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NMR and Theoretical Studies on the Conformational Preferences of Some Non-metal Coordinated *N*-Enoyl Systems Attached to Common Chiral Auxilaries

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Abstract. We report a systematic study of a series of *N*-enoyl systems attached to common oxazolidin-2-ones, oxazolidine-2-thiones and thiazolidine-2-thiones chiral auxiliaries in order to determine the most stable conformation of these compounds. ^{1}H NMR studies show an *anti-s-cis* structure as the most stable conformation for these series of compounds. Density Functional Theory geometry optimizations and vibrational analysis using the B3LYP exchange-correlation functional with the standard 6-31G** basis sets were done, including solvent effects (chloroform and toluene). Gibbs free energy differences show that the *anti-s-cis* structures are the most stable conformers lying, on average, ca. 6 kcal/mol lower in energy than the *syn-s-cis* conformers, widely used to explain the structure and reactivity of *N*-enoyl systems.
Key words: Enoyl systems, conformational preferences, chiral auxiliaries, NMR shifts.

Resumen. Se reporta un estudio sistemático sobre una serie de sistemas tipo *N*-enoilo, unidos a algunos auxiliares quirales comunes como las oxazolidin-2-onas, oxazolidin-2-tionas y tiazolidin-2-tionas para determinar la conformación más estable de estos compuestos. Estudios de RMN ^{1}H muestran a la conformación *anti-s-cis* como la más estable para estas series de compuestos. En el marco de la Teoría de Funcionales de la Densidad se realizaron optimizaciones de geometría y análisis vibracional con el funcional B3LYP y las bases 6-31G**, incluyendo los efectos del disolvente en cloroformo y tolueno. Las diferencias de energía libre de Gibbs muestran que las conformaciones *anti-s-cis* son las más estables, en promedio, ~6 kcal/mol más estables que los confórmeros *syn-s-cis,* generalmente usados para explicar la estructura y reactividad de sistemas tipo *N*-enoilo.
Palabras clave: Sistemas enoilo, preferencias conformacionales, auxiliares quirales, desplazamientos RMN.

Introduction

The 1,4-addition of nucleophiles to *α,β*-unsaturated carboxylic acid derivatives is one of the most useful methods for asymmetric carbon-carbon or carbon-heteroatom bond formation [1]. In this context, the conjugate addition of organometallic reagents to *N*-enoyloxazolidinone systems has been employed in the synthesis of natural products [2]. Metal coordination with one or both oxygens on these systems enhances the electrophilic character of the *β*-carbon, lowering the energy of the molecular orbitals of the conjugated systems and locking these substrates in a specific conformation to ensure facial selectivity during the addition [3].

Nevertheless, in the conjugate addition of some organocopper reagents to this kind of substrates, Williams [4] and Bergdahl [5] have reported a reversed diastereofacial selectivity on some usual 4-alkyl substituted oxazolidinones of the same relative configurations. They suggest that the observed different stereochemical outcomes reflect the presence of different conformers of the unsaturated systems. (Fig. 1).

More recently, Sabala *et al* [6] suggests that *N*-enoyloxazolidinone systems in an *anti-s-cis* conformation lead to *syn* addition products, whereas a *syn-s-cis* conformation lead to *anti* addition products. In both cases addition of the nucleophile always takes place on the face of the double bond opposite to the R group in the chiral auxiliary. (Fig. 2)

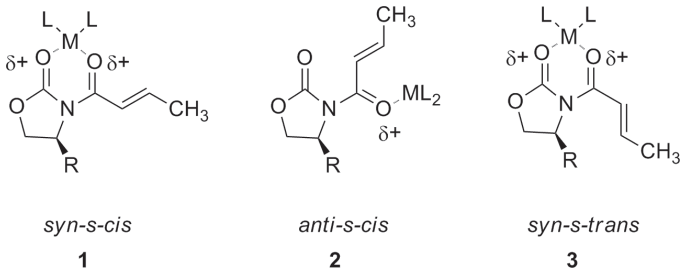


Fig. 1. Common conformers of *N*-enoyl systems.

Moreover, when exploring the synthetic utility of *N*-enoyloxazolidinethiones, the addition of cuprates in the presence of TMSI yields *anti* addition products, suggesting a *syn-s-cis* conformation for this kind of substrates. In the case of *N*-enoylthiazolidinethiones [7], only one example of cuprate addition has appeared in the literature where the addition product seems to be derived from an *anti-s-cis* conformation of the reacting substrate.

Within the context of our medicinal chemistry program whose main goal is the design and synthesis of

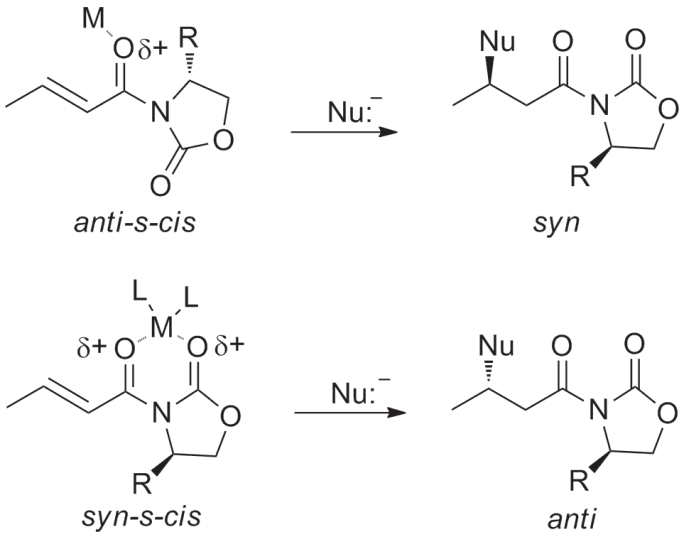


Fig. 2. Conjugate additions of nucleophiles to *N*-enoyl systems.

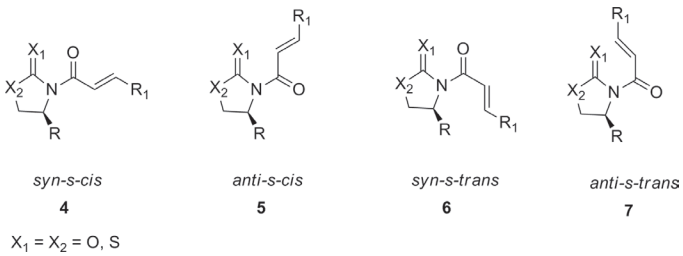


Fig. 3. *N*-enoyl system conformers.

structural analogues of well known pharmacologically active agents, we became interested in this type of analogues, since they are versatile precursors to some active agents.

Although the conformation of the metal coordinated *N*-enoyl and similar species and their ^{1}H NMR spectra have received some attention in the literature [8], to the best of our knowledge, the conformational preferences and energy differences between the possible conformers of the free non-metal coordinated *N*-enoyl systems **4**,**5**,**6** and **7** (Fig. 3) have not been documented.

Intrigued by the different stereochemical behaviors reported in the literature on the addition of cuprates to these systems, we carried out some ^{1}H NMR and theoretical calculations in order to determine the most stable conformers of these conjugated systems [4, 9d].

Results and Discussion

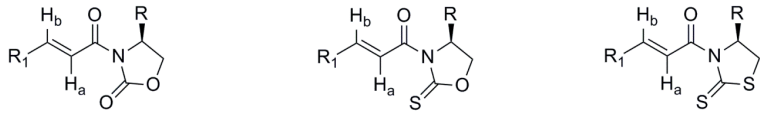
^{1}H NMR Studies

Table 1 shows the compounds chosen for this study, **8-10**. All of them have been prepared following standard literature procedures [2a, 9].

The ^{1}H NMR spectra of α,β-unsaturated derivatives can provide some insight on their conformational preference based on the chemical shifts of the vinylic protons, H_a and H_b. Fig. 4 and 5 show the ^{1}H NMR spectra of some illustrative examples of these compounds. Fig. 4a and 5a show the ^{1}H NMR spectra of crotonic acid **11** and of 4-*p*-chlorophenylpropenoic acid **12** respectively, showing the chemical shift of H_a and H_b for these acids and their derivatives.

As can be seen in Fig 4, the chemical shift of H_a in crotonic acid appears at δ 5.85 ppm (Fig. 4a). However, when the chiral auxiliaries are coupled to crotonic acid, the chemical shift of H_a suffers a significant high frequency shift in their ^{1}H NMR spectra. For example, when (4*S*)-4-phenyl-1,3-oxazolidine-2-one, (4*S*)-4-benzyl-1,3-oxazolidine-2-one or (4*S*)-4-phenyl-1,3-oxazolidine-2-thione are coupled to acid **11**, ^{1}H NMR signal for H_a suffers the high frequency to δ 7.26 in compound **8a**; to δ 7.30 ppm in compound **8e** and to δ 7.68 in compound **9a** (Fig 4b-d). In compound **8e**, H_a and H_b were assigned based on their

Table 1. *N*-enoyl systems attached to chiral auxiliaries.



8 **9** **10**

Compound	R	R_1	Compound	R	R_1	Compound	R	R_1
8a	Ph	Me	**9a**	Ph	Me	**10a**	Ph	Me
8b	Ph	*p*-ClPh	**9b**	Ph	*p*-ClPh	**10b**	Ph	*p*-ClPh
8c	Ph	*i*-Pr	**9c**	Ph	*i*-Pr	**10c**	Ph	*i*-Pr
8d	Ph	*i*-Bu	**9d**	Ph	*i*-Bu	**10d**	Ph	*i*-Bu
8e	Bn	Me	**9e**	Bn	Me	**10e**	Bn	Me
8f	Bn	*p*-ClPh	**9f**	Bn	*p*-ClPh	**10f**	Bn	*p*-ClPh
8g	Bn	*i*-Pr	**9g**	Bn	*i*-Pr	**10g**	Bn	*i*-Pr
8h	Bn	*i*-Bu	**9h**	Bn	*i*-Bu	**10h**	Bn	*i*-Bu

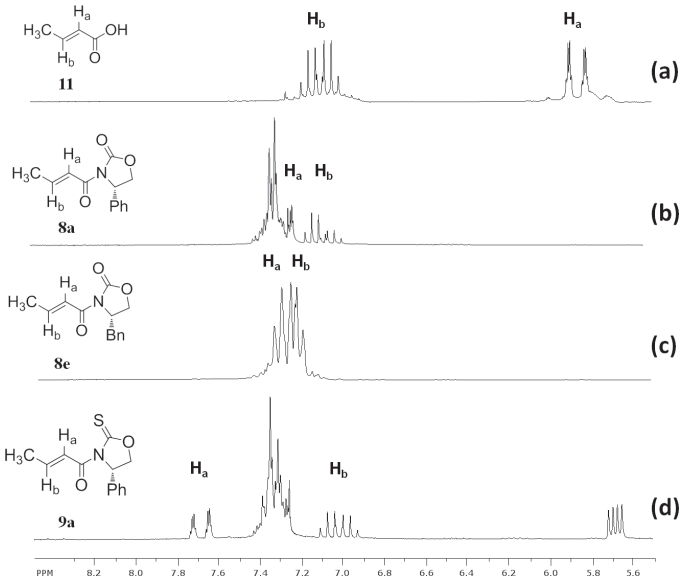


Fig. 4. ^{1}H NMR spectra of crotonic acid **11** (a) and derivatives **8a** (b), **8e** (c) and **9a** (d).

coupling constants, for example, H_a exhibits a single coupling constant of 15.0 Hz showing its coupling to H_b. On the other hand, for H_b two coupling constants can be observed, one of them has a magnitude of 15.0 Hz as expected and the other one showing a coupling constant of 5.2 Hz due to its coupling with the methyl group protons. This is consistent with the ^{1}H NMR spectra reported in the literature for this compound [10].

Fig 5 shows the ^{1}H NMR spectra of 4-*p*-chlorophenylpropenoic acid **12** where the chemical shift of H_a appears at δ 6.54 ppm (Fig. 5a). In a similar manner, when the same chiral

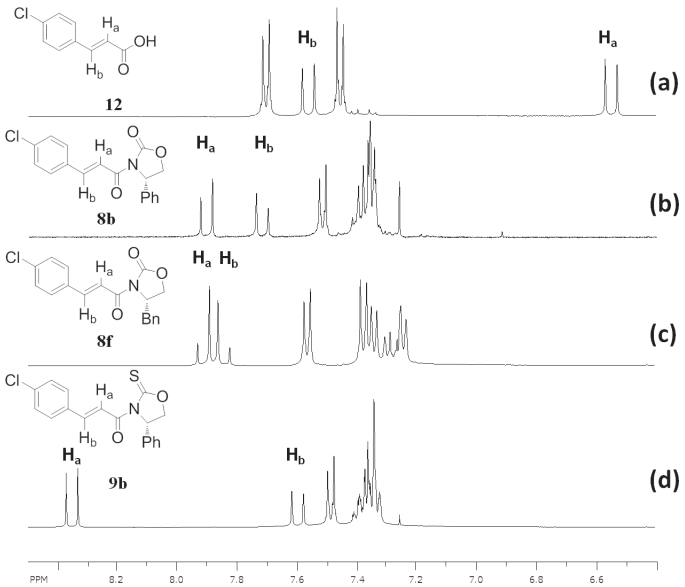


Fig. 5. ^{1}H NMR spectra of 3-*p*-chlorophenylpropenoic acid **12** (a) and derivatives **5a** (b), **5b** (c) and **5c** (d).

auxiliaries are coupled to acid **11**, compounds **8b, 8f** and **9b** are obtained. Once again the chemical shifts of H_a in these compounds suffer the high frequency shift to δ 7.90 in **8b**, to δ 7.90 in **8f** and to δ 8.35 in **9b** (Fig. 5b-d). In all these cases, this represents an average downfield displacement of δ 1.53.

On the other hand, although the chemical shift of H_b experiences some minor displacement, it practically remains the same throughout the entire series, as can be seen on the figures. One possible explanation to the pronounced displacement of H_a is the preferred conformation these molecules may adopt. Once the chiral auxiliaries are introduced to the corresponding carboxylic acids, the molecules adopt an *anti-s-cis* conformation. In this conformation, H_a experiences the proximity of the oxygen carbonyl or the sulfur thionyl group of the chiral auxiliary, where the deshielding effect of these groups induces the downfield displacement of H_a. This type of displacement experienced by H_a when the auxiliaries are introduced is observed throughout all the series, thus supporting the idea of an *anti-s-cis* conformation as the most stable conformation for all these compounds. (Fig. 4 and 5) In addition to the ^{1}H NMR evidence, the *anti-s-cis* conformational preferences shown by these systems may be the result of some C-H_a···O or C-H_a···S hydrogen bond in a cyclic six-membered ring arrangement [11].

Computational studies

We have performed electronic structure calculations within the Density Functional Theory (DFT) in order to determine the energies of all the possible conformers appearing in **8-10**. In particular we used the hybrid B3LYP exchange-correlation functional [12] with the standard 6-31G** basis sets for all atoms. Geometry optimizations for the four conformers of each species were carried out without any symmetry restrictions and the nature of the minima was verified with analytical frequency calculations (no imaginary frequencies) for all the conformers studied here. Gibbs free energies were obtained at T = 298.15 K within the harmonic approximation. These optimizations considered up to 162 degrees of freedom. In the present case all of the critical degrees of freedom are dihedral angles. The calculations were done using the Gaussian03 code [13]. The default code-supplied thresholds (maximum and RMS force/displacements) were used for the convergence criteria.

Based on the results found with the NMR experiments, we now turn our attention to the relative stability of the four possible conformers in each case. Table 2 shows the relative the B3LYP/6-31G* energies of all compounds for the four different conformers of each species obtained at 0 K *in vacuo*. We find that, in all cases, the *anti-s-cis* conformation is the most stable one compared to the other three isomers for each series of molecules (compounds **8-10**). Another important result is that, at 0 K and without solvent effects, the relative stability of these conformers is *anti-s-cis* > *anti-s-trans* > *syn-s-cis* > *syn-s-trans* and the mean relative energies between the four type of conformers are 4.5 (*anti-s-cis*/*anti-s-trans*), 2.2 (*anti-s-trans*/*syn-s-cis*) and 4.6 (*syn-s-cis*/*syn-s-trans*) kcal/mol.

Table 2. Relative energies(kcal/mol) at 0K for the four conformers of each species: **8-10** *in vacuo*.

Compound	*anti-s-cis*	*anti-s-trans*	*syn-s-cis*	*syn-s-trans*
8a	0.0	5.2	7.9	12.0
8b	0.0	6.0	8.3	12.9
8c	0.0	5.8	7.9	11.8
8d	0.0	4.0	8.2	12.3
8e	0.0	5.8	9.5	17.3
8f	0.0	6.6	10.2	18.0
8g	0.0	5.9	9.5	17.6
8h	0.0	5.9	9.4	16.8
9[a]	0.0	4.1	5.4	9.2
9b	0.0	4.9	5.8	10.1
9c	0.0	4.7	5.4	9.1
9d	0.0	3.5	5.7	9.5
9e	0.0	4.3	6.5	11.3
9f	0.0	5.1	7.3	15.0
9g	0.0	4.3	6.5	11.3
9h	0.0	4.3	6.4	13.6
10	0.0	3.4	4.9	4.9
10b	0.0	4.1	5.4	5.8
10c	0.0	4.0	4.9	5.0
10d	0.0	2.7	5.2	5.3
10e	0.0	3.3	5.1	9.2
10f	0.0	4.1	5.9	13.0
10g	0.0	3.4	5.2	9.2
10h	0.0	3.4	5.1	11.7
Average difference	0.0	4.5	6.7	11.3

Regarding the benzyl substituent in compounds **8e** and **8f**, a conformation in which this substituent is oriented further apart from the double bond and the chiral auxiliaris ring systems was considered for the calculations. In all cases, this orientation resulted in the lower energy conformation.

At this point it is interesting to note that the average energy difference *in vacuo* between the most stable conformation (*anti-s-cis*) and the conformation generally used to illustrate the structure and reactivity of *N*-enoyl systems (*syn-s-cis*) [2] is 6.7 kcal/mol and, quite remarkably, the latter is not even the second most stable conformer (see Fig. 6).

In order to study the role of finite temperature on the relative stability of the conformers, we have performed a set of Gibbs free energy calculations at 298.15 K for the four conformers of compounds **8a**, **8e**, **9a**, **9e**, **10a** and **10e**. Table 3 shows a comparison of the relative energies using the internal energy ΔE at 0 K and those obtained including the ZPE and entropic contributions at 298 K, ΔG_{298}.

Note that the largest change with respect to the energy differences at 0 K between the two most stable conformers is <

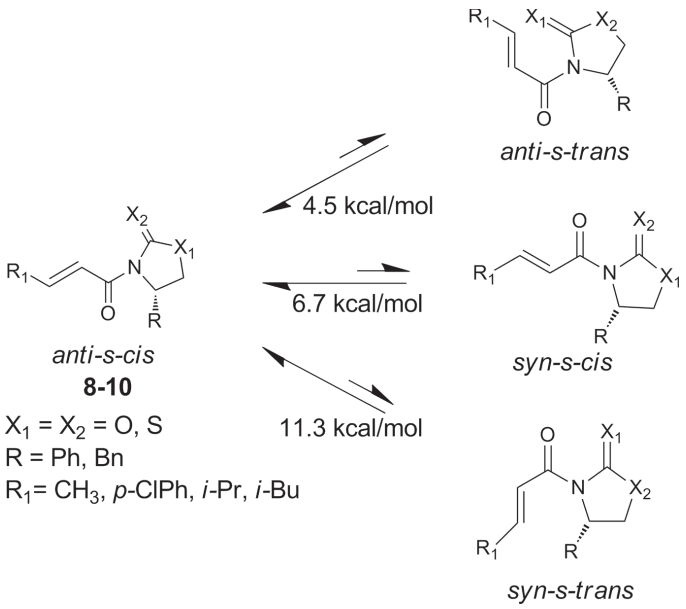


Fig. 6. Average energy difference at 0 K *in vacuo* between the *anti-s-trans*, *syn-s-cis* and *syn-s-trans* conformations with the most stable structure in all cases, the *anti-s-cis* isomer.

0.5 kcal/mol. The important result derived from Table 3 is that the stability order established previously in Table 2 for the four conformers is not modified when considering the Gibbs free energy differences *in vacuo* at room temperature. Fig 7 shows the optimized structures of compounds **8a**, **9a**, **8b** and **9b** compounds whose ^{1}H NMR spectra are given above. The fact that the *anti-s-cis* conformers are the most stable structures in all cases is in good agreement with the experimentally observed ^{1}H NMR chemical shifts. The optimized geometries for all isomers of each species are available upon request from the authors.

Finally, since the NMR spectra were obtained in chloroform, we deemed necessary to verify if the free energy differ-

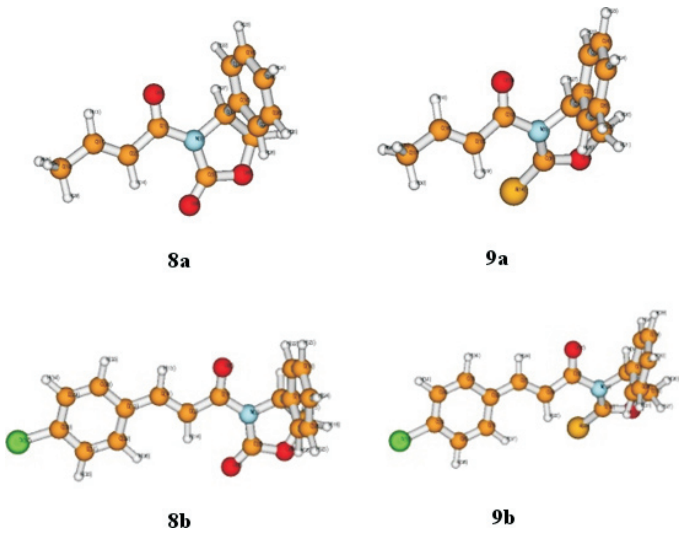


Fig. 7. Optimized structures of compounds **8a**, **9a**, **8b** and **9b**.

Table 3. Relative energies (kcal/mol) for the **8-10** conformers of each species.

Compound	ΔE				ΔG_{298}			
	anti-s-cis	*anti-s-trans*	*syn-s-cis*	*syn-s-trans*	*anti-s-cis*	*anti-s-trans*	*syn-s-cis*	*syn-s-trans*
8a	0.0	5.2	7.9	12.0	0.0	4.8	7.1	11.1
8e	0.0	5.8	9.5	17.3	0.0	5.6	8.8	14.0
9a	0.0	4.1	5.4	9.2	0.0	4.2	5.4	8.9
9e	0.0	4.3	6.5	11.3	0.0	4.4	6.5	10.9
10a	0.0	3.4	4.9	4.9	0.0	3.0	4.7	4.8
10e	0.0	3.3	5.1	9.2	0.0	3.3	5.3	9.0

Table 4. Relative *vacuo*/solvent Gibbs free energies(kcal/mol) of the conformers at 298K.

Compound	*vacuo/chloroform*				*vacuo/toluene*			
	anti-s-cis	*anti-s-trans*	*syn-s-cis*	*syn-s-trans*	*anti-s-cis*	*anti-s-trans*	*syn-s-cis*	*syn-s-trans*
8a	0.0/0.0	4.8/4.4	7.1/5.0	11.1/9.2	0.0/0.0	4.8/4.7	7.1/6.1	11.1/10.3
8e	0.0/0.0	5.6/5.4	8.8/6.2	14.0/11.7	0.0/0.0	5.6/5.6	8.8/7.5	14.0/13.2

ences are modified by the solvent, and if the solvent effects are large enough to qualitatively change the stability order of the conformers. In addition, we also considered toluene since this solvent is used in our medicinal chemistry program. Therefore, for the **8a** and **8e** cases, the Gibbs free energy differences at 298.15 K between the four conformers were also calculated using the Polarizable Continuum Model (PCM) [14] using chloroform and toluene as solvents. The inclusion of the solvent effects in the PCM scheme is done via their dielectric constants. As previously done *in vacuo*, full geometry optimizations and frequency calculations were done considering the solvent effects. We note that the final optimized geometries in the solvents were barely modified from those optimized *in vacuo*. The results of these calculations are presented in Table 4.

Table 4 shows that the inclusion of the solvent effects, for both solvents, diminishes the free energy differences between the conformers; nevertheless, their relative stability is the same as that obtained *in vacuo*. As a byproduct we also find that chloroform has a larger effect on the energy differences among the four conformers of each species than toluene.

In particular, this comparison shows that the energies of the lowest lying conformers, the *anti-s-cis* and *anti-s-trans* structures, are lowered in the solvent by roughly the same amount (< 1 kcal/mol), so that the energy differences *in vacuo* yield a good approximation to the Gibbs free energy differences in solution at 298 K. For instance, in the case of **8a** the free energy difference between the *anti-s-cis* and the *anti-s-trans* conformers at 298 K in chloroform is 4.4 kcal/mol, as compared to the 4.8 kcal/mol value obtained *in vacuo*; for the **8e** case the free energy difference between the *anti-s-cis* and the *anti-s-trans* conformers at 298 K in chloroform is 5.4 kcal/mol, as compared to the 5.6 kcal/mol value obtained *in vacuo*. Therefore, these electronic structure calculations confirm the greater stability of the *anti-s-cis* conformers in all cases, both *in vacuo* and when considering the finite temperature and solvent effects.

Conclusion

In conclusion, an *anti-s-cis* **2** conformation is consistent with the ^{1}H NMR spectra of these compounds where the proximity of the carbonyl or thionyl group of the chiral auxiliaries induces a high frequency chemical shift of the vinylic proton H_a. On the other hand, the systematic electronic structure calculations carried out for the *N*-enoyl systems **8a-h** to **10a-h** confirm the *anti-s-cis* conformation as the most stable one. The stability order found *in vacuo* for the conformers (*anti-s-cis* > *anti-s-trans* > *syn-s-cis* > *syn-s-trans*) is conserved if solvent effects in chloroform and toluene are included. The *anti-s-cis* **5** conformer is, on average, ca. **6 kcal/mol** more stable than the one usually assumed (*syn-s-cis* **4**) to explain the reactivity and stereochemistry of these compounds.

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