

## Computational study of *exo*-selective Diels-Alder cycloadditions, catalyzed by aluminum chloride

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Dedicated to Acad. Ivan Juchnovski on the occasion of his 80<sup>th</sup> birthday

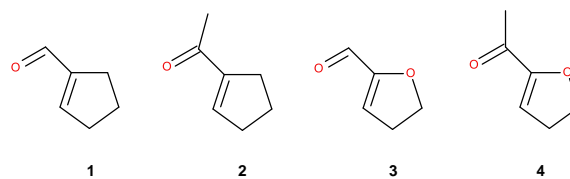
The aluminum chloride catalyzed *exo*-selective Diels-Alder reaction of cyclopentadiene with four dienophiles, with the reactive double bond in a five-membered cyclopentene or dihydrofuran ring, is studied computationally by M06-2x/6-311G(d,p) density functional theory. The electron-withdrawing group in these dienophiles is a carbonyl group, aldehyde or methyl ketone, at the reactive double bond, capable to form complexes by coordination of AlCl<sub>3</sub>. The predicted stabilization energy of the complexes is in the range of 25 to 37 kcal.mol<sup>-1</sup>. Present calculations predict stereoselectivities in very good agreement with experiment for the studied cyclopentene dienophiles. In the cases of dihydrofuran dienophiles calculated selectivities are higher than determined by experiment, although the observed trend of selectivity change between the two dihydrofuran dienophiles is predicted correctly. Free energy differences between located transition structures are interpreted mainly on the basis of steric repulsion. The majority of the studied reaction channels follow a concerted non-synchronous mechanism. In a few cases of highly asynchronous transition structures calculations predict a two-step mechanism.

**Key words:** *exo*-selectivity; Diels-Alder; DFT; cyclopentenal; dihydrofurfural; aluminum chloride; catalysis

### INTRODUCTION

The most significant feature of the Diels-Alder cycloaddition reaction, discovered a century ago, [1] is its capability to generate up to four stereogenic centers in a single reaction step. Indeed, this reaction capability has been and currently is still the focus of intense scrutiny both experimentally and theoretically. The creation of essential natural and biomimetic products is based to a significant extent on Diels – Alder type condensed ring syntheses, due to their high and predictable stereoselectivity. With [4+2] cycloadditions, the predominant stereochemical outcome consists of *endo* – Diels-Alder adducts [2]. In certain cases of synthetic design, this preference may happen to be undesirable. Therefore, cycloadditions of the [4+2] type with *exo* preference are of special interest to synthetic planners. For this reason we attempt to understand the origins of *exo*-selectivity by means of computational theoretical chemistry, applied to some experimentally known examples of this kind of reaction [3-7]. The uncatalyzed reactions of cyclopenten-1-al **1** and the corresponding methylketone **2** with cyclopentadiene, CPD, produce the corresponding adducts with *exo/endo*

selectivity up to 5:1 for the aldehyde, but with practically equal amounts of *exo* and *endo* adducts with the enone [3]. 4,5-Dihydrofurfural **3** and 2-acetyl-4,5-dihydrofuran **4** as dienophiles, Scheme 1, give with CPD, in the presence of dimethylaluminum chloride predominantly the *exo*-adduct [3].



**Scheme 1.** Studied dienophiles in their *s-cis* conformations.

The observed low to moderate selectivity of uncatalyzed additions is increased upon Lewis acid catalysis [3]. We model computationally the reactions of the above dienophiles with CPD catalyzed by AlCl<sub>3</sub> in the attempt to understand the role of Lewis catalysts in reaction stereoselectivity.

### COMPUTATIONAL DETAILS

We study reaction potential energy profiles and surfaces using the Gaussian 09 program system [8]. Our model uses M06-2x/6-311G(d,p) [9]

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calculations to search for minima and transition structures, TSs, on the reaction potential energy surfaces, PES, using the default Berny algorithm and tight optimization criteria [8,10]. Located stationary structures are further identified by vibrational analysis to ensure the presence of a unique imaginary frequency in TSs and no imaginary frequency in the minima. In addition, we characterize TSs by following intrinsic reaction coordinates, IRC, [11–13] to acquire additional information regarding the reaction mechanism from curvatures of the energy profiles. To compute kinetic stereoselectivities of each diastereoisomeric reaction channel, we calculate their respective Gibbs free energies and determine the overall reaction stereochemical distribution from the relative  $\Delta\Delta G^\ddagger$  [14,15]. Relative free energies and kinetic stereoselectivities are calculated at the experimental temperature of 195 K for better comparison with experimental results. [3] The catalytic Lewis acid in our models is  $\text{AlCl}_3$ , a simplification for  $\text{Et}_2\text{AlCl}$  used in experiments [3]. Solvent effects are accounted for using the PCM model [16] as implemented in Gaussian 09.

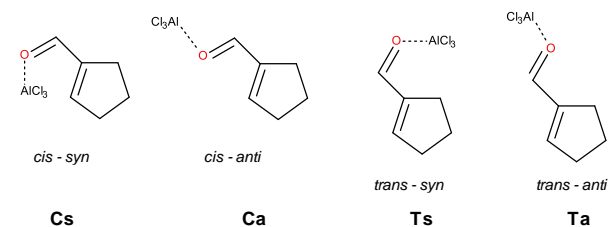
## RESULTS AND DISCUSSION

Dienophiles **1** – **4** (Scheme 1) can exist as mixtures of *s-cis* and *s-trans* isomers, denoted further as C and T. Our calculations show that dienophiles **1** – **3** in dichloromethane (DCM) have an energetic preference for the *s-trans* conformation, with the energy difference between conformers decreasing from **1** to **3**, while for dienophile **4** the *s-cis* rotamer is more stable.

We initiate our modeling of Lewis acid (LA) catalysis of the [4+2] addition with optimization of the structures of the reactant dienophile complexes with  $\text{AlCl}_3$  as starting PES minima of the reaction. Structures of  $\text{AlCl}_3$  complexes are determined by the direction of free electron pairs of carbonyl oxygen atoms, as shown on Scheme 2, and denoted for convenience as *syn* and *anti* relative to the C=C bond. Thus complex **Ca** stands for a complex with *s-cis* conformation and *anti* orientation of the LA relative to the reactive double bond of the dienophile complex. The free energies of complexes with respect to the reactants, as well as their relative free energies are listed in Table 1.

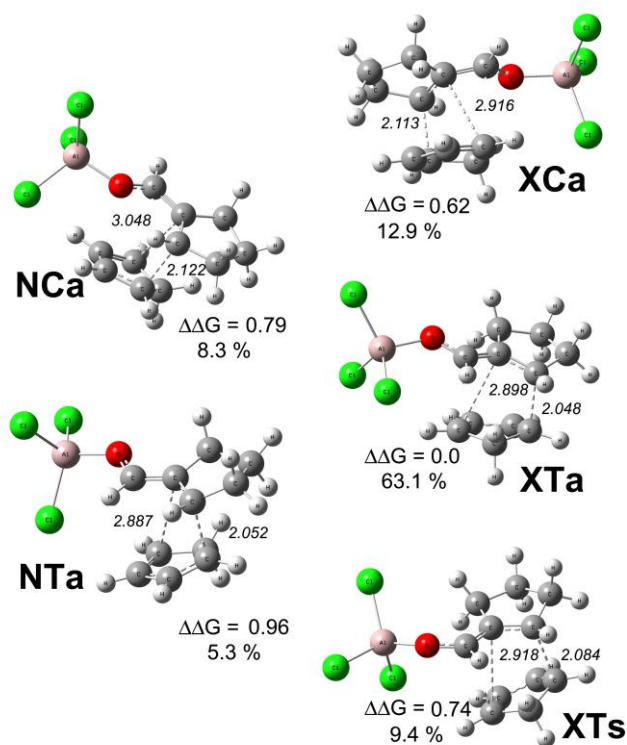
The data in Table 1 shows that the most stable complexes of the cyclopentene dienophiles **1** and **2** have the *s-trans* conformation with *anti* orientation of  $\text{AlCl}_3$ . On the other hand, the most stable complexes of the 4,5-dihydrofuran dienophiles **3**

and **4** have the *s-trans* conformation with *syn* orientation of the LA, although the energy difference between complexes **Ta** and **Ts** in the case of dienophile **3** is minimal.



**Scheme 2.** *Syn*- and *anti*-complexes of **1** with  $\text{AlCl}_3$ .

The more simple examples of *exo*-selective dienophiles are the two 1-carbonyl derivatives of cyclopentene **1** and **2**. Calculated relative free energies of TSs for their additions to CPD are listed in Tables 2 and 3, resp. The favored diastereoisomeric TSs with **1** are shown in Fig. 1 along with their corresponding free energy differences and kinetic percentage contributions at 195 K.

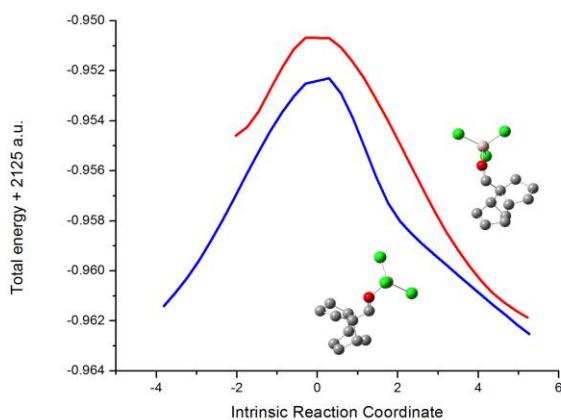


**Fig. 1.** Energetically preferred transition structures for the  $\text{AlCl}_3$  catalyzed addition of **1** to CPD, favored *exo*-isomers on the right. Incipient C-C bonds are denoted by dash lines. The shown relative TS free energies are in kcal.mol<sup>-1</sup> at 195 K. Calculated kinetic product percentage distributions are at 195 K as well.

**Table 1.** Stabilization and relative energies of AlCl<sub>3</sub> complexes of the dienophiles in kcal.mol<sup>-1</sup> at 298K and 195K. Stabilization energies are relative to free dienophiles **1** – **4** and isolated AlCl<sub>3</sub>.

	$\Delta\Delta G_{298}$		$\Delta\Delta G_{195}$		$\Delta\Delta G_{298}$		$\Delta\Delta G_{195}$	
	<b>1</b>				<b>2</b>			
<b>Ca</b>	-30.50	3.13	-34.57	3.11	-32.58	1.18	-36.82	1.09
<b>Cs</b>	-28.35	5.28	-32.60	5.08	-31.36	2.40	-35.60	2.31
<b>Ta</b>	-33.63	0.00	-37.68	0.00	-33.76	0.00	-37.91	0.00
<b>Ts</b>	-31.27	2.36	-35.64	2.04	-32.16	1.60	-36.21	1.70
	<b>3</b>				<b>4</b>			
<b>Ca</b>	-26.86	2.23	-30.89	2.47	-30.82	0.00	-34.55	0.39
<b>Cs</b>	-25.00	4.08	-29.14	4.22	-28.53	2.29	-32.60	2.34
<b>Ta</b>	-29.00	0.08	-33.01	0.35	-28.51	2.32	-32.77	2.17
<b>Ts</b>	-29.08	0.00	-33.36	0.00	-30.67	0.16	-34.94	0.00

Energetically preferred *exo* TSs, contributing to more of 70% of the reaction *exo* outcome, Fig. 1, have the *s-trans* conformation following the relative stability of the LA complexes (Table 1). The most stable *endo* TS however prefers the *s-cis* conformation. The *anti*-orientation of LA is preferred in all TSs. Calculated *exo* : *endo* ratio via all 8 TSs at 195K, 85.44 : 14.56, is in a very good agreement with the experimentally found one, 87.5 : 12.5. [3]. A computation of IRCs from favored *endo* and *exo* TSs is given on Fig. 2. The resulting smooth IRC energy profiles indicate concerted non-synchronous reaction mechanisms.

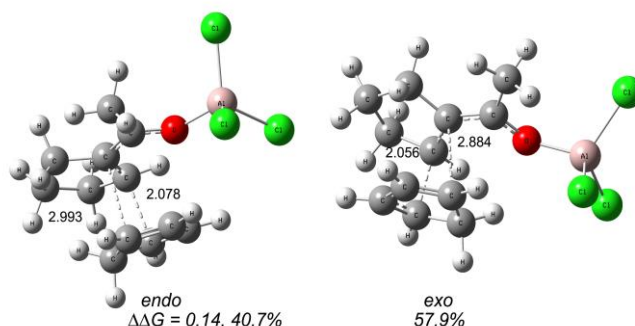
**Fig. 2.** Intrinsic reaction coordinate following for the AlCl<sub>3</sub> catalyzed addition of **1** to CPD, the upper red curve refers to a NT addition, and the bottom blue curve to the XT favored addition. Optimized product structures are shown on the right (product) side of the graphic. Hydrogen atoms are removed for clarity

The less favored TS *endo*-isomers, Fig. 1, left, also indicate the reason for the observed diastereoselectivity, even though these structures satisfy the Alder-rule [2] for “maximum accumulation of unsaturation”, or stacked  $\pi$ -bonds. The bulk of AlCl<sub>3</sub> catalyst, bound to the electron-withdrawing group, brings a strong disadvantage to the corresponding TSs due to steric repulsion.

Fig. 3 depicts favored TSs for the reaction of **2** and CPD with their corresponding kinetic contributions to the reaction stereochemical outcome. Energetically preferred TSs in the case of dienophile **2** have the *s-cis* conformation (Table 2, Fig. 3), although the *s-trans* reactant complexes are more stable than the *s-cis* ones (Table 1).

**Table 2.** Relative free energies of TSs for the addition of **1** to CPD, kcal.mol<sup>-1</sup>, and selected geometry parameters, incipient bonds d<sub>1</sub> and d<sub>2</sub>, numbered in the order of their formation, in Å. *Endo* is denoted N, while *exo* is X. Reaction asynchronicity may be deduced from the difference between lengths of incipient C-C bonds, d<sub>2</sub>-d<sub>1</sub>, or from their ratio d<sub>2</sub>/d<sub>1</sub>.

	$\Delta\Delta G$	$\Delta\Delta G$	d <sub>1</sub>	d <sub>2</sub>	d <sub>2</sub> -d <sub>1</sub>	d <sub>2</sub> /d <sub>1</sub>
	298	195				
<b>NCa</b>	0.88	0.79	2.122	3.048	0.926	1.436
<b>NCs</b>	3.59	3.52	2.159	2.981	0.822	1.381
<b>NTa</b>	1.06	0.96	2.052	2.887	0.835	1.407
<b>NTs</b>	1.89	1.63	2.051	2.973	0.922	1.450
<b>XCa</b>	0.58	0.62	2.113	2.916	0.803	1.380
<b>XCs</b>	3.02	2.89	2.145	2.952	0.807	1.376
<b>XTa</b>	0.00	0.00	2.048	2.898	0.850	1.415
<b>XTs</b>	0.90	0.74	2.084	2.918	0.834	1.400

**Fig. 3.** Dominant TSs for the model reaction of **2** with CPD, catalyzed by AlCl<sub>3</sub>. Relative free energies, in kcal.mol<sup>-1</sup>, and product percentage distributions are at the experimental temperature, 195 K.

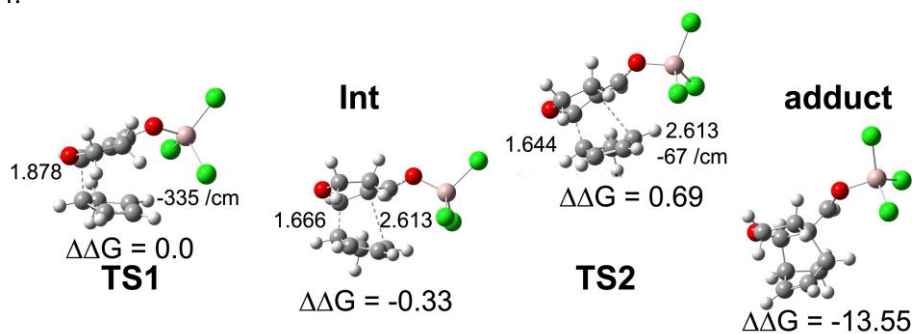
Moreover, at difference to dienophile **1**, only two TSs, **NCa** and **XCa**, contribute to the reaction outcome. The relative stabilities of **NCa** and **NCs**, as well as of **XCa** and **XCs** correspond to these of the *anti* – *syn* isomers of LA complexes, **NCs** being additionally hindered by repulsive interaction with CPD. The *s-trans* isomers, **XT**, suffer a repulsive interaction between their methyl group and the CH<sub>2</sub> fragment of CPD. Calculated *exo* : *endo* ratio via all 8 TSs at 195 K, 41.8 : 58.2, is in reasonable agreement with the experimentally found one, 50 : 50. [3]. Note that the energy difference between **NCa** and **XCa** of only 0.14 kcal.mol<sup>-1</sup> is about the limit of precision of DFT computations. IRC analyses indicate that both **XCa** and **NCa** products are the result of concerted reactions.

**Table 3.** Relative free energies for TSs for the addition of **2** to CPD, kcal mol<sup>-1</sup>, and selected geometry parameters (incipient bonds), Å. For notations see Table 2.

TS	$\Delta\Delta G$	$\Delta\Delta G$	$d_1$	$d_2$	$d_2-d_1$	$d_2/d_1$
	298	195				
<b>NCa</b>	0.00	0.00	2.078	2.993	0.915	1.440
<b>NCs</b>	1.94	1.99	2.109	2.962	0.853	1.404
<b>NTa</b>	3.41	3.03	2.019	2.864	0.845	1.419
<b>NTs</b>	4.75	4.21	2.016	2.964	0.948	1.470
<b>XCa</b>	0.27	0.14	2.056	2.884	0.828	1.403
<b>XCs</b>	1.56	1.55	2.077	2.884	0.807	1.389
<b>XTa</b>	3.28	2.94	2.056	2.923	0.867	1.422
<b>XTs</b>	4.76	4.15	2.050	2.894	0.844	1.412

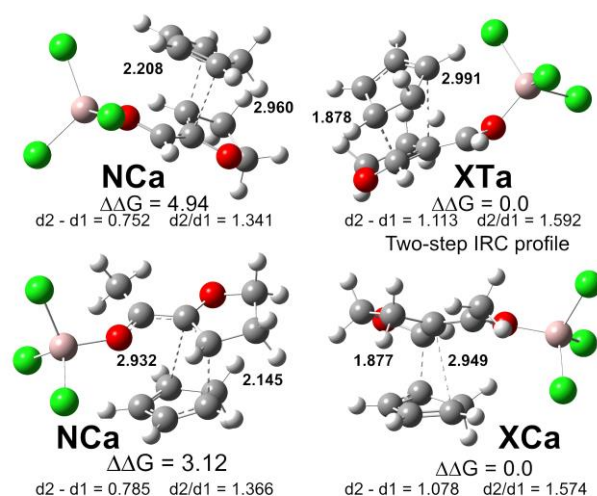
Experimentally determined *exo*-selectivity at 195 K is significantly higher in the [4+2] additions of 4,5-dihydrofurfural **3** (*exo* : *endo* = 97.5 : 2.5) and 4,5-dihydro-2-furylmethylketone **4** (*exo* : *endo* = 93.8 : 6.2) to CPD than in the corresponding reactions of carbonyl-substituted hydrocarbons **1** and **2** [3].

Our M06-2x/6-311G(d,p) model calculations with the AlCl<sub>3</sub> catalyst show overestimated *exo* – selectivity for **3** and **4**, while indicating increased asynchronicity of the favored TSs for the latter reactions, Fig. 4.



**Fig. 5.** Calculated Gibbs free energies of PES stationary points around the rate-determining **TS1** of 4,5-dihydrofurfural with CPD, left, at the experimental temperature, 195 K, catalyzed by AlCl<sub>3</sub>. Relative energies are in kcal.mol<sup>-1</sup>, incipient C-C bond lengths (dashed lines) are in Å. The imaginary frequencies of the two TSs (as negative, in cm<sup>-1</sup>) are also shown. The final product is at the right, with free energy out of scale.

IRC following for the *endo*-TSs shows that the studied [4+2] addition is still a concerted though nonsynchronous reaction. In the two most stable *exo*-TSs the  $d_2/d_1$  ratio is significantly increased to 1.593 for dienophile **3**, and 1.574 for dienophile **4**. IRC following for **4** shows that the reaction still remains a concerted single step addition, while for **3** the product branch of the IRC arrives first at an intermediate, which is ca. 0.5 kcal mol<sup>-1</sup> lower in energy than the TS. Next we find a second TS, indicating that at a ratio of  $d_2/d_1 \geq 1.57$  the concerted mechanism becomes a two-step one, see Fig. 5.



**Fig. 4.** Most stable *endo* and *exo* TSs for the [4+2] additions of **3** (upper row) and **4** to CPD catalyzed by AlCl<sub>3</sub>. Incipient C-C bonds are indicated by dashed lines, with corresponding distances in Å. Relative free energy differences in kcal.mol<sup>-1</sup> are at the experimental temperature, 195 K.

Nevertheless, present calculations predict correctly the experimentally observed reduction of selectivity in the reaction of the methyl substituted dienophile **4** relative to **3** [3].

## CONCLUSIONS

Synthetically important *exo*-selective Diels – Alder additions are reproduced reasonably well using contemporary DFT calculations. This can be meaningful in view of possible synthetic planning of condensed ring compounds, such as alkaloid and polysaccharide systems, [3-7] requiring *exo*-junctions. With the studied dienophiles **1** – **4**, *exo*-selectivity is mostly the result of steric interactions, although the cyclic dienophile C=C bonds with attached electron-withdrawing carbonyl groups could also contribute by reaction strain. [17] Lewis acid catalysis, while enhancing selectivity, does not fundamentally change the reaction outcome, even in the cases of mechanistic changes from a nonsynchronous concerted to a biradicaloid two-step reaction energy profile.

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## ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ НА ЕКЗО-СЕЛЕКТИВНИ ПРИСЪЕДИНЯВАНИЯ ПО ДИЛС – АЛДЕР, КАТАЛИЗИРАНИ ОТ АЛУМИНИЕВ ХЛОРИД

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(Резюме)

Изследвана е катализираната от алуминиев хлорид екзо-селективна реакция на Дилс-Алдер между циклопентадиен и четири диенофила с петатомни пръстени, циклопентен и дихидрофуран, съдържащи диенофилната двойна връзка. Използвана е теорията на функционала на плътността в приближение M06-2x/6-311G(d,p). Електронакцепторната група на използваните диенофили е карбонил, алдехид или кетон, свързан пряко с двойната връзка и способен да образува комплекси чрез координиране с алуминиев хлорид. Стабилизиращите енергии на тези комплекси са в рамките на 25 до 37 ккал.мол<sup>-1</sup>. Пресмятанията предсказват много добре наблюдаваната експериментално селективност на циклопентеновите диенофили, но преувеличават резултатите за дихидрофурановите производни. Независимо от това е предсказано правилно намаляването на селективността при ацетил-4,5-дихидрофуран в сравнение с 4,5-дихидрофурфурал. Разликата между изчислените свободни енергии на намерените преходни структури за реакциите се обяснява главно със стерични взаимодействия. Повечето от изследваните реакционни пътища отговарят на съгласуван несинхронен механизъм. В малкото случаи на силно асинхронни преходни структури пресмятанията предсказват двустепенен механизъм на реакцията.