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N-Alkenyl-2-aziridinylmethyl Radicals and *N*-Alkenylaminyl Radicals in Cascade Cyclizations to Pyrrolizidines and Indolizidines

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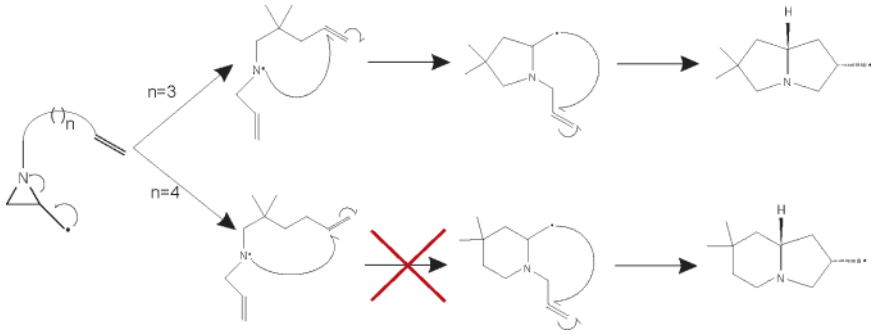


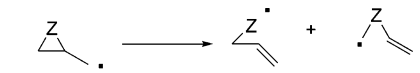
The radical cascade cyclizations of *N*-alkenyl-2-aziridinylmethyl radicals to pyrrolizidines and indolizidines were examined using density functional theory (DFT) calculations. A large preference for cyclization to pyrrolizidines was found. These predictions corroborated very well with experimental results, leading to an efficient synthesis of pyrrolizidines. No radical cascade cyclization to indolizidines could be performed in practice as only ring opening of *N*-alkenyl-2-aziridinylmethyl radicals to *N*-allyl-*N*-alkenylamines occurred.

1. Introduction

2-Oxiranylmethyl radicals[1−5] and their carbon analogues, i.e., cyclopropylmethyl radicals,[1] have received considerable attention in recent years because of their pronounced potential to give rise to ring-opening reactions, the resulting radicals being of utility in a variety of synthetic transformations (Scheme 1; Z = O, CR^1R^2).

The cyclopropylcarbinyl−homoallylic rearrangement has been widely studied, showing that stereoelectronic factors determine the outcome of the reaction.[2,6−8] The related β-cleavage of oxiranylcarbinyl radicals has also been widely reported.[2,3,7,9,10] The ring opening of aziridinylmethyl radicals, i.e., the nitrogen analogues of 2-oxiranylmethyl radicals and cyclopropylmethyl radicals, did not receive such pronounced attention (Scheme 1; Z = NR). The β-cleavage of these aziridinylmethyl radicals has an analogous synthetic potential which has not been unraveled yet. It is known from both ab initio theoretical studies and experimental work that 2-aziridinylmethyl radicals have a kinetic preference to ring

SCHEME 1. Ring Opening of 2-Oxiranylmethyl, Cyclopropylmethyl, and 2-Aziridinylmethyl Radicals



Z = O, CR^1R^2, NR

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(1) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347−357.
(2) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091−2115.
(3) Pasto, D. J. *J. Org. Chem.* **1996**, *61*, 252−256.
(4) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.
(5) Li, J. J. *Tetrahedron* **2001**, *57*, 1−24.
(6) Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380.
(7) Jorgensen, W. L.; Laird, R. E. *J. Org. Chem.* **1990**, *55*, 9−27.
(8) Marples, B. A.; Toon, R. C. *Tetrahedron Lett.* **1999**, *40*, 4873−4876.
(9) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
(10) Bowman, W. R.; Brown, D. S.; Burns, C. A.; Marples, B. A.; Zaida, N. A. *Tetrahedron* **1992**, *48*, 6883.

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opening by cleavage of the C−N bond while a thermodynamic preference for cleavage of the C−C bond is observed.[3,8] The cyclization of *N*-butyl-4-pentenylaminyl radicals is a slow and irreversible process that is accelerated by small amounts of bis(tributyltin) oxide.[11] This was the start of some conflicting reports on such radical cyclizations. Other reports claimed the reversible cyclization of the photochemically generated *N*-butyl-4-pentenylaminyl radical,[12] while failures of similar radicals were reported as well.[13] These reports initiated studies of the kinetics of the 5-exo cyclization of the *N*-alkyl-4-pentenaminyl radical to the corresponding pyrrolidine derivative.[14] In contrast to the conclusions of Maxwell,[11] the latter publication states that all 5-exo cyclizations proceeded in a facile way and that bis(tributyltin)oxide had no catalytic effect. The cyclization of the *N*-methylpent-4-enylaminyl radical was investigated theoretically at the CBS-RAD (B3LYP, B3LYP) level of theory. This radical is predicted to undergo irreversible cyclization through the 5-exo manifold.[15,16] In the latter publication, the irreversible nature of the cyclization of the *N*-methylpent-4-enylaminyl radical was confirmed. Computations of the energies of the *N*-methyl-4-pentenylaminyl radical and the cyclized *N*-methyl-2-pyrrolidinylmethyl radical with a high level of theory (fourth-order Møller−Plesset perturbation theory) indicated that the cyclization is slightly exergonic at 298 K.[14]

Cascade reactions have become an interesting tool to construct more complex compounds. Such domino reactions lead to a minimization of waste as compared to stepwise reactions which consume larger amounts of reagents, solvents, and energy.[17] Radical domino reactions are faced with the problem of the intramolecular cyclizations of *N*-alkenylaminyl radicals.[17,18] Examples of such efficient cyclization in the direction of pyrrolizidines or indolizidines have been reported recently.[19−21]

To gain insight in the radical cascade of carbon-centered and nitrogen-centered radicals en route to pyrrolizidines and related bicyclic compounds, a theoretical study of the radical ring opening of *N*-alkenyl-2-(bromomethyl)aziridines with DFT calculations was undertaken. The purpose of this study was to investigate the synthetic potential of these domino reactions leading to important skeletons in natural product chemistry. In this context, particular attention is paid to the type of substitution in the alkenyl side chain and the alkenyl length.

2. Computational Details

Transition state theory is an adequate method for the evaluation of macroscopic kinetic quantities of chemical reactions.[22−26] It has proven its success in many studies for the quantitative prediction of kinetic parameters.[27] In TST, the rate coefficient for the reaction A → B is given by

$$k(T) = \frac{k_B T}{h} \frac{q_{\ddagger}}{q_A} e^{-\Delta E_0 / k_B T} \quad (1)$$

where k_B represents the Boltzman constant, T is the temperature, h is the Planck constant, ΔE_0 represents the molecular energy difference at absolute zero between the activated complex and the reactant (with inclusion of the zero-point vibrational energies), and $q_{\ddagger}$ and q_A are the molecular partition functions of the transition state and reactant, respectively. The molecular properties, such as geometries (moments of inertia), ground-state energies, and frequencies, required for the evaluation of the partition functions and the reaction barrier ΔE_0 are obtained by ab initio molecular calculations.

All ab initio calculations were carried out with the GAUSSIAN 98 software package[28] within the DFT framework.[29] It is generally accepted that the hybrid functional B3LYP[30] in combination with a sufficiently large basis set is able to reproduce accurate geometries especially for radical structures.[31−33] The vibrational frequencies of the optimized structures are also calculated at the same level of theory. The B3LYP harmonic vibrational frequencies are systematically larger than the observed experimental frequencies. The overestimation, however, is found to be relatively uniform, and as

(11) Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276−4283.
(12) (a) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317. (b) Newcomb, M.; Burchill, M. T.; Deeb, T. *J. Am. Chem. Soc.* **1988**, *110*, 6528. (c) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651.
(13) (a) Bowman, W. R.; Clark, D.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275. (b) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295. (c) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* **1991**, *32*, 6441.
(14) Newcomb, M.; Musa, O. M.; Martinez, F. N.; Horner, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 4569−4577.
(15) Maxwell, B. J.; Smith, B. J.; Tsanaktsidis, J. *Perkin Trans. 2* **2000**, 425−431.
(16) Maxwell, B. J., Schiesser, C. H.; Smart, B. A.; Tsanaktsidis, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2385.
(17) Tietze, L. *Chem. Rev.* **1996**, *96*, 115−136.
(18) Fallis, A. G.; Brinza, E. M. *Tetrahedron* **1997**, *53*, 17543−17594.
(19) Brown, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445−11462.
(20) Kim, S.; Lee, T. A. *Synlett* **1997**, 950.
(21) De Smaele, D.; Bogaert, P.; De Kimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797−9800.
(22) Eyring, H. *J. Chem. Phys.* **1935**, 107. A more comprehensive treatment can be found in: Wynne-Jones, W. F. K.; Eyring, H. *J. Chem. Phys.* **1935**, *3*, 492. This article is reproduced in full in: Back, M. H.; Laidler, K. L. *Selected readings in chemical kinetics*; Pergamon: Oxford, 1967.
(23) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875, **1937**, *33*, 448.
(24) Laidler, K. J. *Chemical kinetics*; HarperCollins Publishers: New York, 1987.
(25) Quarrie, D. A. Mc.; Simon, J. D. *Physical Chemistry—A molecular approach*; University Science Books: Sausalito, CA, 1997.
(26) For reviews, see, for example: (a) Pechukas, P. In *Dynamics of Molecular Collisions, Part B*; Miller, W. H., Ed.; Plenum Press: New York, 1976. (b) Laidler, K. J.; King, M. C. *J. Phys. Chem.* **1983**, *87*, 2657. (c) Truhlar, D. G.; Hase, W. L. Hynes, J. T. *J. Phys. Chem.* **1983**, *87*, 2664. (d) Gilbert, R. G.; Smith, S. C. *Theory of Unimolecular and Recombination Reactions*; Blackwell: Oxford, 1990.
(27) Smith, D. M.; Nicolaides, A.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1998**, *120*, 10223−10233.
(28) Gaussian 98, Revision A.6: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, Jr. R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G.A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E.S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.
(29) An example of a reference work: Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*,; Oxford University Press: New York, 1989.
(30) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(31) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063.
(32) Coote, M. L. *J. Phys. Chem. A* **2004** *108*, 3865−3872.
(33) Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2001**, *105*, 2936−2941.

TABLE 1. Kinetic Parameters of Dialkylaminylradicals Depicted in Scheme 2

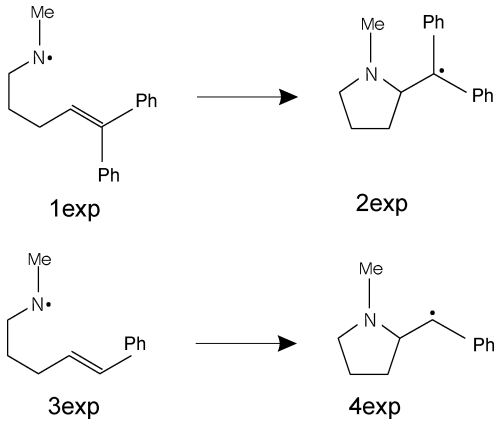
	E_a (exp)	A (exp)	$k_{293.15K}$ (exp)	E_a (theor)	A (theor)	$k_{293.15K}$ (theor)	level of theory
1exp−2exp	22.59	3.40E+09	3.20E+05				B3LYP/6-311G**//B3LYP/6-31G(d)
				41.84		4.89E+02	B3LYP/6-311G**//B3LYP/6-31+G(d)
				43.15		2.84E+02	B3LYP/6-311G**//B3LYP/6-311+g(d,p)
				41.21	1.68E+10	6.34E+02	B3LYP/6-311G**//B3LYP/6-311G**
				25.59		4.19E+05	B3LYP/6-311G**//B3P86/6-31G(d)
				28.78		1.10E+05	B3LYP/6-311G**//B3P86/6-31+G(d)
				29.59		7.87E+04	B3LYP/6-311G**//B3P86/6-311+g(d,p)
3exp−4exp	24.6	4.57E+09	1.90E+05	36.31		9.04E+03	B3LYP/6-311G**//B3LYP/6-31G(d)
				41.64		9.95E+02	B3LYP/6-311G**//B3LYP/6-31+G(d)
				41.17	3.14E+10	1.21E+03	B3LYP/6-311G**//B3LYP/6-311G**
				43.45		4.70E+02	B3LYP/6-311G**//B3LYP/6-311+g(d,p)
				26.31		5.80E+05	B3LYP/6-311G**//B3P86/6-31G(d)
				29.99		1.24E+05	B3LYP/6-311G**//B3P86/6-31+G(d)
				31.17		7.65E+04	B3LYP/6-311G**//B3P86/6-311+g(d,p)

a result generic frequency scaling factors are often applied. A scaling factor of 0.9614 is applied to the frequencies in the evaluation of the partition functions[34] while the zero-point vibrational energies are scaled with 0.9806.[34]

According to specific studies on similar radical reactions,[27] the B3LYP method gives a reliable and quantitatively good description of geometries, frequencies, reaction barriers, and preexponential factors. In the latter study, it concerned a ring-opening reaction of the 2-aziridinylcarbinyl radical toward formation of the aminyl radical. However various conflicting reports appeared on the radical cyclization of *N*-butyl-4-pentenylaminyl radical.[11,14−16] This motivated us to investigate whether B3LYP/6-311G** energies are accurate enough for our applications, i.e., if they are capable of reproducing aminyl radical kinetics within acceptable accuracy from the experimental values. Our reference experiments were taken from the recent literature[35] which concerned a kinetic scale for various dialkylaminyl radical reactions as shown in Scheme 1. The kinetic results are summarized in Table 1. The B3LYP functional largely overestimates the activation barriers of the studied cyclization reactions. Values of about 40 kJ/mol are found whereas the experimental measured barriers are in the order of 20 kJ/mol. For all tested basis sets the activation barrier remains far too high. According to studies on bond dissociation energies of N−H bonds it was found that the B3P86 functional has the potential to provide accurate kinetics for nitrogen centered radicals.[36−38] The B3P86 functional improves the energetic results drastically, and the energy barriers approximate the experimental data very well. The inadequacy of the B3LYP functional for the cyclization of aminyl radicals is quite surprising since the functional has proven to work well for other radical reactions involving carbon-centered radicals.[39,40] The previous discussion points attention to the fact that DFT methods may be very useful but only in combination with a good functional for the application of interest. B3LYP is commonly accepted to produce good results for a lot of applications but the present study shows that despite the common trust it is always needed to test the functional for the given application.

The preexponential factors are quite well predicted within the B3LYP/6-311G** level. This is not too surprising since the latter quantity merely depends on the frequencies and geometries which are commonly accepted to be well predicted with the B3LYP functional. The frequency factor is still slightly too high, but we believe this can be resolved by taking into account internal rotations properly. A similar procedure was shown for the cyclization of the butylbenzene radical.[41] Since the main goal of the paper concerns the reproduction of the synthetic potential of domino reactions, the computationally expensive exact treatment of internal rotations is not performed in this work. The overall agreement for the rate constant at 20° predicted with the B3LYP/6-311G**//B3P86/6-31G(d) method is surprisingly good: the theoretical value of 4.19×10^5 must be compared with the experimental value of 3.20×10^5. The B3LYP/6-311G**//B3P86/6-31G(d) method will be further used throughout the paper.

SCHEME 2. Unimolecular Dialkylaminyl Radical Reactions



3. Results and Discussion

3.1. Cascade Reaction toward the Formation of Pyrrolizidine Radicals. The formation of pyrrolizidine radicals starting from aziridinylmethyl radicals can be interpreted as the result of a cascade of carbon- and nitrogen-centered radicals, as schematically shown in Scheme 3 (reaction 1).

The theoretical predictions of the critical energies of the various steps of the domino reaction (reaction 1) are schematically given in Figure 1, while the kinetic parameters are listed in Table 2.

The 2-aziridinylmethyl radical can occur as its trans and cis isomers (cf. inversion at nitrogen), as depicted in Figure 2.

(34) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.
(35) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862−3868.
(36) Jursic, B. S. *THEOCHEM* **1996**, *366*, 103−108.
(37) Dilabio, G. A.; Pratt, D. A. *J. Phys. Chem. A* **2000** *104*, 1938−1943.
(38) Yao, X. Q.; Hou, X. J.; Jiao, H.; Xiang, H. W.; Li, Y. W. *J. Phys. Chem. A* **2003**, *107*, 9991−9996.
(39) Jursic, B. S. *THEOCHEM* **1999**, *492*, 285−291.
(40) Van Speybroeck, V.; Van Cauter, K.; Coussens, B.; Waroquier, M. *ChemPhysChem* **2005**, *6*(1), 180−189.
(41) Van Speybroeck, V.; Borremans, Y.; Van Neck, D.; Waroquier, M.; Wauters, S.; Saeys, M.; Marin, G. B. *J. Phys. Chem. A* **2001**, *105* (32), 7713−7723.

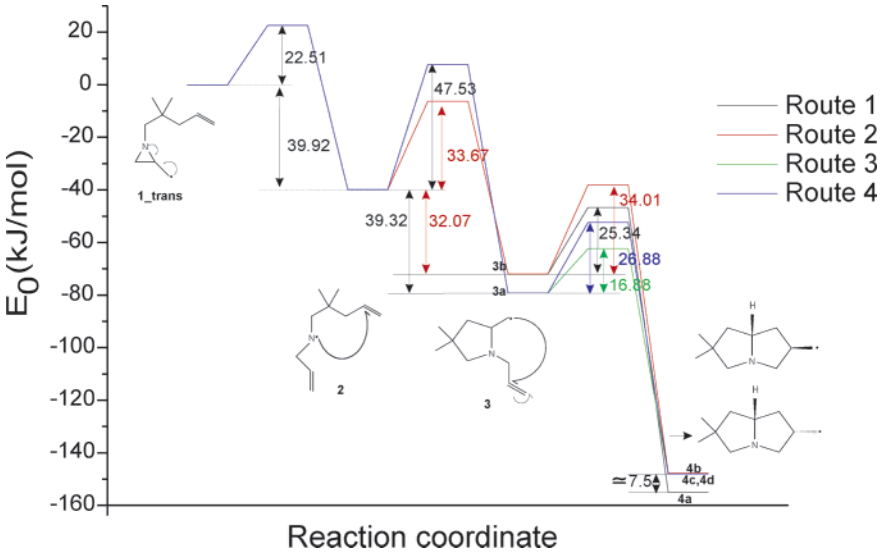
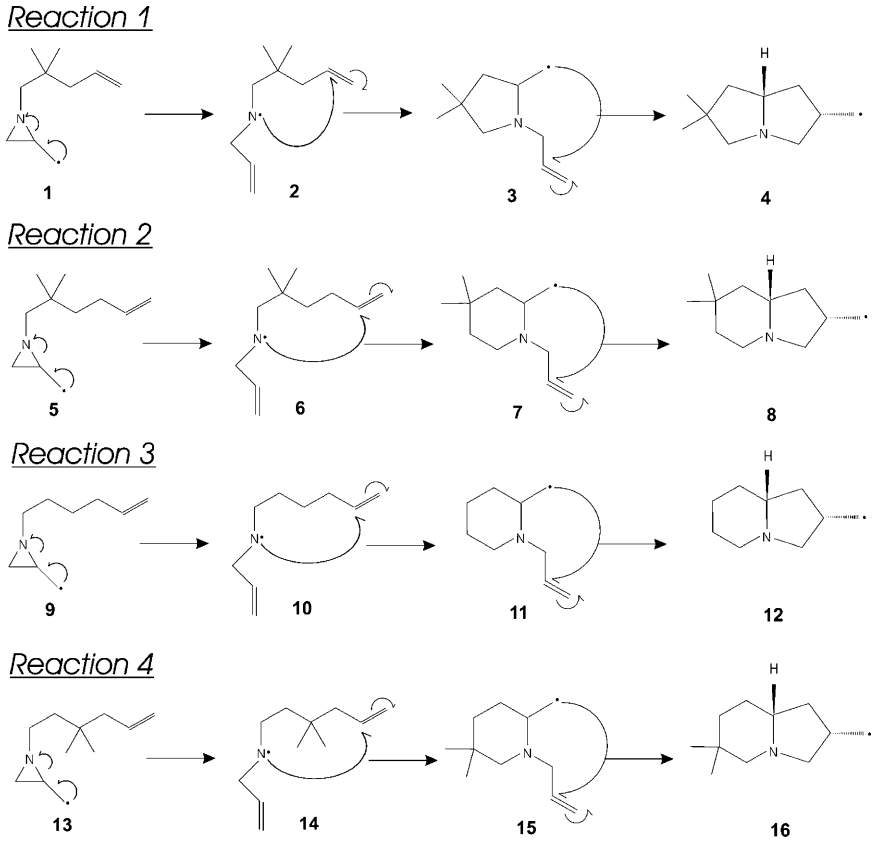


FIGURE 1. Potential of the reaction route leading to pyrrolizidines.

SCHEME 3. Reaction Routes Starting from 2-Aziridinylmethyl Radicals toward Pyrrolizidines and Indolizidines



The trans isomer is energetically favored by 6.22 kJ/mol and is retained for further calculations of the reaction barriers (cfr. Figure 1). In addition, the *trans*-aziridinylmethylradical shows multiple conformers, which can be assessed by applying various internal rotations of main subgroups of the molecule.[42,43] It is well-known that the reaction barriers are slightly altered by explicitly accounting for the internal rotations. Only the frequency factor can be seriously affected depending on the specific nature of the molecule under study. Taking into account the main objective of this paper to study the synthetic potential of the domino reactions and in view of the numerical cost of an exact treatment of internal rotations, only the most stable conformation is retained for further kinetics. The reaction barrier at 0 K is calculated as 22.51 kJ/mol which is in fair agreement with CBS-RAD results (15.4 kJ/mol) given by Smith et al. for the ring opening of the 2-aziridinylcarbinyl radical toward formation of the aminyl radical.[27] The optimized structure of the resulting *N*-allylaminyl radical (**2**) is shown in Figure 2. The

TABLE 2. Kinetic Parameters of Various Domino Reactions Displayed in Scheme 2

reaction 1	1 → 2	2 → 3	3a → 4a	3a → 4b	3b → 4c	3b → 4d
ΔE_0	22.51	33.67	25.34	34.01	16.88	26.88
E_a	23.70	32.62	23.80	32.65	15.87	25.43
A	8.22×10^{12}	6.26×10^{10}	5.90×10^{10}	8.16×10^{10}	3.30×10^{11}	3.14×10^{11}

reaction 2	5 → 6	6 → 7	7 → 8
ΔE_0	23.36	66.52	12.79
E_a	23.58	64.67	12.27
A	9.05×10^{12}	2.09×10^{10}	5.22×10^{11}

reaction 3	9 → 10	10 → 11	11 → 12
ΔE_0	23.73	58.35	13.84
E_a	24.97	60.20	13.33
A	9.41×10^{12}	2.20×10^{10}	7.04×10^{11}

reaction 4	13 → 14	14 → 15	15 → 16
ΔE_0	24.05	48.49	19.55
E_a	25.21	46.88	19.19
A	9.10×10^{12}	1.60×10^{10}	7.92×10^{11}

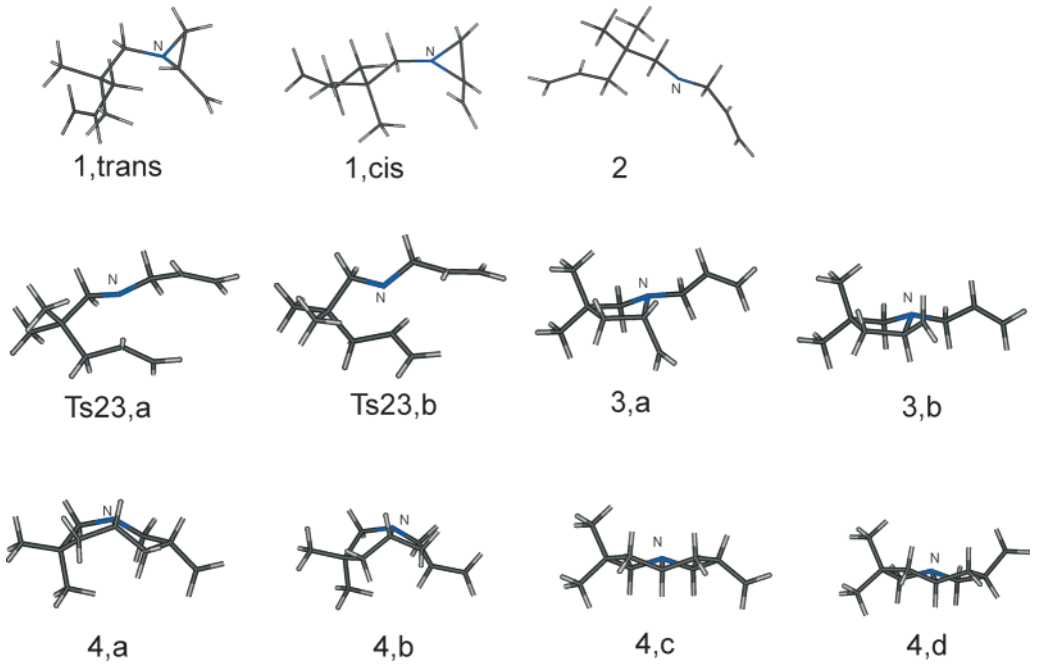


FIGURE 2. Structures of various reactants, products, and transition states leading to pyrrolizidines.

activated complex is characterized by one imaginary frequency at 565.58i 1/cm, corresponding to the cleavage of the C−N bond. This corresponds well with the experimental studies of Toon and Marples on aziridinyl carbinyl radicals, who showed that only products of C−N bond cleavage were found experimentally.[8]

The next step is the cyclization of the aminyl radical (**2**), which is trapped in an intramolecular fashion to give the 2-pyrrolidinylmethyl radical (**3**). According to several references, the cyclization of lower alkenyl and its substituted analogues is a stereoelectronically controlled process.[44,39] Beckwith showed that intramolecular addition of lower alkenyl radicals and related species occurs preferentially in the exo mode rather than in the endo mode. Preferable interactions occur between the radical center and the double bond if the radical's singly occupied orbital (SOMO) and alkene's π^*-molecular orbital are properly aligned. The specific molecular orbital in the transition state resulting from the latter interaction is shown in Figure 3a and is responsible for an extra stabilization of the transition state which is not present for the endo cyclization.[45]

The most stable transition state for 5-exo cyclization is shown in Figure 2 (TS23,a) and resembles a chair conformation as was suggested by Beckwith for the analogous ring-closure reaction of the 5-hexenylradical.[46] Spellmeyer and Houk also postulated a boatlike transition state for the exo cyclization of this radical, which

(42) Van Speybroeck, V.; Van Neck, D.; Waroquier, M.; Wauters, S.; Saeys, M.; Marin, G. B. *J. Phys. Chem. A* **2000**, 104, 10939−10950.
(43) Van Speybroeck, V.; Van Neck, D.; Waroquier, M. *J. Phys. Chem. A* **2002**, *106*, 8945−8950.
(44) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100.
(45) Tuzun, N. S.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2003**, *68*, 6369−6374.
(46) (a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484.

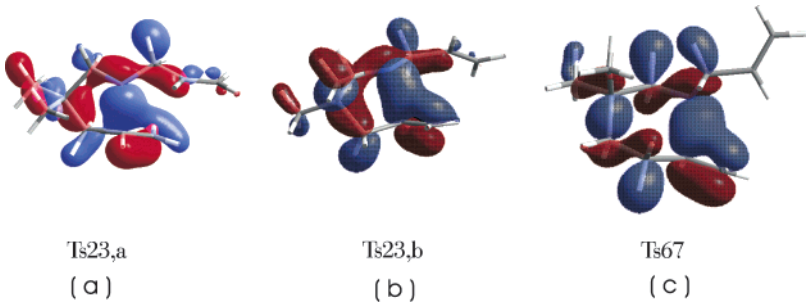


FIGURE 3. Molecular orbitals in the transition state resulting from the interaction of SOMO and π alkene orbital for TS23,a (a), TS23,b (b) and six-membered TS67 (c) ring closure, respectively.

was slightly more activated.[47] To check the validity of the more activated boatlike structures for our systems, we located them on the potential energy surface. It was found that all boatlike structures are about 15 kJ/mol more activated than their corresponding chairlike transition states and are therefore taken out of consideration.

The lowest energy transition state (TS23,a) is characterized by an axial position of the *N*-propenyl side chain and leads to a cis-conformation of the product (**3,a**) that lies ~7 kJ/mol higher in energy than the lowest energy conformer (**3,b**) (schematically depicted in the potential energy diagram of Figure 1). The most stable product resulting from the cyclization of the aminyl radical (**2**) is the trans-conformer in which the propenyl substituent at the nitrogen and the methylene substituent are on the opposite side of the ring (**3,b** in Figure 2). Both product conformers can transform into each other by an inversion at the nitrogen center, while the rest of the molecule relaxes accordingly. The barrier for this inversion was calculated as 7.0 and 14.3 kJ/mol for **3,a** → **3,b** and **3,b** → **3,a** respectively. These values are less than the barrier for cyclization itself. The trans-conformer of the product can be reached directly through a higher energy transition state (TS23,b in Figure 2) that is 13.9 kJ/mol more activated. The origin of this energy difference must again be traced back to stereoelectronic effects in the transition state. This is illustrated in Figure 3b where the molecular orbital resulting from the interaction of the SOMO and the π^* molecular orbital of the alkene is visualized for the higher energy transition state. The orbital overlap is no longer optimal for this transition state. In the case of nitrogen-substituted alkenes the products resulting from cyclization can transform into each other, but for the carbon analogues, i.e., as in 5-hexenyl, the two products cannot transform into each other. In these cases both reaction routes must be taken into consideration.

The activation energy to cyclization via the exo mode trough the transition state TS23,stereo1 is predicted as 33.67 kJ/mol. The reaction enthalpy at 0 K amounts to −39.32 kJ/mol. According to these results, the cyclization of the aminyl radical is an irreversible process ($k_{2\rightarrow3}/k_{3\rightarrow2} \approx 2.2 \times 10^5$). In the literature, many conflicting reports are found on a similar although different reaction, i.e., the cyclization of the *N*-methyl-*N*-4-pentenylaminyl radical through the exo mode. The previous findings can mainly be summarized as follows: Newcomb and co-workers predicted that the cyclization of the latter radical is a reversible process,[12,14] whereas Tsanaktsidis and co-workers revised this reaction and concluded that the cyclization is a slow irreversible process ($k_{\text{forward}} \gg k_{\text{reverse}}$).[11,15,16] Both authors supported their claims by theoretical and experimental findings. From the theoretical point of view the degree of exothermicity raises some questions, since it seems to vary largely in terms of the level of theory used for the molecular orbital calculations. Newcomb and co-workers did not, however, address the transition states, and thus, a direct comparison with experimental data is not possible.

In light of the previous results it is useful to comment further on our energetic results. The degree of exothermicity and the activation barriers seem to depend largely on the functional used. Our B3LYP energetic results can merely be summarized as follows: (i) the activation barrier amounts to approximately 50 kJ/mol and (ii) the reaction is reversible characterized by a reaction enthalpy of 9.6 kJ/mol. On the basis of the level of theory study on the cyclization of dialkyl aminyl radicals for which experimental results are available, it seems that the B3LYP energetic results are highly inaccurate for the type of systems studied here. The energetic results on the B3LYP/6-311G** level are shown in the Supporting Information for the interested reader. The B3P86 functional improves the results substantially and alters the main conclusions for the 5-exo cyclization: (i) the reaction is activated by 34 kJ/mol and (ii) is irreversible with a reaction enthalpy of about 40 kJ/mol. Earlier results by Jursic on bond dissociation energies of nitrogen containing radicals suggest similar findings, although a clear consensus is not available.[36] On the basis of our results, some indications are available to unravel the conflicting discussions found in the literature on the cyclization of the *N*-methyl-*N*-4-pentenylaminyl radical, but no conclusive statement can be made since it concerns a different system.

The next step in the radical cascade is the formation of the bicyclic skeleton, after which the radical cascade terminates into azabicyclic compounds as schematically depicted in Scheme 2. Experimentally the cascade reaction of aziridines to pyrrolizidines was found to be a stereoselective process as it leads to one stereoisomer with respect to the methyl substituent and the bridgehead hydrogen. Theoretically, this stereoselectivity of this process can be validated by calculating the kinetics of both reaction routes.

From the microscopic point of view various reaction routes are possible starting from **3,a** and **3,b**, and for both starting conformers two possible transition states are

(47) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

possible leading to a specific stereoisomer for the bicyclic skeleton. The structures of the final stereoisomers are shown in Figure 2. At 300 K, 6% of **3** will reside in conformer **3,a** and 94% will appear in conformer **3,b**. The latter results are derived from the energetics of the various conformers of **3**. The individual rate constants for the reaction routes leading to **4,a**, **4,b**, **4,c**, and **4,d** can be calculated and are tabulated in Table 1. The structures indicated by **4,a** and **4,d** correspond to a stereoisomer in which the methyl substituent and the bridgehead hydrogen are on the opposite side of the ring, whereas **4,b** and **4,d** are characterized by relative positions of the latter groups on the same side of the ring. The energetically most favored structure **4,a** is characterized by two fused five-membered rings, both of which have an envelope-like form (cf. Figure 2). The latter structure is approximately 7 kJ/mol more stable than the second isomer. The reaction leading to the bicyclic skeleton is, however, kinetically controlled: taking into account the Boltzmann distribution for the various conformers of **3** and the rate constants for the various reaction routes, we find that at 300 K the reaction route leading to the second isomer is 23 times faster than the pathway leading to the first isomer. The reaction route **3** leading to the second isomer has a substantially lower activation energy and slightly higher frequency factor. The exact values for the kinetic parameters are given in Table 1. Experimentally, the cascade reaction of aziridines was also found to be stereoselective leading exclusively to the isomer **2**. The theoretical results clearly show that the process is kinetically controlled since the energetically preferred isomer **1** is not preferentially formed.

3.2. Reaction Preference of Cascade Cyclization toward Pyrrolizidines and Indolizidines. All attempts to synthesize an indolizine experimentally via a similar radical-induced cascade failed, as only the corresponding amounts of the *N*-allyl-2,2-dimethyl-5-hexenylamine (cf. **6** and hydrogen capture) could be isolated from the reaction of 2-(bromomethyl)-1-(2,2-dimethyl-5-hexen-1-yl)aziridine with tributyltin hydride in benzene under reflux in the presence of AIBN. The underlying reaction mechanism was investigated by studying the variations in the synthetic potential in terms of the alkenyl length and the type of substitution in the alkenyl side chain (Scheme 2, reactions 2−4). The kinetic parameters for the various reactions are listed in Table 1, and the synthetic potential of the various reaction routes is shown in Figure 4.

The kinetics of the ring opening reactions (**5** → **6**, **9** → **10**, **13** → **14**) are almost unaltered by varying the length of the alkenyl chain. It can be expected that all suggested aminyl radicals (**6**, **10**, **14**) will undergo regioselective exo ring closure.[44] The ring closure of the aminyl radical with a hexenyl radical attached is clearly much more activated (about 25 kJ/mol) than with an attached pentenyl radical. Beckwith reported rate constants, reaction enthalpies, and entropies for ring-closure reactions in the exo mode of the series from butenyl to octenyl radicals.[44] In general, the reaction barrier reflects the heat of formation of the ring being formed: it is small for cyclopentyl and cyclohexyl rings but much larger for 3- or 4-membered rings. When taking a closer look at his experimental results,[44] it is clear that the reaction barrier for formation of

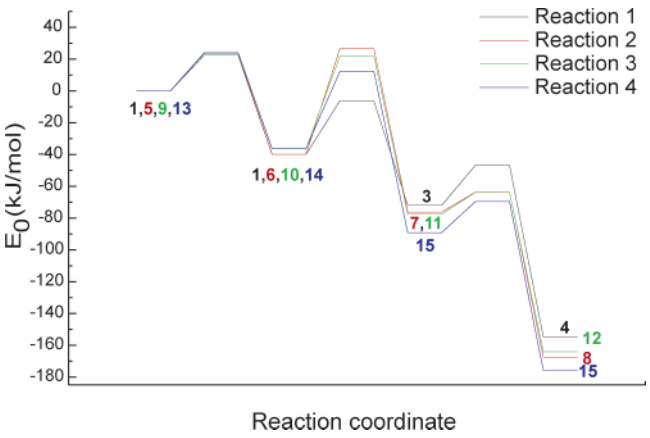


FIGURE 4. Potential of the reaction routes leading to pyrrolizidines and indolizidines.

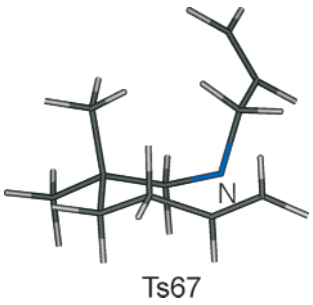


FIGURE 5. Structure of the transition state leading to indolizidines.

cyclohexyl radicals is larger than for cyclopentyl radicals, in accordance with our theoretical results.

The transition states for steps **2** → **3** (**TS2,3**) and **6** → **7** (**TS6,7**) are shown in Figures2 and 5, respectively.

For 5-exo cyclizations of the aminyl radicals the ending 2-propenyl chain is oriented almost trans with respect to the rest of the molecule, while for all 6-exo cyclizations the corresponding angle deviates largely from the trans orientation. These structural changes have a large impact on the degree of delocalization of the molecular orbital resulting from the interaction of the SOMO and π^* molecular orbital that was responsible for the stabilization of the transition state for five-membered ring formation. The specific orbital is shown in Figure 3c. The orbital overlap over the double bond of the propenyl ending chain is no longer present, and thus, the transition state for 5-exo cyclization of the aminyl radical is stabilized over the corresponding 6-exo cyclizations.

The influence of substituents in the alkenyl chain on the reaction barriers was also investigated. By proper substitution, the barrier may be lowered by about 18 kJ/mol (reaction 4) but still remains substantially higher than for the 5-exo cyclization pathway. In the literature, many comments are made on the "5exo : 6endo" rate, but much less is known about the "5exo : 6exo" variation. From the experimental paper of Newcomb and coworkers, it can be derived that the 6-exo cyclization is only 10 kJ/mol more activated than the 5-exo cyclization. At this point it is not clear whether the "5exo : 6exo" rate can be substantially altered by placing other substituents at various positions of the dialkylaminyl radical. This aspect needs further investigation. The preexpo-

nential factors for steps **2** → **3**, **6** → **7**, **10** → **11** and **14** → **15** are all in the same order of magnitude. Our theoretical results confirm the experimental finding that no efficient route toward indolizidines can be established, since the intermediate 6-exo cyclization of the aminyl radicals forms a bottleneck in the radical cascade.

4. Conclusions

In this paper the kinetics and thermodynamics of radical cascade cyclizations of *N*-alkenyl-2-aziridinylmethyl radicals to pyrrolizidines and indolizidines were studied by density functional theory calculations. Experimentally, pyrrolizidines could be synthesized efficiently while the synthesis toward indolizidines failed. In this paper the underlying microscopic reasons for this behavior were investigated, and it was found that the initial ring opening of the *N*-alkenyl-2-aziridinylmethyl radicals is almost unaltered by the length of the alkenyl chain and the type of substituents in the alkenyl side chain. The reaction barrier for cyclization of the formed aminyl radical varies largely in terms of the length of the alkenyl chain, i.e., the route toward indolizidines is characterized by a higher barrier of approximately 35 kJ/mol. Experimentally, the cascade reactions toward pyrrolizidines seem to be a stereoselective process as only one isomer with respect to the methyl substituent and the bridgehead hydrogen was found. Theoretically, a large kinetic preference was also found for formation of this isomer, despite the fact that the second isomer is in principle more stable.

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Supporting Information Available: The energetic results at the B3LYP/6-311g** level for the cyclization toward pyrrolizidines and *Z*-matrixes of all stable structures and transition states together with their energy. This material is available free of charge via the Internet at http://pubs.acs.org.

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