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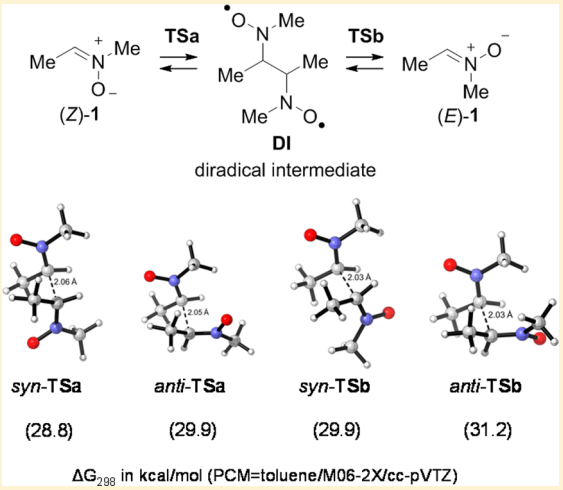
DFT Investigation of the Mechanism of *E*/*Z* Isomerization of Nitrones

David Roca-López, Tomás Tejero, and Pedro Merino*

Laboratorio de Síntesis Asimétrica, Departamento de Síntesis y Estructura de Biomoléculas, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Universidad de Zaragoza, CSIC, Zaragoza, E-50009 Aragón, Spain

Supporting Information

ABSTRACT: The hitherto unknown mechanism of *E*/*Z* isomerization of nitrones, with important implications in 1,3-dipolar cycloaddition chemistry, has been investigated using density functional theory calculations. Unimolecular and bimolecular processes have also been considered. Both concerted and stepwise mechanisms involving either zwitterionic or diradical species have been studied. The unimolecular torsional mechanism and isomerization through intermediate oxaziridines present energy barriers too high to justify the observed experimental results. Several bimolecular processes involving an initial dimerization are possible. Among them, the concerted process can be discarded in terms of energy barrier. Zwitterionic intermediates are too high in energy to be considered. From the two possible diradical approaches consisting of either C−O or C−C coupling, the latter is the most favored. Thus, the mechanism of *E*/*Z* isomerization of nitrones proceeds via a diradical bimolecular process involving an initial dimerization through a C−C coupling followed by a dedimerization, with energy barriers for the rate-limiting step of 29.9 kcal/mol for *C*-methyl nitrones and 25.8 kcal/mol for *C*-(methoxycarbonyl) nitrones. These values are in very good agreement with the experimental data previously measured through kinetic experiments.

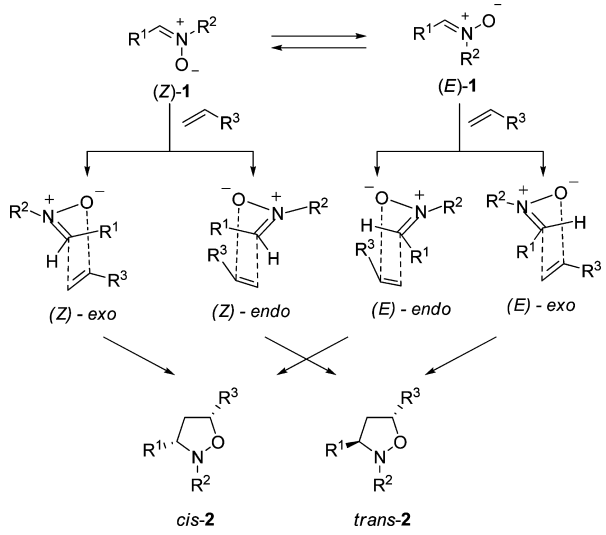


INTRODUCTION

The *E*/*Z* isomerism of nitrones has often occupied a central position in rationalizing the stereoselectivity of the important 1,3-dipolar cycloaddition reactions between those dipoles and alkenes.[1] Indeed, the cycloaddition between a nitrone and an alkene can lead to 3,4- and 3,5-regioisomers. For a given regioselectivity, the reaction of the *Z*-isomer of the nitrone, (*Z*)-**1**, through an *endo* approach gives rise to the *trans* isomer. The same isomer could be obtained from the *E*-nitrone through an *exo* approach. Similarly, the corresponding *cis* adduct could be obtained from either (*Z*)-**1** through an *exo* approach or (*E*)-**1** through an *endo* approach. The reaction is illustrated in Scheme 1 for the 3,5-regioisomer. A similar situation could take place in the case of 3,4-regioisomers.

Despite the impact of *E*/*Z* isomerism of nitrones on cycloaddition chemistry, the mechanism underlying this phenomenon has not yet been elucidated. Nitrones derived from aldehydes (aldonitrones) are found as *Z*-isomers[2−4] with the exception of those having electron-withdrawing groups at the nitrone carbon (particularly, carbonyl-conjugated nitrones), which present a solvent-dependent equilibrium between *E*- and *Z*-isomers.[5,6] In that case, the isomerization can be induced by the use of metals.[7,8] During the oxidation of *N*-methylhydroxylamines to nitrones the initial formation of (*E*)-nitrones has been observed followed by a rapid isomerization to the more stable *Z*-nitrones.[9] *N*-(Alkenylglycosyl) nitrones provided evidence of *E*/*Z* isomerization in intramolecular cycloadditions.[10] The *E*/*Z* isomerization was preferred to competitive 2-aza-Cope rearrangement typical of other *N*-alkenyl nitrones.[11,12]

Scheme 1. Cycloaddition between Nitrones and Alkenes



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Ketonitrones can be found either as pure isomers or as mixtures of *E*- and *Z*-isomers depending on *C*-substituents and the solvent in which they exist.[13,14] In some instances the corresponding *E*- and *Z*-isomers can be resolved by fractional crystallization.[15]

The *E*/*Z* isomerism of a C═N bond has been studied in detail for a variety of systems including imines, hydrazones, and oximes.[16,17] These investigations have been based on dynamic and theoretical studies of barriers to nitrogen inversion. However, the case of nitrones is different since nitrogen inversion is not possible due to absence of a free electron pair at the nitrogen atom. Kinetic investigations on isomerization of ketonitrones showed activation barriers of 33−35 kcal/mol for *E*/*Z* interconversion[18,19] even though in the case of compounds bearing electron-withdrawing grops the barrier decreased to 25 kcal/mol.[20] Kinetic studies with cyclic α-keto-*N*-methylnitrones with an exocyclic nitrone group showed values of activation energy in the range of 23−25 kcal/mol.[21] Similar values (23−29 kcal mol), determined by dynamic ^{31}P NMR spectroscopy, were also found for aldonitrones.[22] Those early kinetic studies pointed to a unimolecular torsional mechanism of isomerization, in agreement with small values of entropy found experimentally.[18,21,23] Semiempirical calculations were made and overestimated the C−N rotational barrier by about a factor of 2.[24] This study also determined experimentally the entropy of activation to be close to zero as expected for a rotational process. On the other hand, a more recent kinetic study[25] showed that the small negative values of entropy (−4 cal/mol·K) already reported by Grubbs[18] are more in agreement with a second-order isomerization, corresponding to a bimolecular mechanism, for which high negative values of entropy of activation should be found.[26] Since the definitive features of the species involved in isomerization have been up to now unknown, an ultimate elucidation of the mechanism is still required.

Herein, we report the first systematic computational study of the mechanism of *E*/*Z* isomerization of nitrones by considering both uni- and bimolecular processes as well as zwitterionic and biradical species. The evidence of the nature of the transition states for such processes is discussed. These mechanistic studies give an insight into the cycloaddition chemistry of nitrones acting as a guide in the consideration of *E*- and *Z*-isomers for both *endo* and *exo* approaches that is essential regarding the stereochemical course of the 1,3-dipolar cycloaddition between a nitrone and an alkene.

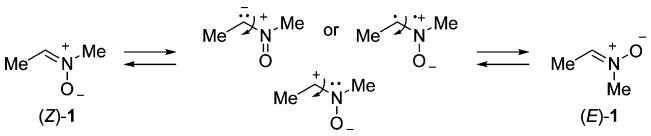
COMPUTATIONAL METHODS

All of the calculations were performed using the Gaussian09 program.[27] Molecular geometries were optimized with the M06-2X functional[28] in conjunction with the cc-pVTZ basis set.[29,30] The M06-2X functional has amply demonstrated its applicability for chemical kinetics and reliability for predicting energy barriers.[28,31] Analytical second derivatives of the energy were calculated to classify the nature of every stationary point, to determine the harmonic vibrational frequencies, and to provide zero-point vibrational energy corrections. The thermal and entropic contributions to the free energies were also obtained from the vibrational frequency calculations, using the unscaled frequencies. All of the located transition states were confirmed to connect to reactants and products by intrinsic reaction coordinate (IRC) calculations.[32,33] For all diradical transition states and intermediates, a spin-projection scheme has been used to estimate energies of singlet diradical structures.[34−36] However, the corresponding free energies are given without spin-correction because its effectiveness has not been completely demonstrated.[35,37,38] Calculations have been carried out both in the gas phase and considering solvent effects (toluene) with the PCM model.[39−41]

RESULTS AND DISCUSSION

Unimolecular Isomerization. There are two possible mechanisms for the *E*/*Z* isomerization of nitrones following a unimolecular process. A torsion mechanism considering biradical or zwitterionic species (Scheme 2) would explain exchange

Scheme 2. Torsional Mechanism for *E*/*Z* Isomerization of Nitrones

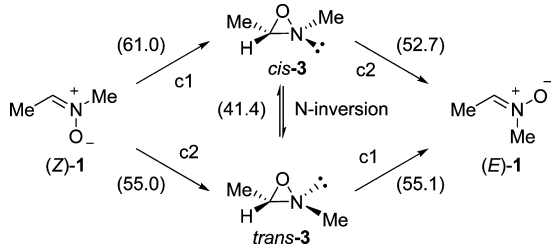


between *E*- and *Z*-isomers, as early studies proposed.[21,24] In particular, Grubbs and co-workers proposed that the torsional process should be accompanied by the formation of intermediate iminoxy radicals.[18]

Unfortunately, neither closed-shell nor open-shell explorations of the potential energy surface (PES) provided clear data for identifying a transition structure. A relaxed dihedral scan provided a pseudo transition structure that could not be confirmed (see Supporting Information for details). Quite likely, these negative results indicate that *E*/*Z* isomerization does not proceed by the simple torsion mechanism. Moreover, following potential energy variations with rotation about C−N bond through the above-mentioned relaxed dihedral scan revealed a value of ca. 46.5 kcal/mol for a hypothetical energy barrier corresponding to that mechanism.

A second possibility consists of the formation of an intermediate oxaziridine that upon nitrogen inversion could reopen to the other isomer (Scheme 3). The photochemical

Scheme 3. *E*/*Z* Isomerization of Nitrones through Intermediate Oxaziridines



isomerization of a nitrone to the corresponding oxaziridine has been reported in the past[20,42−51] and has also been studied theoretically.[52−54] However, there is no experimental evidence that an oxaziridine could be formed from a nitrone under thermal conditions. On the other hand, the thermal isomerization of oxaziridines into nitrones have been reported in several cases.[55−62]

The thermal ring closing of a nitrone to oxaziridine can occur in two possible rotatory modes.[52] Starting from (*Z*)-**1** one rotatory mode (Scheme 3, c1) leads to the oxaziridine *cis*-**3**, and the other one (Scheme 3, c2) to the corresponding *trans*-**3**. The reverse thermal ring opening of oxaziridines **3** to (*E*)-**1** can also take place through the same two different rotatory modes as illustrated in Scheme 3. We have located the four transition structures corresponding to transformations of (*Z*)-**1** and (*E*)-**1** into *cis*- and *trans*-**3**, and the energy barriers are in the range of 55.1−61.0 kcal/mol (for geometry and detailed energy data see

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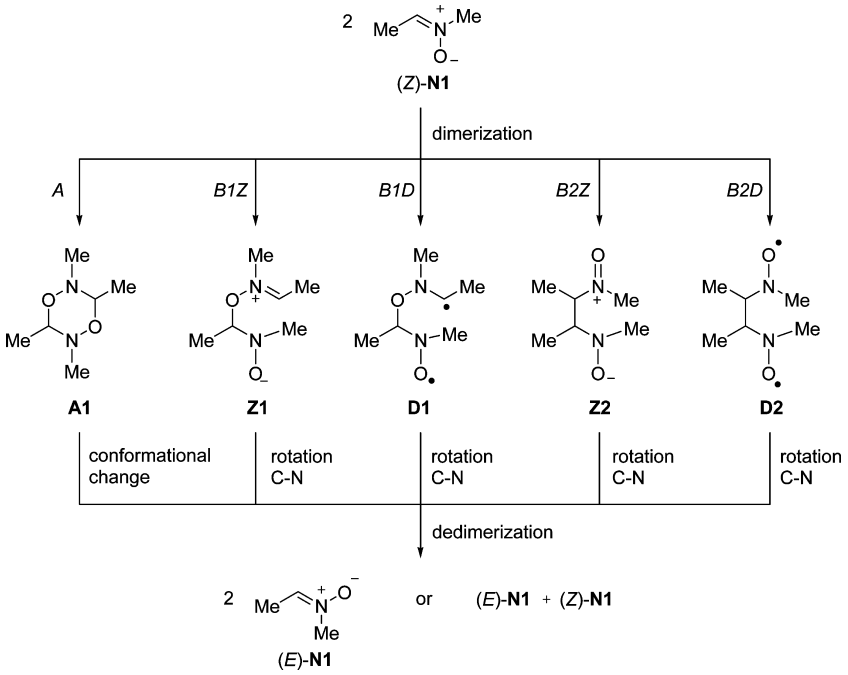
Scheme 4. Bimolecular Mechanisms for the *E*/*Z* Isomerization of Nitrones



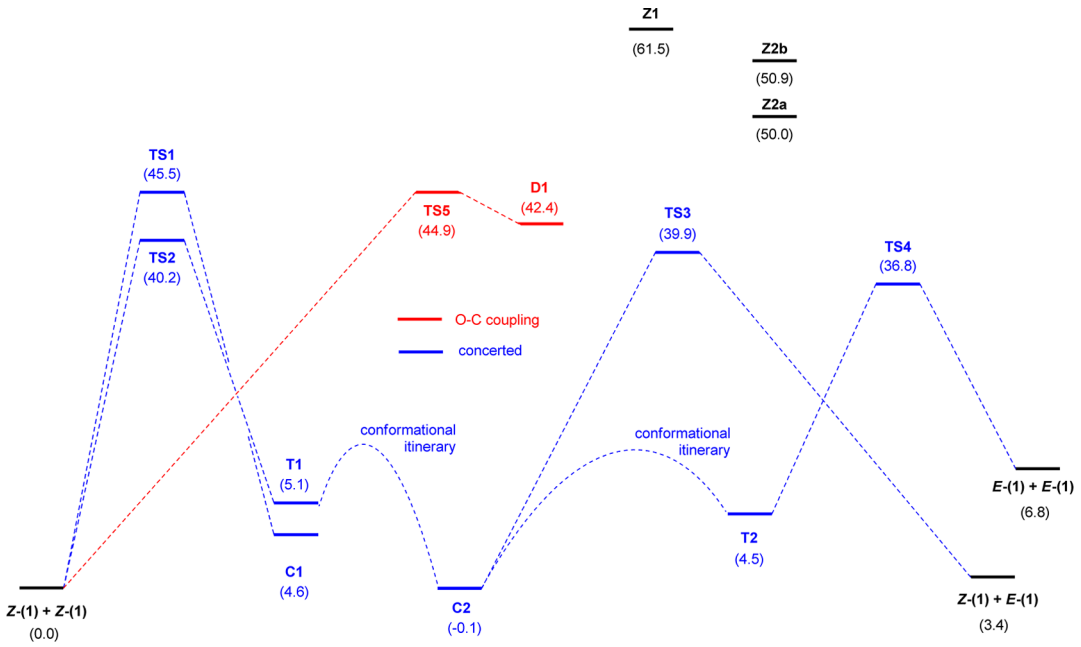


Figure 1. Energy diagrams (PCM=toluene/M06-2X/cc-pVTZ) for bimolecular concerted and C−O stepwise isomerization of nitrones. Relative free energy values (ΔG_{298}) are given in kcal/mol.

Supporting Information). In addition *cis*- and *trans*-**3** can interconvert through a typical nitrogen inversion. The corresponding energy barrier for this process was found to be 41.4 kcal/mol, in agreement with previous experimental data[63] and theoretical calculations.[64] Despite the reversibility of the nitrone-to-oxaziridine conversion, which could explain the interconversion between *E*- and *Z*-isomers, the energy barriers are too high to justify the experimental conditions in which *E*/*Z* isomerization of nitrones has been observed.[25]

Bimolecular Isomerization. The bimolecular isomerization of nitrones has been previously hypothesized by Ali and co-workers.[25] These authors based the hypothesis in kinetic measurements and proposed a zwitterionic bimolecular mechanism. However, in their original report no details about the nature of the species involved in the process are given. Only general references pointing to unreacted hydroxylamine, the nitrone itself, or "any basic entity" (*sic*) are provided. Since the *E*/*Z* isomerization of nitrones takes place not only during their synthesis but under a variety of conditions and in the complete absence of any additive or any other species,[10] it is plausible to consider a bimolecular mechanism involving exclusively two nitrone molecules. In principle, any bimolecular isomerization should involve an initial dimerization followed by a conformational change and finally a dedimerization (Scheme 4). The

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whole process might be concerted (Scheme 4, *A*) to form dimer **A1**, which after a conformational change could dedimerize to form either (*E*)-**1** or a mixure of *E*- and *Z*-isomers. Alternatively, the process might be also stepwise through C−O or C−C couplings (Scheme 4, *B1* and *B2*, respectively). In both cases the mechanism could be zwitterionic (Scheme 4, **B1Z** and **B2Z**) or diradical (Scheme 4, **B1D** and **B2D**). In the case of a stepwise mechanism a rotation around the C−N single bond followed by a dedimerization would lead to the *E*-isomer. In this context, we have recently reported a theoretical study on the dimerization of cyclic nitrones and demonstrated that the process is concerted through a bispseudopericyclic reaction.[65]

For the concerted route (Scheme 4, *A*) the formation of dimer **A1** can account through either **TS1** leading to chair **C1** with a barrier of 45.5 kcal/mol or **TS2** leading to twist **T1** with a barrier of 40.2 kcal/mol. In both cases the process takes place concertedly and corresponds to a typical bispseudopericyclic process as in the case of cyclic nitrones (Figure 1).[65] The geometries of **TS1** and **TS2** are given in Figure 2. For **TS1**, corresponding to the formation of **C1**, the forming C−O bonds are 2.00 Å, the system showing a complete symmetry. Similarly, in **TS2**, leading to **T1**, the C−O forming bonds were found to be 2.02 Å in both cases.

The formation of the dimer is endergonic (4.6 and 5.1 kcal/mol for **C1** and **T1**, respectively), and calculations predict the preferential formation of **T1** through the more stable **TS2**. The more stable chair **C2** is formed from **T1** through a typical conformational course involving *N*-inversion and a conformational change (for details see Supporting Information). Dedimerization of **C2** afforded a mixture of (*E*)-**1** and (*Z*)-**1** through **TS3** with a barrier of 39.9 kcal/mol. Alternatively, **C2** can interconvert into **T2** through a *N*-inversion and two conformational changes (for details see Supporting Information), which dedimerizes to two molecules of (*E*)-**1** through **TS4** with a barrier of 36.8 kcal/mol. As expected, a high degree of symmetry was found for **TS4** with identical forming C−O bond distances (2.01 Å) On the other hand, **TS3**, leading to different (*E*)-**1** and (*Z*)-**1**, presented C−O forming bonds of 1.92 and 2.09 Å. This lack of symmetry can account for the higher energy of **TS3**.

Next, we studied the stepwise mechanism *B1* consisting of a dimerization through C−O coupling. The corresponding zwitterionic intermediate **Z1** was located but lies too high (61.5 kcal/mol) above (*Z*)-**1**, making the zwitterionic path for this mechanism untenable. Several different conformations were found for diradical intermediate **D1**, the most favored being located at 42.4 kcal/mol above the ground state. This intermediate is formed through the corresponding **TS5** with a barrier of 44.9 kcal/mol (Figure 1). The geometry of **TS5** is illustrated in Figure 3 and corresponds to a late transition structure (product-like) with short C−O forming bonds, i.e., 1.54 Å. Since **TS5** is 4.7 kcal/mol higher than the lowest **TS2** of mechanism *A*, the mechanism *B1* was ruled out definitively.

We next considered stepwise dimerization through a C−C coupling (Scheme 4, *B2*). Location of the two isomeric (*R***R**-*syn* and *R***S**-*anti*) zwitterionic intermediates *syn*-**Z2a** and *anti*-**Z2b** was not straightforward. Any attempt to locate the corresponding minima led to separation into the two starting nitrones. In order to estimate what the energy of such intermediates would be, we optimized a partially constrained geometry. In this pseudo minimum the C−C bonds were fixed at 1.57 Å and the rest of the variables were optimized. Under these conditions *syn*-**Z2a** and *anti*-**Z2b** were calculated to be 50.0 and

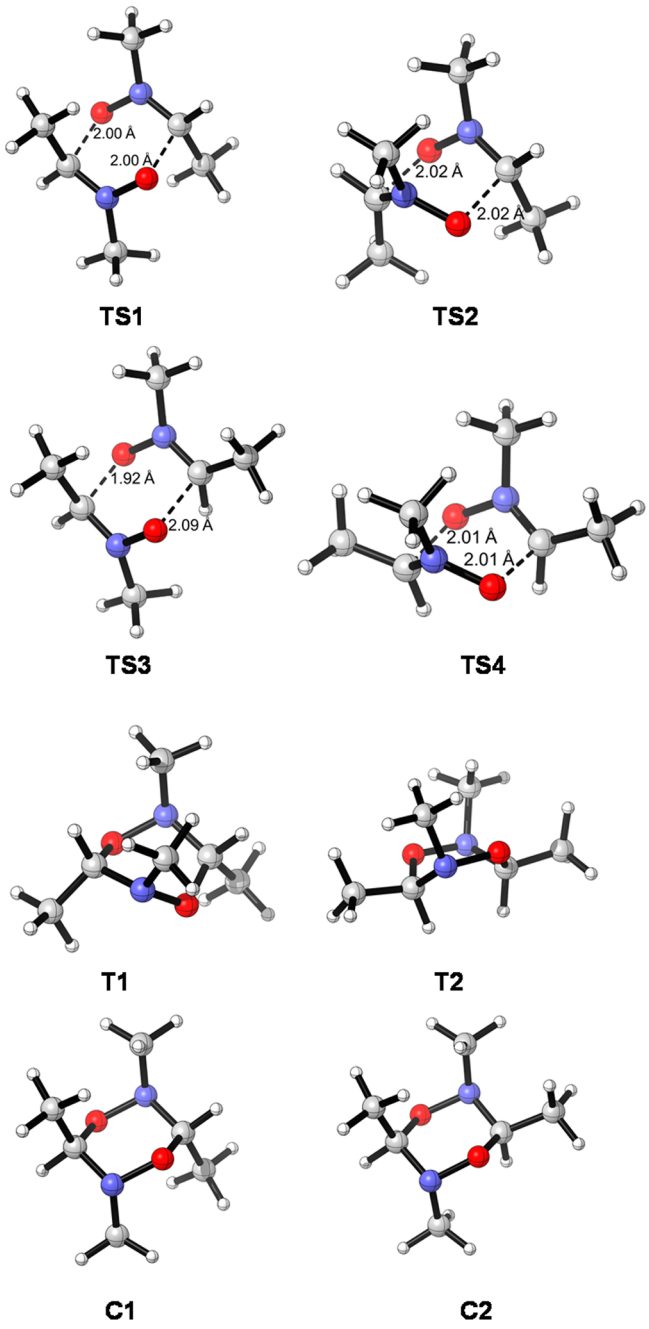

Figure 2. Optimized geometries (PCM=toluene/M06-2X/cc-pVTZ) of **TS1**, **TS2**, **TS3** **TS4**, **T1**, **T2**, **C1**, and **C2**.

50.9 kcal/mol, relative to the isolated two molecules of (*Z*)-**1**, rendering the whole process unfavorable.

On the other hand, two possible diradical intermediates can be formed through diastereomeric channels. The corresponding *syn*-**D2a** and *anti*-**D2b** (Scheme 5) were located at 12.8 and 13.5 kcal/mol, relative to the isolated two molecules of (*Z*)-**1** (Figure 4). The formation of **D2a** and **D2b** can proceed through 6 different transition structures corresponding to 3 staggered approaches and 2 possible nitrone faces. Thus, **TS6a** and **TS6b** correspond to the lowest energy values located at the studied level, corresponding to energy barriers of 28.8 and 29.9 kcal/mol, respectively.

The geometries of **TS6a** and **TS6b** are given in Figure 5, and the corresponding diradical intermediates are in Figure 6. The

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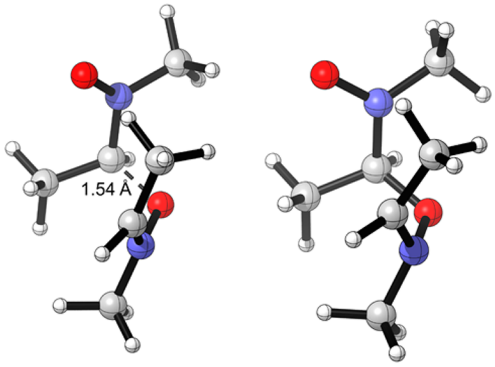
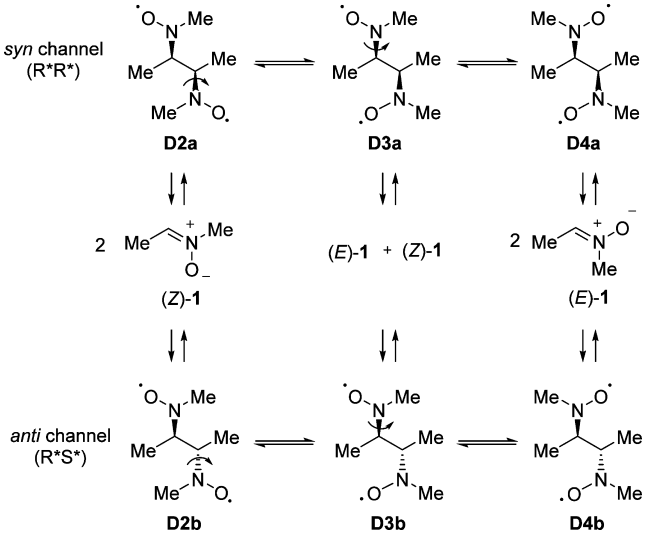


Figure 3. Optimized geometries (PCM=toluene/M06-2X/cc-pVTZ) of **D1** and **TS5**.

Scheme 5. Bimolecular Diradical C−C Stepwise Isomerization of Nitrones



forming C−C bonds in **TS6a** and **TS6b** are 2.06 and 2.05 Å, respectively. Both **TS6a** and **TS6b** are diradical species with single electrons located mainly on the terminal nitrone oxygens. Whereas in **TS6b** the two nitrogen atoms adopt a gauche disposition (N−C−C−N dihedral angle of −93.8°), in **TS6a** they adopt an antiperiplanar orientation (N−C−C−N dihedral angle of 166.3°). Indeed, **D2a** presents a N−C−C−N dihedral angle of 169.5°, and **D2b** presents one of −71.1°. Further rotation of one of the O−N−C−C dihedral angles in **D2a** (O−N−C−C = −89.5°) and **D2b** (O−N−C−C = 83.3°) leads to **D3a** (O−N−C−C = −60.8°) and **D3b** (O−N−C−C = −51.5°), respectively, through the corresponding rotational transition structures **TS-rot1a** and **TS-rot1b** with barriers of 13.7 and 14.9 kcal/mol, respectively. Dedimerization of **D3a** and **D3b** into (*E*)-**1** and (*Z*)-**1** takes place through **TS7a** and **TS7b** with energy barriers of 29.9 and 31.2 kcal/mol. Alternatively, an additional rotation of the second O−N−C−C dihedral angle in **D3a** (O−N−C−C = 91.9°) and **D3b** (O−N−C−C = −86.0°) leads to **D4a** (O−N−C−C = −73.2°) and **D4b** (O−N−C−C = 58.8°), respectively, in this case through **TS-rot2a** and **TS-rot2b** with barriers of 15.8 and 16.5 kcal/mol, respectively. Dedimerization of **D4a** and **D4b** into two molecules of (*E*)-**1** takes place through **TS8a** and **TS8b** with energy barriers of 31.0 and 31.2 kcal/mol. The geometries of **TS7a**, **TS7b**, **TS8a**, and **TS8b** are given in Figure 5. The C−C breaking bonds in **TS7a** and **TS7b** are 2.03 Å in both cases. Similar values were found for **TS8a** (2.04 Å) and **TS8b** (2.02 Å). In all cases (**TS7a,b** and **TS8a,b**) the transition structures are confirmed to be diradical species with the single electrons located on the oxygen atoms. By this path (Scheme 4, mechanism *B2D*) the rate-limiting step corresponds to the dedimerization step, which is in the range of 29.9−31.2 kcal/mol, more than 10 kcal/mol lower than the other possible mechanisms including unimolecular ones.

In order to check the validity of our model, we also located transition state structures in which the methyl group at the nitrone carbon has been replaced by a methoxycarbonyl group, i.e., the corresponding **TS6a-ester**, **TS6b-ester**, **TS7a-ester**, **TS7b-ester**, **TS8a-ester**, and **TS8b-ester**. According to the experimental kinetic experiments[20] the energy barrier should

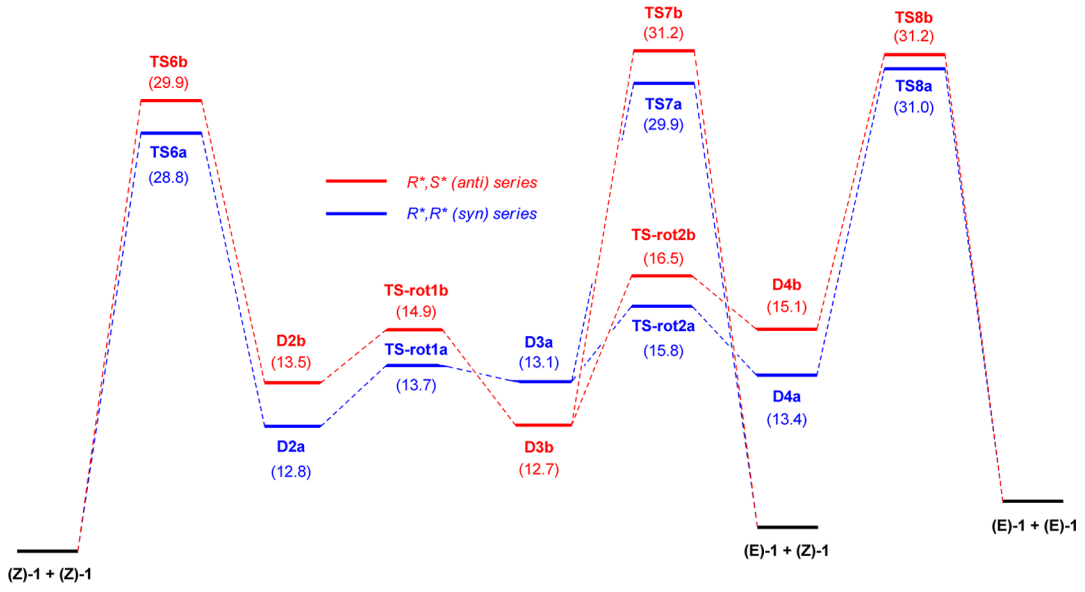


Figure 4. Energy diagrams (PCM=toluene/M06-2X/cc-pVTZ) for bimolecular diradical C−C stepwise isomerization of nitrones. Relative free energy values (ΔG_{298}) are given in kcal/mol.

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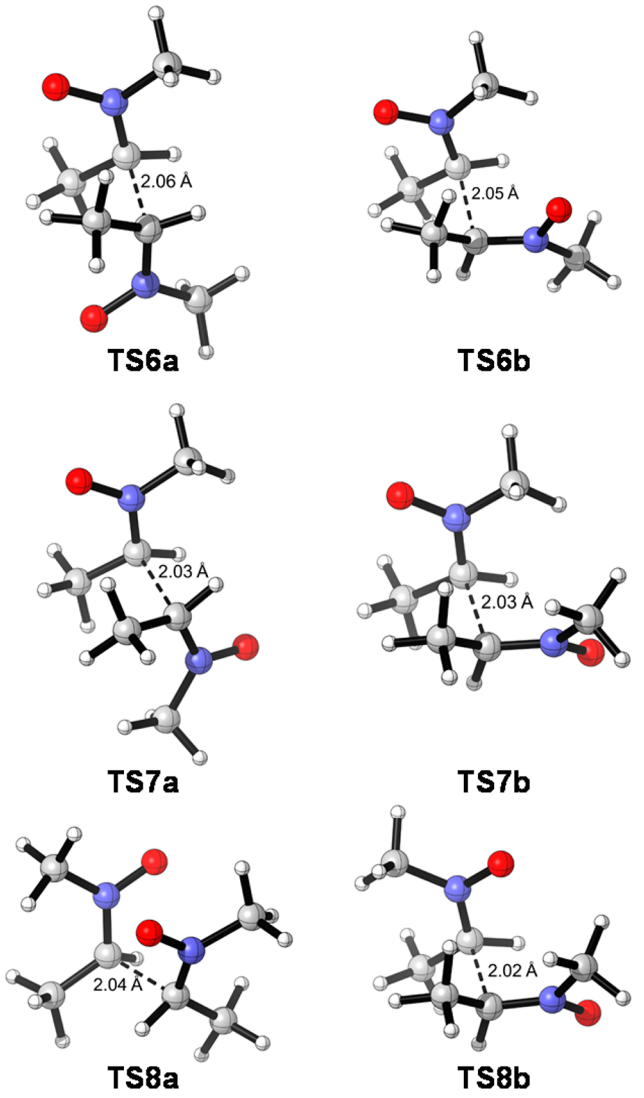

Figure 5. Optimized geometries (PCM=toluene/M06-2X/cc-pVTZ) of **TS6a,b**, **TS7a,b**, and **TS8a,b**.

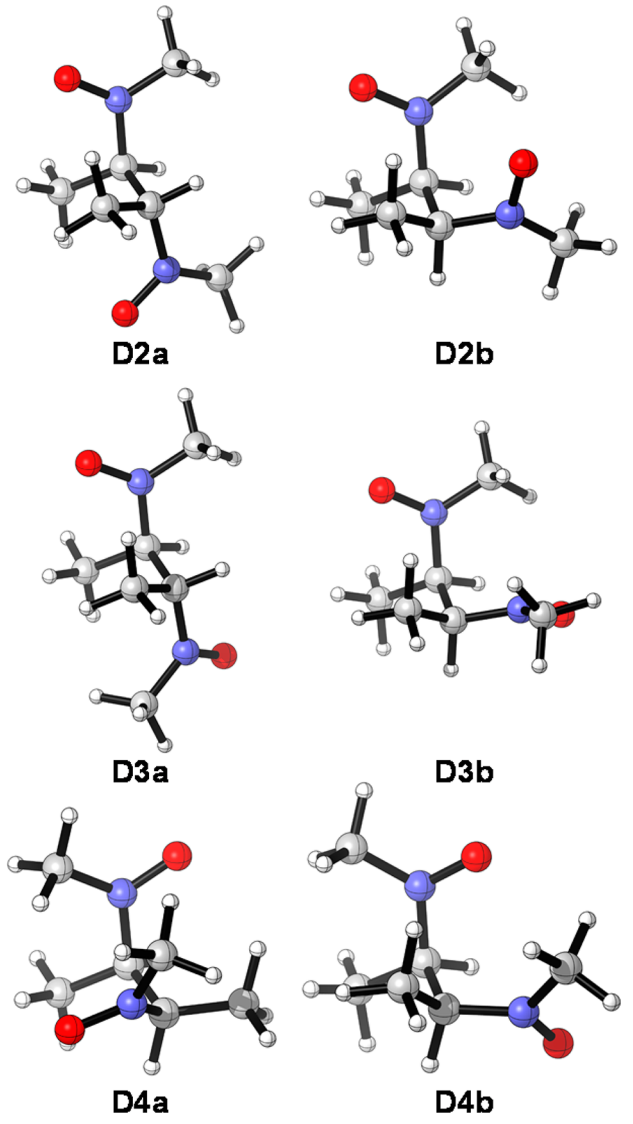

Figure 6. Optimized geometries (PCM=toluene/M06-2X/cc-pVTZ) of **D2a,b**, **D3a,b**, and **D4a,b**.

diminish to ca. 25 kcal/mol. Upon comparison with the corresponding nitrones (*Z*)-**1-ester** and (*E*)-**1-ester**, we found an excellent agreement with the experimental observations with barriers in the range of 25.8−27.9 kcal/mol (Figure 7), thus demonstrating the stabilization exerted by the electron-withdrawing group and consequently the easy *E*/*Z* interconversion for nitrones bearing an electron-withdrawing group at the nitrone carbon. The geometries of **TS6a-ester**, **TS6b-ester**, **TS7a-ester**, **TS7b-ester**, **TS8a-ester**, and **TS8b-ester** are illustrated in Figure 8. The C−C forming/breaking bonds are similar to those observed for the parent **TS6a,b**, **TS7a,b**, and **TS8a,b**. Also, in this case, all of the located transition structures are diradical species with single electrons located at the oxygen atoms.

CONCLUSIONS

The mechanism of *E*/*Z* isomerization of nitrones has been extensively examined to understand spontaneous thermal conversion between the two nitrone isomers. The pathways by which the isomerization could take place have been rationalized on the basis of DFT calculations. The most favored process is a bimolecular one involving a C−C coupling with barriers of ca. 31.0 kcal/mol (25.8 kcal/mol in the case of *C*-(methoxycarbonyl)nitrones). Thereby it has been found that unimolecular processes based on a torsional mechanism or the formation of intermediate oxaziridines show energy barriers too high (46.5−55.0 kcal/mol) for leading to a picture in accord with experimental findings. In a similar way, zwitterionic intermediates formed during a bimolecular process are also too high in energy (50.0−61.5 kcal/mol). Both a concerted bimolecular process and a diradical one involving C−O coupling have also been discarded because of the energy barriers (40.2 kcal/mol for the concerted process and 44.9 kcal/mol for the diradical C−O coupling). It remains a future challenge to demonstrate experimentally that the biradical mechanism is the operational one. Quite probably, the intermediates are not long-lived enough to be detected by conventional techniques such as EPR. However, including external magnetic fields could be an option to change the kinetics of the reaction and thus open a possibility for confirming the biradical mechanism.

In summary, through DFT study of the mechanism of *E*/*Z* isomerization of nitrones, we can conclude that the isomerization is a diradical bimolecular process involving a C−C coupling. This

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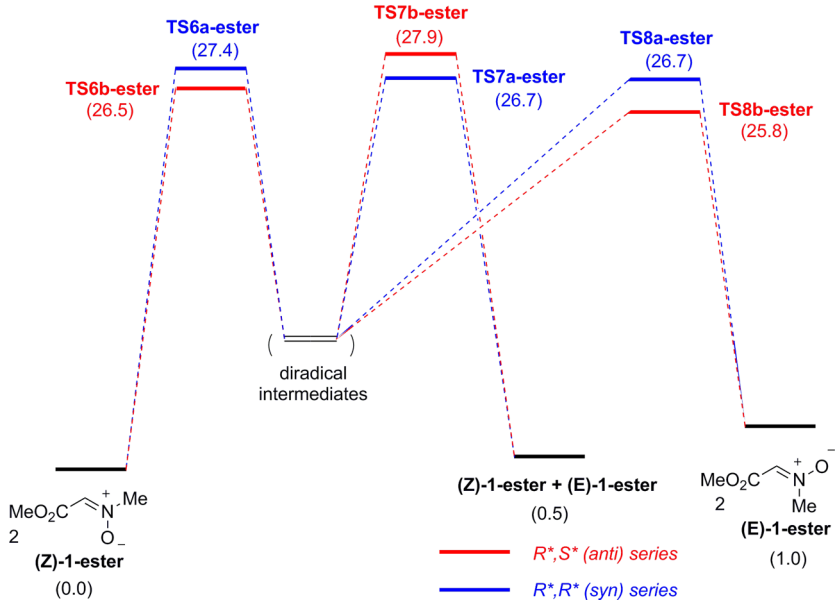

Figure 7. Energy barriers (PCM=toluene/M06-2X/cc-pVTZ) for **TS6a-ester**, **TS6b-ester**, **TS7a-ester**, **TS7b-ester**, **TS8a-ester**, and **TS8b-ester**. Relative free energy values (ΔG_{298}) are given in kcal/mol.

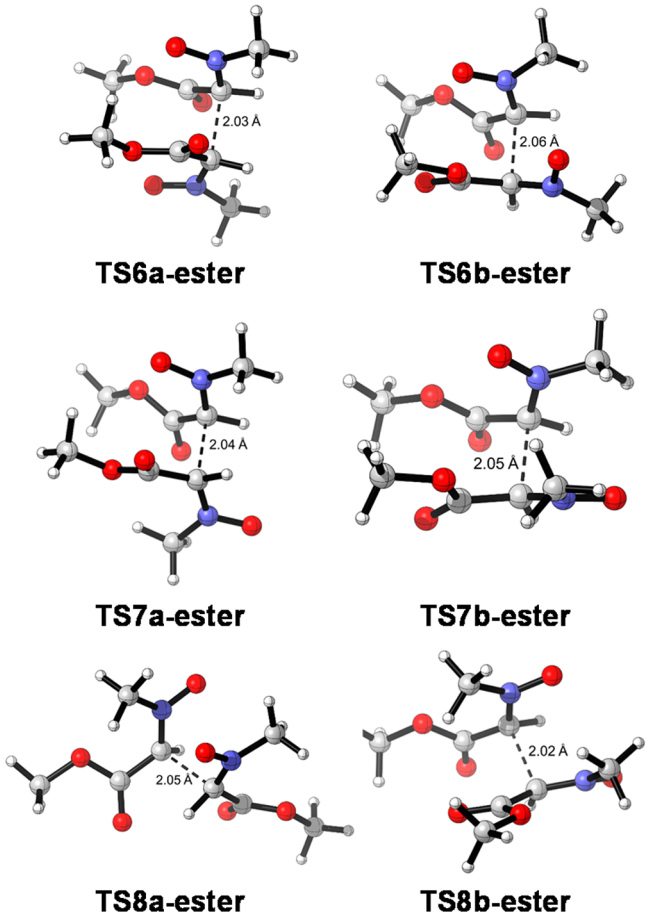

Figure 8. Optimized geometries (PCM=toluene/M06-2X/cc-pVTZ) of **TS6a-ester**, **TS6b-ester**, **TS7a-ester**, **TS7b-ester**, **TS8a-ester**, and **TS8b-ester**.

is due to the easy generation of diradical species **D2a**, only 12.8 kcal/mol above the ground state. The rate-limiting step of the process has an energy barrier of 29.9 kcal/mol for *C*-methyl nitrones and 26.5 kcal/mol for *C*-(methoxycarbonyl) nitrones, in excellent agreement with the experimental results previously reported.

■ ASSOCIATED CONTENT

Supporting Information

Details of calculations corresponding to torsional mechanism and isomerization thorugh intermediate oxaziridines. Detailed conformational itineraries for bimolecular mechanims. Absolute (hartrees) and relative (kcal/mol) electronic and free energies at PCM=toluene/M06-2X/cc-pVTZ level of theory and Cartesian coordinates of optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pmerino@unizar.es.

Notes

The authors declare no competing financial interest.

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