Diels-Alder Reactions of Cycloalkenones. 9. Diastereofacial Selectivity of Mono- and Dialkylated 2-Cyclohexenones[1]

E. Charles Angell,[2b] Francesco Fringuelli,*[2a] Ferdinando Pizzo,[2a] Barry Porter,[2b] Aldo Taticchi,*[2a] and Ernest Wenkert*[2b]

Dipartimento di Chimica, Università degli Studi, 06100 Perugia, Italy, and Department of Chemistry (D-006), University of California—San Diego, La Jolla, California 92093

Received December 17, 1985

The Diels–Alder reactions of 6-methyl-2-cyclohexenone and 2,6-dimethyl-2-cyclohexenone with isoprene and (*E*)-piperylene as well as 2,4-dimethyl-2-cyclohexenone with 1,3-butadiene and (*E*)-piperylene under aluminum chloride catalysis are described. Structure analysis of the adducts and some of their hydrogenation products by NMR spectroscopy is presented. Base-induced isomerization of the octalones and decalones and conformational analysis of the equilibrants have been performed. The syn–anti diastereofacial selectivity of the above and earlier cycloadditions has been interpreted in terms of a unifying stereoelectronic pathway and conformational considerations.

The spatial orientation of the diene and dienophile toward each other determines the stereochemistry of the product of the Diels–Alder reaction. Not only can the disposition of the two reacting species toward each other in the cycloaddition process lead to exo vs. endo isomerism but also syn vs. anti addition may take place. The latter phenomenon manifests itself whenever the plane through the multiple bond system of neither one nor both of the reactants represents a symmetry plane. When the lack of symmetry of one of the reactants, e.g., the dienophile, is due to the presence of a substituent on one face of the π bond system, syn or anti addition would depend on the diene attack occurring on the substituent or opposite side of the dienophile, respectively.[1f] Whereas stereoselectivity of the syn–anti type (i.e., π-facial stereoselectivity or diastereofacial selectivity) has been in the limelight during the last 15 years, difficulties of Diels–Alder adduct isolation and structure elucidation have hampered research in this connection and the majority of the successful studies have involved the use of only rigid unsymmetrical dienes, e.g., inter alia, 1,2,3,4,5-pentachlorocylopentadiene,[3] dienic propellanes,[4] *cis*-hydronaphthalenes,[5] nopadiene,[6] cyclopropano- and cyclopentano-spiro-fused isodicyclopentadienes and their dehydro derivatives,[7] 5,6-bis(deuteriomethylidene)-2-bicyclo[2.2.2]octene,[8] and norbornane- and norbornene-fused cyclopentadienes,[7,9] dimethylfulvenes,[7b,10] furans,[9b,d,h,11] and anthracenes.[12] A limited number of studies have focused on unsymmetrical, conformationally mobile dienes, e.g., cycloheptatriene[13] and some derivatives thereof,[14] cyclooctatetraene,[15] and 4-alkyl-1-vinylcyclohexenes.[16] Finally, a few investigations, mostly directed toward natural products synthesis, have included unsymmetrical, cyclic α,β-unsaturated ketone derivatives as dienophiles and yielded some unconnected stereoselectivity data.[17]

Table I. Aluminum Chloride Catalyzed Diels–Alder Reactions of Dienes 1 with Cyclohexenones 2[a]

reactants	products	product ratios	% anti addition
1a–2b	**3, 4**	1.2:1	55
1b–2a	**5a, 6a, 13**[d]	7.7:15.7:1	35
1b–2c	**5b, 6b**	1.8:1	64
1c–2a	**7, 8, 14**	65:134:1	33
1c–2b	**9a, 10a, 11a, 12a**	4.3:4.4:1.3:1	51
1c–2b[b]	**9a, 10a, 11a, 12a**	5.7:4.2:1:1.5	54
1c–2b[c]	**9a, 10a, 11a, 12a**	4.4:3.5:1:1	54
1c–2c	**9b, 10b, 11b, 12b**	2.5:5:1:1.5	35

[a] Reaction conditions are those presented in Table VII. Reaction temperature, 40 °C. [b] Reaction temperature, 0 °C. [c] Reaction temperature, 75 °C. [d] Another product, probably 8a-*epi*-**6a**, accounts for 2% of the product mixture.

(1) For previous papers, see: (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391. (b) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. (c) Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *Ibid.* **1983**, *48*, 1810. (d) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Ibid.* **1983**, *48*, 2802. (e) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Ferreira, V. F.; Michelotti, E. L.; Porter, B.; Wenkert, E. *Ibid.* **1985**, *50*, 890. (f) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *Ibid.* **1985** *50*, 4686. (g) Angell, E. C.; Fringuelli, F.; Halls, T. D. J.; Pizzo, F.; Porter, B.; Taticchi, A.; Tourris, A. P.; Wenkert, E. *Ibid.* **1985**, *50*, 4691. (h) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *Ibid.* **1985**, *50*, 4696. (i) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1986**, *16*, 245.

(2) (a) Università di Perugia. (b) University of California.

(3) (a) Williamson, K. L.; Li Hsu, Y. F.; Lacko, R.; Youn, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129. (b) Williamson, K. L.; Li Hsu, Y. F. *Ibid.* **1970**, *92*, 7385.

(4) (a) Kalo, J.; Ginsburg, D.; Vogel, E. *Tetrahedron* **1977**, *33*, 1177. (b) Böhm, M. C.; Gleiter, R. *Ibid.* **1980**, *36*, 3209.

(5) Jacobson, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 2579.

(6) (a) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4976. (b) Ashkenazi, P.; Benn, R.; Ginsburg, D. *Helv. Chim. Acta* **1984**, *67*, 583.

(7) (a) Paquette, L. A.; Hayes, P. C.; Charumilind, P.; Böhm, M. C.; Gleiter, R.; Blount, J. F. *J. Am. Chem. Soc.* **1983**, *105*, 3148. (b) Paquette, L. A.; Green, K. E.; Gleiter, R.; Schäfer, W.; Gallucci, J. C. *Ibid.* **1984**, *106*, 8232.

(8) Avenati, M.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1279.

(9) (a) Alder, K.; Flock, F. H.; Janssen, P. *Chem. Ber.* **1956**, *89*, 2689. (b) Sugimoto, T.; Kobuke, Y.; Furukawa, J. *J. Org. Chem.* **1976**, *41*, 1457. (c) Paquette, L. A.; Carr, R. V. C.; Arnold, E.; Clardy, J. *Ibid.* **1980**, *45*, 4907. (d) Paquette, L. A.; Bellamy, F.; Böhm, M. C.; Gleiter, R. *Ibid.* **1980**, *45*, 4913. (e) Paquette, L. A.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *Ibid.* **1980**, *45*, 4922. (f) Paquette, L. A.; Carr, R. V. C.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186, 7218. (g) Paquette, L. A.; Carr, R. V. C. *Ibid.* **1980**, *102*, 7553. (h) Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *Ibid.* **1981**, *103*, 2022. (i) Ermer, O.; Bödecker, C. D. *Helv. Chim. Acta* **1983**, *66*, 943. (j) Bartlett, P. D.; Wu, C. *J. Org. Chem.* **1984**, *49*, 1880. (k) Paquette, L. A.; Green, K. E.; Hsu, L. Y. *Ibid.* **1984**, *49*, 3650.

(10) Paquette, L. A.; Kravetz, T. M.; Böhm, M. C.; Gleiter, R. *J. Org. Chem.* **1983**, *48*, 1250.

(11) (a) Avenati, M.; Hagenbuch, J.-P.; Mahaim, C.; Vogel, P. *Tetrahedron Lett.* **1980**, 3167. (b) Hagenbuch, J.-P.; Vogel, P.; Pinkerton, A. A.; Schwarzenbach, D. *Helv. Chim. Acta.* **1981**, *64*, 1818.

(12) Hayes, P. C.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 1257.

(13) (a) Bellus, D.; Helferich, G.; Weis, C. D. *Helv. Chim. Acta* **1971**, *54*, 463. (b) De Lucchi, O.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1982**, 914.

(14) Goldstein, M. J.; Gevirtz, A. H. *Tetrahedron Lett.* **1965**, 4417.

(15) Avram, M.; Mateescu, G.; Nenitzescu, C. D. *Justus Liebigs Ann. Chem.* **1960**, *636*, 174.

(16) Quin, L. D.; MacDiarmid, J. E. *J. Org. Chem.* **1982**, *47*, 3248.

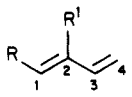
0022-3263/86/1951-2642$01.50/0

Table II. ^{13}C Chemical Shifts of *cis*-Octalones[a]

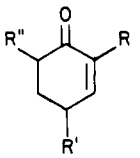
	3	4	5a	5b	6a	6b	7	8	9a	9b	10a	10b	11a	11b	12a	12b
C(1)	215.2	214.5	216.3	216.8	212.5	216.2	214.7	211.8	216.0	216.1	214.0	215.3	215.0	216.1	214.9	216.5
C(2)	37.2	36.3	40.0	39.4	44.8	39.4	45.9	45.9	40.2	44.5	38.1	40.3	37.6	39.5	35.8	39.9
C(3)	34.9	30.0	34.2	34.9	30.9	31.3	30.5	34.0	32.3	33.6	31.0	32.6	35.5	35.3	29.6	29.9
C(4)	29.5	28.0	26.4	28.5	29.7	24.6	25.7	30.0	29.0	28.7	28.2	25.0	29.0	27.9	28.1	24.0
C(4a)	47.0	45.9	36.6	42.4	37.1	40.9	38.7	40.0	45.7	41.2	48.8	43.3	49.6	44.0	40.9	37.2
C(5)	23.6	21.6	34.2	33.2	32.6	33.0	26.6	26.1	23.7	28.7	22.1	27.4	23.9	28.5	22.5	27.5
C(6)	123.2[b]	124.2[b]	131.8	130.5	131.3	130.9	123.5	123.4	122.0	122.3	122.4	122.5	123.5	123.6	122.2	122.4
C(7)	123.8[b]	124.9[b]	117.3	116.5	118.8	119.0	131.2	131.2	130.7	130.3	131.9	131.5	129.8	129.3	132.2	131.7
C(8)	31.9	33.1	24.6	31.8	24.0	32.0	31.8	32.5	37.3	37.0	39.8	39.7	32.7	32.0	32.8	31.6
C(8a)	47.0	48.1	48.0	47.2	47.4	47.0	48.7	53.8	49.5	50.0	51.2	50.8	50.9	51.2	50.6	49.6
2-Me			15.0	15.2	14.5	15.2	16.9	14.2		25.1		14.8		14.8[b]		15.8
4-Me	19.8[c]	18.4							21.2		18.4		19.9		18.3	
6-Me			23.8	23.7	23.5	23.3										
8-Me							18.2	17.7	20.6	16.0	15.9	16.1	14.7	15.2[b]	16.2	16.2
8a-Me	19.9[c]	26.7		19.9		25.9			25.1	21.5	23.1	23.8	14.7	15.1[b]	22.9	20.1

[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b,c] Signals in any vertical column may be interchanged.

The broad study of the acid-catalyzed Diels–Alder reaction of cycloalkenones[1] has included observations of the reactions of 4- and 5-alkyl-2-cyclohexenones with 1,3-butadiene (**1a**), isoprene (**1b**), and (*E*)-piperylene (**1c**)[1f,g] and analysis of the diastereofacial selectivity of these cycloadditions. As an extension of this investigation the reactions of the three dienes with 6-methyl- (**2a**),[18] 2,4-dimethyl- (**2b**),[19] and 2,6-dimethyl-2-cyclohexenone (**2c**)[20] have been examined and the results are presented herewith. The combined data constitute the results of the first systematic study of the behavior of conformationally flexible dienophiles in the Diels–Alder reaction.



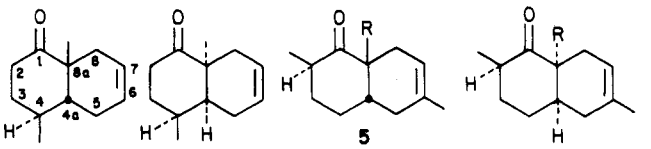
1a, R=R'=H
b, R=H, R'=Me
c, R=Me, R'=H



2a, R=R'=H, R"=Me
b, R=R'=Me, R"=H
c, R=R"=Me, R'=H

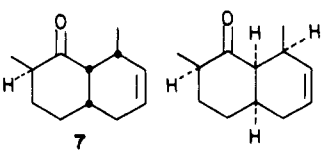
Diels–Alder Reactions and Products

The reactions of the three dienes with the three dienophiles were executed in various diene–dienophile combinations under aluminum chloride catalysis in toluene solution at 40 °C for 3–16 h and led to 80–95% yields of octalones, as shown in Tables I and VII. The stereochemistry of the allylic methyl group of the piperylene-derived products indicated the cycloadditions of the C(2)-unsubstituted ketone **2a** to yield exclusively endo adducts and those of the C(2)-methylated ketones **2b** and **2c** to lead to mixtures of *exo* and *endo* products. The *cis*-octalones were kinetically based Diels–Alder adducts, as shown by the constancy of the product ratios throughout the course of each reaction and the lack of exo–endo isomerization of pure exo products **11a**, **12a**, and **12b** and syn–anti isomerization of pure syn adduct **6b** and anti adducts **5a**, **7**, and **9b** on their exposure to the reaction conditions of the Diels–Alder reaction.

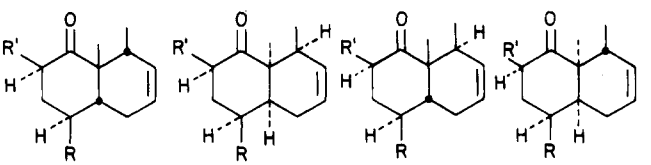


3 **4** **5** **6**

a, R=H;
b, R=Me

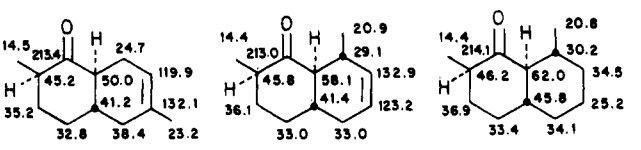


7 **8**

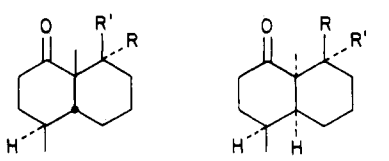


9 **10** **11** **12**

a, R=Me, R'=H; **b**, R=H, R'=Me

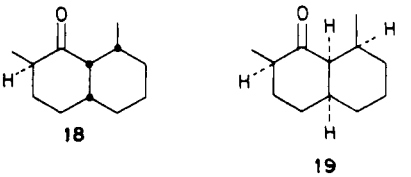


13 **14** **15**



16 **17**

a, R=R'=H; **b**, R=Me, R'=H; **c**, R=H; R'=Me



18 **19**

(17) (a) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722. (b) Harayama, T.; Taketami, M.; Inubushi, Y. *Chem. Pharm. Bull. Jpn.* **1979**, *27*, 730. (c) Grieco, P. A.; Vidari, G.; Ferriño, S. *Tetrahedron Lett.* **1980**, 1619. (d) Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224. (e) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, 1897. (f) Fukumoto, K.; Chihiro, M.; Ihara, M. *J. Chem. Soc., Perkin Trans 1* **1983**, 2569. (g) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252. (h) Boger, D. L.; Mullican, M. D.; Helberg, M. R.; Patel, M. *Ibid.* **1985**, *50*, 1904.

(18) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(19) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(20) Rubotton, G. M.; Juve, H. D., Jr. *J. Org. Chem.* **1983**, *48*, 422.

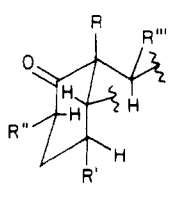
Table III. ^{13}C Chemical Shifts of *cis*-Decalones[a]

	16a	16b	16c	17a	17b	17c	18	19
C(1)	216.3	217.3	216.0	215.9	216.1	215.8	216.6	213.7
C(2)	37.8	39.3	38.3	37.5	36.7	39.1	46.3	46.2
C(3)	34.4	30.8	35.7	29.2	30.1	31.0	29.1	33.1
C(4)	28.9	31.7	28.1	28.8	28.2	28.9	26.2[b]	31.5
C(4a)	48.5	49.3	51.4	50.5	44.1	52.6	42.3	43.7
C(5)	23.3	27.5	22.5	23.1	22.8	22.0	27.9	27.2
C(6)	20.1	19.7	20.5	26.2	20.0	26.5	26.4[b]	26.4
C(7)	21.3	29.7	29.9	22.5	28.3	30.2	28.7	28.8
C(8)	31.3	39.0	32.5	35.4	31.7	43.0	34.9	35.2
C(8a)	48.7	50.8	52.8	49.7	51.9	52.2	49.7	55.0
2-Me							17.1	14.2
4-Me	19.9	18.5	19.6	18.7	19.0	18.9		
8-Me		22.3	16.4		18.0	17.1	19.7	19.7
8a-Me	19.9	25.2	14.1	27.6	24.9	23.6		

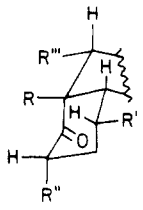
[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Signals may be interchanged.

The structures of the Diels–Alder adducts (**3–12**),[21] the dihydro derivatives (**16–19**),[21] and the trans isomers (**13–15**)[21] were determined by ^{13}C NMR spectroscopy, the carbon shifts of the *cis*-octalones and -decalones being listed in Tables II and III, respectively, and those of the trans compounds appearing on their formulas.

Earlier chemical shift correlations[1f,g] and especially the use of the octalones 4-demethyl-**3** and **11** (R = R′ = H)[1b] as models served as the basis for the shift assignment of octalones **3**, **5b**, **11a**, and **11b** and decalones **16a,c**. The data showed the compounds to posses conformation **20**, a form especially favored by ketones **11a,b** in view of their two equatorial, secondary methyl groups locking the structures into this conformation. The previous carbon shift correlations[1f,g] and the use of the ketones **10** (R = R′ = H) and 4-demethyl-**17a**[1b] as models permitted the shift assignment of octalones **4**, **6b**, **10a**, **10b**, **12a**, and **12b** and decalones **17a–c**. The data revealed all these compounds to prefer conformation **21** (drawn in enantiomeric form with respect to their portrayed configurations, for ease of comparison with conformation **20**, a spatial orientation favored especially by ketones **10a,b**, whose two equatorial, secondary methyl functions anchor this conformation.



20



21

Finally, the δ values of ketones **9a**, **9b**, and **16b** differ enough from those calculated for compounds of either conformation **20** or **21** to preclude the use of the NMR data for rigorous conformational analysis. Whereas these substances might be expected to prefer conformation **21**, the nonbonded repulsions of the two methyl groups in their ketonic rings probably leads to ring distortions away from the normal all-chair conformations.

For the shift assessment of the angularly unmethylated ketones (**5a**, **6a**, **7**, **8**, **18**, and **19**), 2-demethyl-**7**,[1b] 2-demethyl-4α-methyl-**7**,[1g] 2-demethyl-3β-methyl-**18**,[1f] and 2-demethyl-4α-methyl-**18**[1g] served as models. A preference for conformation **21** for the piperylene-derived ketones **7**, **8**, **18**, and **19** could be discerned from the data. The 8-methyl group (oriented axially and in highly unfavorable, nonbonded interaction with C(2) and C(4) in conformation **20**) locks these substances into conformation **21** even in the cases of the α-keto methyl group thereby being forced into an axial orientation. Comparison of the C(4) and C(8a) shifts of ketones **7** and **18** with those of bicycles **8** and **19**, respectively, reveals the γ-effects indicative of the axiality of the 2-methyl group in ketones **7** and **18**. Removal of the 8-methyl group changes the conformational picture. Thus, whereas ketone **6a** prefers conformation **21**, incorporating an equatorial 2-methyl group, its 2-epimer (**5a**) changes into conformation **20**, in order to maintain the equatoriality of its 2-methyl function. Finally, shift assignment and structure analysis of the *trans*-octalones (**13** and **14**) and -decalone (**15**) followed a well-established routine.[1]

The 2-methyl groups of all bicyclic ketones, except for compounds **7**, **9b**, and **18**, show an interesting shift consistency, diagonstic for equatorial α-keto methyl functions. The C_1 units of the trans ketones resonate at 14.4 ± 0.1 ppm and those of the cis ketones of conformation **20** at 15.0 ± 0.2 ppm and of conformation **21** at 14.8 ± 1.0 ppm. The 14–16 ppm shift range appears to reflect the effect of the neighboring carbonyl group on the methyl function in a syn-periplanar relationship thereto, shielding the one-carbon unit by ca. 8 ppm. It is noteworthy that the same effect is exerted by the carbonyl group on the angular methyl function of *cis*-octalones unencumbered by nonbonded interactions with other alkyl groups. Those ketones residing in conformation **20** (i.e., those placing their angular methyl groups into a syn-periplanar orientation with respect to the carbonyl function) exhibits an angular methyl shift of 19.8 ± 0.3 ppm,[1] while the value of the ketones of conformation **21** is 24.3 ± 2.2 ppm.[1] The introduction of an equatorial 8-methyl group shields the angular methyl function of ketones of conformation **20** (14.9 ± 1.0 ppm) and those of conformation **21**, albeit only minimally (23.5 ± 2.0 ppm).

The presence of the Lewis acid in the media of the catalyzed Diels–Alder reactions of cycloalkenones make the cis-bicyclic, ketonic products vulnerable to isomerization at their α-keto carbon centers, e.g., the conversion of angularly unsubstituted compounds into their trans isomers.[1] The possibility of structure change of the Diels–Alder adducts makes interpretation of the results of the cycloadditions of 6-methyl-2-cyclohexenone (**2a**) especially difficult in view of the availability of two sites (carbons 2 and 8a) in the products for stereochemical alteration. Thus not only are the *trans*-octalones products of isomerization but the origin of even the *cis*-octalones is suspect as a consequence of their possible acid-induced interconversion. However, it was possible to prove that

(21) Whereas the pictorialization of the racemic *cis*-octalones (and hence of the the other bicyclic ketones) appears to be based on an arbitrary choice of absolute configurations, the formulas are designed to facilitate the visualization of the syn and anti diene–dienophile relationships from which the Diels–Alder adducts are derived.

Table IV. Equilibrium Constants for C(2) and C(8a) Epimer Pairs of Octalones and Decalones[a]

	K
C(2) Isomer Pair	
5a–6a	5
5b–6b	0.1
7–8	0.2–1.5[b]
9b–10b	5
11b–12b	0.01
18–19	15–80[b]
C(8a) Isomer Pair	
5a–13	60
7–14	≥90
18–15	≥200

[a] In ethanol at 22 °C, based on GC analysis. *K* is the trans ketone/cis ketone ratio with reference to the C(2)-methyl C(8a)-substituent relationship in the C(2) isomer pairs and the bridgehead substituents in the C(8a) isomer pairs. [b] The range is due to the low percentage presence of the compounds at equilibrium.

the *cis*-octalone pairs **5a–6a** and **7–8** were primary products of the reactions with isoprene (**1b**) and (*E*)-piperylene (**1c**), respectively, when it was shown that exposure of ketones **5a** and **7** to the conditions of the Diels–Alder reaction left their C(2) center unaffected and changed their C(8a) site only up to ca. 2%. Furthermore, these results revealed that the *trans*-octalones **13** (4% of the product mixture of the first reaction) and **14** (0.5% of the product mixture of the second reaction) were derived exclusively from *cis*-octalones **5a** and **7**, respectively.

The possiblity of C(2) isomerization beclouded also the cycloadditions of 2,6-dimethyl-2-cyclohexenone (**2c**). However, the absence of structure change on exposure of ketone **6b**, a product of the reaction with isoprene (**1b**), and octalones **9b** and **12b**, products of the reaction with (*E*)-piperylene (**1c**), to the conditions of the Diels–Alder reaction showed these compounds to be primary Diels–Alder products. Thus, luckily, the results of the cycloadditions of 6-methylated cyclohexenones were completely interpretable. Since the reactions of cyclohexenones with C(6)-alkyl groups more bulky than methyl functions could be anticipated to lead to more product C(2) isomerization and hence to mixtures of products whose origin would be difficult to ascertain, the present study was limited to the use of only 6-methyl-2-cyclohexenones despite earlier investigations on 4- and 5-alkyl-2-cyclohexenones[1f,g] having utilized methyl, isopropyl, and *tert*-butyl derivatives.

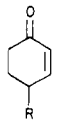
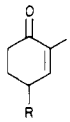
With a fair number of 1-octalones and 1-decalones in hand it was of interest to determine their stabilities with respect to cis–trans or C(2) isomerization. Equilibria were established in ethanolic sodium ethoxide solution, and the results are presented in Table IV.

The equilibration of the angularly unsubstituted octalones (i.e., the **5a–6a–13** and **7–8–14** ketone triads) and decalones (i.e., the **18–19–15** triad) gave four-component mixtures in which a trans-bicycle (**13**, **14**, and **15**, respectively) was the major product (90%, 99%, and 93%, respectively) and the other trans compound appeared in trace, unisolable amount. The equilibrium data for the C(2) isomerizations are in accord with the conformational change attending the alteration of the C(2) sterochemistry (vide supra).

Syn–Anti Diasteroisomerism

Correlation of the stereochemical data from the present and previous studies[1f–h] in terms of the syn–anti diastereoselection associated with the Diels–Alder reaction of variously substituted 2-cyclohexenones leads to the picture presented in Table V. Inspection of the C(2)-unsubstituted 2-cyclohexenone section of the latter reveals that (a)

Table V. Syn–Anti Diastereoselectivity[a]

	dienophile				dienophile			
		R				R		
diene		Me	*i*-Pr	*t*-Bu		Me	*i*-Pr	*t*-Bu
1a		55	67	100		55		
1b		90	91	100		85[b]		
1c		49	61	100		51		
1a		96	92	97		100[c]	>90[d]	
1b		97	92	91			90[d]	
1c		96	98	97			95[d]	
1a								
1b		35				64		
1c		33				35		

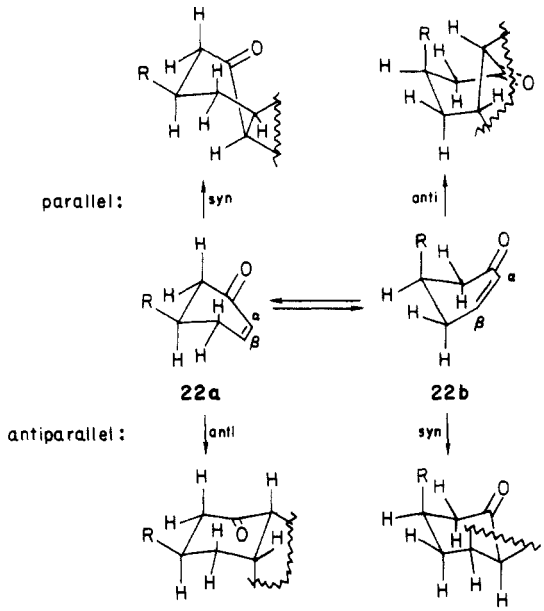
[a] Expressed as % of anti Diels–Alder adducts. [b] Reference 23. [c] From ref 24. [d] R = C(Me)=CH_2.

among the C(4)-substituted dienophiles anti selectivity increases from methyl to *tert*-butyl compounds in the reactions with 1,3-butadiene (**1a**) and (*E*)-piperylene (**1c**) and is high for all substituents in the reactions with isoprene (**1b**), (b) among the C(5)-substituted enones anti selectivity is high for all substituents in all reactions, and (c) among the C(6)-methylated ketones syn selectivity is prevalent for reactions with either (*E*)-piperylene (**1c**) or isoprene (**1b**). Furthermore, the cycloaddition behavior of the 2-methyl-2-cyclohexenones is nearly the same as that of their C(2)-unsubstituted relatives. Finally, it is worthy of note that the diastereoselectivity is nearly independent of the reaction temperature.[22]

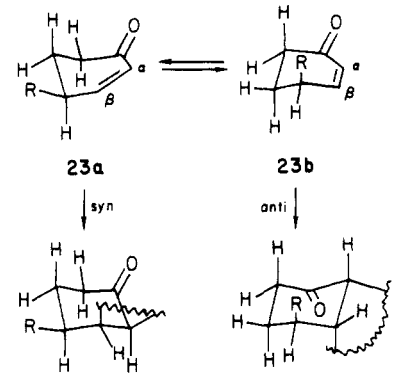
It is accepted generally that [4 + 2] cycloadditions of reactants of low or medium polarity exhibiting minimal electronic and steric effects in solvents of low dielectric constant take place through a one-step mechanism.[25] To explain the diastereoselectivity of these reactions, various hypotheses have been advanced focusing on the following factors: (a) attractive van der Waals–London interactions,[3a,26a] (b) attractive polarizability effects,[26b] (c) attractive or repulsive dipole effects,[3,4b,26b] (d) attractive or repulsive steric effects,[17d,26c–f] (e) entropy and/or enthalpy effects,[26g] (f) thermodynamic control (isomer adduct stabilities),[11b] (g) conformational effects,[16,26h] (h) nonequivalent extension of the π-electron densities (π-anisotropy),[9b,26i] (i) π-orbital distortion,[26j] (j) stabilizing secondary orbital interactions,[26a,k] and (k) σ–π interaction in frontier orbital pairs.[26l,m] Whereas one or more of these parameters

(22) This fact was verified for several reactions. For a striking example see the data on the **1c–2b** reaction at three temperatures in Table I.
(23) Minuti, L.; Pizzo, F.; unpublished observations.
(24) Harayama, T.; Cho, H.; Inubushi, Y. *Chem. Pharm. Bull. Jpn.* **1977**, *25*, 2273.
(25) (a) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70. (b) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157. (c) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523. (d) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
(26) (a) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227. (b) Avenati, M.; Vogel, P. *Helv. Chim. Acta.* **1982**, *65*, 204. (c) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537. (d) Hoffmann, R.; Levin, C. C.; Moss, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 629. (e) Kobuke, Y.; Fueno, T.; Furukawa, J. *Ibid.* **1970**, *92*, 6548. (f) Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *Ibid.* **1972**, *94*, 3633. (g) Mahaim, C.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 866. (h) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Mareda, J.; Muller, P. H.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4974. (i) Ito, S.; Kakehi, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1869. (j) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Roseboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482. (k) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301. (l) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328. (m) *Stereochemistry and Reactivity of Systems Containing π Electrons*; Watson, W. H., Ed.; Verlag Chemie International: Deerfield, FL, 1983. (n) Dewar, M. J. S.; Pierini, A. *J. Am. Chem. Soc.* **1984**, *106*, 203.

Scheme I



Scheme II



may be of importance for any one diene–dienophile combination, caution must be exercised in the adoption of any hypothesis in view of the difference of activation energy for incipient stereoisomers often being less than 1 kcal/mol.[27]

The interpretation of the stereochemistry results of the present and previous studies[1f-h] of the Diels–Alder reactions of 2-cyclohexenones requires the adoption of several, fundamental assumptions. (a) The ketones exist in an envelope conformation in which the carbonyl oxygen and all ring carbons, except C(5), are coplanar (e.g., conformations **22** for 5-alkyl-2-cyclohexenone).[28] (b) The aluminum chloride catalyst complexes the carbonyl oxygen[29] and the complexation influences minimally the conformational equilibrium of the ketones[28a,b,30] and does not affect the reaction mechanism.[3b,29,31] (c) The Curtin–Hammett principle is applicable, the energy of activation of the Diels–Alder reaction (ca. 16–18 kcal/mol[25d,32])being larger than the energy barrier of conformational interconversion of the 4-, 5-, or 6-alkylated 2-cyclohexenones (up to 5–7 kcal/mol[33]), making the cycloaddition product ratio not solely dependent on the enone conformer population ratio. (d) The cycloadditions of the α,β-unsaturated ketones involve a one-step mechanism[25] with an unsymmetrical, nonsynchronous transition state[25,26e,n,35] in which σ-bond formation with the β-carbon is in advance of that at the α-carbon site.[25c,d,26m,n] (e) In analogy with the conformational constraints of carbanion interaction with the β-carbon center in nucleophilic additions of 2-cyclohexenones[36] the diene–dienophile interaction at the same site prefers (in the absence of steric interference) an axial diene approach antiparallel to the pseudoaxial bond at neighboring C(4), thereby creating an incipient fused cyclohexenone in half-chair conformation, over parallel approach producing the same ring in initial half-boat form (implying a transition state in which the dienophile unit possesses a nearly fully formed sp^3-hybridized β-carbon center and a nearly unchanged trigonal α-carbon site) (Scheme I).[26h,34a,37]

5-Alkyl-2-cyclohexenones 22. Scheme I illustrates the cycloaddition chemistry for these unsaturated ketones. The conformer mixture of the starting ketones **22** includes an axially alkylated equilibrant **22b**, whose equilibrium concentration may be appreciable in view of the lack of any energetically unfavorable 1,3-diaxial interaction of its side chain. However, during the reactions under stereoelectronic control (i.e., the "antiparallel" processes) this conformer can be expected to be considerably less reactive than its companion **22a** as a result of the strong 1,3-diaxial involvement of its 5-alkyl group with the developing bond at the β-carbon site and the general, steric crowding of the incoming diene (in endo additions) by the C(5) axial substituent. These arguments are in accord with the high, albeit not exclusive, anti diastereoselectivity of all Diels–Alder reactions of enones **22** (Table V).[1f]

4-Alkyl-2-cyclohexenones 23. The high preference of methyl groups within cyclohexane chairs for equatorial orientation (the equatorial/axial ratio for methylcyclohexane being ca. 20 at room temperature)[34a] drops with an increase of sp^2-hybridized ring carbons,[38a] reaching the

(27) Berson, J. A.; Remanick, A.; Mueller, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 5501.

(28) (a) Paris, C.; Torri, G.; Elegant, L.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1974**, 1450. (b) Torri, J.; Azzaro, M. *Ibid.* **1974**, 1633. (c) Manley, S. A.; Tyler, J. K. *Chem. Commun.* **1970**, 382. (d) Arnaud, C.; Huet, J. *Bull. Soc. Chim. Fr.* **1971**, 4525. (e) Barieux, J.-J.; Gore, J.; Richer, J.-C. *Ibid.* **1974**, 1020. (f) Barieux, J.-J.; Gore, J.; Subit, M. *Tetrahedron Lett.* **1975**, 1835.

(29) Anh, N. T.; Penne, J. S. *Tetrahedron* **1973**, *29*, 3259 and references cited therein.

(30) Torri, J.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1978**, 238.

(31) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *6*, 16. (b) Kojima, T.; Inukai, T. *J. Org. Chem.* **1970**, *35*, 1342; **1971**, *36*, 924. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(32) Whereas the activation energy of reactions catalyzed by aluminum chloride is lower (Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 872), the argument remains unaffected.

(33) Extrapolated from the low-temperature barriers of 10.3, ca. 6, 5.3, and 5.2-6.2 kcal/mol for cyclohexane,[34a] cyclohexanone,[34a] cyclohexene,[34b] and C(4)-substituted cyclohexenes,[34c] respectively.

(34) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1965. (b) Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Weinheim, 1978. (c) Jensen, F. R.; Bushweller, C. H. *Alicycl. Chem.* **1971**, *3*, 190.

(35) Liu, M. T. H.; Schmidt, C. *Tetrahedron* **1971**, *27*, 5289.

(36) (a) Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, 1269. (b) Chamberlain, P.; Whitham, G. *J. Chem. Soc., Perkin Trans 2* **1972**, 130. (c) Nagata, W.; Yoshioka, M.; Terasawa, T. *J. Am. Chem. Soc.* **1972**, *94*, 4672. (d) Hoye, T. R.; Magee, A. S.; Rosen, R. E. *J. Org. Chem.* **1984**, *49*, 3224.

(37) (a) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758. (b) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (c) For ease of pictorialization Scheme I illustrates the cycloaddition processes for only one cyclohexenone (i.e. the 5-alkyl case), for ketones instead of aluminum chloride complexes, and in terms of product structures instead of transition-state pictures.

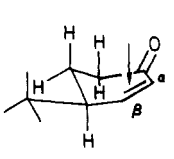
(38) (a) The room temperature equatorial/axial ratios for 4-methylcyclohexanone[39a] and 4-methylcyclohexene[39b] are 7 and 4.2, respectively. (b) At 40 °C.[28a,b] (c) The absence of one of the two, usual 1,3-diaxial interactions of the axial substituent of conformer **23b** (the "3-alkyl ketone effect")[34a] and the remaining one being between a pseudoaxial alkyl group and a pseudoaxial hydrogen (the "4-alkyl ketone effect")[34a] makes this conformer present at equilibrium to a larger extent than in a saturated cyclohexane chair.

Table VI. Syn–Anti and Exo–Endo Diastereoselectivity for the Reactions of 2-Methyl-2-cyclohexenones with (*E*)-Piperylene

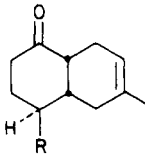
	product yield, %				anti/syn product ratio		% of total product yield	
	syn		anti					
	exo	endo	exo	endo	exo	endo	exo	endo
1c–2b	9	40	12	39	1.3	1	21	79
1c–2c	15	50	10	25	0.7	0.5	25	75

low equatorial/axial ratio of 4 for 4-methyl-2-cyclohexenone (**23**, R = Me).[38b] If it be assumed that this phenomenon applies also to 4-isopropyl- (**23**, R = *i*-Pr) and 4-*tert*-butyl-2-cyclohexenone (**23**, R = *t*-Bu) the energy content of their conformers with axial substituents would be lower than that of the related cyclohexanes,[38c] making their presence felt in the conformational equilibrium. Thus both conformers **23a** and **23b** become important in considering the diastereoselectivity of the reactions of the 4-alkyl-2-cyclohexenones **23**.

As Scheme II illustrates, "antiparallel" operations on conformers **23a** and **23b** give syn and anti products, respectively. In the reactions of 4-methyl-2-cyclohexenone (**23**, R = Me) with 1,3-butadiene (**1a**) and (*E*)-piperylene (**1c**) the predominant conformer (**23a**) would be expected to be less reactive than its coequilibrant in view of nonbonded 1,2-interaction of the developing axial bond at the β-carbon site with the 4-methyl group in the syn addition of conformer **23a**. The opposing forces of the position of the conformational equilibrium and the conformer reactivity appear to balance each other enough to make the reactions diastereounselective (Table V). In the case of the reactions of the 4-isopropyl compound (**23**, R = *i*-Pr) the above 1,2-interaction increases in importance, yielding an anti product preference (the anti–syn ratio being ca. 2; Table V). Finally, 4-*tert*-butyl-2-cyclohexenone (**23**, R = *t*-Bu) exhibits so strong an aversion to the 1,2-interaction, in this instance the equivalent of a 1,3-diaxial interaction with a methyl group within a cyclohexane chair (see formula **24**), as to overcome the effect of the low concentration of conformer **23b** (R = *t*-Bu) at equilibrium and thus reveals complete anti diastereoselectivity (Table V).



24

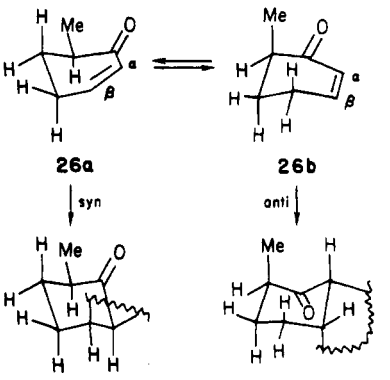


25

The reactions of the 4-alkyl-2-cyclohexenones (**23**) with isoprene (**1b**) reveal uniformly high anti diastereoselectivity (Table V). Since the regiochemistry is such as to lead to products of structure type **25**, it can be expected that the diene's methyl group offers an additional destabilizing factor for the transition state of syn addition, i.e., its proximity to the 4-alkyl group (in an endo addition[40]).

6-Methyl-2-cyclohexenone (2a, 26). Scheme III portrays the stereoelectronically required paths of the reactions of 6-methyl-2-cyclohexenone (**26**) with isoprene (**1b**) and (*E*)-piperylene (**1c**). Whereas in the starting ketone

Scheme III



26a **26b**

the conformer with the equatorial methyl group (**26a**) is favored at equilibrium,[41] the two conformers **26a** and **26b** can be expected to be of comparable reactivity in view of the absence of steric interference by alkyl groups in either equilibrant toward the axial carbon–carbon bond formation at the β-carbon site. Hence syn addition is favored kinetically for both reactions (Table V).

2-Methyl-2-cyclohexenones. The syn–anti diastereoisomerism of Diels–Alder reactions is accompanied often by exo–endo diastereoisomerism.[42] Whereas the reactions of the C(2)-unsubstituted 2-cyclohexenones (vide supra) had involved only endo addition, the introduction of an α-methyl group on the α,β-unsaturated ketone nucleus has resulted in the formation of both exo and endo products.[43] This phenomenon was evident from the results of the reactions with (*E*)-piperylene (**1c**) and, by analogy, was assumed to be valid for the cycloadditions with 1,3-butadiene (**1a**) and isoprene (**1b**) also, especially in view of the observation of both exo and endo product formation in the reaction of carvone (5-isopropenyl-2, R = Me, R′ = R″ = H) with (*E*)-2-methyl-1,3-pentadiene (4-methyl-1, R = H, R′ = Me). The amount of exo addition (20–25%) appears to be nearly independent of the position of a methyl substituent on the diene (the aformentioned reaction of carvone giving 20% of exo product), the presence of an alkyl substituent on the dienophile (2-methyl-2-cyclohexenone itself yielding 30% of exo product) and the position of this alkyl group (Table VI). Furthermore, the presence of the 2-methyl function on the 2-cyclohexenone unit appears to have little influence on the syn–anti diastereoselectivity (Table V) and the anti/syn product ratio remains nearly the same for both exo and endo ad-

(39) (a) Edgard, M. T.; Barth, G.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2680. (b) Fernandez-Gomez, F.; Lysenkov, V. I.; Ulyanova, O. D.; Pertin, Y. A.; Bardyshev, I. I. *Zh. Fiz. Khim.* **1977**, *51*, 2710; *Chem. Abstr.* **1978**, *88*, 21988.

(40) Exo addition cannot be invoked, since for such a process much more syn product (especially with the 4-methyl and 4-isopropyl enones) should have been formed, and the results of the reactions of 6-methyl-2-cyclohexenone could not be justified easily.

(41) At first glance, this equilibrium might be affected by the presence of the Lewis acid catalyst, if it were assumed that complexation of the ketone with aluminum chloride leads to an oxygen–aluminum bond system syn to C(6), thus forcing the methyl group at this center into an axial conformation. However, an exhaustive study[30] of the structure of 2-cyclohexenone–trifluoroborane complexes has revealed that in dichloromethane-d_2 solution the C(3)-unsubstituted compounds are ca. 1:1 syn–anti isomer mixtures and the 2- or 6-methylated enones have their boron attachments oriented anti to the methyl groups.

(42) For a discussion of exo–endo diastereoselectivity, see: Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.*, see following paper in this issue.

(43) The presence of the 2-methyl group appears not to affect the conformational equilibria.[28b]

Table VII. Reaction Conditions of the Diels–Alder Reactions of Dienes 1 with 2-Cyclohexenones 2[a]

reactants	diene/ketone[b]	$AlCl_3$/ketone[b]	ketone concn, M	reaction temp, °C	reaction time, h	product yield, %[c]
1a–2b	6	0.9	0.2	40	16	95
1b–2a	9	0.25	0.1	40	3	80
1b–2c	6	0.25	0.1	40	8	94
1c–2a	3	0.25	0.1	40	5	95
1c–2b	3	0.25	0.2	40	6	95
1c–2c	3	0.25	0.1	40	8	92

[a] Complexation time—40 min; complexation temperature—22 °C.[1b] [b] Ratio of equivalents. [c] GC-based yields.

dition (Table VI). The last fact indicates clearly that the reactions leading to exo products also follow the "axial antiparallel" operation at the enone β-carbon site.

In conclusion it can be stated, that the above survey of a large number of diverse, catalyzed Diels–Alder reactions of 2-cyclohexenones has shown that mere consideration of steric factors is insufficient to explain the diastereofacial selectivity of the cycloaddition processes. Instead, it has been necessary to invoke stereoelectronic control in the transition state of the diene–dienophile interaction and call upon conformational analysis for interpretation of the results. It is hoped that the ideas outlined above will aid in the prediction of product stereochemistry for the Diels–Alder reactions of conformationally mobile and, possibly, polychiral diene and/or dienophile substrates in the future.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared spectra of carbon tetrachloride solutions were recorded on a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra were observed on carbon tetrachloride solutions, containing Me_4Si as internal standard (δ 0), on JEOL JNM-60 HI and Varian EM-390 spectrometers. The ^{13}C NMR spectra of $CDCl_3$ solutions were taken on a Nicolet NT-200, wide-bore, broad-band spectrometer, operating with an Oxford magnet at 50.31 MHz in the Fourier transform mode. The carbon shifts on formulas **13–15** are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. GC analyses were performed on Carlo Erba HRGC-5160 and Hewlett-Packard 5880 A chromatographs with 50-m (0.2 mm diameter) Carbowax 20 M and 25- and 50-m (0.2 mm diameter) SE-30 bonded phase capillary columns, an "on-column" injection system (internal standards: *p*-methoxy- and *p*-chloroacetophenone), and hydrogen as the carrier gas. Absorption chromatography was carried out on 230 mesh Merck silica gel or 4:1 silica gel–silver nitrate columns (elution with pentane–ether gradients). All solid Diels–Alder adducts were crystallized from pentane and the (2,4-dinitrophenyl)hydrazones from 95% ethanol.

Diels–Alder Reactions. The reactions and their workup followed a previous prescription,[1b] and the conditions are detailed in Table VII. The octalones **13** and **14**, obtained in Diels–Alder reactions in low yield (Table I), were isolated in larger quantity for purpose of full characterization by base-induced isomerization of adducts **5a** or **6a** and **7** or **8**, respectively (Table IV).

Octalone 3: IR 3020 (w, olefinic CH), 1710 (s, C=O), 1680 (w, C=C) cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 7 Hz, Me), 1.07 (s, 3, Me), 5.60 (m, 2, olefinic Hs). The (2,4-dinitrophenyl)hydrazone: mp 146–147 °C. Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.15; H, 6.25; N, 15.56.

Octalone 4: IR 3030 (w, olefinic CH), 1710 (s, C=O), 1670 (w, C=C) cm^{-1}; ^1H NMR δ 0.98 (d, 3, J = 7 Hz, Me), 1.30 (s, 3, Me), 5.47 (m, 2, olefinic Hs). The (2,4-dinitrophenyl)hydrazone: mp 162–163 °C. Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.76; H, 6.17; N, 15.51.

Octalone 5a: IR 3019 (w, olefinic CH), 1712 (s, C=O) cm^{-1}; ^1H NMR δ 0.98 (d, 3, J = 7 Hz, Me), 1.65 (s, 3, Me), 5.28 (br s, 1, olefinic H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.67; H, 10.14.

Octalone 5b: mp 27–28 °C; IR 3018 (w, olefinic CH), 1705 (s, C=O), 1663 (w, C=C) cm^{-1}; ^1H NMR δ 0.96 (d, 3, J = 7 Hz, Me), 1.00 (s, 3, Me), 1.66 (s, 3, Me), 5.25 (br s, 1, olefinic H). The (2,4-dinitrophenyl)hydrazone: mp 197–198 °C. Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.26; H, 6.51; N, 15.05. Found: C, 61.25; H, 6.54; N, 14.95.

Octalone 6a: IR 3040 (w, olefinic CH), 1717 (s, C=O), 1680 (w, C=C) cm^{-1}; ^1H NMR δ 0.97 (d, 3, J = 7 Hz, Me), 1.61 (s, 3, Me), 5.23 (br s, 1, olefinic H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.50; H, 10.16.

Octalone 6b: IR 1710 (s, C=O) cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 7 Hz, Me), 1.23 (s, 3, Me), 1.60 (s, 3, Me), 5.20 (br s, 1, olefinic H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.50. Found: C, 80.95; H, 10.40.

Octalone 7: mp 25–26 °C; IR 3023 (w, olefinic CH), 1715 (s, C=O), 1655 (w, C=C) cm^{-1}; ^1H NMR δ 1.15 (d, 3, J = 7 Hz, Me) 1.18 (d, 3, J = 7 Hz, Me), 5.44 (s, 2, olefinic Hs). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.75; H, 10.16.

Octalone 8: IR 3032 (w, olefinic CH), 1716 (s, C=O), 1665 (w, C=C) cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 6 Hz, Me), 1.16 (d, 3, J = 7 Hz, Me), 5.42 (s, 2, olefinic Hs). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.87; H, 10.17.

Octalone 9a: IR 3022 (w, olefinic CH), 1705 (s, C=O), 1662 (w, C=C) cm^{-1}; ^1H NMR δ 0.93 (d, 3, J = 7 Hz, Me), 1.02 (d, 3, J = 7 Hz, Me), 1.15 (s, 3, Me), 5.46 (m, 2, olefinic Hs). The (2,4-dinitrophenyl)hydrazone: mp 188–189 °C. Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.26; H, 6.51; N, 15.05. Found: C, 61.53; H, 6.38; N, 14.96.

Octalone 9b: IR 3020 (w, olefinic CH), 1700 (s, C=O), 1662 (w, C=C) cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 6 Hz, Me), 1.06 (d, 3, J = 7 Hz, Me), 1.17 (s, 3, Me), 5.52 (m, 2, olefinic Hs). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.50. Found: C, 80.95; H, 10.45.

Octalone 10a: IR 3022 (w, olefinic CH), 1714 (s, C=O), 1665 (w, C=C) cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 7 Hz, Me), 1.20 (d, 3, J = 7 Hz, Me), 1.40 (s, 3, Me), 5.33 (s, 2, olefinic Hs). The (2,4-dinitrophenyl)hydrazone: mp 195–196 °C. Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.26; H, 6.51; N, 15.05. Found: C, 60.95; H, 6.46; N, 15.04.

Octalone 10b: IR 3020 (w, olefinic CH), 1715 (s, C=O), 1655 (w, C=C) cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 7 Hz, Me), 1.17 (d, 3, J = 7 Hz, Me), 1.38 (s, 3, Me), 5.38 (m, 2, olefinic Hs). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.50. Found: C, 80.95; H, 10.47.

Octalone 11a: mp 25–26 °C; IR 3020 (w, olefinic CH), 1710 (s, C=O), 1655 (w, C=C) cm^{-1}; ^1H NMR δ 0.75 (d, 3, J = 7 Hz, Me), 0.90 (s, 3, Me), 0.93 (d, 3, J = 6 Hz, Me), 5.33 (m, 2, olefinic Hs). The (2,4-dintrophenyl)hydrazone: mp 186–187 °C. Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.26; H, 6.51; N, 15.05. Found: C, 60.92; H, 6.40; N, 14.98.

Octalone 11b: IR 3020 (w, olefinic CH), 1708 (s, C=O), 1658 (w, C=C) cm^{-1}; ^1H NMR δ 0.77 (d, 3, J = 7 Hz, Me), 0.92 (s, 3, Me), 0.97 (d, 3, J = 6 Hz, Me), 5.40 (m, 2, olefinic Hs). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.50. Found: 81.00; H, 10.52.

Octalone 12a: mp 27–28 °C; IR 3023 (w, olefinic CH), 1712 (s, C=O), 1670 (w, C=C) cm^{-1}; ^1H NMR δ 0.83 (d, 3, J = 7 Hz, Me), 1.00 (d, 3, J = 7 Hz, Me), 1.17 (s, 3, Me), 5.40 (m, 2, olefinic Hs). The (2,4-dinitrophenyl)hydrazone: mp 160–161 °C. Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.26; H, 6.51; N, 15.05. Found: C, 61.47; H, 6.44; N, 15.15.

Octalone 12b: IR 3020 (w, olefinic CH), 1712 (s, C=O), 1656 (w, C=C) cm^{-1}; ^1H NMR δ 0.88 (d, 3, J = 7 Hz, Me), 1.02 (d, 3, J = 7 Hz, Me), 1.10 (s, 3, Me), 5.43 (m, 2, olefinic Hs). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.50. Found: C, 81.05; H, 10.37.

Octalone 13: mp 49–50 °C; IR 3040 (w, olefinic CH), 1715 (s, C=O) cm^{-1}; ^1H NMR δ 0.98 (d, 3, J = 7 Hz, Me), 1.62 (s, 3, Me), 5.33 (br s, 1, olefinic H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.52; H, 10.25.

Octalone 14: mp 56–57 °C; IR 3021 (w, olefinic CH), 1715 (s, C=O), 1656 (w, C=C) cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 6 Hz, Me), 1.01 (d, 3, J = 6 Hz, Me), 5.44 (br s, 2, olefinic Hs). The (2,4-

dinitrophenyl)hydrazone: mp 169-170 °C. Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.10; H, 6.15; N, 15.60.

Hydrogenation of the Octalones. A mixture of 200 mg of octalone and 20 mg of platinum oxide in 10 mL of dry ethanol was hydrogenated at room temperature and atmospheric pressure and the reaction terminated upon the consumption of an equimolar amount of hydrogen. The workup followed normal procedure.

Decalone 15: IR 1714 (s, C=O) cm^{-1}; ^1H NMR δ 0.88 (d, 3, J = 6 Hz, Me), 0.95 (d, 3, J = 6 Hz, Me). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.70; H, 11.15.

Decalone 16a: IR 1710 (s, C=O) cm^{-1}; ^1H NMR δ 0.97 (d, 3, J = 7 Hz, Me), 1.16 (s, 3, Me). The (2,4-dinitrophenyl)hydrazone: mp 147-148 °C. Anal. Calcd for $C_{18}H_{24}O_4N_4$: C, 59.98; H, 6.71; N, 15.54. Found: C, 60.04; H, 6.80; N, 15.46.

Decalone 16b: IR 1710 (s, C=O) cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 6 Hz, Me), 1.10 (d, 3, J = 7 Hz, Me), 1.25 (s, 3, Me). The (2,4-dinitrophenyl)hydrazone: mp 140-142 °C. Anal. Calcd for $C_{19}H_{26}O_4N_4$: C, 60.93; H, 7.01; N, 14.96. Found: C, 60.42; H, 6.99; N, 14.90.

Decalone 17a: IR 1710 (s, C=O) cm^{-1}; ^1H NMR δ 0.91 (d, 3, J = 7 Hz, Me), 1.15 (s, 3, Me). The (2,4-dinitrophenyl)hydrazone: mp 176-177 °C. Anal. Calcd for $C_{18}H_{24}O_4N_4$: C, 59.98; H, 6.71; N, 15.54. Found: C, 59.98; H, 6.70; N, 15.56.

Decalone 17b: IR 1710 (s, C=O) cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 7 Hz, Me), 1.10 (s, 3, Me), 1.33 (s, 3, Me). The (2,4-dinitrophenyl)hydrazone: mp 198-199 °C. Anal. Calcd for $C_{19}H_{26}O_4N_4$: C, 60.93; H, 7.01; N, 14.96. Found: C, 60.64; H, 6.95; N, 14.90.

Decalone 18: mp 28-29 °C; IR 1707 (s, C=O) cm^{-1}; ^1H NMR δ 1.10 (d, 3, J = 7 Hz, Me), 1.20 (d, 3, J = 7 Hz, Me). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.80; H, 11.12.

Decalone 19: mp 25-26 °C; IR 1715 (s, C=O) cm^{-1}; ^1H NMR δ 0.93 (d, 3, J = 7 Hz, Me), 1.10 (d, 3, J = 6 Hz, Me). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.75; H, 11.17.

Epimerization of Diels-Alder Adducts. A 0.1 M solution (6 mL) of sodium ethoxide in dry ethanol was added to a solution of 40 mg of cis bicyclic ketone in 8 mL of absolute ethanol under nitrogen and the mixture stirred at 22 °C for a length of time needed to establish equilibrium (as monitored by GC analysis).

Acknowledgment. F.F., F.P., and A.T. thank the Consiglio Nazionale delle Ricerche and the Ministero Pubblica Istruzione for financial support of the work in Perugia. A.T. and E.W. are indebted to NATO for grant (257.81) support.

Diels-Alder Reactions of Cycloalkenones. 10. Endo-Exo Diastereoselectivity of 2-Cyclohexenones[1]

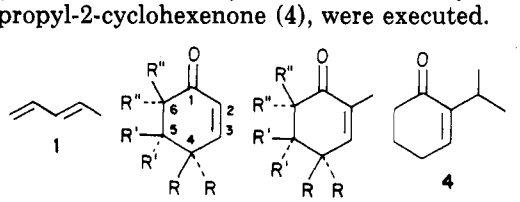
E. Charles Angell,[2b] Francesco Fringuelli,*[2a] Lucio Minuti,[2a] Ferdinando Pizzo,[2a] Barry Porter,[2b] Aldo Taticchi,*[2a] and Ernest Wenkert*[2b]

Dipartimento di Chimica, Università degli Studi, 06100 Perugia, Italy, and Department of Chemistry (D-006), University of California—San Diego, La Jolla, California 92093

Received December 17, 1985

The Diels-Alder reactions of (*E*)-piperylene with 5,5-dimethyl-, 2,4,4-trimethyl-, 2,5,5-trimethyl-, 2,6,6-trimethyl-, and 2-isopropyl-2-cyclohexenone under aluminum chloride catalysis are described. Structure analysis of the adducts and some of their hydrogenation products by NMR spectroscopy is presented. The endo-exo diastereoselectivity of the above and earlier cycloadditions has been interpreted.

It has been known for some time that the Diels-Alder reactions of cyclopentadiene with acrolein, methyl vinyl ketone, and methyl acrylate lead preponderantly to endo products and that the endo-exo product ratio decreases seriously when the dienophiles are changed into methacrolein, methyl propenyl ketone, and methyl methacrylate, respectively.[3] A similar α-methyl effect was noticed during the broad study of the acid-catalyzed Diels-Alder reactions of cycloalkenones and (*E*)-piperylene (1), nearly exclusive endo addition being associated with C(2)-unsubstituted 2-cyclohexenones[1,4] but both endo and exo adducts resulting from reactions of 2-methyl-2-cyclohexenones.[1,4a,5] After a careful analysis of the diastereofacial selectivity of the cycloadditions of the cyclohexenones[1] it became of interest to examine their endo-exo diastereoselectivity, especially from the points of view of its dependence on conformational effects and the substitution pattern of the saturated ring carbons. Prior to consideration of the issue of diastereoisomerism the following additional Diels-Alder reactions of (*E*)-piperylene (1), i.e., cycloadditions with 5,5-dimethyl- (**2c**), 2,4,4-trimethyl- (**3b**), 2,5,5-trimethyl- (**3c**), 2,6,6-trimethyl- (**3d**) and 2-isopropyl-2-cyclohexenone (4), were executed.



Diels-Alder Reaction Products

The reactions of (*E*)-piperylene (1) with the five dienophiles were carried out under aluminum chloride catalysis in toluene solution at 40 °C for 8-90 h and led to 70-96% yields of octalones, as shown in Table III. 5,5-Dimethyl-2-cyclohexenone (**2c**) was converted into a 32:1 mixture of *trans*-octalone **5** and its 8a-epimer. The transformation

(1) For the previous paper, see: Angell E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.*, preceding paper in this issue.

(2) (a) Università di Perugia. (b) University of California.

(3) (a) Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548. (b) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17.

(4) (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. (b) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Ferreira, V. F.; Michelotti, E. L.; Porter, B.; Wenkert, E. *Ibid.* **1985**, *50*, 890. (c) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *Ibid.* **1985**, *50*, 4686. (d) Angell, E. C.; Fringuelli, F.; Halls, T. D. J.; Pizzo, F.; Porter, B.; Taticchi, A.; Tourris, A. P.; Wenkert, E. *Ibid.* **1985**, *50*, 4691. (e) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1986**, *16*, 245.

(5) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4696.

0022-3263/86/1951-2649$01.50/0