Tetrahedron Letters 54 (2013) 4030–4033

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A theoretical study of the mechanism, stereoselectivity and Lewis acid catalyst on the Diels–Alder cycloaddition between furan and activated alkenes

Samir Bouacha [a], Abdelmalek Khorief Nacereddine [a,b,*], Abdelhafid Djerourou [a]

[a] Laboratoire de Synthèse et Biocatalyse Organique, Département de Chimie, Faculté des Sciences, Université Badji Mokhtar Annaba, BP 12, 23000 Annaba, Algeria
[b] Ecole Normale Supérieure d'Enseignement Technologique (ENSET) de Skikda, Azzaba, Skikda, Algeria

ARTICLE INFO

Article history:
Received 15 January 2013
Revised 6 May 2013
Accepted 17 May 2013
Available online 23 May 2013

Keywords:
Diels–Alder cycloadditions
Stereoselectivity
DFT calculations
Lewis acid catalyst
Mechanism
Solvent effects

ABSTRACT

A theoretical study of the mechanism, stereoselectivity, Lewis acid catalysts and solvent effects on the Diels–Alder reactions of methyl acrylate and methyl methacrylate with furan has been carried out through DFT calculations at the B3LYP/6-31G* level of theory. Bond order and charge transfer analysis indicate that these reactions take place via an asynchronous concerted mechanism. The Lewis acid catalyst changes the nature of the mechanism but not the stereoselectivity. The inclusion of solvent effects does not change the obtained results in the gas phase study.

Diels–Alder (DA) cycloaddition reactions are a powerful tool in organic synthesis and in the chemical industry.[1] In addition, they represent a versatile synthetic tool for constructing simple and complex molecules. The use of butadiene and ethylene derivatives to form six-membered carbocycles in a single-step process is often used for the synthesis of natural products and bioactive molecules.[2] Density functional theory (DFT) has become a useful method for explaining the reactivity and selectivity of cycloaddition reactions.[3] There are many experimental and theoretical reports on the study of the origin of the stereoselectivity of Diels–Alder cycloadditions. Recently, we studied the Diels–Alder cycloaddition between difluoromethylenecyclopropane and furan[4] and found that this reaction proceeded via a synchronous concerted mechanism. This reaction favored the formation of the *endo* cycloadduct due to the favorable secondary interaction in the *endo* transition state.

Herein, the DA reactions between furan **3** and methyl acrylate (MA, **1**), and methyl methacrylate (MMA, **2**) in the absence and in the presence of aluminum trichloride ($AlCl_3$) as the catalyst, have been studied (Schemes 1 and 2). The influence of the aluminum trichloride catalyst has been investigated taking into account the formation of a complex between the aluminum atom of the catalyst and the carbonyl oxygen atom of MA (**1**) and MMA (**2**).

The aim in this work was to gain an understanding of the role of the $AlCl_3$ catalyst and solvent effects on the stereoselectivity and mechanism of the DA cycloaddition reactions of MA (**1**) and MMA (**2**) with furan.

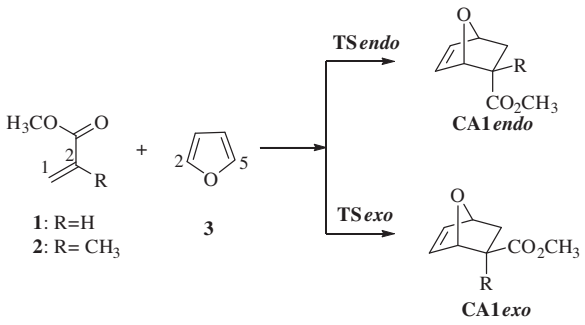
Geometry optimizations of the critical points (reactants, transition states and products) were carried out using DFT methods at the B3LYP/6-31G* level of theory.[5] Frequency calculations were used to confirm the nature of the stationary points. Transition states were found to have only one negative eigenvalue. The electronic populations were computed using NPA (natural population analysis). The electronic structures of the stationary points and bond orders (Wiberg indexes)[6] were analyzed by the natural bond orbital (NBO) method.[7] Solvent effects were evaluated at the same level of theory using the polarized continuum model (PCM).[8] All calculations were performed using GAUSSIAN 03.[9]

Experimentally,[10] the Diels–Alder cycloaddition of furan (**3**) with methylacrylate MA (**1**) in absence of Lewis acid catalyst favoring the formation of the *endo* product gives the ratio (6:4). The Lewis acid catalyst enhances the formation of *endo* cycloadduct (7:1). The reaction between furan (**3**) and methylmetacrylate MMA (**2**) gives only the *endo* cycloadduct in absence of any Lewis acid catalyst (Table 1).

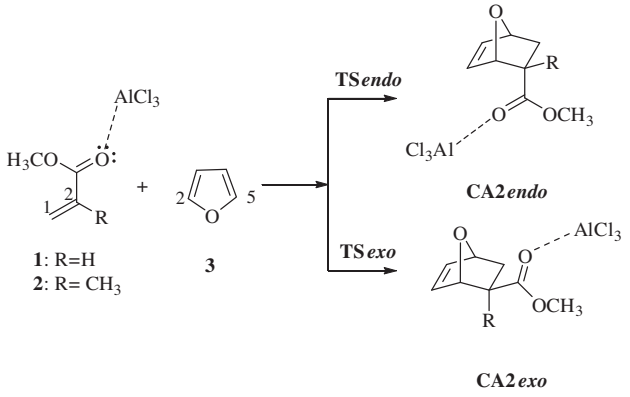
As a computational model, we used the $AlCl_3$ catalyst to investigate the stereoselectivity *endo* and *exo* of these cycloaddition reactions.

* Corresponding author. Tel.: +213 0778787313.
E-mail address: malek_khorief@yahoo.com (A.K. Nacereddine).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.079



Scheme 1. Diels–Alder cycloaddition reaction between methyl acrylate or methyl methacrylate and furan.



Scheme 2. Diels–Alder cycloaddition reaction between methyl acrylate and methyl methacrylate with furan in presence of a Lewis acid catalyst ($AlCl_3$).

Table 1
Experimental stereoselectivity ratio

Reaction	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	*Endo*/*exo* ratio
1 + **3**	––	CH_2Cl_2	27	4	62	6:4
	BF_3–OEt_2	CH_2Cl_2	5	10	75.5	7:3
2 + **3**	––	CH_2Cl_2	rt	8	8	1:0

The nature of the mechanism of these DA cycloaddition reactions has been analyzed using the global indices, as defined in the context of DFT, which are useful tools to understand the reactivity of molecules in their ground states. The global electrophilicity index ω, which measures the stabilization in energy when the system acquires an additional electronic charge, ΔN from the environment, is given by the following expression[11] $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ, and the chemical hardness η. Both quantities may be approached in terms of the one-electron energies of the Frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively.[12] The global hardness η of the system is given by $2\eta = 1/S$.[12] On the other hand, the nucleophilicity index is defined[13] as $N = \varepsilon_{HOMO} - \varepsilon_{HOMO(TCE)}$, where ε_{HOMO} is the HOMO energy of the nucleophile and $\varepsilon_{HOMO(TCE)}$ corresponds to the HOMO energy of tetracyanoethylene (TCE), taken as a reference.

Table 2
Global properties, in eV, of the diene and dienophiles

	HOMO	LUMO	μ	η	ω	N
MMA **2** + LA	−7.75	−3.40	−5.58	4.35	3.57	1.37
MA **1** + LA	−7.75	−3.16	−5.46	4.60	3.24	1.37
MA **1**	−7.37	−1.22	−4.30	6.15	1.50	1.75
MMA **2**	−7.27	−1.03	−4.15	6.23	1.38	1.85
Furan **3**	−6.10	0.52	−2.79	6.61	0.59	3.02

Global properties analysis

The difference between the global electrophilicity indices of the reagents $\Delta\omega$, may be used to predict the polar character of the process.[14] The static global properties: electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and nucleophilicity (N) indices of MA (**1**), MMA (**2**) and the corresponding Lewis acid coordinated complexes of **1**+LA, **2**+LA and furan (**3**) are listed in Table 2. The electronic chemical potential of furan (**3**) ($\mu = -2.79$ eV) is higher than that of dienophiles **1** and **2** ($\mu = -4.30$ and -4.15 eV, respectively), and higher also than the potential of the corresponding LA complexes ($\mu = -5.46$ and -5.58 eV, respectively). Therefore, the charge transfer (CT) of these cycloaddition reactions will take place from furan (**3**) to dienophiles **1** and **2**, and from furan (**3**) to complexes **1**+LA and **2**+LA. These results are in agreement with the CT analysis performed on the TSs (see later).

The global electrophilicity of dienophiles **1** and **2** are $\omega = 1.50$ and 1.40 eV, respectively. According to the absolute scale of electrophilicity, these compounds may be classified as strong electrophiles.[14] The presence of the electron-donating CH_3 group at the α position decreases the electrophilicity of MMA (**2**). Coordination of $AlCl_3$ to the carbonyl oxygen atom increases considerably the electrophilicity of dienophiles **1** and **2** to 3.23 eV for (**1**+LA) and 3.57 eV for (**2**+LA). On the other hand, furan (**3**) has a very low electrophilicity value: 0.582 eV, being classified as a marginal electrophile. While MA (**1**) and MMA (**2**), and the corresponding LA complexes, have very low nucleophilicity indices, furan (**3**) has a high nucleophilicity index, $N = 3.04$ eV. The electrophilicity difference for the couples: MA (**1**)/furan (**3**), MMA (**2**)/furan (**3**), MA **1**+LA/furan (**3**), MMA **2**+LA/furan are 0.92, 0.82, 2.64, and 2.98 eV, respectively. Therefore, the LA increases the polar character of these cycloaddition reactions.

Study of the uncatalyzed DA cycloadditions

Relative energies (in kcal/mol) for the stationary points (reactants, TSs and cycloadducts) involved in these DA reactions, in the gas phase and in a solvent (CH_2Cl_2), are collected in Table 3. The total energies (in a.u) are given in the Table in the Supplementary data. These DA cycloaddition reactions can take place along two stereoisomeric reaction channels, *endo* and *exo* (see Scheme 1). The structures of the TSs are given in Figure 1. From Table 3, we can see that the *endo* stereoisomer is favored over the *exo* stereoisomer by 0.56 kcal/mol. This may be due to the favorable interaction between the secondary orbitals via the *endo* approach. On the other hand, the product formed from the *exo* approach is more

Table 3
Relative energies (kcal/mol) for the stationary points involved in the DA reactions of MA (**1**) and MMA (**2**) with furan (**3**) in the gas phase ΔE and in CH_2Cl_2 [ΔE (CH_2Cl_2)]

System	ΔE	ΔE (CH_2Cl_2)
TS1*endo*	24.86	22.56
TS1*exo*	25.42	23.01
CA1*endo*	−1.22	−2.55
CA1*exo*	−1.73	−3.28
TS2*endo*	27.51	25.41
TS2*exo*	27.77	25.26
CA2*endo*	−1.80	0.75
CA2*exo*	−2.23	0.69