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A DFT study of the asymmetric (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole catalyzed Michael addition of carbonyl compounds to nitroalkenes

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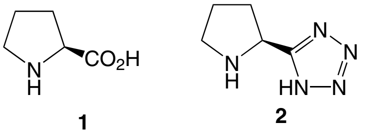
Abstract—The role of the (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole in the asymmetric organocatalyzed Michael addition of carbonyl compounds to nitroalkenes has been studied using DFT methods at the B3LYP/6-31G** computational level. For the C–C bond-formation step, several reactive channels have been analyzed. The B3LYP/6-31G** results, which are in reasonable agreement with the experiments, allow us to explain the stereoselectivity and the increase of the reactivity achieved by an intramolecular HB between the acid hydrogen of the tetrazole moiety and one oxygen atom of the nitroalkene.

1. Introduction

The Michael addition is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] Several reagent systems for this type of transformation, that rely on asymmetric catalysts, have been developed to date.[2] Recently, asymmetric organocatalysis has received much interest because of obvious advantages over its metal-mediated counterpart. It does not need expensive and often toxic metals, and it is generally easier to make and more easily recoverable than usual catalytic reagents. The most extensively studied asymmetric system is based on proline **1** (see Chart 1), which accelerates a range of transformations such as aldol reactions,[3] Robinson annulations,[4] and Mannich reactions.[5] Although these reactions are highly enantioselective, they all require polar solvents, such as dimethylsulfoxide (DMSO), due to the insoluble nature of proline itself.

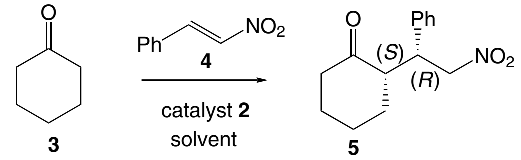


1 2

Chart 1.

Tetrazoles and carboxylic acids have similar structural requirements and aqueous pK_a values. However, the tetrazole group has increased lipophilicity and metabolic stability.[6] These properties have led to a widespread use of tetrazoles as carboxylic acids, and its replacement in medicinal chemistry have been reported very recently. The replacement of the carboxylic acid in proline with the tetrazole unit would give a greater solubility than that shown by proline, and a greater range of solvents can be used with the organocatalyst than it is possible when using proline.

Recently, Ley et al.[7] have reported that the tetrazole derived from proline **2** (see Chart 1) acts as an organocatalyst in the asymmetric Michael addition of ketones to β-nitrostyrene **4** (see Scheme 1). They found that the reaction with (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **2** in several alcoholic solvents outperforms proline **1**, both in terms of product yield and enantioselectivity. The relative configuration of compound **5** determined by X-ray[7] suggests that the approach of β-nitrostyrene **4** to the enamine formed by the condensation between cyclohexanone **3**



Scheme 1.

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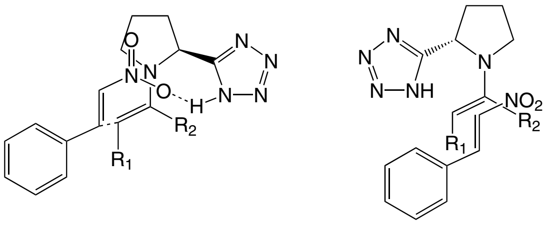
and pyrrolidinyltetrazole **2** takes place through the *re*/*re* faces of both reactant carbon centers. For the formation of stereoisomer **5**, two potential transition state structures (TSs) for C–C bond-formation step were proposed (see **TSA** and **TSB** in Scheme 2). **TSA** corresponds with the approach of β-nitrostyrene **4** by its *re* face to the *re* (β) face of the enamine in the *anti* conformation (for a definition of the *syn*/*anti* conformations of the enamines, the α/β faces of the enamines, and the *re*/*si* faces of nitroalkenes, see Chart 2). This approach mode allows an intramolecular hydrogen bond (HB) formation between the tetrazole and β-nitrostyrene **4**.[8] On the other hand, **TSB** corresponds with the approach of β-nitrostyrene **4** by its *re* face to the *re* (α) face of the enamine in the *syn* conformation. It has been proposed that this approach mode prevents hindrance with the tetrazole group[9].



TSA **TSB**

Scheme 2.

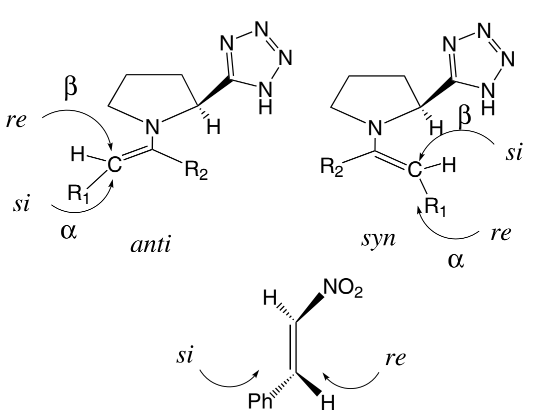


Chart 2.

For the improvement of the pyrrolidinyltetrazole **2** over proline **1**, Ley et al. suggested that there is an inherent difference between the two catalysts that alters the TS.[7] On the one hand, if pyrrolidinyltetrazole **2** participated in a HB as in **TSA**, it would be expected for them to give a similar enantioselectivity unless there is an inherent difference in the HB between pyrrolidinyltetrazole and proline. A second explanation is that the slightly larger tetrazole moiety occupied a larger region of the space than the carboxylic acid, thereby providing more of an α facial preference for a *re*/*re* approaching substrate, see **TSB**.

Our interest in organocatalysis prompted us to carry out theoretical investigations on the intermolecular proline-catalyzed aldol reaction[10] and the proline-catalyzed nucleophilic addition of nitrones to carbonyl compounds.[11] Recently, the replacement of the carboxylic acid functionality by a tretrazole group in the organocatalyst proline-catalyzed asymmetric aldol reaction has been studied.[12] The formation of an intramolecular HB between the acid hydrogen of the tetrazole moiety and the carbonyl oxygen atom of the aldehyde catalyzes very effectively the C–C bond formation by a large stabilization of the negative charge that is developing at the carbonyl oxygen atom along the nucleophilic attack.[12] As a consequence of the HB formation, the reactive channels associated with the *anti* arrangement of the methylene of the enamine are favored over the channels associated with the *syn* arrangement.

Herein, the pyrrolidinyltetrazole catalyzed Michael additions of carbonyl compounds to nitroalkenes are studied using density functional theory (DFT) with the well-established B3LYP/6-31G** method. We have investigated the TSs associated with the C–C bond-formation step of the pyrrolidinyltetrazole catalyzed Michael additions of acetaldehyde to nitroethylene **8**, and acetone to β-nitrostyrene **4**, in the presence of pyrrolidinyltetrazole **2**. Our main purpose is to investigate the role of the tetrazolic acid moiety in these Michael additions to nitroalkenes.

2. Computational methods

Density functional theory[13] calculations have been carried out using the B3LYP[14] exchange-correlation functionals, together with the standard 6-31G** basis set.[15] As these organocatalyzed Michael reactions are carried out in polar solvents, which can modify both gas phase activation energy and stereoselectivity, their effects have been considered by using a relatively simple self-consistent reaction field (SCRF) method[16] based on the polarizable continuum model (PCM) of Tomasi et al.[17] As the solvent used in the experimental work is ethanol, we have used its dielectric constant $\varepsilon = 24.55$. Implicit solvent effects were considered by intermolecular HB formation of a methanol molecule, as a model of ethanol used experimentally, to one oxygen atom of nitroethylene. The values of the relative enthalpies, ΔH, and free energies, ΔG, in ethanol were calculated with the standard statistical thermodynamics[15] at 298.15 K. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[18] All calculations were carried out with the Gaussian 03 suite of programs.[19]

3. Results and discussion

Two reaction models have been studied. The first one, *Model I*, is the Michael addition of enamine **6**, obtained by condensation of the acetaldehyde with pyrrolidinyltetrazole **2**, to the simplest nitroethylene **8**. For this reaction a number of TSs associated with the C–C bond formation, in which the two reactant molecules adopt different arrangements, are considered. The role of the intramolecular HB by tetrazole will be analyzed. In the second model, *Model II*, the four more favorable intramolecular HB reactive channels associated with the

Michael addition of enamine **7**, obtained by condensation of acetone with pyrrolidinyltetrazole **2**, to β-nitrostyrene **4** are studied. Finally, the factors responsible for the stereoselection found in these organocatalyzed Michael additions are also discussed.

3.1. Study of the C–C bond-formation step associated with the Michael addition of acetaldehyde to nitroethylene 8 in the presence of pyrrolidinyltetrazole 2. Reaction Model I

Pyrrolidinyltetrazole **2** can exist mainly as two tautomeric forms in equilibrium; in the gas phase, the tetrazolic acid form **2** is 2.4 kcal/mol lesser in energy than the isomeric form **2′** (Chart 3). With the inclusion of the solvent, ethanol, this difference becomes 3.3 kcal/mol. For enamine **6**, obtained by condensation between acetaldehyde and pyrrolidinyltetrazole **2**, two conformational structures are feasible due to the restricted rotation around the C6–N7 single bond (see Scheme 3). These conformers are related to the *syn*, **6s**, and *anti*, **6a**, arrangement of the active methylene group relative to the tetrazole group. In ethanol, conformer **6s** is 0.8 kcal/mol more stable than conformer **6a** (see Table 1); however, the easy C6–N7 bond-rotation allows the equilibration between these conformers.

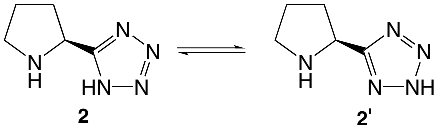


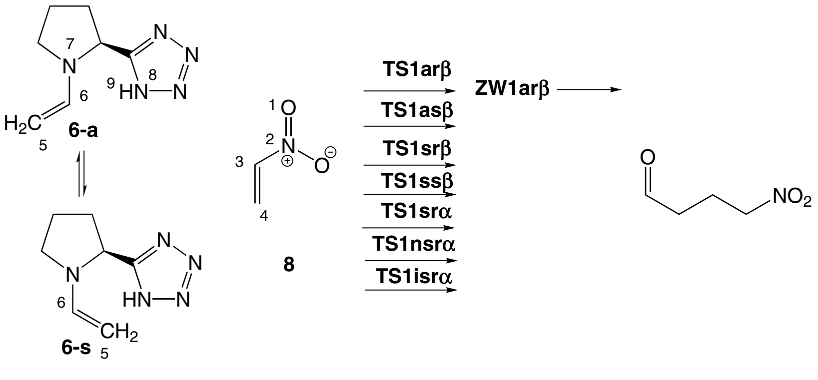
Chart 3.

The C–C bond-formation step corresponds with the stereocontrol step for the pyrrolidinyltetrazole catalyzed Michael addition. Taking into account the *syn* and *anti* conformations and the α and β faces of the chiral enamines, and the *re* and *si* faces of the β-substituted nitroalkenes, there are eight approach modes for the attack of the enamine to nitroalkenes. In addition, if we consider the possible rotamers along the C–C forming bond, the number of TS increases considerably. This fact justifies the use of a reduced model for an initial study. For this step, a large number of TSs have been studied; here the more relevant ones are presented. They are related mainly with the nucleophilic attack of active methylene of enamine **6** in the *syn* or *anti* conformations, named as **a** and **s** to the *re* or *si* faces of the β-conjugated position of nitroethylene **8**, named as **r** and **s**, and by the α or β faces of the chiral enamine, named as **α** and **β**, respectively. Note that the β-conjugated position of nitroethylene **8** is not prochiral; however, we have used the descriptors *re*/*si* to a further comparison of the TSs with those associated with the attack of enamine **7** to β-nitrostyrene **4**, see Chart 2. At the TSs associated to the approach by the β face of the *syn*/*anti* enamines **6**, one oxygen atom of nitroethylene **8** is involved in an intramolecular HB to the acid hydrogen atom of pyrrolidinyltetrazole **2**. In addition, other three TSs associated to the approach of nitroethylene **8** by its *re* face to the α face of the *syn* enamine **6** are also discussed. Finally, the zwitterionic intermediate associated with the more favorable reactive channel has been located in order to obtain information about the thermochemistry of the C–C bond-formation step. Therefore, seven TSs, **TS1srβ**, **TS1ssβ**, **TS1arβ**, **TS1asβ**, **TS1srα**, **TS1nsrα**, and **TS1isrα**, and one intermediate, **ZW1srβ**, have been studied (see Scheme 3).

Table 1. Entropies and free energies (*H* and *G*, in au) and relative entropies and free energies (Δ*H* and Δ*G*, in kcal/mol) in ethanol at 25 °C and 1 atm for the stationary points involved in the Michael addition of enamines **6** and **7** to nitroethylene **8** and β-nitrostyrene **4**, respectively

	H	Δ*H*	*G*	Δ*G*
4	−514.031865		−514.077336	
8	−283.041731		−283.075190	
6s	−546.885840		−546.935998	
6a	−546.885749	0.1	−546.934694	0.8
TS1arβ	−829.921692	3.7	−829.981428	18.7
TS1asβ	−829.919394	5.1	−829.979761	19.7
TS1srβ	−829.916363	7.0	−829.976442	21.8
TS1ssβ	−829.919377	5.1	−829.977704	21.0
TS1srα	−829.917466	6.3	−829.976380	21.8
TS1nsrα	−829.913213	9.0	−829.973194	23.8
TS1isrα[a]	−945.596643	5.0	−945.668443	28.7
ZW1arβ	−829.941446	−8.7	−829.997317	8.7
7s	−586.173703		−586.226396	
7a	−586.172819	0.6	−586.225760	0.4
TS2ar	−1100.192042	8.5	−1100.265411	24.0
TS2as	−1100.190066	9.7	−1100.264023	24.9
TS2sr	−1100.188560	10.7	−1100.260909	26.9
TS2ss	−1100.187813	11.1	−1100.261669	26.4
ZW2ar	−1100.205039	0.3	−1100.277939	16.2

[a] The free energy of methanol is −115.704249 au.



Scheme 3.

The activation free energies associated with the C–C bond-formation step via these TSs are 18.7 (**TS1arβ**), 19.7 (**TS1asβ**), 21.8 (**TS1srβ**), 21.0 (**TS1ssβ**), 21.8 (**TS1srα**), 23.8 (**TS1nsrα**), and 28.7 (**TS1isrα**) kcal/mol (see Table 1). These energetic results indicate that the formation of the intramolecular HB by the β face of enamine **6** favors C–C bond formation. The more favorable reactive channel corresponds to the approach of nitroethylene **8** by its *re* face to the β face of enamine **6** in the *anti* conformation, via **TS1arβ**. This TS presents the same approach mode as that proposed for the formation of the Michael adduct **5**, via **TSA**.[7] However, **TS1asβ** and **TS1ssβ** are 1.0 and 2.3 kcal/mol above **TS1arβ**; therefore, these reactive channels appear to also be competitive at this reduced model. On the other hand, the more energetic TSs correspond with the approach of nitroethylene **8** to the α face of the *syn* enamine **6**. **TS1srα**, which presents the approach of nitroethylene **8** to enamine **6** by the opposite face that possesses the tetrazole group is 3.1 kcal/mol higher in energy than **TS1arβ**. Note that **TS1srα** also has an intramolecular HB. The non-HB **TS1nsrα** is located 5.2 kcal/mol above **TS1arβ**. Therefore, the formation of the intramolecular HB by the β face clearly accelerates the Michael addition.[12] In addition, although the formation of the intermolecular HB to one methanol molecule, as a model of ethanol used in the experiments, favors enthalpically the C–C bond-for-

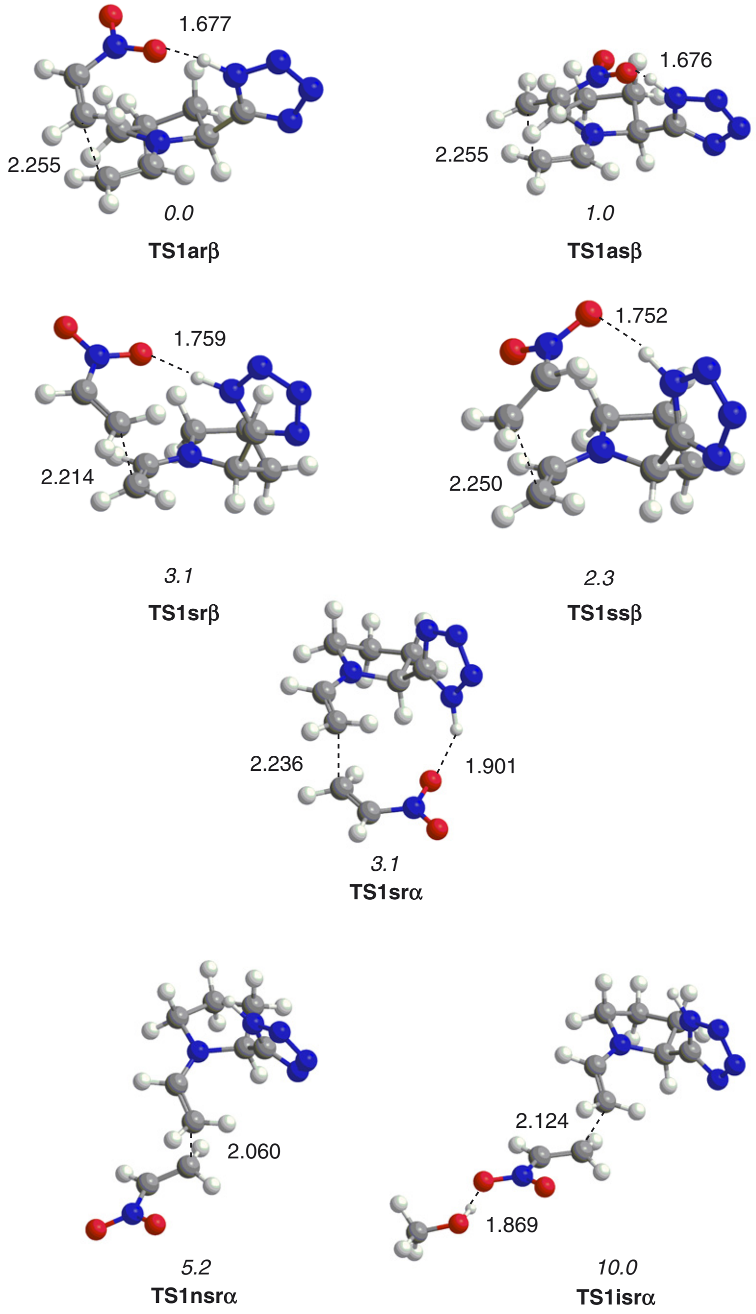


Figure 1. Transition structures associated with the Michael addition of enamine **6** to nitroethylene **8** (reaction *Model I*). Values in italics correspond with the relative free energies, in kcal/mol. The lengths of the forming bonds and the HBs are given in angstroms.

mation process, the activation enthalpy associated to **TS1isrα** is 1.3 kcal/mol higher in energy than that associated with **TS1arβ**, the intramolecular nature of the HB process means that the activation free energy associated to **TS1isrα** rises 10 kcal/mol above **TS1arβ**. These energy results allow us to discard for the reaction *Model II* (see later) to study the reaction paths in which nitroethylene **4** is not involved in an intramolecular HB to the tetrazole by the β face of the *syn*/*anti* enamine. Finally, the intermediate **ZW1arβ** is located 8.7 kcal/mol above the reagents, the C–C bond formation being endergonic.

The lengths of the C4–C5 forming bonds at the TSs are given in Figure 1. At the intramolecular HB TSs, these lengths are a narrow range, 2.21–2.26 Å. The lengths of the O1–H9 HBs at the TSs associated to the approach of nitroethylene **8** by the β face of enamine **6** are in the range 1.68–1.76 Å. At the intramolecular HB **TS1srα**, the length of the intramolecular O1–H9 HB, 1.901 Å, is larger than those at the TS associated to the approaches by the β face. This distance that is even slightly larger than that at the intermolecular HB **TS1isrα**, 1.869 Å, points out a strain associated to the HB formation as a consequence of the tetrazole group and nitroethylene is located in opposite faces of enamine **6**. At the intermediate **ZW1arβ**, the length of the C4–C5 bond is 1.570 Å. The length of the C6–N7 bond at this intermediate, 1.295 Å, points out the double-bond character of the C6–N7 bond. Finally, the distances between the H9 hydrogen and the tetrazolic N8 nitrogen, 1.083 Å, and the H9 and the O1 oxygen at **ZW1arβ**, 1.459 Å, point out a strong O1–H9 HB interaction as a consequence of the large change transferred to the NO_2 group along the Michael addition (see later).

Table 2. Bond order values (BO) of the C–C forming bond and charge transfer (CT, in e) at the TSs and zwitterionic intermediates involved in the Michael addition of enamines **6** and **7** to nitroethylene **8** and β-nitrostyrene **4**, respectively

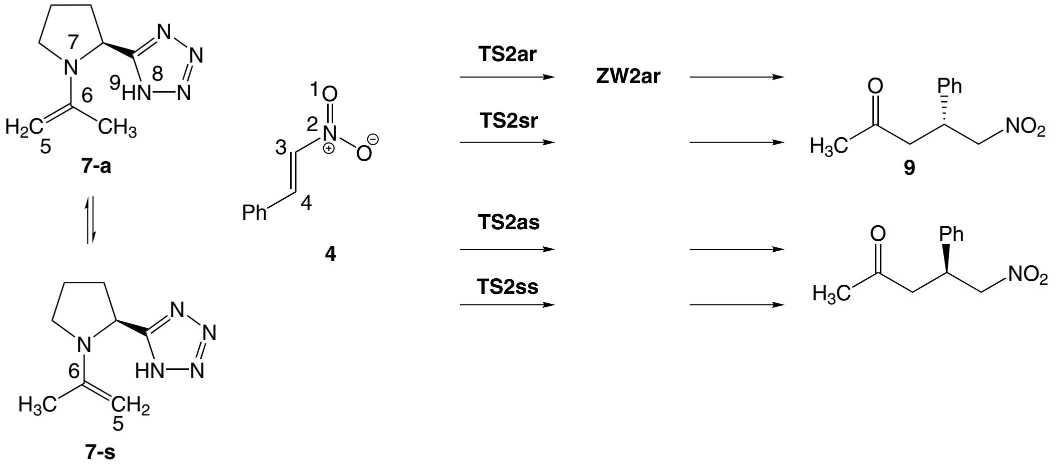
	BO	CT		BO	CT
TS1arβ	0.33	0.31	**TS2ar**	0.40	0.36
TS1asβ	0.32	0.29	**TS2as**	0.41	0.38
TS1srβ	0.35	0.32	**TS2sr**	0.43	0.41
TS1ssβ	0.33	0.31	**TS2ss**	0.42	0.40
TS1srα	0.35	0.33			
TS1nsrα	0.45	0.44			
TS1isrα	0.41	0.42			
ZW1arβ	0.96	0.68	**ZW2ar**	0.92	0.75

The Wiberg bond order (BO) values[20] of the C–C forming bond at the TSs are in the range of 0.32–0.45 (see Table 2). The more defavored **TS1nsrα** is more advanced than of the HB TSs. At these TSs, the C6–N7 BO values, in the range 1.27–1.32, point out a π character of the C6–N7 bond as a consequence of the participation of the N7 lone pair along the C–C bond-formation process. At the intermediate **ZW1arβ**, the BO value of the C4–C5 bond indicates that this bond is already formed. An analysis of the natural charges at the atoms belonging to nitroethylene **8** and enamine **6** allows us to evaluate the charge transfer (CT) along the nucleophilic attack of enamine **6** to nitroethylene **8**. At the TSs, the CT are in the range 0.29–0.44 e (see Table 2). **TSnrsα** and **TSisrα** present the larger CT as a consequence of the more advanced character. At the zwitterionic intermediate **ZW1arβ**, the CT arises to 0.68 e.

3.2. Study of the C–C bond-formation step associated with the Michael addition of acetone to β-nitrostyrene 4 in the presence of pyrrolidinyltetrazole 2. Reaction Model II

In the reaction *Model II*, the C–C bond-formation step associated with the Michael addition of enamine **7**, formed by condensation of acetone with pyrrolidinyltetrazole **2**, to β-nitrostyrene **4** was studied. For this step, the four reactive channels associated with the attack of the *syn*/*anti* enamine **7** by its β face were considered. Therefore, four TSs, **TS2sr**, **TS2ss**, **TS2ar**, and **TS2as**, and one intermediate, **ZW2ar**, were studied (see Scheme 4).

The activation free energies associated with the C–C bond-formation step are 24.0 (**TS2ar**), 24.9 (**TS2as**), 26.9 (**TS2sr**), and 26.4 (**TS2ss**) kcal/mol (see Table 1). As *Model I*, the more favorable reactive channel corresponds to the approach of β-nitrostyrene **4** by its *re* face to the β face of enamine **7** in the *anti* conformation, via **TS2ar**. Note that the **TS2ar** presents the same approach mode of the

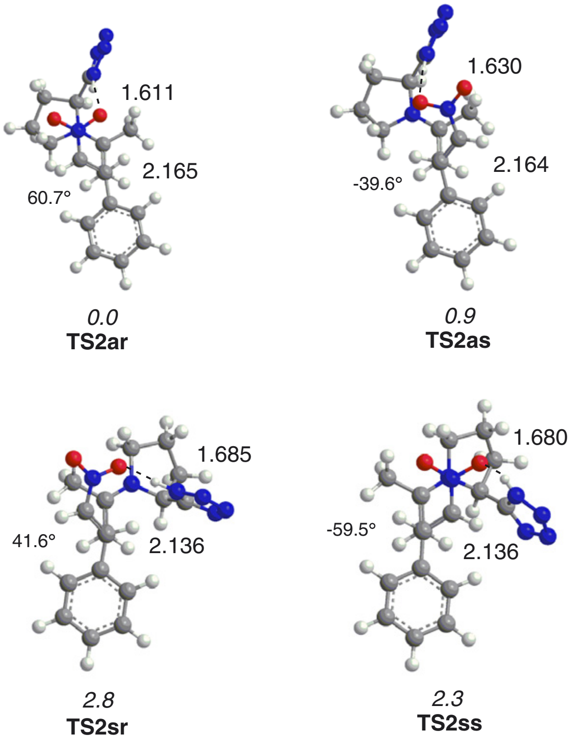


Scheme 4.

reagents than that at **TSA**, which has been proposed as a potential TS for the organocatalyzed Michael addition given in Scheme 1.[7] The intermediate **ZW2ar** is located 16.2 kcal/mol above the reagents. Further hydrolysis of the iminium group present in **ZW2ar** affords the Michael adduct **9**, which has the same configuration at the C4 carbon atom than that at the Michael adduct **5**.[7]

The relative free energy of the TSs indicates that the presence of the methyl group on enamine **7** and phenyl substituent present on β-nitrostyrene **4** does not substantially modify the stereochemistry. However, the presence of the phenyl group has a large incidence on the activation free energies. The activation free energy associated with **TS2ar** is 5.3 kcal/mol higher than that associated with **TS1arβ**. In addition, the intermediate **ZW2ar** is located 16.2 kcal/mol above the reagents. These energetic results can be related to the loss of conjugation of the phenyl substituent of β-nitrostyrene **4** along the C–C bond formation.

The geometry of the TSs is given in Figure 2. The lengths of the C–C forming bond at the TSs are 2.165 Å at **TS2ar**, 2.164 Å at **TS2as**, 2.136 Å at **TS2sr** and 2.136 Å at **TS2ss**. The lengths of the O1–H9 HB at the TSs are in the range 1.61–1.69 Å. These lengths are slightly shorter than those found at the TSs associated with the reaction between enamine **6** and nitroethylene **8**. At the intermediate **ZW2ar**, the length of the C4–C5 bond is 1.592 Å. The length of the C6–N7 bond at this intermediate, 1.306 Å, points out the large π character of this bond. Finally, the distances between the H9 hydrogen and the tetrazolic N8 nitrogen, 1.102 Å, and the H9 and the O1 oxygen, 1.462 Å, indicate a strong O1–H9 HB interaction as a consequence of the large CT to the NO_2 group along the Michael addition.



0.0
TS2ar

0.9
TS2as

2.8
TS2sr

2.3
TS2ss

Figure 2. Transition structures associated with the Michael addition of enamine **7** to β-nitrostyrene **4** (reaction *Model II*). Values in italics correspond with the relative free energies, in kcal/mol. The lengths of the forming bonds and the HBs are given in angstroms, while the C3–C4–C5–C6 dihedral angles are given in degrees.

The BO values of the C5–C6 forming bond at the TSs, between 0.40 and 0.43, indicate that the C–C bond-formation process is more advanced than that at the TSs associated with the Michael addition of enamine **6** to nitroethylene **8** (see Table 2). The CT from the donor enamine **7** to the acceptor β-nitrostyrene **4** at the TSs are in the range 0.36–0.41 e, while at the intermediate **ZW2ar** it is 0.75 e (see Table 2). These values are slightly larger than those found at reaction *Model I*, as a consequence of the presence of the electron-releasing methyl group on enamine **7**, and the electron-withdrawing phenyl group on β-nitrostyrene **4**, which favor the CT from nucleophile **7** to electrophile **4**.

3.3. Analysis of the factors responsible for the relative energies of the stereoisomeric TSs

Analysis of the relative energies of the TSs for the two reaction models indicates that both models give similar trends. The inclusion of the methyl group on acetone and the phenyl group on the β-nitrostyrene does not cause significant changes in the relative free energies. In order to explain these energy results, a global analysis of the structure of the TSs was performed. Firstly, the HB formation clearly plays a relevant role on the activation free energy through a larger stabilization of these zwitterionic TSs.[10–12] Along the nucleophilic attack of the enamines to nitroethylenes, the CT is being located on the electron-withdrawing NO_2 group. The HB formation at the oxygen atom allows a larger stabilization of the negative charge that is developing at the oxygen atoms.[11,12] Formation of the intramolecular HB by the β face of the enamines is favored over its formation by the α face as a consequence of the larger hindrance at the latter. In addition, these intramolecular HB formation modes appear to be more favorable than that at alcohols used as solvents. Two factors are responsible for this differentiation: tetrazole is more acid than alcohols, and the intramolecular HB is entropically more favorable than the intermolecular one.

From the geometries of the four TSs for the reaction *Model II*, some conclusions can be drawn. (i) In these TSs, the phenyl group presents an *anti* conformation relative to the C5–C6 double bond of enamines. Since this disposition is invariant relative to enamines **6** and **7**, the presence of the phenyl group on the nitroalkene does not cause a noticeable distinction between these TSs. (ii) The C3–C4 and C5–C6 double bonds present a *gauche* relation along the C4–C5 bond formation. However, while along the attack of the *anti* enamine to the *re* face of β-nitrostyrene, the NO_2 group is located over the amine group, see **TS2ar**, along the attack to the *si* face these groups are more far away, see **TS2as**. Note that the distance between the nitro N2 and amine N7 nitrogen atoms at **TS2ar** and **TS2as** is 3.327 and 3.980 Å, respectively. The favorable electrostatic interactions that appear between the NO_2 group that is being negatively charged and the amine group that is being positively charged at the **TS2ar** can contribute to a large stabilization of this TS than **TS2as**. Note that the C3–C4–C5–C6 dihedral angle at **TS2as**, 39.6°, present a large deviation of the 60°, probably as a consequence of these electronic interactions that close the corresponding dihedral angle in order to approach the ends of this zwitterionic TS. (iii) Finally, for the two reaction models, the *syn* TSs are ca. 2 kcal/mol more energetic than the *anti* ones.[12] Note that the presence of the methyl group on the enamine **7** does not cause a substantial energy difference between the *anti* and *syn* TSs, the methylene group being responsible for the diastereoselection.

4. Conclusions

The role of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole in the asymmetric organocatalyzed Michael addition of carbonyl compounds to nitroalkenes has been studied using DFT methods at the B3LYP/6-31 G** computational level. Two reaction models have been considered. They are related to the additions of the enamines formed by the condensation of acetaldehyde and acetone with (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole to nitroethylene and β-nitrostyrene, respectively. For the C–C bond-formation step several reactive channels have been analyzed. Formation of an intramolecular HB between the acid hydrogen of tetrazol and the oxygen atom of nitroalkene by the β face of the chiral enamine favors the C–C bond-formation step by a large stabilization of the negative charge that is being developed at the electron-withdrawing NO_2 group along the nucleophilic attack of these enamines to the nitroalkenes. For the two reaction models, the more favorable reactive channel corresponds to the approach of β-nitrostyrene by its *re* face to the β face of the enamine in the *anti* conformation. The TS associated to this channel corresponds to **TSA**, which has been proposed by the experimentalists as a potential TS for these Michael additions. Although the major stereoisomer can also be obtained by the approach of β-nitrostyrene by its *re* face to the α face of the enamine, via the proposed **TSB**, the hindrance that appears along this approach mode associated to HB formation prevents this channel from being competitive. The present theoretical study, which agrees with the experimental outcome, allows an explanation for the role of the tetrazole on the stereochemistry course of the reactions.

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