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Understanding the Chemoselectivity and Stereoselectivity in Michael Addition Reactions of β-Hydroxyparthenolides and Amines such as Pyrrolidine, Morpholine, Piperidine and 1-Methylpiperazine: a DFT Study.

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Abstract

The chemoselectivity and stereospecificity of the Michael addition of the 9β-hydroxyparthenolides with amines such as pyrrolidine, morpholine, piperidine and 1-methylpiperazine were studied with several theoretical approaches, activation energies and reactivity indexes derived from the DFT. The calculations were performed using DFT B3LYP / 6-31G (d, p) and the results were in agreement with experimental observations.

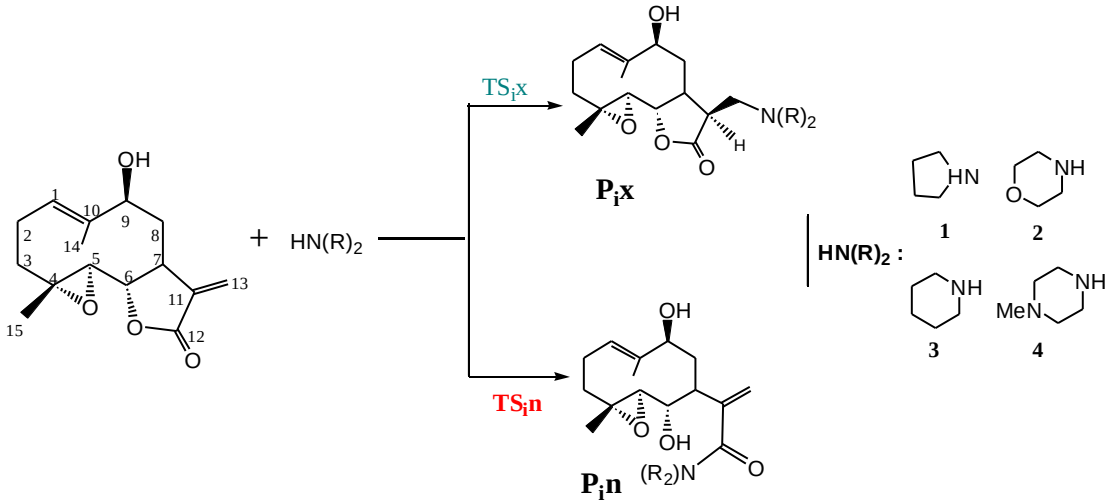
1. Introduction

The Michael addition reaction is a versatile synthetic methodology for the efficient coupling of electron poor olefins with a vast array of nucleophiles. This is one of the most important carbon–carbon bond-forming reactions. A variety of Michael acceptors [1], such as α,β-unsaturated ketones, aldehydes, esters, and nitrils, can be used in this reaction, which can be readily transformed into a range of different functionalities. [2] A large number of methods have been reported quite recently for 1,4-conjugate addition to electron-deficient olefins.
In this work we report on the Michael addition of secondary amines (scheme 1) to 9β-hydroxyparthenolides, the major compounds isolated from Anvillea radiata species [3]. The result obtained showed that the reactions were stereospecific and yielded exclusively a single stereoisomer with the R-configuration at the newly formed C-11 chiral carbon. The products obtained were evaluated as novel anticancer agents [4], and we used DFT calculations to obtain information about the factors affecting reactivity and selectivity in these reactions.

2. Computational methods

We used Gaussian 09 [5] to carry out DFT calculations using the B3LYP functional [6], together with the standard 6-31G(d,p) basis set [7]. The optimizations were carried out using the Berny analytical gradient optimization method [8]. The global electrophilicity index ω is defined as $\omega = \frac{\mu^2}{2\eta}$, where μ is the electronic chemical potential and η the chemical hardness [9]. Both μ and η are determined in terms of the one-electron energies of the HOMO and LUMO frontier molecular orbital, E_{HOMO} and E_{LUMO}, as $\mu = \frac{\varepsilon_{HOMO} - \varepsilon_{LUMO}}{2}$ and $\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO}$ [10]. The empirical nucleophilicity index N [11] based on the HOMO energies obtained within the Kohn–Sham scheme [12] is defined as $N = \varepsilon_{HOMO}(\mathrm{Nu}) - \varepsilon_{HOMO}(\mathrm{TCE})$. Nucleophilicity was referred to tetracyanoethylene (TCE). Electrophylic P_k^+ and nucleophilic P_k^- Parr functions [13-20] were obtained by

analysis of the Mullikan atomic spin density (ASD) of the radical anion and radial cation of the reactants. The local electrophilicity and nucleophilicity indices were calculated as $\omega_K = \omega.P_k^+$, $N_K = N.P_k^-$ respectively. The stationary points were characterized by frequency computations in order to verify that the transition states have one and only one imaginary frequency. Intrinsic reaction coordinates (IRC) [21] pathways were plotted to verify the connectivity between the minima and associated transition states. Solvent effects of ethanol were taken into account through single point energy calculations using the polarizable continuum model (PCM) developed by Tomasi's group in the framework of the self consistent reaction field [22].



Scheme 1. Competitive chemio-isomeric pathways associated with the Michael addition reaction of β-hydroxyparthenolideswith amines such as pyrrolidine, morpholine, piperidine and 1-methylpiperazine

3. **Results and discussion**

3.1. *DFT analysis based on the global and local reactivity indexes*

In order to analyze the mechanism of the Michael reactions studied, we used DFT B3LYP/6-31G (d, p) to calculate the global indices shown in Table 1 the electronic chemical potential μ, chemical hardness η, global electrophilicity ω and nucleophilicity N of the 9β-hydroxyaminoparthenolides and the amines pyrrolidine (R1), morpholine (R2), piperidine (R3) and 1-methyl-piperazine (R4).

Table 1. Electronic chemical potential μ, chemical hardness η, electrophilicity ω and nucleophilicity N calculated using DFT B3LYP/6-31G (d, p) (eV)

System	μ	η	N	ω
9β-hydroxyparthenolides	-4.05	4.96	2.99	1.65
Pyrrolidine (R_1)	-1.88	7.22	4.03	0.24
Morpholine (R_2)	-1.91	7.63	3.79	0.23
Piperidine**(**R_3**)**	-1.70	7.57	4.03	0.19
1-methylpiperazine (R_4)	-1.46	7.03	4.54	0.15

Table 1 shows that:

- The electronic chemical potential of the 9β-hydroxyparthenolides is smaller than that of the four amines. Thereby, a very high the global electron-density transfer GEDT will be expected during the reaction, suggesting a polar mechanism for these reactions and implying that electron transfer takes place from the amines towards the 9β-hydroxyparthenolides.
- The electrophilicity index of the 9β-hydroxyparthenolides is greater than that of the amines, implying that in these reactions, the 9β-hydroxyparthenolides behave as electrophiles while the amines as nucleophiles.

3.2. Prediction of the chemioselectivity of the reaction using Parr functions

In polar organic reactions the most favorable reactive channel is that involving the initial two-center interaction between the most electrophilic and nucleophilic centers of the two reactants. Recently, Domingo et al. [23] proposed that the electrophilic and nucleophilic Parr functions, derived from the changes of spin

electron-density, reached via the GEDT process from the nucleophile to the electrophile as powerful tools in the study of the local reactivity in polar processes. We therefore analyzed the electrophilic Parr functions for 9β-hydroxyamino-parthenolides in order to predict the most favorable electrophile/nucleophile two-center interaction in these reactions and so explain the regioselectivity which was found experimentally (Figure 1).

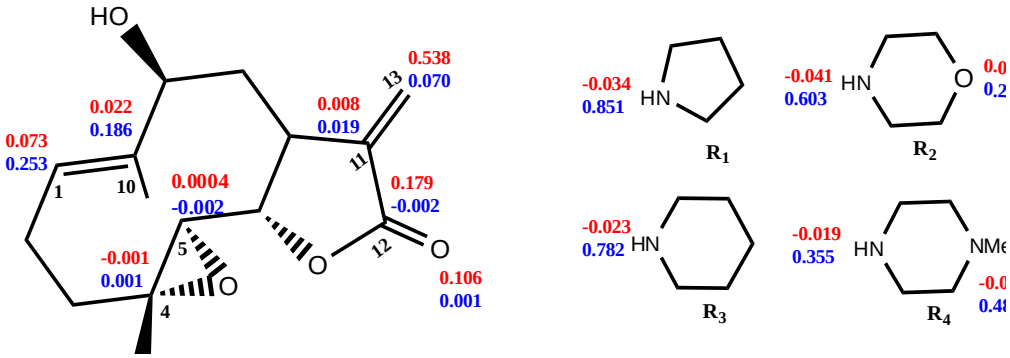


Figure 1. Electrophilic Parr functions in red and nucleophilic Parr functions in blue of 9β-hydroxyparthenolides and the amino-compounds

Analysis of the electrophilic Parr functions of the 9β-hydroxyparthenolides indicates that the C13 carbon atom is the most electrophilic center of the molecule, P_{13}^{+} =0.538, while analysis of the nucleophilic Parr functions of the amino-compounds indicates that the NH nitrogen is the most nucleophilic center of pyrrolidine, morpholine, piperidine and 1-methylpiperazine, P_{NH}^{-} = 0.851, 0.603, 0.782 and 0.355 respectively. Consequently, the most favored nucleophilic/electrophilic two-center interaction along an asynchronous single bond formation will take place between the C13 carbon of the 9β-hydroxyparthenolides and the NH nitrogen atom of the amino-compounds, leading to the formation of Pix chemoisomers. This is in good agreement with the experimental results.

3.3. Kinetic study

The kinetic study has been divided. Indeed, the Michael addition reaction between 9β-hydroxyparthenolides and the amino-compounds (R1, R2, R3 and R4) was studied and the solvent effects on these reactions were also discussed. In the second hand, the reaction was stereospecific and yielded exclusively a single stereoisomer with the R-configuration at the newly formed C-11 chiral carbon. We have analyzed the energetic aspects and geometrical parameters of the transition states.

3.3. What is the origin of the chemoselectivity?

The values of the enthalpies, entropies and Gibbs free energies and the relative ones of the stationary points involved in the Michael addition reactions of β-hydroxyparthenolides with amines (*pyrrolidine, morpholine, piperidineand 1-methylpiperazine*) are summarized in Table2. The Gibbs free energy profiles of these reactions are given in Figure 2. From Table 2, a comparison between the relative activation enthalpies associated with the two reactive pathways of the Michael addition reactions of β-hydroxyparthenolides with *pyrrolidine* indicates that the most favorable approach mode is now that associated with **TS1x** (ΔH =12.55 kcal mol^{-1}). Addition of the entropic contribution to the enthalpy increases the activation Gibbs free energy of this reactive channel to 32.63 kcal mol^{-1}. However, the analysis of the activation Gibbs free energies indicates that although the *isomer P1x* becomes the most favorable one as the consequence of the unfavorable negative activation entropy associated with **TS1n**, ΔS = -53.53cal mol^{-1} K^{-1}. These Michael addition reactions of β-hydroxyparthenolides with *pyrrolidine*shows a high selectivity as **TS1x** is 26.98 kcal mol^{-1} more favorable than **TS1n**. This is similar for the reactions of β-hydroxyparthenolides with *morpholine, piperidineand 1-methylpiperazine.* Consequently, the analysis of the thermodynamic parameters indicates that reactions of β-hydroxyparthenolides with amines (*pyrrolidine, morpholine, piperidineand 1-methylpiperazine*) are very chemoselective.

Table2 showed that the formation of products P_{1x}, P_{2x}, P_{3x}, P_{4x}, P_{2n} and $P_{3n}$was exothermic, while the formation of P_{1n} and P_{4n} was endothermic.

The activation barriers calculated showed that the formation of the chemoisomers P_{1x}, P_{2x}, P_{3x} and P_{4x} was kinetically favored relative to the formation of P_{1n}, P_{2n}, P_{3n} and P_{4n}.

A comparison between the relative activation enthalpies associated with the two reaction pathways of the Michael reaction between 9β-hydroxyparthenolides and amines(R_1, R_2, R_3 and R_4) indicated that the most favorable approach was associated with $TS_{1\alpha}$(ΔH = 12.55 kcal mol^{-1},10.66 kcal mol^{-1} , 12.55 kcal mol^{-1} and

6.27 kcal mol^{-1}). The addition of the entropic contribution to the enthalpy increased the activation Gibbs free energy of this reactive channel to 32.63 kcal mol^{-1}. Analysis of the Gibbs free energy of activation indicated that the attack at double bond C_{11}= C_{13} was the most favored. In addition, this reaction was exothermic by -6.27kcal.mol^{-1}. We would therefore expect to obtain a single isomeric compound from this addition reaction.

Table 2. Relative enthalpy (ΔH kcal mol^{-1}), relative Gibbs free energy (ΔG kcal mol^{-1} K^{-1}) and relative entropy (ΔS cal mol^{-1}), computed in gas and ethanol, for the stationary points involved in the Michael addition reaction between the 9β-hydroxyparthenolidesand the four amino-compounds (R_1, R_2, R_3 and R_4)

	Gas phase			Ethanol		
	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS
TS_1x	**12.55**	32.63	-47.07	13.17	25.72	-42.66
TS_1n	43.92	59.61	-53.53	44.55	58.35	-53.50
P_1x	-9.41	-6.27	-59.63	-5.64	-5.27	-56.50
P_1n	-7.53	8.35	-56.20	12.55	5.14	-50.46
TS_2x	**10.66**	4.39	-16.72	8.15	2.94	-11.02
TS_2n	11.23	29.49	-15.95	9.41	21.25	-11.73
P_2x	-21.96	-23.84	-18.36	-50.20	-28.86	-9.18
P_2n	-18.82	-21.37	-14.72	-30.12	-21.62	-9.18
TS_3x	**12.55**	22.59	-40.23	8.78	14.43	-43.03
TS_3n	25.10	40.16	-49.17	26.98	38.31	-48.96
P_3x	-12.55	-18.82	-40.16	-13.17	-16.31	-57.54
P_3n	-6.27	-19.22	-49.62	-8.78	-8.78	-51.70
TS_4x	**6.27**	19.45	-45.28	2.51	15.68	-43.74
TS_4n	16.94	30.74	-47.71	13.80	30.00	-49.98
P_4x	-13.80	-1.88	-49.58	-1.25	-18.19	-56.75
P_4n	-2.51	11.2	-49.62	-4.39	-11.29	-41.34

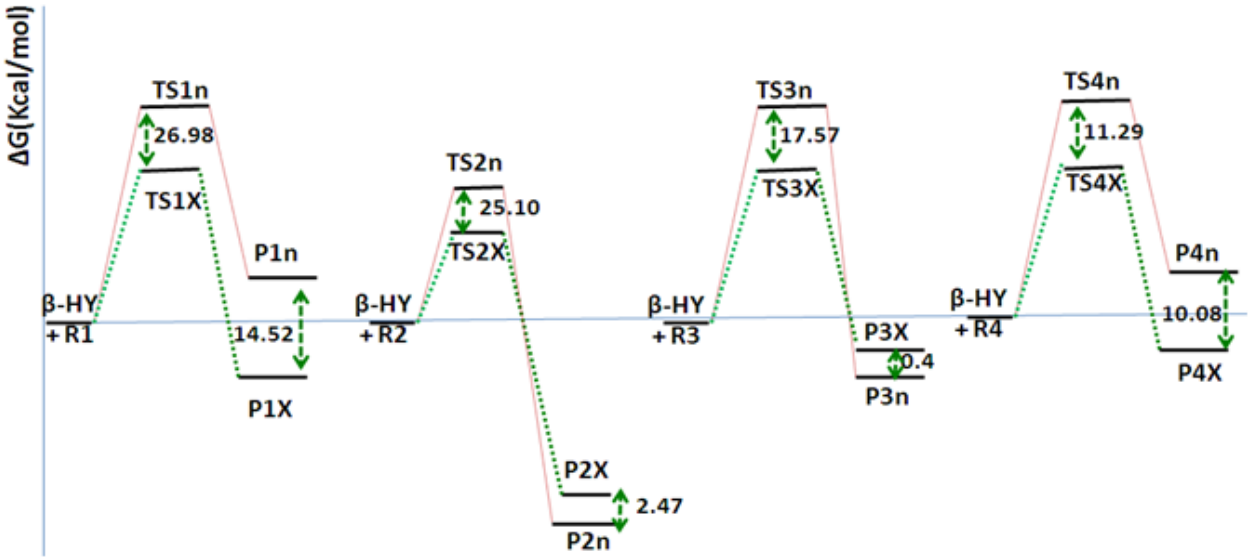


Figure 2. Gibbs free energy profile (ΔG, in kcal mol^{-1}) of the Michael addition reactions between β-hydroxyparthenolides and amines (*R1*: *pyrrolidine, R2: morpholine, R3: piperidineand R4: 1-methylpiperazine*).

3.3. **Understanding the origin of the α/β selectivity**

The calculation of the energies of the reactants, the energies of the products obtained, TSiα and TSiβ transition energies at the C_{11}= C_{13} double bond of 9β-hydroxyparthenolides and the difference in transition energy showed that the attack was kinetically preferred at the α side (Table 3).

According to transition state theory (TST), the second order rate constant (k_{TST}) at a given temperature (T) can be determined using the following equation [24] :

$$K_{TST} = \frac{k_B T}{h C_0} e^{\frac{-\Delta G^{\#}}{RT}} \quad (1)$$

Where k_B, h, C_0, and R denote Boltzmann's constant, Planck's constant, standard concentration (1 mol l^{-1}) and the universal gas constant, respectively. Using equation (1), the ratio of the products Pα and Pβ can be calculated as follows:

$$\frac{K\alpha}{K\beta} = e^{\frac{\Delta\Delta G^{\#}}{RT}} = 10^{\frac{TS\beta - TS\alpha}{RT.Ln10}} \approx 10^{\frac{(TS\beta - TS\alpha)1000}{1358.6}} \quad (2)$$

The results (table 3) showed that the reaction rate was higher on the α side than on the β side. In other words, the formation of $P_{i\alpha}$ products (α side) was favored relative to formation of $P_{i\beta}$ products (β side): this agrees with experimental results [4, 25-27].

Table 3. Relative Gibbs free energy (kcal mol^{-1}) for the stationary points of the α and β sides to the double bond C_{11}= C_{13} involved in the Michael reaction between hydroxyparthenolides and amino-compounds (R_1, R_2, R_3 and R_4) calculated in gas using DFT B3LYB/6-31G (d, p)

System	ΔG (α side) (kcal mol^{-1})	ΔG (β side) (kcal mol^{-1})	TSβ - TSα	Kα/Kβ
TS_{1x}	32.63	34.17	1.54	$10^{1.133}$ = 13.58
P_{1x}	-6.27	-5.64		
TS_{2x}	4.39	8.15	3.76	$10^{2.767}$ = 585.5
P_{2x}	-23.84	-21.20		
TS_{3x}	22.59	23.78	1.19	$10^{0.875}$ = 7.5
P_{3x}	-18.82	-13.17		
TS_{4x}	19.45	20.51	1.06	$10^{0.780}$ = 6
P_{4x}	-1.88	-1.25		

The results obtained showed that the activation energy leading to products $P_{ix\alpha}$ ($P_{1x\alpha}$, $P_{2x\alpha}$, $P_{3x\alpha}$ and $P_{4x\alpha}$, namely the products obtained at α side) was lower than the activation energy leading to $P_{ix\beta}$ products ($P_{1x\beta}$, $P_{2x\beta}$, $P_{3x\beta}$, and $P_{4x\beta}$, namely the products obtained at the β side). Indeed, the energy barriers of the $P_{ix\alpha}$productsare32.63, 4.39, 22.59 and 19.45 kcal/mol for products $P_{1x\alpha}$, $P_{2x\alpha}$, $P_{3x\alpha}$ and $P_{4x\alpha}$ respectively, while those for $P_{ix\beta}$ products are 33.17, 8.15, 23.78and20.51kcal/mol assigned to $P_{1x\beta}$, $P_{2x\beta}$, $P_{3x\beta}$ and $P_{4x\beta}$ respectively, showing that the α side was kinetically favored. The reaction energy for the α side was-6.27, -23.84, -18.82 and- 1.88 kcal/mol for the $P_{1x\alpha}$, $P_{2x\alpha}$, $P_{3x\alpha}$ and $P_{4x\alpha}$ respectively, while equivalent values for the β side were -5.64, -21.20, -13.17 and -1.25 kcal/mol for $P_{1x\beta}$, $P_{2x\beta}$, $P_{3x\beta}$ and $P_{4x\beta}$ respectively, showing that the attack at the α side was thermodynamically favored.

To better understand the difference between the transition state energies, we optimized the most stable structure of 9β-hydroxyparthenolides (figure 3).

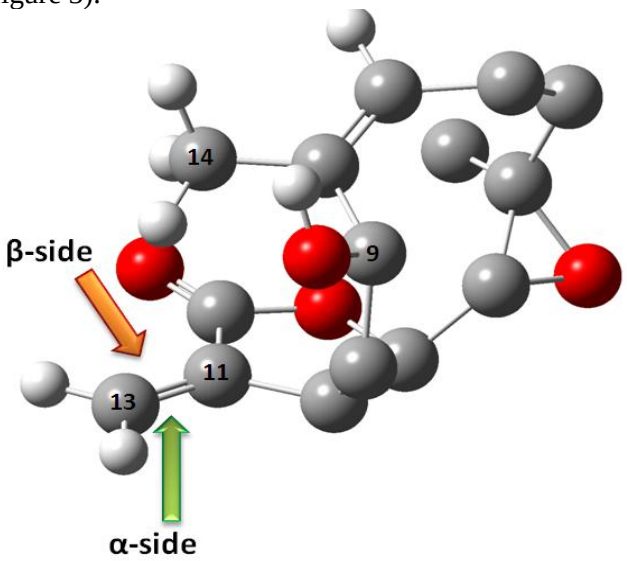


Figure 3. Optimized equilibrium structure of 9β-hydroxyparthenolides

We see from the optimized structure that the methyl C_{14} and hydroxyl carried by thecarbonC_9 represent asteric hindrance at the β side, but there was no such hindrance at α side which was preferred.

The bond lengths for reaction stationary points in gas phase and in solvent are given in Figure 4.

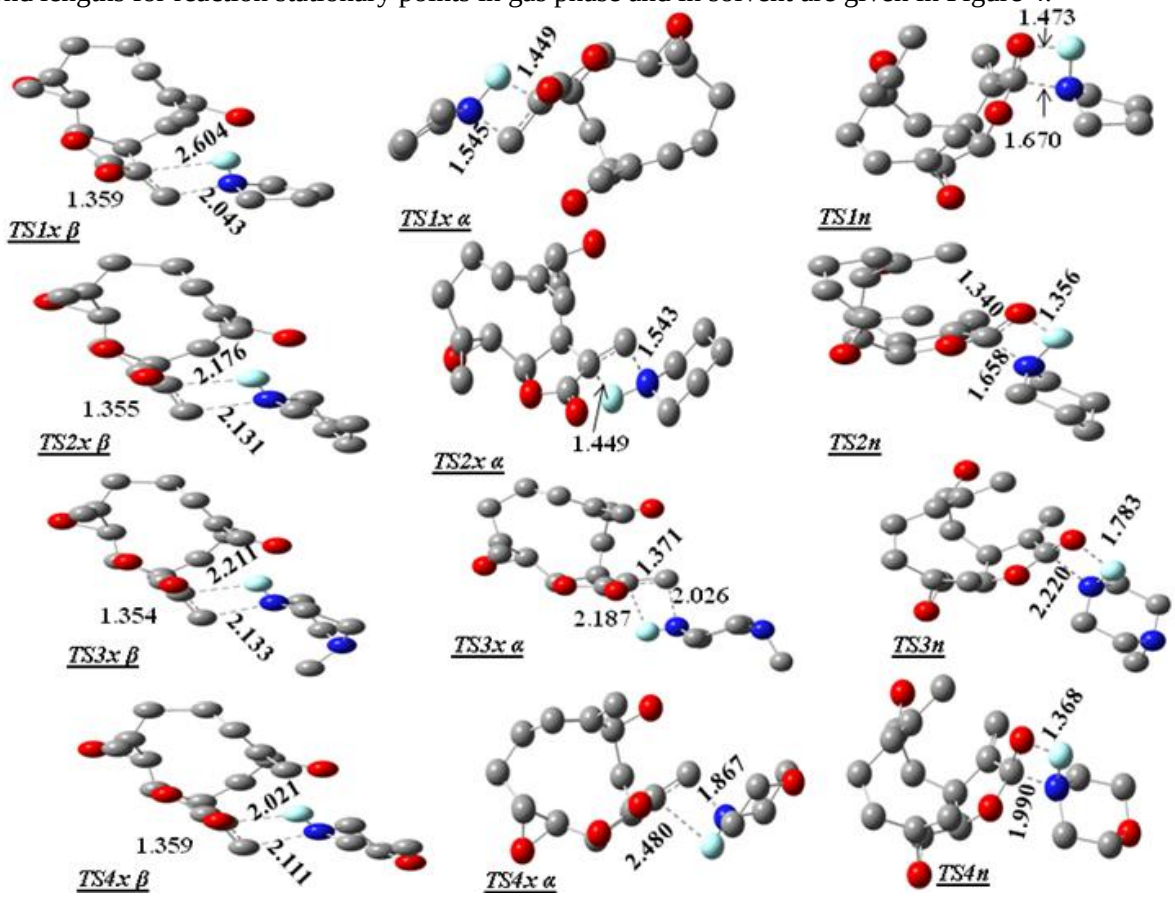


Figure 4. B3LYP/6-31G(d,p) optimized geometries of the TSs in the Michael addition reactions of β-hydroxyparthenolides with amines (*pyrrolidine, morpholine, piperidineand 1-methylpiperazine*)

As shown in figure 4, the lengths of the NH–C11 and NH–C12 forming bonds are 2.043, 1.545 and 1.670 at TS_1xβ, TS_1xα and TS_1n respectively, the NH–C11 and NH–C12 forming bonds are 2.131, 1.543 and 1.6580 at TS_2xβ, TS_2xα and TS_2n respectively, the NH–C11 and NH–C12 forming bonds are 2.133, 2.026 and 2.220 at TS_3xβ, TS_3xα and TS_3n respectively, the NH–C11 and NH–C12 forming bonds are 2.111, 1.867 and 1.990 A at TS_4xβ, TS_4xα and TS_4n respectively. It is obvious that the most favorable TS_1xα displays the highest degree of asynchronicity.

Conclusion

The mechanism of the chemoselectivity and the stereoselectivity for the Michael addition reaction leading to the formation of the 9β-hydroxyamino-parthenolides derivatives was studied using DFT B3LYP/6-31G (d, p).
The theoretical results obtained enabled us to conclude that the activation energies and reactivity indices calculated correctly predicted the chemoselectivity experimentally observed in these reactions. The analysis of the substituent effect on the α/β stereoselectivity of the double bond C_{11}= C_{13} for various amines derivatives showed that the α-side was favored, in agreement with the experimental results

References

1. Saidi M. R., Pourshojaei Y., Aryanasab F., *Synthetic Communications*, 39 (2009) 1109.
2. Yadav J. S., Reddy R. A., GopalRao Y., Narsaiah A. V., Reddy B. V. S., *Lett. Org. Chem*., 4 (2007) 462.
3. Moumou M., Benharref A., Daran J. C., Mellouki F., Berraho M., *ActaCryst*. E68 (2012) o386.
4. Moumou M., El Bouakher A., Allouchi H., El Hakmaoui A., Benharref A., Mathieu V., Guillaumet G., Akssira M., *Bioorg. Med. Chem. Lett*., 24 (2014) 4014.

5. Zhao Y., Truhlar D.G., *J PhysChem A*, 108, (2004) 6908.
6. Hehre W.J., Radom L., Schleyer P.V.R., J.A. Pople, Ab Initio Molecular Orbital Theory.Wiley, New York, 1986.
7. Schlegel H.B., *J ComputChem*, 3, (1982) 214.
8. Frisch M. J. et al., Gaussian 09, Revision A 02, Gaussian Inc., Wallingford CT, 2009.
9. Parr R. G., Szentpaly L. V., Liu S., *J. Am. Chem. Soc*., 121 (1999) 1922.
10. Parr R. G., Pearson R. G., *J. Am. Chem. Soc*., 105 (1983) 7512.
11. Domingo L. R., Pérez P., *Org BiomolChem*, 9 (2011) 7168.
12. Kresse G., Furthmuller J., *J; Com. Mat. Sci*., 6 (1996) 50.
13. Zeroual A., Benharref A., El Hajbi A., *J Mol Model*.21 (2015) 2594.
14. Domingo L. R., Rios-Gutierrez M., Emamian S., *RSC Adv*., 6 (2016) 17064.
15. Jornet D., Bosca F., Andreu J. M., Domingo L. R., Tormos R., Miranda M. A., *J. Photochem. Photobiol., B*,155 (2016) 1.
16. Zeroual A., Hammal R., El Hajbi A., *J. Com. M. M. D*., 15 (2015) 97.
17. Zeroual A., Hammal R., Benharref A., El Hajbi A., *Mor. J. Chem*. 3 (2015) 698.
18. Domingo L. R., Ríos-Gutiérrez M., Pérez P., *Tetrahedron*, 72 (2016) 1524.
19. Zeroual A., Zoubir M., Hammal R., Benharref A., El Hajbi A., *Mor. J. Chem*. 3 (2015) 356.
20. Zeroual A., Hammal R., Ryachi K., Barhoumi A., Benharref A., El Hajbi A., *I. J. I. A. S*., 8 (2014) 750.
21. Fukui K., *J. Phys. Chem*., 74 (1970) 4161.
22. Tomasi J., Persico M., *Chem. Rev*. 94 (1994) 2027.
23. Domingo L. R., Perez P., Saez J. A., *RSC Adv*., 3 (2013) 1486.
24. Zeroual A., El Hajbi A., *Can. Chem. Trans*. 3 (2015) 430.
25. Moumou M., Benharref A., Daran J. C., Elhakmaoui A., Berraho M., *Acta Crysta*. E67 (2011) o2768.
26. Moumou M., Benharref A., Avignant D., Oudahmane A., Akssira M., Berraho M., *Acta Cryst*. E67 (2011) o2226.
27. Moumou M., Benharref A., Oudahmane A., Mellouki F., Berraho M., *Acta Cryst*. E68 (2012) o167.

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