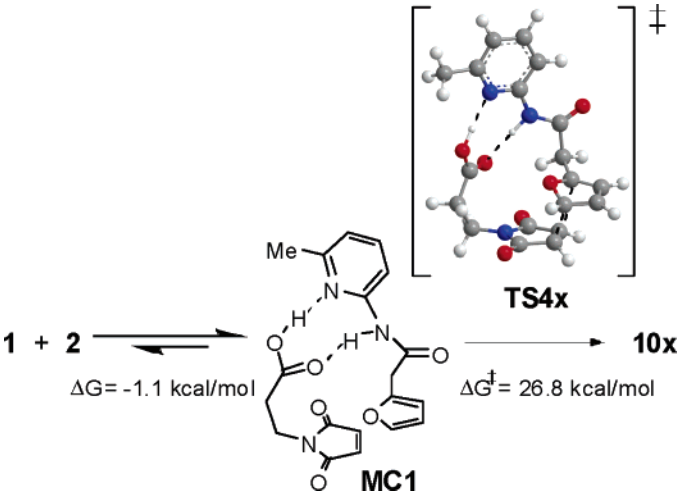
Toward an Understanding of the Acceleration of Diels−Alder Reactions by a Pseudo-intramolecular Process Achieved by Molecular Recognition. A DFT Study

Luis R. Domingo,* M. José Aurell, Manuel Arnó, and José A. Sáez

Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

domingo@utopia.uv.es

Received February 23, 2007



The pseudo-intramolecular Diels−Alder (DA) reaction between a 2-substituted furan (**1**) and a *N*-maleimide derivative (**2**) has been analyzed using DFT methods. Formation of two hydrogen bonds between the appendages on furan and maleimide derivatives favors thermodynamically the formation of a molecular complex (**MC1**) through an efficient molecular recognition process. The large enthalpy stabilization associated with the molecular recognition overcomes the unfavorable activation entropy associated with the bimolecular process. As a consequence, the subsequent DA reaction is clearly accelerated through a pseudo-intramolecular process.

Introduction

The Diels−Alder (DA) reaction is one of the most useful synthetic reactions in organic chemistry. It corresponds to one of a general class of cycloaddition reactions.[1] By varying the nature of the diene and dienophile, many different types of six-membered carbocyclic structures can be built up. However, not all possibilities take place easily. For instance, the DA reaction between butadiene and ethylene must be forced to take place: after 17 h at 165 °C and 900 atm, a yield of 78% is obtained.[2] Although this DA reaction is exothermic by 40 kcal/mol, it has a large activation energy of 27.5 kcal/mol.[3]

For the DA reaction, the negative activation entropy associated with the bimolecular process also plays a negative role. In this way, for the DA reaction between butadiene and ethylene, the activation entropy of the concerted process has been estimated to be −40.6 eu.[4] This unfavorable value, together with the high temperature required by the reaction, increases the activation free energy of this DA reaction to 42.6 kcal/mol. There are two different ways to reduce this large energy: (i) reduce the unfavorable activation enthalpy associated with the

---

[1] (a) Carruthers, W. *Some Modern Methods of Organic Synthesis*; 2nd ed.; Cambridge University Press: Cambridge, 1978. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.

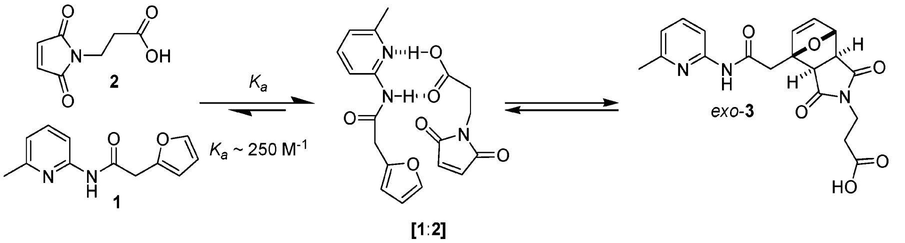
[2] (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

[3] Rowley, D.; Steiner, H. *Discuss. Faraday Soc.* **1951**, *10*, 198−235.

[4] Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036−6043.

10.1021/jo070373j CCC: $37.00

SCHEME 1



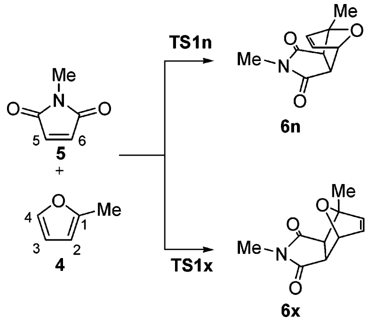
two σ bond formations and/or (ii) decrease the unfavorable activation entropy associated with the bimolecular process. Several strategies have been developed to reduce the activation enthalpy. They include the adequate substitution over the ethylene and/or the butadiene reagents and the use of Lewis acids.

In order to diminish the unfavorable activation entropy associated with the bimolecular process, several strategies are employed. They include the use of high pressure and the use of water as solvent for the reaction in order to produce hydrophobic effects and to perform the process in an intramolecular manner. The intramolecular DA (IMDA) reaction represents an interesting variant of the DA reaction in which the 1,3-butadiene and ethylene are linked by a tether. The IMDA reaction does not only modify the reaction rate, but the stereo- and regioselectivity can change with regard to the intermolecular mode due to the strain imposed by the tether along the approach of the diene/dienophile fragments. Nonactivated DA reactions involving nonsubstituted hydrocarbon reagents, which require drastic reaction conditions in the intermolecular mode, are performed through an IMDA reaction under milder conditions. Recently, several theoretical works have been devoted to study the IMDA reactions.[5]

The pseudo-intramolecular DA (PIMDA) reactions are achieved by a molecular recognition process in solution and constitute a synthetic strategy capable of accelerating the reaction. The location of complementary recognition sites on the reactive partners permits the association of the reagents in an early step of the reaction, which shifts some of the entropic cost of organizing the reagents to a binding event early in the reaction sequence. In addition, the use of molecular recognition should permit the control of the stereo- and/or regiochemical outcome of the reaction through the previous orientation of the reagents.

The induction of DA reactions using molecular recognition has been widely studied by Philp and co-workers.[6] Recently, they have presented the dramatic acceleration suffered by the DA reaction between furan **1** and maleimide **2**, which presents complementary hydrogen bonding sites (see Scheme 1).[7] In addition, the formation of the binary complex [**1**:**2**] induces solely the formation of the stereoisomer *exo*-**3**.

SCHEME 2



Our interest about the mechanism of cycloaddition reactions, and especially for the effects of the catalysts over the course of the reaction, instigated us to perform a theoretical study of the reactions experimentally studied by Philp (see Scheme 1).[7] In the present study, the PIMDA reaction between the furan **1** and the maleimide **2** is studied using the density functional theory (DFT) at the B3LYP/6-31G** level. First, the intermolecular DA reaction between 2-methylfuran **4** and *N*-methylmaleimide **5** is studied as a reference model of the intermolecular mode (see Scheme 2). The effects of the hydrogen bond (HB) formation over the activation energy have been considered by the HB formation between a formic acid molecule and *N*-methylmaleimide **5** (see Scheme 3). Then, formation of several precursor complexes by molecular recognition between the furan **1** and maleimide **2** studied by Philp is considered to understand the factor responsible of the acceleration and stereocontrol observed experimentally (see Scheme 4).

Results and Discussions

The Diels−Alder Reaction between 2-Methylfuran 4 and *N*-Methylmaleimide 5. First, the DA reaction between 2-methylfuran **4** and *N*-methylmaleimide **5** was studied. Due to the asymmetry of both reagents, two stereoisomeric reactive channels are feasible: *endo* and *exo*. An analysis of the stationary points found along the two reactive channels indicates that these DA reactions take place along concerted bond-formation processes. Thus, two TSs, **TS1n** and **TS1x**, and two cycloadducts, **6n** and **6x**, associated with the *endo* and *exo* channels, named **n** and **x**, were located and characterized (see Scheme 2).

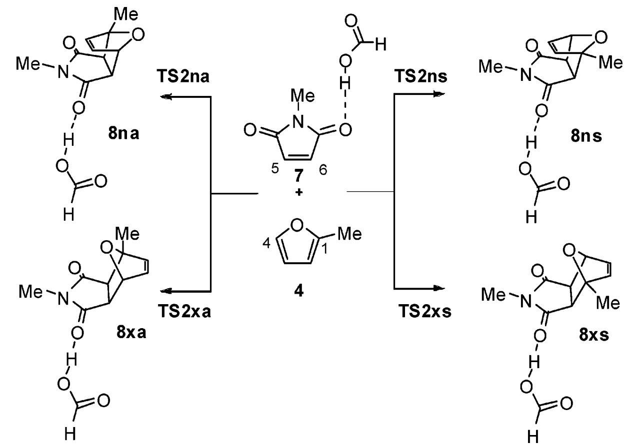
---

(5) (a) Domingo, L. R.; Sanz-Cervera, J. F.; Williams, R. M.; Picher, M. T.; Marco, J. A. *J. Org. Chem.* **1997**, *62*, 1662−1667. (b) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938−1940. (c) Cayzer, T.; Wong, L. S. M.; Turner, P.; Paddon-Row, M. N.; Sherburn, M. S. *Chem.−Eur. J.* **2002**, *8*, 739−750. (d) Limanto, J.; Tallarico, J. A.; Porter, J. R.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 14748−14758. (e) Domingo, L. R.; Zaragozá, R. J.; Williams, R. W. *J. Org. Chem.* **2003**, *68*, 2895−2902. (f) Su, M. D. *Organometallics* **2004**, *23*, 2507−2509. (g) Khuong, K. S.; Beaudry, C. M.; Trauner, D.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 3688−3689. (h) Cayzer, T. N.; Paddon-Row, M. N.; Moran, D.; Payne, A. D.; Sherburn, M. S.; Turner, P. *J. Org. Chem.* **2005**, *70*, 5561−5570. (i) Paddon-Row, M. N.; Moran, D.; Jones, G. A.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 10841−10853. (j) Padwa, A.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 5432−5439. (k) Pearson, E. L.; Kwan, L. C. H.; Turner, C. I.; Jones, G. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2006**, *71*, 6099−6109.

(6) (a) Philp, D.; Robertson, A. *Chem. Commun.* **1998**, 879−880. (b) Bennes, R.; Philp, D.; Spencer, N.; Kariuki, B. M.; Harris, K. D. M. *Org. Lett.* **1999**, *1*, 1087−1090. (c) Robertson, A.; Philp, D.; Spencer, N. *Tetrahedron* **1999**, *55*, 11365−11384.

(7) (a) Pearson, R. J.; Kassianidis, E.; Philp, D. *Tetrahedron Lett.* **2004**, *45*, 4777−4780. (b) Pearson, R. J.; Kassianidis, E.; Slawin, A. M. Z.; Philp, D. *Org. Biomol. Chem.* **2004**, *2*, 3434−3441.

SCHEME 3



SCHEME 4

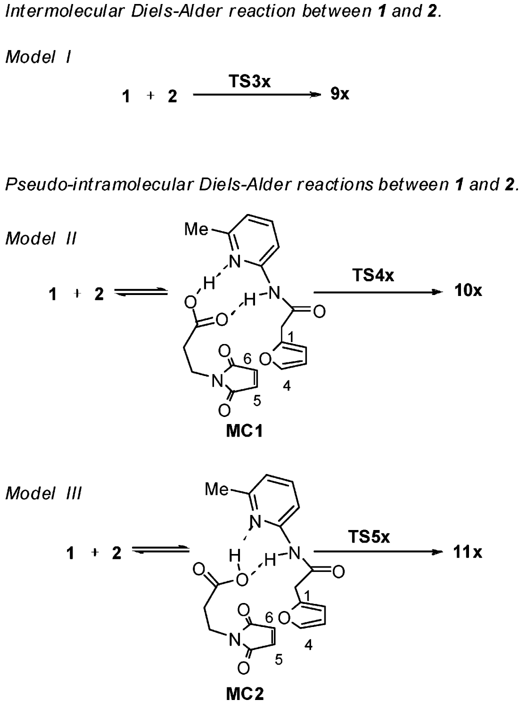


TABLE 1. Relative[a] Energies (ΔE and ΔE_{sol}, in kcal/mol), in the Gas Phase and in Chloroform, and Relative[a] Enthalpies, Entropies, and Free Energies (ΔH, ΔG, in kcal/mol and ΔS in cal/mol·K) for the TSs and Cycloadducts Involved in the DA Reactions between 2-Methylfuran 4 and *N*-Methylmaleimide 5, in the Absence and in the Presence of Formic Acid

	ΔE	ΔE_{sol}	ΔH	ΔS	ΔG
TS1n	18.8	18.7	19.4	−47.4	34.0
TS1x	18.0	18.1	18.6	−47.3	33.2
6n	−5.8	−5.5	−3.5	−50.0	11.9
6x	−7.8	−7.5	−5.4	−50.8	10.2
TS2ns	17.1	16.9	17.5	−47.1	32.0
TS2xs	15.6	16.0	16.1	−47.5	30.7
TS2na	16.4	17.2	16.8	−47.9	31.5
TS2xa	15.5	16.6	16.0	−48.8	31.0
8ns	−5.7	−5.8	−3.5	−52.6	12.7
8xs	−8.4	−8.0	−6.1	−52.8	10.2
8na	−6.0	−5.8	−3.8	−51.6	12.1
8xa	−8.7	−8.0	−6.4	−52.1	9.6

[a] Relative to **4** + **5** or **4** + **7**.

The activation energies associated with the intermolecular DA reactions between 2-methylfuran **4** and *N*-methylmaleimide **5** are 18.8 (**TS1n**) and 18.0 (**TS1x**) kcal/mol (see Table 1). This DA reaction is slightly *exo* selective. The activation energies associated with these concerted processes are ca. 7 kcal/mol lower than that associated with the butadiene/ethylene reaction.[4] This acceleration is a consequence of the large nucleophilic character of 2-methylfuran **4** and the large electrophilic character of *N*-methylmaleimide **5**. These behaviors increase the Δω of the reaction relative to that for the butadiene/ethylene pair, favoring the cycloaddition along a more polar process (see later).[8]

Inclusion of the thermal corrections to the energies increases the activation enthalpy of **TS1x** to 18.6 kcal/mol (see Table 1). A more drastic change is observed on the computed activation free energy associated with these intermolecular processes. The inclusion of the activation entropy to the enthalpy increases the activation free energies to 34.0 (**TS1n**) and 33.2 (**TS1x**) kcal/mol, as a consequence of the large negative activation entropy associated with these bimolecular processes. Note that the activation entropy values associated with these DA reactions, −47.4 and −47.3 eu, are larger than that computed for the butadiene/ethylene DA reaction, −40.6 eu,[4] probably as a consequence of the restricted rotation of the methyl substituents on the TSs. These DA reactions are slightly exothermic, −3.5 (**6n**) and −5.4 (**6x**) kcal/mol. However, with the inclusion of the entropy to the free energy, the processes become endergonic at 11.9 (**6n**) and 10.2 (**6x**) kcal/mol.

The geometries of the TSs are given in Figure 1. The lengths of the C1−C6 and C4−C5 forming bonds at the TSs are 2.182 and 2.080 Å at **TS1n** and 2.321 and 1.995 Å at **TS1x**, respectively. The extent of the asynchronicity of the cycloadditions can be measured through the difference between the lengths of the two σ bonds that are being formed, that is, $\Delta r = d\text{C1}-\text{C6} - d\text{C4}-\text{C5}$. The asynchronicity at the TSs are $\Delta r =$ 0.10 (**TS1n**) and 0.33 (**TS1x**). The more favorable **TS1x** has the large asynchronicity in the bond-formation process. The symmetric substitution of the ethylene framework of *N*-methylmaleimide is responsible for the synchronicity of these processes.[9] In addition, at the more asynchronous **TS1x**, the shorter distance corresponds to the C4−C5 forming bond because the C4 position corresponds to the more nucleophilic center of 2-methylfuran.[10]

The extent of bond formation along the reaction pathway is provided by the concept of bond order (BO). The BO values of the C1−C6 and C4−C5 forming bonds at the TSs are 0.39 and 0.45 at **TS1n** and 0.33 and 0.50 at **TS1x**. These values point to concerted but asynchronous bond-formation processes. The more favorable **TS1x** is more advanced and more asynchronous.

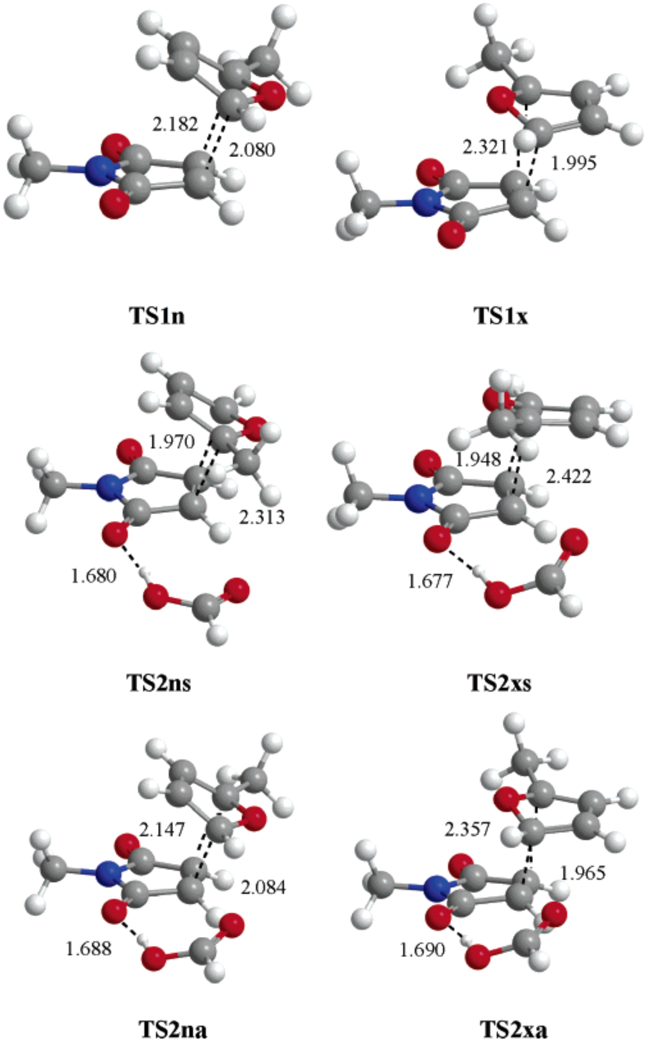
The natural population analysis (NPA) allows us to evaluate the charge transfer (CT) along these DA reactions. The natural charges at the TSs appear to be shared between the electron-rich diene **4** and the electron-poor dienophile **5** (see later). The CT from 2-methylfuran **4** to *N*-methylmaleimide **5** at the TSs is 0.23 e at **TS1n** and 0.24 e at **TS1x**. These values indicate

---

[8] (a) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417−4423. (b) Pérez, P.; Domingo, L. R.; Aizman, A.; Contreras, R. In *Theoretical Aspects of Chemical Reactivity*; Toro Labbé, T., Ed.; Elsevier Science: Amsterdam, 2006; Vol. 19, pp 167−238.

[9] Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 3884−3890.

[10] Domingo, L. R.; Aurell, M. J. *J. Org. Chem.* **2002**, *67*, 959−965.



TS1n **TS1x**

TS2ns **TS2xs**

TS2na **TS2xa**

FIGURE 1. Structures of the transition states involved in the Diels−Alder reactions between 2-methylfuran **4** and *N*-methylmaleimide **5**, in the absence, **TS1n** and **TS1x**, and in the presence, **TS2ns**, **TS2xs**, **TS2na**, and **TS2xa**, of formic acid. The distances are given in angstroms.

that these TSs have some zwitterionic character. The CT is slightly larger at the more favorable **TS1x**.

As these DA reactions have some polar character, and solvent effects can have some incidence on the activation energies and stereoselectivity, effects of chloroform in these DA reactions were also considered. The relative energies are summarized in Table 1. In chloroform, all species are stabilized between 2 and 7 kcal/mol. With the inclusion of solvent effects, the activation energy of the cycloaddition increases only to 0.1 kcal/mol (**TS1x**). In addition, solvent effects have also a small impact in the *exo* selectivity since **TS1x** is 0.6 kcal/mol lower than **TS1n**. Thus, inclusion of solvent effects on the activation parameters does not modify substantially the gas-phase results.

The Diels−Alder Reaction between 2-Methylfuran 4 and *N*-Methylmaleimide 5 in the Presence of Formic Acid. Formation of a HB to carbonyl compounds increases the reactivity of the electron-deficient reagent, accelerating the DA reaction through a more polar process.[11] Maleimide **2** possesses a carboxylic acid appendage, which can form a HB with one oxygen atom of maleimide. Therefore, the catalytic effect of the HB was considered to be forming a HB between *N*-methylmaleimide **5** and one molecule of formic acid (see complex **7** in Scheme 3). Formation of the HB to one of the carbonyl oxygen atoms of **5** breaks the symmetry of *N*-methylmaleimide **5**. Consequently, four reactive channels are feasible for the DA reaction between 2-methylfuran **4** and the complex **7**. They are related to the *endo* and *exo* stereoisomeric approach modes of the π system of the furan **4** relative to the amide group of **5**, named **n** and **x**, respectively, and to the *syn* and *anti* regioisomeric approach modes of the methyl group of **4** relative to the hydrogen-bonded carbonyl group of the complex **7**, named **s** and **a**, respectively (see Scheme 3). The four reactive channels were explored. An analysis of the stationary points found along the four reactive channels indicates that these DA reactions take place along concerted bond-formation processes. Thus, four TSs, **TS2ns**, **TS2xs**, **TS2na**, and **TS2xa**, and the corresponding cycloadducts, **8ns**, **8xs**, **8na**, and **8xa**, were located and characterized.

Formation of the HB stabilizes the complex **7** at −12.3 kcal/mol, with regard to the separated reagents. The activation energies associated with the intermolecular DA reactions between 2-methylfuran **4** and the complex **7** are 17.1 (**TS2ns**), 15.6 (**TS2xs**), 16.4 (**TS2na**), and 15.5 (**TS2xa**) kcal/mol (see Table 1). All of these TSs are in a narrow range of energies: 1.6 kcal/mol. Formation of the HB decreases the activation energy associated with the more favorable *anti*/*exo* reactive channel, via **TS2xa**, at 2.5 kcal/mol. The HB has a smaller effect on the thermochemistry of the reaction. In this sense, the exothermic character of the formation of the *exo* [4 + 2] cycloadducts increases only to 0.5 kcal/mol relative to that of **6x**.

The lengths of the two forming bonds at the TSs are given in Figure 1. The asynchronicity at the TSs is $\Delta r = 0.34$ (**TS2ns**), 0.47 (**TS2xs**), 0.06 (**TS2na**), and 0.39 (**TS2xa**). The TSs associated with the *syn* reactive channels are more asynchronous than those associated with the *anti* one. In all of these TSs, the shorter forming bond distance corresponds to that involving the C4 carbon, which is the most nucleophilic center of 2-methylfuran **4**.[10] The lengths of the HBs at the TSs are in the narrow range of 1.68−1.69 Å. These lengths are shorter than that at the complex **7**, 1.761 Å.

The BO values of the C1−C6 and C4−C5 forming bonds at the *syn* TSs are 0.32 and 0.52 at **TS2ns** and 0.28 and 0.53 at **TS2xs**, respectively, while BO values of the C1−C5 and C4−C6 forming bonds at the *anti* TSs are 0.41 and 0.45 at **TS2na** and 0.32 and 0.52 at **TS2xa**, respectively. The more favorable *exo* TSs are more asynchronous than the *endo* ones. The CT from 2-methylfuran **4** to the complex **7** at these TSs is 0.27 e at **TS2ns**, 0.30 e at **TS2xs**, 0.27 e at **TS2na**, and 0.29 e at **TS2xa**. These CTs are slightly larger than those obtained in the DA reaction between **4** and **5**, as a consequence of the larger electrophilic character of the complex **7** compared to that of the maleimide **5** (see later). The decrease of the activation energy associated with these cycloadditions can be related to the increase of the polar character of the DA reaction.[11]

Finally, in chloroform, all species are stabilized between 2 and 8 kcal/mol. The TSs associated with the *syn* channels are ca. 1 kcal/mol more solvated than the *anti* ones. As a consequence, in chloroform, the more favorable reactive channel corresponds to the *syn*/*exo* one (see Table 1). In addition, due

---

[11] Domingo, L. R.; Andrés, J. *J. Org. Chem.* **2003**, *68*, 8662−8668.

TABLE 2. Relative[a] Energies (ΔE and ΔE_{sol}, in kcal/mol), in the Gas Phase and in Chloroform, and Relative[a] Enthalpies, Entropies and Free Energies (ΔH, ΔG, in kcal/mol and ΔS in cal/mol·K) for the TSs and Cycloadducts Involved in the Intermolecular and Pseudo-intramolecular DA Reactions between the Furan Derivative 1 and the Maleimide Derivative 2

	ΔE	ΔE_{sol}	ΔH	ΔS	ΔG
TS3x	18.9	19.5	19.5	−47.9	34.3
9x	−8.7	−8.3	−6.4	−52.7	9.9
MC1	−16.8	−9.8	−15.4	−46.4	−1.1
TS4x	4.6	9.7	5.3	−66.2	25.7
10x	−19.7	−14.5	−17.3	−70.1	4.3
MC2	−10.6	−4.3	−9.1	−42.2	3.8
TS5x	10.5	15.0	11.2	−63.8	30.9
11x	−14.1	−9.4	−11.6	−67.3	9.1

[a] Relative to **1** + **2**.

to the fact that the reagents are more solvated than **TS2xs**, the activation energy of the reaction increases slightly to 16.0 kcal/mol.

The Diels−Alder Reaction between Furan 1 and Maleimide 2. For the study of the DA reaction between the furan derivative **1** and the maleimide derivative **2**, we have considered three reaction models. In Model I, the intermolecular DA reaction without formation of HB is studied (see Scheme 4), while in Models II and III, the formation of two HBs between the pyridinylcarboxamide susbtituent in the furan **1** and the carboxylic acid susbtituent in maleimide **2** is considered (see Scheme 4). For these PIMDA reactions, only the *exo* reactive approach mode of **2** relative to the dienic system of **1** is feasible due to the geometrical restrictions imposed by the HB formation. An analysis of the stationary points found along *exo* reactive channels associated with the three reaction models indicates that these DA reactions take place along concerted bond-formation processes. Therefore, one TS and one cycloadduct were characterized for each reaction model. In addition, for the Models II and III, one precursor complex in which the two reactant molecules are coupled by two HBs was also characterized. The corresponding stationary points are **TS3x** and **9x** for Model I, **MC1**, **TS4x**, and **10x** for Model II, and **MC2**, **TS5x**, and **11x** for Model III (see Scheme 4).

The activation energy associated with the intermolecular DA reaction between the furan **1** and the maleimide **2**, Model I, via **TS3x** is 18.9 kcal/mol (see Table 2). Inclusion of the thermal corrections to the free energies increases the activation free energy associated with this intermolecular process to 34.3 kcal/mol (see Table 2). Formation of the [4 + 2] cycloadduct **9x** is exothermic at −6.4 kcal/mol. These energies are similar to those obtained for the cycloaddition between 2-methylfuran **4** and *N*-methylmaleimide **5**. For the two intermolecular DA reactions, both enthalpic and entropic kinetic factors are unfavorable.

The PIMDA reaction between furan **1** and maleimide **2** via Model II takes place through the early formation of the **MC1** complex, achieved by the formation of two HBs between the susbtituents present in both reagents. While the carboxylic acid hydrogen of **2** forms a HB with the pyridine nitrogen atom of **1**, the relatively acidic hydrogen of the carboxamide of **1** forms a second HB with the carbonyl oxygen atom of the carboxylic acid of **2** (see Scheme 4). Formation of the two HBs stabilizes the **MC1** complex at −16.8 kcal/mol. After inclusion of the thermal corrections to the enthalpy and the entropy associated with the formation of **MC1**, it is located −1.1 kcal/mol below the reagents, **1** + **2**. Therefore, the exothermic character of the formation of the two HBs overcomes the unfavorable reaction entropy associated with the **MC1** formation, −46.4 eu, and as a consequence, it is located thermodynamically below the reagents.

The activation energy associated with **TS4x** from **MC1** is 21.4 kcal/mol (see Table 2). This value is 2.5 kcal/mol higher in energy than that associated with **TS3x**; a part of this increase can be associated with some strain imposed by the tether. However, if we include the thermal corrections to the activation enthalpy and the activation entropy, the activation free energy associated with **TS4x** increases only to 26.8 kcal/mol. This value, that is 7.5 kcal/mol lower than that associated with **TS3x**, justifies the large acceleration observed experimentally in the PIMDA reaction reported experimentally by Philp.[7] Despite the fact that the activation enthalpy of the pseudo-intramolecular process is 2.5 kcal/mol higher in energy than that for the intermolecular one, the activation entropy decreases to −19.8 eu. Therefore, *this PIMDA reaction is strongly accelerated by the decrease of the unfavorable activation entropy associated with the intermolecular process*. It is interesting to remark that the activation free energy associated with **TS4x**, 26.8 kcal/mol, is 3.9 kcal/mol lower than that associated with **TS2xs**. As a consequence, there is a larger acceleration at the PIMDA reaction achieved by molecular recognition via **MC1** than at the process via the activated maleimide **7**. Formation of the [4 + 2] cycloadduct **10x** is exothermic at −1.9 kcal/mol.

Finally, a second model of the PIMDA reaction between furan **1** and maleimide **2**, Model III, proposed also by Philp,[7] was considered. In this model, the relatively acidic hydrogen of the carboxamide in **1** forms a second HB with the hydroxyl oxygen atom of the carboxylic acid of **2** (see Scheme 4). Formation of the two HBs stabilizes the **MC2** complex at −10.6 kcal/mol. After inclusion of the thermal corrections to the enthalpy and the entropy associated with the **MC2** formation, it is located 3.8 kcal/mol above reagents **1** + **2**. Therefore, formation of **MC2** is an endergonic process. **MC2** is located 4.9 kcal/mol above **MC1**. These energy results indicate that the HB formation to the hydroxyl oxygen atom is less favorable than the formation of the HB to the carbonyl oxygen atom of the carboxylic acid.

The activation energy associated with **TS5x** from **MC2** is 21.1 kcal/mol (see Table 2). If we include the thermal corrections to the enthalpies and the entropies to the free energies, the activation free energy associated with **TS5x** increases to 27.1 kcal/mol. This value is only 0.3 kcal/mol higher than that associated with **TS4x**. However, the **MC2** formation is endergonic, and the energy reference for **TS4x** must be the separated reagents, **1** + **2**. As a consequence, the activation free energy for **TS5x** from **1** + **2** is 30.9 kcal/mol, a value that is 3.4 kcal/mol lower in energy than that for the intermolecular process via **TS3x**, but 4.1 kcal/mol higher in energy than that for the pseudo-intramolecular process via **TS4x**.

Table 2 shows that the PIMDA reaction represented by the Model II is endergonic at 4.3 kcal/mol. As a consequence, under reversible conditions, the reaction should go through **MC1**. Recent computational studies have indicated that the B3LYP functionals fail to calculate energies associated with carbon−carbon bond-forming/breaking processes.[12] In this way, we have found that B3LYP calculations do not explain correctly the thermodynamic control of a DA reaction, while HF and MP2 calculations explain the experimental results.[13] However, while

---

(12) (a) Izgorodina, E. I.; Coote, M. L.; Radom, L. *J. Phys. Chem. A* **2005**, *109*, 7558−7566. (b) Check, C. E.; Gilbert, T. M. *J. Org. Chem.* **2005**, *70*, 9828−9834.

TABLE 3. Relative[a] Energies and Relative Free Energies[a] (ΔE and ΔG, in kcal/mol) for the Stationary Points Involved in the Reaction Models II and III for the Diels−Alder Reaction between the Furan Derivative 1 and Maleimide Derivative 2

	B3LYP/6-31G**		MP2/6-31G**		MP3/6-31G**	
	ΔE	ΔG	ΔE	ΔG^b	ΔE	ΔG^b
			Model II			
MC1	−16.8	−1.1	−22.4	−6.4	−18.5	−2.5
TS4x	4.6	25.7	−13.9	4.6	2.5	21.0
10x	-19.7	4.3	−41.9	−20.2	−36.5	−14.7
			Model III			
MC2	−10.6	3.8	−16.7	−0.9	−13.0	2.8
TS5x	10.5	30.9	−7.3	11.0	8.6	26.9
11x	−14.1	9.1	−34.4	−13.0	−29.7	−8.3

[a] Relative to **1** + **2**. [b] Free energies obtained from the MP2 and MP3 electronic energies plus the HF thermal correction to the energies.

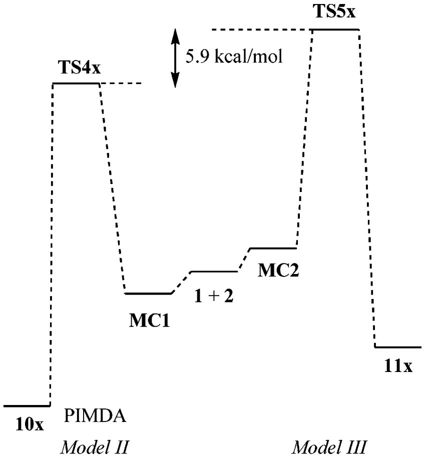


FIGURE 2. Free energy reaction profiles for the Model II and Model III channels of the Diels−Alder reactions between **1** and **2**.

HF overestimates the activation energies, MP2 underestimates them,[14] being necessary to perform MP3 calculations to obtain reasonable energies.[15] As a consequence, we have calculated the free energies of the stationary points involved in the reaction Models II and III at the MP2/6-31G** and MP3/6-31G** levels. The relative energies and free energies are given in Table 3. Taking as a reference the high MP3 computational level, it can be seen that MP2 calculations overestimate all relative energies. Although MP2 calculations consider the formation of **MC1** and **10x** to be exothermic, the corresponding values are 3.9 and 5.4 kcal/mol more exothermic than MP3 ones. The worst result corresponds to the computed relative energy of **TS4x**, as MP2 calculations give a value 16.4 kcal/mol lower in energy than the MP3 ones. On the other hand, B3LYP calculations give a relative energy for **MC1** of only 1.7 kcal/mol higher than MP3. The relative energy of **TS4x** is only 2.1 kcal/mol higher than that obtained at the MP3 level. The large discrepancy of the DA reaction is found on the relative energy of the cycloadduct **10x** since B3LYP underestimates it at 16.8 kcal/mol. Inclusion of the thermal corrections to the free energy of the MP3 electronic energies states that this PIMDA is strongly exergonic, −14.7 kcal/mol (see Table 3). As a consequence, considering the MP3 energies, the cycloaddition is irreversible under the reaction conditions. Note that the unique discrepancy between the B3LYP and the MP3 energies is found in the total electronic energy associated with the cycloadduct **10x**. Therefore, the kinetic analysis of the PIMDA reaction between **1** and **2** via **MC1** based on the B3LYP energies is validated by means of the MP3 results. It is interesting to remark that the MP3/6-31G** free energy for the **MC1** formation gives a K_a value at 35 °C of 60 M^{-1}, a value that is in reasonable agreement with that calculated by the experiment in $CDCl_3$, $K_a = 250\ M^{-1}$.[7a] Similar results were obtained for the reaction Model III at the MP2/6-31G** and MP3/6-31G** levels (see Table 3). Note that formation of **MC2** at the MP3/6-31G** level is endergonic at 2.8 kcal/mol. Therefore, the large effectiveness of the HB formation achieved by molecular recognition at **MC1** makes the DA reaction between **1** and **2** occur through the PIMDA represented by the Model II. A schematic representation of the MP3 free energy profiles for the DA reactions between **1** and **2**, via the Models II and III, is given in Figure 2. It shows that the observed acceleration found by the experiment is due to the molecular recognition.

The geometries of the TSs involved in the three reaction models are given in Figure 3. The lengths of the C1−C6 and C4−C5 forming bonds are 2.289 and 2.033 Å at **TS3x**, 2.332 and 1.992 Å at **TS4x**, and 2.277 and 2.018 Å at **TS5x**. The asynchronicities of the bond formation at the TSs, Δr, are 0.26 at **TS3x**, 0.34 at **TS4x**, and 0.26 at **TS4x**. At the reaction Model II, the lengths of the NH···O═C and OH···N HBs are 1.876 and 1.690 Å at **MC1** and 1.785 and 1.755 Å at **TS4x**, respectively. These short distances point out strong HB interactions. At the reaction Model III, the lengths of the NH···OH and OH···N HBs are 2.250 and 1.730 Å at **MC2** and 2.250 and 1.731 Å at **TS5x**, respectively.

The BO values of the C1−C6 and C4−C5 forming bonds at the TSs are 0.35 and 0.47 (**TS3x**), 0.33 and 0.50 (**TS4x**), and 0.35 and 0.49 (**TS5x**), respectively. These values are closer to those found at **TS1x**. The CT from the donor furan **1** to the acceptor maleimide **2** is 0.22 (**TS3x**), 0.24 (**TS4x**), and 0.28 e (**TS5x**), values closer to that obtained at **TS1x**. These data indicate that the PIMDA processes have a small impact on the electronic structure of TSs. These results are in clear agreement with the similar activation enthalpies found at these DA reactions. At the reaction Model II, the BO values of the NH···O═C and OH···N HBs are 0.06 and 0.14 at **MC1** and 0.07 and 0.12 at **TS4x**, respectively. At these species, the NH···OH HB is weaker than the OH···N one. The formation of the HBs was characterized by a topological analysis of the electron density, $\rho(r)$, using Bader's theory of atoms in molecules (AIM).[16] At **MC1**, the electron density at the bond critical points (BCP) between the NH···O═C and OH···N was found to be 0.0536 and 0.0323 e, respectively, while the values of the density of Laplacian were 0.0897 and 0.1016, respectively. These values (>0) indicate that the charges are locally depleted to an atom, which is characteristic of noncovalent interactions such as HBs.[17]

---

(13) Arroyo, P.; Picher, M. T.; Domingo, L. R.; Terrier, F. *Tetrahedron* **2005**, *61*, 7359−7365.

(14) (a) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B.; Wolber, G. J. *J. Org. Chem.* **1989**, *54*, 2931−2935. (b) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 6736−6744. (c) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478−7485. (d) Bachrach, S. M. *J. Org. Chem.* **1994**, *59*, 5027−5033.

(15) (a) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936−2942. (b) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Am. Chem. Soc.* **1998**, *120*, 1617−1618.

(16) (a) Bader, R. F. W. *Acc. Chem. Res.* **1985**, *18*, 9−15. (b) Bader, R. F. W. *Atoms in Molecules. A Quantum Theory*; Claredon Press: Oxford, U.K., 1990.

(17) Polo, V.; Domingo, L. R.; Andrés, J. *J. Phys. Chem. A* **2005**, *109*, 10438−10444.

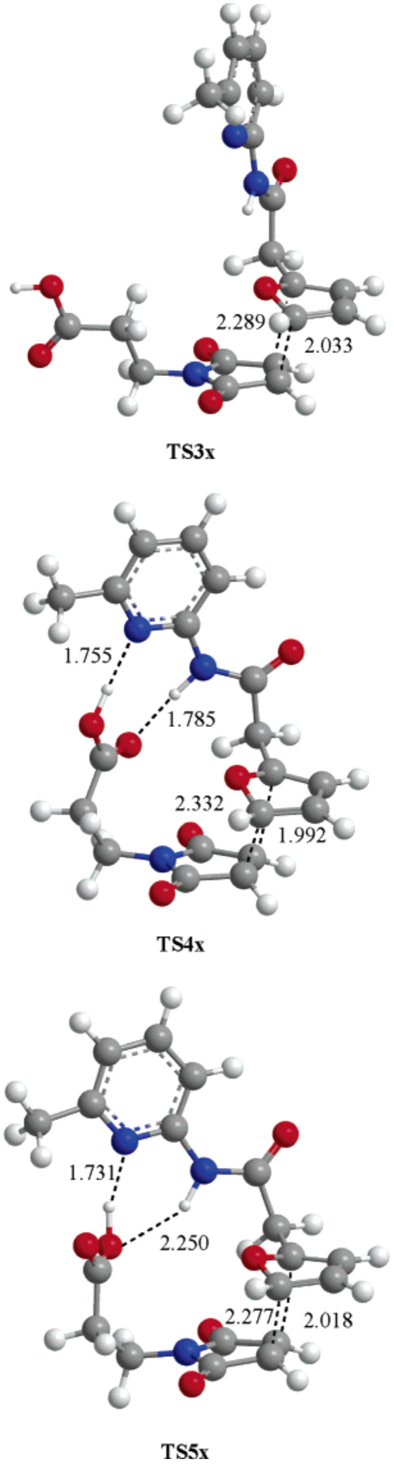


FIGURE 3. Structures of the transition states involved in the intermolecular, **TS3x**, and pseudo-intramolecular, **TS4x** and **TS5x**, Diels−Alder reactions between the furan derivative **1** and maleimide derivative **2**. The distances are given in angstroms.

For the reaction Model I, the reagents become slightly more solvated than **TS3x**. As a consequence, in chloroform, the activation energy associated with the intermolecular DA reaction increases to 0.6 kcal/mol (see Table 2). For the intramolecular processes, **TS4x** and **TS5x** are slightly more solvated than the corresponding MCs; as a consequence, the activation energies associated with the PIMDA reactions decrease by 1.9 and 1.8 kcal/mol, respectively (see Table 2).

TABLE 4. Electronic Chemical Potential (μ, in au), Chemical Hardness (η, in au), and Global Electrophilicity (ω, in eV) of the 2-Furan Derivatives 1 and 4 and the *N*-Maleimide Derivatives 2, 5, and 7

	μ	η	ω
7	−0.1920	0.1683	2.98
2	−0.1880	0.1747	2.75
5	−0.1840	0.1749	2.63
1	−0.1223	0.2012	1.01
4	−0.0950	0.2355	0.52

Analysis Based on the Global Electrophilicity at the Ground State of Reagents. These DA reactions were analyzed using the global electrophilicity index[18] defined within the context of the conceptual density functional theory.[19] In Table 4, the electronic chemical potential, μ, chemical hardness, η, and the global electrophilicity, ω, are displayed.

The electronic chemical potential, μ, of the furan derivatives **1** and **4**, −0.1223 and −0.0950 au, are higher than those of the *N*-methylmaleimide derivatives **2**, **5**, and **7**, between −0.1840 and −0.1920 au, indicating that, along a polar cycloaddition, the CT will take place from these furan derivatives to the *N*-methylmaleimide ones, in clear agreement with the CT found at the TSs.

The electrophilicity of 2-methylfuran **4** is 0.52 eV, a value that falls into the range of marginal electrophiles (good nucleophiles), within the ω scale (see Table 4).[8] On the other hand, the electrophilicity of furan derivative **1** is 1.01 eV. This large electrophilicity value, compared to that for **4**, is a consequence of the presence of the carboxamide group on the compound **1**. The electrophilicity of *N*-methylmaleimide **5** is 2.63 eV, a value that falls into the range of strong electrophiles. Coordination of the formic acid to maleimide **5** increases the electrophilicity of **7** to 2.98 eV, being the most electrophilic species of this series. The electrophilicity of maleimide derivative **2** is 2.75 eV, a value closer to that for **5**.

The difference of electrophilicity, $\Delta\omega$, between 2-methylfuran **4** and *N*-methylmaleimide **5**, 2.11 eV, indicates that this DA reaction will have some polar character.[8] Coordination of the formic acid to maleimide **5** increases the $\Delta\omega$ of the reactions to 2.46 eV. Therefore, it is expected that the HB formation accelerates the DA reaction through a more polar process,[11] in agreement with the activation energies and CTs associated with **TS2n** and **TS2x**. Finally, the similar electrophilicity values found at the maleimides **2** and **5** indicate that both DA reactions, **1** + **2** and **4** + **5**, will have similar electronic structures at the corresponding TSs, in clear agreement with the closer activation energies and charge transfer obtained for these DA reactions.

Conclusions

The pseudo-intramolecular Diels−Alder reaction between a 2-furan derivative **1** and a *N*-maleimide derivative **2**, experimentally studied by Philp, has been analyzed using DFT methods at the B3LYP/6-31G** level. Formation of two hydrogen bonds between the 2-pyridinylcarboxamide residue and the carboxylic acid appendage present on furan and maleimide, respectively, favors thermodynamically the forma-

---

[18] Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922−1924.

[19] (a) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793−1873. (b) Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, *348*, 2337−2361.

tion of a molecular complex through an efficient molecular recognition process. The large enthalpy stabilization caused by the formation of the two hydrogen bonds along the molecular recognition, −15.4 kcal/mol, overcomes the unfavorable activation entropy associated with the bimolecular process, −46.4 eu. As a consequence, the subsequent DA reaction takes place through a pseudo-intramolecular process, being the activation free energy for the DA reaction, 26.8 kcal/mol, 7.5 kcal/mol lower in energy than that for the intermolecular process. DFT calculations show that, although the activation enthalpy associated with the intramolecular process is slightly larger than that for its intermolecular counterpart, the large reduction of the negative entropy activation associated with the intermolecular process is responsible of the acceleration experimentally observed with the molecular recognition.

Acknowledgment. This work was supported by research funds provided by the Ministerio de Educación y Ciencia of the Spanish Government (project CTQ2006-14297/BQU), the Generalidad Valenciana (ACOMP/2007/082), and the Universidad de Valencia (project UV-AE-06-3). J.A.S. thanks to the Ministerio de Educación y Ciencia for his doctoral fellowship.

Supporting Information Available: Computational methods; total energies in the gas phase and in chloroform, and total enthalpies, entropies, and free energies for the transition states and cycloadducts involved in the Diels−Alder reactions between 2-methylfuran **4** and *N*-methylmaleimide **5**, in the absence and presence of formic acid, and in the intermolecular and pseudo-intramolecular Diels−Alder reactions between the furan derivative **1** and maleimide derivative **2**; B3LYP/6-31G** Cartesian coordinates of the structures involved in the DA reactions between between 2-methylfuran **4** and *N*-methylmaleimide **5**, and furan derivative **1** and maleimide derivative **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070373J