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5-*Endo-trig* Radical Cyclizations: Disfavored or Favored Processes?

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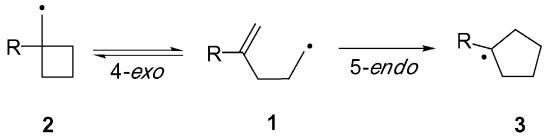
Abstract: Relative kinetic data were determined for the 5-*endo-trig* cyclization of radical **12** compared to hydrogen abstraction from $(TMS)_3SiH$ in the temperature range of 344−430 K, which allows for the estimation of a rate constant of 2×10^4 s^{-1} at 298 K with an activation energy of ca. 9 kcal/mol for the cyclization process. The 5-*endo-trig* cyclization of a variety of radicals that afford five-membered nitrogen-containing heterocycles was addressed computationally at the UB3LYP/6-31G* level. The 5-*endo* vs 4-*exo* mode of cyclication and the effect of delocalization of the unpaired electron in the transition state were investigated. Because the ring formed during cyclization contains five sp^2 centers, electrocyclization via a pentadienyl-like resonance form was also considered. For comparison, similar calculations were performed for 4-penten-1-yl and related radicals. The factors that affect the activation energies of homolytic 5-*endo-trig* cyclization were determined. In the absence of steric or conformational effects, the *endo* cyclization to form the five-membered ring was strongly favored over *exo* cyclization to form the four-membered ring not only on thermodynamic grounds but also kinetically. When a substituent on the double bond was able to delocalize the unpaired electron in the transition state of the 4-*exo* path, the two modes of cyclization became kinetically comparable. These results have an important bearing on the generalization of the Baldwin−Beckwith rules, which classified the 5-*endo-trig* radical cyclization as a "disfavored" process.

Introduction

The 5-*endo-trig* mode of radical cyclization has been known as a "disfavored" process because of the Baldwin−Beckwith set of empirical rules that predicts ring closures in radical reactions.[1] For example, the prototype 4-pentenyl radical (**1**, R = H) meets the stereoelectronic requirements for a 4-*exo-trig* cyclization to give radical **2**, although it is unfavorable on thermodynamic grounds and the equilibrium lies well to the right (Scheme 1).[2,3] On the other hand, the formation of **3** is a thermodynamically favorable process, although there are many cases in the literature where the 5-*endo* cyclization in such systems has not been observed.[4] Some substituted 4-pentenyl

Scheme 1



2 **1** **3**

radicals (i.e., R = Ph) that could afford stabilized radicals have been reported to give 5-*endo* cyclization products in low yield,[5] and it was suggested that these reactions involve competing equilibria and fall under thermodynamic control.[6] In recent years, some synthetically useful all-carbon 5-*endo*-ring closures have been reported and the efficiency of these "exceptional" cases has been attributed to a particularly congested transition

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(1) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482−483.
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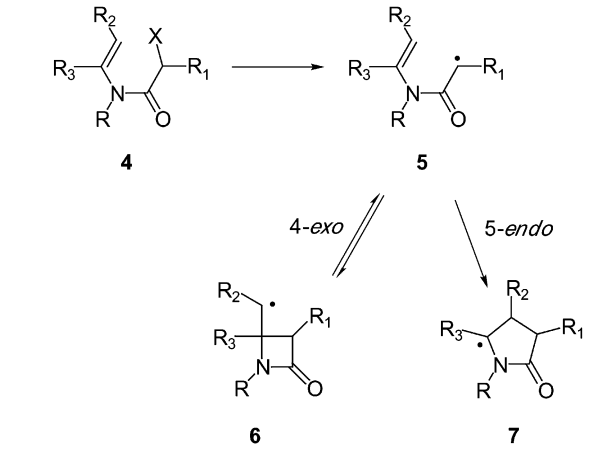
state, to a rate enhancement induced by an extensive Thorpe−Ingold effect, or to the application of bicontinuous microemulsions.[7] A good number of efficient and synthetically useful 5-*endo* radical cyclizations have also been discovered in systems other than all-carbon atoms, i.e., sulfur- and silicon-centered radicals[8] or heteroatom-containing double bonds.[9−11]

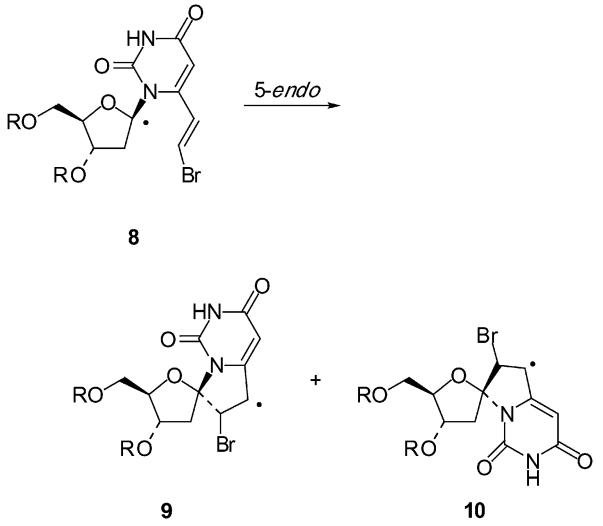
The most widely applied 5-*endo* radical cyclization is by far the synthesis of saturated five-membered nitrogen-containing heterocycles.[12] Ikeda, Ishibashi, and co-workers were the first to show that a variety of halo-enamides of type **4** afford γ-lactams in good yields under free-radical reducing conditions.[13] These 5-*endo* cyclizations can be highly diastereoselective or moderately enantioselective in the presence of chiral auxiliaries. Scheme 2 depicts the generally accepted reaction path, i.e., a competition between a kinetically favored and reversible 4-*exo* cyclization and a 5-*endo* ring closure that is under thermodynamic control.[14] The regioselectivity of the cyclization of radical **5** (4-*exo* vs 5-*endo*) has been studied in some detail by varying the substituents and temperature.[13] Indeed, the quenching of radical **6** in a few cases afforded the β-lactam as the major product. Parsons and co-workers extended this approach to the synthesis of substituted pyroglutamates.[15,16]

Another efficient 5-*endo* cyclization, which is similar to the above-discussed system in that the ring formed during cyclization contains a nitrogen atom and five sp^2 centers, has been discovered in the field of modified nucleoside synthesis. Scheme 3 shows the 5-*endo* ring closure proposed independently by two groups as the key step within a radical cascade sequence for the synthesis of anomeric spironucleosides.[20,21] It should be

Scheme 2



Scheme 3



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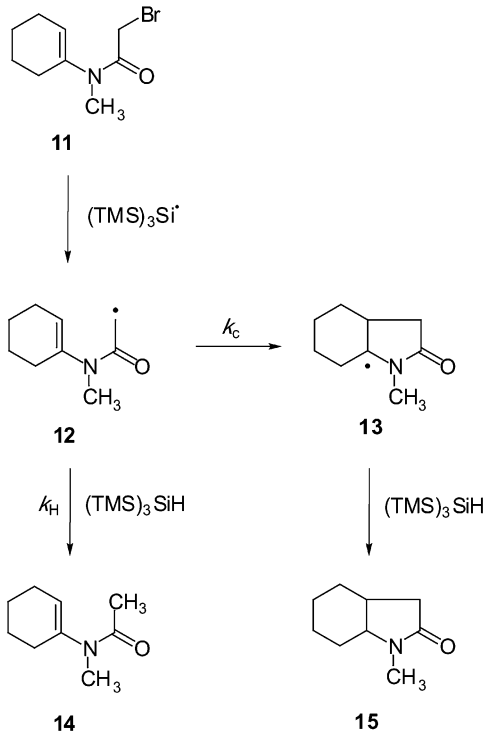
Scheme 4



noted that the two interpretations for the diastereochemical outcome (**9**/**10** = 2:1) of these cyclizations are in contrast.

Despite the extensive synthetic applications of the 5-*endo* radical cyclizations, it is worth pointing out that kinetic information regarding these transformations is limited, and the reasons behind the efficiency of this disfavored process are still unknown.[22] Herein, we report a detailed theoretical study of the parameters involved in these transformations, together with some experiments leading to the establishment of rules that, in turn, might have synthetic utility. We anticipate that 5-*endo-trig* radical cyclization is both the kinetically and thermodynamically favored path.

Results and Discussion

5-*Endo-trig* Radical Cyclization of Enamides. For a detailed kinetic study of the radical cyclization of halo-enamides of type **4**, we chose the bromo derivative **11** reported by Ikeda and co-workers. An indirect procedure for measuring the rate constant of a unimolecular process involves competition between this process and a bimolecular path of the radical (*free-radical clock methodology*).[23] In his reviews, Newcomb summarized competition methods for this purpose.[23] Relative rate constants for the 5-*endo* cyclization can be obtained, provided that conditions can be found in which the intermediate radical **12** is partitioned between the two reaction channels, i.e., the reaction with $(TMS)_3SiH$ and the cyclization (Scheme 4).

This scenario can be achieved in the temperature range 344−430 K if the $(TMS)_3SiH$ concentration remains essentially constant during the course of the reaction (bimolecular process under pseudo-first-order conditions). Under these conditions, eq 1 holds

$$[\mathbf{14}]/[\mathbf{15}] = k_H[(TMS)_3SiH]/k_c \quad (1)$$

Table 1. Kinetic Data for the Reaction of Bromide **11** with $(TMS)_3SiH$ in *tert*-Butylbenzene[a]

T, K	initiator[b]	k_H/k_c,[c] M^{-1}
344	AIBN	7.79 ± 1.53
353	AIBN	5.91 ± 1.49
395	BOOB	3.25 ± 0.49
403	BOOB	2.96 ± 0.20
421	BOOB	2.29 ± 0.14
430	BOOB	2.02 ± 0.09

[a] Conditions: $[(TMS)_3SiH] \geq 12 \times [\mathbf{11}]$ and $(TMS)_3SiH$ concentration in the range of 0.130−0.454 M. [b] AIBN = azobis(isobutyronitrile); BOOB = di-*tert*-butyl peroxide. [c] Average of six different experiments. Errors correspond to one standard deviation.

The quantities of **14** and **15** were obtained by GC analysis, following the thermally initiated radical reaction, by using an internal standard. The ratio [**14**]/[**15**] varied in the manner expected with a change in the silane concentration. The k_H/k_c ratios reported in Table 1 were obtained as the averages of six different experiments. Linear regression analysis of a plot of $\log(k_H/k_c)$ vs $1/T$ yields the relative Arrhenius parameters given by eq 2, where $\theta = 2.3RT$ kcal/mol and the errors correspond to one standard deviation

$$\log k_H/k_c\ (M^{-1}) = -(1.93 \pm 0.09) + (4.41 \pm 0.16)/\theta \quad (2)$$

Unfortunately, the rate constant k_H for the reaction of α-amide primary carbon-centered radicals with $(TMS)_3SiH$ and its temperature dependence are unknown, although they are needed to obtain the Arrhenius expression for k_c from the eq 2.[24] Newcomb and co-workers have shown that the rate constants of α-amide secondary carbon-centered radicals with Bu_3SnH are similar to those of alkyl radicals with Bu_3SnH.[25] Because the reactivity scales of alkyl radicals with Bu_3SnH and $(TMS)_3SiH$ are *parallel*,[24] it is reasonable to assume that the rate constants for the reactions of radical **12** and of a primary alkyl radical with $(TMS)_3SiH$ are similar. From eq 2, a value of $k_H/k_c = 20.1\ M^{-1}$ is calculated at 298 K. Taking[26] $k_H = 3.8$

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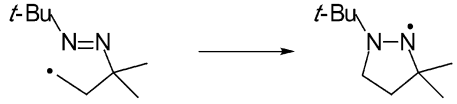
(22) Engel et al.[9b] reported a rate constant of $1.3 \times 10^9\ M^{-1}\ s^{-1}$ at 110 °C for the following 5-*endo* cyclization:



Ab initio calculations at UQCISD/6-31G*//UHF/6-31* level on the 5-*endo* cyclization of the prototype 4,5-diaza-4-penten-1-yl radical and the all-carbon analogue 4-penten-1-yl radical suggest that the former radical cyclize 7−8 orders of magnitude faster mainly because of a smaller C−N=N than C−C=C angle.

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(25) Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022−1025.

(26) The temperature-dependent function for the reaction of 5-hexenyl radicals with $(TMS)_3SiH$ is as follows: $\log k_H(M^{-1}\ s^{-1}) = (8.86 \pm 0.36) - (4.47 \pm 0.53)/\theta$, where $\theta = 2.3RT$ kcal/mol. See: Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399−6403. Errors correspond to one standard deviation.

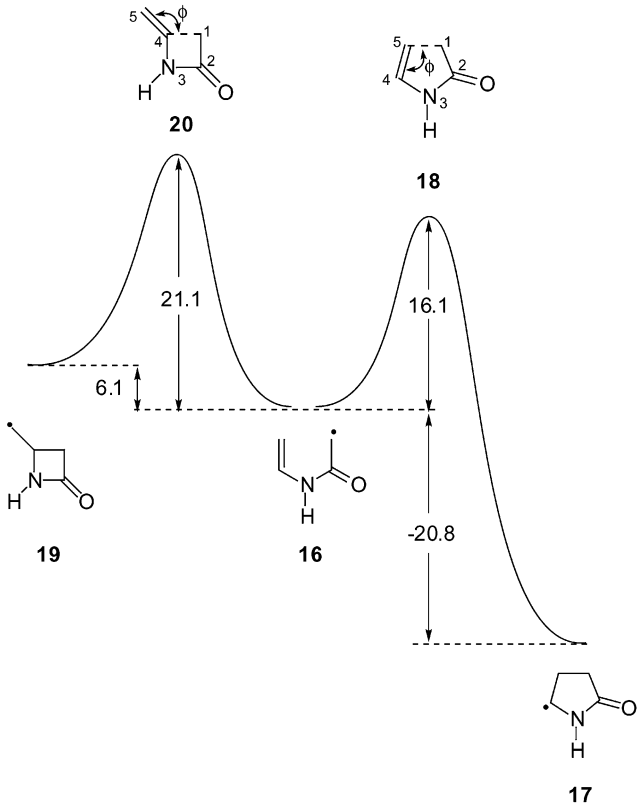


Figure 1. Energy profiles (kcal/mol) for the 4-*exo* and 5-*endo* cyclizations of radical **16** at the UB3LYP/6-31G* level.

$\times 10^5$ M^{-1} s^{-1}, we obtain a value of 1.9×10^4 s^{-1} for the rate constant of the 5-*endo* cyclization of radical **12** at 298 K. Similarly, the combination of eq 2 with the known Arrhenius parameters for the reaction of the primary alkyl radical with $(TMS)_3SiH$[26] yields $\log(A/s^{-1}) = 10.8$ and $E_a = 8.9$ kcal/mol.

MO calculations were performed to determine the factors that affect the activation energy of the 5-*endo* cyclization in radical **12**.[27] Initially, we carried out calculations on the cyclization of the model radical **16** to give the γ-lactam radical **17** via the transition state **18** (see Figure 1) at different levels of theory. Table 2 shows that UB3LYP/6-31G* calculations provide the values of reaction barriers for ring closure (E_a), reaction enthalpies (H_r), and partial bond lengths in the transition state (d_{TS}) comparable to those computed with the more reliable ab initio correlated method UQCISD. Its performance is better than that obtained with ab initio correlated methods in which electron correlation is estimated using perturbation theory [UMP2, UMP4(SDQ)] to reduce computational costs. Furthermore, enlargement of the basis functions to the valence triple-ζ 6-311G* basis set or addition of diffuse functions on heavy atoms (6-31+G*) has negligible effects. Finally, the E_a value computed at the UB3LYP/6-31G* level differs only by 0.6 kcal/mol from that computed using the more flexible 6-311G** basis set in single-point UQCISD calculations (UQCISD/6-311G**//UQCISD/6-31G*).

Table 2. Reaction Barriers (E_a), Reaction Enthalpies (H_r), and Partial Bond Lengths in the Transition State (d_{TS}) for the 5-*Endo* Cyclization of Radical **16** Computed at Different Levels of Theory

method	E_a, kcal/mol	H_r, kcal/mol	d_{TS}, Å
UMP2/6-31G*	22.3	−28.4	2.225
UMP4(SDQ)/6-31G*	21.3	−26.1	2.235
UB3LYP/6-31G*	16.6	−22.8	2.265
	(16.1)[a]	(−20.8)[a]	
UB3LYP/6-31+G*	16.6	−21.8	2.262
UB3LYP/6-311G*	16.5	−21.9	2.256
UQCISD/6-31G*	17.6	−24.9	2.244
UQCISD/6-311G**// UQCISD/6-31G*	17.2	−24.9	

[a] Value corrected for the difference in ZPVE (cf. ref 27).

Table 3. Reaction Barriers (E_a), Reaction Enthalpies (H_r), and Angles of Attack in the Transition State (ϕ) for the Cyclizations Computed at the UB3LYP/6-31G* Level[a]

radical	cyclization	E_a, kcal/mol	H_r, kcal/mol	ϕ, degrees
16	5-*endo*	16.1	−20.8	88.1
	4-*exo*	21.1	6.1	118.9
21	5-*endo*	13.6	−24.0	87.4
	4-*exo*	17.5	2.2	118.1
12	5-*endo*	10.3	−18.5	87.5
22	5-*endo*	11.1	−24.3	87.4
23	5-*endo*	19.4	−18.4	89.0
24	5-*endo*	9.5	−31.1	86.0
	4-*exo*	16.3	2.7	112.0
25	5-*endo*	13.5	−17.2	87.8
	4-*exo*	14.2	−6.1	118.3
26	5-*endo*	13.3	−16.5	88.1
	4-*exo*	12.8	−9.7	111.7
27	5-*endo*	14.9	−12.1	88.7
	4-*exo*	14.8	−5.9	118.6

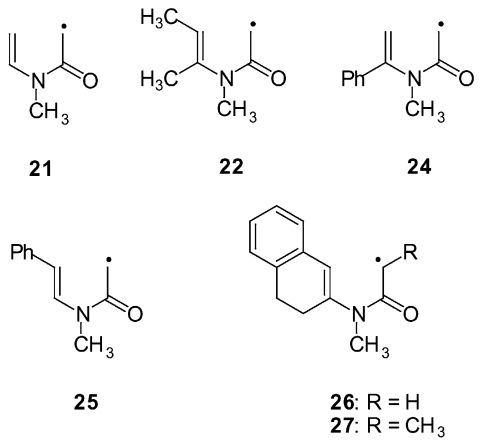
[a] E_a and H_r values corrected for the difference in ZPVE (cf. ref 27).

The UB3LYP/6-31G* calculations were extended to the 5-*endo* vs 4-*exo* radical cyclization for a variety of enamide-type radicals and are reported in Table 3. A comparison of the first two rows that refer to radical **16** and to the corresponding paths represented in Figure 1 shows that the 4-*exo* mode is disfavored compared to the 5-*endo* mode by 5 kcal/mol, in contrast with the Baldwin−Beckwith rules.[1] Furthermore, the formation of a β-lactam radical **19** is 6.1 kcal/mol endothermic, whereas the 5-*endo* cyclization is computed to be strongly exothermic. The angle of attack ϕ in the transition states **18** and **20** is 88.1° and 118.9°, respectively, indicating that the disposition of the three interactive atoms in the 5-*endo* cyclization is considerably less than normal (109.47°) and that the 4-*exo* fashion meets the stereoelectronic requirements according to Baldwin's hypothesis. The replacement of the NH moiety by NCH_3 in radical **21** decreases both the E_a and H_r values by 2.5−3.9 kcal/mol in both modes of cyclization (Chart 1 and Table 3). The reason for the effect on E_a by this replacement is 2-fold. For the 5-*endo* cyclization, one-third of the decrease (0.8 kcal/mol) is due to geometrical changes, whereas two-thirds is due to the polar contribution. That is, from the values of the dihedral

(27) Unrestricted DFT calculations have been carried out with the Gaussian 98 system of programs[28] running on DEC-Alpha 500 computers employing the B3LYP functional and the valence double-ζ basis set supplemented with polarization *d*-function on heavy atoms (UB3LYP/6-31G*). The nature of the transition states has been verified by frequency calculations (one imaginary frequency), and energy values have been corrected for the zero-point vibrational energy (ZPVE).

(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, 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.; 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 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

Chart 1



Scheme 5

angle, $\omega(C_1C_5C_4N_3)$, formed between the plane of the olefinic moiety and the radical center (cf. the transition state **18** in Figure 1), the dispositions of the double bond and the radical center in the unrearranged radical (ω_{UR}) and in the transition state (ω_{TS}) are more similar for radical **21** ($\omega_{UR} = -32.7°$, $\omega_{TS} = -40.0°$) than for radical **16** ($\omega_{UR} = -21.3°$, $\omega_{TS} = -38.9°$). In addition, the replacement of NH by NCH_3, despite having no influence on the electrophilicity of the radical (EA = 0.53 and 0.54 eV for radicals **16** and **21**, respectively), destabilizes the π-orbital of the double bond by 0.19 eV, thus favoring the attack of the electrophilic radical center.[29]

Table 3 also shows that replacement of the vinyl moiety in **21** with the cyclohexenyl group, as in radical **12** (Scheme 4), further decreases the E_a value for the 5-*endo* cyclization by 3.3 kcal/mol. The computed reaction barrier for radical **12** is similar to that estimated from the relative kinetic data, i.e., 10.3 vs 8.9 kcal/mol. One can argue that conformational interconversions by rotation about the carbonyl carbon-to-nitrogen bond could play an important role in the experimental value (Scheme 5). In this respect, Newcomb and co-workers measured rate constants in the range of $3-16 \times 10^5\ s^{-1}$ for the C−N bond rotation in an α-amide primary carbon-centered radical similar to radical **12** in the temperature range of 283−340 K. These values are ca. 30 times higher than the corresponding rate constants estimated for the 5-*endo* cyclization of radical **12**. Furthermore, the UB3LYP/6-31G* calculations show that rotamer **12a** should be not populated, its energy being 4.5 kcal/mol higher than that of rotamer **12,** which is the most stable conformer (Scheme 5). To evaluate the contribution of ring conformation and of the olefin substitution to the reaction barrier of radical **12**, the cyclohexenyl was replaced with the 2-butenyl group (**22**). E_a decreases by 2.5 kcal/mol on going from radical **21** to **22**. This decrease is attributed to the destabilization of the π-orbital of the double bond by 0.16 eV and, therefore, to more favorable polar effects. The decrease of E_a by 3.3 kcal/mol going from radical **21** to **12** is slightly larger, although the destabilization of the π-orbital of the double bond is similar (0.15 eV). It is reasonable to assume that the larger decrease is due to a partial distortion of the double bond within the cyclic moiety. This decreases the energy of the excited triplet state and might also diminish the barrier for the addition of carbon-centered radicals to alkenes.[29] It is worth mentioning that, in both radicals **22** and **12**, the dispositions of the double bond and the radical center in the unrearranged radical (ω_{UR}) and in the transition state (ω_{TS}) are similar, as expected from the presence of the *N*-methyl group (see the Supporting Information).

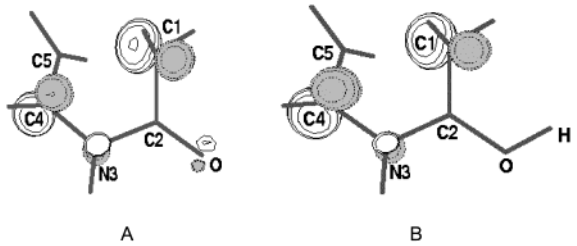
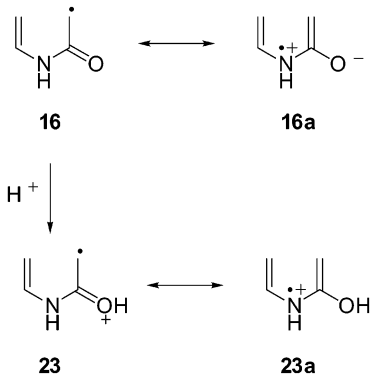


Figure 2. Picture of the SOMO of the UB3LYP/6-31G* transition states for the 5-*endo* cyclizations of (A) radical **16** and (B) radical **23**.

Scheme 6



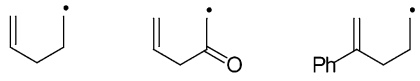
The possibility of an electrocyclization via the pentadienyl structure in the resonance form **16a** (Scheme 6) could also be considered.[30] However, the electron distribution in the SOMO reveals the radical nature of this reaction. In the transition state, the unpaired electron is localized at both the carbons at which the unpaired electron is localized in the unrearranged and rearranged radicals (Figure 2A for radical **16**). It should be remarked that the SOMO should be of the allyl type in the transition state of an electrocyclic mechanism, i.e., spin density at C_2 and C_4. To force this situation, radical **16** was considered as protonated at the oxygen atom (**23**), so that the pentadienyl-type resonance structure **23a** should prevail compared to radical **16**. However, the calculations show that the E_a value significantly increases upon protonation (Table 3) and that the electron distribution in the SOMO resembles that of radical **16** (Figure 2B for radical **23**).

The effect of delocalization of the unpaired electron in the transition state was then investigated by carrying out calculations initially on model radicals **24** and **25**, where a phenyl group is attached to the olefinic moiety. 4-Phenyl substitution (radical

(29) (a) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340−1371.

(30) (a) For a review, see: Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 45, Chapter 1, pp 1−158. (b) For a recent ab initio study of 1,4-pentadienyl electrocyclic reaction, see: Martinez, C.; Cooksy, A. L. *J. Org. Chem.* **2002**, *67*, 2295−2302.

Chart 2



28 **29** **30**

Table 4. Reaction Barriers (E_a), Reaction Enthalpies (H_r), and Angles of Attack in the Transition State (ϕ) for the Cyclizations Computed at the UB3LYP/6-31G* Level[a]

radical	cyclization	E_a, kcal/mol	H_r, kcal/mol	ϕ, degrees
28	5-*endo*	16.3	−19.0	88.9
	4-*exo*	18.1	4.5	115.0
29	5-*endo*	17.9	−14.1	87.9
30	5-*endo*	12.2	−30.7	88.9

[a] E_a and H_r values corrected for the difference in ZPVE (cf. ref 27).

24) considerably decreases the E_a value of 5-*endo* cyclization. E_a is about 4 kcal/mol lower than in radical **21**. The phenyl group stabilizes the transition state by delocalizing the unpaired electron. Indeed, 15% of the unpaired electron is localized at the phenyl group in the transition state. Thus, the energy difference between the 5-*endo* and 4-*exo* cyclizations significantly increases up to 6.8 kcal/mol in radical **24**. On the other hand, 5-phenyl substitution (radical **25**) is expected to favor the 4-*exo* mode to a larger extent over 5-*endo* ring closure, as only in the first case can the unpaired electron in the transition state be delocalized to the phenyl group. Indeed, E_a of 5-*endo* cyclization does not change significantly on going from radical **21** to radical **25**, and the two mechanistic paths now have comparable E_a values. To compare these findings with experimental data, we also investigated the cyclization of radicals **26** and **27**, because it has been reported that the nature of substituent R on the radical center influences the 4-*exo*/5-*endo* product ratio.[13h] When the substituent R was H (**26**), β-lactam was the only cyclic product formed, whereas the introduction of methyl substituent (**27**) led to the formation of both β- and γ-lactams in similar amounts. Indeed, Table 3 shows that, for radical **26**, the 4-*exo* cyclization is favored and that, for radical **27**, the reaction barriers for the two modes of cyclization are about the same.

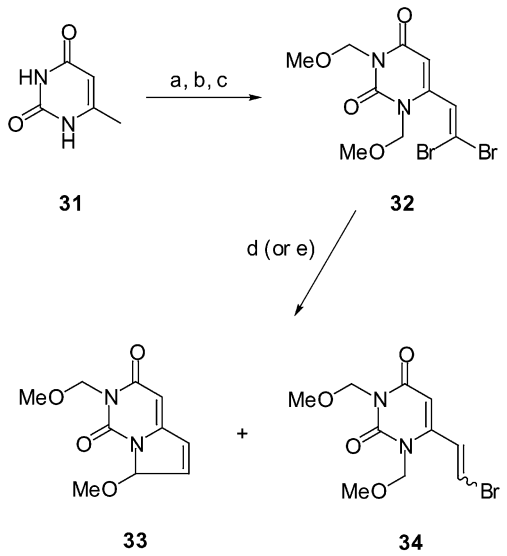
5-*Endo-trig* Cyclization of 4-Penten-1-yl and Related Radicals. For comparison of the all-carbon analogues with the 5-*endo* cyclization of enamides, the ring closures of radicals **28**−**30** (Chart 2) were also considered, and the results are summarized in Table 4. Previous ab initio calculations at the UQCISD/6-31G*//UHF/6-31* level on the 5-*endo* cyclization of radical **28** gave $E_a = 19.5$ kcal/mol and $\phi = 88.8°$.[9b]

The trend found for radical **28** is the same as for radical **16**. The difference between the E_a values of the 5-*endo* and 4-*exo* cyclizations is reduced to 1.8 kcal/mol in the carbon analogue. Interestingly, 4-penten-1-yl radical was found to produce the 5-*endo* cyclic radical in vibronically excited states in the gas phase. Moreover, the UB3LYP/6-31G* E_a value of 16.3 kcal/mol is in the range estimated experimentally for this process (18 ± 3 kcal/mol).[31] The angles of attack ϕ in the transition states of 5-*endo* and 4-*exo* closure for radical **28** are 88.9° and 115.0°, respectively, indicating that the disposition of the three interactive atoms in the 5-*endo* cyclization is considerably less than normal (109.47°) and that the 4-*exo* fashion meets the stereoelectronic requirements according to Baldwin's hypothesis. In 4-phenyl-4-penten-1-yl radical (**30**), the E_a decreases by ∼4 kcal/mol because the phenyl group stabilizes the transition state by delocalizing the unpaired electron. Indeed, it was found that 5-*endo* cyclization occurs in a moderate yield (19%).[5b] Therefore, the 5-*endo* ring closure is again favored over the 4-*exo* mode, in contrast to the Baldwin−Beckwith rules.[1] This is probably due to an increase of the energy strain in the transition state, which involves all of the atoms in the chain of the 4-*exo* mode compared to the 5-*endo* mode. Indeed, the strain energy due to stretching and bending computed with the MM3 parameters[32] increases by only 0.8 kcal/mol on going from the ground state to the transition state geometry for the 5-*endo* cyclization of **28**, whereas the increment is 6.1 kcal/mol for the 4-*exo* mode.

As noted above, the five sp^2 atoms are not coplanar in the transition state for the cyclization of radical **12**, the dihedral angle between the olefinic plane and the radical center being about 40°. This suggests that a change of hybridization of the central atom should not considerably affect the E_a value. Table 4 shows that the E_a value increases by less than 2 kcal/mol on replacing the NH moiety in radical **16** (sp^2 hybridization at N) with a CH_2 group (sp^3 hybridization at C in radical **29**).

5-*Endo-trig* Radical Cyclization of 6-Vinyluridines and Related Compounds. Protected 6-dibromovinyluridines react under free-radical conditions to provide the corresponding anomeric spironucleosides through a cascade reaction including an efficient 5-*endo* radical cyclization (Scheme 3).[20,21] To determine experimentally the structural requirements for efficient radical cascades and investigate in particular the influence of the sugar moiety, we proceeded to the synthesis of the uracil derivative **32**. Compound **32** was prepared in a three-step procedure starting from the commercially available compound **31** according to Scheme 7 with a 36% overall yield.

Scheme 7 [a]



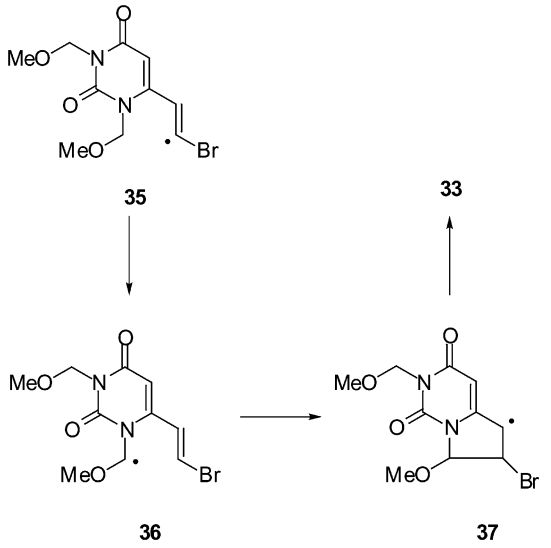
31 **32** **33** **34**

[a] (a) i. NaH, DMF; ii. MOMCl, room temperature, 4 days, 65%. (b) SeO_2, dioxane/AcOH (11:1), reflux, 8 h, 72%. (c) CBr_4, PPh_3, Et_3N, CH_2Cl_2, −60 to 20 °C, 3 h, 77%. (d) (n-$Bu_3Sn)_2$, $h\nu$, toluene, 48 h, 110 °C, 70% (**33**/**34** = 6:4). (e) $(TMS)_3SiH$, AIBN, toluene, 5 h, 80 °C, 87% (ratio **33**/**34** =1:9).

(31) Watkins, W. K.; Olsen, D. K. *J. Phys. Chem.* **1972**, *76*, 1089−1092.

(32) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8566.

Scheme 8



Reaction of the dibromo derivative **32** with Bu_3Sn• radicals, generated by photolysis of hexabutylditin with 300-W visible light in refluxing toluene for 48 h, afforded two products, which were isolated in a 70% combined yield and in a ratio **33**/**34** = 6:4. The vinyl bromide **34**, in turn, is present in an *E*/*Z* ratio of 78:22. Alternatively, upon reaction of compound **32** with $(TMS)_3SiH$ in toluene under standard free-radical conditions (AIBN, 80 °C, 5 h), we isolated two products in an 87% combined yield and in a ratio of **33**/**34** = 1:9, the vinyl bromide **34** being in an *E*/*Z* ratio of 46:54. According to the previous proposals,[20,21] the mechanism comprises a cascade of free-radical reactions shown in Scheme 8, which involves bromine abstraction by stannyl or silyl radical to generate the vinyl radical **35**, followed by a 1,5-radical translocation, 5-*endo* cyclization of radical **36**, and finally product formation by bromine-atom ejection from radical **37**.[33] Upon comparison of these data with an analogous atom dispositon at the reactive centers but in the nucleoside case (Scheme 3),[20,21] it appears that the replacement of a ribose moiety with a methoxymethylene group results in a significantly less efficient radical cascade sequence, with the cyclized product formed in a low yield. Therefore, the ribose moiety in the nucleoside case possibly creates a more crowded transition state that is suitably positioned for a radical translocation and/or cyclization.

The UB3LYP/6-31G* calculations were performed to examine the factors that influence the 5-*endo* radical cyclization in such a system. Chart 3 shows the structures under consideration. First, we studied the 5-*endo* cyclization of the simplest α-aminyl radical **38** containing a dienic moiety. In this radical, the delocalization of the unpaired electron in the transition state is limited to a single double bond. Furthermore, the radical center does not carry substituents, and the nitrogen lone pair cannot be delocalized to a carbonyl group. Surprisingly, as shown in Table 5, E_a was found to be 19.4 kcal/mol, which is 3.3 kcal/mol higher than the value for radical **16** (cf. Table 3). Substitution of the double bond with a methyl group in radical **39** decreases the E_a value. This indicates that delocalization of the unpaired electron to the double bond in the transition state

(33) For some structurally analogous uracil derivatives obtained by 5-*exo* radical cyclization, see: Fenick, D. J.; Falvey, D. E. *J. Org. Chem.* **1994**, *59*, 4791−4799.

Chart 3

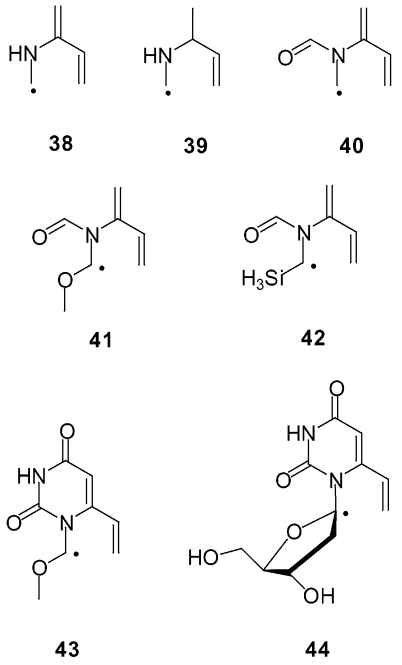


Table 5. Reaction Barriers (E_a), Reaction Enthalpies (H_r), and Angles of Attack in the Transition State (ϕ) for the Cyclizations Computed at the UB3LYP/6-31G* Level[a]

radical	cyclization	E_a, kcal/mol	H_r, kcal/mol	ϕ, degrees
38	5-*endo*	19.4	−23.0	88.4
39	5-*endo*	18.4	−11.1	88.2
40	5-*endo*	17.7	−25.5	88.1
41	5-*endo*	13.0	−30.9	89.5
42	5-*endo*	20.2	−16.4	88.7
43	5-*endo*	8.4	−33.3	90.2
44	5-*endo*	8.5	−28.6	89.7

[a] E_a and H_r values corrected for the difference in ZPVE (cf. ref 27).

is not efficient. The presence of the carbonyl group in **40** decreases E_a by about 2 kcal/mol. The carbonyl group should delocalize the nitrogen lone pair, thus reducing its interaction with the radical center and, consequently, increasing the percentage of the unpaired electron at the carbon. This favors the interaction between the radical center and the double bond in the transition state. Interestingly, the methoxy substituent in **41** further decreases E_a by about 5 kcal/mol. This should be due to both the enthalpic factor and the strong pyramidalization that this electronegative group induces at the radical center because radical **40** is nearly planar. Calculations on radical **42,** where a silyl group is located α to the radical center, confirmed this hypothesis. In this case, the radical center is planar because of the presence of a strongly electropositive silyl group, and the E_a value increases by about 7 kcal/mol on going from an electronegative to an electropositive α-substituent. Interestingly, the energy required to bend the radical centers to the same extent as in their corresponding transition-state geometries is estimated to be 3.6, 1.6, and 5.3 kcal/mol for radicals **40**−**42**, respectively. However, as shown in Table 5, variations of the enthalpy factor on going from radicals **40** and **41** to radical **42** are too large if compared to the difference in the activation energy barriers. This could suggest that polar effects play a significant role in the cyclization of radical **42**.[34]

On the basis of this discussion, it is not surprising that vinyl uridines can undergo a facile 5-*endo* radical cyclization, because the uridinyl group can delocalize the unpaired electron in the transition state. Indeed, the uridine group in the transition state of radical **43** further decreases the E_a value. A comparison of 5-*endo* cyclization of radicals **41** and **43** indicates that the E_a and H_r values decrease by 4.6 and 2.4 kcal/mol, respectively. Furthermore, substitution of the methoxy group with a ribosyl group in radical **44** does not affect the E_a value. This confirms that the inductive effect exercised by the oxygen atom is responsible for the sizable lowering (45%) of the activation energy on going from radical **38** to radicals **43** and **44**.

The factors controlling the diastereochemical outcome of the 5-*endo* cyclization in Scheme 3 deserve some comments. The ratio **9**/**10** = 2:1 is independent of the experimental conditions, and the two interpretations for such a selectivity are somewhat in contrast.[20c,21b] Chatgilialoglu et al. suggested a pyramidal C1′ radical where the inversion of configuration at C1′ radical is the main factor controlling the outcome of the stereochemistry, although the relative populations of the rotamers around the C1′−N1 bond might play a minor role.[20c] In the limit of rapid inversion of the C1′ radical, the product distribution is controlled only by the difference between the total free energy of activation for each pathway (Curtin−Hammett principle).[35] On the other hand, Kittaka et al. proposed that a planar C1′ radical with rapid C1′−N1 rotation operates and that the cyclic product ratio depends simply on the different repulsions between the C2 carbonyl and the 2′-substituent in the two transition states.[21b] We have recently shown that the C1′ radical in 2′-deoxyuridine case is indeed pyramidal (the C1′−N1 bond is about 30° out of the plane OC1′C2′) and exists in two stable conformations (α- and β-anomers).[36] The α/β conversion proceeds via a roto-inversion pathway with a low activation energy. The UB3LYP/6-31G* calculations on radical **44** show that, also in the vinyl derivative, the radical center is strongly pyramidal both in the ground and in the transition state, the C1′−N1 bond being 28.1° and 35.1° out of the plane OC1′C2′, respectively. It is also worth mentioning that the enhancement of reactivity noted for the radical cascade sequence involving the intermediate **8** (Scheme 3) with respect to the analogous reaction of radical **36** (Scheme 8) is probably due to an entropic factor, because the presence of a sugar substituent should increase the rigidity about the radical center.

Conclusions

We have faced the question: Is 5-*endo-trig* radical cyclization a disfavored process? Our results show that these reactions are not only thermodynamically but also kinetically favored. Baldwin−Beckwith rules favor a 4-*exo* mode on stereoelectronic grounds. Indeed, the 4-*exo* mode of cyclization meets the stereoelectronic requirements, but this is not enough to make this mode kinetically favored. The four-membered strain in the transition state induces a higher activation energy than the five-membered ring formation (cf. Figure 1). Only substituents that strongly delocalize the unpaired electron in the transition state of 4-*exo* cyclization and/or bulky substituents that play an important conformational role in the transition state of 5-*endo* cyclization can significantly change the reaction course. We are confident that similar guidelines will be useful to both homolytic and heterolytic cyclizations, because the same factors should govern both classes of reactions.[37]

Acknowledgment. We thank Prof. Scott E. Denmark for helpful discussions of electrocyclization reactions. T.G. thanks the Greek General Secretariat for Research and Technology for a "Career Award" grant and Prof. M. Orfanopoulos for generous hosting at the University of Crete.

Supporting Information Available: Experimental procedures, preparation and characterization of materials, and structural parameters (d_{TS}, ω_{UR} and ω_{TS}) related to Tables 3−5 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0261731

(34) Fischer and Radom found that radicals with high electron affinities exhibit an electrophilic behavior that lowers the activation energy for radical addition.[29] The ionization potential computed for the radical center was similar for these three radicals (7.00, 7.00, and 7.05 eV for radicals **40**−**42**, respectively), whereas the electron affinity of the silyl derivative **42** is much larger (0.17 eV) than those of the other two radicals (−0.51 and −0.59 eV for **40** and **41**, respectively).

(35) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

(36) (a) Chatgilialoglu, C.; Ferreri, C.; Bazzanini, R.; Guerra, M.; Choi, S.-Y.; Emanuel, C. J.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 9525−9533. (b) Chatgilialoglu, C.; Gimisis, T.; Guerra, M.; Ferreri, C.; Emanuel, C. J.; Horner, J. H.; Newcomb, M.; Lucarini, M.; Pedulli, G. F. *Tetrahedron Lett.* **1998**, *39*, 3947−3950.

(37) For recent examples, see: (a) Graig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, *55*, 13471−13494. (b) Dell'Elba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Pedrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **2000**, 903−912.