Highly Selective Diels-Alder Cycloadditions of Captodative Dienophiles 1-Acetylvinyl Arenecarboxylates to Unsymmetrically Substituted Butadienes[1]

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Thermal Diels-Alder cycloadditions of captodative olefins 1-acetylvinyl arenecarboxylates, CH_2=C(COCH_3)OCOAr, **1a** (Ar = $C_6H_4pNO_2$), **1b** (Ar = α-naphthyl), and **1c** (Ar = β-naphthyl), with isoprene (**2**) were shown to be regioselective. This regioselectivity was greatly improved by using Lewis acids catalysis ($ZnCl_2$, BF_3·Et_2O), the para adduct being the main isomer. The addition of dienophile **1a** to 1-substituted dienes **3**, **4**, and **6** and 1,3-disubstituted butadiene **5** was highly regioselective too, and the ortho isomer was the only observed adduct. Stereoselectivity of these reactions was examined, and it was determined for all of these dienes, including the 1,4-diacetoxybutadiene (**7**), that the endo stereoisomer was obtained in a high proportion (>80%). The structure of major adducts **8a**, **18a**, **20a**, **22a**, **26a**, and **29a** was established by ^1H and ^{13}C NMR spectroscopy. Regioselectivity of these cycloadditions has been rationalized in terms of the FMO theory by MO calculations of dienophiles **1**, using MINDO/3 and ab initio methods. It is suggested that secondary orbital interactions might be responsible for the observed endo selectivity.

Profound interest has always been shown in the mechanism of the Diels-Alder reaction, in order to understand the participating factors that contribute to regioselectivity, stereoselectivity, and reactivity of this process.[2] Thus, it has been firmly established that the rate of cycloaddition depends on the substitution of the reactants: electron-releasing groups at the diene and/or electron-withdrawing groups at the dienophile accelerate the reaction, in contrast with dienophiles having electron-donor groups that retard it.[2c] This is a brief statement of Alder's rule,[3] which has demonstrated its effectiveness in predicting the reactivity of Diels-Alder cycloadditions.[4] Recently, great interest has been devoted to the captodative olefins[5] as dienophiles in Diels-Alder reactions.[6] These are olefins geminally substituted by both an electron-acceptor and an electron-donating group and, in principle, an unimportant reactivity and selectivity would be expected due to this opposite electronic effect. On the other hand, we reported the preparation of captodative dienophiles: 1-acetylvinyl arenecarboxylates **1a-e**.[7] They were shown to be as reactive as methyl vinyl ketone (MVK) and more reactive than analogous derivatives **1f-i**[8] in these reactions. Nevertheless, we found a low stereoselectivity of these molecules toward cyclopentadiene.[7]

We hereby report an extensive study on regioselectivity and stereoselectivity of Diels-Alder additions of dienophiles **1a-c** to nonsymmetrical dienes.[9] And we disclose full details about our MO calculations, which rationalize the experimental results. We have chosen different conjugated dienes, distinguished by their functional groups and by their position within the conjugated system. Thus, we took isoprene (**2**) and 1-acetoxybutadiene (**3**) as not very strong electron-rich dienes,[2d,10] 1-methoxybutadiene (**4**) and 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (**5**)[11] as monosubstituted and disubstituted dienes, respectively, with strong electron-donating groups,[2d] 1-(methoxycarbonyl)-1,3-butadiene (**6**), considered as a nonactivated diene, and finally, 1,4-diacetoxybutadiene (**7**), a symmetrical disubstituted diene, to test stereoselectivity only.

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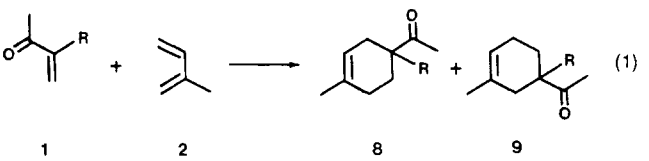
Results

The dienophiles **1a-c** were prepared according to the general procedure.[7]

The thermal cycloadditions between dienophiles **1a-c** and an excess of isoprene (**2**) gave mixtures of adducts **8a/9a**, **8b/9b**, and **8c/9c** (see eq 1). Reaction conditions



(1)

1 2 8 9

a, R = $OCOC_6H_4pNO_2$
b, R = OCOα-naphthyl
c, R = OCOβ-naphthyl
d, R = OCOPh
e, R = $OCOC_6H_3$-2,4-$(NO_2)_2$
f, R = $OCOCH_3$
g, R = OMe
h, R = OEt
i, R = $OSiMe_3$

(1) Presented in part at the 3rd Chemical Congress of North America, Toronto, Canada, June 1988; Résumé No. 351.
(2) (a) Wollweber, H. *Diels-Alder Reactions*; Georg Thieme Verlag: Stuttgart, 1972. (b) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16-33. (c) Sauer, J.; Sustmann, R. *Ibid.* **1980**, *19*, 779-807. (d) Sustmann, R. *Tetrahedron Lett.* **1971**, 2721-2724.
(3) Alder, K. *Experientia* **1955**, Suppl. II, 86.
(4) (a) Eisenstein, O.; Anh, N. T. *Bull. Soc. Chim. Fr.* **1973**, 2721-2723, and references cited therein; (b) **1973**, 2723-2726. (c) Anh, N. T.; Canadell, E.; Eisenstein, O. *Tetrahedron* **1978**, *34*, 2283-2288.
(5) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148-154.
(6) (a) Stella, L.; Boucher, J.-L. *Tetrahedron Lett.* **1982**, 953-956. (b) Boucher, J.-L.; Stella, L. *Ibid.* **1985**, 5041-5044; (c) *Tetrahedron* **1985**, *41*, 875-887; (d) **1986**, *42*, 3871-3885; (e) **1988**, *44*, 3595-3605; (f) **1988**, *44*, 3607-3615. (g) Mertes, J.; Mattay, J. *Helv. Chim. Acta* **1988**, *71*, 742-748. For related studies, see: (h) Trost, B. M.; Ippen, J.; Vladuchik, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 8116-8118. (i) Quick, J.; Jenkins, R. *J. Org. Chem.* **1978**, *43*, 2275-2277.
(7) Tamariz, J.; Vogel, P. *Helv. Chim. Acta* **1981**, *64*, 188-197.
(8) (a) Brodsky, L.; Agosta, W. C. *J. Org. Chem.* **1974**, *39*, 2928-2930. (b) Wharton, P. S.; Aw, B. T. *Ibid.* **1966**, *31*, 3787-3790. (c) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, 1693-1696.
(9) For a preliminary report, see: Aguilar, R.; Reyes, A.; Tamariz, J.; Birbaum, J.-L. *Tetrahedron Lett.* **1987**, 865-868.
(10) Houk, K. N.; Munchausen, L. L. *J. Am. Chem. Soc.* **1976**, *98*, 937-946.
(11) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808. Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406.

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Table I. Reaction Conditions and Product Ratios for the Diels–Alder Additions of Dienophiles 1a, 1b, and 1c with Isoprene (2)[a]

entry	dienophile	2 (molar equiv)	solvent	catalyst[b]	temp (°C)	reactn time (h)	products (rel yield)[c] 8	9	yield,[d] (%)
1	**1a**	7	xylene	none	130	35	**8a** (75)	**9a** (25)	77
2	**1a**	4	CH_2Cl_2	$ZnCl_2$	25	36	**8a** (94)	**9a** (6)	98
3	**1a**	5	CH_2Cl_2	$BF_3{\cdot}Et_2O$	−50	7	**8a** (98.5)	**9a** (1.5)	81
4	**1a**	5	CH_2Cl_2	$BF_3{\cdot}Et_2O$	−78	10	**8a** (99)	**9a** (1)	89
5	**1b**	15	xylene	none	130	70	**8b** (67)	**9b** (33)	70
6	**1b**	6	CH_2Cl_2	$BF_3{\cdot}Et_2O$	−78	10	**8b** (98)	**9b** (2)	88
7	**1c**	10	xylene	none	130	72	**8c** (70)	**9c** (30)	69
8	**1c**	5	CH_2Cl_2	$BF_3{\cdot}Et_2O$	−78	10	**8c** (99)	**9c** (1)	90

[a] All under N_2 atmosphere. Thermic trials in the presence of 1–2% hydroquinone. [b] 5 molar equiv of catalyst in all cases. [c] Proportions as determined by GLC of the crude reaction mixture. [d] As isolated product mixture 8 + 9 after purification by column chromatography on silica gel or Florisil.

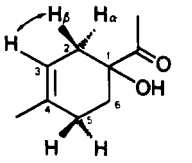
and corresponding isolated yields are reported in Table I. The reactions were carried out in xylene solutions, under nitrogen, and a catalytic amount of hydroquinone was put in, in order to minimize secondary radical processes. The reactions were stopped when the dienophile had disappeared, yielding a mixture of adducts **8a/9a** as light-yellow crystals, and mixtures of adducts **8b/9b** and **8c/9c** were isolated as colorless oils (Experimental Section).

In order to enhance the reactivity and the selectivity of these reactions, we decided to employ Lewis acid catalysts.[12] Previous studies on the reaction of captodative olefins showed little improvement in the reactivity and/or regioselectivity in the presence of Lewis acids,[6c,i] because of easy decomposition of the dienophile.[6a,c,8c] Nevertheless, in a recent report[6d] there was observed a large reactivity and stereoselectivity in additions of α-(methylthio)acrylonitrile with several Lewis acids. In our case, the reaction carried out with $ZnCl_2$ was slower than that with $BF_3{\cdot}Et_2O$ (Table I), but in all the experiments, the dienophiles were highly stable under these conditions, even at room temperature, giving better yields than the thermal trials. The reactivity was dramatically increased when $BF_3{\cdot}Et_2O$ was added. The cycloaddition took place even at −78 °C, and in shorter times than under thermal and $ZnCl_2$ catalysis conditions (Table I).

The ratio of regioisomers obtained under thermal conditions was quite close to that reported in the cases of cycloadditions of MVK[13] and acrylic derivatives[14] to **2**, and the para mode of addition was always preferred. In contrast, the cycloadditions of **1a** to exocyclic dienes remotely perturbed were not regioselective.[15] It should be noticed that the best regioselectivity (para/meta, 75:25) was found for dienophile **1a** (Table I), and, as expected, this latter corresponds to more the reactive dienophile of the series.[7] Entries 2–4, 6, and 8 in Table I also reveal that the presence of Lewis acids greatly improved regioselectivity. In this sense, $BF_3{\cdot}Et_2O$ was an even better catalyst than $ZnCl_2$. Indeed, in the presence of 5 equiv of $BF_3{\cdot}Et_2O$, **1a** added to **2** (5-fold excess) at −78 °C, giving a mixture of adducts **8a/9a** (99:1) (entry 4, Table I).

The adducts ratio **8/9** could not be determined either by ^1H NMR spectroscopy or by gas chromatography (GLC). Thus, it was necessary to convert them to the corresponding alcohols **10/11** and calculate their proportion by GLC. These were prepared in an almost quantitative yield by saponification of the mixtures **8/9**.

The structure of the main para isomer **8** was initially assigned on the basis of the following ^1H NMR (360 MHz) arguments. The spectrum of a mixture of **10/11** (98:2) displayed a multiplet at 5.2 ppm assigned to the vinylic proton H-3 and two multiplets at 2.2 and 2.16 ppm corresponding to the allylic protons H-2β and H-5α, respectively. Nuclear Overhauser effect difference (NOED)[16] experiments furnished a spatial proximity relationship between protons labeled as H-2β and H-3. A NOED spectrum shows an enhancement in the magnitude of signal at 2.2 ppm (H-2β) when the multiplet signal at 5.2 ppm (H-3) was irradiated. This is only consistent with the structure **10**, resulting from dienophile attack on the diene



10

in the para orientation. This assignment was confirmed by converting a mixture of alcohols **10/11** to the corresponding aromatic compounds **16/17**, in a ratio that did not differ from that of the starting mixture. Thus, when a mixture of alcohols **10/11** (98:2) was treated with thionyl chloride in methylene chloride at room temperature for 5 h, it afforded a mixture of chloro derivatives **12** and **13**, accompanied by a minor fraction of cyclohexadiene isomers **14** and **15**. The whole mixture was heated at reflux in benzene and in the presence of DBN for 4 h, giving a mixture of **16/17** (98:2) in 62% yield.

For the case of 1-substituted dienes, the additions were carried out with the most reactive and selective dienophile, **1a**. The experimental results are summarized in Table II. Under thermal conditions, **1a** added to dienes **3**, **4**, and **6**, providing the corresponding adducts as mixtures of diastereoisomers. While the ortho regioisomers **18**, **20**, and **22** were the observed products, no trace of the respective meta regioisomers, **19**, **21**, and **23**, could be detected by NMR spectroscopy. The reactions were monitored by

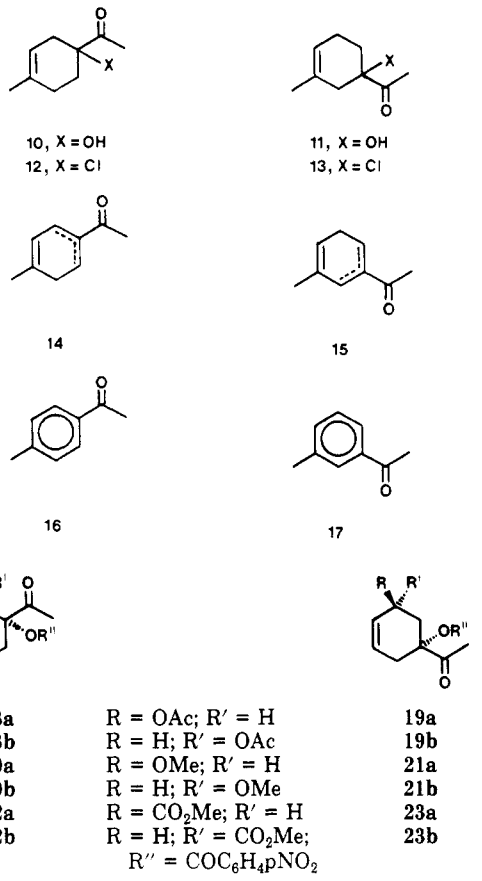
(12) (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437. (b) Houk, K. N.; Strozier, R. W. *Ibid.* **1973**, *95*, 4094–4096. (c) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 1121–1123. (d) Alston, P. V.; Ottenbrite, R. M. *Ibid.* **1975**, *40*, 1111–1116. (e) Anh, N. T.; Seyden-Penne, J. *Tetrahedron* **1973**, *29*, 3259–3265.

(13) Lutz, E. F.; Bailey, G. M. *J. Am. Chem. Soc.* **1964**, *86*, 3899–3901.

(14) Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924–928, and references cited therein.

(15) Tamariz, J.; Vogel, P. *Tetrahedron* **1984**, *40*, 4549–4560.

(16) Sanders, J. K. M.; Mersh, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *15*, 353–400.



18a	R = OAc; R′ = H	**19a**
18b	R = H; R′ = OAc	**19b**
20a	R = OMe; R′ = H	**21a**
20b	R = H; R′ = OMe	**21b**
22a	R = CO_2Me; R′ = H	**23a**
22b	R = H; R′ = CO_2Me; R″ = $COC_6H_4pNO_2$	**23b**

TLC and were terminated when a conversion rate better than 70% was reached. Yields were optimized as isolated products, considering the recovered dienophile. The cycloaddition with **4** had to be made at lower temperature because if above 110 °C the diene quickly decomposed.

Unsuccessful results were obtained by using Lewis acids catalysis ($ZnCl_2$, $AlCl_3$, and BF_3·Et_2O) with dienes **3** and **4**, inasmuch as these were rapidly decomposed even at lower temperature than −50 °C. A much better result was furnished when the reaction with diene **6** was made in the presence of BF_3·Et_2O at 40 °C for 15 h (entry 4, Table II), giving the adducts **22** in 90% yield.

The structures of the major ortho regioisomers were established by high-field ^1H NMR spectroscopy. Double irradiation experiments were carried out to correlate the cyclohexene protons, showing signals for two vicinal methylene groups, demonstrating their ortho orientation. The chemical shifts and the coupling constants of **18a**, **20a**, and **22a** are tabulated in Table III. Typical coupling constants between methyne HC-2 and methylenes H_2C-5,6 confirm a half-chair conformation of the cyclohexene systems[17] and allow a distinction between pseudo-axial and pseudo-equatorial protons. Interestingly, a long-range $^5J_{H,H}$ coupling constant of ca. 1.0 Hz was measured at **18a** and **20a** between the pseudo-equatorial H-2α and the pseudo-axial H-5α. The same coupling constant for **22a** was much larger (J = 2.5 Hz). In contrast, the coupling constant between the pseudo-equatorials H-2α and H-5β was smaller (<1.0 Hz), which agreed with preceding ex-

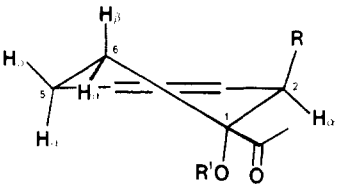


Figure 1. Half-chair conformation of cyclohexene system of adducts **18a** (R = OAc), **20a** (R = OMe), and **22a** (R = CO_2Me) (R′ = $COC_6H_4pNO_2$).

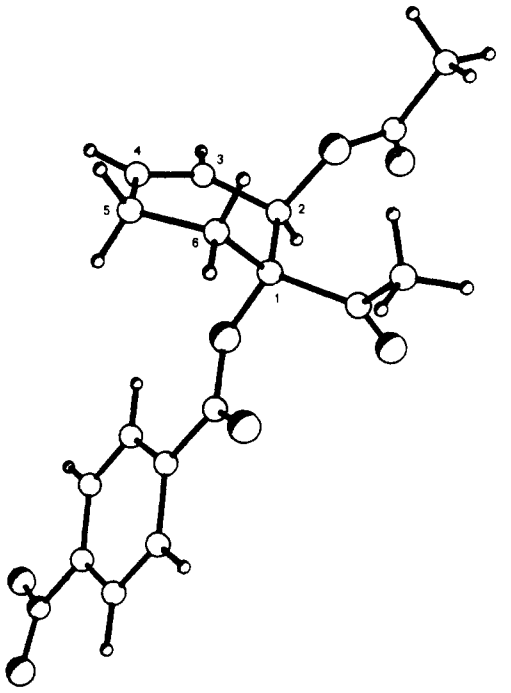


Figure 2. Stereoscopic view of the X-ray crystal structure of **18a**.

amples.[18] Double "W" coupling constant was registered between H-6α and the vinylic proton H-4 (ca. 1.0 Hz) and the allylic proton H-2α (ca. 1.5 Hz), the latter suggesting that the conformational equilibrium of the half-chair is shifted toward maintaining a pseudo-axial position of corresponding R and OR′ groups on C-1 and C-2 (Figure 1).

Diastereoisomeric ratios of mixtures **18a**/**18b**, **20a**/**20b**, and **22a**/**22b** were determined by ^1H and ^{13}C NMR spectroscopy, showing a good selectivity (>80%) (Table II) for the endo isomers **18a**, **20a**, and **22a**. No significant enhancement of stereoselectivity was shown on the addition of diene **6** (entry 4, Table II) by Lewis acid catalysis. Even though the regiochemistry was unambiguously established by ^1H NMR spectroscopy, the relative configuration of substituted centers C-1 and C-2 could not be assigned by this means. Lanthanide-induced shift was not a useful technique, because of the great number of complexing sites present in the molecule. Then, we decided to undertake the structural determination of adducts **18a** and **18b** by selective ketalization of the corresponding diols **24a** and **24b**. If the hydroxy groups had a syn relationship, as in **24b**, it could be expected that ketalization would take place to give **25b**; in contrast, if they are in an anti position, the ketal derivative **25a** would not be formed. Indeed, when a mixture of **18a**/**18b** (>95:<5) was saponified (K_2CO_3/

(17) (a) Günther, H.; Jikeli, G. *Chem. Rev.* **1977**, *77*, 599–637. (b) Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1978**, *43*, 4052–4057. (c) Bäckvall, J.-E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396–6403. (d) Johansson, A. M.; Nilsson, J. L. G.; Karlén, A.; Hacksell, U.; Sanchez, D.; Svensson, K.; Hjorth, S.; Carlsson, A.; Sundell, S.; Kenne, L. *J. Med. Chem.* **1987**, *30*, 1827–1837.

(18) Mahaim, C.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 866–886. Mahaim, C.; Carrupt, P.-A.; Vogel, P. *Ibid.* **1985**, *68*, 2182–2194, and references cited therein.

Table II. Reaction Conditions and Product Ratios for the Diels–Alder Additions of Dienophile 1a with 1-Acetoxy-1,3-butadiene (3), 1-Methoxy-1,3-butadiene (4), and 1-(Methoxycarbonyl)-1,3-butadiene (6)[a]

entry	diene (molar equiv)	solvent	catalyst (molar equiv)	temp (°C)	reactn time (h)	products (rel yield)[b] ortho	products (rel yield)[b] meta	yield[c] (%)
1	**3** (3)	xylene	none	130	11	**18a/18b** (>95) (>95:<5)	**19a/19b** (<5)	79
2	**4** (2)	xylene	none	110	31	**20a/20b** (>95) (86:14)	**21a/21b** (<5)	89
3	**6** (3)	xylene	none	130	53	**22a/22b** (>95) (80:20)	**23a/23b** (<5)	81
4	**6** (3)	CH_2Cl_2	$BF_3{\cdot}Et_2O$ (3.5)	40	15	**22a/22b** (>95) (84:16)	**23a/23b** (<5)	90

[a] All under N_2 atmosphere. Thermic trials in the presence of 1–2% hydroquinone. [b] Relative proportions as determined from the ^1H NMR spectrum of the crude reaction mixture. [c] As isolated mixtures after purification by column chromatography on Florisil or silica gel/10% K_2CO_3.

Table III. ^1H NMR (360 MHz) Spectral Data of Major Adducts 18a, 20a, 22a, and 29a and Their Assignments[a]

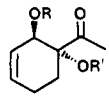
δ_H[b]	H-2	H-3	H-4	H-5α	H-5β	H-6α	H-6β	H-2′	H-3′	CH_3CO	R-C-2	CH_3CO_2
18a	5.47	5.95	6.16	1.97	2.31	2.65	2.37	8.15	8.31	2.27	2.07[c]	
20a	3.90	6.06	6.11	1.95	2.25	2.65	2.35	8.11	8.27	2.37	3.40[d]	
22a	3.77	5.80	5.98	2.03	2.30	2.67	2.51	8.10	8.27	2.43	3.70[e]	
29a	5.48	6.07	6.10	5.23		3.04	2.42	8.15	8.31	2.26	2.08[c,f]	2.06[f]

$J_{H,H}$ (Hz)	2,3	2,4	2,5α	2,5β	2,6α	3,4	3,5α	3,5β	4,5α	4,5β	4,6α	5α,5β
18a	4.8	<1.0	1.0	<1.0	1.4	10.0	2.5	1.5	2.6	4.5	~1.0	18.0
20a	4.25	~0.5	1.0	<1.0	1.4	10.0	2.0	1.0	2.3	4.5	~1.0	18.3
22a	5.0	<1.0	2.5	1.0	2.0	10.0	2.0	1.5	2.1	5.0	1.2	18.5
29a	4.2	<1.0	1.2		1.6	10.0	1.4		1.2		1.5	
calcd[g]	4.7[h]	0.5[h]	2.1[i]	1.2[i]			2.2[j]	1.0[j]	2.9[h]	4.4[h]		

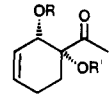
$J_{H,H}$ (Hz)	5α,6α	5β,6α	5α,6β	5β,6β	6α,6β
18a	6.1	3.0	11.4	6.7	14.3
20a	6.1	1.3	11.4	5.8	13.5
22a	6.3	1.5	11.5	6.3	14.2
29a	6.0		10.4		14.0
calcd[g]	6.5[k]	2.3[k]	10.2[k]	6.5[k]	

[a] Spectra were determined in deuteriochloroform. For further data of minor isomers, see Experimental Section. [b] Chemical shifts in ppm and are relative to Me_4Si (δ = 0.0). [c] For R = CH_3CO_2. [d] For R = CH_3O. [e] For R = CH_3O_2. [f] These assignments may be reversed. [g] The coupling constants were calculated by using the Karplus equation modifications[20] and including the torsional angles given by the X-ray structure of **18a**.[19] [h] See ref 20a. [i] See ref 20b. [j] The value of the coupling constant is negative, see ref 20a. [k] See ref 20c.

MeOH, 25 °C, 10 min), it provided a mixture of diols **24a/24b** (>95:<5). In order to increase the proportion



24a, R = R′ = H
25a, R = R′ = $C(CH_3)_2$



24b, R = R′ = H
25b, R = R′ = $C(CH_3)_2$

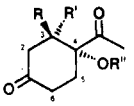
of isomer **24b**, we found that the isomerization of **24a**, to **24b** took place in a reverse aldol fashion when the mixture was introduced into a column of Florisil containing 10% of anhydrous K_2CO_3. The ratio of the mixture **24a/24b** depended on the time spent in the column; thus, from a typical experiment with 1.2 g of mixture **24a/24b** (>95:<5), after elution we obtain a mixture of **24a/24b** (40:60). This could be separated by medium pressure chromatography (Lobar system). Of both diols only the less polar one, corresponding to the original minor isomer **24b**, was quantitatively protected when the mixture **24a/24b** (40:60) was treated with 2,2-dimethoxypropane, in the presence of a catalytic amount of pTsOH (0 °C, 11 h), affording **25b**. Hence, these results suggested that the major adduct obtained from Diels–Alder addition corresponded to isomer **18a** with an anti relationship between alkoxy groups. This assignment was confirmed by single-crystal X-ray diffraction[19] of adduct **18a**, which could be separated from **18b** by recrystallization to give colorless monoclinic crystals (mp 121–122 °C). The X-ray structure of **18a** is illustrated in Figure 2. The cyclohexene ring exhibits a half-chair conformation; the acetoxy and *p*-nitrobenzoyloxy groups are trans-diaxial and consequently the acetyl group is in the equatorial position. The normally more hindered axial positions are, in this case, occupied by the two bulkier groups, presumably to avoid the sterically less favored gauche interaction between them. At the same time, this structure confirms the equatorial position of H-2, which was anticipated by ^1H NMR spectroscopy. Therefore, the main stereoisomer corresponded to the endo adduct, with regards to the acetyl group.

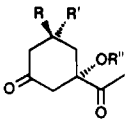
The torsion angles provided by the X-ray structure were used to calculate the coupling constants for the cyclohexene protons and, therefore, it could be correlated with experimental data. Table III shows both the calculated[20] and experimental data series, which correlate quite well. These results suggest that the cyclohexene moiety has the same conformation in all cases and presumably the same configuration.

The thermal (120 °C, 11 h) cycloaddition of dienophile **1a** with 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (**5**) carried out in xylene as solvent turned out to be also highly regio- and stereoselective, because it afforded only a mixture of stereoisomer ketones **26a/26b** in a ratio of 93:7, as determined from the ^{13}C NMR spectrum of the crude

(19) Soriano-García, M.; Toscano, R. A.; Reyes-Arellano, A.; Salgado-Zamora, H.; Tamariz-Mascarúa, J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988**, *44*, 1293–1295.

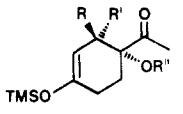
(20) (a) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561–5564. (b) Barfield, M.; Sternhell, S. *Ibid.* **1972**, *94*, 1905–1913. (c) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.

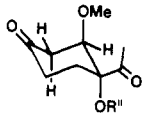




26a R = OMe; R′ = H **27a**
26b R = H; R′ = OMe; **27b**
R″ = $COC_6H_4pNO_2$

reaction mixture. The isomer **27** was not detected by ^1H NMR spectroscopy. It was not possible to isolate the corresponding cyclohexene adducts **28a/28b** presumably on account of their instability upon conditions of isolation.

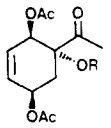




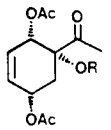
28a, R = OMe; R′ = H **26a**
28b, R = H; R′ = OMe; R″ = $COC_6H_4pNO_2$

The structure elucidation was readily made by ^1H NMR spectroscopy, since the H-3 base proton of the methoxy group with a signal at 4.13 ppm is shown as a triplet (J = 2.9 Hz), corresponding to a coupling with only one vicinal methylene. Considering that this coupling constant is not very large, it could result from the average of two gauche couplings between H-3 in the equatorial position and the H-2 protons, so then an axial configuration of the methoxy group on C-3 is expected. On the other hand, with regards to the conformational preference of groups on C-3 and the *p*-nitrobenzoyloxy group on C-4 to be trans-diaxials, as in **18a**, it is somewhat suggestive that the relative configuration of these centers on the major isomer **26a** would also correspond to the endo one, as indicated.

The endo mode of cycloaddition seems to be prefered for a large range of noncyclic butadienes, as was also the case for 1,4-diacetoxybutadiene (**7**), which added to **1a**, in xylene at 130 °C for 16 h, to yield a mixture of adducts **29a/29b** (90:10). Heating was maintained up to 65% of



29a



29b

conversion of diene, because longer times of reaction provided a great number of side products. Attempts to accelerate the reaction with Lewis acids was unsuccessful, since a rapid diene decomposition was observed. The structure of major endo stereoisomer **29a** was deduced from the NOED experiments in the ^1H NMR spectrum (Table III). Double irradiation on the signal of aromatic protons H-2′ at 8.15 ppm produced an enhancement of the signals at 5.48 and 5.23 ppm assigned to base protons of the acetoxy groups, H-2 and H-5, respectively. A simple Dreiding models analysis shows that the benzoyloxy group in the axial position permits the aromatic protons to come close to both allylic protons H-2 and H-5, so allowing an induced relaxation.

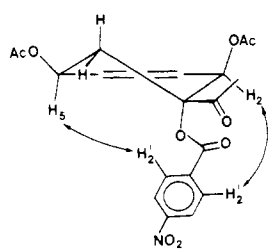


Table IV. Carbon NMR Spectral Data of Major Adducts 8a, 18a, 20a, 22a, 26a, and 29a and Their Assignments[a]

	8a	18a	20a	22a	26a	29a
C-1	85.2	84.0	83.9	83.7	204.7	84.0
C-2	31.7	67.9	76.0	48.4	40.7*	67.3
C-3	116.5	121.7	122.6	120.9	82.0	124.1
C-4	133.3	133.2	132.2	129.0	82.9	132.9
C-5	26.5*	21.9	22.1*	21.9*	26.0	66.7
C-6	27.7*	21.9	22.2*	23.3*	36.3*	28.0
C-7	205.7	203.2	205.4	205.7	206.9	201.9
C-8	24.1	25.3	26.7	25.9	27.6	25.2
$ArCO_2$	163.9	163.0	163.0	163.2	163.2	163.0
Ar	150.8	150.8	150.7	150.7	151.0	151.1
	135.2	134.1	134.6	134.5	143.3	133.6
	130.9	130.7	130.8	130.7	131.0	131.1
	123.6	123.5	123.5	123.5	123.8	123.8
CH_3	23.1	20.4				21.0
						20.6
CH_3O			56.9	52.2	57.3	
CO_2		169.0		170.4		170.1
						169.1

[a] δ values downfield of Me_4Si and $CDCl_3$ as solvent and internal standard. Those marked with an asterisk for each compound may be interchanged. For further signals of minor isomers and coupling constants, see Experimental Section.

The chemical shifts of ^{13}C NMR spectra for the major adducts obtained in this study are displayed in Table IV. Assignments of signals corresponding to the olefinic carbons are based on substituent effects[21] and on $^3J_{C,H}$ coupling differences. Vinylic carbons in isoprene adduct **8a** could be easily distinguished because of their substitution. While the assignment of the vinylic carbons of **18a**, **20a**, **22a**, and **29a** was more difficult, it could be established that C-4 carbons were shifted ca. 10 ppm downfield with respect to C-3 carbons. Allylic substitution on C-2 by OAc, OMe, and CO_2Me groups causes a decrease in the β shift (C-3) and promotes a deshielding effect on γ (C-4).[21b] This could be supported by observing a lower $\Delta\delta_{C\text{-}4/C\text{-}3}$ (8.8 ppm) in **29a** with respect to **18a** (11.5 ppm), hence the former has a second OAc group on C-5, which produces an opposite shift effect. On the other hand, homoallylic substitution on C-1 with both acetyl and aroyloxy groups could produce a similar effect on the shifts of the vinylic carbons:[21b,c] shielding C-3 carbons upfield and shifting carbon C-4 downfield. Long-range $^3J_{C,H}$ couplings of C-4 was shown to be a multiplet signal, instead of a simple pattern corresponding to C-3 signals; for example, the coupled spectrum of **20a** (Experimental Section) showed at 132.2 ppm a three-bond C–H coupling as a quintuplet (ca. 6.0 Hz), arising from coupling with the two methylenic protons H-6 and with the allylic proton H-3, while the signal for C-3 at 122.6 ppm showed only two $^3J_{C,H}$ (5.5 and 9.2 Hz) couplings, attributed to interactions with the two H-6 protons. Assignment of the aliphatic carbons of ketone **26a** was based on analogy with substituted cyclohexanones.[22]

Discussion

The regioselectivity of the Diels–Alder reaction has been successfully rationalized in terms of the frontier molecular orbital (FMO) theory, by considering only interactions between HOMO-diene and LUMO-dienophile,[23] under

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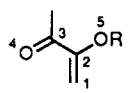
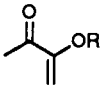
Table V. Ab Initio STO-3G Calculations of Energies (eV) and Coefficients (C_i) of the Frontier Molecular Orbitals for Captodatives Dienophiles 1 and MVK



s-cis



s-trans

dienophile	conformational isomer	ΔH_f[b] (kcal/mol)	HOMO[a] E	C_1	C_2	C_3	C_4	C_5	ΔC_i[c]
1a	s-cis	−97.970	−7.530	0.589	0.478	−0.092	−0.265	−0.495	0.111
1a	s-trans	−95.961	−7.558	−0.590	−0.471	0.086	0.257	0.503	0.119
1d	s-cis	−85.825	−7.520	0.556	0.389	0.078	−0.214	−0.498	0.167
1d	s-trans	−89.172	−8.116	0.573	0.447	−0.098	−0.254	−0.412	0.126
1f	s-cis	−128.192	−7.660	−0.583	−0.423	0.091	0.234	0.494	0.160
1f	s-trans	−123.763	−7.569	−0.591	−0.399	0.064	0.203	0.543	0.192
1g	s-cis	−71.130	−7.119	−0.627	−0.339	0.071	0.209	0.569	0.228
1g	s-trans	−66.028	−7.185	0.627	0.388	0.054	−0.190	−0.582	0.239
MVK	s-cis	−29.220	−8.608	0.583	0.552	−0.209	−0.408		0.031
MVK	s-trans	−27.028	−8.671	−0.588	−0.548	0.211	0.404		0.040

dienophile	conformational isomer	LUMO[a] E	C_1	C_2	C_3	C_4	C_5	ΔC_i[c]
1a	s-cis	6.350	0.520	−0.341	−0.536	0.594	0.175	0.179
1a	s-trans	6.316	0.495	−0.330	−0.526	0.578	0.186	0.165
1d	s-cis	6.260	−0.497	0.368	0.495	−0.557	−0.190	0.129
1d	s-trans	5.847	−0.602	0.442	0.478	−0.553	−0.080	0.160
1f	s-cis	6.005	0.599	−0.437	−0.492	0.572	0.099	0.162
1f	s-trans	5.884	−0.598	0.437	0.480	−0.551	−0.089	0.161
1g	s-cis	6.462	0.553	−0.416	−0.538	0.608	0.186	0.137
1g	s-trans	6.333	−0.559	0.425	0.537	−0.600	−0.188	0.134
MVK	s-cis	6.215	0.620	−0.428	−0.508	0.589		0.192
MVK	s-trans	6.182	0.615	−0.433	−0.510	0.592		0.182

[a] These are the absolute values of the p_z coefficients. [b] Calculated by MINDO/3. [c] Carbon 1 − carbon 2.

normal electronic demand (NED) conditions.[2d,24] In addition, secondary orbital interactions have been considered to eliminate some discrepancies found in applying this approach.[25] More recently, a reactivity model has been proposed to account for the observed regiochemistry of a large amount of mono- and disubstituted dienes.[26] This model, based on electrostatic potentials, seems to be particularly successful for disubstituted dienes, which are improperly described by the FMO treatment. However, both this model and the FMO theory predict a nearly correct orientation of addition of 1-substituted dienes by strong electron-donor groups.[24]

In order to explain the observed regioselectivity of our dienophiles, we decided to estimate the eigenvalues and eigenvectors of their MOs. Initially, we have calculated them aided by the semiempirical method MINDO/3,[27] choosing four representative dienophiles **1a**, **1d**, **1f**, and **1g**, which are differentiated by the electron-releasing force of the donor substituent.[9] Now, we also present the data obtained by the ab initio STO-3G method[28] for the aforementioned dienophiles (Table V).

Geometries of the conjugated enone system of the dienophiles were assumed to be planar, in the two possible s-cis and s-trans conformations.[29] The enthalpies for all these olefins were obtained by completely optimized geometries with the MINDO/3 technique.

The raising of both HOMO and LUMO energies by α-substitution of the enone system of the MVK by electron-releasing groups seems to be a general tendency (Table V), as has been reported from experimental IPs and EAs of analogous olefins.[10] Nevertheless, a larger STO-3G stabilization of LUMO energies for dienophiles *s-trans*-**1d** and *s-cis*- and *s-trans*-**1f** than for MVK was observed. Also, MINDO/3 calculations seem to have a similar trend, overstabilizing the LUMO energies for **1a** and **1f**.

We have examined the basic FMO assumption that one of the two frontier interactions involves orbitals that are much closer in energy than in the other interaction and hence is likely to be significantly more important.[2d,30] To assess these energy gaps, we considered the ab initio STO-3G calculations, because these molecular orbital methods have provided a reasonable account of the relative energy separations between competing frontier orbital interactions.[31] Frontier orbital energies for dienophiles **1a**, **1d**, **1f**, and **1g**, and for dienes used in this study, **2**, **3**, **4**, and **6**, are furnished in Tables V and VI, respectively. For the dienes only s-cis conformations have been taken into account, because they are those in which the dienes

(23) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57–64. (b) Alston, P. V.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1973**, *38*, 4075–4077. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361–369, and references cited therein. (d) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523–531. (e) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, 1313–1314. (f) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092–4094.

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(25) Alston, P. V.; Ottenbrite, R. M.; Cohen, T. *J. Org. Chem.* **1978**, *43*, 1864–1867. Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M.; Cohen, T. *Ibid.* **1983**, *48*, 5051–5054.

(26) Kahn, S. D.; Pan, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381–7396. Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 663–666.

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(28) Newton, M. D.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1970**, *52*, 4064–4072. Hehre, W. J.; Stewart, R. F.; Pople, J. A. *Ibid.* **1969**, *51*, 2657–2664. Hehre, W. J. *Acc. Chem. Res.* **1976**, *9*, 399–406.

(29) Initially, standardized geometrical parameters were used; see: Pople, J. A.; Gordon, M. *J. Am. Chem. Soc.* **1967**, *89*, 4253–4261. Then, an exhaustive optimization was carried out by MINDO/3, and the afforded geometrical data were feeded to ab initio STO-3G calculations.

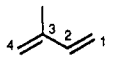
(30) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.

(31) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

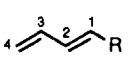
(32) Gift of Clark Still (Columbia University).

(33) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

Table VI. Ab Initio STO-3G Calculations of Energies (eV) and Coefficients (C_i) of the Frontier Molecular Orbitals for Monosubstituted Dienes



2



3, R = OAc
4, R = OMe
6, R = CO_2Me

	HOMO[a]						LUMO[a]					
diene	E	C_1	C_2	C_3	C_4	diff[b]	E	C_1	C_2	C_3	C_4	diff[c]
2[d]	−7.292	0.492	0.369	−0.421	−0.552	0.060	6.884	−0.626	0.477	0.469	−0.618	0.008
3[e]	−6.068	0.278	0.279	−0.192	−0.294	0.017	5.992	0.364	−0.260	−0.240	0.343	0.021
4[f]	−5.605	0.441	0.496	−0.297	−0.503	0.062	6.558	0.644	−0.396	−0.468	0.609	0.035
6[f]	−6.775	0.525	0.384	−0.366	−0.498	−0.027	4.952	0.505	−0.523	−0.311	0.542	−0.037

[a] These are the absolute values of the p_z coefficients. [b] Carbon 4 − carbon 1. [c] Carbon 1 − carbon 4. [d] Geometric parameters for calculations were taken from: Kavana-Saebø, K.; Saebø, S.; Boggs, J. E. *J. Mol. Struct.* **1984**, *15*, 259–269. [e] The geometry was obtained by complete optimzation of all atomic coordinates using the MODEL program,[32] which is an extended version of the MM2 program.[33] [f] See ref 43.

Table VII. Energy Gaps (eV) of Frontier Orbitals for Monosubstituted Dienes and Dienophiles 1a, 1d, 1f, and 1g[a]

	energy gaps to 1a[b]			energy gaps to 1d[c]		
diene	HOMO–LUMO	LUMO–HOMO	diff	HOMO–LUMO	LUMO–HOMO	diff
2	13.642	14.414	0.772	13.139	15.000	1.861
3	12.418	13.522	1.104	11.915	14.108	2.193
4	11.955	14.088	2.133	11.452	14.674	3.222
6	13.125	12.482	−0.643	12.622	13.068	0.446
	energy gaps to 1f[b]			energy gaps to 1g[b]		
diene	HOMO–LUMO	LUMO–HOMO	diff	HOMO–LUMO	LUMO–HOMO	diff
2	13.297	14.544	1.247	13.754	14.003	0.249
3	12.073	13.652	1.579	12.530	13.111	0.581
4	11.610	14.218	2.608	12.067	13.677	1.610
6	12.780	12.612	−0.168	13.237	12.071	−1.166

[a] Method: ab initio STO-3G. [b] The FMO energies of the more stable s-cis conformation are only considered. HOMO-diene/LUMO-dienophile and LUMO-diene/HOMO-dienophile. [c] The FMO energies of the most stable s-trans conformation are only considered.

are presumed to react. In Table VII energy gaps are tabulated for the two possible HOMO–LUMO interactions between these cycloaddends. These data show that for electron-rich dienes (i.e., **2**, **3**, and **4**) the energy gaps HOMO-diene/LUMO-dienophile are smaller than those of LUMO-diene/HOMO-dienophile, by approximately 2.0 eV. In contrast, for the electron-deficient diene **6**, these energy differences are inverted in practically all cases: the LUMO-diene/HOMO-dienophile interaction being closer than the other by only a small amount (ca. 0.5 eV). According to these results, it could be assumed that a single frontier interaction, involving normal electronic demand,[2d] should control additions with electron-releasing dienes **2**, **3**, and **4**. Besides, they also suggest that probably both interactions (neutral electronic demand)[2d] play important roles for the addition of electron-poor diene **6**.

Regioselectivity could then be estimated on the basis of coefficient differences for the proper frontier orbital interaction between diene and dienophile, and also considering that the larger terminal coefficient on each addend will become bonded preferentially in the transition state.[23,24a,34] It can be observed from Table V that the geminal substituents in dienophiles **1** increase the relative magnitude of the coefficient of the olefin unsubstituted terminus (C-1) at the expense of the coefficient of the substituted terminus (C-2), in both HOMO and LUMO. The origin of this polarization of π-system of captodative olefins seems to be easily comprehensible from a qualitative perturbational approach.[6c,23c]

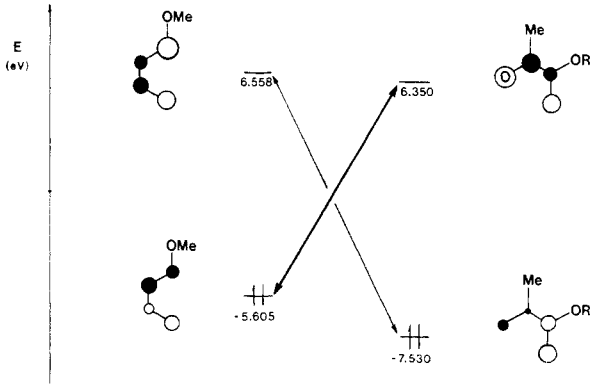


Figure 3. Ab initio frontier molecular orbital interactions for the Diels–Alder reaction between dienophile **1a** and diene **4** in the concerted transition state.

Therefore, according to coefficient polarization for the LUMOs of dienophiles **1** and for the HOMOs of electron-donor dienes (**2**–**4**), the expected major regioisomers for the additions of these cycloaddends must correspond to para or ortho adducts, when the reaction is carried out with isoprene (**2**) or 1-substituted dienes **3** and **4**, respectively. This is due to the main interactions between carbon C-4 or **2** and C-4 of 1-substituted dienes **3** and **4** with C-1 of dienophiles **1** (Figure 3).

Even when steric effects have been invoked[35] to control regioselectivity for the isoprene (**2**) additions, these effects do not seem to opperate in our case since, on the other hand, the ortho isomer is the only adduct formed for the

(34) Calculations of FMOs of both transition-state and ground-state geometries for some dienes and dienophiles have shown similar π-coefficient magnitudes:[37a] Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129–1134.

(35) Bachler, V.; Mark, F. *Theoret. Chim. Acta* **1976**, *43*, 121–135, and references cited therein.

1-substituted dienes, in spite of being the more crowded one.[36]

Undoubtedly, a more difficult case to predict is the addition of dienophiles 1 to the electron-withdrawing diene 6. Several reports have shown that FMO theory has not completely accounted for regioselectivity of this kind of dienes.[23e,37] In our ground-state structures, not only one single FMO interaction but both HOMO-diene/LUMO-dienophile and LUMO-diene/HOMO-dienophile interactions would be taken into account, because the energy gaps for both HOMO–LUMO interactions are very close. However, two opposite predictions arise. Indeed, for the HOMO-6/LUMO-1 interaction the greatest terminal coefficient in diene 6 is on carbon C-1 (Table VI), leading to overlap on carbon C-1 of dienophile; hence, the major expected adduct would be the unobserved meta isomer. In the energetically more favorable interaction; LUMO-diene/HOMO-dienophile (**1d** being an exception), the largest coefficients involved in both cycloaddends are located to give the experimentally observed ortho isomer: C-1 of dienophile and C-4 of diene (Tables V and VI). Furthermore, when the secondary interactions are considered,[12d,23d] greater preference for the ortho regioisomer would be predicted, since the largest secondary coefficient is located on carbon C-2 of the diene in both HOMO and LUMO. Thus, interaction between this secondary carbon and the carbonyl carbon of the dienophile will provide the greatest stabilization of the transition state. This is in agreement with transition-state geometry optimizations for 1-substituted dienes by electron-withdrawing groups.[37a]

The results given in Table II show that **1a** undergoes cycloaddition with several acyclic dienes in a highly stereoselective way, with the endo adduct the prefered isomer. These results contrast with the lower stereoselectivities of the addition of dienophiles 1 toward cyclopentadiene (**30**)[7] and with the exo-favored addition of other captodative olefins.[6d,f]

The endo/exo selectivity of Diels–Alder reactions has generally been explained by secondary orbital interactions, i.e., additional overlap between orbitals of atoms not directly intervening in bond formation.[2c,38] However, other hypotheses have been proposed as responsible for the endo-Alder rule,[39] as attractive van der Waals,[40] dipole–dipole,[41] steric[42] interactions and closed-shell repulsions[43] between the dienophile substituents and the diene in the transition state. Recently, it has been shown that secondary orbital interactions from the donor group of captodative dienophiles might stabilize the exo transition state with **30**.[44] The exo isomer (with regards to electron-attractive group) is also present in slightly higher amounts in additions of dienophiles 1[7] and could also be explained as a balance of two antagonistic effects: steric repulsions of the crowded interaction of the aroyloxy group of 1 and the methylene bridge of **30**[45] favoring the exo isomer, and, in contrast, repulsive interactions between π-orbitals of the aroyloxy group and the diene system would destabilize it.

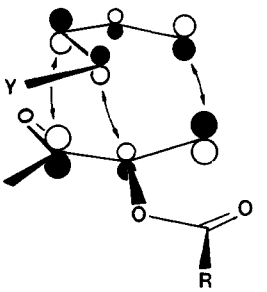


Figure 4. Orbital interaction between LUMO of **1a** and HOMO of dienes **3** (Y = OAc) and **4** (Y = OMe).

Nevertheless, whereas in the case of cycloaddition of 1 with acyclic dienes **3–7**, steric repulsions are not present as concerns the methylene bridge, secondary orbital interactions might be a factor that would stabilize the endo transition state,[34,46] since the appropriate secondary orbitals in both 1-substituted dienes and dienophiles are larger (Tables V and VI). Assuming an NED interaction, the coefficient of the C-2 center in the HOMOs of electron-donor dienes **3–5** has a size as large as the terminal coefficient (Table VI), and the former could interact with the larger secondary lobe in the LUMO of the corresponding dienophile. It can be noticed in Table V that the largest LUMO secondary orbital coefficients in the dienophiles are found in the carbonyl of the acetyl group, while a great contribution of O-5 center is observed in the HOMOs. Hence, and assuming a small change of π-coefficients in the transition state, an efficient interaction could take place, stabilizing particularly the endo transition state (Figure 4). Moreover, in this geometrical approach, the biggest and electron-rich center of aroyloxy group, e.g., the lone pair on oxygen, is placed far from any possible steric[47] and/or electrostatic[26] repulsions with the π-system of the diene and/or with its substituent groups.

The enhancement of the reactivity, regioselectivity, and stereoselectivity of Diels–Alder additions by the presence of Lewis acids has been well documented,[12a,48] and some hypotheses based on FMO framework have been given in the past[49] to rationalize it. The complexing of dienes and dienophiles by Lewis acids modifies the energy position and the relative magnitudes of the eigenvector coefficients of the frontier orbitals and consequently it can improve both reactivity and selectivity. Calculations made for

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(42) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537–562.
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(46) Güner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1988**, *53*, 5348–5351.
(47) While experimental results[12e,37b] have consistingly shown that steric factors can be neglected in determining regiochemistry, many studies[45,47a-c] have considered them to play an important role in controling stereoselectivity in catalyzed and uncatalyzed Diels–Alder reactions. (a) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14–23. (b) Tripathy, R.; Franck, R. W.; Onan, K. D. *Ibid.* **1988**, *110*, 3257–3262. (c) Fox, M. A.; Cardona, R.; Kiwiet, N. J. *J. Org. Chem.* **1987**, *52*, 1469–1474.
(48) For examples of Lewis acid catalyzed cycloadditions, see: Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306–1307, and references cited therein. Dieck, H. T.; Dietrich, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 781–783. Oppolzer, W. *Ibid.* **1984**, *23*, 876–889. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802–2808. Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700–1706, and references cited therein.
(49) For example, see ref 12b,d,e, 17b, 23b, 25, and: Güner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1987**, *52*, 391–394.

analogous captodative olefins showed that coordination at the amide unit of the donor group is energetically more favored.[44] In our case, the Lewis acid could complex both acceptor and donor groups of the dienophile 1, because an excess (5 molar equiv) of catalyst was added. So, it should be expected that this double-induced electron-withdrawing effect would show a significant rate and regioselective enhancement.

Conclusion

The present study thus reveals that the captodative dienophiles **1a–c** undergo Diels–Alder cycloaddition with acyclic substituted dienes, giving the corresponding adducts with very high regio- and stereoselectivities. Besides, ab initio STO-3G and MINDO/3 calculations provided energetic and polarization parameters of MOs for dienophiles 1, affording an FMO interpretation about regioselectivity in agreement with results. Thus, primary orbital interactions of FMOs cycloaddends seem to be the reason for controlling the orientation of the additions, and also secondary orbital interactions could be the factor to permit the endo preference. Further theoretical and experimental efforts are being carried out to obtain much more evidence about participating effects in the stereoselectivity of additions of olefins 1 to acyclic and cyclic dienes.

Experimental Section

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. Infrared spectra (IR) were recorded on a Perkin-Elmer 599B spectrophotometer. ^{1}H NMR spectra were obtained on either Varian EM-390 (90 MHz) or Bruker WH-360 FT (360 MHz) spectrometers, chemical shifts are quoted in ppm downfield from TMS as internal standard (δ, apparent multiplicity, apparent coupling constants, number of protons, and tentative structure assignment). The ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.49 MHz) instrument operated in pulsed FT mode and locked on solvent deuterium. The mass spectra (MS) were taken on a Hewlett-Packard 5985-A spectrometer in electron-impact ionization (70 eV) or chemical ionization modes (CI) (m/e, rel intensity). GLC analyses were performed on a Varian Vista 6000 chromatograph equipped with a OV-17, 12% (4 m × $^1/_8$ i.d.) on a Chromosorb WHP 100/120-mesh column; 60–135 °C, 12 mL/min N_2. Medium pressure chromatography separations were performed on a Lobar-Merck (LiChroprep. Si60, 40–63 m, 1.5 cm × 25 cm) column. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) with potassium permanganate spray and/or short- and long-wave ultraviolet light to visualize the spots. Microanalyses were performed by the laboratory Ilse Beetz in Kronach (Germany). Abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintuplet, m = multiplet, br = broad.

Isoprene Adducts with Dienophiles 1. General Procedures. 1-Acetyl-4-methyl-3-cyclohexen-1-yl *p*-Nitrobenzoate (8a) and 1-Acetyl-3-methyl-3-cyclohexen-1-yl *p*-Nitrobenzoate (9a). Method A. A mixture of **1a** (0.2 g, 0.85 mmol), **2** (0.41 g, 6.0 mmol), and hydroquinone (3 mg) in anhydrous xylene (5 mL) was placed in a 25-mL round-bottom flask provided with a rubber septum, under an N_2 atmosphere. After being stirred at 130 °C for 35 h, the mixture was diluted with EtOAc (150 mL) and washed with ice-cold water (2 × 50 mL). The solvent was evaporated in vacuo and the residue was purified by column chromatography (40 g of Florisil, petroleum ether/EtOAc, 9:1) to furnish 0.198 g (77%) of a mixture of adducts **8a/9a** (75:25).

Method B. To a mixture of **1a** (0.05 g, 0.21 mmol) and **2** (0.05 g, 0.73 mmol) in dry CH_2Cl_2 (3 mL) under an N_2 atmosphere was added anhydrous $ZnCl_2$ (0.1 g, 1.1 mmol). After being stirred at room temperature for 36 h, H_2O (5 mL) was added and then EtOAc (250 mL). The organic layer was separated and washed until neutral with water (2 × 20 mL) and aqueous 5% $NaHCO_3$ (10 mL). The organic extracts were combined and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by column chromatography on Florisil (10 g, petroleum ether/EtOAc, 9:1), yielding 0.063 g (98%) of pale yellow crystals of a mixture of **8a/9a** (94:6).

Method C. A degassed solution of **1a** (0.3 g, 1.27 mmol) and **2** (0.43 g, 6.32 mmol) in anhydrous CH_2Cl_2 (4 mL) was cooled at −78 °C. Freshly distilled BF_3·Et_2O (0.9 g, 6.34 mmol) was added dropwise under an N_2 atmosphere and the mixture was stirred at −78 °C for 10 h. The cold mixture was poured at once in a separatory funnel containing EtOAc (250 mL) and water (100 mL). After vigorous shaking, the organic layer was separated and washed until neutral with aqueous 5% $NaHCO_3$. After drying (Na_2SO_4) the solvent was evaporated in vacuo, and the residue was purified by column chromatography on Florisil (60 g, petroleum ether/EtOAc, 9:1), yielding 0.34 g (89%) of a mixture of adducts **8a/9a** (99:1), as a pale yellow powder. Pure **8a** was obtained as pale yellow crystals (83%) by recrystallization from EtOH: R_f 0.44 (1/4 ethyl acetate–hexane); mp 77–78 °C; IR (KBr) 3060, 1680, 1580, 1500, 1280, 710 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.7 (br s, 3 H), 1.9–2.1 (m, 3 H), 2.2 (s, 3 H), 2.3–2.8 (m, 3 H), 5.4 (m, 1 H), 8.26 (m, 4 H); ^{13}C NMR ($CDCl_3$), see Table IV; δ 205.7 (br s), 163.9 (s), 150.8 (t, $^3J_{C,H}$ = 6.7 Hz), 135.2 (t, $^3J_{C,H}$ = 6.7 Hz), 133.3 (m), 130.9 (dd, $^1J_{C,H}$ = 169.0 Hz, $^3J_{C,H}$ = 5.5 Hz), 123.6 (dd, $^1J_{C,H}$ = 169.7 Hz, $^3J_{C,H}$ = 2.5 Hz), 116.5 (dm, $^1J_{C,H}$ = 155.6 Hz), 85.21 (br s), 31.7 (tt, $^1J_{C,H}$ = 128.2 Hz, $^3J_{C,H}$ = 5.0 Hz), 27.7 (tm, $^1J_{C,H}$ = 131.8 Hz), 26.5 (tm, $^1J_{C,H}$ = 129.4 Hz), 24.1 (q, $^1J_{C,H}$ = 128.2 Hz), 23.1 (qd, $^1J_{C,H}$ = 125.7 Hz, $^3J_{C,H}$ = 7.2); MS (70 eV) 150 (M$^+$ − $C_9H_{13}O_2$, 72), 136 (35), 121 (100), 104 (34), 93 (32). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.64. Found: C, 63.34; H, 5.71.

1-Acetyl-4-methyl-3-cyclohexen-1-yl α-Naphthoate (8b) and 1-Acetyl-3-methyl-3-cyclohexen-1-yl α-Naphthoate (9b). Method A. The same procedure as for **8a/9a** was used, with 0.08 g (0.33 mmol) of **1b** and 0.34 g (5 mmol) of **2**. The cycloaddition was carraied out for 70 h. Column chromatography on silica gel (10 g, petroleum ether/EtOAc, 8:2) yielded 0.072 g (70%) of a mixture of **8b/9b** (67:33) as a colorless oil.

Method C. The same procedure as for **8a/9a** was used, with 0.2 g (0.83 mmol) of **1b** and 0.34 g (5 mmol) of **2**. The reaction was carried out for 10 h. Column chromatography on silica gel (15 g, petroleum ether/EtOAc, 8:2) yielded 0.225 g (88%) of a mixture of **8b/9b** (98:2) as a colorless oil: R_f 0.53 (1/4 ethyl acetate–hexane); IR (film) 3070, 3000–2850, 1700, 1510, 1310, 1270, 1225, 820 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.76 (br s, 3 H, CH_3C=), 2.3 (s, 3 H), 1.8–2.5 (m, 4 H), 2.65 (m, 2 H), 5.5 (m, 1 H, HC-3), 7.5–8.4 (m, 6 H), 9.0 (m, 1 H); MS (70 eV) 308 (M$^+$, 2), 172 (19), 155 (100), 136 (67), 127 (89), 121 (91), 91 (67). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.89; H, 6.53. Found: C, 77.84; H, 6.51.

1-Acetyl-4-methyl-3-cyclohexen-1-yl β-Naphthoate (8c) and 1-Acetyl-3-methyl-3-cyclohexen-1-yl β-Naphthoate (9c). Method A. The same procedure as for **8a/9a** was used, with 0.08 g (0.33 mmol) of **1c** and 0.23 g (3.3 mmol) of **2**. The reaction was carried out for 72 h. Column chromatography on silica gel (10 g, petroleum ether/EtOAc, 8:2) yielded 0.07 g (69%) of a mixture of **8c/9c** (70:30) as a colorless oil.

Method C. The same procedure as for **8a/9a** was used, with 0.1 g (0.42 mmol) of **1c** and 0.14 g (2.0 mmol) of **2**. The reaction was carried out for 10 h. Column chromatography on silica gel (10 g, petroleum ether/EtOAc, 8:2) yielded 0.115 g (90%) of a mixture of **8c/9c** (99:1) as a colorless oil: R_f 0.51 (1/4 ethyl acetate–hexane); IR (film) 3100–2800, 1700, 1625, 1450, 1160, 820 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.7 (br s, 3 H, CH_3C=), 2.2 (s, 3 H), 1.8–2.5 (m, 4 H), 2.6 (m, 2 H), 5.4 (m, 1 H, HC-3), 7.4–8.1 (m, 6 H), 8.6 (br s, 1 H); MS (70 eV) 308 (M$^+$, 2), 172 (41), 156 (91), 137 (83), 128 (100), 122 (84), 91 (43). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.89; H, 6.53. Found: C, 77.94; H, 6.68.

1-Acetyl-1-hydroxy-4-methylcyclohex-3-ene (10) and 1-Acetyl-1-hydroxy-3-methylcyclohex-3-ene (11). A solution of a mixture of 0.2 g (0.65 mmol) of **8b/9b** (98:2) in dry THF (5 mL) under nitrogen at 0 °C was treated with anhydrous K_2CO_3 (0.27 g, 1.95 mmol) in dry MeOH (2 mL). After being stirred for 3 h at 0 °C, EtOAc (80 mL) was added, and the mixture was washed until neutral with aqueous 5% HCl (2 × 10 mL) and with aqueous 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by column chromatography on silica gel (10 g, petroleum ether/EtOAc, 8:2), yielding 0.1 g (97%) of a mixture of **10/11** (98:2) as a pale yellow oil: R_f 0.32 (1/4 acetyl acetate/hexane); IR (KBr)

3400, 2960–2800, 1675, 1330, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.36 (dddd, J = 2.1, 2.5, 6.0, 13.0 Hz, 1 H, H-6α), 1.5 (ddd, J = 6.0, 11.0, 13.0 Hz, 1 H, H-6β), 1.58 (br s, 3 H, CH_3C=), 1.67 (m, 1 H, H-5β), 1.73 (m, 1 H, H-2α), 1.8 (s, 3 H, CH_3CO), 2.16 (m, 1 H, H-5α), 2.2 (m, 1 H, H-2β), 3.3 (br s, 1 H, OH), 5.2 (m, 1 H, H-3); MS (70 eV) 136 ($M^+ - H_2O$, 20), 121 (17), 111 (94), 93 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.93; H, 9.20.

4-Methylacetophenone (16) and 3-Methylacetophenone (17). To a solution of a mixture of **10**/**11** (98:2) (0.1 g, 0.65 mmol) in dry CH_2Cl_2 (6 mL) under an N_2 atmosphere at 0 °C was added dropwise $SOCl_2$ (0.32 g, 2.7 mmol). After 5 h of stirring at room temperature, the mixture was diluted with CH_2Cl_2 (100 mL) and washed until neutral with aqueous 5% HCl (2 × 10 mL) and aqueous 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was diluted with dry benzene (8 mL) and DBN (5 drops) was added. The mixture was gently refluxed for 4 h, diluted with CH_2Cl_2 (100 mL), and washed until neutral with aqueous 5% HCl (2 × 10 mL) and with aqueous 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by column chromatography on silica gel (7 g, petroleum ether/EtOAc, 8:2), yielding 0.054 g (62%) of a mixture of **16**/**17** (98:2) as a pale yellow oil. The resultant mixture was 98% pure (GLC), and its constituents were identified by comparison of their ^1H NMR, IR, and GLC retention times (32.5 min for **16** and 31.2 min for **17**) with those of authentic samples (Aldrich Chemical Co.).

General Procedure for the Diels–Alder Reaction of Dienophile 1a with Substituted Butadienes. [1*R,2*R**]-2-Acetoxy-1-acetyl-3-cyclohexen-1-yl *p*-Nitrobenzoate (18a) and [1*R**,2*S**]-2-Acetoxy-1-acetyl-3-cyclohexen-1-yl *p*-Nitrobenzoate (18b).** A mixture of **1a** (4.2 g, 17.9 mmol), **3** (6.01 g, 53.6 mmol), and hydroquinone (5 mg) in anhydrous xylene (12 mL) was placed under an N_2 atmosphere in a 50-mL round-bottom flask provided with a rubber septum. After being stirred at 130 °C for 11 h, the solvent was evaporated in vacuo and the residue was purified by column chromatography on Florisil/10% K_2CO_3 (30 g, petroleum ether/EtOAc, 9:1), furnishing 4.8 g (79%) of a mixture of adducts **18a**/**18b** (>95:<5) as pale yellow crystals. The major isomer **18a** was isolated by recrystallization from petroleum ether/EtOAc, 8:2, as colorless prism: R_f 0.54 (3/7 ethyl acetate–hexane); mp 121–122 °C; IR (KBr) 3080, 2900, 1715, 1705, 1695, 1280, 855 cm^{-1}; ^1H NMR, see Table III; ^{13}C NMR ($CDCl_3$), see Table IV; δ 203.2 (m), 169.0 (m), 163.0 (br s), 150.8 (m), 134.1 (t, $^3J_{C,H}$ = 8.6 Hz), 133.2 (dm, $^1J_{C,H}$ = 163.1 Hz), 130.7 (dd, $^1J_{C,H}$ = 174.6 Hz, $^3J_{C,H}$ = 6.6 Hz), 123.5 (dd, $^1J_{C,H}$ = 172.3 Hz, $^3J_{C,H}$ = 4.4 Hz), 121.7 (ddd, $^1J_{C,H}$ = 167.0 Hz, $^3J_{C,H}$ = 4.5, 6.6 Hz), 84.0 (m), 67.9 (dm, $^1J_{C,H}$ = 153.3 Hz), 25.3 (q, $^1J_{C,H}$ = 128.5 Hz), 21.9 (t, $^1J_{C,H}$ = 131.3 Hz), 20.4 (q, $^1J_{C,H}$ = 129.6 Hz); MS (70 eV) 245 ($M^+ - C_4H_6O_3$, 20), 151 (13), 150 (100), 104 (30), 95 (19), 77 (24). Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.90. Found: C, 58.97; H, 4.91.

[1*R,2*R**]-1-Acetyl-2-methoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (20a) and [1*R**,2*S**]-1-Acetyl-2-methoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (20b).** The same procedure as for **18a**/**18b** was used, with 0.1 g (0.42 mmol) of **1a** and 0.07 g (0.84 mmol) of **4**. The mixture was heated at 110 °C for 31 h. Column chromatography on Florisil/10% K_2CO_3 (12 g, petroleum ether/EtOAc, 9:1) yielded 0.03 g of unreacted **1a** and 0.085 g (89%) of a mixture of **20a**/**20b** (86:14) as pale yellow crystals. Pure major isomer **20a** was isolated by recrystallization from petroleum ether/EtOAc, 8:2, as colorless prisms: R_f 0.60 (3/7 ethyl acetate–hexane); mp 137–138 °C; IR (KBr) 3060, 3010, 2960, 1710, 1695, 1295, 1110, 855 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) data of **20a**; see Table III. Further signals attributed to isomer **20b**: 2.36 (s, CH_3CO). The other signals are completely or partially overlaped by those of **20a**. ^{13}C NMR ($CDCl_3$) see Table IV, data of **20a**: δ 205.4 (m), 163.0 (m), 150.7 (t, $^3J_{C,H}$ = 8.5 Hz), 134.6 (br s), 132.2 (dqi, $^1J_{C,H}$ = 160 Hz, $^3J_{C,H}$ = 6.0 Hz), 130.8 (dd, $^1J_{C,H}$ = 169.0 Hz, $^3J_{C,H}$ = 6.1 Hz), 123.5 (dd, $^1J_{C,H}$ = 171.0 Hz, $^3J_{C,H}$ = 3.7 Hz), 122.6 (ddd, $^1J_{C,H}$ = 162.0 Hz, $^3J_{C,H}$ = 5.5, 9.2 Hz), 83.9 (m), 76.0 (d, $^1J_{C,H}$ = 145.3 Hz), 56.9 (qd, $^1J_{C,H}$ = 142.0 Hz, $^3J_{C,H}$ = 4.8 Hz), 26.7 (q, $^1J_{C,H}$ = 128.0 Hz), 22.2 (t, $^1J_{C,H}$ = 131.0 Hz), 22.1 (t, $^1J_{C,H}$ = 131.0 Hz). Further signals attributed to isomer **20b**: 128.8 (d, $^1J_{C,H}$ = 160.0 Hz), 124.4 (d, $^1J_{C,H}$ = 165.0 Hz), 57.5 (q, $^1J_{C,H}$ = 145.0 Hz), 26.0 (q, $^1J_{C,H}$ = 128.0 Hz). MS (70 eV): 217 (M^+ – 102, 16), 150 (100), 120 (10), 104 (33), 84 (36), 76 (22). Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.19; H, 5.33. Found: C, 60.22; H, 5.41.

[1*R,2*R**]-1-Acetyl-2-(methoxycarbonyl)-3-cyclohexen-1-yl *p*-Nitrobenzoate (22a) and [1*R**,2*S**]-1-Acetyl-2-(methoxycarbonyl)-3-cyclohexen-1-yl *p*-Nitrobenzoate (22b). Method A.** The same procedure as for **18a**/**18b** was used, with 0.5 g (2.13 mmol) of **1a** and 0.715 g (6.38 mmol) of **5**. After being heated for 53 h, the residue was purified by column chromatography on Florisil/10% K_2CO_3 (26 g, petroleum ether/EtOAc, 9:1), yielding 0.11 g of unreacted **1a** and 0.466 g (81%) of a mixture of **22a**/**22b** (80:20) as pale yellow crystals.

Method B. A degassed solution of **1a** (2.3 g, 9.78 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled at 0 °C and BF_3·Et_2O (4.86 g, 34.2 mmol) was added dropwise under an N_2 atmosphere. Then, diene **5** (3.28 g, 29.3 mmol) was slowly added, and the mixture was heated at 40 °C for 15 h. After being cooled down to room temperature, CH_2Cl_2 (50 mL) was added, and the mixture was washed with brine (3 × 10 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo and the residue purified by column chromatography on Florisil/10% K_2CO_3 (45 g, petroleum ether/EtOAc, 9:1), giving 3.05 g (90%) of a mixture of **22a**/**22b** (84:16). Pure major isomer **22a** was isolated by recrystallization from petroleum ether/EtOAc, 8:2, as colorless needles: R_f 0.62 (3/7 ethyl acetate/hexane); mp 139–140 °C; IR (KBr) 3100, 3070, 2940, 1730, 1710, 1530, 1315, 1190 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) data of **22a**, see Table III. Further signals attributed to isomer **22b** are completely overlapped by those of **22a**. ^{13}C NMR ($CDCl_3$), see Table IV, data of **22a**: δ 205.7 (dd, $^3J_{C,H}$ = 6.3, 9.0 Hz), 170.4 (m), 163.2 (t, $^3J_{C,H}$ = 4.3 Hz), 150.7 (tt, $^3J_{C,H}$ = 2.0, 8.6 Hz), 134.5 (br s), 130.7 (dd, $^1J_{C,H}$ = 169.7 Hz, $^3J_{C,H}$ = 6.1 Hz), 129.0 (dm, $^1J_{C,H}$ = 160.0 Hz), 123.5 (dd, $^1J_{C,H}$ = 170.9 Hz, $^3J_{C,H}$ = 3.7 Hz), 120.9 (ddd, $^1J_{C,H}$ = 166.0 Hz, $^3J_{C,H}$ = 6.1, 13.4 Hz), 83.7 (br s), 52.2 (q, $^1J_{C,H}$ = 147.7 Hz), 48.4 (dm, $^1J_{C,H}$ = 135.0 Hz), 25.9 (q, $^1J_{C,H}$ = 129.0 Hz), 23.3 (tm, $^1J_{C,H}$ = 133.0 Hz), 21.9 (tm, $^1J_{C,H}$ = 128.8 Hz). Further signals attributed to isomer **22b**: 172.4 (m), 166.5 (m), 148.9 (m), 131.6, 129.5, 126.3, 122.7, 121.3, 51.3 (q, $^1J_{C,H}$ = 147.0 Hz), 44.4, 24.9, 22.7. MS (70 eV): 244 (M^+ – 103, 2), 180 (10), 163 (11), 150 (100), 121 (12), 104 (49). Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.90. Found: C, 58.67; H, 4.86.

[1*R,2*R**,5*R**]-1-Acetyl-2,5-diacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (29a) and [1*R**,2*S**,5*S**]-1-Acetyl-2,5-diacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (29b).** The same procedure as for **18a**/**18b** was used, with 0.675 g (2.87 mmol) of **1a** and 0.23 g (1.35 mmol) of **7**. The mixture was heated at 130 °C for 16 h. Column chromatography on Florisil/10% K_2CO_3 (45 g, petroleum ether/EtOAc, 9:1) yielded 0.47 g of unreacted **1a** and 0.19 g (53.6%) of a mixture of **29a**/**29b** (90:10) as a pale yellow oil: R_f 0.53 (2/3 ethyl acetate/hexane); IR ($CHCl_3$) 3050, 2930, 1710, 1520, 1280, 855 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) data of **29a**: see Table III. Further signals attributed to isomer **29b**: 1.97 (s). The other signals are completely or partially overlaped by those of **29a**. ^{13}C NMR ($CDCl_3$) data of **29a**: δ 201.9 (br s), 170.1 (br s), 169.1 (br s), 163.0 (s), 151.1 (m), 133.6 (t, $^3J_{C,H}$ = 8.5 Hz), 132.9 (ddd, $^1J_{C,H}$ = 165.0 Hz, 5.0, 10.6 Hz), 131.1 (dd, $^1J_{C,H}$ = 166.0 Hz, $^3J_{C,H}$ = 6.0 Hz), 124.1 (ddd, $^1J_{C,H}$ = 169.0 Hz, $^3J_{C,H}$ = 4.0, 4.5 Hz), 123.8 (dd, $^1J_{C,H}$ = 173.0 Hz, $^3J_{C,H}$ = 4.0 Hz), 84.0 (br s), 67.3 (dm, $^1J_{C,H}$ = 155.5 Hz), 66.7 (d, $^1J_{C,H}$ = 149.5 Hz), 28.0 (t, $^1J_{C,H}$ = 134.7 Hz), 25.2 (q, $^1J_{C,H}$ = 128.0 Hz), 21.0 (q, $^1J_{C,H}$ = 130.0 Hz), 20.6 (q, $^1J_{C,H}$ = 130.5 Hz); MS (70 eV) 243 (M^+ – 162, 9), 150 (100), 136 (13), 121 (26), 104 (38), 94 (78). MS (CI, NH_3): 423 ($M^+ + NH_4^+$, 78), 346 (8), 200 (29), 138 (100), 121 (36), 105 (27), 93 (11). Anal. Calcd for $C_{19}H_{19}NO_9$: C, 56.29; H, 4.72. Found: C, 56.40; H, 4.95.

[3*R,4*R**]-4-Acetyl-3-methoxy-4-[(*p*-nitrobenzoyl)oxy]-cyclohexan-1-one (26a) and [3*R**,4*S**]-4-Acetyl-3-methoxy-4-[(*p*-nitrobenzoyl)oxy]cyclohexan-1-one (26b).** The same procedure as for **18a**/**18b** was used, with 2.5 g (10.6 mmol) of **1a** and 1.82 g (10.6 mmol) of **5**. The mixture was heated at 120 °C for 11 h. Column chromatography on Florisil/10% K_2CO_3 (15 g, petroleum ether/EtOAc, 9:1) yielded 0.70 g of unreacted **1a** and 2.1 g (70%) of a mixture of **26a**/**26b** (93:7) as pale yellow crystals. Recrystallization from petroleum ether/EtOAC, 8:2, afforded **26a** as colorless prisms: R_f 0.44 (2/3 ethyl acetate–hexane); mp 141–142 °C; IR (KBr) 3075, 3040, 2920, 1700, 1690, 1510, 1350, 1280, 1105, 860, 740 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.37–2.52 (m, 2 H), 2.4 (s, 3 H), 2.85 (m, 4 H), 3.35 (s, 3 H, OMe),

4.13 (t, J = 2.9 Hz, 1 H), 8.2 (d, J = 9.0 Hz, 2 H), 8.33 (d, J = 9.0, 2 H). ^{13}C NMR ($CDCl_3$) data of **26a**: δ 206.9 (m), 204.7 (qi, $^3J_{C,H}$ = 6.0 Hz), 163.2 (s), 151.0 (t, $^3J_{C,H}$ = 7.3 Hz), 134.3 (t, $^3J_{C,H}$ = 6.1 Hz), 131.0 (dd, $^1J_{C,H}$ = 169.0 Hz, $^3J_{C,H}$ = 5.5 Hz), 123.8 (dd, $^1J_{C,H}$ = 170.9 Hz, $^3J_{C,H}$ = 3.7 Hz), 82.9 (s), 82.0 (d, $^1J_{C,H}$ = 150.1 Hz), 57.3 (qd, $^1J_{C,H}$ = 142.8 Hz, $^3J_{C,H}$ = 4.3 Hz), 40.7 (br t, $^1J_{C,H}$ = 129.4 Hz), 36.3 (t, $^1J_{C,H}$ = 130.6 Hz), 27.6 (q, $^1J_{C,H}$ = 128.6 Hz), 26.0 (t, $^1J_{C,H}$ = 133.7 Hz). Further signals attributed to isomer **26b**: 205.9, 204.0, 33.8. MS (CI, NH_3): 353 ($M^+ + NH_4^+$, 45), 306 (9), 188 (100), 171 (11), 156 (19). Anal. Calcd for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11. Found: C, 57.05; H, 5.44.

[1*R,2*R**]-1-Acetyl-1,2-dihydroxycyclohex-3-ene (24a) and [1*R**,2*S**]-1-Acetyl-1,2-dihydroxycyclohex-3-ene (24b).** To a solution of **18a/18b** (>95:<5) (2.3 g, 6.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was added MeOH (1 mL) and anhydrous K_2CO_3 (0.5 g). After being stirred at room temperature for 10 min, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (3 × 5 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was divided in two parts, the first one (1.2 g) was purified by column chromatography on Florisil (14 g, petroleum ether/EtOAc, 85:15), yielding 0.49 g (95%) of **24a/24b** (>95:<5) as a light-yellow oil. The second part (1.2 g) was purified on Florisil/10% K_2CO_3 (16 g, petroleum ether/EtOAc, 9:1), providing 0.5 g (97%) of a mixture of **24a/24b** (40:60). This mixture was separated by medium pressure chromatography (petroleum ether/EtOAc, 85:15), yielding 0.19 g of **24a** as colorless crystals and 0.29 g of **24b** as a colorless oil.

24a: R_f 0.34 (1/1 ethyl acetate–hexane); mp 60–61 °C; IR (film) 3400, 3010, 2900, 1685, 1350, 1200, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.7–2.7 (m, 6 H, 2 CH_2, 2 OH), 2.35 (s, 3 H, CH_3CO), 4.1 (br s, 1 H, C-2), 5.95 (m, 2 H, H-3, H-4); MS (70 eV) 156 (M^+, 0.2), 138 ($M^+ - H_2O$, 0.3), 95 (8), 85 (29), 43 (36), 40 (100). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.56; H, 7.79.

24b: R_f 0.4 (1/1 ethyl acetate–hexane); IR (film) 3400, 3010, 2900, 1690, 1370, 1250 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.4 (m, 5 H, 2 CH_2, OH), 2.35 (s, 3 H, CH_3CO), 4.0 (br s, 1 H, OH), 4.6 (br s, 1 H, C-2), 5.68 (dm, J = 10.0 Hz, H-3), 5.98 (dm, J = 10.0 Hz, H-4); MS (70 eV) 156 (M^+, 3), 113 (55), 96 (17), 95 (100), 87 (12), 70 (41), 67 (89). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.64; H, 7.86.

[1*R,2*S**]-1-Acetyl-1,2-(isopropylidenedioxy)-3-cyclohexene (25b).** To a solution of a mixture of **24a/24b** (4:6) (0.35 g, 2.2 mmol), p-TsOH (0.15 g, 0.87 mmol), and anhydrous DMF (0.6 mL) in dry CH_2Cl_2 (2 mL) at 0 °C was slowly added 2,2-dimethoxypropane (0.58 g, 5.6 mmol). After being stirred at this temperature for 19 h, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with aqueous 5% NH_4OH (2 × 2 mL) and brine (2 × 3 mL). The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo. The obtained oil was purified by column chromatography on Florisil/10% K_2CO_3 (30 g, petroleum ether/EtOAc, 7:3) and afforded 0.26 g (98%) of **25b** as a colorless oil and 0.13 g (93%) of unreacted **24a**.

25b: R_f 0.6 (1/4 ethyl acetate–hexane); IR (film) 3020, 2940, 1700, 1390, 1260, 1240, 1120, 1080 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.4 (s, 3 H), 1.5 (s, 3 H), 1.8 (m, 2 H), 2.1 (m, 2 H), 2.36 (s, 3 H, CH_3CO), 4.86 (m, 1 H, H-2), 6.1 (m, 2 H); MS (70 eV) 181 ($M^+ - CH_3$, 1), 153 (38), 138 (1), 123 (3), 96 (20), 95 (100), 67 (31). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.57; H, 8.16.

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Supplementary Material Available: Table of MINDO/3 calculations of energies and coefficients of the FMOs for dienophiles 1 and MVK (1 page). Ordering information is given on any current masthead page.

AM1 Calculations of Substituent Effects in Retro-Diels–Alder Reactions

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The AM1 method has been used for investigating the effects of substituents on retro-Diels–Alder reactions, and the results have been compared with experimental data. Transition structures for butadiene reacting with ethylene and acrolein are quite close to those obtained with ab initio methods. The calculated asynchonicity of the retro-Diels–Alder reaction of substituted bicyclo[2.2.2]octa-2,5-dienes and ethanoanthracenes depends on substituents, with electron-donating groups making the TS more asymmetrically. The calculated activation energies for these reactions are too high compared to experimental data, but trends in relative activation energies for different substituents are reproduced reasonably well, although there are exceptions. Calculated activation entropies for unsubstituted systems are in good agreement with ab initio values and experimental data, but the variation of activation entropy with substituents is not reproduced.

Introduction

The Diels–Alder (DA) reaction continues to be one of the more popular reactions in organic synthesis due to the control of stereochemistry it provides,[1] and the reverse reaction has been used for protecting a diene moiety during synthetic sequences.[2] The qualitative effects of different functional groups on the reaction rate are well known,[3] electron donors on the diene and electron acceptors on the dieneophile accelerate the reaction,[4] and these effects can be rationalized by FMO theory.[6] Despite the large number of DA reactions known, very few systematic studies of the effects of different functional groups have appeared, but

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