

Tandem Diels–Alder Aromatization Reactions of Furans under Unconventional Reaction Conditions – Experimental and Theoretical Studies

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Dedicated to Prof. Luis Oro^[‡]

Keywords: Cycloadditions / Density functional calculations / Furans / Heterogeneous catalysis / Lewis acids / Microwaves

Silica-supported Lewis acids are good catalysts for Diels–Alder reactions between furan and acrylonitrile and methyl acrylate at room temperature. When 2,5-dimethylfuran is used as the diene, yields of the Diels–Alder adducts with methyl acrylate are lower, due in part to the appearance of aromatization products. The use of microwave activation results in some cases in good yields of aromatic products and, as such, constitutes a good synthetic route to polysubstituted

aromatic compounds. Computational studies on the reaction mechanism and the role of the catalyst on the product distribution show that “hard” Lewis acids, such as aluminum derivatives, make ring-opening of the adduct much easier, affording aromatic products. The theoretical results are in excellent agreement with the relative reactivity observed for the different dienes and dienophiles.

Introduction

Diels–Alder reactions of furan and its derivatives have received a great deal of attention; this interest is for two main reasons. Firstly, furan and some of its derivatives are inexpensive compounds obtained from agricultural by-products.^[1] Secondly, the cycloadducts are versatile intermediates in the preparation of carbohydrates and other biologically active compounds.^[2]

The use of furans as dienes has resulted in some problems related to their sensitivity to the most common Lewis acid catalysts, the ease of reversibility of their reactions, and the formation of by-products. In view of these drawbacks, a range of special reaction conditions has been developed including, for instance, very long reaction times,^[3] high pressure,^[4,5] ZnI₂ in sealed tubes,^[6] cupric fluoroborate and long reaction times,^[7] cation-exchanged K10 clays,^[8] Y zeolite,^[9] and, more recently, chiral bis(oxazoline)copper catalysts.^[10] We have shown that ZnCl₂,^[11] TiCl₄, and Et₂

AlCl₃^[12,13] supported on silica gel are suitable catalysts for Diels–Alder reactions between furan and a number of dienophiles,^[14] including chiral acrylates,^[15] under mild but unconventional reaction conditions (use of a solid catalyst in the absence of a solvent). In view of these results, we considered it interesting to explore the use of silica-supported Lewis acids as catalysts in Diels–Alder reactions of 2,5-dimethylfuran.

Results and Discussion

Experimental Reactivity Results

Firstly, we compared the behavior of furan (**1**) and 2,5-dimethylfuran (**2**) in their reactions with methyl acrylate (**3a**) and acrylonitrile (**3b**), catalyzed by silica and by three silica-supported Lewis acids (Scheme 1 and Table 1). The catalysts were obtained by treatment of silica with ZnCl₂, Et₂AlCl, and TiCl₄, and are henceforth denoted as Zn(Si), Al(Si), and Ti(Si), respectively.

The results obtained depend on the nature both of the diene and of the dienophile. As previously reported,^[16] Zn(Si) is a better catalyst than Al(Si) and Ti(Si) for Diels–Alder reactions involving α,β -unsaturated nitriles such as acrylonitrile, and good yields of the corresponding cycloadducts were obtained with this catalyst. With this dienophile, the reactions carried out using furan as the diene produced the *endo* cycloadduct (**4bn**) as the major product, the situation being reversed in the case of 2,5-dimethylfuran, with which the *exo* cycloadduct (**5bx**) was the major product. Any catalysis due to the support can be ruled out, because the reaction is not promoted by silica gel (Table 1).

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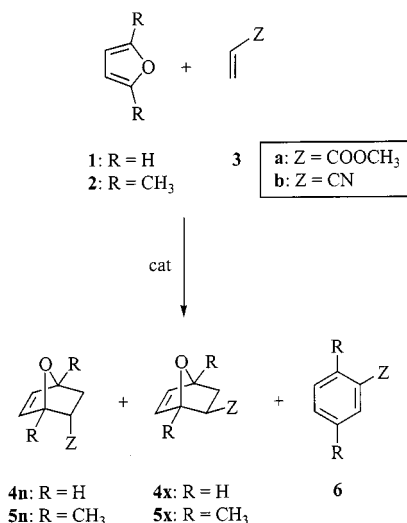
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Table 1. Results obtained on treatment of furan (**1**) and 2,5-dimethylfuran (**2**) with methyl acrylate (**3a**) and acrylonitrile (**3b**), carried out at room temperature; **n** = *endo*, **x** = *exo*

Diene	Dienophile	Catalyst	<i>t</i> [h]	Yield of 4 or 5 (%) ^[a]	n/x ^[a]	Yield of 6 (%) ^[a]
1	3a	SiO ₂	24	75	86:14	—
		Zn(Si) ^[b]	24	75	81:19	—
		Ti(Si) ^[c]	24	71	73:27	—
1	3b	Zn(Si)	3	78	67:33	—
		Ti(Si)	24	—	—	—
2	3a	SiO ₂	24	24	66:34	—
		Zn(Si)	24	25	63:37	—
		Al(Si) ^[c]	24	32	75:25	6
		Ti(Si)	2	8	62:38	—
			24	—	—	14
2	3b	SiO ₂	3	—	—	—
		Zn(Si)	3	79	37:63	—
		Al(Si)	3	—	—	—
		Ti(Si)	3	15	38:62	—

[a] Determined by NMR. — [b] Ref.^[11]. — [c] Ref.^[12,13]



Scheme 1

In the reactions carried out with methyl acrylate as the dienophile, the use of silica-supported Lewis acids resulted in good yields of the corresponding cycloadducts **4an** and **4ax** when furan was used as the diene,^[14,15] but the yields obtained with this dienophile and 2,5-dimethylfuran were much lower. These results do not indicate that 2,5-dimethylfuran is necessarily less reactive than furan, but more that the difficulty in obtaining good yields was due to competition from other reactions.

The first of these reactions is the retro Diels–Alder reaction. The equilibrium position changes from one diene and one dienophile to another. Cook and Cracknell have described^[17] reactions of fumaronitrile in which there was a greater yield of cycloadducts with 2,5-dimethylfuran than with furan. On the other hand, Dewar and Pierini^[18] have reported that this behavior was reversed when maleic anhydride (a dienophile more similar to methyl acrylate) is used as a dienophile. Furthermore, both the forward and reverse reactions are faster with 2,5-dimethylfuran, meaning that equilibrium is also reached more quickly.

The second competing reaction, not observed in the case of acrylonitrile, is ring-opening of the cycloadducts, followed by aromatization to yield methyl 2,5-dimethylbenzoate (**6a**).

In order to modify the results, we decided to assess the effect of temperature on the reactions. However, we found that the use of conventional heating gave irreproducible results. It is known that mineral oxides are poor heat conductors and that conventional methods result in inhomogeneous heating and even in overheating. Microwave irradiation is an unconventional source of energy, the usefulness of which in synthetic organic chemistry has been increasingly recognized in recent years.^[19,20] This energy source is particularly suitable for reactions carried out with a solid catalyst in the absence of a solvent.^[21] In fact, metal oxides do absorb microwaves efficiently and this phenomenon results in rapid and homogeneous heating of the reaction mixture. In this manner, microwave activation in the presence of silica gel has enabled a furan derivative to undergo successful intramolecular Diels–Alder reaction even though failing to undergo the reaction under normal thermal treatment.^[22] Microwave activation has also recently been employed to carry out Diels–Alder reactions of furans promoted by K10^[23] or without a catalyst.^[24]

First of all, we used microwave activation in the treatment of 2,5-dimethylfuran with methyl acrylate and acrylonitrile, using a focused microwave reactor, and the results obtained in these experiments are collected in Table 2.

In agreement with previous studies, silica gel was not very efficient in the promotion of the reactions. With methyl acrylate, an increase in the amount of aromatic product was observed, probably accompanied by an increase in the retro Diels–Alder reaction. In fact, a small amount of cycloadduct was only obtained when the Zn(Si) catalyst was used. In the reactions involving acrylonitrile, the corresponding aromatic product was not obtained. Nevertheless, the reaction results were not noticeably improved and only with Zn(Si) were cycloadducts achieved, in a yield of 80%, in this case using a relatively low temperature and a reaction

Table 2. Results obtained on treatment of 2,5-dimethylfuran (**2**) with methyl acrylate (**3a**) and with acrylonitrile (**3b**), carried out in a focused microwave reactor under argon pressure; **n** = *endo*, **x** = *exo*

Dienophile	Catalyst	<i>T</i> [°C]	<i>p</i> [bar]	<i>t</i> [min]	Yield of 5 (%) ^[a]	5n/5x ^[a]	Yield of 6 (%)
3a	SiO ₂	90	3	15	8	—	—
	SiO ₂	70	3	30	9	—	—
	Ti(Si)	85	—	45	—	—	[b]
	Al(Si)	70	—	45	—	—	[b]
	Zn(Si)	50	—	15	10	67:33	—
	Zn(Si)	70	—	15	29	65:35	[b]
3b	SiO ₂	70	3	15	24	48:52	—
	Ti(Si)	70	3	15	11	50:50	—
	Al(Si)	70	3	15	15	50:50	—
	Zn(Si)	70	3	15	65	50:50	—
	Zn(Si)	40	3	7	80	48:52	—

[a] Determined by NMR. — [b] The appearance of more than 20% of **6a** was observed, but the appearance of other by-products did not allow accurate determination.

time of only 7 min. We also used a domestic microwave oven, permitting the use of a closed vessel in which high pressures are probably reached. Under these conditions, aromatic compounds were the only products obtained. The best yields were obtained with the aluminum- and titanium-immobilized catalysts, Al(Si) and Ti(Si). With regard to the reagents, aromatization was achieved more easily with the methyl acrylate adducts than with the acrylonitrile adducts (Table 3).

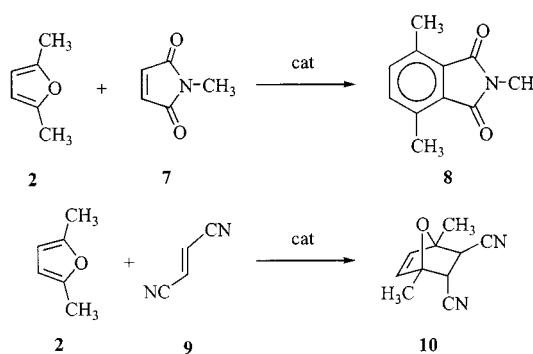
Table 3. Results obtained on treatment of 2,5-dimethylfuran (**2**) with methyl acrylate (**3a**) and with acrylonitrile (**3b**), carried out in a domestic microwave oven at 780 W in a closed Teflon vessel

Dienophile	Catalyst	<i>t</i> [min] ^[a]	Yield of 6 (%) ^[b]
3a	SiO ₂	45	—
	Zn(Si)	45	24
	Al(Si)	35	64
	Ti(Si)	45	80
3b	SiO ₂	45	—
	Zn(Si)	45	23
	Al(Si)	35	50
	Ti(Si)	45	50

[a] Final temperature: 120 °C. — [b] Determined by NMR using CH₂Br₂ as the internal standard.

The different behavior of nitrile and carbonyl compounds is rather surprising. We therefore decided to explore this area further by investigating the reactions with 2,5-dimethylfuran of a dicarbonyl dienophile, namely *N*-methylmaleimide (**7**), and of a dinitrile dienophile, namely fumaronitrile (**9**) (Scheme 2), using the same immobilized Lewis acids under microwave activation conditions. The results obtained in these experiments are collected in Table 4.

The differences found in these reactions were very significant. With *N*-methylmaleimide, high yields of the aromatic compound **8** were obtained, with Al(Si) and Ti(Si) once again proving to be more efficient catalysts than Zn(Si). It can be seen that the differences between the two kinds of microwave activation are not due to the reaction temperature reached, because with the focused microwave reactor lower yields were obtained even at 150 °C. Cintas et al.



Scheme 2

have studied the reaction between 2,5-dimethylfuran and *N*-methylmaleimide under microwave activation conditions in the presence of K10-montmorillonite, and they did not observe any aromatization product.^[23] It is important to note the clear differences between a solid with strong Brønsted acid properties, such as the K10, and the immobilized Lewis acids used in this work. Surprisingly, with fumaronitrile the aromatic product was not obtained, and the Diels–Alder cycloadduct **10** was the only product observed with all three immobilized Lewis acids. Whereas the aromatization of the corresponding cycloadduct was easily effected in the presence of a strong base, as described previously,^[17] the same reaction was not facile when an acid catalyst was used.

The observed differences between carbonyl and nitrile compounds are not easy to explain, and we therefore considered it interesting to carry out some theoretical calculations on the aromatization process.

Computational Results

The first step of the mechanism proposed for the aromatization of the Diels–Alder adducts consists of the breaking of one of the O–C bonds of the C–O–C bridge to give an intermediate zwitterion (Scheme 3). Given the electron-withdrawing character of the CN and COOMe groups, it would seem logical to conclude that the C–O bond broken should be that producing the most stable zwitterion.

Table 4. Results obtained on treatment of 2,5-dimethylfuran (**1b**) with *N*-methylmaleimide (**7**) and with fumaronitrile (**9**), under microwave activation conditions

Dienophile	Catalyst	<i>E</i> [W] (<i>T</i> [°C])	<i>t</i> [min]	Yield of 8 (%) ^[a]	Yield of 10 ^[b] (%)
7	Ti(Si)	780 (120) ^[c]	45	80	—
	Ti(Si)	240 (90) ^[d]	45	11	—
	Ti(Si)	270 (150) ^[d]	45	55	—
	Al(Si)	780 (120) ^[c]	45	83	—
	Zn(Si)	780 (120) ^[c]	45	50	—
9	Ti(Si)	780 (120) ^[c]	45	—	60
	Al(Si)	780 (120) ^[c]	45	—	50
	Zn(Si)	780 (120) ^[c]	45	—	20

^[a] Determined by NMR using CH₂Br₂ as the internal standard. — ^[b] Determined by NMR using fumaronitrile as the internal standard. — ^[c] Reactions carried out in a domestic microwave oven in a closed Teflon vessel; the temperature refers to the final temperature measured. — ^[d] Reactions carried out in a focused microwave reactor under 3 bar of argon.

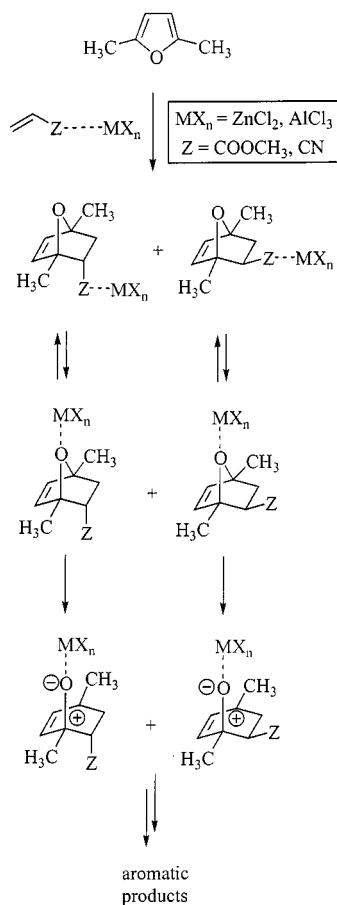
terion, namely the one with the greater separation between the positive charge and the electron-withdrawing group (Scheme 3). However, in the case of the acrylonitrile cycloadducts, we calculated both ring-opening possibilities in order to confirm this hypothesis.

As shown in Scheme 3, the ring-opening should be favored by the coordination of the Lewis acid to the bridge oxygen atom, as should the stabilization of the final zwitterion. Consequently, we calculated the structures and energies of the Diels–Alder adducts with the Lewis acid coordinated to that oxygen atom. However, in all cases the energies

of these structures were found to be higher than those corresponding to the Diels–Alder cycloadduct with the Lewis acid coordinated to the cyano or carbonyl groups. Thus, because of the Curtin–Hammett principle,^[25] these latter structures and energies were taken as starting points to calculate the activation barriers of the aromatization reactions provided that a rapid preequilibrium exists between both types of complexes. In the case of the ester group, both the *syn* and *anti* conformations of the carbonyl group were considered in the search of the corresponding transition structures.

Structural features of the Lewis acids supported on silica are not easy to elucidate. However, it is generally accepted that ZnCl₂ supported on silica mainly consists of very small isolated particles of ZnCl₂ dispersed on the silica surface. On the other hand, when the silica is treated with Et₂AlCl, attachment of the Al onto the surface through reaction of the silanol groups and displacement of the alkyl and/or chlorine groups takes place. A recent theoretical and experimental study^[26] has shown that the acidity of the resulting aluminum centers is at least as high as, if not superior to, that of aluminum trichloride. We therefore decided to use two simple models for the Lewis acid, namely the molecules of ZnCl₂ and AlCl₃ coordinated to the corresponding cycloadducts. This approach has previously been used successfully.^[27]

Given the high number of stationary points (minima and transition structures) that must be considered throughout the work (see below), we explored the possibility of using a mixed scheme of calculations. Thus, the stationary points in the potential energy reaction surface were located at the HF/3-21G(d) theoretical level, which has been found to be suitable for the description of common Diels–Alder reactions.^[28] Next, single point calculations were carried out at the B3LYP/6-31G(d) theoretical level, which is known to provide good estimates for activation barriers.^[29] This scheme has proven to give results similar to those found at the full B3LYP/6-31G(d) theoretical level for the Diels–Alder reaction between 1,3-butadiene and acrolein, both uncatalyzed and catalyzed by BF₃.^[30] In order to test the validity of this scheme, some calculations were also performed at the full B3LYP/6-31G(d) theoretical level.



Scheme 3

Figure 1 and 2 show some selected structures and Table 5 collects calculated activation and relative TS energies together with some selected geometrical parameters (full description of the energy results can be obtained as Supporting Information for this paper) for the ring-opening reactions of the cycloadducts **5a** and **5b**. Compounds **5a** and **5b** were formed from Diels–Alder reactions between 2,5-dimethylfuran (**2**) and methyl acrylate (**3a**) and acrylonitrile (**3b**), respectively, catalyzed by ZnCl_2 and AlCl_3 .

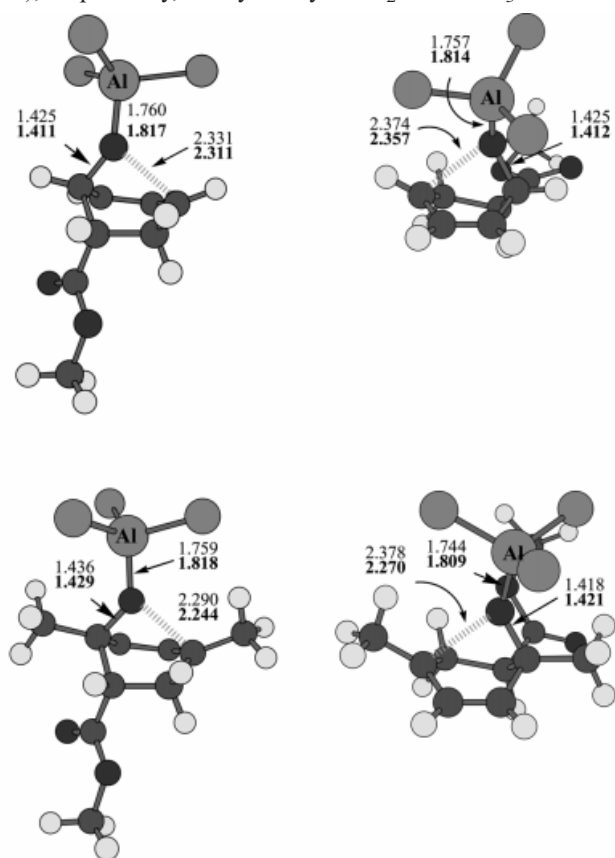


Figure 1. Some geometrical parameters of the transition structures in the ring-opening reactions of cycloadducts **5a**, catalyzed by AlCl_3 , calculated at the HF/3-21G(d) (normal typeface) and B3LYP/6-31G(d) (bold) theoretical levels

First of all, it is necessary to verify our starting hypotheses. As far as the theoretical level is concerned, it can easily be seen that the full B3LYP/6-31G(d) calculations produce activation energies very similar to those obtained at the B3LYP/6-31G(d)//HF/3-21G(d) level. Furthermore, the transition structures (TSs) do not display any significant differences from a geometrical point of view. In any case, the slight geometrical differences do not result in any noticeable energy differences, as shown by the calculated relative TS energies. We thus confirmed that the mixed scheme proposed works well, and it was consequently used throughout the work described here.

From the mechanistic point of view, the two possibilities for ring-opening were considered in the case of the ring-opening reactions of the acrylonitrile *endo* and *exo* cycloadducts. As can be seen, ring-opening by the C–O bond near

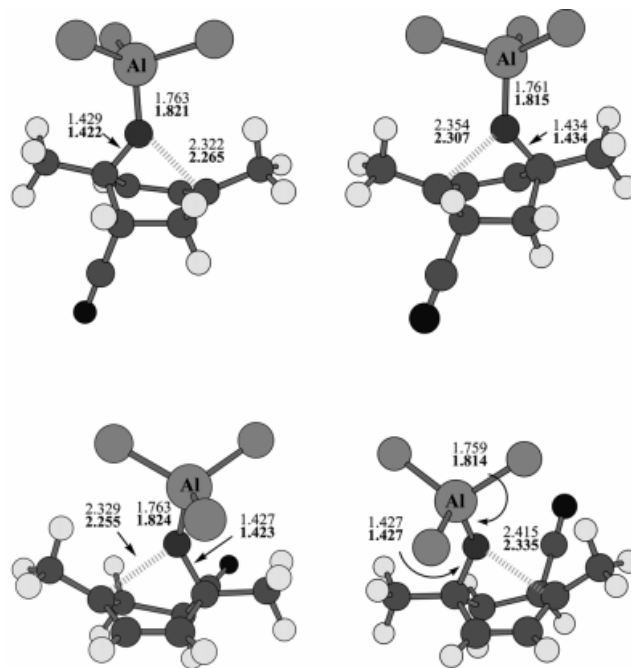


Figure 2. Some geometrical parameters of the transition structures in the ring-opening reactions of cycloadducts **5b**, catalyzed by AlCl_3 , calculated at the HF/3-21G(d) (normal typeface) and B3LYP/6-31G(d) (bold) theoretical levels

the cyano group is disfavored by ca. 3 kcal mol^{−1} in both cases, as one would expect from the predicted destabilization of the incipient positive charge (Scheme 3). We will therefore henceforth consider only the ring-opening reaction through the C–O bond situated on the side opposite to the electron-withdrawing group.

From a structural viewpoint, it can be seen that the C–O distance, corresponding to the breaking bond (Table 5), is always shorter in the case of the aluminum-catalyzed processes than in that of the zinc-catalyzed ones. This indicates that the TSs are earlier in the former cases, and so the catalytic effect is greater with the aluminum catalyst. This trend is also corroborated by examination of the metal–oxygen (M–O) bond length (Table 5), which is always shorter for aluminum complexes and gives rise to stronger Lewis acid activation.

These observations are in line with the calculated energy profiles. Thus, activation barriers are always lower for aluminum-catalyzed reactions, a situation in agreement with the experimental results and showing that aromatization reactions are easier with $\text{Al}(\text{Si})$ than with $\text{Zn}(\text{Si})$. If one compares the behavior of the two dienophiles, it can be seen that barriers to the aromatization of ester adducts are always lower than those for nitrile adducts, a fact that is also in good agreement with the experimental observations.

In order to compare the relative reactivity of the furan and 2,5-dimethylfuran cycloadducts, the transition structures of the aromatization reactions of the Diels–Alder adducts of furan with methyl acrylates were also calculated, and the results are collected in Table 5. As expected, the activation barriers for the furan adducts are much higher than those for their 2,5-dimethylfuran counterparts and are

Table 5. Activation and relative TS energies [kcal mol⁻¹] along with some geometrical parameters for the Lewis acid catalyzed ring-opening reactions of the Diels–Alder cycloadducts of furan (**1**) and 2,5-dimethylfuran (**2**) with methyl acrylate (**3a**) and acrylonitrile (**3b**), calculated at the B3LYP/6-31G(d)//HF/3-21G(d) and full B3LYP/6-31G(d) theoretical levels

Diene	Dienophile	Catalyst	TS	dC _O –C HF/3-21G(d)	dC _M –O	$\Delta E^\ddagger$ [a] B3LYP/6-31G(d)// HF/3-21G(d)	B3LYP/6-31G(d)	$\Delta\Delta E^\ddagger$ B3LYP/6-31G(d)// HF/3-21G(d)	B3LYP/6-31G(d)
2	3a	AlCl ₃	<i>endo s-cis</i>	2.346	1.756	19.1	19.0	0.0	0.0
		AlCl ₃	<i>endo s-trans</i>	2.290	1.759	<i>19.1</i>	19.7	0.0	0.7
		AlCl ₃	<i>exo s-cis</i>	2.403	1.746	22.1	21.1	2.2	1.7
		AlCl ₃	<i>exo s-trans</i>	2.378	1.744	<i>21.9</i>	20.6	2.0	2.0
		ZnCl ₂	<i>endo s-cis</i>	2.507	1.821	31.9	31.4	4.5	4.8
		ZnCl ₂	<i>endo s-trans</i>	2.447	1.819	25.5	26.2	5.0	4.9
		ZnCl ₂	<i>exo s-cis</i>	2.574	1.885	31.1	32.1	0.0	0.0
		ZnCl ₂	<i>exo s-trans</i>	2.554	1.858	<i>24.7</i>	24.8	2.8	2.2
2	3b	AlCl ₃	<i>endo</i>	2.322	1.763	22.5	21.9	0.0	0.0
		AlCl ₃	<i>endo</i> ^[b]	2.354	1.761	25.8	25.2	2.8	3.3
		AlCl ₃	<i>exo</i>	2.329	1.763	24.0	23.3	2.6	2.4
		AlCl ₃	<i>exo</i> ^[b]	2.416	1.824	26.8	26.1	2.8	3.3
		ZnCl ₂	<i>endo</i>	2.485	1.823	32.4	31.3	0.0	0.0
		ZnCl ₂	<i>exo</i>	2.498	1.822	33.6	32.1	2.3	2.1
	3a	AlCl ₃	<i>endo s-trans</i>	2.331	1.760	23.3	—	0.0	—
		AlCl ₃	<i>exo s-trans</i>	2.374	1.757	27.7	—	2.3	—

[a] Values in italics correspond to the lower activation energy for a given final configuration. — [b] Ring-opening takes place at the C–O bond adjacent to the CN group.

even higher than those for the adducts of 2,5-dimethylfuran with acrylonitrile. This is in good agreement with the lack of aromatic products observed in the reactions of the furan adducts, and can be ascribed to the lower stabilization of the incipient positive charge created during the ring-opening process.

The next step was to compare these reactivities with those found in the cases of *N*-methylmaleimide (**7**) and fumaronitrile (**9**). To this end, the corresponding TSs were located at the same theoretical level for the corresponding cycloadducts. These calculations were only performed for catalysis by AlCl₃, given that this catalyst is more active than ZnCl₂. Figure 3 shows some selected structures and Table 6 gathers the calculated activation energies, together with some selected geometrical parameters (full description of the energy results can be obtained as Supporting Information for this paper).

From a structural viewpoint, it can be seen that the C–O distance, corresponding to the breaking bond, in the case of the *N*-methylmaleimide *exo* cycloadduct is shorter than that calculated for the methyl acrylate *exo* cycloadduct, but the reverse holds for the *endo* cycloadducts. The activation barrier calculated for the *endo* cycloadduct is similar to those found for the methyl acrylate cycloadducts, which is in agreement with an easy aromatization reaction. The activation barrier for the *exo* cycloadduct is slightly higher and is similar to those found in the case of the acrylonitrile cycloadducts – hence this is still compatible with a direct aromatization reaction. Given the reversibility of the Diels–Alder reaction, and the irreversibility of the aromatization reaction, aromatization of the *exo* cycloadduct by cycloreversion and formation of the *endo* cycloadduct cannot be completely discounted.

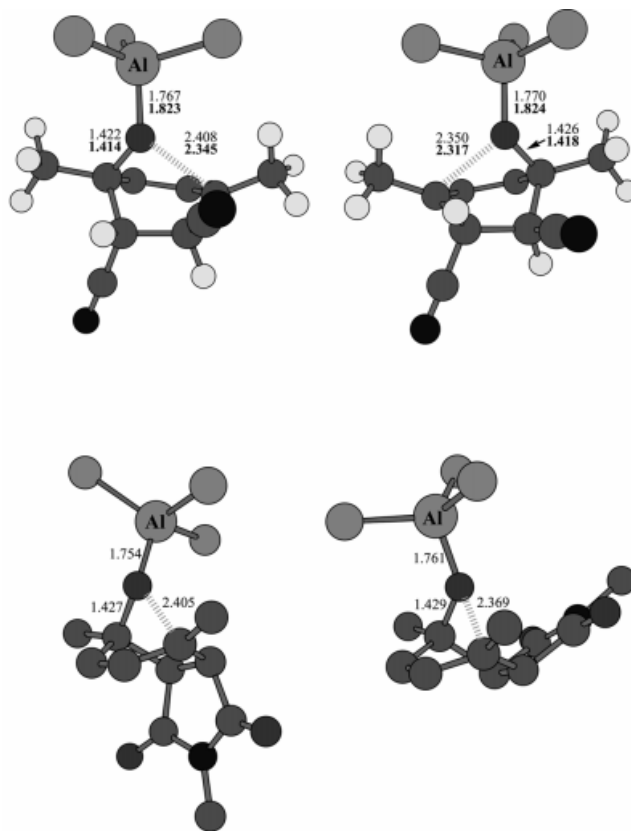


Figure 3. Some geometrical parameters of the transition structures in the ring-opening reactions of the cycloadducts corresponding to the Diels–Alder reactions between 2,5-dimethylfuran (**2**) and *N*-methylmaleimide (**7**) or fumaronitrile (**9**), catalyzed by AlCl₃, calculated at the HF/3-21G(d) (normal typeface) and B3LYP/6-31G(d) (bold) theoretical levels

Table 6. Activation energies [kcal mol^{−1}] and some geometrical parameters for the Lewis acid catalyzed ring-opening reactions of the Diels–Alder cycloadducts of 2,5-dimethylfuran (**2**) with *N*-methylmaleimide (**7**) and fumaronitrile (**9**), calculated at the B3LYP/6-31G(d)//HF/3-21G(d) and (in part) full B3LYP/6-31G(d) theoretical levels

Dienophile	Catalyst	TS	$d_{\text{C-O-C}}$ HF/3-21G(d)	$d_{\text{C-M-O}}$	$\Delta E^\ddagger$ B3LYP/6-31G(d)// HF/3-21G(d)	B3LYP/6-31G(d)
7	AlCl ₃	<i>endo</i>	2.405	1.754	21.6	—
	AlCl ₃	<i>exo</i>	2.369	1.761	24.8	—
9	AlCl ₃	<i>endo</i> ^[a]	2.350	1.770	28.7	27.8
	AlCl ₃	<i>exo</i> ^[b]	2.408	1.767	27.8	27.0

^[a] Ring-opening takes place at the C–O bond adjacent to the *endo*-CN group. – ^[b] Ring-opening takes place at the C–O bond adjacent to the *exo*-CN group.

In the case of the ring-opening reactions of fumaronitrile cycloadducts, there are two possible TSs; that in which the cleaved C–O bond is on the side of the *endo*-cyano group, and that in which this bond is on the side of the *exo*-cyano group. In neither case is there any great benefit from the point of view of the stabilization of the transient positive charge being formed during the bond-breaking. From the geometrical point of view, if we compare the C–O distances corresponding to the breaking bond with those calculated for the ring-opening of the acrylonitrile cycloadducts, it can be seen that they are closer to those calculated for the cases in which ring-opening takes place at the same side as the cyano group. As a consequence, the activation barriers are the highest calculated in this work, at 28.0 and 28.7 kcal mol^{−1}, respectively. This result is in excellent agreement with the experimental observations in terms of the experimentally found difference between carbonyl and cyano groups.

Conclusion

Silica-supported Lewis acids are good catalysts for Diels–Alder reactions between furan and acrylonitrile and methyl acrylate at room temperature. When 2,5-dimethylfuran is used as a diene the yields of acrylonitrile Diels–Alder adducts are also very good. However, the corresponding yields are lower with methyl acrylate and this is in part due to the appearance of aromatization products that are not observed with furan. The use of microwave activation in some cases results in good yields of aromatic products and thus constitutes a good synthetic route to polysubstituted aromatic compounds.

Computational studies of the reaction mechanism and the role of the catalyst on the product distribution show that “hard” Lewis acids, such as aluminum derivatives, make ring-opening of the adduct easier and result in aromatic products. The theoretical results are in excellent agreement with the relative reactivities observed for the different cycloadducts. In particular, the different reactivities towards aromatization exhibited by carbonyl and cyano cycloadducts can easily be interpreted on the basis on the energies of the corresponding transition structures for the ring-opening reactions.

Experimental Section

General Remarks: ¹H NMR spectra were recorded at 299.94 MHz and ¹³C NMR spectra at 75.429 MHz with a Varian Unity 300 spectrometer. Chemical shifts (δ) are reported in ppm using Me₄Si as the standard internal reference, and coupling constants *J* are given in Hz. Complete assignment was achieved by acquisition of NOE difference spectra and 2D NMR correlation experiments such as COSY and HETCOR. – Column chromatography was carried out with SiO₂ (silica gel, Merck type 60 230–240 mesh). – Microwave irradiation was conducted in a Miele Electronic M720 domestic oven or a focused microwave reactor (Prolabo MX350) with measurement and control of power and temperature by infrared detection. – Catalysts modified with Lewis acids were obtained by treating silica gel with 1 M solutions of ZnCl₂, AlEt₂Cl, or TiCl₄, following the previously described method.^[11–13] The silicas contained 1.5 mmol of Zn g^{−1}, 1.4 mmol of Al g^{−1}, or 1.2 mmol of Ti g^{−1}, respectively. For Zn(Si) catalyst an activation of 2 h at 150 °C under vacuum was necessary before use. In all the reactions a diene/dienophile molar ratio of 6:1 was used. Reagents were purchased from commercial suppliers.

Diels–Alder Reactions at Room Temperature: The dienophile **3a** or **3b** (0.25 mmol) and the corresponding amount of furan (**1**) or dimethylfuran (**2**) were added to the catalyst (250 mg) under argon in a Schlenk tube. The reaction mixtures were stirred for the times and temperatures indicated (Table 1, 3 and 4). CDCl₃ (2 mL) was added in all cases, and the catalyst was separated by filtration. The crude reaction mixtures were analyzed by ¹H and ¹³C NMR spectroscopy. Yields and selectivities were determined by integration of the ¹H NMR signal of the vinyl protons [**3a**: δ = 6.39 (H_{cis}); **5an**: δ = 6.25 (5-H); **5ax**: δ = 6.32 (5-H) for reactions with methyl acrylate; **3b**: δ = 5.63 (H_{gem}); **5bn**: δ = 6.12 (6-H); **5bx**: δ = 6.38 (6-H) for reactions with acrylonitrile]. A pure mixture of *endo* and *exo* cycloadducts was obtained by extraction of the reaction mixture with CH₂Cl₂, filtration, and removal of the solvent and unchanged reagents under reduced pressure. For reactions with methyl acrylate, chromatographic separation using “end-capped” silica gel^[15] as a stationary phase and hexane/ethyl ether (7:3) as an eluent was necessary.

Diels–Alder Reactions in a Domestic Microwave Reactor: A Teflon vessel was charged with the dienophile (**3a**, **3b**, **7** or **9**, 1.5 mmol), the corresponding amount of dimethylfuran (**2**), and the catalyst (500 mg) and then closed. The reaction mixture was irradiated in a domestic microwave oven at 780 W for the indicated time (Table 3 and 4). In all cases, CH₂Cl₂ (50 mL) was added and the catalyst was separated by filtration. The solvent was removed under reduced pressure and the crude reaction mixtures were analyzed by

^1H and ^{13}C NMR spectroscopy in CDCl_3 . Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 ($\delta = 4.93$) as an internal standard. For reactions involving fumaronitrile (**9**) the degree of conversion was determined using the signal at $\delta = 6.31$ from fumaronitrile as the internal standard and the signal at $\delta = 6.45$ (6-H) from the cycloadduct (**10**). The crude reaction mixture was purified by flash chromatography using hexane/ethyl acetate (9:1) as eluent.

Diels–Alder Reactions in a Focused Microwave Reactor with Temperature Control: A modified Fischer–Porter reaction vessel was charged with a mixture of the dienophile (**3a** or **3b**, 0.25 mmol), the corresponding amount of furan (**1**) or 2,5-dimethylfuran (**2**), and the catalyst (250 mg). The vessel was then closed and placed under pressure with argon (3 bar). The reaction mixtures were irradiated in a focused microwave reactor (Prolabo) for the time and temperature indicated (Table 3 and 4). In all cases, CDCl_3 (2 mL) was added and the catalyst was separated by filtration. The crude reaction mixtures were analyzed by ^1H and ^{13}C NMR spectroscopy. Yields and selectivities were determined by integration of the ^1H NMR signals of the vinyl protons as described above.

Methyl 2-endo-1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (5an): The data for this product were obtained from a mixture of **5an** and **5ax**. – ^1H NMR (CDCl_3): $\delta = 1.59$ (s, 3 H, 4- CH_3), 1.73 (s, 3 H, 1- CH_3), 1.83 (dd, $J = 11.47$ and 3.91 Hz, 1 H, 3- H_{ax}), 1.99 (dd, $J = 11.47$ and 9.03 Hz, 1 H, 3- H_{eq}), 2.92 (dd, $J = 9.03$ and 3.91 Hz, 1 H, 2-H), 3.64 (s, 3 H, OCH_3), 6.07 (d, $J = 5.61$ Hz, 1 H, 6-H), 6.25 (d, $J = 5.61$ Hz, 1 H, 5-H). – ^{13}C NMR (CDCl_3): $\delta = 18.5$ (1- CH_3), 18.7 (4- CH_3), 38.3 (C-3), 51.0 (C-2), 51.6 (OCH_3), 85.9 (C-4), 87.1 (C-1), 136.2 (C-6), 140.1 (C-5), 172.8 (COO).

Methyl 2-exo-1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (5ax): The data for this product were obtained from a mixture of **5ax** and **5an**. – ^1H NMR (CDCl_3): $\delta = 1.53$ (s, 3 H, 1- CH_3), 1.67 (s, 3 H, 4- CH_3), 1.62–1.75 (m, 1 H, 3- H_{ax}), 1.98–2.07 (m, 1 H, 3- H_{eq}), 2.55 (dd, $J = 7.81$ and 3.66 Hz, 1 H, 2-H), 3.72 (s, 3 H, OCH_3), 6.15 (d, $J = 5.61$ Hz, 1 H, 6-H), 6.21 (d, $J = 5.61$ Hz, 1 H, 5-H). – ^{13}C NMR (CDCl_3): $\delta = 16.3$ (1- CH_3), 18.5 (4- CH_3), 38.3 (C-3), 49.7 (C-2), 51.6 (OCH_3), 85.7 (C-4), 87.9 (C-1), 139.1, 140.5 (C-5 and C-6), 173.9 (COO).

2-endo-1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile (5bn): The data for this product were obtained from a mixture of **5bn** and **5bx**. – ^1H NMR (CDCl_3): $\delta = 1.62$ (s, 3 H, 1- CH_3), 1.74 (s, 3 H, 4- CH_3), 1.78 (br. s, 1 H, 3- H_{ax}), 2.15 (dd, $J = 11.48$ and 9.28 Hz, 3- H_{eq}), 2.77 (dd, $J = 9.28$ and 3.91 Hz, 1 H, 2-H), 6.31 (d, $J = 5.62$ Hz, 1 H, 5-H), 6.38 (d, $J = 5.62$ Hz, 1 H, 6-H). – ^{13}C NMR (CDCl_3): $\delta = 17.6$ (4- CH_3), 18.1 (1- CH_3), 35.3 (C-2), 40.2 (C-3), 86.7 (C-4), 87.3 (C-1), 120.4 (CN), 136.4 (C-5), 141.0 (C-6).

2-exo-1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile (5bx): The data for this product were obtained from a mixture of **5bx** and **5bn**. – ^1H NMR (CDCl_3): $\delta = 1.65$ (s, 3 H, 4- CH_3), 1.78 (s, 3 H, 1- CH_3), 1.97–1.99 (m, 2 H, 3- H_{ax} and 3- H_{eq}), 2.55 (dd, $J = 7.08$ and 5.61 Hz, 1 H, 2-H), 6.12 (d, $J = 5.62$ Hz, 1 H, 6-H), 6.25 (d, $J = 5.62$ Hz, 1 H, 5-H). – ^{13}C NMR (CDCl_3): $\delta = 16.5$ (1- CH_3), 18.2 (4- CH_3), 35.5 (C-2), 40.3 (C-3), 85.9 (C-4), 86.8 (C-1), 120.5 (CN), 137.3 (C-6), 140.8 (C-5).

Methyl 2,5-Dimethylbenzoate (6a): This product was separated from the reaction mixture as described above. – ^1H NMR (CDCl_3): $\delta = 2.34$ (s, 3 H, 2- CH_3), 2.54 (s, 3 H, 5- CH_3), 3.88 (s, 3 H, OCH_3), 7.12 (d, $J = 7.8$ Hz, 1 H, 4-H), 7.21 (dd, $J = 7.8$ and 1.7 Hz, 1 H, 3-H), 7.70 (d, $J = 1.7$ Hz, 1 H, 6-H). – ^{13}C NMR (CDCl_3): $\delta = 20.8$ (2- CH_3), 21.2 (5- CH_3), 51.7 (OCH_3), 131.0 (C-

6), 131.6 (C-4), 132.7 (C-3), 135.2 (C-5), 137.0 (C-2), 168.2 (COO).

2,5-Dimethylbenzonitrile (6b): This product was separated from the reaction mixture as described above. – ^1H NMR (CDCl_3): $\delta = 2.34$ (s, 3 H, 2- CH_3), 2.50 (s, 3 H, 5- CH_3), 7.21 (d, $J = 8.3$ Hz, 1 H, 3-H), 7.27 (d, $J = 8.3$ Hz, 1 H, 4-H), 7.40 (s, 1 H, 6-H). – ^{13}C NMR (CDCl_3): $\delta = 19.7$ (2- CH_3), 20.4 (5- CH_3), 112.3 (C-1), 118.1 (CN), 129.9 (C-3), 132.5 (C-6), 133.4 (C-4), 135.9 (C-5), 138.6 (C-2).

2,4,7-Trimethylisindole-1,3-dione (8): M.p. 168–169 °C (from hexane). – ^1H NMR (CDCl_3): $\delta = 2.63$ (s, 6 H, 3- CH_3 , 6- CH_3), 3.12 (s, 3 H, NCH_3), 7.28 (s, 2 H, 4-H, 5-H). – ^{13}C NMR (CDCl_3): $\delta = 17.3$ (3- CH_3 , 6- CH_3), 23.4 (NCH_3), 129.0 (C-5, C-4), 135.1 (C-3, C-6), 135.8 (8-C, 9-C), 169.2 (2 $\times$ CO).

2-endo,3-exo-1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarbonitrile (10): Yellow oil. – ^1H NMR (CDCl_3): $\delta = 1.79$ (s, 3 H, 1- CH_3), 1.80 (s, 3 H, 4- CH_3), 2.89 (d, $J = 11.48$ Hz, 1 H, H_{ax}), 3.05 (d, $J = 9.28$ Hz, 1 H, H_{eq}), 6.39 (d, $J = 5.6$ Hz, 1 H, 5-H), 6.45 (d, $J = 5.6$ Hz, 1 H, 6-H). – ^{13}C NMR (CDCl_3): $\delta = 16.0$ (4- CH_3), 16.9 (1- CH_3), 41.6 (C-2), 42.1 (C-3), 88.3 and 88.4 (C-1 and C-4), 117.3 (2 $\times$ CN), 138.9 (C-6), 139.7 (C-5).

Theoretical Calculations: Theoretical calculations were carried out using the Gaussian 94^[31] and Gaussian 98^[32] programs. Geometrical optimizations (minima and transition structure searches) were performed at the Hartree–Fock theory level, using the standard 3-21G(d) basis set and, in some cases, using a Density Functional Theory (DFT) method based on the three-parameter hybrid correlation functional developed by Becke^[33] plus the Lee–Yang–Parr^[34] exchange functional (B3LYP) as implemented in the Gaussian program, with the standard 6-31G(d) basis set. In the case of the transition structures, frequency calculations were carried out in order to ensure the presence on only one negative eigenvalue of the Hessian matrix. The vibration associated with the imaginary frequency was checked to correspond to a movement in the direction of the reaction coordinate. Single point energy calculations were performed on the HF/3-21G(d)-optimized structures at the B3LYP/6-31G(d) theoretical level.

Acknowledgments

This work was made possible by the generous financial support of the Comisión Interministerial de Ciencia y Tecnología (Projects MAT99-1176 and PB97-0429). Technical assistance from Mr. Alfonso Saiz is also acknowledged.

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Received February 20, 2001

[O01084]