



Diels-Alder cycloaddition versus ring-opening esterification: A computational study of the mechanism of formation of oxa-norbornene lactones from the reaction of furfuryl alcohol and itaconic anhydride

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ABSTRACT

The reactions of furfuryl alcohol with itaconic anhydride can proceed *via* four plausible pathways – two pathways involving initial Diels-Alder cycloaddition followed by lactonization and two pathways involving initial esterification followed by intramolecular Diels-Alder cycloaddition – to afford two distinct norbornene products bearing either a five- or six-membered butyrolactone ring respectively. DFT calculations reported herein show that the first-step Diels-Alder cycloaddition reactions have barriers of 8.5 and 11.8 kcal/mol which are far lower than the barriers of 29.6 and 36.9 kcal/mol for the esterification pathways. The calculated energies for the experimentally observed five- and six membered oxa-norbornene lactone isomers are exergonic with reaction energies of -17.1 and -12.8 kcal/mol respectively. Thermodynamically the five-membered isomer is more stable adduct than the six-membered adduct. Thus the most preferred pathway is the one involving initial $[4 + 2]$ cycloaddition followed by lactonization to form the five-membered butyrolactone ring. Substitution of methyl groups on the carbon bearing the hydroxyl group shows that the substituents do not affect the reaction pathways markedly.

1. Introduction

Furfuryl alcohol (a derivative of furan in which $-\text{CH}_2\text{OH}$ is substituted on C_1 of the furan and itaconic acid are bio-based chemicals that are very abundant in nature [1,2]. Furfuryl alcohol and itaconic acid react to form products that serve as precursors for some bio-based polymers with extensive applications in drug design, consumer science and industry [3]. There is growing interest in the use of furan-based compounds for the development of platform molecules and polymers due to the fact that they are aromatic and can function as dienes, they have a large structural variation and they are easily accessible from renewable resources. The reaction of furfuryl alcohols with itaconic anhydride forms two distinctive oxa-norbornene products bearing a five- or six-membered butyrolactone ring [4–6], which are known to be valuable intermediates for the production of biologically active compounds.

Although the five-membered isomer is known to be the dominant adduct, the exact pathway through which the reaction proceeds is not known yet. The reaction could either proceed by Diels-Alder cycloaddition followed by lactonization or it could proceed by the ring-opening of the acid anhydride to form the ester followed by the intramolecular

Diels-Alder reaction. Bai et al. [5] studied the ring opening metathesis polymerization of a new bio-derived monomer from itaconic anhydride and furfuryl alcohol and achieved 100% atom economy through a tandem Diels-Alder addition and lactonisation but were unable to ascertain the specific reaction pathway, i.e. whether the reaction followed a $[4 + 2]$ cycloaddition or ring opening esterification.

Taffin et al. [7] conducted experimental and theoretical studies on a Diels-Alder reaction between 2,5-dimethylfuran and vinylene carbonate and reported that the reaction slowly reaches a thermodynamic equilibrium which gives rise to the formation of the *exo* isomer. Peheré and coworkers [8] studied reactions of furans with itaconic anhydride and observed that thermodynamic instability renders furans labile in high yielding Diels-Alder (DA) cycloaddition reactions, but for itaconic anhydride and furfuryl alcohol the opening of the anhydride portion drives the reaction to completion. It is known from previous experimental studies that itaconic anhydride reacts with bases like alcohol and amines to undergo regioselective ring-opening esterification reaction whereas in the presence of dienes or nitrones the itaconic anhydride could act as dienophile or dipolarophile in the cycloaddition reactions. However, the case of itaconic anhydride reacting with furfuryl alcohol is of special interest because furfuryl alcohol could act as both a

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diene and a base and therefore the mechanism of such reaction must be thoroughly investigated.

Undesirable *trans*-esterification of tricyclic anhydrides with excess propylene oxide using aluminum salen catalysts has been investigated where the structure of the tricyclic anhydride, the ratio of the addition of aluminum catalyst to the nucleophilic cocatalyst, and the acidic properties of the aluminum catalyst were all reported to have contributed to the rates of side reactions [9]. Han and coworkers [10] investigated chromium complex-based binary catalytic ring-opening copolymerization of epoxide and norbornene anhydride and reported that the chelating between the endo-diester unit of the polyester chain and the metal center plays an important role in the stereoselectivity. Domingo et al. [11] studied molecular mechanism for the cycloaddition reaction between 2-methylfuran and acetylene dicarboxylic acid using density functional theory at B3LYP/6-31 + G* level of theory. Their results revealed that the reaction proceeds along a stepwise mechanism with the initial step corresponding to the nucleophilic attack on C₅ of the furan ring to one carbon atom of the conjugated acetylenic carbon to give a zwitterionic intermediate. The nucleophilic attack on the acetylenic carbon to the substituted carbon of the furan ring was reported to have afforded the Diels-Alder cycloadduct.

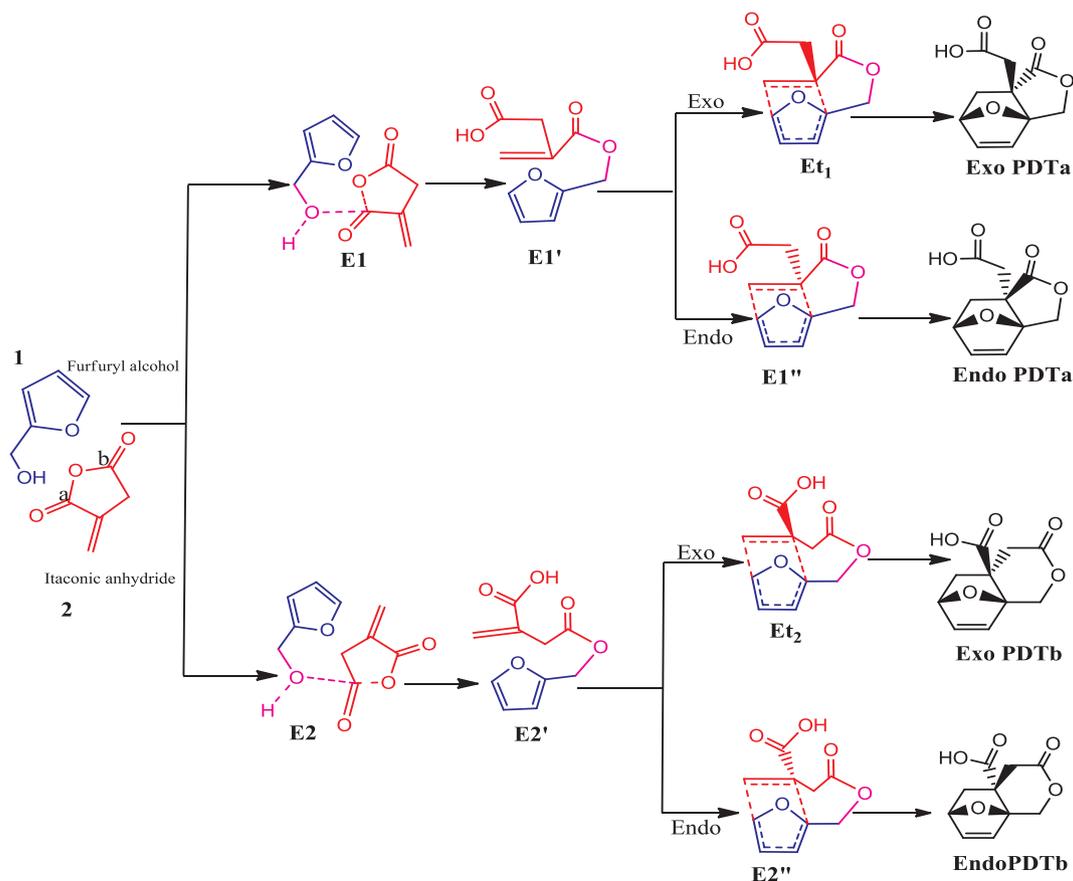
Some studies have been conducted to determine the special reactivity, regio- and stereoselectivity of itaconic anhydride to form oxanorbornene lactone. However, there has been no consensus with regards to mechanistic channel of the reaction of furfuryl alcohol and itaconic acid anhydride to ascertain the first stage of the reaction (that is whether the reaction proceeds via the Diels-Alder cycloaddition first before esterification pathway or vice versa) to form oxanorbornene lactones. Through quantum chemical calculations at the M06/6-31G(d) and M06-2X/6-31G(d) levels of theory, this work aims at investigating the pathways for the reactions of furfuryl alcohol and itaconic acid anhydride according to the proposed schemes 1 and 2. Moreover, the

nature of the alcohol (whether primary, secondary or tertiary) is also taken into account in this work (Scheme 3). It should be noted that Diels-Alder reactions can proceed via a number of mechanisms other than the one shown in Scheme 3, the complete repertoire embracing non-polar mechanisms (synchronical mechanism, biradicaloidal one step-mechanism, stepwise biradical mechanism) [29,30], and polar mechanisms (one step-two stage mechanism, stepwise zwitterionic mechanism) [31,32], but it is the well-known concerted (one-step) mechanism that has been investigated.

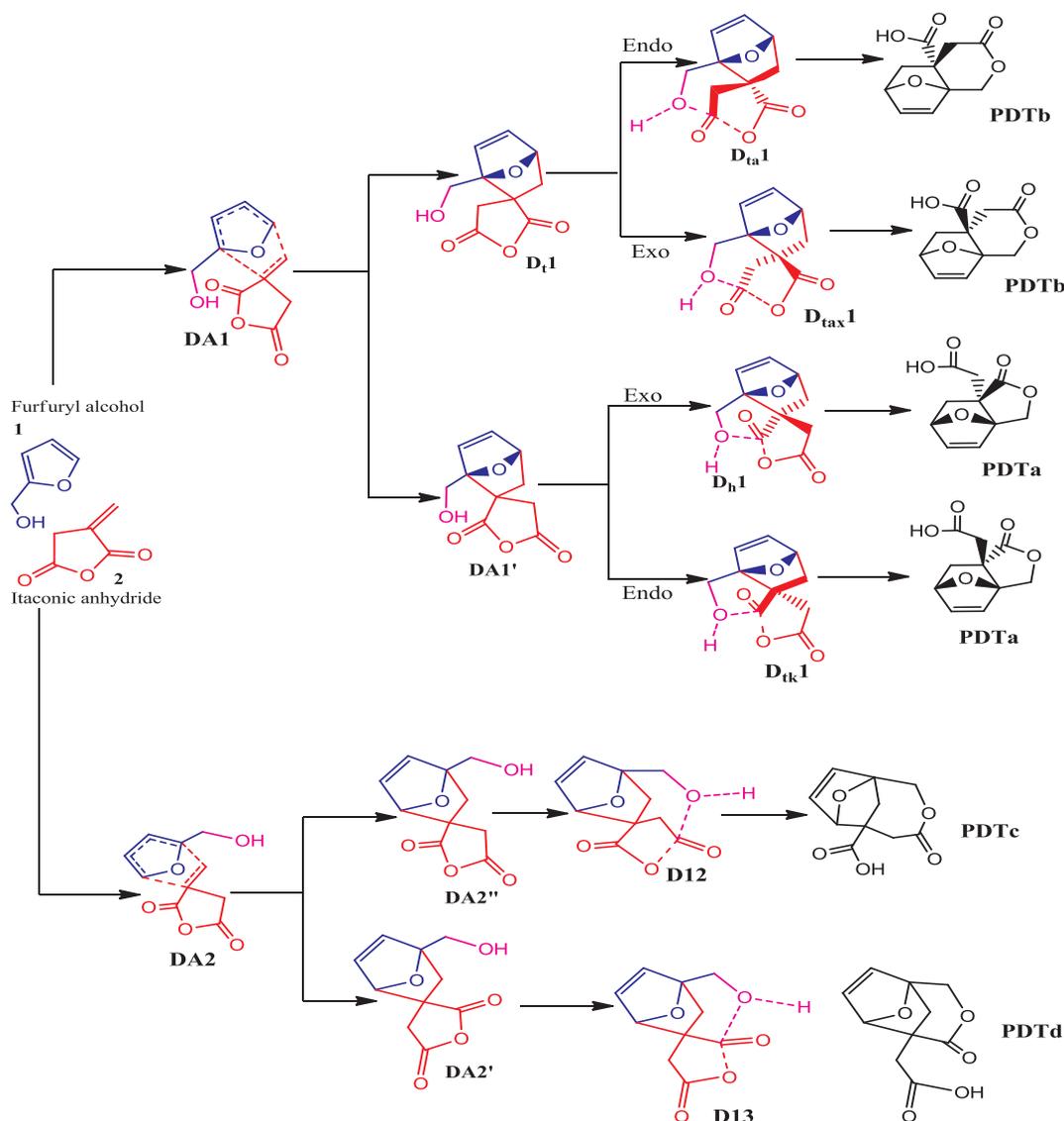
2. Details of calculations

DFT calculations were carried out using the Spartan '14 Molecular Modeling program [12] and Gaussian 09 [13] package at the M06-2X/6-31G(d) and M06/6-31G(d) levels of theory.

The selection of hybrid density functional theory method was based on efficiency and accuracy. DFT calculations generally offer better and more reliable description of the geometries and relative energies than either Hartree-Fock or MP2 methods even though it might underestimate weak interaction such as van der Waals interaction [14–18]. Hybrid and gradient-corrected DFT methods often outperform MP2 while using less computer time. The M06 and M06-2X functionals are the most versatile of the Minnesota 06 functionals of Donald Truhlar, and the work of Ken Houk on the applications of these functionals on organic reactions has shown that these functionals have comparable accuracies to higher levels of theory [19–21] and that it is possible to obtain relatively accurate activation and reaction energies for cycloadditions at the M06-2X/6-31G(d) level [20]. With regard to the relatively modest 6-31G(d) basis set, Houk et al. compared energetics at this level with single point calculations with the larger 6-311G(d,p) basis set and confirmed that the larger basis set size does not affect the conclusions [22]. Some authors have however reported small



Scheme 1. Proposed pathways for the esterification reactions of furfuryl (1) alcohol with itaconic acid anhydride (2).



Scheme 2. Proposed pathways for the Diels-Alder reactions of furfuryl (1) alcohol with itaconic acid anhydride (2).

overestimation of activation barriers with the M06-2X functional [23].

The starting geometries of the molecular systems were constructed using Spartan's graphical model builder and minimized interactively using the sybyl force field [24]. No symmetry restrictions were imposed during geometry optimizations. Vibrational frequencies were calculated to verify the true nature of each stationary point located on the potential energy surface (PES). For minima on the PES, which present reactants, intermediates or products, it was verified that no structure has an imaginary vibrational frequency. For first-order saddle points, which represent transition states it was verified that each structure has one and only one imaginary frequency which correspond to vibration along the reaction coordinate.

Transition state structures were computed by first obtaining guess input structures. This was done by constraining specific internal coordinates of the molecules (bond lengths, bond angles, dihedral angles) while fully optimizing the remaining internal coordinates. This procedure gives appropriate guess transition state input structures which are then submitted for full transition state calculations without any geometry or symmetry constraints. Full vibrational frequency calculations verified that each transition state structure had a Hessian matrix with a single negative eigen value, characterized by an imaginary vibrational frequency along the respective reaction coordinate. Intrinsic reaction coordinate calculations were then performed to ensure that each

transition state smoothly connects the reactants and products along the reaction coordinate [25–27].

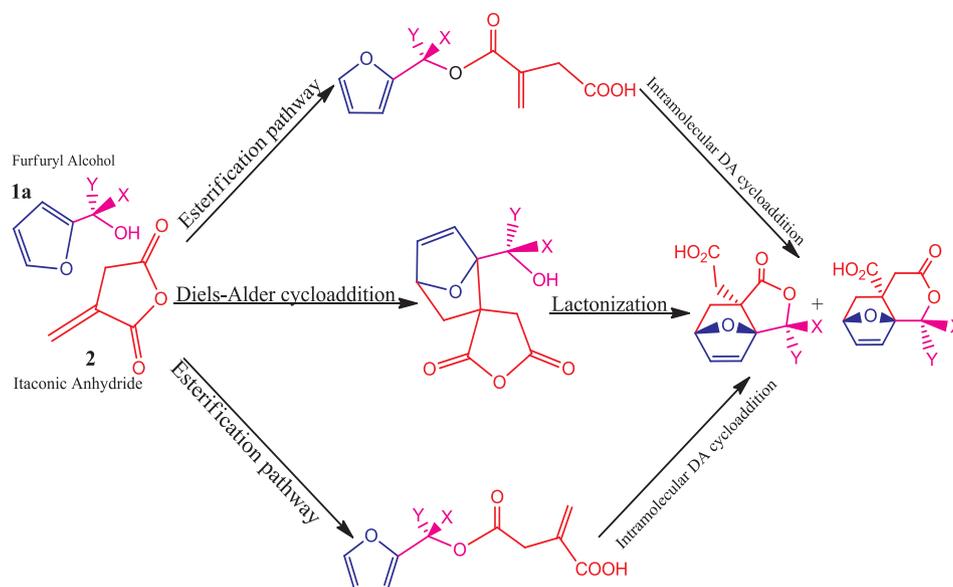
3. Results and discussion

3.1. Regio- and stereoselectivity of esterification reactions of furfuryl alcohol with itaconic acid anhydride

Scheme 1 shows the proposed pathways for esterification reactions of furfuryl alcohol and itaconic acid anhydride.

In the esterification pathways, the alcoholic oxygen of the furfuryl alcohol acts as a nucleophile and attacks either carbonyl carbon a or b of the acid anhydride (Scheme 1) to open the ring of the acid. The ring-opening esterification occurs through either transition state E1 or E2 to give intermediate E1' or E2' (Scheme 1). The E1' and E2' can also undergo intramolecular Diels-Alder [4 + 2] cycloaddition reaction through *endo* or *exo* transition states E1'' or E1' to give either product PDTa or PDTb.

Fig. 1 shows the optimized geometries of the stationary points related to the proposed mechanistic pathways (Scheme 1). Zero-point-corrected Gibbs free energies of the reaction of furfuryl alcohol and itaconic acid anhydride are presented on the energy profiles. Esterification pathways which lead to the formation of the five- and six-



Scheme 3. Proposed pathways for the reactions of mono and di-substitution of methyl (CH₃) group on the carbon atom bearing the hydroxyl group of the furfuryl alcohol.

membered oxa-norbornene lactone products are shown on Fig. 1. The results shown on the energy profiles are the M06-2X results.

From the profile, the energy barrier through the E2 transition state is 29.6 kcal/mol while that through the E1' transition state is 36.9 kcal/mol, making the E2' kinetically favorable over the E1 by 7.3 kcal/mol. The formation of the ester intermediates E1' and E2' are seen to have

the same reaction energy of -13.1 kcal/mol. The facial regioselectivity of the ring-opening of E2' regioisomer has been reported experimentally, in which the itaconic anhydride was reacted with amines base to afford amide which successively underwent lactamization to give succinimide anhydride [28]. The results of this present study confirm the regioselectivity patterns for itaconic anhydride with furfuryl alcohol

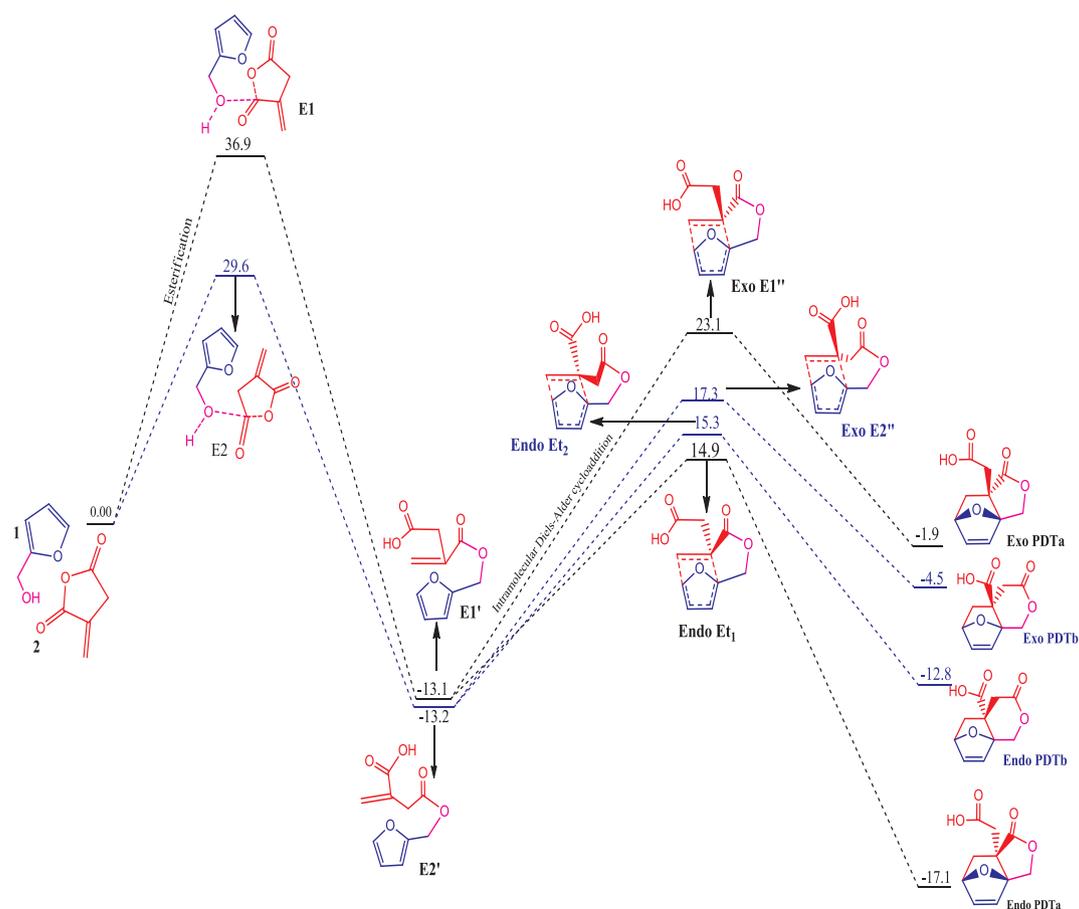


Fig. 1. Energy profile for the Gibbs free energies of the transition states and products of furfuryl alcohol with itaconic acid anhydride.

acting as nucleophile.

The intermediate **E1'** and **E2'** undergo intramolecular Diels-Alder cycloaddition reaction to form five- or six-membered oxa-norbornene lactone products. The intramolecular Diels-Alder cycloaddition reaction of **E1'** goes through the *endo* or *exo* transition states in which the energy barrier through *exo* **Et₁** is 36.2 kcal/mol while that through *endo* **E1''** gives an energy barrier of 28.0 kcal/mol. Thus the conversion of the ester intermediate **E1'** is favoured kinetically along the *endo* **E1''** pathway compared to the *exo* **Et₁** pathway. Thermodynamically, the formation of the *endo* and *exo* five-membered oxa-norbornene isomers from intermediate **E1'** are exergonic with reaction energies of -17.1 and -1.9 kcal/mol respectively. This implies that the *endo* isomeric pathway is both kinetically and thermodynamically more favourable than the *exo* isomeric pathway.

The ester intermediate **E2'** is also seen to have the same *endo/exo* isomeric pathways along intramolecular DA rearrangement where the *exo* **E2''** gives higher energy barrier than the *endo* **E₁₂**. The rearrangement of intermediates *exo* **E2''** and *endo* **E₁₂** to form the six-membered oxa-norbornene lactone product have barriers of 30.3 kcal/mol and 28.4 kcal/mol respectively. The rearrangement of **E2'** is also seen to be exergonic whereby the *endo* isomer is thermodynamically more favourable than the *exo* isomer by about 8.3 kcal/mol. Therefore, in the reaction of furfuryl alcohol with itaconic acid anhydride to form the five- and six-membered oxa-norbornene lactones, **E2** routes serves as a better pathway than the **E1** for the esterification reaction pathways.

The energetics at the M06/6-31G(d) level of theory show the same trends as those at the M06-2X/6-31G(d) level of theory even though the energies at the M06/6-31G(d) level are slightly higher. For instance, the M06/6-31G(d) calculations gave activation barriers of 37.1 kcal/mol and 30.5 kcal/mol along transition states **E1** and **E2** respectively. This paper therefore discusses the M06-2X results while the M06 results have been included in the supplementary electronic information (Fig. S1) for comparison, which will be useful for benchmarking purposes of the two methods.

3.2. Regio- and stereo-selectivity of Diels-Alder cycloaddition reactions of furfuryl alcohol with itaconic acid anhydride

Scheme 2 shows the proposed pathways involved in the reaction of furfuryl (**1**) alcohol with itaconic acid anhydride (**2**) along the Diels-Alder cycloaddition pathway and Fig. 2 presents the zero-point-corrected Gibbs free activation and reaction energies. The [4 + 2] cycloaddition occurs when the vinyl portion of the acid anhydride **2** adds across the furan part of the alcohol **1** through either transition state **DA1** or **DA2** (depending on the orientation of approach of the itaconic acid) to form intermediate **DA1'** or **DA2'** (Scheme 2). The formation of the **DA1** and **DA2** regioisomers have activation energies of 8.5 kcal/mol and 11.8 kcal/mol respectively which show that the **DA1** pathway is favored over the **DA2** if the reaction is kinetically controlled. The cycloadducts formed from these two transition states have almost the same reaction energy of about -14.7 kcal/mol even though the orientation of the isomers are different (see Fig. 3).

The Diels-Alder cycloadducts **DA1'** and **D_f1** undergo lactonization to produce four regioisomers through *endo* and *exo* transition states (structures in Fig. 2). The formation of the *endo* or *exo* transition states are achieved based on the approach of the alcoholic oxygen which acts as nucleophile to attack the carbonyl carbons of the acid portion. If the OH group of the furfuryl alcohol approaches the carbonyl carbons from the top it forces the acid group on the oxa-norbornene ring to give the *endo* orientation whereas the back attack of the OH group gives *exo* conformation. Also, the rearrangement of the intermediates **D_f1** through transition states **D_{tax}1** and **D_{ta}1** give product **PDTb**. The activation barrier through the cycloaddition **D_{tax}1** is 52.9 kcal/mol which is 12.9 kcal/mol higher than that of the **D_{ta}1** lactonization. Energetically, the lactonization of **DA1'** through transition states **D_{tk}1** and **D_h1** are of lower energy than its corresponding **D_{ta}1** and **D_{tax}1**

isomeric pathways.

Attempts to locate transition states structures of **D12**, **D13** and their corresponding isomers did not yield any result and therefore it is inferred that those pathways may not exist. The computed energies of the products **PDTc** and **PDTd** (structures in scheme 2) are 37.1 and 110.0 kcal/mol and 11.2 and 66.3 kcal/mol also indicate that these molecules cannot be formed experimentally.

Jasiński [31] has demonstrated quantitatively that furane derivatives react relatively slower than respective 5-membered dienes. This, according to the authors, is a consequence of the tendency to preserve the aromatic system in the furan molecule.

3.3. Comparison between Diels-Alder cycloaddition and esterification reaction of itaconic acid anhydride with furfuryl alcohol to form five and six-membered oxa-norbornene lactones

The energetics presented in Figs. 1 and 2 indicate that the Diels-Alder cycloaddition pathways have relatively lower energies compared to the ring-opening esterification reaction pathways. The structure of the ester intermediates **E1'** and **E2'** reveal that the intramolecular Diels-Alder rearrangement would also lead to oxa-norbornene product bearing five and six-membered lactone isomers respectively. The activation barrier for the intramolecular Diels-Alder reaction of the **E2'** for the formation of six-membered lactone isomers is lower than the energy barrier for the lactonization of the DA cycloaddition adduct of **D_{ta}1** by about 16.6 kcal/mol. Adducts formed from the two esterification and the DA cycloaddition reactions have the same intermediate energies of -13.1 kcal/mol and -14.7 kcal/mol in that order.

The lactonization of **D_f1** and intramolecular DA reaction of **E2'** give reaction energies of -4.5 and -12.8 kcal/mol for the six-membered oxa-norbornene lactones whereas the rearrangement of **DA1'** and **E1'** give -1.9 and -17.2 kcal/mol energy for the five-membered oxa-norbornene isomers.

Thermodynamically, the five-membered oxa-norbornene *endo* adduct is more stable than its corresponding six-membered *endo* isomer which is in good agreement with experimental result [5,8]. Our computed results also point out that the intermediate **DA1'** and **D_f1** are the kinetic products and therefore should be observed, as they were in the experimental work of Peheré et al. [8]. For the reaction of 2-methylfuran with acetylene dicarboxylic acid, Domingo et al. [11] reported that the 2-methylfuran acts as a nucleophile instead of a diene. However, with the reaction of furfuryl alcohol with itaconic anhydride, the furfuryl alcohol serves as a better diene rather than a nucleophile as is seen from the fact that the first transition states of the Diels-Alder pathway (where furfuryl alcohol acts as a diene) are of lower energies than the corresponding transition states of the esterification where furfuryl alcohol acts as a nucleophile, even though there are lone pairs of electrons on the alcoholic oxygen. Also, the thermal reactions of furfuryl alcohol with itaconic acid anhydride were reported in the same Peheré et al. [5] study and it was observed that two mono furfuryl itaconate esters (labelled as **15a** and **15b** in that work) are formed at temperature of 80 °C. Our calculations suggest that among the two ester isomers, the **15a** should be able to form the experimentally observed adduct since what impedes its progress under normal conditions is the initial activation energy. Moreover, this also reveals that the rate-determining step for the reaction of these two reactants is the first step.

3.4. Diels-Alder cycloaddition and esterification reactions of mono and dimethyl substituted furfuryl alcohol with itaconic acid anhydride

Scheme 3 shows the proposed pathways involved in the reaction of itaconic anhydride with mono- and di-substitution of methyl (CH₃) group on the furfuryl alcohol **1a** and Table 1 presents the Gibbs free activation and reaction energies. The reaction of monomethyl and dimethyl furfuryl alcohols with itaconic anhydride maintain the oxa-norbornene lactone rings and no distortion is seen to have occurred in

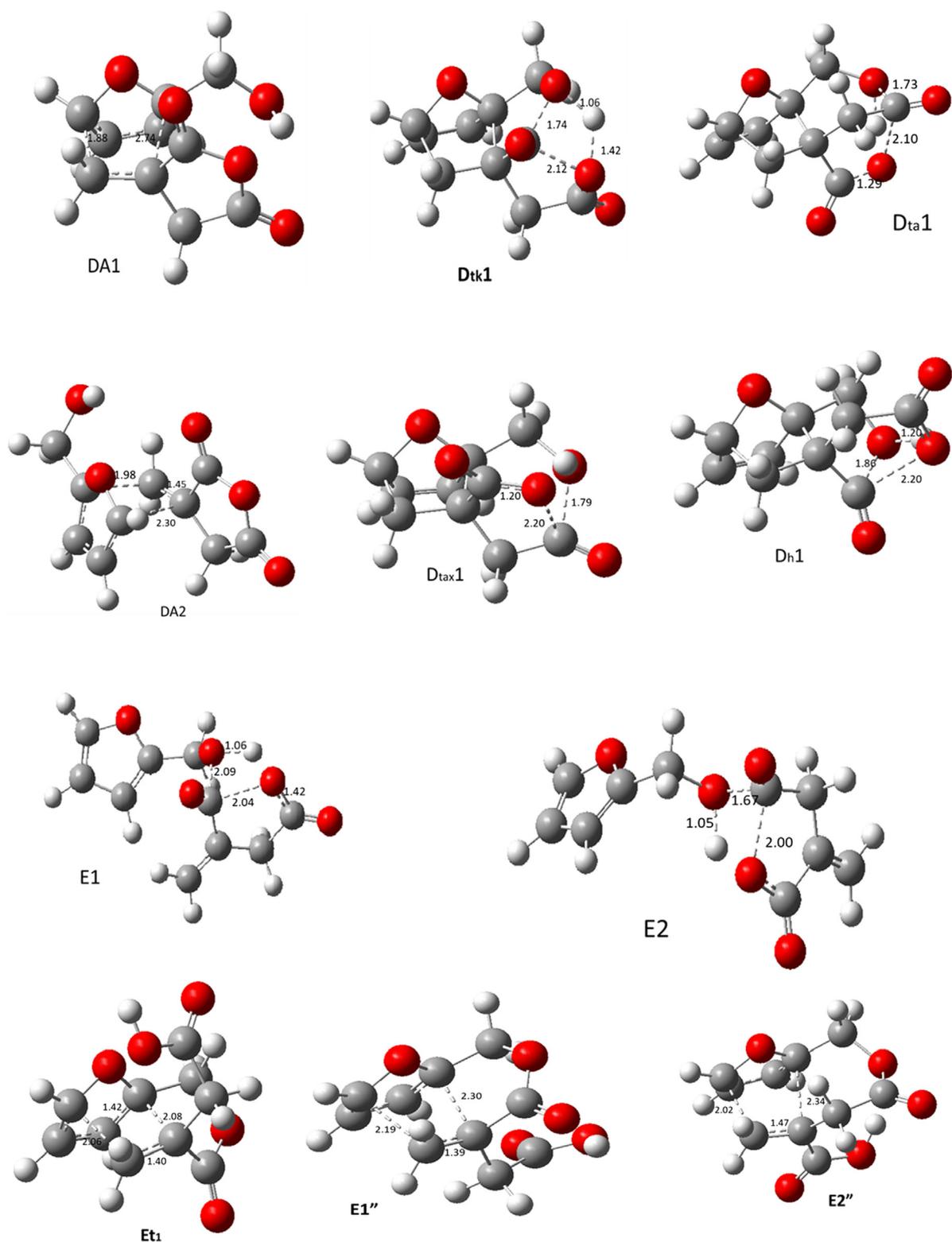


Fig. 3. Optimized geometries of the transition states and products involved in the reaction of furfuryl alcohol and itaconic anhydride.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.comptc.2018.05.019>.

Table 1

Energetics of the reactions of 2°(X = H, Y = CH₃) and 3°(X = Y = CH₃) furfuryl alcohol with itaconic anhydride which yield five- and six-membered oxa-norbornene lactone products /kcal/mol.

Alcohol	Activation energy (ΔG^\ddagger)/kcal/mol							Reaction energy (ΔG_{rxn})/kcal/mol				
	E1	E1'	E1''	E _{t1}	E2	E2'	Et ₂	E2''	Endo PDTa	Exo PDTa	Endo PDTb	Exo PDTb
2°alcohol	36.4	-13.2	14.5	27.5	29.3	-13.4	15.7	-	-17.9	2.4	-14.2	0.02
3°Alcohol	36.5	-10.9	15.6	28.7	30.7	-11.7	15.4	-	-15.3	5.1	-14.0	-3.4
Alcohol	DA1	DA1'	D _{tk} 1	D _h 1	D _{ta} 1	D _{tax} 1	-	-	-	-	-	-
2°Alcohol	11.7	-14.7	23.5	40.9	26.1	31.8	-	-	-	-	-	-
3°Alcohol	12.2	-14.4	23.8	43.2	26.7	31.7	-	-	-	-	-	-

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