



The origin of diastereoselectivity in the Michael addition reaction: a computational study of the interaction between CH-acidic Schiff base and α,β -unsaturated ketones

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ABSTRACT

Theoretical quantum chemical computations were applied in answering a question set from the experiment: why the Michael addition to chalcones is a highly diastereoselective process? Density functional theory methods were used to examine the mechanistic pathways for the Michael reaction of [(diphenylmethylene)amino]acetonitrile—CH-acidic Schiff base with α,β -unsaturated ketones (enones). Transition state structures, prereactive complexes and reaction path energetics for different channels of the reaction are determined. The theoretical predictions reveal that the difference in the stabilization of the prereactive complex explains adequately the experimental findings for diastereoselectivity of the addition to benzylideneacetophenone (chalcone), compared to the nonselective process in the case of 4,4-dimethyl-1-phenyl-1-pentene-3-one.

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1. Introduction

The conjugate addition (Michael reaction) is one of the fundamental C–C bond-forming reactions in organic chemistry.^{1,2} The diastereoselective Michael reaction of stabilized carbanions with α,β -unsaturated ketones (enones) and esters, followed by hydrolysis, is one of the most important methods for preparation of 2-alkyl-2-aminoacids and their derivatives.^{3–5} Due to its importance in synthetic organic chemistry, the enantioselective Michael addition to α,β -unsaturated carbonyl compounds has been extensively studied.^{6–8} The role of the catalyst, as well as the origin of enantioselectivity, has been studied for the Michael addition of malonitrile to α,β -unsaturated imides catalyzed by bifunctional thiourea catalysts.⁹ Theoretical methods have been applied to studies of the Michael addition mechanism involving different substrates, and for rationalising experimental observation.^{9–13} The mechanism of the enantioselective control of an organocatalyst with central and axial chiral elements in the Michael addition of 2,4-pentandione to a nitroalkene is investigated using density functional theory (DFT) calculations.¹⁰ Density functional based numerical approaches for computing orbital and atomic reactivity

indices are employed in the study of selectivity descriptors for the 1,4 Michael addition reaction.¹⁴

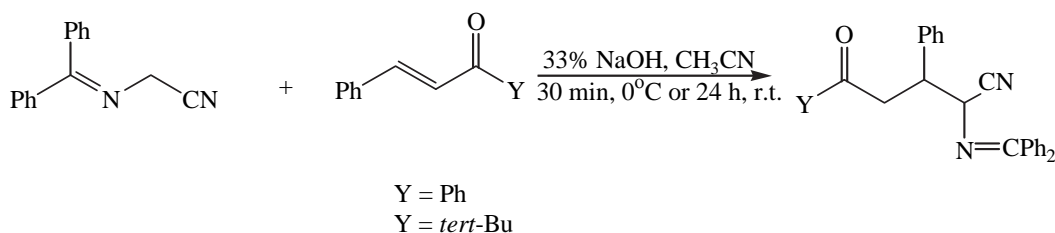
Recently we reported a synthesis of the substituted 2-amino-5-oxonitriles by the reaction of [(diphenylmethylene)amino]acetonitrile and some α,β -unsaturated ketones.^{15,16} Selective removal of the diphenylmethylene protecting group, followed by in situ cyclization gave 3,5-disubstituted-3,4-dihydro-2H-pyrrole-2-carbonitriles. The present computational study has been initiated by the experimentally established highly diastereoselective Michael addition of [(diphenylmethylene)amino]acetonitrile to chalcones, compared to the nonselective addition to an alkyl containing α,β -unsaturated ketone. It was of interest to compare the energy profiles of the Michael addition reaction of [(diphenylmethylene)amino]acetonitrile to α,β -unsaturated ketones (enones) of two types: (1) benzylideneacetophenone (chalcone); (2) α,β -unsaturated ketone containing *t*-Bu and Ph groups—4,4-dimethyl-1-phenyl-1-pentene-3-one. In this way it would be possible to assess the influence of the substitution at both sides of the enone system, on the energy characteristics and diastereoselectivity of the addition reaction.

2. Results and discussion

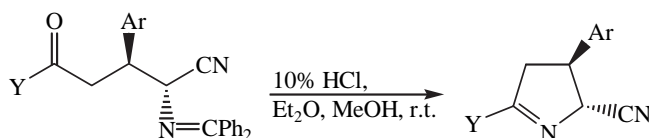
The Michael reaction of [(diphenylmethylene)amino]acetonitrile (CH-acidic Schiff base) with enones was carried out in aqueous conditions (33% NaOH, CH₃CN, 0 °C) in our laboratory.¹⁵ In the present paper, the mechanism of Michael addition of the CH-acidic

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Schiff base to two types of substrates is studied (Scheme 1): (1) diaryl α,β -unsaturated ketone (benzylideneacetophenone, chalcone) and (2) alkyl containing α,β -unsaturated ketone (4,4-dimethyl-1-phenyl-1-pentene-3-one). With benzylideneacetophenone and substituted arylmethylenacetophenones (chalcones) (Scheme 1) the reaction proceeds with high diastereoselectivity—the diastereoisomeric ratio 99:1 (^1H NMR Spectroscopy) was observed for the crude products. In this conditions the reaction proceeds under kinetic control—the diastereoisomeric ratio is constant with the time (99:1, ^1H NMR). The stereochemistry of the obtained 2-amino-5-oxonitriles (Scheme 1) was proved from the established stereochemistry of the respective substituted 3,4-dihydro-2*H*-pyrrole-2-carbonitriles (Scheme 2).¹⁵



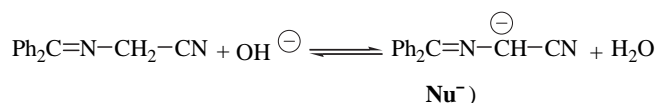
Scheme 1. Michael addition of CH-acidic Schiff base to α,β -unsaturated ketones (enones): enone **A**: Y=Ph and enone **B**: Y=*t*-Bu.



Scheme 2. Cyclisation of 2-amino-5-oxonitriles to 3,5-disubstituted 3,4-dihydro-2*H*-pyrrole-2-carbonitriles.

On the other hand, under the same reaction conditions, the interaction between the starting CH-acidic Schiff base and alkyl containing α,β -unsaturated ketone—4,4-dimethyl-1-phenyl-1-pentene-3-one (Scheme 1) gives a diastereoisomeric mixture (diastereoisomeric ratio 1:1) of the substituted 2-amino-5-oxoheptanenitrile.¹⁶

In order to understand the stereoisomerism of the Michael 1,4-addition reaction, the mechanism of the process has to be studied in details. In the course of our calculations, we presume that the reactants are deprotonated Schiff base and the corresponding α,β -unsaturated ketone. This is due to the high experimental reactivity of the starting CH-acidic Schiff base in the presence of OH^- species in the two phase system ($\text{CH}_3\text{CN}/\text{aq NaOH}$). In fact immediate deprotonation of the starting nitrile occurs, on and an activated nucleophile (further denoted as Nu^-) is formed (Scheme 3).



Scheme 3. Deprotonation of CH-acidic Schiff base and formation of the active nucleophile.

In general, depending on the mutual orientation of the reactants (substituted enone and Nu^-), two diastereoisomers resulted as reaction products: RS (SR) and SS (RR). For convenience, the reaction path leading to the diastereomeric product RS (SR) is denoted as channel 1 and the path resulting in the SS (RR) diastereoisomer—as channel 2 (Scheme 4).

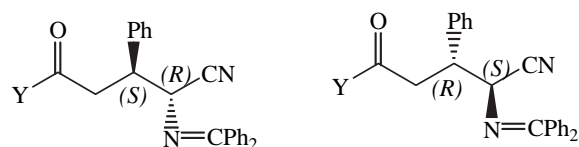
As already mentioned, it is experimentally proven that the diastereoisomeric excess of the 2*R*,3*S* (2*S*,3*R*) form is 98% when the reaction takes place with chalcone—enone **A**.¹⁵ The two

channels for the addition reaction with formation of RS (channel 1) or SS (channel 2) diastereoisomers are explored here, studying the reaction of benzylideneacetophenone (chalcone) and 4,4-dimethyl-1-phenyl-1-pentene-3-one (alkyl containing α,β -unsaturated ketone) with Nu^- by applying DFT quantum chemical calculations with B3LYP¹⁷ and M05¹⁸ functional and 6-31G(d,p)^{19–21} basis set. Single point calculations at B3LYP/6-31+G(d,p)//B3LYP/6-31 G(d,p) and M05/6-31+G(d,p)//M05/6-31 G(d,p) have been carried out in order to check the energetic results.²² Conformational analysis for the chalcone showed that *trans* isomer is energetically favoured. This is also a well established experimental fact.⁵ Therefore, *trans* configurations for the reacting α,β -unsaturated ketones are considered as substrates in theoretical

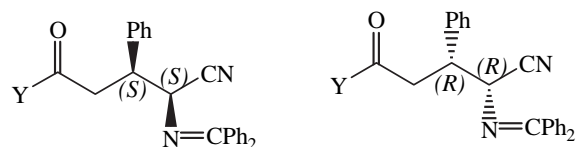
calculations. The optimised structure of the base Nu^- is shown in Figure 1.

Transition state structures for both channels of the addition leading to RS (channel 1) and SS (channel 2) diastereoisomers for substrates enone **A** (chalcone) and enone **B** (alkyl containing α,β -unsaturated ketone) are optimised at B3LYP/6-31G(d,p) and M05/6-31G(d,p) levels of theory. The optimised structure of the transition state for reaction channel 1 for enone **A** (chalcone)—TS_RS is

Channel 1: Diastereoisomer 2*R*, 3*S* (2*S*, 3*R*)



Channel 2: Diastereoisomer 2*S*, 3*S* (2*R*, 3*R*)



Scheme 4. Diastereoisomers of 2-amino-5-oxonitriles.

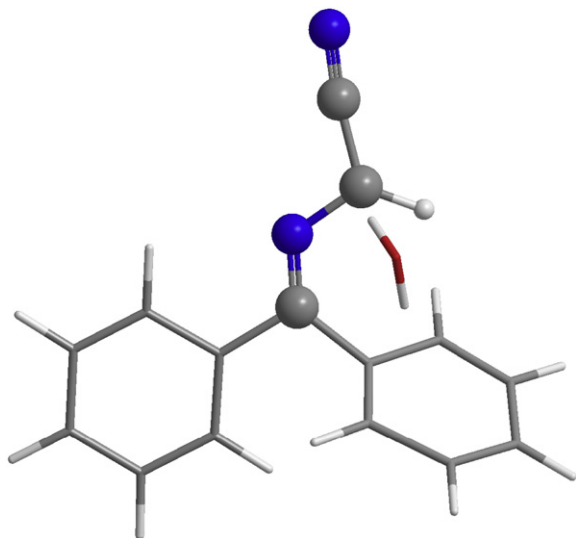


Figure 1. Optimised structure of the deprotonated Schiff base from DFT computations.

depicted in Figure 2. The main vector of the imaginary vibrational frequency, characterising the transition state TS_RS is also shown in Figure 2. It can be seen from the figure that the principal component of the transition vector corresponds to a C–C bond formation. The length of this newly created bond in the transition state structures for the two channels of the reaction is about 2.1 Å, compared to R_{C-C} in the next forming intermediates being ~ 1.6 Å.

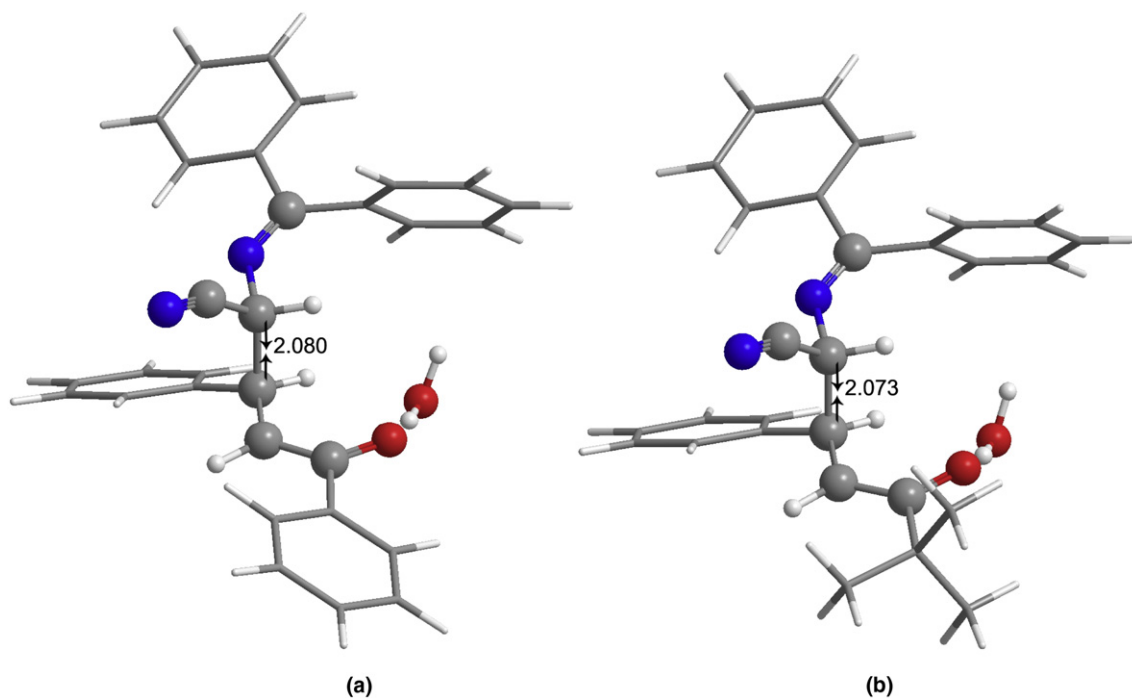


Figure 2. B3LYP/6-31G(d,p) optimised transition state structure TS_RS for channel 1 of the reaction between [(diphenylmethylene)amino]acetonitrile and (a) enone A—benzylideneacetophenone (chalcone) and (b) enone B.

In all cases, IRC calculations in the forward direction from the transition states lead to intermediate structures of respective enolates I_SS and I_RS. The products of the addition reaction—respective 2-amino-5-oxonitriles are experimentally isolated and the stereochemistry of the structures has been proven by NMR spectroscopy.¹⁵ IRC calculations backward from the transition states

leads to prereactive complexes C_RS for channel 1 and C_SS for channel 2.

Computed, relative to reactants, energies for all structures along the reactions pathways are summarised in Table 1. Because of the ionic nature of some species, as well as taking into account that the

Table 1

B3LYP/6-31G(d,p) optimised, relative to reactants, energies (kcal/mol) for stationary points along the reaction pathway of Michael addition of deprotonated Schiff base Nu[−] to enone A: benzylideneacetophenone (chalcone) and enone B: 4,4-dimethyl-1-phenyl-1-pentene-3-one

| Structure | enone A | | | | enone B | | | |
|----------------|------------|------------|---------------------|-----------------------|------------|------------|---------------------|-----------------------|
| | ΔE | ΔG | $\Delta G_{H_2O}^a$ | $\Delta G_{CH_3CN}^a$ | ΔE | ΔG | $\Delta G_{H_2O}^a$ | $\Delta G_{CH_3CN}^a$ |
| R ^b | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| C_SS | −16.30 | −3.60 | 9.05 | 8.36 | −8.36 | 5.95 | 17.31 | 16.06 |
| C_RS | −11.96 | 0.74 | 14.09 | 12.53 | −6.27 | 7.44 | 17.52 | 15.87 |
| TS_SS | −1.72 | 15.15 | 25.62 | 24.39 | 1.98 | 17.89 | 27.67 | 26.74 |
| TS_RS | −1.12 | 14.87 | 24.62 | 23.39 | 0.63 | 17.16 | 27.60 | 26.54 |
| I_SS | −9.04 | 7.55 | 15.71 | — | −9.76 | 9.50 | 18.40 | 17.84 |
| I_RS | −9.79 | 6.53 | 14.20 | 14.39 | −7.51 | 9.08 | 19.46 | 19.52 |

^a From SP IEFPCM B3LYP/6-31G(d,p) computations.

^b Reactants are: respective enone and the complex [Nu[−]⋯H₂O].

reaction is carried out in solution, it is important to evaluate the solvent effect on the energetics of the reaction. Results from SP IEFPCM calculations in water and acetonitrile are also presented in Table 1. For more precise energy estimation, SP calculations with 6-31+G(d,p) basis set has also been done and the data are given in Table 2.

It can be seen from data in Table 1 that for both substrates enone A and enone B relative to reactants energies and Gibbs free energies for the transition states, TS_RS (channel 1) and TS_SS (channel 2) are very close in the gas phase as well as in solution. Therefore for both substrates activation energies for the two channels of the reaction are very close. This conclusion disagrees with the

Table 2

Transition states energies (relative to the respective prereactive complex, kcal/mol) for channel 1 and channel 2 of the addition of Nu⁻ to enone **A**: benzylideneacetophenone and enone **B**: 4,4-dimethyl-1-phenyl-1-pentene-3-one

| | B3LYP/6-31G(d,p) | | | B3LYP/6-31+G(d,p)// B3LYP/6-31G(d,p) | M05/6-31G(d,p) | | |
|----------------|------------------|-----------------------------------|-------------------------------------|---|----------------|-----------------------------------|--|
| | ΔG | $\Delta G_{\text{H}_2\text{O}}^a$ | $\Delta G_{\text{CH}_3\text{CN}}^a$ | $\Delta G_{\text{H}_2\text{O}}^a$ | ΔG | $\Delta G_{\text{H}_2\text{O}}^a$ | |
| enone A | | | | | | | |
| Channel 1 (RS) | 14.13 | 10.53 | 10.86 | 9.17 | 13.84 | 11.97 | |
| Channel 2 (SS) | 18.75 | 16.57 | 16.03 | 15.81 | 15.69 | 13.62 | |
| enone B | | | | | | | |
| Channel 1 (RS) | 9.73 | 10.09 | 10.68 | 9.42 | 9.81 | 11.01 | |
| Channel 2 (SS) | 11.94 | 10.36 | 10.68 | 9.40 | 12.60 | 11.83 | |

^a From SP IEFPCM calculations at the respective level of theory.

experimental finding that the diastereomeric ratio for the addition reaction to benzylideneacetophenone (enone **A**) is 99:1 in favour of RS (SR) diastereomer.

In contrast to energies of the transition states, we found that the energies of the prereactive complexes C_RS (channel 1) and C_SS (channel 2) differ substantially for substrate benzylideneacetophenone (enone **A**), but these quantities are very close for substrate 4,4-dimethyl-1-phenyl-1-pentene-3-one (enone **B**), (Table 1). The energies of the transition states relative to respective prereactive complex—C_RS for channel 1 and C_SS for channel 2 for the two substrates are given in Table 2.

The data in Table 2 clearly show that the intrinsic free energy barriers in the gas phase as well as in solution for the reaction with substrate enone **B**: 4,4-dimethyl-1-phenyl-1-pentene-3-one are

the respective energy barrier for channel 2 (leading to SS diastereomer) by 4.62 kcal/mol in the gas phase and 6.04 kcal/mol in water at the DFT level of theory. B3LYP/6-31+G(d,p) computations also confirm this energy estimation showing difference in the intrinsic energy barriers of 6.64 kcal/mol (Table 2). The predicted difference in energy barriers for channel 1 and channel 2 is in accord with the experimentally obtained diastereoselectivity of the Michael reaction for enone **A**: chalcone. Diastereoisomeric excess of 98 % in favour of diastereomer 2R,3S (2S,3R) (channel 1) is experimentally obtained.¹⁵ The theoretically predicted energy difference can be explained with the structures of prereactive complexes for channel 1 and 2 for substrate benzylideneacetophenone (chalcone). The optimised structures of the two complexes C_RS and C_SS are shown in Figure 3.

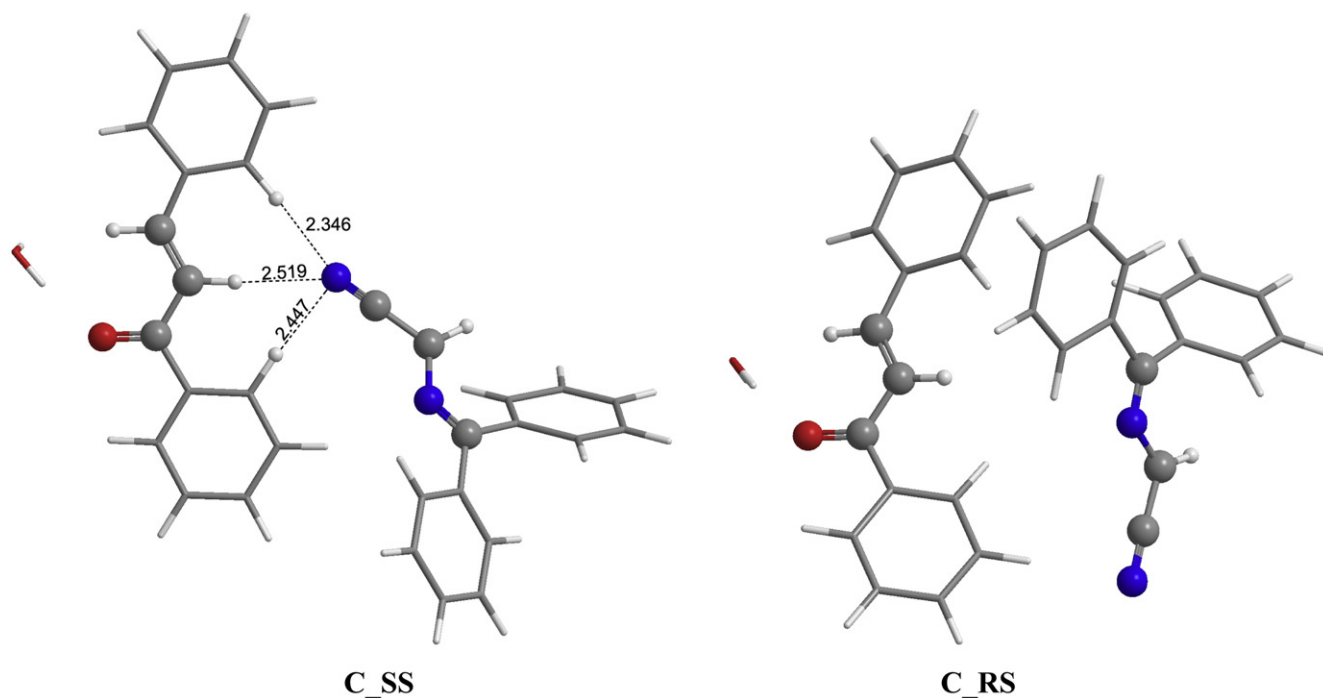


Figure 3. B3LYP/6-31G(d,p) optimised structures of the prereactive complexes C_SS and C_RS for the addition of [(diphenylmethylene)amino]acetonitrile to benzylideneacetophenone (chalcone).

almost equal for both channels leading to RS and SS diastereoisomers. These data correspond to the experimentally obtained diastereoisomeric ratio 1:1 for that reaction.

In the case of enone **A**: benzylideneacetophenone (chalcone) theoretical prediction shows that the intrinsic activation free energy for channel 1 (leading to RS diastereomer) is lower than

It can be seen from Figure 3 that complex C_SS is more stable than C_RS because of weak hydrogen bonds between chalcone and the nitrile group from the nucleophile. These stabilising associations do not occur in complex C_RS due to unfavourable spatial orientation of the two molecules. Such hydrogen bond associations do not exist in the prereactive complexes for enone **B**. The

optimised structures of the prereactive complexes C_SS and C_RS for the addition of [(diphenylmethylene)amino] acetonitrile to enone **B**: 4,4-dimethyl-1-phenyl-1-pentene-3-one are given in Figure S1 in the Supplementary data.

Thus, theoretical results show that the diastereoselectivity of Michael addition of CH-acidic Schiff base [(diphenylmethylene)amino]acetonitrile to chalcone can be explained in terms of stability of the prereactive complexes formed along the reaction path.

3. Conclusions

Density functional and ab initio methods were applied in examining the possible mechanistic pathways for the Michael reaction of [(diphenylmethylene)amino]acetonitrile (CH-acidic Schiff base) with two substrates: enone **A**: benzylideneacetophenone (chalcone) and enone **B**: 4,4-dimethyl-1-phenyl-1-pentene-3-one (alkyl containing α,β -unsaturated ketone).

Transition state structures and energies were determined for the two channels of the reaction leading to RS and SS diastereoisomers. Diastereoselectivity of the Michael addition to chalcones is rationalised and explained in terms of stability of the prereactive complexes formed. The theoretical predictions reveal that for benzylideneacetophenone, the RS diastereomeric channel results in considerable energy savings, and this is the most favourable pathway of the reaction in full agreement with the experiment showing a diastereoisomeric excess of 98% in favour of the 2R,3S (2S,3R) diastereomer. Comparisons are made with the energetics of the Michael addition to 4,4-dimethyl-1-phenyl-1-pentene-3-one. In contrast to benzylideneacetophenone, Michael reaction proceeds via two energetically equal channels, in agreement with the experimentally obtained diastereoisomeric ratio of 1:1.

4. Computational methods

Computations were carried out with Gaussian 03 program package.²³ Stable structures and transition states along the reaction pathways were fully optimised by applying DFT^{24,25} method with two functionals B3LYP¹⁷ and M05¹⁸ in conjunction with the 6-31G(d,p)^{19–21} basis set. The critical points along the reaction path were further characterised by analytic computations of harmonic vibrational frequencies at the same level/basis set. Transition state structures were located by the traditional transition state optimisation using the Berny algorithm,²⁶ and then checked by intrinsic reaction coordinate (IRC) computations at the same level of theory.²⁷ Single point computations at DFT level with 6-31+G(d,p) basis set were performed for more precise energy prediction.²²

The effect of solvent was assessed by using the Polarized Continuum Model (IEFPCM) incorporated in the Gaussian package.^{28,29} The standard dielectric constants for water and acetonitrile implemented in the Gaussian program were employed. Single point IEFPCM B3LYP/6-31+G(d,p) computations on the optimised B3LYP/6-31G(d,p) geometry were performed for estimating the changes in

energy profile of the reaction in the presence of water, as far as experimentally reaction was carried out in the alkaline water solution.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.107. These data include MOL files and InChiKeys of the most important compounds described in this article.

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