A Theoretical Kinetic and Thermodynamics Study about the Effect of Substituents in the Synthesis of Chalcones

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Introduction

Chalcones are natural compounds found in plants with two aromatic rings united by a fragment of three *α,β*-unsaturated carbons with one carbonyl. They can be formed by the chemical modification of several precursors. The most common path of synthesizing this compound is from aldol condensation of aromatic ketones and aromatic aldehydes1 – Claisen-Schmidt mechanism[4] (Figure 1).

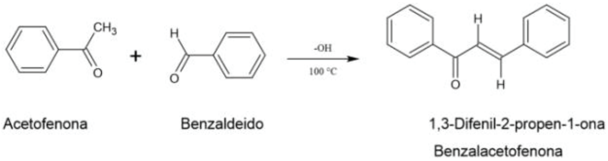

Figure 1. Generic Claisen-Schmidt reaction

Some chalcones are biologically active, and among these activities we can mention the following characteristics: cytotoxicity, antimicrobial, anti-inflammatory and antimalarial. Sofalcone, for example, was approved for clinical trials of anti-Helicobacter pylori (H. pylori activity)[6]. An essential aspect of chalcone studies is understanding their reaction mechanisms; the kinetic study of this reaction is very important for the elucidation of the step-by-step synthesis of these molecules.

Although there are several experimental works that estimated the kinetic rate constant[1,2,5,7] and proposed mechanisms[1,2] for this reaction, there are few theoretical studies4 in this reaction.

In this paper, we reported an understanding of the effect of the different substituents on these reactions and an estimative of the kinetic rate constant. It was characterized by the main reactive channels of the studied reactions. Then, we predicted if the condensation is viable, if it is energetically favorable, and what more stable compound among the studied.

Methods

To develop this work, we characterized the transition states with the Density Functional Theory (DFT) from the existence of only one negative frequency for each substituent. The quantum calculations were performed at the B3LYP /6-311++G** level of calculation as implemented in the GAUSSIAN09 suit of programs.

The transition states were located using the 'Synchronous transit-guided quasi-Newton' method. The transition states were used to estimate the activation energies and build an energetic profile of these reactions using different substituents - NO_2, Cl, OH, H, NH_2 and

CH_3O (MeO). The Zero Point of Energy (ZPE) was used to correct the activation energies.

The estimative of the rate constant considered only the first step (abstraction of hydrogen of ketone molecule by anion hydroxyl) of the reaction (hypothesis of the rate determining step, see Figure 2). The rate constant was calculated using the Transition State Theory (TST)3 including Wigner correction tunneling.[8]

Results and Discussion

In the first step of the Claisen-Schmidt mechanism for the formation of a generic chalcone, the anion hydroxyl OH-, a basic catalyst, abstracts hydrogen of ketone molecule. The first transition state, which was found, and the mechanism of the first step of chalcone synthesis are represented in Figure 2.

With the description of the first step study of these reactions using DFT and QST2 methodology, it was possible to estimate the rate constant. This kinetic data is temperature dependent and was fitted with models of Arrhenius law, obtaining values for the activation energy (Ea) for each substituent in meta position of the aromatic ring of the ketones, as can be seen in Table 1.

Table 1. Values of barrier height and activation energy (Arrhenius law) in the first step of synthesis of chalcones. Units are in kJ.mol^{-1}.

Chalcones	Barrier Height	Activation Energy	Literature
Chalc-NO2	8.0	16.5	-
Chalc-Cl	15.3	22.7	-
Chalc-OH	17.9	24.8	-
Chalc-H	18.2	25.1	32,61
Chalc-NH2	20.4	27.3	-
Chalc-MeO	23.5	30.5	41,02

Based on the analysis of the first step of the formation mechanisms of chalcones in Table 1, it was perceived that the barrier height and the activation energy tend to be smaller when the substituents are withdrawing groups and to favor the reaction, making it faster.

Thermodynamic parameters of energy variation between products and reactants have been calculated for the first step of the reaction (Table 2). All of the process is exothermic and spontaneous.

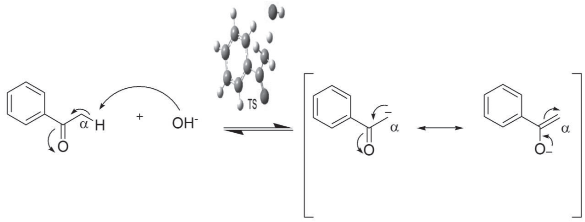

Figure 2. First step of Claisen-Schmidt mechanism for the formation of a generic chalcone, and the transition state which been found

Table 2. Enthalpy and Gibbs free variation energy for first step of synthesis of chalcone. Units are in kJ.mol-1.

Chalcones	ΔH	ΔG
Chalc-NO2	-45.9	-46.1
Chalc-Cl	-26.8	-28.5
Chalc-OH	-23.2	-25.6
Chalc-H	-22.1	-25.3
Chalc-NH2	-18.3	-25.5
Chalc-MeO	-14.3	-17.2

Conclusions

The preliminary results show that the use of aromatic ketones substituted at the meta position by withdrawing groups favors the reaction, making it faster, because they reduce the activation energy. The complete study of the reaction becomes necessary once the remaining steps of the reaction can be more decisive in the kinetics of this reaction. We expect that these results will orient futures experimental works.

Acknowledgments

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