

## Computational efforts towards the thermodynamic analysis of product preference for chalcones formed from the p-anisaldehyde and ketones: acetophenone, p-methylacetophenone, and indanone.

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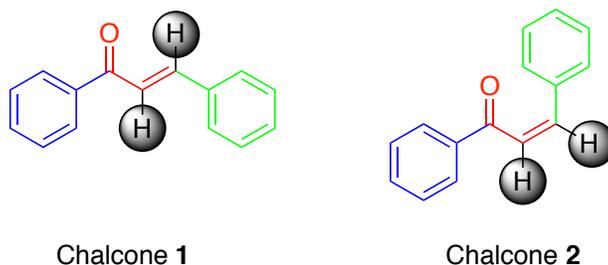
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### ABSTRACT

Chalcones are molecules consisting of an unsaturated carbonyl compound coming off an aromatic region. Usually synthesized from starting materials of an aldehyde and ketone, chalcones have affects that can play a significance to biological aspects of life through their chemotherapeutic characteristics. Due to the unsaturated double bond within the molecule, chalcones can exist as stereoisomers from one another: giving one molecule both a cis- and trans- formation. This project focuses on computational syntheses of three different chalcones in both their cis- and trans- forms to determine which stereoisomer has a more thermodynamically preferred synthesis: determined by Gibbs Free Energy values ( $\Delta G$ ) from each synthesis. For each chalcone studied, results showed all  $\Delta G$  values were negative yet the values for the trans- isomer had a larger magnitude. This tells us that both cis- and trans- chalcone syntheses are exergonic however the trans- chalcone ends up releasing more heat and is therefore more preferred. This supported our hypothesis that trans- chalcones would have a more preferred synthesis which was made based off the fact that trans- molecules are more stable as they have less steric strain relative to the cis- isomer.

### INTRODUCTION

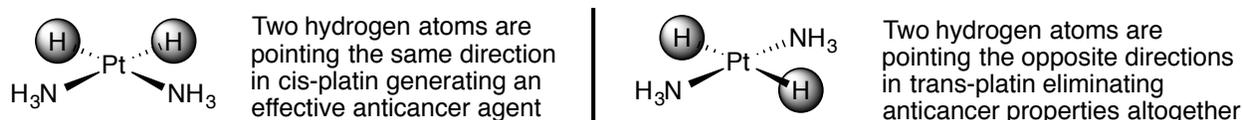
Chalcones (1,3-diaryl-2-propen-1-ones) are small organic molecules with a typical formula weight in the range of 200 – 400 g/mol. Although substitution with heavy atoms, e.g. halogens, can quickly increase their mass (Tekale 2020). In general, as a functional group one can describe a chalcone as a combination of an aromatic ketone and a,b-unsaturated components in one organic molecule (Scheme 1) and as a functional class they often are referred to as chalconoids. The bridge connecting the two rings contain three unsaturated atoms that dictate the overall nearly planar geometry of the molecule. In Scheme 1, we illustrate the structural build of a sample chalcone where each aromatic ring is highlighted in blue if it originated from an aromatic ketone during synthesis and green if it originated from an aromatic aldehyde. The conjugated bridge between the rings is emphasized in red. Due to the planar arrangement of the bridge the attachment of two hydrogens (shown in black) can occur in a trans fashion where they are pointing in the opposite directions (left, chalcone 1) or in a cis fashion where they are pointing in the same direction (right, chalcone 2).



**Scheme 1.** A general example of a chalcone and its structural functional group build.

These two compounds are stereoisomers, and the phenomenon is known as cis-trans isomerism in a chalcone. Stereoisomers are molecules that consist of the same molecular formula and connectivity of atoms; however, they differ in three-dimensional orientation. The two isomers of chalcones cannot interconvert once the lock of the

conjugated bridge is installed. However, in the beginning of the reaction either form can be theoretically formed. In general, the geometry of isomers can be exceptionally important where the well-known example of cisplatin and transplatin isomers show complete opposite chemotherapeutic affects all due to the change in geometry (Scheme 2, Pracharova 2015).



**Scheme 2.** Effect of cis-trans isomerism on biological properties of platinum complex.

Many of chalcones were first found in plants as a natural defense mechanisms or relevant intermediates and have demonstrated valuable biological properties, such as anti-cancer, anti-diabetic, and anti-inflammatory activities in clinical trials (Gaonkar 2017, Rammohan 2020). In addition, chalcones can be used as synthons or building blocks for synthesis of other chemotherapeutic drugs (Tajuddeen 2018). Since the biological activity can be highly dependent on the geometry around the double bond as demonstrated in example of cis-platin (Scheme 2) in this project we investigated cis-trans isomerism of several chalcones. *The goal of our study was to identify, if possible, any thermodynamic trends on preference of one isomer versus another using computational methods.* Our previous experimental data allowed isolation of only trans isomers in moderate to good yields. Formation of a cis isomer was not detected on an appreciable level. The innovation of this study is the use of computational methods for modeling of a cis isomer that can be modeled side-by-side with a related trans isomer even if we are not able to isolate it from reaction mixtures. Although synthesis and biological properties are vastly explored (Gaonkar 2017, Rammohan 2020) to the best of our knowledge there have been no previously reported examples of computational modeling for the compounds chosen in this study.

## METHODS

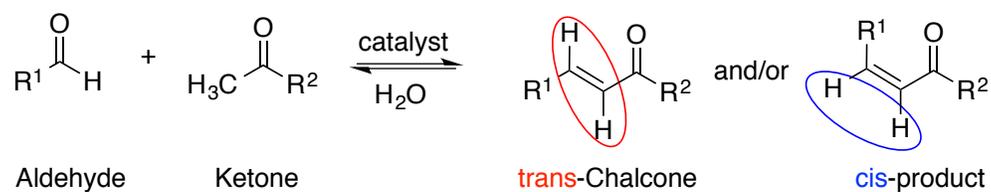
All starting materials and products were generated and optimized using Avogadro and saved as an input file. All structures were modeled at the HF/3-21G level of theory (Binkley, 1990) using the computational chemistry suite GAMESS (5 Dec 2014 R1, Barca 2020). All structures were verified as true minima as indicated by the absence of any imaginary vibrational frequencies. Structures were pre-optimized and output visualizations were created using Avogadro (Hanwell 2012). All calculations used the header demonstrated on Figure 1. All output files were opened using TextEdit to extract the necessary thermodynamic parameters information.

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**Figure 1.** The exact Header information used for calculation of all compounds in the project.

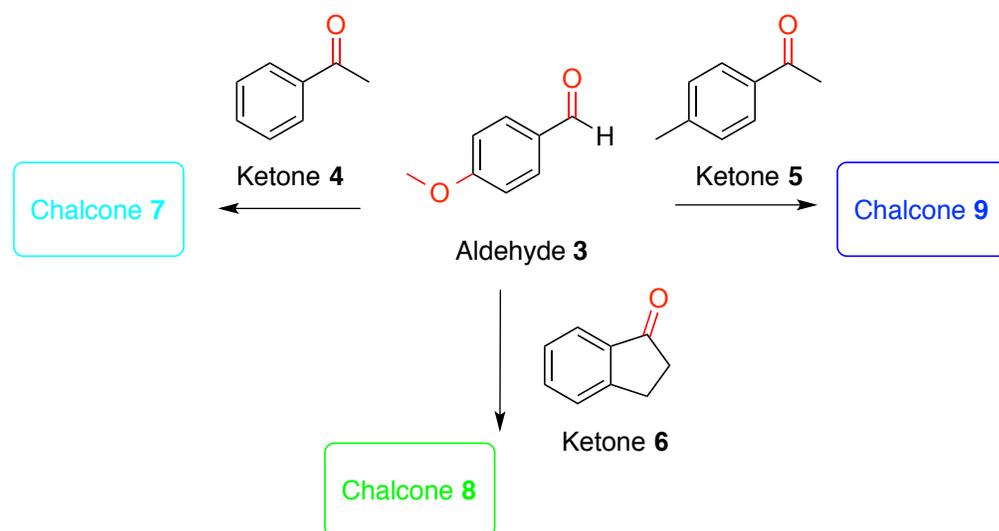
## RESULTS AND DISCUSSION

For this study we have modeled a general aldol condensation reaction between one aldehyde and several ketones. The general reaction using generic aldehyde/ketone pairing is demonstrated in Scheme 3. The different geometric arrangement at the double bond bridge and the 3D difference between hydrogen atom orientation in trans and cis isomers is highlighted, as well as the formation of water as byproduct.



**Scheme 3.** Synthesis of trans and cis isomers of chalcones via aldol condensation.

Although multiple combinations of aldehydes and ketones are possible, in our study we used a single aldehyde while varying the ketone structure (Scheme 4) to maintain some similarity in the structures of the chalcone products. The starting compounds and both chalcone isomers were modeled to identify individual thermodynamic parameters. Prior to that each structure was built and optimized in Avogadro (Hanwell 2012). The obtained optimized geometries are shown on Tables 1 and 2 alongside of the corresponding structural drawings.



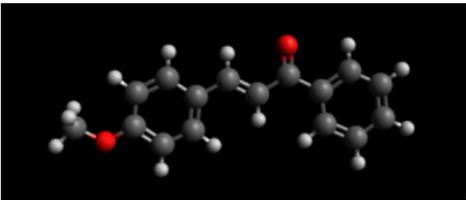
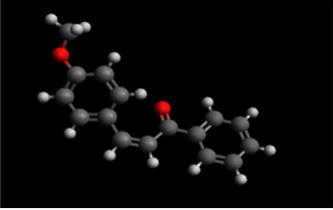
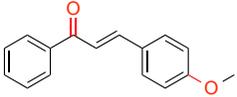
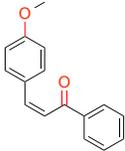
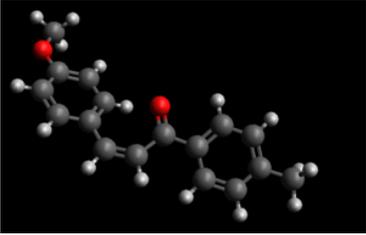
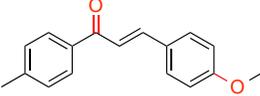
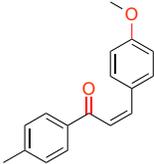
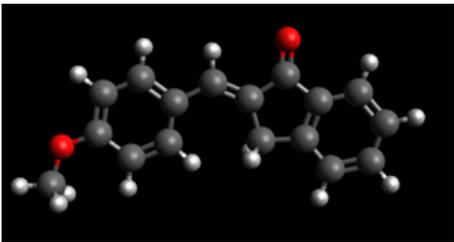
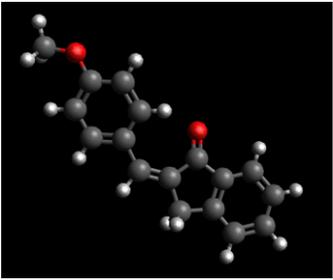
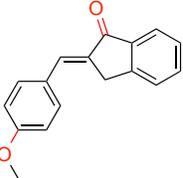
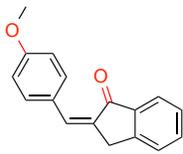
**Scheme 4.** Exact combinations of starting materials used in the study and corresponding products.

**Table 1.** Optimized geometry and corresponding structural drawings\* of starting materials.

Aldehyde 3	Ketone 4	Ketone 5	Ketone 6

\*All structural drawings were completed using ChemDraw, the coloring scheme matches the atoms in both types of visual representation of the molecules.

**Table 2.** Optimized geometry and structural drawings of products.

trans-isomer of chalcone 7	cis-isomer of chalcone 7
	
	
trans-isomer of chalcone 8	cis-isomer of chalcone 8
	
	
trans-isomer of chalcone 9	cis-isomer of chalcone 9
	
	

In this project, we obtained thermodynamic parameters, including the change in Gibbs free energies ( $\Delta G$ ) for the syntheses of three different chalcones 7–9 in both their cis and trans isomer forms (Scheme 3 and Table 2). The change in Gibbs free energy ( $\Delta G$ ) allows one to determine the thermodynamic probability of a spontaneous reaction or in

technical terms, whether a reaction can be classified as endergonic or exergonic one. In endergonic reactions, products have more free energy than reactants and therefore will require energy for the reaction to occur to an appreciable extent (Peters 2018). On the other hand, in exergonic reactions products have less free energy than reactants and as a result reaction will self-sustain and can proceed spontaneously. Although it is understood that even if a reaction is thermodynamically possible, there can still be kinetical limitations.

In addition to investigating the spontaneity of the reactions we analyzed the reaction heats or enthalpies. The summary of calculated enthalpies (H) for the substances involved in the formation of chalcones products is shown in Table 3. Our calculations determined the enthalpy (H) for water at 67.1 kJ/mol. Since water is the byproduct in all reactions it is not included in Table 3 but is included in all the following calculations for the reactions.

**Table 3.** Total enthalpy values (H, KJ/mol) for the studied reactions.

	Aldehyde	Ketone	Trans-Isomer	Cis-Isomer
Chalcone 7*	429.195	411.281	773.435	768.539
Chalcone 8*	429.195	494.724	852.286	855.573
Chalcone 9*	429.195	433.662	791.949	791.968

\*For exact structures please refer to Table 2.

The changes in enthalpies of the reactions using all combinations of starting materials were calculated using the equation 1 with an assumption of 1:1 stoichiometry of a general aldol reaction (Scheme 3) and are summarized in Table 4. The data is organized to demonstrate a side-by-side comparison of calculated parameters for each isomer.

$$\Delta H = \sum H_{Products} - \sum H_{Reactants} \quad \text{Eq. 1}$$

**Table 4.** Calculated change in enthalpy ( $\Delta H$ , kJ/mol) for the studied reactions.

Chalcone Isomer	$\Delta H$	Chalcone Isomer	$\Delta H$	Chalcone Isomer	$\Delta H$
cis-7	-4.851	cis-8	-1.26	cis-9	-3.803
trans-7	+0.045	trans-8	-4.547	trans-9	-3.822

Our data demonstrates that five out of six modeled reactions have negative sign of enthalpy change, meaning they are exothermic and release heat upon formation of the product. The overall trend is that the formation of trans-isomer generates more heat than observed for the cis-isomer, except for the chalcone 7. It is unclear what is the reasoning behind the difference as there is a lot of structural similarity between chalcones 7 and 8.

In addition to investigating the heat production for the target reactions we analyzed the entropy changes. The summary of calculated entropies (S) for the compounds involved in the formation of chalcone products is shown in Table 6. Our calculations determined the entropy (S) for water is 194.407 J/mol•K. Since water is the byproduct in all reactions it is not included in Table 5 but is included in all the following calculations for the reactions.

**Table 5.** Total entropy values (S, J/mol•K) for the studied reactions.

	Aldehyde	Ketone	Trans-Isomer	Cis-Isomer
Chalcone 7*	376.649	346.093	535.855	472.381
Chalcone 8*	376.649	395.394	553.264	564.236
Chalcone 9*	376.649	353.585	518.725	511.164

\*For exact structures please refer to Table 2.

The changes in entropies of the reactions using all combinations of starting materials were calculated using the equation 2 with an assumption of 1:1 stoichiometry of a general aldol reaction (Scheme 3) and are summarized in the Table 6. The data organized to demonstrate a side-by-side comparison of calculated parameters for each isomer.

$$\Delta S = \sum S_{Products} - \sum S_{Reactants} \quad \text{Eq. 2}$$

**Table 6.** Calculated change in entropy ( $\Delta S$ , J/mol•K) for the studied reactions.

Chalcone Isomer	$\Delta S$	Chalcone Isomer	$\Delta S$	Chalcone Isomer	$\Delta S$
cis-7	-55.594	cis-8	-13.400	cis-9	-24.663
trans-7	+7.520	trans-8	-24.372	trans-9	-17.102

The collected data indicate negative sign of entropy changes for five out of six reactions, similarly to the trend observed earlier for the changes in enthalpy. Interestingly, a somewhat anomaly was again observed for the combination of cis- and trans-isomers of chalcone 7, where the entropy change for trans-isomer came out as a positive value. Considering the endothermic character of enthalpy change for the reaction with chalcone 7, these findings indicate that formation of trans-chalcone 7 might become less probable at lower temperature as indicated in the equation 3.

$$\Delta G = \Delta H - T\Delta S \quad \text{Eq. 3}$$

The summary of calculated Gibbs free energies (G) for the substances involved in the formation of chalcone products is shown in Table 7. Our calculations determined the Gibbs free energy (G) for the formation of water at 9.124 kJ/mol. Since water is the byproduct in all reactions it is not included in Table 8 but is included in all the following calculations for the reactions.

**Table 7.** Total Gibbs free energy values (G, kJ/mol) for the studied reactions.

	Aldehyde	Ketone	Trans-Isomer	Cis-Isomer
Chalcone 7*	316.897	308.094	613.670	627.699
Chalcone 8*	316.897	376.837	687.330	687.346
Chalcone 9*	316.897	328.240	637.291	639.565

\*For exact structures please refer to Table 2.

The changes in Gibbs free energy of the reactions using all combinations of starting materials were calculated using the equation 4 and are summarized in the Table 8. The data organized to demonstrate a side-by-side comparison of calculated parameters for each isomer.

$$\Delta G = \sum G_{Products} - \sum G_{Reactants} \quad \text{Eq. 4}$$

**Table 8.** Calculated change in Gibbs free energy ( $\Delta G$ , kJ/mol) for the studied reactions.

Chalcone Isomer	$\Delta G$	Chalcone Isomer	$\Delta G$	Chalcone Isomer	$\Delta G$
cis-7	+11.832	cis-8	+2.736	cis-9	+3.552
trans-7	-2.197	trans-8	+2.720	trans-9	+1.278

Our data indicate that for five out of six reactions the change in Gibbs free energy was calculated as positive, although values for four out of those five reactions appear to be relatively small. When interpreting the data, one should consider that computational methods provide thermodynamic parameters at standard conditions, known as  $\Delta G^\circ$ , related to the equilibrium state of the reaction. This indicates that even when reaction does achieve equilibrium it will favor reactants over the products. In addition, the general trend of trans-isomer being more energetically favorable (lower  $\Delta G$  values) and formation of trans-chalcone 7 is determined to be spontaneous at standard conditions.

## CONCLUSION

Chalcones have demonstrated numerous biological properties and, therefore, acquired a strong interest in academia and industry. The typical structure of chalcone is presented as a trans-isomer even though the cis arrangement is also possible. Knowing that stereoisomerism can have a dramatic effect on the biological properties of the resulting molecule, we conducted a study probing the preference for synthetic formation of cis-isomers of several chalcones. Our results support an experimental trend for the thermodynamic preference for the formation of trans-isomers of chalcones. However, for chalcones **8** and **9** the difference in changes of Gibbs free energy between the formation of cis and trans isomers is very small. This indicates that given the right conditions synthesis of cis-isomer for those chalcones can be potentially achieved. Another implication of our data is that the trans-form is kinetically preferable. This can explain why there is isolation of only the trans-product when cis-isomers are not that much higher in energy. The results of this study will be used as preliminary data to further investigate the factors governing the formation of these biologically relevant compounds.

## ACKNOWLEDGEMENT

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