Hydrogen Bond Stabilization in Diels-Alder Transition States. The Cycloaddition of hydroxy-*ortho*-quinodimethane with Fumaric acid and Dimethylfumarate

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Abstract

DFT investigations on the mechanism of Diels-Alder reactions of a hydroxy-*ortho*-quinodimethane with fumaric acid derivatives were performed to understand the origin of the *syn* or *anti* configuration of the adducts. The diene hydroxyl group and the dienophile carboxyl group show hydrogen bonding in the transition state, significantly favouring the *syn* product. This reaction is poorly diastereoselective for $R = CO_2Me$ (ratio *syn/anti* = 57:43) and significantly improved for $R = CO_2H$ (ratio *syn/anti* = 71:29). The stereoselectivities are properly predicted from transition structures calculated at B3LYP/6-31G(d) level of approximation.

Keywords: Diels-Alder, DFT, stereoselectivity, Transition states, *ortho*-quinodimethane

INTRODUCTION

The photochemical excitation of *ortho*-tolualdehyde is well known to generate a highly reactive *ortho*-quinodimethane (QDM) type intermediate, readily trapped by an alkene in a Diels-Alder reaction. This process is an efficient way to assemble a dihydronaphthalene skeleton bearing three contiguous chiral centers. The cycloaddition could, in principle, lead to two enantiomeric pairs of diastereomers, as seen in Fig 1.

The Diels-Alder reactions are amongst the most useful and versatile in organic synthesis, for their remarkable stereoselectivity[1–4] and atom economy[5]. Inter [6–8] and intramolecular [9, 10] Diels-Alder reactions are well documented and they have been investigated both experimentally and theoretically [11–14]. Further, there are many reports of catalysts [15–17] and solvents [18] impacting upon the rates and stereoselectivities of Diels-Alder reactions through various interactions including hydrogen bonding. Gain or loss of aromaticity also plays an important role in Diels-Alder transition states and adducts[19]. In the photochemically assisted cycloaddition of **2** with **3**, we noticed an interesting change in the product distribution when switching from fumaric acid (FA) **3a** (ratio **4a/5a** = 71:29) to dimethyl fumarate(DMF) **3b** (ratio **4b/5b** = 57:43)[20]. The goal of the present work is to rationalize this observation computationally, and to understand the factors controlling the stereospecificity and, in particular, the influence of hydrogen bonding on the *endo* vs *exo* transition states (TS).

COMPUTATIONAL DETAILS

DFT calculations were carried out using Gaussian03, Revision B.01 and C.01 [21], transition states have been located using Berny's algorithm [22]. All calculations were carried out on a cluster of AMD Opteron(tm) Processors 246, 2.0 GHz CPU. The hybrid B3LYP functional-Becke's three parameter exchange functional (B3) [23, 24] with the non-local correlational functional of Lee, Yang and Parr (LYP)[25] and a 6-31G(d) basis set was used throughout. Stationary points that were located have been characterized by computing the vibrational frequencies. In all cases reactants and products had real frequencies and the transition states had a single imaginary frequency. Furthermore TSs have been confirmed by animating the imaginary frequency in MOLDEN[26]. After locating a TS, intrinsic reaction

coordinate (IRC) [27] calculations were also carried out along the corresponding Minimal Energy Path (MEP) in order to identify its respective reactant and product. Bond orders (BO) were calculated as the Wiberg [28] indices which are derived from the natural atomic orbitals analysis, and from them bond formation index BF_i or bond cleavage index BC_j have been calculated as described below [29, 30]:

$$BF_i \text{ or } BC_j = \frac{BO_i^{TS} - BO_i^{R}}{BO_i^{P} - BO_i^{R}} \times 100$$

$$BF_{Ave} = \frac{1}{n} \sum_{i=1}^{n} BF_i$$

where the summation is over the "forming bonds."

$$BC_{Ave} = \frac{1}{n} \sum_{i=1}^{n} BC_i$$

where the summation is over the "cleaving bonds."

Bond formation-cleavage average(BFC_{Ave}) values have been calculated as

$$BFC_{Ave} = \frac{1}{2}(BF_{Ave} + BC_{Ave})$$

RESULTS AND DISCUSSION

Reactions of *ortho*-QDM with FA and DMF

ortho-QDM undergoes Diels-Alder reaction with FA and DMF to form the diastereomeric *syn/anti* adducts, depending on the relative orientation of the reactants (Fig.2). The substituent on the dieneophile may be directed away from the diene (*exo* approaches A and C) or towards the diene (*endo* approaches B and D) with respect to the OH group. A careful consideration of the dieneophile structure reveals that it has three types of conformations as described in Fig. 3: namely *S-cis/S-cis*, *S-cis/S-trans*, *S-trans/S-trans* in which the *S-cis/S-cis* conformation was calculated as the most stable one. Hence, we have investigated all the possible approaches(A-D) for the reactions of *ortho*-QDM with FA and DMF with the *S-cis/S-cis* conformation. In addition, the favourable *exo* approach C has been investigated for all other conformations. The *S-trans/S-cis* conformation can react with the diene in

two possible ways; either with the *cis* or *trans* part of the dieneophile leaning towards the OH termination of the diene. One important point to be mentioned here, is that we have two types of dienes with OH groups outside the ring and inside the ring. The calculation shows that the diene with the OH group inside ((Z)-enol) is more stable than its isomer with the OH outside ((E)-enol) and that the *exo* approach C is kinetically favored. However, it has been established experimentally that this isomer has a very short lifetime by way of quantum tunneling [31]. As a consequence, we considered only the isomer with the OH outside as experimentally relevant. Hence, the application of the Arrhenius equation [33] to the activation energy differences for approaches A and B predicts the ratios **4a/5a** = 85:15 (0.6 kcal/mol) and **4b/5b** = 70:30 (0.52 kcal/mol), in accordance to the trend observed experimentally. The rate of a chemical reaction is often sensitive to the nature of the solvent. However, rates of pericyclic reactions are not very sensitive to solvents [32]. This insensitivity is related to the mechanism of this type of reaction because there is little charge development in the reacting system during the activation process. We have therefore omitted the solvent effect in our calculations.

Transition state geometry

The reactions were found to occur in a concerted fashion, through an asynchronous transition state due to the asymmetrical nature of the diene. The terminal carbon of the diene reacts first, as can be seen from the predicted bond lengths of the newly forming bonds in the TSs (Fig. 4) as compared to the hydroxy terminal carbon. This is due to the fact that the charges on the terminal carbon and hydroxy terminal carbon are -0.461 and 0.009 respectively, which clearly indicates the increased nucleophilicity of the former compared to the latter one. The twist angles are high in *exo* TSs as can be seen from Table I. Also hydrogen bonding is present in them. The bond distance between O and H is 1.675 Å for FA and 1.680 Å for DMF. The bond angles (OHO) are 148.83, 149.29 degrees respectively.

Energetics

The FOE (frontier orbital energy) gaps presented in Table I suggest that these reactions are "normal electron demand" cycloadditions meaning that the electrons move from the

HOMO of the diene to the LUMO of the dieneophile. The negative reaction energy values for these reaction is characteristic of an exothermic reaction. The activation energies presented in Table I reveal that *S-cis/S-cis* TS C is kinetically more favorable, both for FA and DMF when compared to all the other three pathways (Fig. 5). Moreover, this reaction path shows an intramolecular hydrogen bond interaction between the dieneophile oxygen and the proton from the hydroxyl group in the diene of OH. For $R = CO_2H$ (series a) the activation energy of the *exo* approach C is 0.77 kcal/mol, whereas the *exo* approach A has an activation energy of 3.21 kcal/mol. Furthermore, the stereoselectivity decreases for $R = CO_2Me$. In that case, the activation energy of the *exo* approach C 2.31 kcal/mol and the *exo* approach A 3.99 kcal/mol. For both series, the *exo* approach C is kinetically more favored. The stereoselectivity depends on the kinetic control of the reaction. During this reaction, the ring becomes partially aromatic in the TS and this results in considerable stabilization of the TS. Owing to this extra stabilization, the activation energy is significantly lowered. The ring becomes fully aromatic in the product and this gain in aromaticity from the TS to the product makes the reaction highly exothermic.

Bond order analysis

Based on the bond order analysis, the BC_j, BF_i and BFC_{Ave} values are presented in Table II. The developing $C_5 - C_6$ π bond is more pronounced than the $C_8 - C_{11}$ and $C_{10} - C_7$ σ bonds. This shows that the ring starts to gain aromaticity in the TS itself. In this reaction, the diene cleaves ($C_7 - C_5$, $C_6 - C_8$, $C_{11} - C_{10}$) to a higher extent than the newly forming bond($C_5 - C_6$, $C_8 - C_{11}$, $C_{10} - C_7$). The relatively low BFC_{Ave} values indicate that the transition states are early transition states. Hydrogen bond is forming between the hydroxyl proton and dieneophile oxygen. The bond order of hydrogen bonds in the TSs for the reaction with FA and DMF are 0.0975, 0.0955 respectively.

CONCLUSIONS

We have theoretically investigated a reaction, the cycloaddition between *ortho*-QDM with FA and DMF using DFT, the B3LYP functional and a 6-31G(d) basis set. Our results reveal that the quasi-absence of diastereoselectivity for the reaction with $R = CO_2Me$ (ratio

4b/5b = 57:43) becomes modest with $R = CO_2H$ (ratio **4a/5a** = 71:29) which is in good agreement with experiment and that the *exo* approach is kinetically more favored over the *endo*, for both FA and DMF. Due to the hydrogen bond stabilization and gain of aromaticity the activation energy barriers are very low. These stereoselectivities are correctly predicted from transition structures. Computed energy barrier explains very well the experimental stereoselectiyity of the reaction. Bond order analysis shows clearly the formation of the new bonds and the cleavage of the reacting double bonds

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FIG. 1: Reaction of *ortho*-tolualdehyde.

a: R= CO$_2$H
b: R=CO$_2$Me

(±)-*syn-trans* **4**   (±)-*anti-trans* **5**
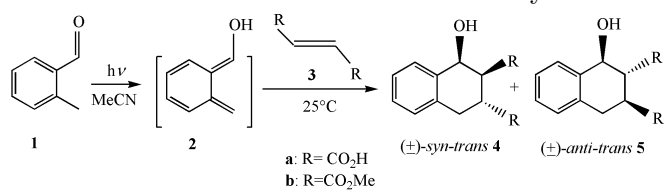
FIG. 2: Possible approaches for the reaction of *ortho*-hydroxy quinodimethane.

S-cis/S-cis = 0.0 kcal/mol   S-cis/S-trans = 0.57 kcal/mol   S-trans/S-trans = 0.58 kcal/mol
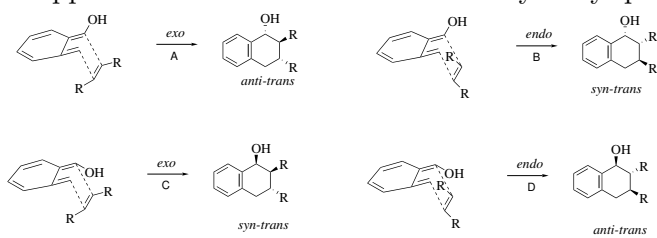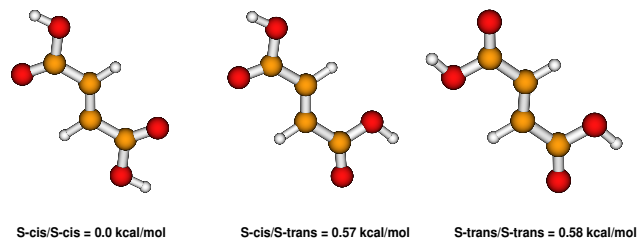
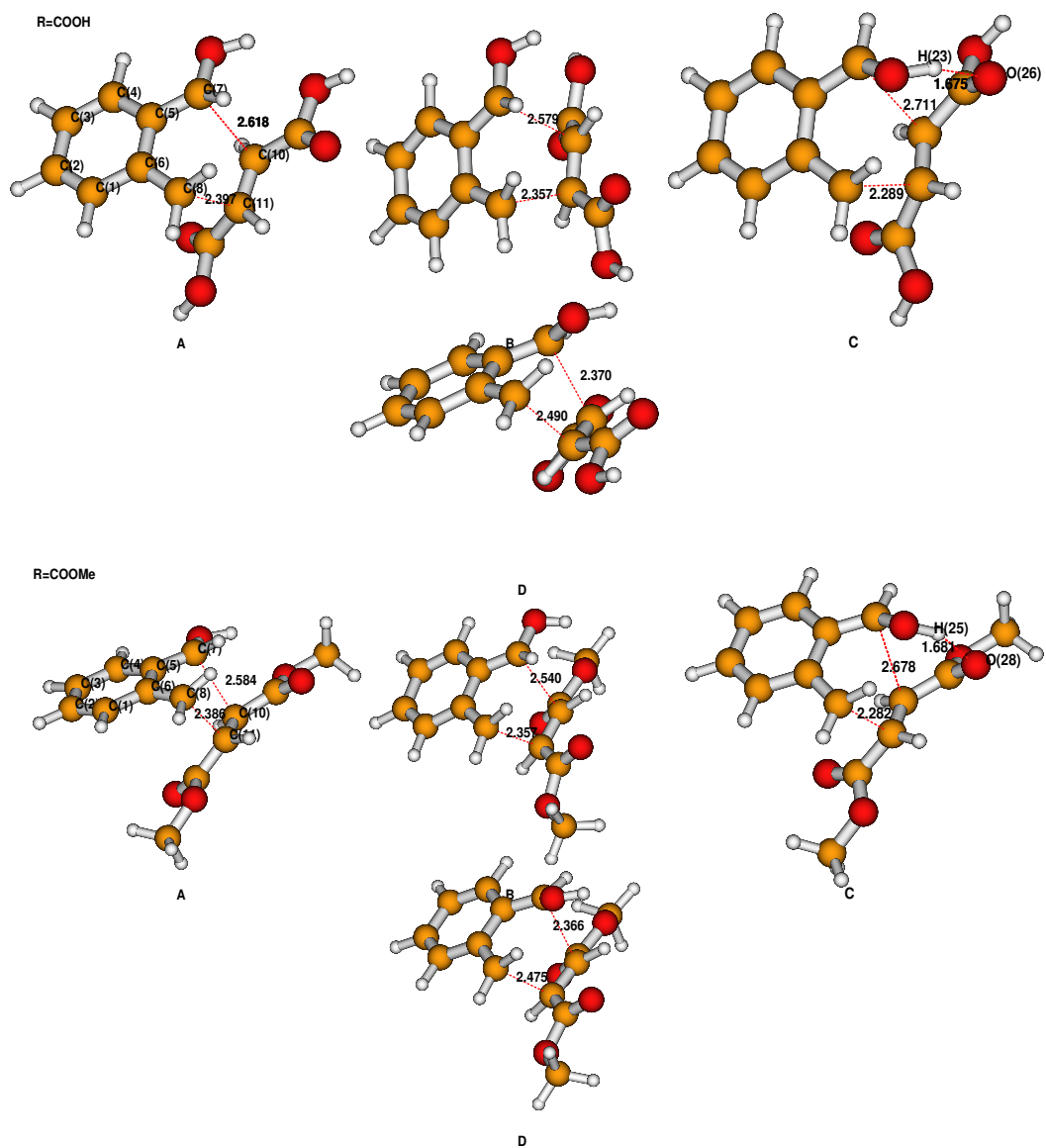FIG. 3: Possible conformations of Fumaric acid.
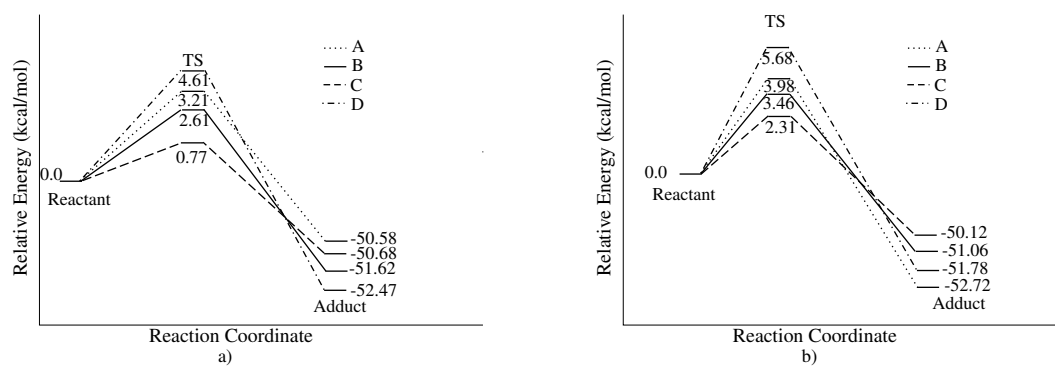
FIG. 4: Optimized Transition State Geometries.

FIG. 5: Schematic energy diagrams for a) R=CO_2H and b) R=CO_2Me.

TABLE I: Calculated Activation, Reaction energies (kcal/mol), twist angle (degrees), $\nu(\mathrm{cm}^{-1})$ and Frontier orbital energy gaps (eV).

Substrate	Conformation	Approach	$\Delta E^{\neq a}$	$\Delta E_r{}^a$	Twist angle	ν	$\Delta E_1{}^b$	$\Delta E_2{}^c$
R=COOH	S-cis/S-cis	A	3.21	-50.58	-7.83	-229.98	0.08	0.24
		B	2.16	-51.62	0.50	-284.96	0.08	0.24
		C	0.77	-50.68	19.90	-295.61	0.08	0.24
		D	4.61	-52.47	22.35	-330.66	0.08	0.24
	S-cis/S-trans	C	1.08	-53.02	13.48	-302.60	0.09	0.29
	S-trans/S-trans	C	5.78	-50.58	-17.73	-372.90	0.09	0.29
	S-trans/S-cis	C	5.75	-52.58	-17.75	-365.59	0.09	0.29
R=COOMe	S-cis/S-cis	A	3.98	-52.72	-8.51	-254.62	0.08	0.28
		B	3.46	-51.06	5.13	-302.75	0.08	0.28
		C	2.31	-50.12	18.95	-312.55	0.08	0.28
		D	5.68	-51.78	19.09	-345.25	0.08	0.28
	S-cis/S-trans	C	2.35	-54.50	22.99	-320.13	0.09	0.23
	S-trans/S-trans	C	7.04	-52.59	-18.14	-382.87	0.07	0.23
	S-trans/S-cis	C	6.73	-52.12	-18.42	-381.39	0.09	0.23

[a]zero-point energy corrected

[b]$E_{HOMO}(Diene) - E_{LUMO}(Dieneophile)$

[c]$E_{HOMO}(Dieneophile) - E_{LUMO}(Diene)$

TABLE II: Percentage of bond formation and cleavage in the TS.

Substrate	Conformation	Approach	BF_i			BC_j			BFC_{Ave}
			C_5-C_6	C_8-C_{11}	$C_{10}-C_7$	C_7-C_5	C_6-C_8	$C_{11}-C_{10}$	
R=COOH	S-cis/S-cis	A	29.75	26.24	19.16	32.11	37.37	38.35	31.75
		B	32.64	29.02	18.67	34.14	39.98	39.66	32.36
		C	34.85	33.90	15.64	39.14	47.26	46.71	36.25
		D	34.49	26.77	26.78	42.63	38.34	43.38	35.40
	S-cis/S-trans	C	36.12	33.87	15.33	38.61	47.51	45.19	36.11
	S-trans/S-trans	C	35.85	39.88	17.48	36.13	51.78	48.31	38.24
	S-trans/S-cis	C	35.74	53.26	48.88	35.74	53.26	48.88	38.58
R=COOMe	S-cis/S-cis	A	30.54	27.03	17.38	32.61	37.89	38.53	30.66
		B	33.38	29.29	19.89	35.08	40.00	39.76	32.90
		C	36.36	34.32	16.89	39.37	47.25	45.99	43.26
		D	35.03	27.32	27.18	42.76	38.71	43.02	35.67
	S-cis/S-trans	C	33.61	34.15	16.13	38.80	47.34	44.61	44.24
	S-trans/S-trans	C	36.55	40.28	17.93	36.72	51.68	47.84	38.50
	S-trans/S-cis	C	36.11	41.27	17.62	36.24	52.57	47.70	44.63

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