A Combined Density Functional and ab initio Quantum Chemical Study of the Brandi Reaction

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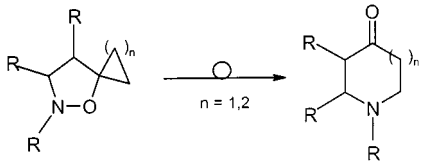
The Brandi reaction is the transformation of spiro[cyclopropane-1,5′-isoxazolidines] into tetrahydropyridones under thermal conditions. According to calculations performed by the restricted and unrestricted density functional theory and post-Hartree–Fock single- and multireference methods of ab initio quantum chemistry, the reaction proceeds through two biradical intermediates. These intermediates result from the homolytic cleavage of the N–O bond of the isoxazolidine ring in the first step, and the homolytic cleavage of one of the C–C bonds of the spiro-fused cyclopropane in the second. The activation energy of the rate-determining first step of the parent reaction amounts to about 40 kcal mol^{-1} at the RDFT/UDFT level of theory. This energy is not much higher than the energy of the first biradical intermediate relative to the reactants. The relative energies calculated at the quadratic CI and coupled cluster ab initio level were of the same order of magnitude. The effects of structural modification of spiro[-cyclopropane-1,5′-isoxazolidines] by substitution at carbon or nitrogen in the five-membered ring, introduction of a double bond into the five-membered ring and replacement of the spiro-cyclopropane by spiro-cyclobutane are discussed. The theoretical results reflect Brandi's experimental findings on the reactivity of the compounds under conventional thermal or flash vacuum thermolysis conditions and his hypothesis about the reaction mechanism reasonably well.

Introduction

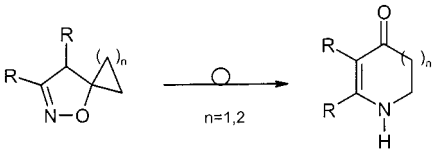
The Brandi reaction is the thermal rearrangement of spiro[cyclopropane-1,5′-isoxazolidines] to tetrahydropyridones [Equation (1), $n = 1$] and related rearrangements that are commonly observed at temperatures of about 110 °C in solution under conventional reflux conditions or between 400 and 700 °C when flash vacuum thermolysis (FVT) is employed.[1−2] This reaction is obviously unique, proceeding in a complex way through intermediates. The precondition is a strained spiro-fused ring in the 5-position. Regioisomeric spiro compounds do not react.[1d] The reaction is also disfavoured if spiro[cyclopropane-1,5′-...] ($n = 1$) is replaced by spiro[cyclobutane-1,5′-...] ($n = 2$).



(1)

R = aliphatic or aromatic residues

The same type of reaction was observed with isoxoazolines in place of isoxazolidines [Equation (2)]. The reaction with $n = 1$ results in dihydropyridones.[2] As can be seen in their required reaction temperatures of between 170 and 200 °C, spiro[cyclopropane-1,5′-isoxoazolines] are less reactive than the corresponding dihydro analogues.



(2)

R = aliphatic or aromatic residues

Some examples collected in Scheme 1 illustrate the characteristic change in reactivity. 2′-Methyl-3′-phenyl-spiro[cyclopropane-1,5′-isoxazolidine (**1a**) is a typical starting compound, with which the reaction occurs easily at about 100 °C.[1b] As shown with **2** and related compounds, the reactivity of the isoxazolidines is considerably greater if donor-substituted phenyl groups are present at nitrogen. The reaction then proceeds smoothly even at room temperature.[3]

In contrast, compounds such as the bicyclic spiro[cyclopropane-1,5′-isoxazolidine] **3** are less reactive than **1a**.[4] A slight increase in the reaction temperature is also necessary on changing from the isoxazolidine **1a** (about 100 °C) to the isoxazolines **4a** (about 200 °C).[2] When spiro-cyclopropane is replaced by spiro-cyclobutane, as in **1b** and **4b**, the reactivity is much more sharply reduced;[5] reactions of these compounds could only be achieved by use of FVT techniques at higher temperatures. The compound **4b**, for example, reacts at temperatures of 600−700 °C.[1c] In some

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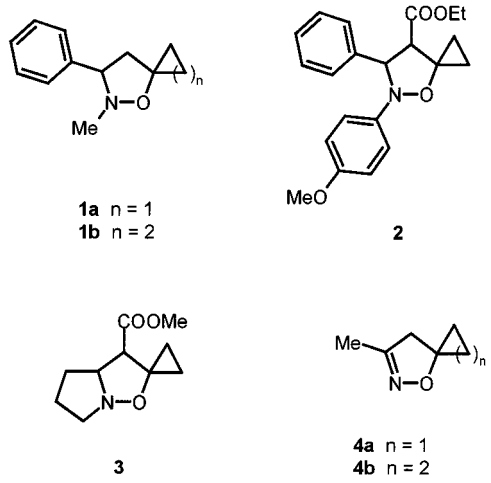


Scheme 1. Some compounds studied experimentally

cases spiro[cyclobutane-1,5′-isoxazolines] do not react at all.

Broadly, three mechanisms may be envisaged (Scheme 2). In the first, initial homolytic cleavage of the N−O bond of the five-membered ring of the reactant (**R**) to give the biradical species **Int1** is followed by homolytic cleavage of the C−C bond of the cyclopropyloxy group; cyclization of the resulting biradical **Int2** finally provides the product **P** (path 1). This mechanism was previously advocated by Brandi et al.[1c]

Another mechanism may consist of the inverse order of breakage of the two bonds and formation of the biradical **Int3** by way of **TS3** in the first step of the reaction (path 2). Finally, the question of whether the change of the bonds proceeds in a concerted manner through a transition structure **TS1a** (path 3) has to be addressed.

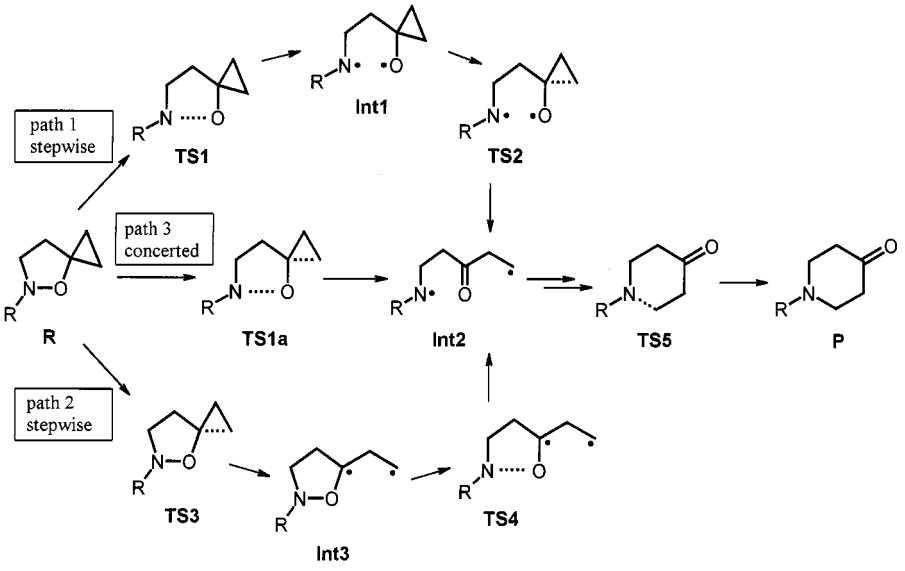
The aim of this paper is to discuss the mechanism of the reaction by means of first-principles methods. Below, the parent reaction − that of the unsubstituted compounds − is considered. Substituents are then introduced to reveal structure-reactivity relationships. To examine the various structures along the reaction path, spin-restricted and spin-unrestricted density functional theory methods (RDFT and UDFT, respectively) were used. Emphasis has been placed on general trends in reactivity and on qualitative relationships. For comparative purposes, calculations at higher levels of ab initio quantum chemistry were also performed.

Methodological and Computational Details

Calculation of biradical or biradical-like species is more difficult than that of conventional structures. Because of the near-degeneracy problem, the Hartree−Fock method is bound to fail. As a consequence, results of post-Hartree−Fock methods are less reliable.[6,7] The HF solutions of biradicals become singlet-triplet unstable.[8] Theoretical indices such as the Lee-Taylor-T_1 diagnostic criterion at the coupled cluster CCSD(T)[9] level were used to examine the multiconfigurational character of the structures. With regard to experimental results, the low singlet-triplet (S/T) splitting energy may also indicate the biradical character. To cope with cases of near-degeneracy, two distinctly different approaches appeared to be most attractive:

The first was the use of the most reliable multireference-based methods, such as the complete-active-space self-consistent-field method (CASSCF), and also the second-order perturbation theory method (CASPT2).[10] Both dynamic and static (nondynamic) correlation are considered in these cases.[11] Calculation requires extended basis sets and becomes computationally very demanding for larger compounds. The method is less well suited for study of series of compounds.

The second was use of the Kohn−Sham density functional theory method. The commonly used spin-restricted approximation (RDFT) with consideration of dynamic cor-



Scheme 2. Alternative reaction paths

relation,[12] however, is only well suited in calculations of chemical transformations with more conventional structures.[13,14] Although the RDFT solutions are much more singlet-triplet stable than those of the restricted HF method,[15] regions of instability are found with biradical species. The RDFT solutions are then externally unstable and collapse into the unrestricted DFT solutions (UDFT) upon release of spin restriction. Although the expectation values $<S^2>$ of the spin square operator $\mathbf{S^2}$ may be as large as unity,[7] UDFT performs much better than UHF. As discussed recently, $<S^2>$ values calculated from KS Slater determinants have no physical significance[16a] and should be disregarded.[16b]

UDFT has been successfully used in the past few years for treatment of various chemical transformations such as torsion around double bonds,[17a] singlet/triplet splitting[17b] and various ring-opening (ring-closure) and rearrangement reactions proceeding through biradical intermediates and transition structures. Houk et al.[13,18] demonstrated the usefulness of this approach in calculating organic reactions early on. Biradical structures involved in reactions have been calculated by UDFT and nonbiradical ones by RDFT; the mixed RDFT/UDFT description is denoted below as (U)DFT. The excellent performance of (U)DFT has been shown with investigation of Diels–Alder,[19a][19b] *retro*-Diels–Alder[19c][19d] and other cycloaddition[19e–19g] and ring-opening reactions,[19h–19i] as well as with various rearrangement reactions.[19c][19j–19o] Where data were available for comparison, UDFT performed well with respect to QCISD and CASSCF (CASPT2) ab initio calculations. Reliable experimental data are available for the enediyne-to-benzyne cyclization (Bergman reaction). As shown by Cremer et al.,[16a] UDFT showed excellent agreement both with respect to experiment and to the results of high level ab intio quantum chemical calculations; UDFT results proved to be more accurate than those of CCSD(T). According to ref.[16a], UDFT indirectly covers static correlation effects as well as dynamic correlation effects and has proved to be a good basis for compounds of multireference character.

In this study, the Brandi reaction was investigated on the basis of the experience discussed above. Unless mentioned otherwise, the B3LYP hybrid functional[20,21] was employed in conjunction with the 6–31G* basis set.[22] (U)DFT calculations were performed using the A7 release of the Gaussian98 program.[23] To destroy the α,β-spin symmetry of biradical intermediates and transition structures, the GUESS=MIX option was used. In the preparation of (U)DFT calculations, semiempirical (U)AM1 and (U)PM3 calculations[24] were also performed, and the results are mentioned in passing. The structures of the reactants, intermediates and products were fully optimized at semiempirical and DFT levels and the minima were confirmed by frequency analysis. To establish the nature of the biradical transition structures, some reaction path calculations were also carried out by scanning the intrinsic reaction coordinates (IRC). As shown below, the IRC exhibits a continuous crossover from the UDFT to the RDFT energy surface. The same holds for the scan of a two-dimensional area performed with respect to the relevant changes of the N–O and C–C bond lengths of the three alternative reaction paths (Scheme 2). To avoid early crossover from unrestricted to restricted solutions in the border region, the SCF=(NoDIIS,QC) option in Gaussian was used in some cases.

Results and Discussion

Energetics of the Parent Reaction

The parent reaction considered below is that of the unsubstituted spiro[cyclopropane-1,5′-isoxazolidine] **5**. Relative energies for the parent reaction along reaction paths 1 and 2 are depicted in Figure 1. The results of the DFT and the AM1 calculations have some features in common. Thus, principally the same stationary points were found by both theoretical models. However, the results of the two methods differ if the energies of paths 1 and 2 are compared in detail. As shown in Figure 1, (U)DFT clearly favours reaction path 1 over reaction path 2, while the opposite holds for (U)AM1, and correspondingly for (U)PM3. According to the (U)DFT calculations, the first rate-determining barrier is about 20 kcal mol^{-1} higher in energy in the case of reaction path 2 than it is in reaction path 1.

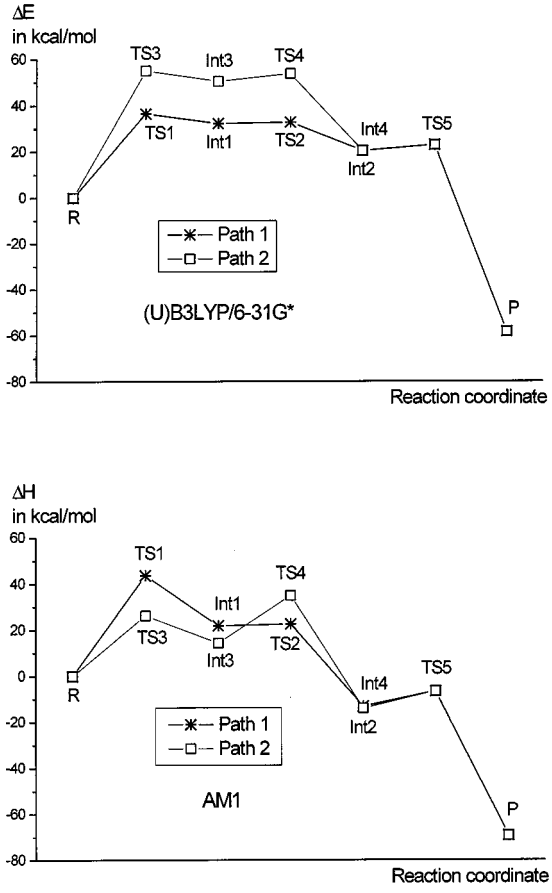


Figure 1. Energy profiles for the parent reaction at the DFT (upper part) and AM1 levels (lower part). For short notations see Scheme 2

The following discussion first deals with reaction path 1 as calculated by the (U)DFT method. The homolytic cleavage of the N−O bond of the five-membered isoxazolidine ring of reactant **R** results in the biradical intermediate **Int1** (cf. Scheme 2). A *cisoid* intermediate is expected to be formed first with ring-opening. A *transoid* conformer is 1 kcal mol^{-1} higher in energy at the DFT level. The $<S^2>$ values of the intermediates amount to about 1 and the Lee-Taylor-T_1 diagnostic of these intermediate structures is as large as 0.035. Such a value signals a multiconfigurational character for this intermediate. As found for nonconjugated biradicals,[25] the S/T-splitting energy of **Int1** conformers is extremely low. This holds for other intermediates of this study as well, and all these species have therefore been calculated by spin-unrestricted DFT. At the (U)DFT level, the first intermediate **Int1** is about 31 kcal mol^{-1} higher in energy than the reactant **R** (cf. Table 1). The energy of the first-order saddle point (**TS1**) of this reaction is only about 5 kcal mol^{-1} higher than that of the first intermediate (37 kcal mol^{-1} relative to the reactant). The energy of the intermediate **Int1** therefore approximately reflects the reaction barrier of the first step of the Brandi reaction.

Table 1. Energies (kcal mol^{-1}) of relevant structures on reaction path 1 of the parent reaction relative to the reactant, calculated at different levels of theory

	TS1	Int1	TS2	Int2	TS5	P
(U)HF/6-31G*	19.6	4.4	10.6	−11.0	−	−65.9
(U)B3LYP/6-31G*	36.5	31.1	32.8	20.4	22.9	−58.4
QCISD/6-31G*// (U)B3LYP/6-31G*	41.7	36.7	38.3	20.3	21.4	−60.7
QCISD/6-31G*// QCISD/6-31G*	−	34.9	−	19.5	−	−60.0
QCISD(T)/6-31G*// (U)B3LYP/6-31G*	40.9	37.1	38.0	22.6	25.2	−58.9
CCSD(T)/6-31G*// (U)B3LYP/6-31G*	41.0	37.3	38.4	24.3	−	−58.8

The transition structure **TS1** is confirmed by the imaginary frequency indicating the reaction path towards N−O bond cleavage. The nature of the transition structure was established by the intrinsic reaction coordinates (IRC) of **TS1**. As shown in Figure 2, the IRC approach either resulted in the reactant, on the left, or moved towards the N−O bond-broken species with increasing N−O atomic distances. Although $<S^2>$ is not a diagnostic for the quality of the calculated DFT energies,[16a] this value displays a remarkable continuous change along the reaction path. Thus, the first transition structure on path 1 described by the spin-unrestricted DFT solution undergoes a smooth change to the reactant structure defined by the spin-restricted solution.

This outcome encouraged us to perform a relaxed scan of a part of the hypersurface with the interatomic distances N−O and C−C as variables. The result is displayed in Figure 3. The scan provided information about the three al-

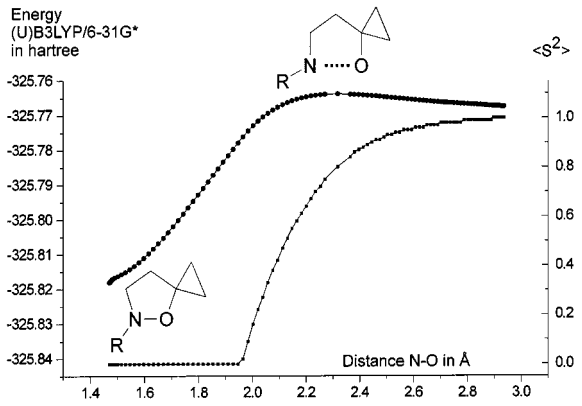


Figure 2. Changes in energy along the intrinsic reaction coordinate with respect to the first order saddle point TS1 of the reaction (upper curve, left scale) and change of expectation value $<S^2>$ of the spin operator $\mathbf{S^2}$ (lower curve, right scale)

ternative reaction paths of Scheme 2. The reaction with primary N−O bond splitting follows the path of lowest energy from the reactant minimum at the left through the saddle point **TS1** at the bottom of Figure 3. The path in the direction towards the saddle point **TS3** shown on the left (path 2) clearly needs more activation energy. This is consistent with the calculated higher energy of the transition structure **TS3** at (U)DFT level. Since all attempts to calculate transition structure **1a** of the concerted reaction between the left-hand corner at the bottom and the right-hand corner on top of Figure 3 failed, this part of the scan was of particular interest (path 3). The problems are explained by the results shown in Figure 3; the energies in the relevant region do not indicate a first order saddle point. However, the energies of the hypothetical path 3 are not much higher than those in the first step of path 1.

Torsion around the C−C bonds of the intermediate **Int1** is nearly barrierless. The next step of the reaction is the breakage of a C−C bond in passing from the intermediate **Int1** to the intermediate **Int2** through the transition structure **TS2**. The barrier to this ring-opening reaction is very low, amounting only to about 1 kcal mol^{-1}. **TS2** is an early transition structure. The easiness of cyclopropyl ring-opening in **Int1** is not surprising in view of the fact that the same type of reaction occurs rapidly with the cyclopropyloxy radical.[26] The energies of **TS2** and **Int2** are lower than that of **Int1**, and so the second step of the reaction is therefore not rate-determining. The barrier to conformational change in **Int2** is low and the formation of a *cisoid* conformation should easily occur, followed by the final ring-closure to the product through the transition structure **TS5**. It should be mentioned that the nudged elastic band method of Henkelman and Jónson[27] for reaction path calculations resulted in the same stationary points for reaction path 1, with a region of low energy conformational change before the last reaction barrier defined by **TS5** was reached.[28]

In agreement with the calculated barrier of the rate-determining step (37 kcal mol^{-1}), the reaction is thermally allowed. One of the most important results of the study of the parent reaction is the conclusion that the homolytic

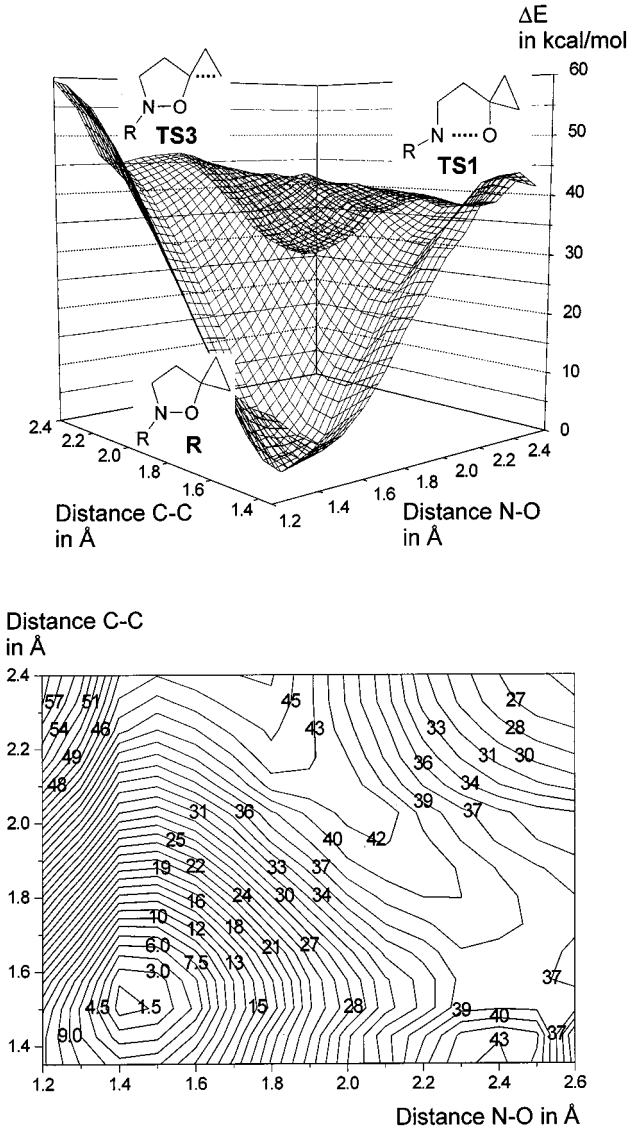


Figure 3. Part of the energy hypersurface (relaxed scan) of the first step of the parent Brandi reaction with respect to relevant changes in the N−O and C−C bond lengths at the (U)B3LYP/6-31G* level (upper part: three-dimensional surface, lower part: contour lines in plane). Energies in kcal mol^{-1}

cleavage of the O−N bond occurs more easily than the C−C cleavage in the first step, favouring reaction path 1. This is in agreement with early conclusions of Brandi et al., based on experimental experience.[1a] Extension of the study to the methyl-substituted compounds **8** and **9** produced closely similar reaction parameters.

The question may be asked of why N−O bond cleavage of the isoxazolidine ring occurs at relatively low energies. In cases of unstrained open-chain structures containing N−O bonds, the corresponding energy is considerably higher. Dissociation of the N−O bond of hydroxylamine and *N*,*O*-dimethylhydroxylamine into the hydroxyl and aminyl radicals requires energies of 64.2 and 56.5 kcal mol^{-1}, respectively, calculated at the same level of theory. These energies are significantly higher than the N−O ring-splitting energy of 31.1 kcal mol^{-1} calculated for **5**. However, if hydroxylamine is calculated with an N−O torsional angle reduced to that of isoxazolidine, the dissociation energy becomes considerably lower (20 kcal mol^{-1}). In other words, the relatively low ring-splitting energy of isoxazolidine is in part due to the destabilization of the N−O bond in the strained isoxazolidine ring structure. As shown below, the energy of the N−O cleavage in the ring is also considerably reduced by the spirocyclopropyl group.

C−C ring cleavage in the cyclopropyloxy fragment of intermediate **Int2** occurs rapidly. The activation energy amounts to 0.9 kcal mol^{-1} at the (U)DFT level. Without doubt, this step of the reaction is favoured by the strain relief and the formation of the energetically favoured C=O bond in place of the C−O bond. The high reactivity of the related monoradicals is well known experimentally.[29] In sharp contrast, ring-opening of the unsubstituted cyclopropane needs a comparatively high energy. According to experimental heats of formation, the dissociation energy amounts to 50 kcal mol^{-1}.[29] For that reason the regioisomeric spiro[cyclopropane-1,4′-isoxazolidines] **12** with isolated three-membered rings are not reactive.

The results reported at the DFT level were obtained by employing the 6−31G* basis set. Basis set extension did not essentially change the relative DFT energies. DFT calculations were also compared with single-point ab initio calculations based on RDFT and UDFT optimum geometries. As is known, results of DFT calculations agree satisfactorily well with those of higher level ab initio calculations including QCISD(T)[30] and CCSD(T)[31] calculations for closed-shell structures, and also for open-shell radical structures.[7] However, the results of HF-based ab initio open-shell calculations of the singlet molecules at the *post*-HF level are not free of spin contamination that may affect the energies. Remarkably, however, the relative energies of (U)DFT and ab initio calculations are in reasonably good agreement. The heights of the barriers to the rate-determining N−O bond cleavage calculated by the ab initio methods are greater than those calculated by DFT calculations. Thus, relative energies of 40.9 and 42.0 kcal mol^{-1} were calculated by QCISD(T) and CCSD(T), respectively, to be compared with 36.5 kcal mol^{-1} calculated by (U)DFT (cf. Table 1). The results achieved at different levels of theory were consistent and support the application of (U)DFT. The results of ab initio HF calculations differ greatly from those mentioned above, demonstrating the well-known weaknesses or failure of the method in calculating biradical species.

Structures of the Compounds Involved in the Parent Reaction

Selected bond lengths of the most interesting parent structures along reaction path 1 as calculated by (U)DFT are listed in Figure 4. Whereas molecular geometries of conventional structures with first row elements are very well reproduced by RDFT,[32] there is no experimental knowledge available concerning biradical structures calculated by UDFT. N−O bond cleavage results in elongation of the N−O bond from 1.44 to 2.32 Å on passing from the react-

ant structure **R** to the transition structure **TS1**. Remarkably, two of the C−C bonds of cyclopropane involved in the spiro bond are considerably lengthened (by about 0.06 Å) while the third bond is shortened (0.04 Å). The same holds for the intermediate **Int1**. The lengthening of the C−C bonds obviously prejudices the following cleavage of one or the other bond. The intermediate **Int1** does not display any marked change in the bond lengths with conformational change. The length of the C−O bond is significantly greater than that of the C=O bond and corresponds closely to that of cyclopropyloxy radical. The C−C bond length increases from 1.61 Å in the first intermediate to 1.77 Å in the transition structure of C−C ring-opening (**TS2**). In the subsequent formation of the second intermediate **Int2**, the most striking change is the formation of the C=O bond, connected with a shortening of the bond length from 1.29 Å in **Int1** to 1.21 Å in **Int2**. The C=O bond length in **Int2** is similar to that in the product after cyclization.

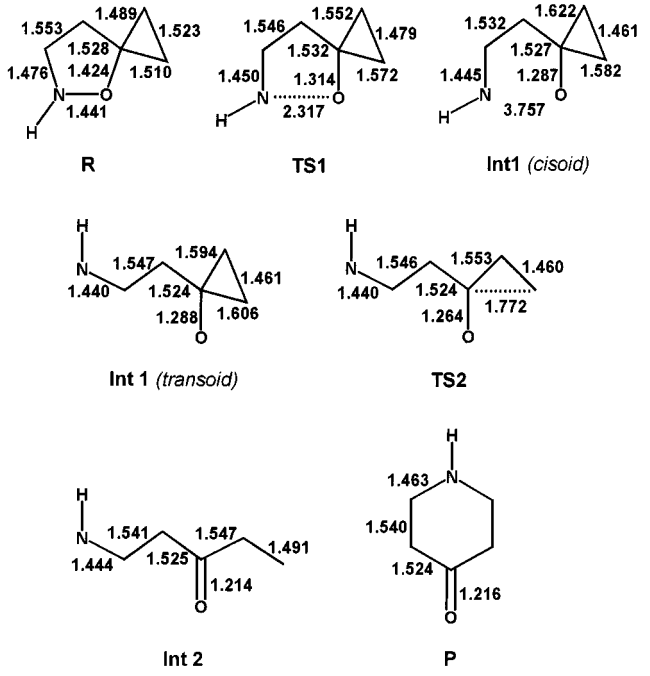


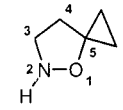
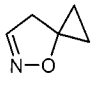
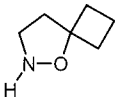
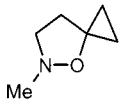
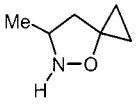
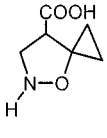
Figure 4. Selected bond lengths (Å) of nonbiradical compounds calculated by RDFT, and of biradical compounds calculated by UDFT (B3LYP/6-31+G*)

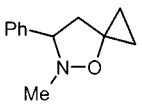
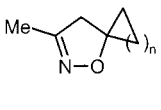
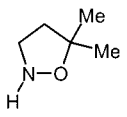
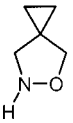
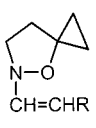
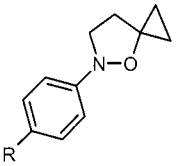
Effects of Donor and Acceptor Substitution

The experimental study of the Brandi reaction revealed specific substituent effects. To avoid large computational demands, appropriate model-type substituted compounds were studied. There are several possibilities for structural modification, such as substitution of hydrogen at the nitrogen or substitution of hydrogen at different positions in the carbon skeleton of the ring. If cleavage of the N−O bond is the rate-determining step of the reaction, the effect of donor and acceptor substitution at nitrogen warrants particular interest, and so the difference in energy between intermediate **Int1** and reactant **R** was calculated. This energy is the dissociation energy of the N−O bond of the heterocyclic compound. The results are given in Table 2.

Substitution of H at nitrogen by a methyl group results in a lowering of the dissociation energy and in a decrease in the activation energy defined by the transition structure **TS1**. The relative energies between the different stationary points of the reaction are essentially the same as in the parent reaction. More pronounced effects are encountered on introduction of electron-donating or electron-withdrawing substituents at nitrogen. This is demonstrated with the model-type compounds **13**. The dissociation energy of the N−O bond calculated at the DFT level for compound **13**

Table 2. (U)DFT reaction parameters of N−O bond cleavage in isoxazolidines and isoxazolines (Energies of the biradical transition structure **TS1**, of the biradical intermediates **Int1** and **Int2** and of the product **P** relative to the reactant **R** in kcal mol)$^{-1}$

	 **5**	 **6**	 **7**	 **8**	 **9**	 **10**
Int1	31.1	30.4	44.1	28.2	34.8	33.0
TS1	36.5	34.8	-	32.8	-	-
Int2	20.4	20.8	27.1	16.5	20.6	23.2
P	-58.4	-55.4	-49.6	-61.8	-58.7	-56.2

	 **1a**	 **4**	 **11**	 **12**	 **13**	 **14**
Int1	27.9	**a** n=1 31.3 **b** n=2 44.0	48.4	46.0	R=H 14.4 R=NH_2 3.6 R=CHO 13.8	R=H 17.4 R=OMe 14.5

($R = NH_2$) is 3.6 kcal mol^{-1}, in comparison with 31.1 kcal mol^{-1} for **5**. In the case of acceptor substitution (**13**, R = CHO) the dissociation energy is higher than in the case of the donor-substituted compound and amounts to 13.8 kcal mol^{-1}. Electron donor substitution at nitrogen favours the cleavage of the N−O bond. This is in good agreement with the reactivity of more complex aryl-substituted compounds. The effect of aryl substitution has been shown with calculations performed on **14**. The dissociation energy decreases from 31.1 to 14.5 kcal mol^{-1} on passing from **5** to **14** (cf. Table 2). However, a dramatic reduction in the dissociation energies from 31.1 to 17.4 kcal mol^{-1} is also calculated for substitution by the phenyl group itself. According to the experimental studies, *N*-aryl-substituted spiro[cyclopropane-1,5′-isoxazolidines] in fact react at room temperature.

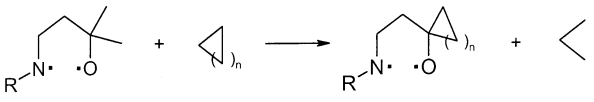
Substitution at other positions in the isoxazolidine ring has only minor effects on the reactivity. As demonstrated in Table 2, introduction of a methyl group in position 3 does not markedly change the dissociation energy. According to experimental studies methoxycarbonyl substitution at carbon 4 disfavours the reaction, the calculated dissociation energy being increased by only 2 kcal mol^{-1}. The electronic effect of the substituent group COOMe is obviously underestimated in the calculations. According to the theoretical results, the reactivity is also not reduced by introduction of CN as an acceptor group.

Replacement of the Isooxazolidine by Isooxazoline and of Cyclopropyl by Cyclobutyl

Introduction of a double bond into the isoxazolidine ring results in **4a**. The experimental reaction temperature has to be elevated in this case, from 80−160 °C to about 200 °C for reactions in solution. The N−O dissociation energy of **4a** ($n = 1$) calculated by DFT amounts to 31.3 kcal mol^{-1}, to be compared with 34.8 kcal mol^{-1} for the dihydro compound **9**. This energy is nearly the same for **5** and **6** (cf. Table 2). Thus the theory predicts a small effect from the double bond on the activation energies.

As mentioned earlier, Brandi reactions of the spiro-cyclobutane-fused compounds such as spiro[cyclobutane-1,5′-isoxazolidine] (**4b**, $n = 2$) can only be carried out at elevated temperatures, by employing FVT techniques. N−O bond-cleavage in **4b** is actually disfavoured relative to **4a**. The calculated N−O dissociation energy is 11 kcal mol^{-1} higher than that of the spiro-cyclopropane-fused compound (cf. Table 2). As is to be expected, the absence of the spiro-cycloalkane ring also increases this energy strongly. This is demonstrated with compound **11**, the N−O dissociation energy of which amounts to 48 kcal mol^{-1}, in comparison with 31 kcal mol^{-1} calculated for **5**. Thus, the dissociation energy of **11** is 17 kcal mol^{-1} higher.

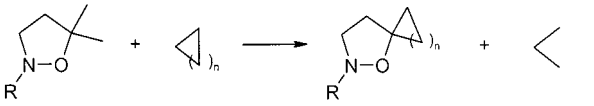
The theoretical results are in harmony with the low reactivities of the compounds of the spiro[cyclobutane-1,5′-isoxazolidine] and spiro[cyclobutane-1,5′-isoxoazoline] series. This result may suggest that the three-membered ring may be primarily involved in the Brandi reaction (reaction path 3). However, the reaction intermediate **Int1** in reaction path 1, with the oxyl group at cycloalkanes, is also definitely more stabilized by cyclopropyl than by cyclobutyl. This is supported by isodesmic reactions.[30] According to the DFT reaction energy calculated for the reaction of Equation (3), the cyclopropyl group ($n = 1$) stabilizes the spirocyclo-substituted biradical compounds better than the cyclobutyl ($n = 2$) compound.



(3)

n = 1: -16.2 kcal mol^{-1}
n = 2: -6.5 kcal mol^{-1}

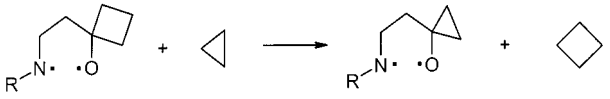
On the other hand, the reactants are hardly effected by the cycloalkyl residues [Equation (4)]:



(4)

n = 1: 1.2 kcal mol^{-1}
n = 2: -2.1 kcal mol^{-1}

The stabilizing effect of spirocyclopropyl with respect to spirocyclobutyl is estimated by Equation (5).



(5)

-9.7 kcal mol^{-1}

Remarkably, the reaction energy corresponds closely to the analogous transformation of the cyclobutanoxyl into the cyclopropanoxyl radical. In these calculations, the monoradicals were also calculated by UDFT. (The application of UDFT is better supported for radicals than for biradicals.[7]) Similarly to what was found for the isodesmic reaction of Equation (5), the reaction is exothermic, again indicating the specific stabilization effect of the three-membered ring [Equation (6)].

(6)

-7.6 kcal mol^{-1}

The close correspondence in the changes for the biradical and monoradical reactivity is closely reflected in the molecular structure of the compounds. The C−O bond lengths are listed in Figure 5. The relatively small bond lengths to the radical oxygen are in agreement with the stronger stabil-

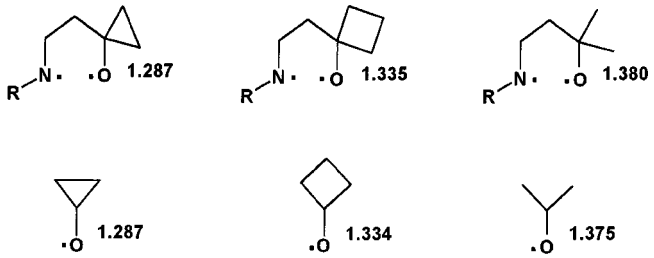


Figure 5. Comparison of carbon-oxygen bond lengths (Å) of some biradical and monoradical species related to TS1, calculated by UDFT (B3LYP/6-31G*)

izing interaction. The strength of the interaction obviously decreases on going from cyclopropyl through cyclobutyl to propyl.

Thus, the greater stabilizing effect of cyclopropyl relative to cyclobutyl can explain the high reactivity of the spirocyclopropyl compound along reaction path 1. On the other hand, the larger ring strain of cyclopropyl does not necessarily favour reaction path 2 over reaction path 1.

Conclusions

Mixed RDFT/UDFT calculations confirmed the Brandi reaction as a multistep reaction. The first step of the reaction is N−O bond cleavage of the isoxazolidine ring (reaction path 1). The biradical intermediate in the rate-determining step of the parent reaction is 31 kcal mol^{-1} higher in energy than the reactant. The activation energy is relatively low because of the weakened N−O bond of the isoxazolidine ring and stabilization of the cyclopropane substituted by oxygen. The subsequent rapid opening of the cyclopropane ring and cyclization of the open-chain biradical results in tetrahydropyridone.

Experimentally observed substitution effects are essentially reproduced. The calculations clearly show that the cleavage of the N−O bond is highly favoured by donor substitution at nitrogen whereas replacement of cyclopropyl by cyclobutyl strongly disfavours the reaction.

As shown for the parent reaction, both the alternative nonconcerted reaction with primary cleavage of a spirocyclopropane C−C bond and the concerted reaction with simultaneous cleavage of the C−C and N−O bonds are less favoured than the reaction with primary cleavage of N−O.

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