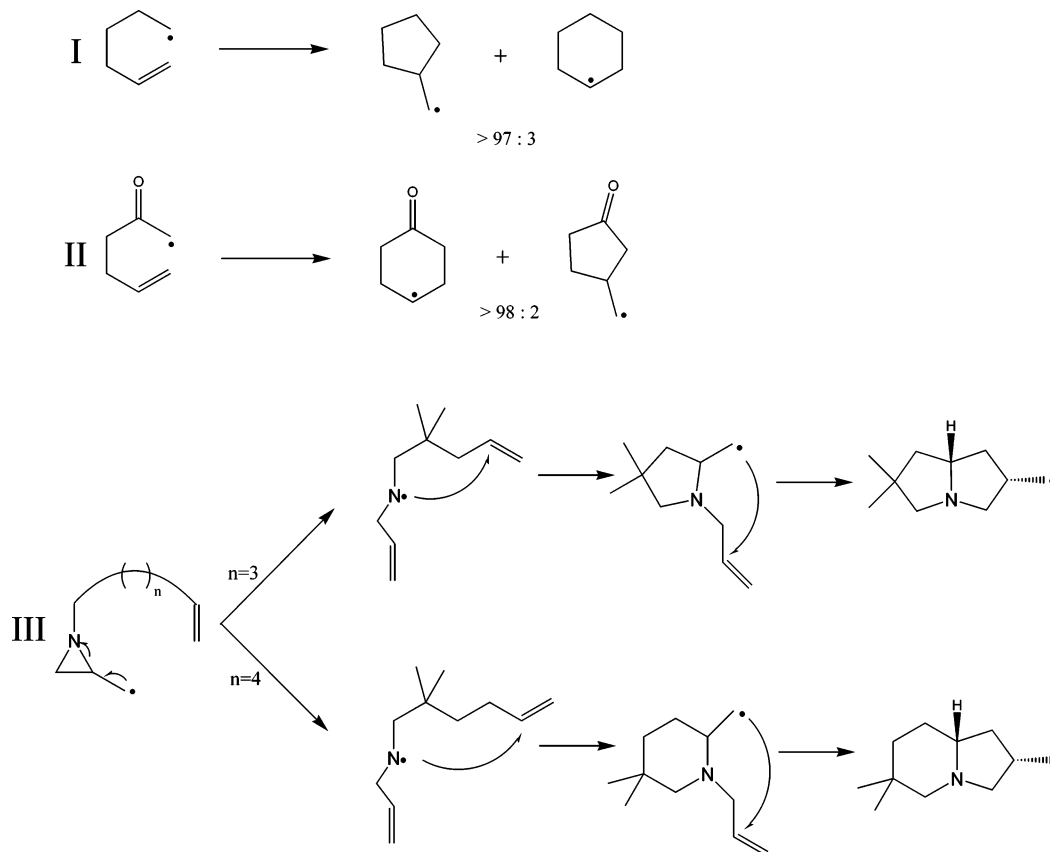


FIGURE 1. Different cyclization reactions involving radicals: (I) cyclization of hexenyl radicals, (II) cyclization of acyl-substituted hexenyl radicals, and (III) cascade radical reactions.

constructed some practical guidelines considering the influence of steric and electronic factors on the regioselectivity; they stated that the reaction occurs preferentially in the *exo* mode, that substituents on the double bond have an unfavorable effect, that adjacent semioccupied orbitals, filled nonbonding or orbitals containing lone pairs favor the homolytic cleavage, and that the stereochemical outcome of the reaction depends on the substituents at different position. A series of other contributions have investigated the aspects of regioselectivity of these reactions. Houk and co-workers⁶ expanded the MM2 force field⁷ to describe the rate of product formation in the cyclization of alkyl- and aryl-substituted radicals. The MM2 force field with fixed transition state parameters was also used to describe the regioselectivity.⁸ The 6-*endo* versus 5-*exo* modes of the *dig* process (i.e., the cyclization of hexenyl and related radicals) has attracted considerable attention.^{9,10} Generally, 5-hexenyl radicals cyclize with high regioselectivity to give five-membered rings rather than six-membered rings (Figure 1, reaction I).¹¹

Such cyclizations are usually kinetically controlled.^{12,5} The overwhelming preference for 5-*exo* ring closure over the 6-*endo* cyclization is a consequence of the interplay of three main factors, the stereoelectronic,¹³ polar,¹⁴ and steric effects.¹⁴ All three effects favor the five-membered ring formation, i.e., the thermodynamically less stable products. Note that these cyclizations need to follow the Bürgi–Dunitz trajectory,¹⁵ which suggests that a nucleophile will approach the C=C double bond at roughly the tetrahedral angle (rather than perpendicular). This was supported by theoretical investigations of transition structures for radical additions to unsaturated systems, where it was established that angles of attack of the reagents are close to tetrahedral.¹⁶ Considering the reaction path of an intramolecular radical “ene” addition, two different transition states, chair-like and boat-like, were found in both (*exo* and *endo*) processes.¹⁷ The formation of these transition states is the first step of two different processes that finally produce two regiochemically different products. It is generally accepted that the chair-like

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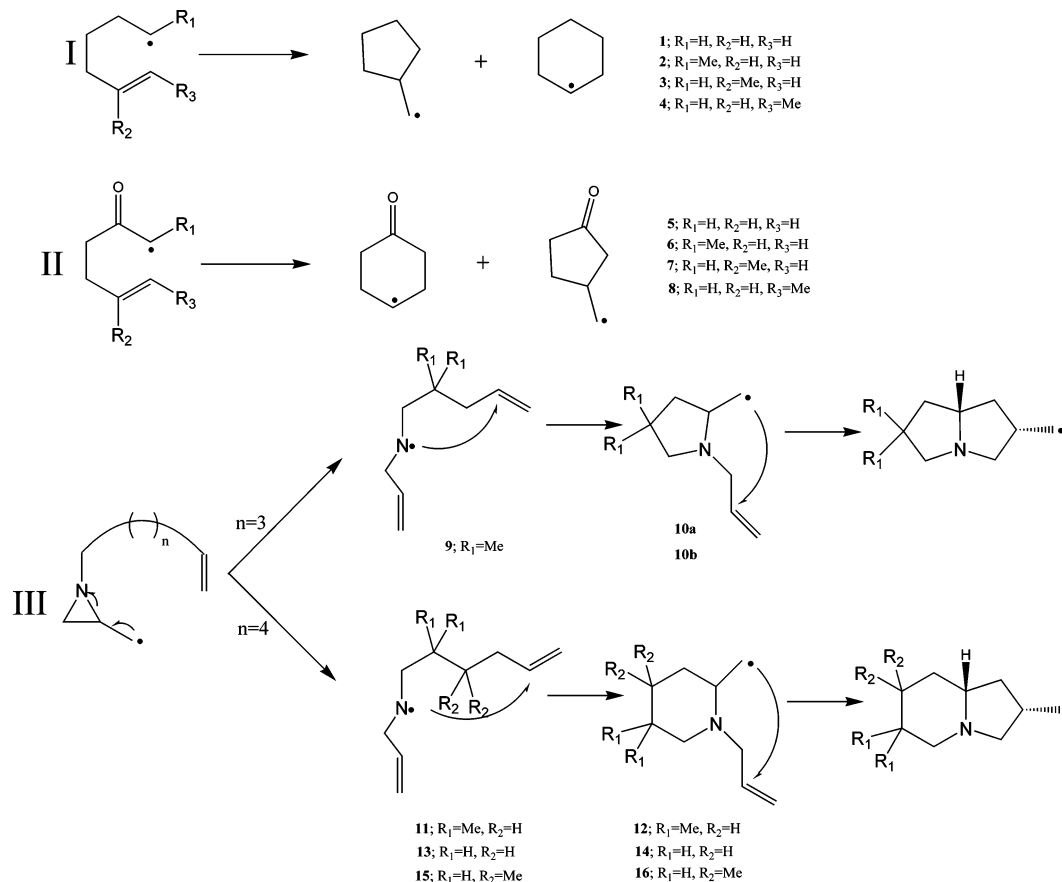
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SCHEME 1. Different Radical Cyclizations Investigated



orientation of the transition state is more stable than the boat-like (also suggested by Beckwith), and the former clearly suggests a preferable interaction between the reacting centers in the transition state, i.e., more favorable overlap between the π -orbital of the ene part and the SOMO (where the radical is localized).^{18,4c} In contrast, for the 5-*exo* pathways of acyl-substituted radicals, the boat-like conformation of TS has the lowest energy. These systems are also in contrast with the prediction of Baldwin's rules and undergo a 6-*endo*¹⁹ ring-forming process (Figure 1, reaction II) via a chair-like transition state.

At this point it is also worthwhile to mention that the analogous ring closure of the prototypical 1,3-hexadiene-5-yn-1-yl radical, which gives the phenyl radical in a regioselective manner,²⁰ occurs in a multistep mechanism.²¹ Theoretical work showed that the latter process occurs in the 5-*exo* mode (contrary to common belief) followed by two additional steps (rearrangement via cyclization and ring-opening steps) resulting in the formation of the phenyl radical.²¹ For the cyclization of 1-vinyl-5-methyl-5-hexenyl radicals²² Gomez, Lopez and co-workers demonstrated that the "direct" 6-*endo-trig* ring closure is an

effective competing reaction²³ among the rapid rearrangement of the methylenecyclopentyl radical via a reversible 3-*exo-trig* cyclization following the 5-*exo* attack, which was supposed by Beckwith and O'Shea.²⁴ For competitive 5-*exo-dig* and 6-*endo-dig* cyclizations of vinyl and aryl radicals,²⁵ no rearrangement-type reactions were reported, and the trends in the activation barriers indicate a strong stereoelectronic preference for the 5-*exo-dig* cyclizations. This is fully consistent with the shorter incipient $C_1 \cdots C_{exo}$ distances in the starting materials and with the smaller deformation needed to form the new bonds via transition state.²⁶

From a stereochemical point of view one of the guidelines of Beckwith states that "1- or 3-substituted systems afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted systems give mainly *trans*-products."²⁵ Experimental studies have shown that the chair-like transition state conformation is energetically unfavorable with bulky substituents, as it would force the bulky phenyl group into an axial position. The unexpected stereochemistry can be rationalized if one assumes a boat-like transition state for the cyclization.²⁷

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The kinetics and mechanism of the analogous reactions of nitrogen-centered radicals are not well established.²⁸ Previously, some of the present authors have examined the cascade cyclizations of *N*-alkenyl-2-aziridinylmethyl radicals²⁹ (Figure 1, reaction III) using density functional theory (DFT) calculations. In this contribution, they reviewed the details of three-membered ring-opening processes, primarily the β -cleavage of aziridinyl radicals, and the above-mentioned unclarified treatment of cyclization of nitrogen-centered radicals.

In the present contribution, the regioselectivity of two distinct types of radical cyclization reactions (both alkyl- and acyl-substituted radical cyclizations (“simple”^{3a,30}) and the above-mentioned cascade reactions, depicted in Figure 1) will be investigated using reactivity indices introduced within the framework of spin-polarized DFT. It will be shown that the regioselectivities estimated using this approach are in good agreement with the experimental results. The different nitrogen- and carbon-centered radicals investigated in this work are depicted in Scheme 1. Radicals **9**, **11**, **13**, and **15** are the intermediates of the second step, whereas **10**, **12**, **14**, and **16** correspond to the intermediates of the third step of the cascade reactions. Radicals **1–4** and **5–8** are the alkyl- and acyl-substituted model systems, respectively, and **10a** and **10b** are the *trans* and *cis* conformers of radical **10**, respectively. We briefly discuss the effect of the orientation of the attacking radical relative to the double bond on the regioselectivity prediction. We also discuss why the non-spin-polarized Fukui functions seem to be inefficient for these systems and why, on the other hand, the spin-polarized indices give the correct regioselectivity.

Theory and Computational Details

Density functional theory provides a very convenient framework for the discussion of chemical reactivity. A series of global and local quantities, the so-called reactivity descriptors or indices, have been introduced to describe the extent of the response of a molecular system toward perturbations in either its number of electrons, *N*, its external (i.e., due to the nuclei) potential, $v(r)$, or both.³¹ An important example of these reactivity indices is the Fukui function, introduced by Parr and Yang,³² defined as the response of the system’s electron density $\rho(r)$ due to a perturbation in its total

number of electrons *N* at a constant external potential $v(r)$. Due to the discontinuity of the electron density with respect to the number of electrons, three different Fukui functions can be introduced, representing the case of a nucleophilic $f^+(r)$, electrophilic $f^-(r)$, and a neutral (radical) attack $f^0(r)$:

$$f^+(r) = (\partial\rho(r)/\partial N)_{v(r)}^+ \approx \rho_{N+1}(r) - \rho_N(r) \quad (1)$$

$$f^-(r) = (\partial\rho(r)/\partial N)_{v(r)}^- \approx \rho_N(r) - \rho_{N-1}(r) \quad (2)$$

$$f^0(r) = \frac{1}{2}(f^+ + f^-) \approx \frac{1}{2}(\rho_{N+1}(r) - \rho_{N-1}(r)) \quad (3)$$

where $\rho_{N+1}(r)$, $\rho_N(r)$, and $\rho_{N-1}(r)$ are the electron densities of the *N* + 1, *N*, and *N* – 1 electron system, respectively, all obtained at the geometry of the *N* electron system, due to the fact that the derivative is taken at a constant external potential. However, in chemistry it is customary to work with properties associated with atoms and functional groups in the molecule. In this context, a useful approximation to describe the site reactivity is given by the condensed-to-atom Fukui indices by using an atomic charge partitioning scheme:³³

$$f_k^+ \approx N_k(N + 1) - N_k(N) \quad (4)$$

$$f_k^- \approx N_k(N) - N_k(N - 1) \quad (5)$$

$$f_k^0 \approx \frac{1}{2}(N_k(N + 1) - N_k(N - 1)) \quad (6)$$

where $N_k(N + 1)$, $N_k(N)$, and $N_k(N - 1)$ represent the electron populations on atom *k* in the *N* + 1, *N*, and *N* – 1 electron system.

Another related quantity is the local softness,^{34,35} $s(r)$:

$$s(r) = (\partial\rho(r)/\partial\mu)_{v(r)} = (\partial\rho(r)/\partial N)_{v(r)} (\partial N/\partial\mu)_{v(r)} = Sf(r) \quad (7)$$

where *S* is the global softness, which can be computed using the vertical ionization energy (IE) and electron affinity (EA) of the system:³⁴

$$S \approx 1/(\text{IE} - \text{EA}) \quad (8)$$

One can interpret the reaction ability toward soft reagents of the different parts of the molecules with the condensed form of the local softness, written as

$$s_k^i = Sf_k^i \quad (9)$$

where *i* equals either +, –, or 0 depending on whether the system undergoes a nucleophilic, electrophilic, or radical attack. In addition to the Fukui function, this quantity permits comparison of the reactivity of different sites in different molecules and is thus preferred to study intermolecular reactivity.

When using these indices to describe the molecular site selectivity, one usually works within the framework of the hard and soft acids and bases (HSAB) principle³⁶ for which theoretical justifications have been provided in recent years.^{36c–e} One can also adopt

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a local version of this principle,³⁷ as will be discussed later on in this contribution.

For the title reactions, it is natural to explore the condensed-to-atoms electronic Fukui functions within the framework of spin-polarized DFT,³⁸ since in addition to the above-mentioned indices, these explicitly consider responses of the systems to changes in the spin number N_s (i.e., the difference between the number of α and β electrons).⁴⁰

In this approach, four types of “spin-polarized” Fukui functions can be written as

$$f_{NN}(r) \equiv \left[\frac{\delta \mu_N}{\delta v(r)} \right]_{N,N_s,B(r)} = \left[\frac{\delta \rho(r)}{\delta N} \right]_{N_s,v(r),B(r)} \quad (10)$$

$$f_{SN}(r) \equiv -\frac{1}{\mu_B} \left[\frac{\delta \mu_N}{\delta B(r)} \right]_{N,N_s,B(r)} = \left[\frac{\delta \rho_S(r)}{\delta N} \right]_{N_s,v(r),B(r)} \quad (11)$$

$$f_{NS}(r) \equiv \left[\frac{\delta \mu_S}{\delta v(r)} \right]_{N,N_s,v(r)} = \left[\frac{\delta \rho(r)}{\delta N_s} \right]_{N,v(r),B(r)} \quad (12)$$

$$f_{SS}(r) \equiv -\frac{1}{\mu_B} \left[\frac{\delta \mu_S}{\delta B(r)} \right]_{N,N_s,v(r)} = \left[\frac{\delta \rho_S(r)}{\delta N_s} \right]_{N,v(r),B(r)} \quad (13)$$

In these equations, $B(r)$ is the external magnetic field, μ_B is the Bohr magneton,

$$\mu_N = \left(\frac{\partial E}{\partial N} \right)_{N_s,v(r),B(r)} \quad \text{and} \quad \mu_S = \left(\frac{\partial E}{\partial N_s} \right)_{N,v(r),B(r)} \quad (14)$$

are the chemical and spin potentials, and

$$\rho(r) = \rho^\uparrow(r) + \rho^\downarrow(r) \quad \text{and} \quad \rho_S(r) = \rho^\uparrow(r) - \rho^\downarrow(r) \quad (15)$$

are the electron and spin densities, respectively. μ_N is associated with the energy change upon electron-transfer processes at constant multiplicity, whereas μ_S measures the energetic cost for the system to change its spin number, i.e., to undergo a spin polarization at a constant number of electrons.

One of the aims of this paper is the application of the latter “spin-polarized” Fukui function describing the chemical reactivity for a process at constant spin number N_s , i.e., f_{NN} , to systems undergoing intramolecular radical addition reactions.

Within a frozen orbital approximation, the spin Fukui functions can be computed using the HOMO and LUMO shape factors,

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proposed by Galván et al.^{39a}

$$f_{NN,k}^- = \frac{1}{2} [\sigma_k^{\text{HOMO},\uparrow} + \sigma_k^{\text{HOMO},\downarrow}] \quad (16)$$

$$f_{NN,k}^+ = \frac{1}{2} [\sigma_k^{\text{LUMO},\uparrow} + \sigma_k^{\text{LUMO},\downarrow}] \quad (17)$$

In ref 39j, a comparison between the frozen orbital approximation and the finite difference approximation was presented, showing that similar results for both methods are obtained when occupied orbitals are involved. Very recently, both approximations were studied for a set of carbene and related systems and were found to give similar results.⁴⁰ As such, the FOA can be considered to be a viable approach for the present set of molecules.

The spin-polarized Fukui function for a radical attack is the average of these two functions:

$$f_{NN,k}^0 = \frac{1}{2} [f_{NN,k}^+ + f_{NN,k}^-] \quad (18)$$

To calculate the shape factors via molecular spin orbital approximation, different partitioning schemes have been introduced.⁴¹ For instance, summing the basis-set components corresponding to atom k :

$$\sigma_k^{\text{HOMO},\uparrow} = \frac{1}{n_{\text{deg,HOMO},\uparrow}} \sum_{g_{\text{HOMO},\uparrow}}^{n_{\text{deg,HOMO},\uparrow}} \sum_{\mu \in k} \sum_{\nu} c_{\mu,g_{\text{HOMO},\uparrow}} c_{\nu,g_{\text{HOMO},\uparrow}} S_{\mu\nu} \quad (19)$$

$$\sigma_k^{\text{HOMO},\downarrow} = \frac{1}{n_{\text{deg,HOMO},\downarrow}} \sum_{g_{\text{HOMO},\downarrow}}^{n_{\text{deg,HOMO},\downarrow}} \sum_{\mu \in k} \sum_{\nu} c_{\mu,g_{\text{HOMO},\downarrow}} c_{\nu,g_{\text{HOMO},\downarrow}} S_{\mu\nu} \quad (20)$$

$$\sigma_k^{\text{LUMO},\uparrow} = \frac{1}{n_{\text{deg,LUMO},\uparrow}} \sum_{g_{\text{LUMO},\uparrow}}^{n_{\text{deg,LUMO},\uparrow}} \sum_{\mu \in k} \sum_{\nu} c_{\mu,g_{\text{LUMO},\uparrow}} c_{\nu,g_{\text{LUMO},\uparrow}} S_{\mu\nu} \quad (21)$$

$$\sigma_k^{\text{LUMO},\downarrow} = \frac{1}{n_{\text{deg,LUMO},\downarrow}} \sum_{g_{\text{LUMO},\downarrow}}^{n_{\text{deg,LUMO},\downarrow}} \sum_{\mu \in k} \sum_{\nu} c_{\mu,g_{\text{LUMO},\downarrow}} c_{\nu,g_{\text{LUMO},\downarrow}} S_{\mu\nu} \quad (22)$$

where σ_k represents the shape factors of corresponding molecular orbitals, $c_{\mu,g}$ are the molecular orbital coefficients, $n_{\text{deg,mo}}$ is the number of degenerate frontier orbitals of the given specified spin state (i.e., a crude average for possible effects due to the presence of degenerate molecular frontier spin orbitals).

These expressions constitute condensed-to-atom k Fukui responses where condensation is achieved by summing overall the basis-set components centered at the k th atom of interest and that the overlap integral $S_{\mu\nu}$ is performed over entire three-dimensional molecular space.⁴² This partitioning scheme has also been found particularly useful to compute condensed values of DFT-based reactivity indices.^{42,43} Note that these equations are obtained by applying a Mulliken type of approach; a revival of interest for Mulliken type of projection operators exists recently.⁴⁴

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TABLE 1. Relative Energies and Free Energies of the Different Conformers of a Series of Simple Alkyl- and acyl-substituted Model Systems^a

reaction	structure	B3LYP/6-311++g(d,p)		MP2/6-311++g(d,p)	
		ΔE	ΔG	ΔE	ΔG
I	1a	6.24	5.95	2.20	3.43
	1b	1.65	1.89	0.00	0.00
	1c	0.35	0.00	0.42	1.17
	1d	6.80	7.63	2.06	2.88
	1e	0.00	0.46	0.63	1.20
II	5a	1.15	2.93	0.00	0.00
	5b	5.94	7.26	1.00	2.55
	5c	0.00	0.00	0.55	0.51
	5d	2.81	2.31	0.45	1.27

^a At the (U)B3LYP/6-311++g(d,p) and (U)MP2/6-311++g(d,p) levels. For the numbering of the different conformers, see Figures 2 and 3. All values are in kcal/mol.

Note from eqs 10–13 that $f_{NN}(r)$ is the equivalent of the Fukui function in the non-spin-polarized case but with the additional restriction that the spin number N_s should also remain constant. It is thus more suited to describe charge-transfer processes without a change in the total spin multiplicity of the system. Hence, it measures the initial response in the reorganization of the charge density upon removing (f_{NN}^-) or adding (f_{NN}^+) exactly the same fraction of the number of electrons to the spin-up and spin-down frontier molecular orbitals. For the description of a radical attack, one uses the average of f_{NN}^- and f_{NN}^+ .

All calculations were performed using the Gaussian03⁴⁵ software package. For the intermediates of the cascade reactions, i.e., for radicals **9–16**, we used the (U)B3LYP/6-311G(d,p) level (see ref 30), whereas radicals **1–8** were optimized at the (U)B3LYP/6-311++G(d,p) level⁴⁶ of theory. In these cases a frequency analysis was performed, and all structures were verified as minima on the potential energy surface. For radical systems, one could expect a less optimal performance of DFT-based calculation methods.⁴⁷ In order to confirm the level of theory, the different conformations of reactants of simplest cyclizations (**1** and **5**) were optimized at (U)MP2/6-311++g(d,p). As can be seen from Table 1, the relative energies change within a few kcal/mol, the difference between geometries calculated with both methods being negligible.

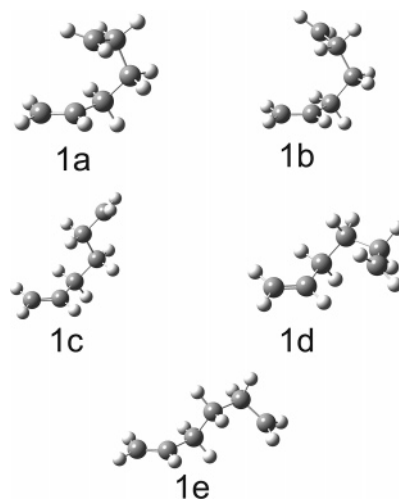
Natural population analysis (NPA)⁴⁸ charges were obtained on all radicals with the NBO program in Gaussian03 at the B3LYP/

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**FIGURE 2.** Different conformers of **1** for the doublet ground state at the (U)B3LYP/6-311++g(d,p) level.

6-311++G(d,p) level,⁴⁹ in order to compute the condensed Fukui functions. Although the differences in the optimized geometries for these systems are negligible as far as the inclusion of diffuse functions in the basis set is concerned, their inclusion is important in the computation of the Fukui functions, as this involves the calculation of a stable radical anion. CASSCF(3,3)/6-311++G// (U)MP2/6-311++g(d,p) and CASSCF(5,5)/6-311++G// (U)MP2/6-311++g(d,p) calculations were carried out for **1a** and **5d**, respectively, to make sure that these systems can be described by a single determinant; the weights of the ground state configuration are 0.975 and 0.96 for **1a** and **5d**, respectively, confirming the assumed single-reference character of these species. The spin-polarized Fukui functions f_{NN} were computed using approximations (eqs 16 and 17); to calculate the $S_{\mu\nu}$ values simple modifications to the 1601.F routine of Gaussian have been introduced.^{41b} According to the results of CASSCF calculations, the required population analysis can be performed with confidence.

Results and Discussion

In the first part, we have investigated the importance of the orientation of the attacking radical relative to the double bond, considering the cases of both a single cyclization and a domino reaction.

We will first discuss the results for the single cyclization. The reactants in different conformations were identified for the two simplest model systems (**1** and **5**) shown in Figures 2 and 3.

In Figure 2, the five investigated orientations of the alkyl toward the double bond (which can be found after applying two internal rotations) for the additions of alkyl-substituted radicals are depicted: **a**, **b**, and **c** correspond to conformers generated by rotating around the C₂–C₃ bond (see Scheme 2) in the most curved chain, while **d** and **e** correspond to one of the “near-attack” orientations and the linear conformer, respectively.

As expected, the most stable conformer of **1** is the linear conformer (see Table 1 for the relative energies and relative free energies) at the B3LYP level; at the MP2 level, conformer **b** is the more stable one, the difference with the linear conformer is only 0.63 kcal/mol. For the two near-attack conformations (**a** and **d**), the Bürgi–Dunitz angles and

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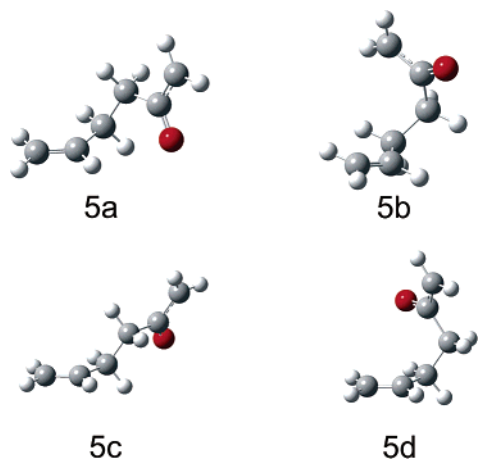
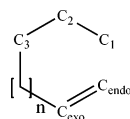


FIGURE 3. Different conformers of **5** for the doublet ground state at the (U)B3LYP/6-311++g (d) level.

SCHEME 2. Numbering of Structures Studied



C_1 – C_{exo} distances are equal to $\alpha = 106.5^\circ$ and 138.7° and $r_{C_1-C_{exo}} = 3.156$ and 3.244 Å, respectively. This suggests that the cyclization of alkyl-substituted radicals starts from the **a** type conformers, since for these structures the angle α is the closest to the tetrahedral angle. Very recently Guan et al.⁵⁰ studied the 6,6-diphenyl-5-hexenyl radical systems to determine the rate constant of the 5-*exo* radical cyclizations with different substituents. Our near-attack orientation conformer is the equivalent of their radical reactant (RR), and comparing the geometrical data, one can find that the geometry turns out to be relatively insensitive for the substitutions.

Similarly, **5** was used to determine the most beneficiary initial structure for acyl-substituted radicals. These conformers are depicted in Figure 3, and the relative energies and free energies are again listed in Table 1. In this case the in-plane geometry at the radical center (C_1 , C_2 , C_3 , and O are in plane) causes a longer distance between the acceptor and donor part of the molecule. The linear orientation (conformer **c**) again is the most stable conformer at the B3LYP level; **b** and **d** are the two near-attack conformations with $\alpha = 98.04^\circ$ and 106.1° , $r_{C_1-C_{exo}} = 3.896$ and 4.036 Å, respectively. The radical cyclization of acyl-substituted chains occurs via the **d** conformer, because it is more stable than **b**, and the corresponding Bürgi–Dunitz angle is closer to the favored tetrahedral angle than in **b**. These comparisons establish the further investigation of the methyl-substituted alkyl and acyl radicals for only the linear (**1e**, **2e**, **3e**, **4e**, **5c**, **6c**, **7c**, **8c**) and in the most favored near-attack initial orientations (**1a**, **2a**, **3a**, **4a**, **5d**, **6d**, **7d**, **8d**).

In the case of the cascade reactions the radicals **9–16** are the intermediates, located on the reaction coordinate after the three-membered ring opening. These structures were used to predict the regioselectivity for the addition of the nitrogen radical to the double bond.

Next, we assess the regioselectivity of the intramolecular addition of the carbon or nitrogen radical to the ene side of the compound using the non-spin-polarized DFT-based reactivity

TABLE 2. Condensed Fukui Functions for Both Model and Cascade Cyclizations^a

				f^0		
		experimentally preferred carbon		N, C	C_{exo}	C_{endo}
I	linear	1e	exo	0.585	−0.004	0.113
		2e	exo	0.486	−0.017	0.094
		3e	exo	0.565	0.002	0.107
I	near-attack	4e	exo	0.553	0.001	0.094
		1a	exo	0.525	−0.018	0.118
		2a	exo	0.457	−0.019	0.089
		3a	exo	0.545	−0.007	0.086
II	linear	4a	exo	0.502	−0.017	0.103
		5c	endo	0.474	0.017	0.112
		6c		0.407	−0.003	0.090
		7c		0.466	0.030	0.113
		8c	endo	0.452	0.029	0.101
II	near-attack	5d	endo	0.468	0.023	0.090
		6d		0.401	−0.001	0.066
		7d		0.446	0.045	0.095
		8d	endo	0.443	0.040	0.082
III	2 step	9	exo	0.447	0.002	0.092
		11	exo	0.456	0.010	0.071
		13	exo	0.452	0.012	0.072
		15	exo	0.443	0.004	0.068
III	3 step	10a	exo	0.554	−0.027	0.036
		10b	exo	0.514	−0.019	0.101
		12	exo	0.524	−0.018	0.062
		14	exo	0.542	−0.016	0.093
		16	exo	0.531	−0.020	0.090

^a At the (U)B3LYP/6-311++g (d,p) level. All values are in au.

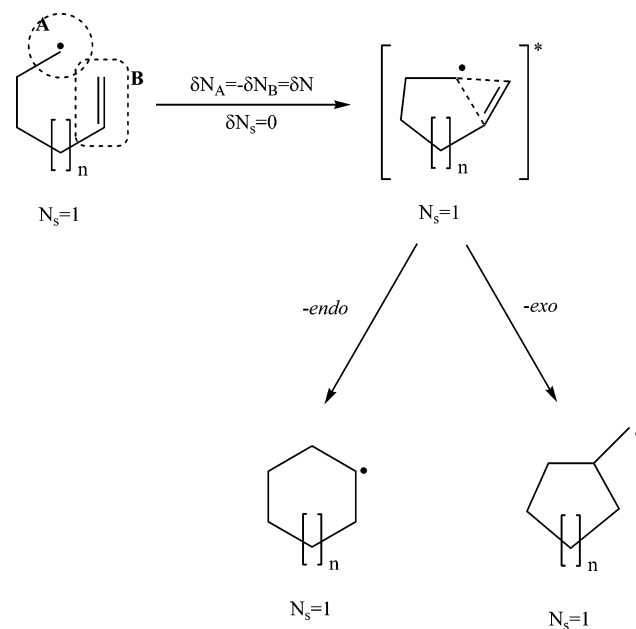


FIGURE 4. Spin-polarized specification of the initial stage in the radical cyclizations.

indices and the local hard and soft acids and bases principle.³⁷ In our case, following the finite difference approach, the smallest absolute value of the difference in local Fukui functions between the nitrogen or carbon radical on one hand and one of the carbon atoms of the double bond (C_{exo} or C_{endo}) on the other corresponds to the atom more susceptible to radical attack. One should however note that, in some cases, this principle was found to be problematic, indicating that a nonreactive site will be the most important.⁵¹ One should indeed carefully check that the smallest difference in Fukui functions corresponds to the

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TABLE 3. Condensed Spin-Polarized Fukui Functions f_{NN}^0 for Both Model and Cascade Cyclizations^a

				f_{NN}^0				
experimentally preferred carbon				N, C	C _{exo}	C _{endo}	Δf_{NN} (exo)	Δf_{NN} (endo)
I	linear	1e	exo	0.283	0.480	-0.134	0.197	0.417
		2e	exo	0.825	0.438	-0.066	0.387	0.891
		3e	exo	0.329	0.627	-0.147	0.298	0.476
		4e	exo	0.358	0.094	0.059	0.264	0.299
I	near-attack	1a	exo	0.337	0.438	-0.055	0.101	0.392
		2a	exo	0.691	0.279	-0.016	0.412	0.707
		3a	exo	0.385	0.494	-0.079	0.109	0.464
		4a	exo	0.324	0.304	0.112	0.020	0.212
II	linear	5c	endo	-0.002	0.136	0.051	0.138	0.053
		6c		0.521	0.131	-0.015	0.390	0.536
		7c		0.092	0.361	0.139	0.269	0.047
		8c	endo	-0.046	0.156	0.189	0.202	0.235
II	near-attack	5d	endo	0.072	0.188	0.042	0.116	0.030
		6d		0.359	0.145	-0.156	0.214	0.515
		7d		0.028	0.406	0.101	0.378	0.073
		8d	endo	0.026	0.239	0.158	0.213	0.132
III	2 step	9	exo	0.411	0.162	0.070	0.249	0.341
		11	exo	0.434	0.050	0.061	0.384	0.373
		13	exo	0.444	0.139	0.066	0.305	0.378
		15	exo	0.485	0.126	0.030	0.359	0.455
III	3 step	10a	exo	0.094	0.157	-0.110	0.063	0.204
		10b	exo	0.275	0.244	-0.077	0.031	0.352
		12	exo	0.175	0.142	-0.132	0.033	0.307
		14	exo	0.099	0.163	-0.127	0.064	0.226
		16	exo	0.105	0.180	-0.095	0.075	0.200

^a At the (U)B3LYP/6-311++g (d,p) level. Also given are the Fukui function differences $\Delta f_{NN}(\text{exo}) = |f_{NN}^0(\text{N, C}) - f_{NN}^0(\text{exo})|$ and $\Delta f_{NN}(\text{endo}) = |f_{NN}^0(\text{N, C}) - f_{NN}^0(\text{endo})|$. All values are in au.

combination of the Fukui function on the radical center with the highest value of the Fukui function on the atoms of the double bond, corresponding to a soft–soft interaction (i.e., an interaction between atoms of similar (high) softness). Moreover, it should be remarked that this proposed Δf criterion (i.e., smallest absolute difference between the Fukui functions of the different interacting sites) only makes sense in the case of an intramolecular interaction; for an intermolecular process, one should use the difference of the condensed local softness values computed with this Fukui function. Table 2 shows the condensed f_k^0 values (calculated using NPA charges) for the simple cyclization in two different orientations, alkyl- and acyl-substituted chains in near-attack and in linear arrangements and for the cascade intermediates. The numbering of all the analyzed atoms is depicted in Scheme 2.

From Table 2, it can be seen that the carbon atom at the *exo* position (C_{exo}) has a f_k^0 value smaller than that of the carbon atom at the terminal position (C_{endo}). Hence the C_{endo} atom is more susceptible to radical attack than C_{exo}. Thus, the prediction for the alkyl-substituted hexenyl radical (I) based on the non-spin-polarized Fukui function is not in agreement with the experimentally observed outcome that the hexenyl radical and its substituted analogues cyclize with high regioselectivity to give five-membered rings. For acyl-substituted radicals (II), where experimentally a clear preference for the 6-*endo* process is found, the calculated regioselectivity is in good agreement with experiment. The calculated Fukui functions for the second and third step of radical cascade cyclizations of *N*-alkenyl-2-aziridinylmethyl radicals to pyrrolizidines and indolizidines show that in both steps the f_k^0 value of the C_{endo} is always higher than that of the C_{exo}. It is thus expected that the radical

attack will preferentially be at the C_{endo} carbon atom. These results are not in agreement with experimental data, because the observed regioselectivity and the calculated activation barriers show that the cyclization of the nitrogen radical (second step) and the carbon radical (third step) always prefer the attack on the C_{exo} resulting in the formation of the “smaller” ring.

Next, we tried to gain more insight in the failure of the condensed Fukui function in the prediction of the regioselectivity of these radical cyclization reactions. In a bimolecular radical addition one can expect little charge transfer between the two molecules. When charge is transferred from the donor to the acceptor, the spin state of both of the reactants is changing. Thus, considering the separated reactants, the nonpolarized Fukui function measures the response of the density for each reactant to a change in number of electrons at fixed external potential but variable spin number and can be expected to give the right regioselectivity. In the reaction studied in this work, part of the molecule acts as an electron acceptor and another part as an electron donor. In an intramolecular addition, during the charge transfer from the donor part to the acceptor part of the molecule, the spin state of the molecule remains constant (Figure 4).

In our case the approaching radical (nucleophilic, electrophilic) adds to the π bond of the carbon–carbon double bond to form a closed-ring doublet radical. In such a process, the number of electrons is changing from a local point of view (charge transfer occurs from one part of the molecule to another one) at constant global spin number N_s (both the reactant and the closed ring are in the doublet state), and the generalized Fukui function $f_{NN}(r)$ should be used to investigate the regioselectivity. This index measures the initial response of the electron density to a constrained charge transfer, i.e., the spin number N_s remains constant during the change in the number

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of electrons. An example is the modeling of an intramolecular rearrangement (which occurs at constant multiplicity).

We have consequently studied the regioselectivity in the different cases considered above using the spin-polarized reactivity indices, as this cyclization involves a doublet radical compound. Also in this case, the smallest absolute value of the difference in local spin-polarized Fukui functions between the nitrogen or carbon radical on one hand and one of the carbon atoms of the double bond (C_{exo} or C_{endo}) on the other should identify the atom more susceptible to radical attack. The calculated $f_{\text{NN}}(r)$ values for the simple cyclization of alkyl-substituted radicals (I) in linear and in near-attack orientation are given in Table 3. One can indeed observe that $\Delta f_{\text{NN}}^0(r)$ is always smaller between the radical and C_{exo} of the double bond than between the radical and the terminal carbon atom (C_{endo}), i.e., it shows a preference for the formation of 5-*exo* rather than the 6-*endo* products, in good agreement with the experimental results.

The non-spin-polarized Fukui functions are relatively insensitive to structural orientation in radicals **1–9**, whereas $f_{\text{NN}}(r)$ changes significantly when going from the linear to the other conformer generated by performing the internal rotations. In the near-attack conformers C_{exo} is softer or more susceptible to radical attack than in linear conformers.

At this point we have to note that the investigations of the cyclization of 5-methyl-5-hexenyl radical (**3**) from different groups come to different conclusions; Beckwith at al. supposed a preferential *endo* ring closure⁵² supported by theoretical calculations, whereas work from Walling at al. clearly showed¹¹ the exclusive formation of the cyclopentylmethyl radical in agreement with Baldwin's rules. In the results of the latter paper one can realize the influence of the methyl substituent, maintaining the steric effect, but the reaction occurs in *exo* mode and our calculations are in agreement with their results.

In the case of acyl-substituted radicals (Table 3, II), in the near-attack orientation the terminal carbon (C_{endo}) atom has a much better "matching" for radical attack, except for **6**, than C_{exo} . According to the computational results the 6-*endo* pathway is generally favored in this case; the only exception occurs when an alkyl substituent connects to the radical carbon atom. However, there are no available experimental data for this system, and theoretical calculations showed that the lowest activation barrier corresponds to the *endo* cyclization. Note that in the more complex Jung–Rayle radical cyclization⁵³ (where, instead of a methyl group, a five-membered ring is connected to the carbon-centered radical), only 5-*exo* cyclization was mentioned. The $f_{\text{NN}}^0(r)$ values for the linear conformation are very different from the $f_{\text{NN}}^0(r)$ values for the near-attack orientation and thus clearly show their usefulness for prediction.

The $f_{\text{NN}}^0(r)$ values for the nitrogen radical and for the carbon 6-*endo* and 5-*exo* cyclizations of the cascade reaction are also given in Table 3. Experimentally both cyclization steps of the

domino reaction (III) were found to be a regioselective process as it leads, if it occurs, always to the smaller ring. One can find a good agreement between our computational results and available experimental data. The better matching always corresponds to the *exo* ring closure. In the case of **11** the $f_{\text{NN}}^0(r)$ values are quite similar for both C_{exo} and C_{endo} carbon atoms.

Conclusion

In this contribution, we have presented a study of the regioselectivity of the radical cyclizations of alkyl- and acyl-substituted hexenyl radicals and the regioselectivity of the cascade radical reaction of *N*-alkenyl-2-aziridinylmethyl radicals, using DFT-based reactivity descriptors. In the first part, we analyzed the different initial orientations for the two simplest alkyl- and acyl-substituted systems. The two near-attack conformations **1a** and **5c** match the Bürgi–Dunitz trajectory. In the case of the second and third step of the cascade reactions, we used the geometry of the intermediates.

In the next step, we investigated the regioselectivity using the Fukui functions within the framework of the local hard and soft acids and bases (HSAB) principle. The interaction was investigated as the interaction of two radical species in both near-attack and linear conformations. The Fukui indices predict that both alkyl- and acyl-substituted radicals occur via 6-*endo* mode. A similar preference was found in the cascade reaction; the ring-forming steps occur on the terminal carbon. This result indicates that the regioselectivity can be explained only in the case of the intramolecular addition of acyl-substituted systems.

Finally, we applied the reactivity descriptors emerging from spin-polarized density functional theory because in an intramolecular process the number of electrons is changing from a local point of view at a constant global spin number N_s . The analysis of the condensed-to-atom spin-polarized Fukui functions indicates that the correct regioselectivity of the intramolecular radical additions emerges from considering the interaction of two radical species in the near-attack conformation. In these cases, good agreement was found when comparing the predicted regioselectivities with experimental data.

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Supporting Information Available: Optimized geometries and energies of all compounds considered in this work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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