A Biradical Mechanism in the Diels−Alder Reactions of 5-Methylene-2(5*H*)-furanones: Experimental Evidence and Theoretical Rationalization

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Abstract: Reactions of protoanemonin, **1**, and 3-bromo- and 3-methoxy-5-methylene-2(5*H*)-furanones, **2** and **3**, with dienes have been performed under both thermal and photochemical activation conditions. Photochemical cycloadditions of butadiene and *trans*-piperylene to this kind of furanones have afforded 1,2-adducts, **10**−**13**, as stereoisomeric mixtures, in 40−60% yields, and have shown that furanones **1**−**3** react specifically at the exocyclic double bond as they do in thermal conditions. Furthermore, thermal cycloadditions have led to the production of the corresponding 1,4-adducts, **4**−**7**, in good yields, but **10**−**13** have also been detected at the initial stages of these reactions. Compounds **10**−**13** have been proved to be intermediates in the production of adducts **4**−**7**, isomerization taking place under heating and involving the formation of biradical species as intermediates. Moreover, cycloreversion from 1,4-adducts has not been observed, and only very small proportions (1−8%) of the corresponding furanones have been found when 1,2-adducts have been heated. In good agreement with these results, CASSCF and DFT *ab initio* theoretical calculations, performed on the reaction of **1** and butadiene to give **4**, have shown the nonconcerted mechanism to be more favorable than the concerted process, and have allowed the location of all intermediates and transition states involved in the overall process. Since, in addition, the presence of radicals in the isomerization of 1,2-adducts to 1,4-adducts has been confirmed with ESR spin trapping techniques, we can conclude that the resulting Diels−Alder adducts are mainly produced *via* a biradical mechanism. To our knowledge, this is the first time that a biradical mechanism *operating* in a Diels−Alder cycloaddition and *accounting for* the production of 1,4-adducts has been evidenced and rationalized.

Introduction

(a) General Considerations on the Diels−Alder Reaction Mechanism. The mechanism of the Diels−Alder cycloaddition has been the subject of a lot of investigations and controversial interpretations.[1] Historically, the studies on the possible mechanisms operating in these reactions began in 1935 when Wassermann proposed the first model for the involved transition states, assuming a synchronic concerted process since small values for the Arrhenius probability factor were determined.[2] Only one year later, Littmann postulated a two-step mechanism through a biradical intermediate,[3] this hypothesis being also supported by Kistiakowsky.[4] Subsequently, between 1965 and 1969, Woodward and Hoffmann defined the term *pericyclic reaction* and stated the rules for conservation of the orbital symmetry in this kind of process.[5]

Up to date, this last theory has been successfully applied to explain most Diels−Alder cycloadditions, but other nonconcerted mechanisms involving zwitterions as intermediates in the 1,4-cycloadditions of tetracyanoethylene and 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene to dienes have also been invoked.[6] Moreover, formation of radicals as intermediates in the reactions between dienes and perhalogenated ethylenes has been described in the works of Bartlett *et al.*[7] These authors studied the competition of a 1,2- and a 1,4-cycloadditon to afford the respective adducts, and proposed a radical mechanism to produce cyclobutane derivatives whereas cyclohexene (Diels−Alder) adducts would be the result of a concerted process.

In the last decades, many theoretical studies have been carried out to rationalize the Diels−Alder reactions of the great variety of dienes and dienophiles. Calculations are mainly referred to the activation parameters to justify the prevalence of a one-step or a biradical mechanism leading, in some cases, to passionate defenses of one or another mechanistic pattern.[1b,8]

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(3) Littmann, E. R. *J. Am. Chem. Soc.* **1936**, *58*, 1316.
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High-level *ab initio* calculations[8g,j] for the parent Diels−Alder reaction (butadiene plus ethylene) show that a concerted mechanism through a symmetric transition state and a two-step mechanism through a biradical intermediate can coexist. The proper description of biradical or biradicaloid structures requires the use of Multiconfigurational SCF (MCSCF) methods to take into account the nondynamical electron correlation. At the CASSCF (Complete Active Space Self Consistent Field)/6-31G* level of calculation, the concerted mechanism is more favorable than the two-step mechanism by only 1.9 kcal/mol.[8j] However, the lack of dynamic correlation leads to an overestimation of the stability of biradicaloid structures. When the energies of the concerted transition state and of the transition state leading to the formation of the biradical are recomputed at the QCISD-(T) (Quadratic Configurational Interaction with Single and Double Excitations and a Perturbative Estimate of Triple Excitations) level, the difference between both mechanisms increases to 10.2 kcal/mol, in favor of the concerted mechanism. From these results it seems clear that the reaction between butadiene and ethylene takes place through a concerted mechanism.

In addition to conventional *ab initio* methods, the density functional theory (DFT) has also been used to study the reaction between butadiene and ethylene.[9] With this kind of method, a concerted mechanism through a symmetric transition state is also predicted. DFT methods have also been sucessfully applied to other Diels−Alder reactions.[10] Moreover, Goldstein *et al.*[11] have recently shown that DFT methods can also be used in the study of the biradical mechanism of the Diels−Alder reaction between butadiene and ethylene, obtaining results in very good agreement with those previously reported by Houk and Li.[8j]

(b) Behavior of 5-Methylene-2(5H)-furanones as Dieno-philes. In 1990 we reported the first Diels−Alder cycloadditions of 5-methylene-2(5H)-furanones to afford exclusively spiro adducts in high yields as the result of an excellent site selectivity.[12] Reactions of the parent compound, protoanemonin **1**, were exhaustively studied in our laboratory with use of open-chain *C*-substituted[12,13] or hetero-substituted dienes[14] as well as cyclic dienes[13,15] (Scheme 1). *Endo/exo* stereoselectivity and regioselectivity in the cycloadditions to asymmetric dienes were also investigated. Theoretical calculations on these reactions were also carried out with the MNDO and AM1 semiempirical

Scheme 1
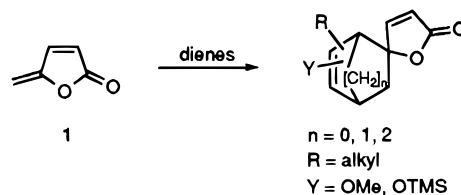
methods, allowing us to postulate a possible biradical mechanism or, at least, a very asynchronous pathway through a biradicaloid transition state for the Diels−Alder cycloadditions of such a captodative system.[16]

The effects of the extended and cross conjugation, two features present in the structure of protoanemonin **1**, were investigated in open-chain related dienophiles, the obtained results not accounting for the enhanced reactivity of the exocyclic double bond in **1**.[17] On the other hand, this reactivity was substantially decreased when substituents were incorporated to that double bond. Thus, 5-ethylidene-2(5H)-furanone afforded mixtures of Diels−Alder adducts coming from reactions at the exo- or the endocyclic double bond, in poor total yields. On the other side, 5-(methoxycarbonyl)methylene-2(5H)-furanone afforded good yields of adducts which resulted from addition to the endocyclic double bond showing, therefore, a reverse site selectivity with respect to **1**.[18]

The study was subsequently extended to other *C-3*-substituted related dienophiles. Thus, when 3-acetoxy-5-methylene-2(5H)-furanone was reacted with butadiene and cyclopentadiene, the same site selectivity and a similar reactivity to that of **1** was observed.[18] More recently, we reported[19] the detection and isolation of the cyclobutane adducts **11** and **12** in the reactions of butadiene with both 3-bromo- and 3-methoxy-5-methylene-2(5H)-furanone, **2**[20] and **3**.[21] These compounds were observed to evolve toward the corresponding Diels−Alder adducts, **5** and **6**, under the reaction conditions. Since a thermal 1,2-cycloaddition is forbidden by the Woodward−Hoffmann selection rules, we postulated a biradical mechanism both for the obtention of the cyclobutane derivatives and for their later conversion into the 1,4-adducts.

These findings led us to kinetic studies and additional experimentation on this kind of reaction to establish a reliable mechanistic pathway accounting for the overall process. The cycloaddition of butadiene to protoanemonin was revisited and *ab initio* theoretical calculations on this reaction were now carried out. As a result, the work reported herein shows for the first time that 1,2-adducts are intermediates in the production of the 1,4-adducts in the Diels−Alder reactions of 5-methylene-2(5H)-furanones. Such intermediates are formed, either under thermal or photochemical activation conditions, by addition of the dienes to the exocyclic double bond of the dienophiles. It is noteworthy that the ability of these furanones to undergo photochemical 1,2-cycloadditions, affording spiro[3.4]octane derivatives with total site selectivity, was unexplored prior to our work. In addition, radical species have also been detected

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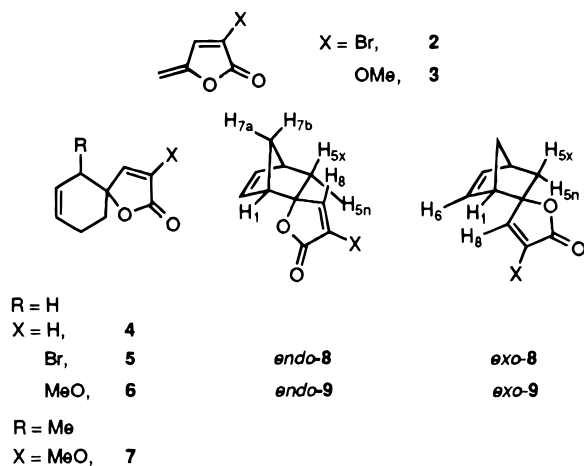
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Chart 1

in the thermal isomerization of the vinyl cyclobutanes to cyclohexene derivatives (Diels−Alder adducts). In conclusion, the results described in the present paper provide evidence of a biradical mechanism operating in the production of both 1,2- and 1,4-adducts.

Results and Discussion

1. Thermal Cycloadditions of Furanones 1, 2, and 3 to Dienes. Bromofuranone **2** and methoxyfuranone **3** (Chart 1) were chosen as representative dienophiles. These molecules are captodative systems containing substituents at *C-3* providing further stabilization for a possible radical at *C-5*, thus influencing the rate and/or the course of the process. The behavior of protoanemonin, **1**, was also reinvestigated.

(a) Reactions with Butadiene. In a previous article,[12] we reported that the reaction between protoanemonin **1** and butadiene, at 150 °C for 4 h, afforded the corresponding Diels−Alder adduct **4** in 85% yield (Chart 1). More recently, we found that bromofuranone **2** gives adduct **5**, in 90% yield, as the only identified product, by reaction with excess butadiene in dichloromethane at 150 °C for 1 h. Methoxyfuranone **3** was shown to be less reactive, and longer reaction times were required to give adducts in good yields. Thus, a mixture of the 1,4- and 1,2-adducts **6** and **12**, respectively, was obtained in 85% yield along with a 5% recovered starting material, after 20 h of reaction at 155 °C.

1,4-Adducts **5** and **6** have not previously been described. These products are solids whose identification was easily achieved by comparison of their spectroscopic data with the adducts coming from furanone **1**.[12,13,22] The ratio of minor vinyl cyclobutane derivative **12** obtained as a mixture of *cis/trans* stereoisomers was observed to be time dependent as deduced from inspection of Table 1 (entries 7−9). Thus, a 1:1 mixture of both 1,4- and 1,2-adducts was produced after 4 h of reaction at 155 °C. Then, thermal reactions between butadiene and furanones **1** and **2** were reconsidered to show the production of similar 1,2-adducts. Cyclobutanes **10** and **11** (Chart 2) were, indeed, detected at shorter reaction times as shown in Table 1 (entries 1−6).

Compounds **10**, **11**, and **12** were isolated and identified as stereoisomeric mixtures. Separation of *cis/trans* isomers and their total characterization, as well as stereochemical assignments, was achieved on larger amounts of these products obtained under photochemical conditions (*vide infra*).

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(b) Reaction of Furanone 3 with *trans*-Piperylene. Similarly to protoanemonin, **1**,[13] furanone **3** added to *(E)*-1,3-pentadiene (*trans*-piperylene) at 155 °C for 6 h afforded the corresponding adduct **7** (60% yield), as a mixture of diastereoisomers from which the major isomer was isolated by crystallization (Chart 1). It is noteworthy that dienophile **3** is much more reactive toward piperylene than toward butadiene as deduced from comparison of this result with those in entries 7−8, Table 1. Cyclobutane 1,2-adducts **13** were detected by HPLC of the reaction mixture before completion of the process.

(c) Reactions with Cyclopentadiene. The cycloadditions of protoanemonin **1** to cyclopentadiene and cyclohexadiene had previously been studied in our laboratory, focussing our attention on the *endo/exo* stereoselectivity. This was enhanced at low temperature, the ratio of *endo/exo* adducts being the result of the kinetic control of the reaction since interconversion between both stereoisomers was not observed.[15] In the reaction with cyclopentadiene, optimal conditions for synthetic purposes involved the use of excess diene in dichloromethane at 90 °C for 2.2 h, affording the corresponding adduct in 75% yield, as a 70:30 mixture of *endo/exo* diastereoisomers. In a similar manner, bromofuranone **2** reacted with 75 equiv of cyclopentadiene in dichloromethane at 90 °C for 2 h to give adduct **8** in 90% yield, also as a 70:30 mixture of diastereoisomers. In turn, methoxyfuranone **3** reacted with 80 equiv of cyclopentadiene in dichloromethane at 155 °C for 10 h, affording the corresponding adducts **9** in 48% yield, as a 58:42 mixture of stereoisomers, along with 24% recovered dienophile. The lower excess of diene resulted in a smaller conversion. Results were not improved by using 120 equiv of cylopentadiene, with a large quantity of polymer being produced in this case. Therefore, besides the low reactivity of **3**, the almost lack of stereoselectivity in this cycloaddition is also noticeable.

Four new compounds, *endo-* and *exo-* **8** and -**9** (Chart 1), were isolated by column chromatography from the corresponding reaction crudes and characterized as crystalline solids. Stereochemical assignments were made by comparison of their spectroscopic data with those previously described for the *endo/exo* adducts from protoanemonin **1** and cyclopentadiene. Identification of each stereoisomer was accomplished on the basis of their ^1H NMR data and differential NOE experiments. Thus, selective irradiation of H_8 in *endo* adducts produced significant NOE on H_1, H_{5x}, and H_{7b}, while NOE was observed on H_1, H_{5n}, and H_6 when H_8 was selectively irradiated in *exo* adducts.

2. Photocycloadditions of Furanones 1, 2, and 3 to Dienes. To the best of our knowledge, photochemically induced cycloadditions involving 5-methylene-2(5*H*)-furanones and dienes to afford 1-oxaspiro[3.5]octane derivatives had not been described prior to our work, although they constitute an efficient method for synthesizing this family of compounds. Butadiene, *trans*-piperylene, and cyclopentadiene were used in this study.
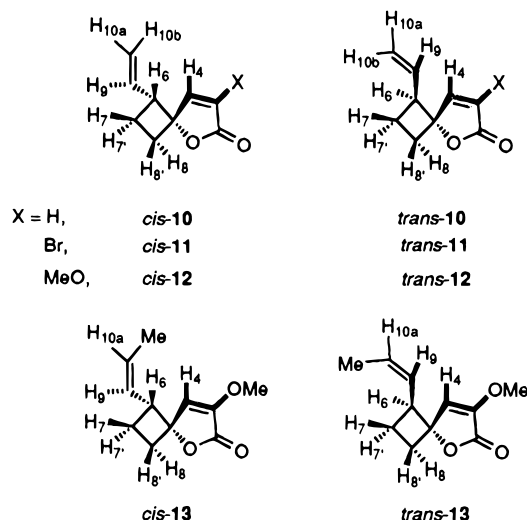
(a) Reactions with Butadiene. Irradiation of furanones **1**−**3**, as THF solutions containing excess butadiene in a Pyrex reactor at −78 °C, with a medium-pressure mercury lamp produced spiro vinyl cyclobutanes **10**−**12**, respectively, as 3:2 mixtures of *cis/trans* stereoisomers (Chart 2). The yield and *cis/trans* ratio in every case are listed in Table 2.

It is remarkable the high site selectivity of the cycloaddition since cyclobutane derivatives coming from reaction at the endocyclic double bond were not detected. *Cis* stereoselectivity was predominant in all cases, contrary to the thermal 1,2-cycloadditions in which *trans* adducts were the major compounds. *Cis/trans* stereochemistry was assigned on the basis of differential NOE experiments. Thus, presaturation of H_4

Table 1. Thermal Cycloadditions of Butadiene to Furanones **1−3**

entry no.	furanone	temp (°C)	time (°C)	% yield[a]	% starting material[a]	1,4-adduct	1,2-adduct	[1,4]:[1,2] ratio[a]
1	**1**	150	45 min	77	21	**4**	**10**	2:3
2	**1**	150	90 min	80	15	**4**	**10**	2:1
3	**1**	150	135 min	90	4	**4**	**10**	15:1
4	**2**	150	10 min	44	46	**5**	**11**	2:1
5	**2**	150	20 min	69	18	**5**	**11**	5:1
6	**2**	150	40 min	84	6	**5**	**11**	15:1
7	**3**	155	4 h	54	34	**6**	**12**	1:1
8	**3**	155	8 h	65	12	**6**	**12**	2:1
9	**3**	155	20 h	85	5	**6**	**12**	8:1

[a] Determined by HPLC.

Chart 2

X = H,	*cis*-**10**	*trans*-**10**
Br,	*cis*-**11**	*trans*-**11**
MeO,	*cis*-**12**	*trans*-**12**

cis-**13**   *trans*-**13**

Table 2. Photocycloadditions of Furanones **1−3** to Dienes Affording 1,2-Adducts

furanone	diene	temp (°C)	time (h)	% yield[a]	adduct	*cis/trans* ratio[b]
1	butadiene	−78	10	61	**10**	60:40
2	butadiene	−78	8	46	**11**	60:40
3	butadiene	−78	20	40	**12**	60:40
3	*trans*-piperylene	0	18,5	56	**13**	60:40

[a] Isolated yield. [b] Determined on isolated stereoisomers.

produced 3% NOE on H$_6$ in *cis* isomers and 2% NOE on H$_9$ in *trans* isomers.

(b) Reaction with *trans*-Piperylene. 1,2-Cycloaddition of *trans*-piperylene to furanone **3** was performed by irradiation of a solution of both components in THF at 0 °C for 18.5 h to afford a 3:2 mixture of *cis/trans*-**13** (56% yield) that was isolated by column chromatography. A very large excess of diene, *ca.* 45 equiv, was crucial to obtain good yields of **13** in shorter reaction times. Both site selectivity related to furanone **3** and regioselectivity concerning the diene were excellent. Tables 3 and 4 summarize the most relevant spectroscopic data for these new compounds.

(c) Reaction with Cyclopentadiene. Irradiation of a solution of furanone **3** and excess cyclopentadiene in THF at −78 °C for 8 h led to 15% **3** recovered and *endo*-**9** produced in 8% yield, as the only defined reaction product, along with some unreacted cyclopentadiene and a large quantity of polymer. It is interesting to note that the obtained compound corresponds to the *endo* diastereoisomer **9** coming from the thermal cycloaddition of **3** to cyclopentadiene (Chart 1).

3. Mechanistic Study of the Thermal Cycloadditions of Furanones 1−3. The results listed in Table 1 account for an important ratio of vinyl cyclobutanes at short reaction times in

the thermal cycloadditions to butadiene, the proportion decreasing progressively with time. The opposite occurs in the case of the cyclohexene derivatives, in such a way that they are the only reaction products in the case of furanones **1** and **2** after 4 and 1 h, respectively, in the presence of butadiene at 155 °C. Similar results were obtained from the reaction of furanone **3** and *trans*-piperylene.

Nishida *et al.* had reported the production of vinyl cyclobutanes along with 1,4-adducts in the reactions between tetracyanoethylene and 1,1-disubstituted butadienes, with the ratio of products depending on the diene, solvent polarity, and reaction time in each case.[6b] Such results led these authors to postulate a two-step mechanism through a zwitterionic intermediate for the production of 1,2-adducts. These products isomerize to 1,4-adducts in polar solvents. Moreover, since this interconversion was not observed in nonpolar solvents, the competition of two mechanistic pathways, concerted for 1,4-adducts and ionic for 1,2-adducts, was invoked to explain the experimental findings with the later conditions.[23]

According to our results it seems feasible that 1,2-adducts are kinetically favored and, consequently, that they are formed in the earlier stages of the reaction. Two possible mechanistic hypotheses emerge. One of them involves the vinyl cyclobutanes as intermediates in the production of the Diels−Alder adducts. Thus, compounds **10−13** would isomerize into the corresponding cyclohexene derivatives **4−7** *without* reversion to the starting materials. The second hypothesis would assume cycloreversion of the 1,2-adducts to the starting diene and dienophile and their later recombination to afford the 1,4-adducts, which are thermodynamically more stable, through a concerted process.

To verify which of these two hypotheses prevails, several experiments were carried out to establish the role of the vinyl cyclobutanes in the overall process leading to the production of the Diels−Alder adducts.

First of all we confirmed that cyclobutane derivatives isomerize to cyclohexene compounds in the reaction conditions. Thus, a mixture of bromo derivatives *cis/trans*-**11** in dichloromethane was heated at 155 °C for 1 h to obtain cyclohexene **5** as the only product as shown by ¹H NMR. Compound **5** could have been produced, however, *via* cycloreversion of **11** to furanone **2** and butadiene and subsequent recombination of these reactants to afford the Diels−Alder adduct. Such a possibility was rejected in view of the following results. A mixture of *cis/trans*-**11** in a chlorobenzene solution contained in an open system, instead of a sealed reactor as in the preceding reactions, was heated to reflux (132 °C) for 1.5 h with the purpose of removing the butadiene produced in the cycloreversion, if any. Once again, compound **5** was the sole identified product, neither **11** nor furanone **2** being detected by ¹H NMR.

Furthermore, crossover experiments were also carried out

(23) In our case, lack of solvent effect was observed.

Scheme 2

X = H, **10**	3 h	**4** (94%)		**14** (6%)
Br, **11**	1 h	**5** (94%)		**15** (6%)
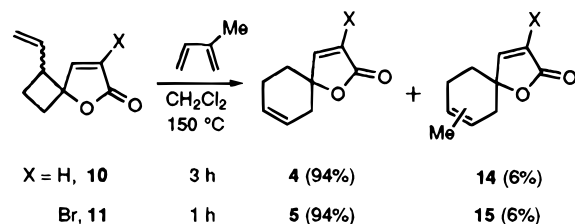
Table 3. Evolution of 1,2-Adducts to 1,4-Adducts and to Corresponding Furanones in Several Conditions

entry no.	1,2-adduct	temp (°C)	time	1,4-adduct (%)[a]	furanone (%)[a]
1	**11**	110	6 h	**5** (61)	**2** (3)
2	**11**	120	3,2 h	**5** (71)	**2** (4)
3	**11**	130	1,5 h	**5** (72)	**2** (6)
4	**11**	150	45 min	**5** (79)	**2** (8)
5	**13**	155	5 min	**7** (4)	
6	**13**	155	30 min	**7** (21)	**3** (1)
7	**13**	155	1 h	**7** (49)	**3** (2)
8	**13**	155	5 h	**7** (74)	**3** (6)

[a] Determined by HPLC.

(Scheme 2). Thus, in separate experiments, *cis/trans*-**10** and *cis/trans*-**11** in dichloromethane solutions were heated in the presence of a large excess of isoprene at 150 °C for 3 and 1 h, respectively. Whereas the ^{1}H NMR spectra of the resultant crudes showed the sole absorptions of products **4** and **5** as previously reported,[19] GC analysis revealed, in both cases, the presence of a 94:6 mixture of the respective Diels−Alder adducts from furanones and butadiene, **4** and **5**, and the corresponding adducts with isoprene **14** and **15**, both as a mixture of regioisomers. Identification of **14** and **15** was done by comparison with the adducts obtained by reaction between excess isoprene and furanones **1**[12] and **2**, respectively.

Moreover, cyclobutanes **11** were heated in sealed reactors at different temperatures for appropriate time periods (Table 5). In all cases, 1,4-adduct **5** was the major product (61−79%), but a small percentage (3−8%) of the precursor furanone **2** was detected in the resulting mixtures by HPLC. Since we observed isomerization of the vinyl cyclobutanes to cyclohexene derivatives to take place in the GC conditions, the use of this analytical technique was precluded for quantitative determinations. Similarly, cyclobutanes **13** coming from furanone **3** and *trans*-piperylene were heated at 155 °C and their evolution was monitored by HPLC. After 30 min of heating, 78% of the **13** remained but 1,4-adduct **7** (21%) as well as furanone **3** (1%) were detected. Furthermore, cyclohexene derivative **7** was the major product (74%) after 5 h at 155 °C (Table 3, entries 6 and 8).

Therefore, some little cycloreversion was detected, but it was necessary to discern if it occurred from the 1,2-adducts or from the 1,4-adducts. To this aim, in separate experiments, solutions of the 1,4-adducts **4, 5,** and **6** in dichloromethane were heated at 150 °C for 3 h, 45 min, and 24 h, respectively, these times being selected according to the reactivity previously observed for each precursor furanone. Analysis by HPLC of the resultant crudes revealed the presence of only the starting Diels−Alder adduct in every case.

All these results are consistent with the formation of the vinyl cyclobutanes as intermediates in the production of the Diels−Alder adducts. This hypothesis is confirmed by studying the evolution of all the components of the reaction including the starting dienophile, the diastereoisomeric vinyl cyclobutanes, and the corresponding Diels−Alder adduct.
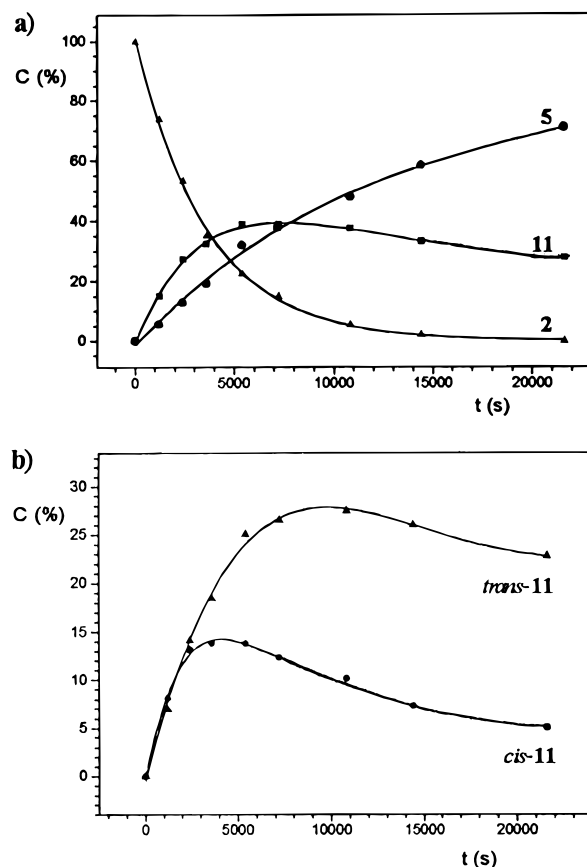
Figure 1. Plot of the relative concentrations (%) corresponding to (a) the starting dienophile **2**, the vinyl cyclobutanes **11**, and the Diels−Alder adduct **5** and (b) the mixture of stereoisomeric cyclobutanes *cis*-**11** and *trans*-**11** *vs* time for the reaction between bromofuranone **2** and butadiene at 110 °C.

Bromofuranone **2** was chosen to carry out such a study due to its suitable reactivity and stability, these characteristics allowing better quantitative determinations to be achieved. Protoanemonin **1** was too unstable and evolved, under the reaction conditions, toward dimers and polymers,[24] thus precluding its use in a similar study. In turn, furanone **3** was much less reactive. Reactions were performed with 1,3-butadiene as the simplest diene, at 110, 120, 130, 140, and 150 °C, and quantitative analyses were carried out by using HPLC.

Figure 1a shows the evolution of the system **2**/*cis/trans*-**11**/**5** throughout the reaction at 110 °C. This plot corresponds clearly to a process going on through an intermediate species in good agreement with the above-mentioned experiments. Although the exponential disappearance of furanone **2** corresponds well to a first-order process, the production of cyclohexene adduct does not seem to follow a simple kinetics.

Furthermore, whereas the initial ratio of both stereoisomeric cyclobutanes is similar, it becomes very different at larger time periods, as shown in Figure 1b. Additional experiments permitted us to demonstrate that consumption of *cis*-**11** is faster than that of *trans*-**11**. Moreover, evolution of *cis/trans*-**11** involves two competing processes, *i.e.* interconversion of each cyclobutane into the other one and isomerization of both *cis* and *trans* intermediates into the corresponding 1,4-adduct. These experiments were carried out as follows. Pure *cis*-**11** and *trans*-**11** in toluene were heated at 90 °C for 3 h in separated

(24) See, for instance: (a) Asahina, Y.; Fujita, A. *Acta Phytochim.* **1922**, *1*, 1. (b) Moriarty, R. M.; Romain, C. R.; Karle, J. *J. Am. Chem. Soc.* **1965**, *87*, 3251. (c) Lustig, E.; Moriarty R. M. *J. Am. Chem. Soc.* **1965**, *87*, 3252. (d) Camps, P.; Font, J.; Marqués, J. M. *Tetrahedron* **1975**, *31*, 2581.
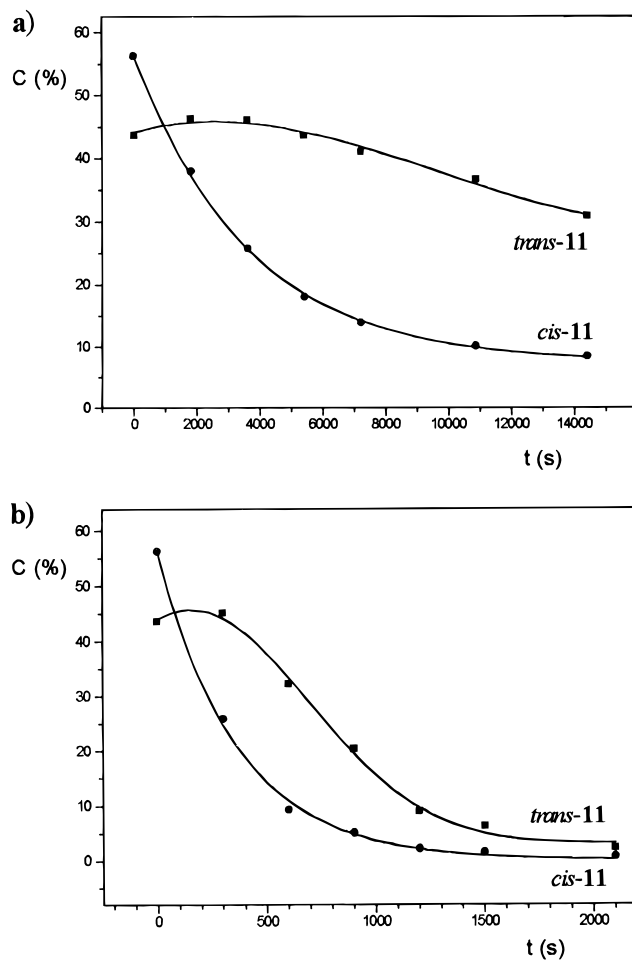
Figure 2. Plot of the relative composition (%) of a mixture of *cis*-**11** and *trans*-**11** *vs* time at 110 (a) and 150 °C (b).

reactors and the composition of the resultant mixture was then determined by HPLC. The obtained data verify the interconversion between the two stereoisomeric cyclobutanes and show that both the interconversion and the isomerization rates for *cis*-**11** are greater than those corresponding to *trans*-**11**. In addition, the evolution of mixtures of *cis/trans*-**11** was studied at 110, 120, 130, 140, and 150 °C. Results are shown in Figure 2 for the extreme temperatures.

It is interesting to note that the rates of disappearance of the two stereoisomeric cyclobutanes become closer as the temperature increases. Moreover, the percentage of cycloreversion from the mixture *cis/trans*-**11**, measured as a ratio of furanone **2** at the reaction times required for almost completion at each temperature, is shown in Table 5 (entries 1−4). One can observe that this ratio increases with temperature in good agreement with the results of crossover experiments (*vide supra*). Nevertheless, cycloreversion is low enough in all cases to assume that the rate constants associated with these processes are very small

Scheme 3 summarizes all the reactions involved and gives an idea of the high complexity of the overall kinetic process since at least six main rate constants must be considered. Such a complexity impeded the determination of the rate constants for each individual reaction.

Production of *cis/trans* vinyl cyclobutanes **10**−**12** results from the reactions between furanones **1**−**3** and *s-trans*-butadiene. Obtaining such compounds in this kind of thermal processes led us to assume the presence of biradical species as intermediates[7a,b] (Chart 3). According to our assumption, the first bond is formed between *C-1* in butadiene (shown as *C(a)*
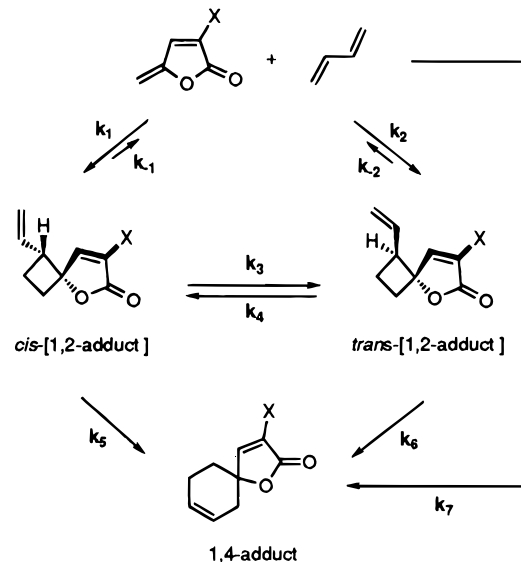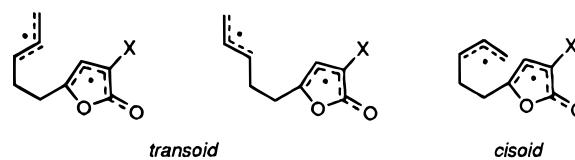
Scheme 3

Chart 3

in Figure 3) and *C-6* in the corresponding furanone. The resultant biradical is stabilized by conjugation with the vinyl group in the diene moiety and with the unsaturated lactone, the *C-3* carbon atom bearing the substituent being involved in this stabilization. This biradical would mainly exist as the average of *transoid* conformers in equilibrium, all of them evolving toward 1,2-adducts, the 1,4-adduct being only produced from the *cisoid* conformer, which must be a higher-energy intermediate.[7d] The results of our kinetic study account for a rapid reversible process affording *cis/trans* cyclobutanes, whereas formation of the thermodynamically more stable cyclohexene would be achieved according to a slower irreversible process.

A similar explanation accounts for the production of stereoisomeric 1,2-adducts **13** from furanone **3** and *trans*-piperylene, as well as for their isomerization to 1,4-adduct **7**. The presence of radicals in these Diels−Alder reactions is also consistent with the production of 1,4-adduct **9** from furanone **3** and cyclopentadiene under photochemical activation, the outcome of such a process presumably involving radical species as intermediates since, under these conditions, a 1,4-concerted cycloaddition is forbidden by orbital symmetry considerations.

Biradicals have been postulated by Hall *et al*. in the reactions of some electron-rich dienes with electron-poor olefins, accounting for the copolymerizations that often accompany their Diels−Alder reactions. Nevertheless, 1,4-cycloadducts were assumed to be produced exclusively through a concerted process, the copolymerization and the [4 + 2]-cycloaddition proceeding as two parallel independent reactions.[25]

Therefore, if our mechanistic hypothesis is reliable, cyclobutanes should be able to revert to the biradical intermediates in the reaction conditions.[7e,f] At this point, two mechanistic possibilities must be considered: (a) The biradicals revert, in turn, to the initial diene and dienophile and these react to afford Diels−Alder adducts according to a one-step process. Never-

(25) (a) Li, Y.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1993**, *58*, 7049. (b) Padias, A. B.; Hall, H. K., Jr. *Aldrichim. Acta* **1995**, *28*, 37.
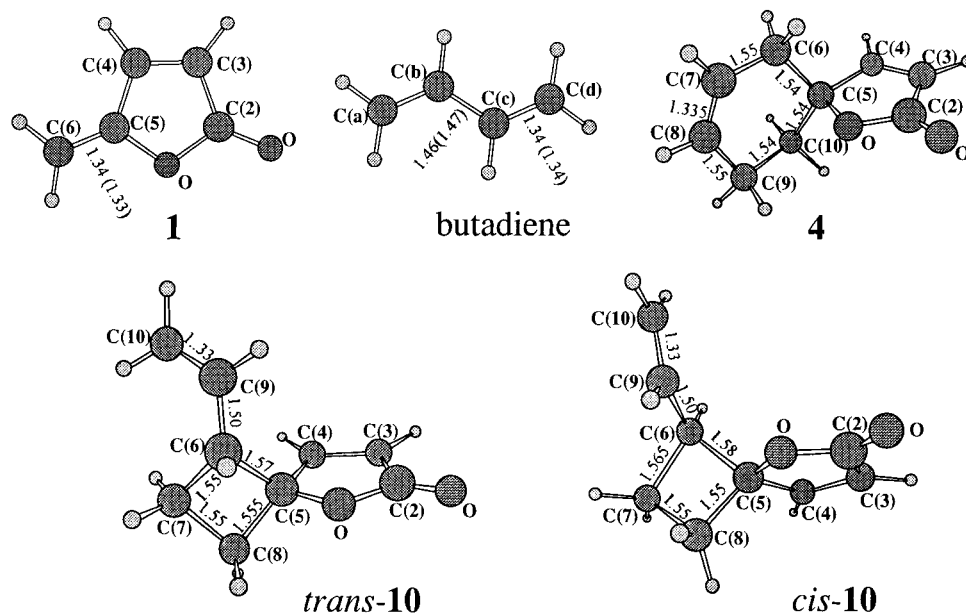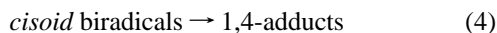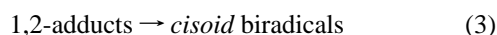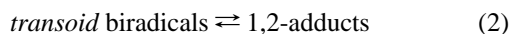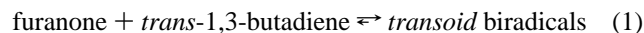
Figure 3. Geometries optimized at the B3-LYP/6-31G* (CASSCF/3-21G) level of calculation for furanone **1**, butadiene, 1,4-adduct **4**, and the 1,2-adducts *trans*-**10** and *cis*-**10**. Selected bonds lengths in Å.

Table 4. Selected Geometry Parameters[a] for the B3-LYP/6-31G* Intermediates and Transition States

reaction	structure	C(6)-C(a)	C(5)-C(d)	C(5)-C(b)	C(5)-C(6)	C(a)-C(b)	C(b)-C(c)	C(c)-C(d)
4 + 2	concerted T.S. (**14**)	1.97	2.93		1.40	1.40	1.42	1.365
	1st T.S. (*endo*-**15**)	1.985 (2.01)	4.86 (3.24)		1.40 (1.37)	1.40 (1.39)	1.43 (1.44)	1.36 (1.35)
	intermediate (*endo*-**16**)	1.56 (1.56)	5.20 (3.40)		1.48 (1.48)	1.49 (1.51)	1.39 (1.39)	1.38 (1.39)
	2nd T.S. (*endo*-**17**)	1.59	2.70		1.475	1.49	1.38	1.395
2 + 2	1st T.S. (*trans*-**18**)	1.97		4.73	1.40	1.405	1.425	1.36
	intermediate (*trans*-**19**)	1.57		3.86	1.48	1.49	1.39	1.38
	2nd T.S. (*trans*-**20**)	1.535		2.31	1.51	1.52	1.42	1.36
	1st T.S. (*cis*-**18**)	1.97		4.77	1.40	1.40	1.425	1.36
	intermediate (*cis*-**19**)	1.57		3.855	1.48	1.49	1.39	1.38
	2nd T.S. (*cis*-**20**)	1.54		2.34	1.51	1.52	1.41	1.37
10 → 4	1st T.S. (*trans*-**21**)	1.535		2.32	1.51	1.51	1.42	1.36
	intermediate (*exo*-**16**)	1.57		4.78	1.48	1.50	1.40	1.38
	2nd T.S. (*exo*-**17**)	1.59	2.68		1.49	1.48	1.38	1.40
	1st T.S. (*cis*-**21**)	1.535	3.72	2.35	1.51	1.52	1.41	1.37

[a] Bond lengths in Å. Values corresponding to the *gauche-in* CASSCF/3-21G structures are given in parentheses.

theless, on the basis of the previous experiments described above, the ratio of 1,4-adducts resulting from a concerted process must be almost negligible, if any, due to the low cycloreversion observed from cyclobutanes. (b) Direct collapse of *cisoid* biradical gives the cyclohexene structure in each case.[7d] This mechanism is given in eqs 1−4.

$$\text{furanone} + trans\text{-1,3-butadiene} \rightleftharpoons transoid \text{ biradicals} \quad (1)$$

$$transoid \text{ biradicals} \rightleftharpoons \text{1,2-adducts} \quad (2)$$

$$\text{1,2-adducts} \rightarrow cisoid \text{ biradicals} \quad (3)$$

$$cisoid \text{ biradicals} \rightarrow \text{1,4-adducts} \quad (4)$$

To realize the feasibility of these hypotheses it was useful to determine the energy barriers associated with all these processes as well as the geometry of the transition states. An accurate theoretical study was carried out with this purpose.

4. Theoretical Calculations. CASSCF and DFT calculations were done on the reaction between butadiene and the parent dienophile **1**. Results on the most favorable mechanism must be extended to the other furanones.

Figure 3 shows the optimized geometries of **1** and butadiene at the B3-LYP and CASSCF levels of calculation. We can observe that both lead to similar results. The optimized geometries of the Diels−Alder adduct **4** and those of the *cis*- and *trans*-1,2-adducts **10** are also shown. Several conformations related to the rotation around the *C(6)−C(9)* bond, involving the vinyl group, have been considered for the two cyclobutane derivatives, and those presented in Figure 3 correspond to the most stable ones.

At the B3-LYP/6-31G* level of calculation, the 1,4-adduct is 35 kcal/mol below the reactants, while the reaction energy corresponding to the 1,2-adducts is −11.1 (*trans*-**10**) and −9.8 (*cis*-**10**) kcal/mol. These results show that the Diels−Alder product is thermodynamically the most favorable.

We began the exploration of the potential energy surface leading to the formation of the Diels−Alder adduct by locating the transition state at the HF/3-21G level, starting from the previously calculated AM1 structure.[16a] This HF/3-21G structure and the corresponding Hessian matrix have been used to locate the transition states on the CASSCF/3-21G and B3-LYP/6-31G* potential energy surfaces. Selected geometry parameters are collected in Table 4, and the B3-LYP structure obtained, **14**, is represented in Figure 4. Both CASSCF and B3-LYP structures are highly asynchronous, while the HF/3-21G struc-
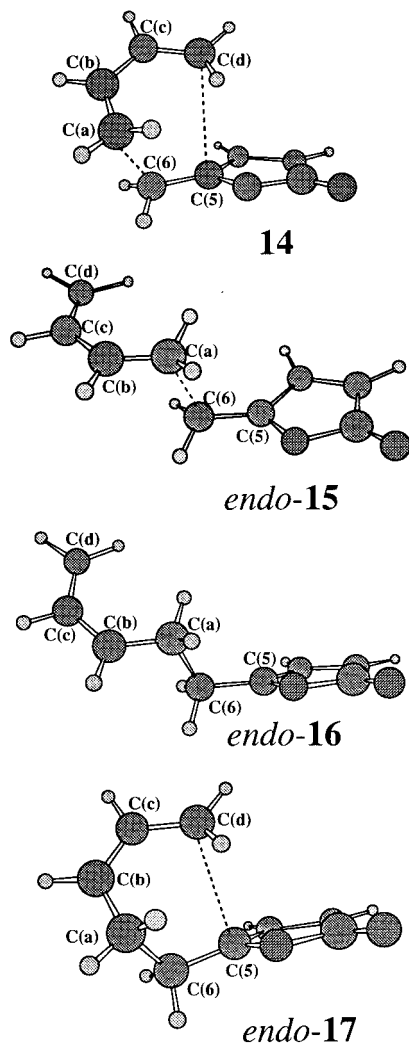
14

*endo-***15**

*endo-***16**

*endo-***17**

Figure 4. Structures of the B3-LYP/6-31G* stationary points corresponding to the Diels−Alder cycloaddition of furanone **1** to butadiene.

Table 5. Energies and Thermodynamic Parameters, Computed at 1 atm and 298.15 K, Relative to the Reactants for the Stationary Points of the B3-LYP/6-31G* Potential Energy Surface Corresponding to the Reaction between **1** and Butadiene

reaction	structure	ΔE^a	ΔH^b	ΔS^c	ΔG^b
4 + 2	concerted T.S. (**14**)	20.0 (22.5)	23.3	−42.9	36.1
	1st T.S. (*endo*-**15**)	21.6 (24.0)	24.2	−36.4	35.1
	intermediate (*endo*-**16**)	10.0 (13.5)	14.6	−35.2	25.1
	2nd T.S. (*endo*-**17**)	12.4 (15.9)	16.7	−45.6	30.3
	product (**4**)	−35.0 (−30.2)	−26.4	−48.9	−11.8
2+2	1st T.S. (*trans*-**18**)	19.5 (21.9)	22.0	−37.1	33.1
	intermediate (*trans*-**19**)	9.2 (12.8)	13.8	−35.7	24.4
	2nd T.S. (*trans*-**20**)	17.5 (21.3)	21.9	−42.1	34.5
	product (*trans*-**10**)	−11.1 (−6.5)	−3.6	−44.8	9.8
	1st T.S. (*cis*-**18**)	19.5 (21.9)	22.0	−37.0	33.0
	intermediate (*cis*-**19**)	8.9 (12.5)	13.4	−35.8	24.1
	2nd T.S. (*cis*-**20**)	14.9 (18.6)	19.3	−42.9	32.1
	product (*cis*-**10**)	−9.8 (−5.4)	−2.6	−43.7	10.4

[a] In kcal mol^{-1}. Values computed at the B3-LYP/6-311G**//B3-LYP/6-31G* level are given in parentheses. [b] In kcal mol^{-1}. Computed from the B3-LYP/6-311G**//B3-LYP/6-31G* energies and the B3-LYP/6-31G* vibrational frequencies. [c] In cal K^{-1} mol^{-1}.

Figure 4, and selected geometry parameters as well as the corresponding energies are presented in Tables 4 and 5, respectively.

The first transition state corresponding to the biradical mechanism of the Diels−Alder reaction, **15**, is 21.6 kcal/mol above the reactants, being slightly higher than the B3-LYP concerted transition state, **14** (*c.f.* 20 kcal/mol). This result differs from that obtained at the same level of calculation for the butadiene plus ethylene cycloaddition,[11] where the concerted transition state was much more favorable (10.6 kcal/mol below). The biradical intermediate **16** is also much more stable than that corresponding to this reaction: while biradical **16** is 11.6 kcal/mol below the transition state **15**, the energy difference was only 4.6 kcal/mol for the butadiene plus ethylene reaction. The energy barrier corresponding to the second transition state, **17,** is 2.4 kcal/mol. This barrier should be lower for the butadiene plus ethylene reaction, thus explaining the difficulty in locating such a structure.[11] The use of the larger basis set produces an increase of all relative energies by 2.5−5 kcal/mol. The inclusion of zero-point and thermal corrections to the energy, as well as the entropy, changes the relative order between the concerted transition state **14** and the first transition state of the biradical mechanism **18** (Figure 5) in such a way that the biradical mechanism becomes the most favorable one. In the reaction between butadiene and ethylene, the inclusion of entropy corrections favors the biradical mechanism, but the concerted transition state remains lower in terms of Gibbs energy. As a summary of the comparison with the butadiene plus ethylene reaction, we can conclude that the reaction between protoanemonin and butadiene presents a clear tendency toward a biradical mechanism.

Let us now consider the stationary points leading to the formation of the cyclobutane adducts **10**. One can observe in Table 5 that all structures are lower in energy than those corresponding to the [4 + 2] reaction, suggesting that the formation of the [2 + 2] adducts is kinetically more favorable. Thus, the first transition states **18** (Figure 5) are lower in energy than the concerted transition state of the [4 + 2] reaction, **14**. On the other hand, the barriers corresponding to the formation of the second C−C bond are notably larger than that corresponding to the [4 + 2] reaction (8.3 and 6.0 kcal/mol *vs* 2.4 kcal/mol). This fact can be related to the differences between the C(5)−C(d) and C(6)−C(a) bond lenghts at the transition states (Table 4) and to the fact that this step is less exothermic

tures were nearly synchronous with C(6)−C(a) and C(5)−C(d) bond lengths of 2.066 and 2.363 Å, respectively. The CASSCF transition structure is 34 kcal/mol above the reactants, while the energy barrier corresponding to B3-LYP/6-31G* transition structure **14** is 20 kcal/mol.

For the CASSCF structure, a small displacement of the nuclear coordinates toward the reaction product followed by a full geometry optimization leads to a biradical intermediate in a *gauche-in* conformation[8g] located 14.8 kcal/mol above the reactants and 19.2 kcal/mol below the transition state. These results seem to indicate that there is not a concerted transition state in the CASSCF potential energy surface.

On the other hand, the same kind of displacement on the nuclear coordinates starting from the B3-LYP transition state leads to the Diels−Alder adduct **4** even if the symmetry between α and β electron densities is broken. According to these results, a very asynchronous concerted reaction path exists in the B3-LYP/6-31G* potential energy surface.

Spin-unrestricted B3-LYP/6-31G* calculations have been undertaken to study the two-step reaction paths leading to the formation of the 1,4-adduct **4** and the 1,2-adducts *cis*-**10** and *trans*-**10**. In all cases, the transition state corresponding to the formation of the first C−C bond, the biradical intermediate, and the transition state corresponding to the formation of the second C−C bond have been located. We have only considered the *anti* conformations of the biradicals and the transition states leading to them.[8g,11] The structures obtained are shown in
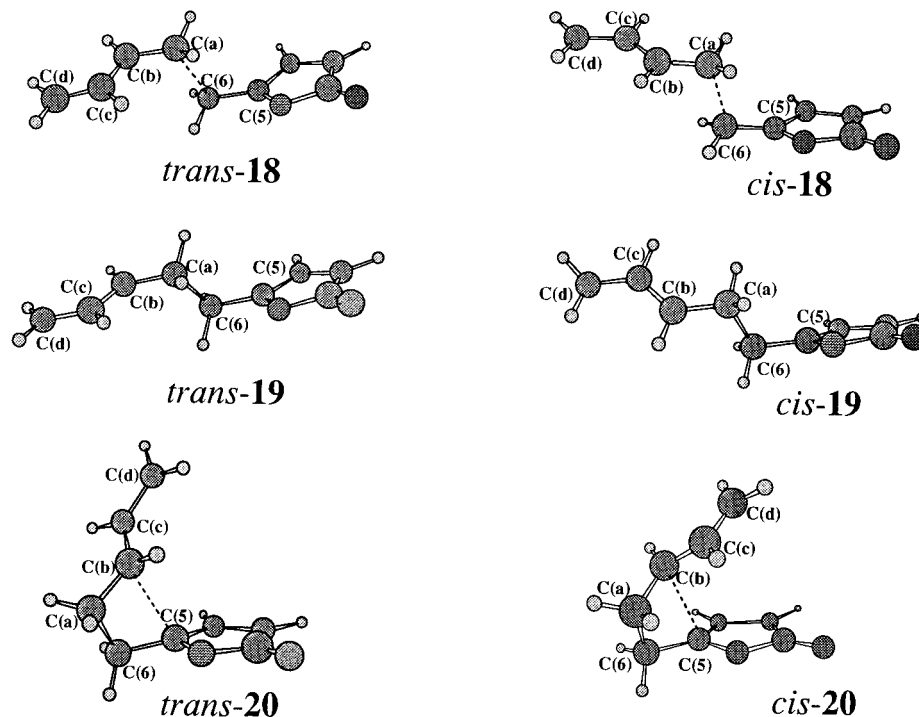
Figure 5. Structures of the B3-LYP/6-31G* stationary points corresponding to the [2 + 2] cycloaddition of furanone **1** to butadiene.

in the [2 + 2] reactions. Moreover, the energy difference between the first and the second transition states is notably lower than that for the [4 + 2] reaction. The use of a larger basis set has the same effect in the computed energies as those observed for the [4 + 2] reaction. The inclusion of zero-point and thermal contributions to the energy, as well as the entropy, makes the cyclobutanes **10** less stable than the reactants. For the formation of *trans*-**10**, the second transition state, *trans*-**20** (Figure 5), becomes the highest one in terms of Gibbs energy, while the first transition state, *cis*-**18**, is the highest one for the formation of *cis*-**10**. As a consequence of these facts, the Diels–Alder adduct **4** becomes the only stationary point that is thermodynamically more stable than the reactants, while the [2 + 2] cycloaddition is the kinetically favored process. This fact is consistent with the experimental observation of the production of cyclobutane adducts in the early stages of the reaction, *trans*-**10** being thermodynamically slightly more stable than *cis*-**10**, while kinetically less favorable.

Concerning the isomerization of the 1,2-adducts **10** into the 1,4-adduct **4**, there are several possible paths. One of them would involve the reversion from *trans*-**10** to biradical **19** (Figure 5), with a Gibbs activation energy of 24.7 kcal/mol, followed by a *transoid* **19** to *cisoid* **16** rearrangement. This process involves a rotation around the C(b)−C(c) bond from an *s-cis* to an *s-trans* conformation, this bond having an important double bond character. From calculations on the allyl radical, we can estimate the barrier of this process to be about 15 kcal/mol, this barrier being larger than those leading to the decomposition of both biradicals. An alternative path would be a direct evolution of *trans*-**10** to an *s-cis* biradical intermediate. In the most stable conformation of the 1,2-adduct (*trans*-**10**, Figure 3), the C(10)−C(9)−C(6)−C(7) dihedral angle is −10.5°, very close to the value corresponding to the *s-cis* conformation of butadiene. The cleavage of the C(5)−C(6) bond in this product would lead to an intermediate with an *s-cis* arrangement of the butadiene moiety that is necessary to lead to the 1,4-adduct. We have located the transition state corresponding to this process (*trans*-**21**) and the corresponding biradical intermediate (*exo*-**16**). This intermediate can evolve
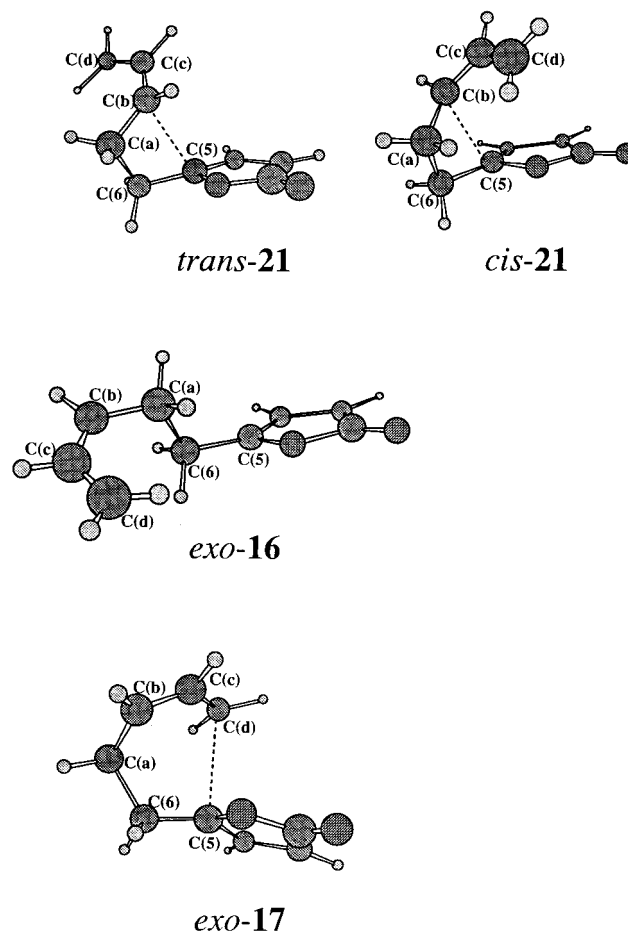

Figure 6. Structures of the B3-LYP/6-31G* stationary points corresponding to the isomerization of the 1,2-adducts **10** into the 1,4-adduct **4**.

to the 1,4-adduct through a second transition state (*exo*-**17**). These structures are represented in Figure 6, selected geometry parameters, and the corresponding energies being shown in Tables 4, 5, and 6, respectively. The activation parameters

Table 6. Energies and Thermodynamic Parameters, Computed at 1 atm and 298.15 K, Relative to **1** and Butadiene for the Stationary Points of the B3-LYP/6-31G* Potential Energy Surface Corresponding to the **10** → **4** Rearrangement

structure	ΔE^a	ΔH^b	ΔS^c	ΔG^b
1st T.S. (*trans*-**21**)	17.5 (21.2)	21.9	−42.8	34.7
intermediate (*exo*-**16**)	9.9 (13.4)	14.5	−36.5	25.4
2nd T.S. (*exo*-**17**)	15.8 (19.3)	20.0	−45.1	33.4
1st T.S. (*cis*-**21**)	15.8 (19.5)	20.2	−43.0	33.0

a In kcal mol^{-1}. Values computed at the B3-LYP/6-311G**//B3-LYP/6-31G* level are given in parentheses. *b* In kcal mol^{-1}. Computed from the B3-LYP/6-311G**//B3-LYP/6-31G* energies and the B3-LYP/6-31G* vibrational frequencies. *c* In cal K^{-1} mol^{-1}.

corresponding to transition state *trans*-**21** are very similar to those for *trans*-**20**, while biradicals *exo*-**16** and *trans*-**19** have similar stabilities. The transition state *exo*-**17** is higher in energy and Gibbs energy than *endo*-**17**.

This direct conversion from *trans*-**10** to an *s-cis* biradical seems the most feasible path for its isomerization into the 1,4-adduct **4**. A similar process starting from a *C(10)−C(9)−C(6)−C(7) s-cis* conformation of cyclobutane adduct *cis*-**10**, which is only 0.8 kcal/mol higher in energy than the most stable conformation shown in Figure 3, would directly lead to the biradical *endo*-**16** and, subsequently, to the Diels−Alder adduct. The transition structure *cis*-**21**, corresponding to the *cis*-**10** → *endo*-**16** rearrangement, is also represented in Figure 6.

In conclusion, these **10** → **4** rearrangements are controlled by the transition states **21**. The Gibbs activation energies corresponding to the decomposition of **10** are 22.6 (*cis*) and 24.9 (*trans*) kcal/mol. This result is in excellent agreement with the experimental observation that the rate of decomposition of the *cis* product is larger than that of the *trans* isomer (Figure 2).

The whole mechanism is summarized in Figure 7 wherein a schematic Gibbs energy profile is presented.

5. Detection by ESR Spectroscopy of Intermediate Radical Species. At this point, both kinetic and theoretical studies seemed to point to a biradical mechanism to explain the thermal production of 1,2-adducts and their isomerization into 1,4-adducts. The next step was, therefore, to perform several experiments to detect such biradical intermediates.

The addition of radical scavengers, such as galvinoxyl radical, to the reaction mixtures of **1** and **2** as well as to **10** and **11** did not produce significant changes in the resultant cycloadducts. This result contrasts with other results previously reported in which the aminoxyl radical was used as a radical scavenger for trapping a biradical intermediate produced in the reaction between *p*-methoxystyrene and dimethyl cyanofumarate.[26] Our results were not surprising, however, since concentration of biradical intermediates produced under the reaction conditions must be extremely low due to their rapid intramolecular collapse to the cyclobutane or cyclohexene derivatives. This fact was also an inconvenience for the direct detection of such short lived intermediate species by Electron Spin Resonance (ESR) spectroscopy despite the high sensibility of this technique.

Nevertheless, the use of ESR spin trapping technique[27] allowed us an indirect detection of these transient species. We limited the experiments to the study of isomerization of cyclobutanes **10** and **11** into the corresponding Diels−Alder adducts because they can be isolated as pure products and are

the key intermediates in the proposed mechanism (see Scheme 3). Different *C*-nitroso and nitrone compounds were used as spin trapping agents since they add efficiently to transient free radicals producing, as spin adducts, substituted aminoxyl (or nitroxide) free radicals of longer lifetimes which are easily characterized by ESR and, in some cases, provide valuable information about the trapped transient radicals.[27] The temperatures for these spin trapping experiments were chosen in such a way that reactions could be performed inside the ESR cavity at a fast enough rate, avoiding at the same time the complete annihilation of the resultant aminoxyl spin adducts.

In thet first series of experiments, we used *N-tert*-butyl-α-nitrone as a spin trap in a 10/1 molar ratio with respect to the cyclobutane derivatives. Thus, 0.5 M solutions of *cis*-**10** and *cis*-**11** in chlorobenzene were heated at 77 °C for 1.5 h with an exces of such a spin trap and, then, the corresponding spectra were recorded. The spectra resulting from both reactions were very similar and consisted of a set of three equally spaced doublets centered at $g = 2.0056(3)$ due to the coupling with one *N* and one *H* nuclei with hyperfine coupling constants $a_N = 14.9$ G and $a_H = 3.3$ G. Figure 8 shows the spectrum of the spin adduct derived from *cis*-**10**.

These spectra are clear proof of the formation of free radicals as intermediates during the thermal isomerization of cyclobutanes. Unfortunately, the observed hyperfine couplings of the spin adducts correspond only to the nuclei belonging to the nitrone moiety and not to the trapped moiety, thus preventing the elucidation of the exact nature of the intermediate species. To avoid such a limitation, we turned our attention to the use of *C*-nitroso derivatives as spin trapping agents since the ESR spectra of the resultant spin adducts provide, in general, more structural information.[28] In fact, the group that was originally the transient radical is directly bonded to the aminoxyl function and the *H* atoms of that group are generally coupled with the unpaired electron of the resultant spin adduct in such a way that the ESR spectra are now suitable to elucidate some structural aspects of the transient species.

The first *C*-nitroso compound assayed was 2-methyl-2-nitrosopropane, but unfortunately this product is unstable at the temperatures required to promote the isomerization of the cyclobutanes. Experiments were then repeated with a more stable spin trapping agent such as nitrosobenzene. Thus, 0.5 M solutions of cyclobutanes *cis*-**10** and *cis*-**11** in chlorobenzene were heated at 77 °C for 30 min in the presence of 10-fold excess of nitrosobenzene. In both reactions, the resultant spectra were quite similar and consisted of a very complex system of overlapped signals centered at $g = 2.0055(3)$ as shown in Figure 8. Both spectra have the characteristic ESR pattern of the spin adducts derived from the addition of an alkyl radical to nitrosobenzene.[28,29]

Attempts to simulate such spectra as pure spin adducts failed. This fact suggests that several spin adducts are simultaneously formed in both reactions. This is in agreement with the fact that the proposed biradical intermediate is susceptible to linking to the spin trapping agent at two centers of the side chain coming from butadiene as well as at two other centers of the furanone moiety. In fact, the observation of small differences in the

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(29) ESR spectra in aromatic hydrocarbons of spin adducts between alkyl radicals and nitrosobenzene appear centered at $g = 2.0060(4)$ and show hyperfine couplings with the five aromatic protons—$a_{H(para)} \approx a_{H(orto)} \approx 2.7 \pm 0.1$ G (3H) and $a_{H(meta)} \approx 1.0 \pm 0.1$ G (2H)—of the phenyl group and with the nitrogen nucleus—$a_N \approx 10.5 \pm 0.1$ G (1N)—of the *NO* group as well as with some other *H* nuclei of the alkyl substituent close to the *NO*. See ref 28.
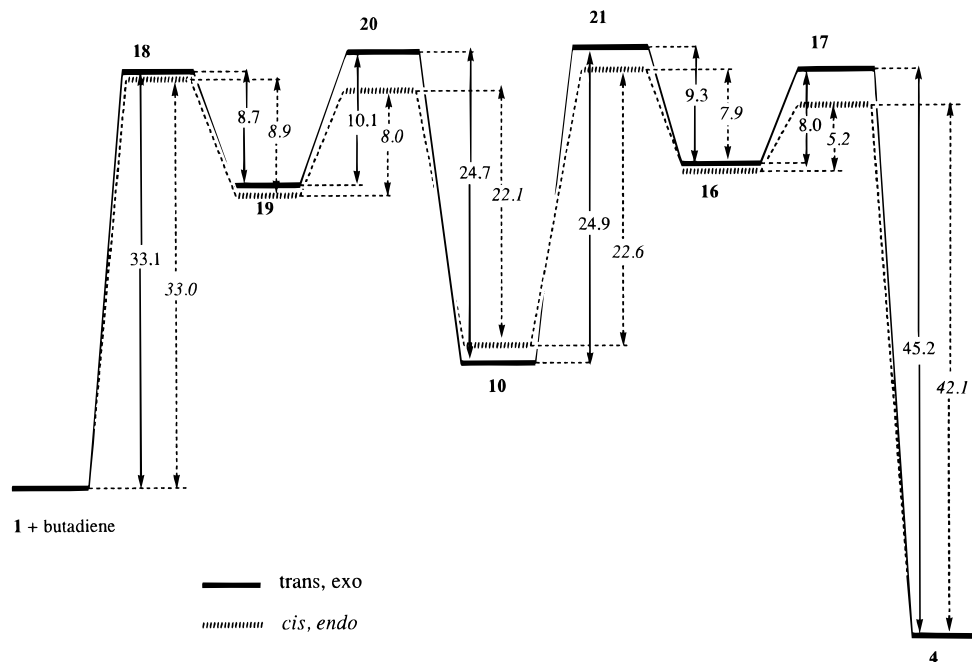
Figure 7. Schematic Gibbs energy profile corresponding to the whole mechanism for the Diels−Alder reaction between furanone **1** and butadiene. Relative Gibbs energies in kcal mol⁻¹ at 298.15 K and 1 atm.
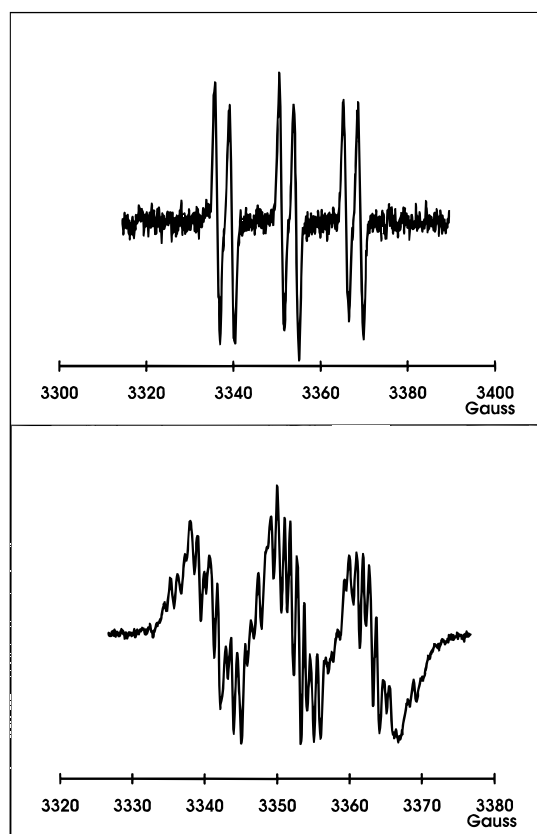

Figure 8. ESR spectra obtained in the spin trapping experiments performed during the thermal isomerization of the cyclobutane derivative *cis*-**10** in chlorobenzene with *N-tert*-butyl-α-phenylnitrone (upper) and nitrosobenzene (lower) as spin trapping agents.

spectra of the spin adducts derived from cyclobutanes *cis*-**10** and *cis*-**11** indicates that the addition to the furanone fragment occurs, although the exact nature of these adducts remains unknown.

From these experiments, the formation of radical species when cyclobutanes were heated was clearly shown and allowed us to

postulate biradical species to be intermediates in the production of the Diels−Alder adducts.

6. Concluding Remarks. 5-Methylene-2(5*H*)-furanones, both the parent compound protoanemonin, **1**, as well as the 3-bromo and the 3-methoxy derivatives, **2** and **3**, have shown for the first time their ability to undergo photochemically induced 1,2-addition of dienes, *i.e.* butadiene and *trans*-piperylene, giving the corresponding vinyl cyclobutane spiro adducts in acceptable yields and excellent site selectivity as the result of specific reaction at the exocyclic double bond. Moreover, the same cyclobutanes have been detected and isolated from the thermal cycloadditions of these furanones to the dienes mentioned above. Such compounds are intermediates in the production of the corresponding Diels−Alder adducts, isomerization taking place with heating and involving intermediary radical species as verified by ESR spectroscopy.

All these results, jointly with those of additional experiments, evidence unequivocally a biradical mechanism operating in the Diels−Alder reactions of such furanones that has been rationalized on the basis of theoretical calculations allowing the proposal of a detailed mechanistic profile for the whole process. Thus, for each reaction, *transoid* biradicals are produced by formation of a first bond between *C-6* in the corresponding furanone and the diene. These biradicals lead to the stereoisomeric vinyl cyclobutanes which are the kinetically most favored products. These compounds can evolve directly to the *cisoid* biradical by breaking the bond that involves the spiro ring junction carbon, the overall process being rate controlled by the Gibbs energy of the transition state associated with this step. In turn, the *cisoid* biradical is an unstable species and evolves rapidly to the Diels−Alder adduct, which is the thermodynamically most stable component of the system, according to a high exothermic reaction.

Experimental Section

Computational Details. In the CASSCF calculations[30] the active space for butadiene contains all π electrons, *i.e.* four electrons in four orbitals. We have considered six electrons in six orbitals for pro-

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toanemonin, **1**. We have also done calculations with an active space containing eight electrons in eight orbitals, but the occupation of the two natural orbitals corresponding to the additional orbitals in the active space was 1.99 and 0.01, respectively. For the transition state location, the active space consisted of ten electrons in ten orbitals . The 3-21G basis set has been used in these calculations.[31]

In the DFT calculations,[32] we have used the hybrid Becke's[33] three-parameter functional for exchange and the gradient corrected functional of Lee, Yang, and Parr[34] for correlation (B3-LYP). The calculations on biradicaloid structures have been carried out by using a spin unrestricted formalism and breaking the spacial symmetry between α and β electron densities. The 6-31G* basis set has been used in the geometry optimization and frequency calculation and single point calculations have been carried out by using the larger 6-311G** basis set.[31]

The CASSCF calculations have been carried out by using the GAMESS program,[35] while the Gaussian-94 program[36] has been used in the DFT calculations.

Isomerization and Interconverson of the Cyclobutane Adducts. The different rates concerning the interconversion of cyclobutanes *cis*-**11** and *trans*-**11** as well as their isomerization to give cyclohexene **5**

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were verified by heating pure *cis*-**11** and *trans*-**11** in separated dichloromethane solutions at 90 °C for 3 h. Thus, starting from *cis*-**11**, a mixture of adduct **5** (22%), *trans*-**11** (16%), and remaining *cis*-**11** (62%) was obtained. Similarly, a mixture containing compound **5** (4%) and *cis*-**11** (6%), along with *trans*-**11** (90%), was obtained after heating pure *trans*-**11**. Quantitative determinations were made by HPLC.

Crossover Experiments. These experiments were carried out by heating (150 °C) dichloromethane solutions of a mixture of *cis/trans*-**10** (for a 1-h period) and a mixture of *cis/trans*-**11** (for 3 h) in the presence of a large excess of isoprene. After the solvent and unreacted diene were removed, the residue was analyzed by GC revealing, in both cases, the presence of the Diels−Alder adduct from isoprene and the corresponding furanone, **14** or **15** (6%), along with adducts **4** and **5**, respectively (94%).

Supporting Information Available: General experimental details and procedures for thermal and photochemical reactions as well as yield, physical and spectroscopic data, and elemental analysis for the new products **5**, **6**, **7**, *endo*-**8**, *exo*-**8**, *endo*-**9**, *exo*-**9**, *cis*-**10**, *trans*-**10**, *cis*-**11**, *trans*-**11**, *cis*-**12**, *trans*-**12**, *cis*-**13**, and *trans*-**13**; Cartesian coordinates of products **4**, *cis*-**10**, and *trans*-**10**, and transition states **14**, *endo*-**15**, *endo*-**17**, *exo*-**17**, *cis*-**18**, *trans*-**18**, *cis*-**20**, *trans*-**20**, *cis*-**21**, and *trans*-**21**, and intermediates *endo*-**16**, *exo*-**16**, *cis*-**19**, and *trans*-**19** (18 pages). See any current masthead page for ordering and Internet access instructions.

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