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Notable Effect of an Electron-Withdrawing Group at C3 on the Selective Formation of Alkylidenecyclobutanes in the Thermal Denitrogenation of 4-Spirocyclopropane-1-pyrazolines. Nonstatistical Dynamics Effects in the Denitrogenation Reactions

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Abstract: A detailed study of the thermal denitrogenation of 3-carbomethoxy-substituted 4-spirocyclopropane-1-pyrazolines **6** was conducted. Alkylidenecyclobutane derivatives **7** were selectively formed in a stereospecific manner. Unrestricted density functional calculations for a 1-pyrazoline **10a** indicated that the concerted cleavage of two C−N bonds is the energetically favored process for the denitrogenation reaction to give the 2-spirocyclopropyl 1,3-diyl, followed by a conrotatory ring-closure process, which was calculated to be the energy minimum pathway, to afford a spiropentane derivative. The calculated energy minimum pathway is largely inconsistent with the experimental results observed for the denitrogenation of **6** and **10a**. The contradiction between the experimental and standard computational results was solved by considering nonstatistical dynamics effects in the concerted denitrogenation reactions. Although the energy minimum pathway from the transition states of the concerted denitrogenation of the 3-carboalkoxy-substituted 1-pyrazolines involves generation of the corresponding 1,3-diradicals, many trajectory calculations using the Bohn−Oppenheimer molecular dynamics model from the transition state for the concerted denitrogenation led directly to the formation of alkylidenecyclobutanes at the UB3LYP/6-31G(d) level of theory.

Introduction

The denitrogenation of azo compounds (RN═NR′) is an important reaction for the clean generation of radical species, which has been utilized for synthetically useful radical-chain reactions as well as the preparation of strained molecules.[1] The focus of recent research interest in denitrogenation reactions is on the mechanism of the C−N bond cleavage step, that is, stepwise C−N bond cleavage versus a concerted two C−N bond cleavage.[2,3] The studies clarify that the product distributions, including stereoselectivity, are largely dependent on the preferred mechanism.

In 1977, Bergman and co-worker[4] reported on the selective formation of spiropentane (**2**) (**2**/**3** = 99/1) in the thermolysis of 4-spirocyclopropane-1-pyrazoline (**1**) (Scheme 1). In contrast, the exclusive formation of methylenecyclobutane derivatives **5** was reported by Tokuda and co-workers in the thermal denitrogenation of 3-carboalkoxy-substituted 4-spirocyclopropane-1-pyrazolines **4**.[5] The 2-spirocyclopropane-1,3-diyl derivatives **DR** have been proposed as plausible intermediates. The dramatic substituent effects of an electron-withdrawing group at C3 on product selectivity prompted us to examine the role of the carboalkoxy group in the thermal decomposition of the 4-spi-

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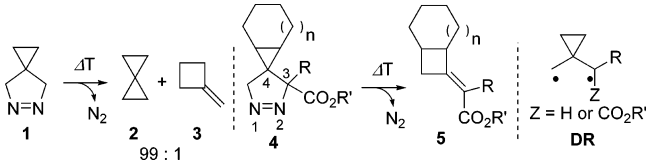
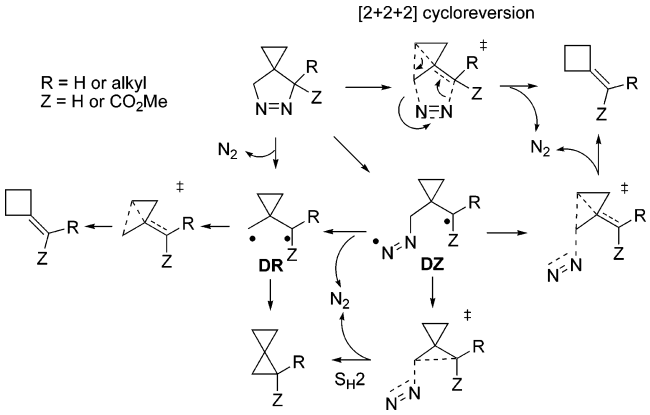
Scheme 1. Denitrogenation of 4-Spirocyclopropane-1-pyrazolines



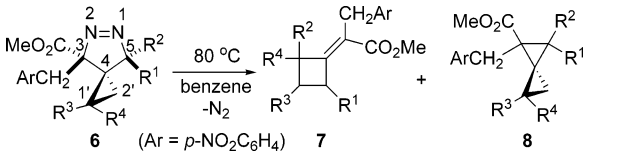
Scheme 2. Possible Mechanism for the Thermal Denitrogenation of 4-Spirocyclopropane-1-pyrazoline



rocyclopropane-1-pyrazolines more closely. On the basis of recent studies of the thermal denitrogenation mechanism of azoalkanes,[2] possible mechanisms for the denitrogenation reaction of 4-spirocyclopropane-1-pyrazolines are summarized in Scheme 2. The spiropentane can be formed via 2-spirocyclopropyl-1,3-diyl **DR** which may be generated by the concerted[6] or stepwise denitrogenation of the 1-pyrazoline. An S_H2 process[7] involving the diazenyl diradical **DZ** would be also possible for the formation of the spiropentane. Three pathways are possible for the formation of the alkylidenecyclobutane derivative: (1) ring-opening of the cyclopropane in the 1,3-diradical **DR**; (2) ring-opening and concomitant elimination of nitrogen via the diazenyl diradical **DZ**; (3) a concerted [2 + 2 + 2] cycloreversion[2e] reaction from the 1-pyrazoline, in which the ring-enlargement of the cyclopropane participates in the concerted denitrogenation.

In the present study, the 1-pyrazoline derivative **6a** and stereochemically labeled **6b**−**e**, which have no extra-ring on the cyclopropane moiety, were prepared and the product distributions in the thermal denitrogenation reactions were investigated, to better understand the effects of an electron-withdrawing group at C3 on the denitrogenation mechanism (Table 1). The selective formation of alkylidenecyclobutanes **7** was observed (Table 1), which clearly indicates that the electron-withdrawing group at C3 plays an important role in controlling product distribution, the spiropentane versus alkylidenecyclobutane. Computational studies provide a reasonable explanation for the notable effects of substituents on the denitrogenation mechanism, in which nonstatistical dynamics[8] plays an important role in controlling the product selectivity in the denitrogenation reactions.

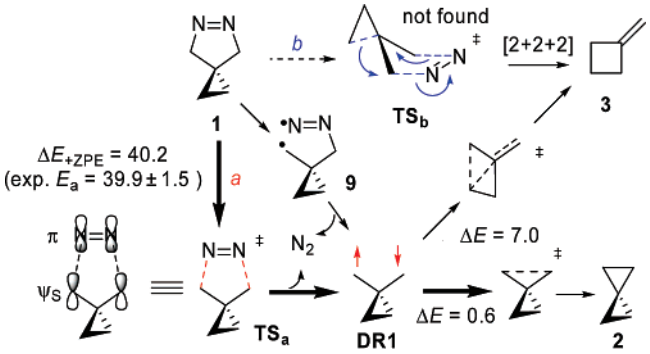
Table 1. Thermal Denitrogenation of 1-Pyrazolines **6** at 80 °C in Benzene



							product (%)[a]	
entry	**6**	R^1	R^2	R^3	R^4	time /h	**7**	**8**[b]
1	**a**	H	H	H	H	16	**7a** (90)	**8a** (10)
2	**b**	Me	H	H	H	2	**7b** (86)	**8b** (14)
3	**c**	H	Me	H	H	20	**7c** (93)	**8c** (7)
4	**d**	H	H	Me	H	3	**7d** (>95)	
5	**e**	H	H	H	Me	24	**7d** (50)	
							7e (50)	

[a] Product ratios were determined by ^{1}H NMR, mass balance >95%. [b] The configuration of **8** was not assigned because of the low yield of **8**.

Scheme 3. Summary for the Computational Results of the Denitrogenation of **1**



Results and Discussion

Thermolysis of 1-Pyrazolines 6. 1-Pyrazolines **6a**−**e** were synthesized by the 1,3-dipolar cycloaddition of diazomethane or diazoethane with the corresponding methylenecyclopropanes[9] (Supporting Information). The structures of **6a**−**e** were unequivocally confirmed by spectroscopic analyses including NOE measurements. When pyrazoline **6a** was heated at 80 °C in benzene for 16 h, methylenecyclobutane **7a** was formed in 90% yield, along with a small amount of the spiropentane derivative **8a** (10%), mass balance >95% (entry 1 in Table 1). Prolonging the thermolysis at 80 °C resulted in no isomerization between **7a** and **8a**, indicating that they are primary products in the thermal decomposition of **6a**.

The stereochemically labeled trans-configured **6b** and cis-configured **6c** underwent decomposition with the stereospecific ring-enlargement of the cyclopropane ring to give the cis-configured methylenecyclobutanes **7b** (86%) and the trans-configured **7c** (93%), respectively (entries 2−3). The configurations of the methylenecyclobutanes were unequivocally confirmed by ^{1}H NMR NOE measurements (Supporting Information). In addition, spiropentanes **8b** and **8c** were also formed as minor products. Configurational determination was, however, difficult because of the low yields of **8**. It should be noted that the decomposition of the cis-isomer **6c** required 20 h for complete decomposition to occur, while the corresponding trans-

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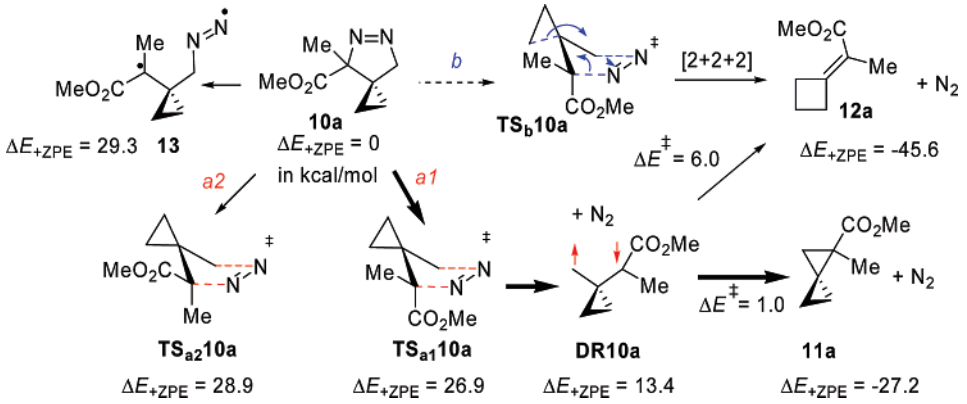
Scheme 4. Summary for the Computational Results of the Denitrogenation of **10a**



isomer **6b** decomposed completely within 2 h (entries 2−3). Prolonging the thermolysis did not change the product ratios of **7** and **8**, and no configurational changes were observed in the products.

Finally, the thermal decomposition of 1-pyrazolines **6d**,**e** bearing a methyl group on the spirocyclopropane ring were performed, in an attempt to determine the regioselectivity of the migrating carbon of the cyclopropane ring in the formation of methylenecyclobutanes (entries 4−5). The decomposition of **6d** gave methylenecyclobutane **7d** exclusively (entry 4). The regioselective formation of **7d** clearly indicates that the C1′ carbon of the cyclopropane ring selectively migrates to the C5 position of **6d**. In contrast, the decomposition of **6e** gave a 1:1 mixture of the methylene-cyclobutanes **7d** and **7e** under similar conditions (mass balance >95%, entry 5). The formation of regioisomers indicates that carbons C1′ and C2′ both migrate equally to the C5 position. The decomposition of **6e** required 24 h for complete decomposition, whereas pyrazoline **6d** was completely denitrogenated within 3 h at 80 °C (entries 4−5). All of the products were stable under the conditions used for the thermolysis. The experimental results for the thermal denitrogenation of 3-methoxycalbonyl-substituted 1-pyrazolines **6** are summarized as follows: (1) The selective formation of methylenecyclobutanes **7** was observed. (2) The stereospecific formation of cis-configured **7b** and trans-configured **7c** was observed in the denitrogenation of trans-configured **6b** and cis-configured **6c**. (3) The regioselective formation of **7d** was observed in the denitrogenation of **6d**, while a mixture of **7d** and **7e** was produced in the reaction of **6e**. (4) The thermal decomposition of **6b** and **6d** was faster than that of **6c** and **6e**, respectively.

To understand the notable substituent effects on product selectivity and the rate of the thermal denitrogenation of 1-pyrazolines **6**, computational studies on the denitrogenation of **1** and model pyrazolines **10** were performed with the Gaussian 03[10] suite of programs (Schemes 3, 4; Supporting Information).

Molecular Orbital Calculations for the Denitrogenation Reaction of 1. First of all, the denitrogenation reaction of the parent 1-pyrazoline **1** and the reactivity of the diradical **DR1** were calculated by using density functional theory (DFT) at the (U)B3LYP/6-31G(d)[11] level (Scheme 3). The adequacy of the DFT calculations for such denitrogenation reactions can be judged by the comparison of the calculated results with the experimental facts,[4] for example, product distribution and activation energy that were determined by Bergman and co-worker. High-level ab initio calculations with configuration interaction, that is, CASPT2 method, were also reported for the reactivity of the diradical **DR1** by Borden and co-workers.[12] Thus, the DFT predictions for such an open-shell molecule can be compared with predictions computed by the CASPT2 level of theory.

The transition state $\mathbf{TS_a}$ ($S^2 = 0.40$) for the concerted denitrogenation, producing singlet propane-1,3-diyl **DR1** (path *a*), was found at the UB3LYP/6-31G(d) level of theory. The energy barrier of the two-bond cleavage was calculated to be $\Delta E_{+ZPE} = 40.2$ kcal/mol. The calculated value is in very good agreement with the experimental value[4] of $E_a = 39.9 \pm 1.5$ kcal/mol reported by Bergman for the denitrogenation of 1-pyrazoline **1**, to produce spiropentane (**2**); see, Scheme 1. Although the diazenyl diradical **9** was found as an equilibrated structure, the energy was calculated to be 2.1 kcal/mol higher than the energy of the transition state $\mathbf{TS_a}$ at the same level of theory. The computational calculations clearly suggest that the pathway involving diazenyl diradical **9** can be excluded for the formation of spiropentane. The favored two C−N bond cleavage is consistent with our previous findings on the effect of an electron-donating substituent at C4, for example, cyclopropane, in the denitrogenation mechanism.[2g] Thus, the concerted two C−N bond cleavage is a symmetry-allowed process, since the phases of the diyl **DR1** LUMO (ψ_S) and the N_2 HOMO (π) match (Scheme 3).[2g] The energy barrier for the formation of spiropentane from **DR1** was computed to be a very small, that is, $\Delta E = 0.6$ kcal/mol, at the same level of theory, which is consistent with Borden's CASPT2 value[12] of 0.8 kcal/mol. The calculated barrier is much lower than the ΔE value of 7.0 kcal/mol for the 1,2-migration, to produce methylenecyclobutane **3**. Thus, the UB3LYP calculations were strongly supportive of the experimental results for the selective formation of spiropentane (**2**) from **1** (Scheme 1).[13,14] The potential energy surface of the three-bond pericyclic denitrogenation, that is, a [2 + 2 + 2]

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(12) Johnson, W. T. G.; Hrovat, D. A.; Borden. W. T. *J. Am. Chem. Soc.* **1999**, *121*, 7766−7772.

(13) For the accuracy of DFT calculations for other open-shell molecules, see ref 2e and: Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036−6043.

cycloreversion[2e] (path *b*) via $\mathbf{TS_b}$, was not found even at the RB3LYP/6-31G(d) level of theory. Although the transition state ($\Delta E_{+ZPE} = 41.1$ kcal/mol) of the two bond cleavage producing the diyl **DR1** was located at the restricted DFT level of theory, the wavefunction was calculated to be unstable.

Molecular Orbital Calculations and Experimental Studies on the Denitrogenation of 10a. To obtain information concerning the role of the carbomethoxy group on the selective formation of alkylidenecyclobutane derivatives (Table 1), the denitrogenation of a 1-pyrazoline **10a** and the reactivity of the 1,3-diyl **DR10a** were examined at the UB3LYP/6-31G(d) level of theory (Scheme 4). As found in pyrazoline **1** (Scheme 3), the concerted denitrogenation (path *a*) was calculated to be the energetically more favored pathway than the stepwise denitrogenation for producing diazenyl diradical **13** ($\Delta E_{+ZPE} = 29.3$ kcal/mol). The transition state $\mathbf{TS_{a1}}$**10a**, in which the carbomethoxy group is located in a pseudoaxial position, was lower in energy by 2.0 kcal/mol than the transition state $\mathbf{TS_{a2}}$**10a**, in which the methyl group is located in a pseudoaxial position. The five-membered pyrazoline ring of the precursor **10a** was optimized to be in an almost planar conformation. Intrinsic reaction coordinate (IRC) calculations for $\mathbf{TS_{a1}}$**10a** revealed that the energy minimum pathway for the denitrogenation of **10a** involves the generation of the singlet state of 1,3-diyl **DR10a** via $\mathbf{TS_{a1}}$**10a**. The [2 + 2 + 2] cycloreversion via $\mathbf{TS_b}$**10a** (path *b*) was not found at either the RB3LYP/6-31G(d) or the RMP2/6-31G(d) level of theory. As found for the reactivity of the parent diradical **DR1**, the energy barrier ($\Delta E^{\ddagger} = 1.0$ kcal/mol) for the conrotatory ring closure of the diradical **DR10a** was found to be lower than that for the ring-enlargement of the cyclopropane ring in the diradical **DR10a** ($\Delta E^{\ddagger} = 6.0$ kcal/mol). Thus, the computational results, again, clearly indicate that the energy minimum pathway of the denitrogenation of **10a** is the generation of the diradical **DR10a** by concerted denitrogenation, followed by ring-closure occurs to selectively give the spiropentane derivative **11a**. The results of the statistical calculations are apparently inconsistent with the experimental results, that is, the selective formation of alkylidenecyclobutanes **7** in the denitrogenation of **6** (Table 1). To exclude an effect of *p*-nitrophenyl group, which is necessary for the separation of stereoisomers in **6b**−**e** by recrystallization, on the product selectivity in the denitrogenation of **6a**, 1-pyrazoline **10a** was prepared (see, Supporting Information) and the product analysis and the determination of the activation parameters (E_a and ln *A*) was performed for the denitrogenation reaction in toluene solution (Figure 1). Thus, one can compare directly the DFT calculations (Scheme 4) with the experimental results. As shown in Figure 1, the activation energy (E_a) for the denitrogenation was determined to be 26.8 ± 0.5 kcal/mol according to the Arrhenius plot, which is very closed to the value ($\Delta E^{\ddagger}_{+ZPE} = 26.9$ kcal/mol) obtained by the DFT calculations (Scheme 4). However, the statistical calculations did not accurately predict the product selectivity. Thus, the theory predicts that the exclusive formation of spiropentane **11a** (Scheme 4), although the slightly favored formation of methylenecyclobutane **12a** was experimentally observed in the denitrogenation of **10a** (Figure 1). The product ratio of **11a** and **12a** were virtually temperature-independent at least in the reaction-temperature range from

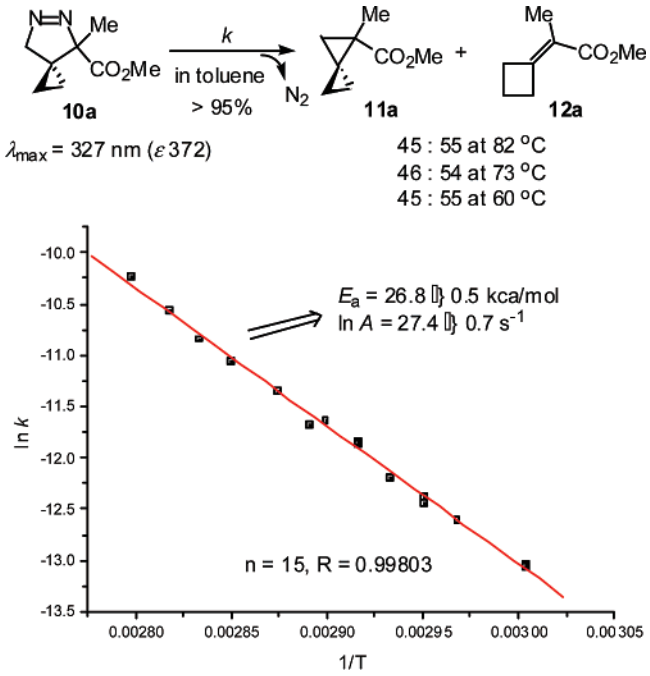


Figure 1. Arrhenius plot for the denitrogenation of 1-pyrazoline **10a** in toluene. The first-order rate constants (*k*) were determined by the decay traces of the band of the azo-chromophore at 327 nm.

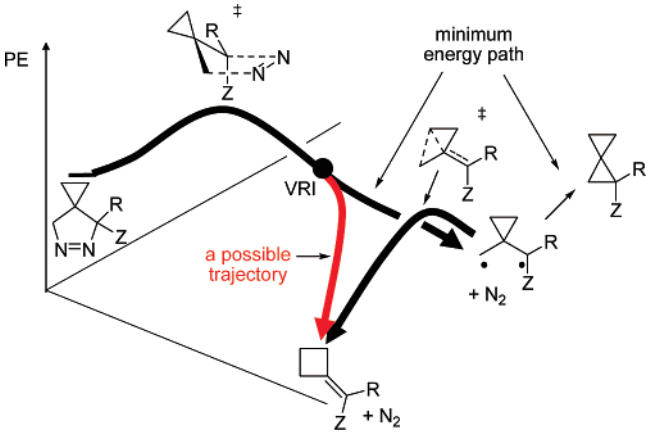


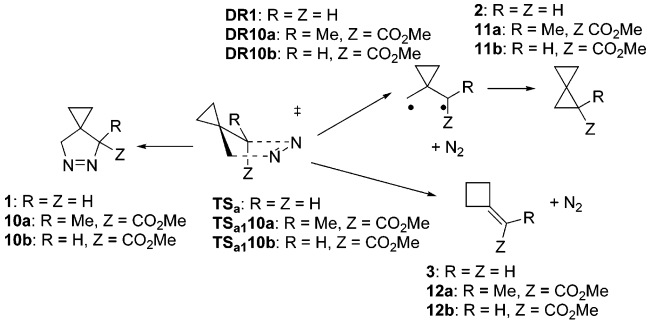
Figure 2. A schematic potential energy (PE) surface for the denitrogenation reaction of 1-pyrazolines.

60 °C to 82 °C. Prolonging the thermolysis resulted in no isomerization between **11a** and **12a**, indicating that they are primary products in the thermal decomposition of **10a**. Although DFT is known to handle properly open-shell structures and their reactivities,[13] the MO calculations did not reproduce the product selectivity in the denitrogenation of 1-pyrazolines **6** and **10a**.

On the basis of the computational results for the pyrazolines **1** and **10a**, the potential energy (PE) surface in the denitrogenation reaction can be drawn as shown in Figure 2. A large activation energy is required for the first concerted-denitrogenation step to generate the unstable diradical with kinetic energy, which affords the spiropentane derivative with a small activation energy. The alkylidenecyclobutane may be formed from the diradical intermediate with a small activation energy. Therefore, it would be possible that the trajectory passing through the denitrogenation transition-state could lead directly to the alkylidenecyclobutane via the valley-ridge inflection point (VRI).[15] Such a reaction has a high probability of exhibiting nonstatistical dynamic effects.[8,16]

(14) An unreliability of the DFT energies for strained molecules was reported by Schreiner and coworkers, see: Schreiner, P. R.; Fokin, A. A.; Pascal, R. A., Jr.; de Meijere, A. *Org. Lett.* **2006**, *8*, 3635−3638.

Scheme 5. Bohn−Oppenheimer Molecular Dynamics Simulations in the Denitrogenation of 1-Pyrazolines **1**, **10a**, and **10b**



transtion state	total number of trajectories	number of trajectories: pyrazoline	diradical (spiropentane)	alkylidene-cyclubutane
TSa	10	1	9*	0
TS$_{a1}$10a	31	25	1	5
TS$_{a1}$10b	36	0	11	25

Nonstatistical Dynamics Effects in the Denitrogenation of 1-Pyrazolines. To study the question of dynamics effects, the transition-states of the concerted denitrogenation, **TS$_a$**, **TS$_{a1}$10a**, **TS$_{a1}$10b**, were used as starting points for trajectory calculations using a Bohn−Oppenheimer molecular dynamics (BOMD) model[17] at the UB3LYP/6-31G(d) level of theory, 0.2-fs steps (Scheme 5). The direct dynamics trajectories were initiated with conditions chosen from a 353 K Boltzmann distribution for the reaction coordinate translation.[18] Although the energy minimum pathway from the denitrogenation transition-state involves generating the 1,3-diradical, that is, the precursor of the spiropentane derivative, the chemical dynamics calculations showed that two products, 1,3-diradical and alkylidenecyclobutane, were formed from the transition state. From the transition state **TS$_a$**, 1 out of 10 trajectories afforded the starting 1-pyrazoline (**1**) after 120 fs; 8 in 10 trajectories produced diradical **DR1** after 100 fs. One trajectory gave spiropentane (**2**) directly with conrotatory ring-closure from the transition state **TS$_a$** (Scheme 6a). Thus, the trajectory calculation results are in good agreement with Bergman's experiment, that is, the selective formation of spiropentane (**2**) from 1-pyrazoline (**1**) (see Scheme 2). In the trajectory calculations from the transition state **TS$_{a1}$10a**, which contains a carbomethoxy group, the results were striking (Scheme 5). Five out of 31 trajectories produced alkylidenecyclobutane **12a**. Twenty-five trajectories went back to the pyrazoline **10a**. One trajectory gave the diradical **DR10a**, which is the precursor of the spiropentane **11a**. Thus, the results of the trajectory calculations are in good agreement with the selective formation of an alkylidenecyclobutane derivative in the denitrogenation of 3-carboalkoxy-substituted 1-pyrazolines **4**,**6**, and **10a**. It should be noted that the C5 carbon selectively migrates to the C2 carbon from the backside of the departing nitrogen atom, as shown in Scheme 6b. Thus, a formal [2 + 2 + 2] cycloreversion reaction is proposed for the selective formation of alkylidenecyclobutane derivatives in the denitrogenation of the 3-carbomethoxy-substituted 1-pyrazoline. To examine the generality of the selective formation of alkylidenecyclobutane derivatives, trajectory calculations were performed at the same level of theory for the transition state **TS$_{a1}$10b**. Eleven of 36 trajectories produced the 1,3-diradical **DR10b** after 120 fs. One of the trajectories afforded spiropentane derivative **11a** after 350 fs (Figure S1 in Supporting Information). The remaining 25 trajectories afforded the expected alkylidenecyclobutane **12b**. Thus, an electron-withdrawing group at C3 in the 1-pyrazolines plays an crucial role in the selective production of alkylidenecyclubutanes, although the energy minimum path affords the corresponding 1,3-diradical.

Effects of an Electron-Withdrawing Group at C3 on the Selective Formation of Alkylidenecyclobutane Derivatives in the Denitrogenation of 1-Pyrazoline. To obtain information on the role of the electron-withdrawing substituent at C3 on changing the product distribution in the denitrogenation reactions, spiropentane versus alkylidenecyclobutane, the singlet−triplet energy gaps (ΔE_{ST} in kcal/mol = $E_S - E_T$) were calculated for the 2-spirocyclopropane-substituted propane-1,3-diyls **DR1** (Z = H) and **DR10b** (Z = CO_2Me) at the UB3LYP/6-31G(d) level of theory, in which the magnitude of the hyperconjugative interaction[19] between the symmetric nonbonding molecular orbital (ψ_S) of the diyl and the C−C σ orbital of the cyclopropane ring can be evaluated precisely (Scheme 7).

The parent 1,3-diradical **DR1** was calculated to be the triplet ground-state molecule, ΔE_{ST} = +1.5 kcal/mol. The value for the preference for the triplet state is close to the CASPT2 value[12] of +2.0 kcal/mol.[20] In contrast, the singlet ground state was calculated for the carbomethoxy-substituted diradical **DR10b**,

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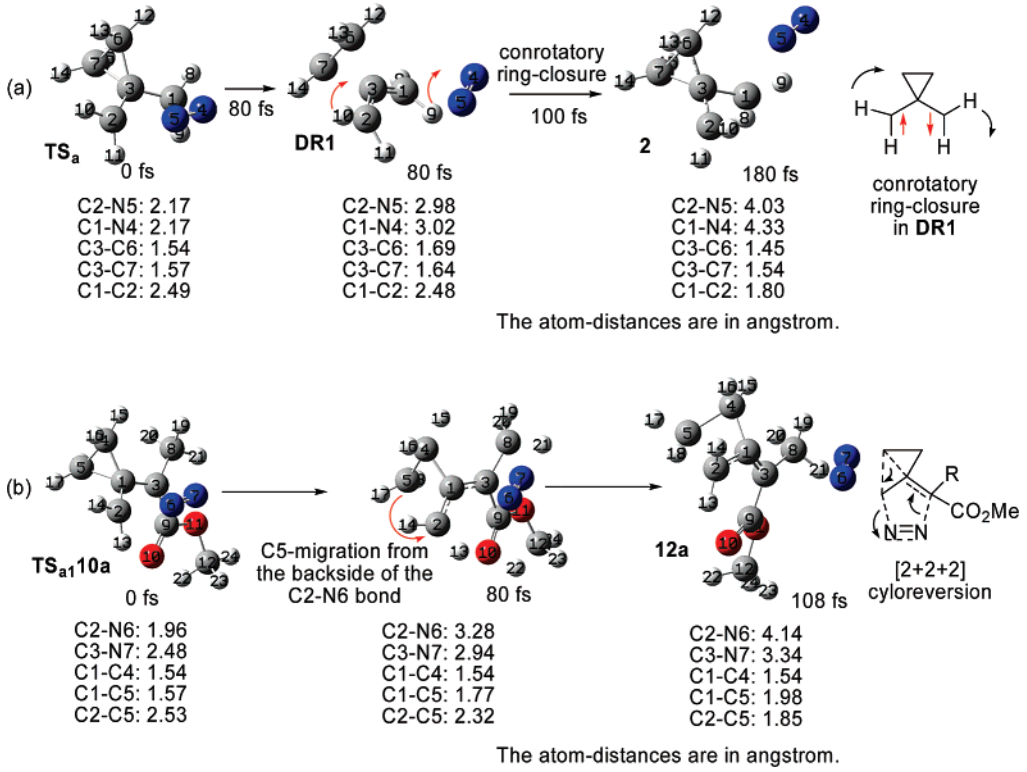
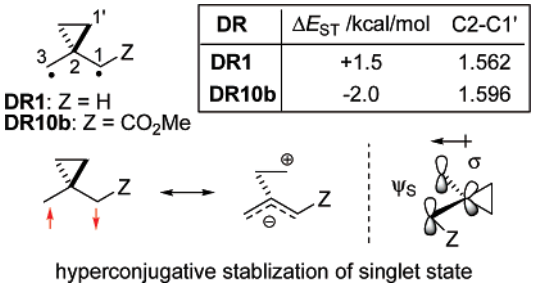
Scheme 6. Selected Structures in the Bohn−Oppenheimer Molecular Dynamics Simulations in the Denitogenation of (a) 1-Pyrazolines **1** and (b) 3-Carbomethoxy-substituted 1-Pyrazoline **10a**



Scheme 7. *Z*-group Effect on the Singlet−Triplet Energy Gap in 2-Spirocyclopropane-1,3-diyls



DR	ΔE_{ST} /kcal/mol	C2-C1′
DR1	+1.5	1.562
DR10b	-2.0	1.596

$\Delta E_{ST} = -2.0$ kcal/mol, after spin-correction.[21,22] The notable substituent effect on the ground state spin-multiplicity can be rationalized by the larger hyperconjugative stabilization of the singlet state in **DR10b**, compared to that for **DR1**. Since the energy level of the orbital ψ_S of **DR10b** (Z = CO_2Me) is lower than that of **DR1** (Z = H), a stronger hyperconjugative interaction with the C−C σ orbital of the electron-donating cyclopropane would be expected for **DR10b**. In fact, the C2−C1′ bond length in **DR10b** (C2−C1′ = 1.596 Å) was calculated to be significantly longer than that in **DR1** (C2−C1′ = 1.562 Å). Such a hyperconjugative interaction should also be operative in the ring-enlargement reaction of the cyclopropane ring, which affords the alkylidenecyclubutane derivative. In fact, the energy barrier for the ring-cleavage in **DR10a** was calculated to be lower than that for the diradical **DR1** (see Schemes 3 and 4). Thus, cyclopropane σ bond-breaking would be prone to participate in the concerted denitrogenation of the 3-carbomethoxy-1-pyrazolines.

Stereospecific Formation of Alkylidenecyclobutanes in the Denitrogenation of 3-Carbomethoxy-Substituted 1-Pyrazolines. As shown in Table 1, the thermal denitrogenation of the trans-configured **6b** and the cis-configured **6c** gave stereospecifically the cis-configured **7b** and the trans-configured **7c**, respectively (entries 2, 3 in Table 1). The regioselective formation of **7d** was observed in the denitrogenation of **6d**, while the regiorandom migration of the carbon in the cyclopropane ring was verified by the formation of a 1:1 mixture of **7d** and **7e** (entries 4, 5 in Table 1). To clarify the origin of the stereospecific and regioselective formation of the alkylidenecyclobutanes **7**, the structures of the transition states for the concerted denitrogenation of the model 1-pyrazolines **10c**−**f**, which correspond to **6b**−**e** (Table 1), were optimized at the UB3LYP/6-31G(d) level of theory (Scheme 8).

For the concerted denitrogenation of the trans-configured **10c**, the transition-state structure **TS$_{a1}$10c**, which would be the precursor of the cis-configured alkylidenecyclobutane **12c**, was successfully optimized at the UB3LYP/6-31G(d) level of theory. However, the transition state **TS$_{a2}$10c**, in which the two methyl groups are located in the pseudoaxial positions, could not be found as a transition state for the denitrogenation at the same level of theory. The transition state **TS$_{a1}$10c** was finally obtained during the optimization of the transition state **TS$_{a2}$10c**. The energetically disfavored structure of **TS$_{a2}$10c** can be reasonably explained by the severe 1,3-diaxial repulsions between the two

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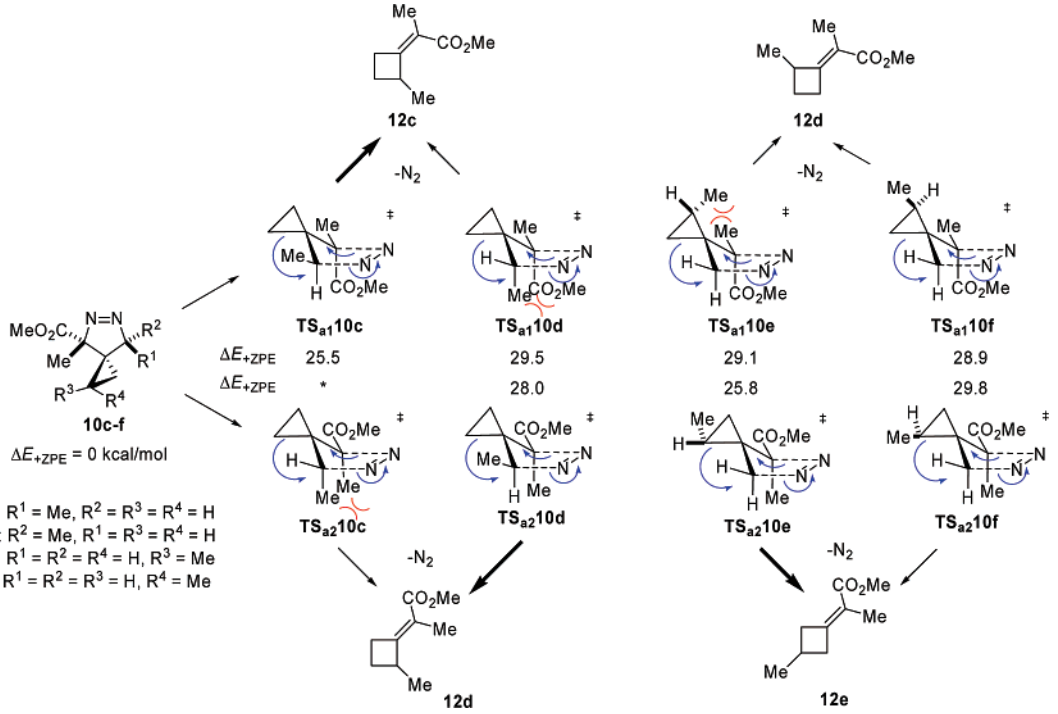
Scheme 8. Summary of Computational Studies for the Denitrogenation of Model 1-Pyrazolines **10c**−**f** at the UB3LYP/6-31G(d) Level of Theory



*Although the location of such a structure **TS$_{a2}$10c** was attempted, the transition state **TS$_{a1}$10c** was finally obtained after the optimization.

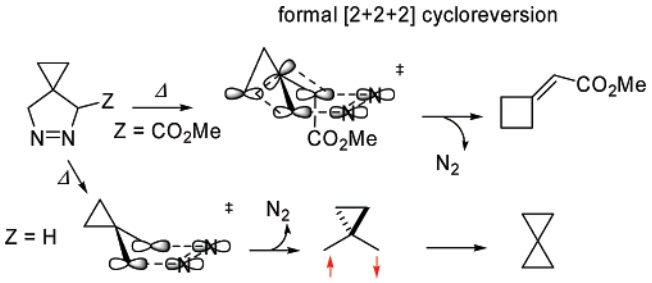
methyl groups. The energetic preference of the transition state **TS$_{a1}$10c** is in very good agreement with experimental results for the selective formation of the cis-configured **7b** from the trans-configured 1-pyrazoline **6b** (see entry 2 in Table 1). In the case of the denitrogenation of the cis-configured **10d**, the transition state **TS$_{a2}$10d**, which would be the precursor of the trans-configured **12d**, was calculated to be energetically more stable than the transition state **TS$_{a1}$10d** by 1.5 kcal/mol including zero-point energies. Thus, the theoretical prediction reproduced the selective formation of the *trans*-configured **7c** in the denitrogenation of the *cis*-configured **6c** very well (entry 3 in Table 1). The energy barrier for the *trans*- configured **10c** was calculated to be smaller than that of the *cis*-configured **10d**, compare the relative energy of **TS$_{a1}$10c** and **TS$_{a2}$10d**. In fact, the denitrogenation of the *trans*-configured **6b** was much faster than that of the *cis*-configured **6c** (entries 2,3 in Table 1).

The theoretical calculations for a model **10e**, which possesses a methyl group at the spirocyclopropane ring, predicted the selective formation of **12e**, since the energy of **TS$_{a2}$10e** was calculated to be more stable than the transition state **TS$_{a1}$10e** by 3.3 kcal/mol (Scheme 8). The significant substituent effect is rationalized by the severe steric repulsion of the substituents between the two methyl groups in **TS$_{a1}$10e**. In fact, the selective formation of **7d** was observed in the denitrogenation of **6d** (entry 4 in Table 1). In the case of the denitrogenation of **10f**, the energy difference between the transition states **TS$_{a1}$10f** and **TS$_{a2}$10f** was calculated to be relatively small, $\Delta\Delta E_{+ZPE} = 0.9$ kcal/mol (Scheme 8). As predicted by the computational results, a mixture of **7d** and **7e** was obtained in the denitrogenation of **6e** (entry 5 in Table 1). The energy barrier for **10e** was calculated to be smaller than that for **10f**; compare the relative energy of **TS$_{a2}$10e** and **TS$_{a2}$10f** (Scheme 8). In fact, the denitrogenation of **6d** was much faster than that of **6e** (entries 4,5 in Table 1).

Summary

The mechanism of the denitrogenation of 4-spirocycloproane-1-pyrazolines was investigated in detail in combined experimental and computational studies. For the reaction of the parent 1-pyrazoline **1**, the selective formation of spiropentane (**2**) was rationalized by the generation of the singlet 1,3-diyl **DR1** via the concerted denitrogenation transition-state **TS$_a$**, followed by the fast radical-coupling reaction of the diyl. The mechanism was strongly supported by standard computational calculations at the UB3LYP/6-31G(d) level of theory. The stepwise formation of spiropentanes was also calculated to be the energy minimum pathway for the denitrogenation of 3-carboalkoxy-substituted 1-pyrazolines, although the selective formation of alkylidenecyclobutanes was observed in experiments. The contradiction between the experimental and standard computational results was solved by considering nonstatistical dynamics effects in the denitrogenation reactions. In classical trajectory calculations using the Bohn−Oppenheimer molecular dynamics model, the product distribution varies greatly. Although the energy minimum path from the transition states of the concerted denitrogenation of the 3-carboalkoxy-substituted 1-pyrazolines involves generating the corresponding 1,3-diradicals, many trajectories led directly to the alkylidenecyclobutane, in which the migration of the carbon occurs from the backside of the departing C−N bond. Thus, the formal [2 + 2 + 2] cycloreversion reaction mechanism adequately explains the selective formation of alkylidenecyclobutanes in the thermal denitrogenation of the carboalkoxy-substituted 1-pyrazolines (Scheme 9). The stereospecific formation of alkylidenecyclobutanes **6b**,**c** supports the formal [2 + 2 + 2] cycloreversion reaction. The notable electron-withdrawing group effects on product distribution can be rationalized by the large contribution of the hyperconjugative resonance structure in the singlet state of the

Scheme 9. *Z*-group Effect on the Denitrogenation Mechanism



1,3-diyl (Scheme 7). The importance of dynamics effects should stimulate future calculations and experiments on the mechanistically and synthetically fascinating denitrogenation reactions of azoalkanes.

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Supporting Information Available: Complete ref 10, experimental, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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