Stereoselective Diels−Alder Reactions of Hexachlorocyclopentadiene with Chiral Alkenes: New Insights Into the "Inside-Alkoxy" Model of Stereoselectivity

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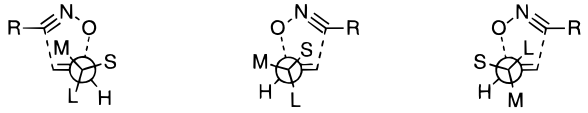
Hexachlorocyclopentadiene undergoes Diels−Alder reactions with dienophiles possessing allylic chiral centers with moderate to excellent *anti* selectivity. Ab initio calculations on model systems elucidate the origin of this stereoselectivity which follow the "inside-alkoxy" model.

The control of diastereofacial selectivity in cycloadditions is important for the development of efficient routes for the synthesis of chiral natural products. Cycloadditions of chiral molecules possessing stereogenic centers at allylic positions have attracted considerable interest.[1] Many previous experimental studies involved 1,3-dipolar cycloadditions to chiral alkenes, or the Diels−Alder reactions of chiral dienes. We report ab initio calculations on transition states of model systems for the cycloaddition of hexachlorocyclopentadiene to chiral dienophiles, which lead to refinement of models to understand stereoselectivity.

Facial selectivity in cycloadditions has been rationalized based on the conformational analysis of transition states.[1] Over a decade ago, we proposed the "inside-alkoxy" effect to explain the stereoselectivities of cycloadditions of chiral allylic ethers to electrophilic 1,3-dipoles, based on experimental results and theoretical studies.[2a] This model accounted for the stereoselectivity observed in a series of 1,3-dipolar cycloadditions of nitrile oxides to chiral allylic alcohols and ethers;[2a] later it was extended to dipolarophiles with two different-sized alkyl groups at the allylic chiral center. The transition state models are shown in Figure 1. **A′** gives the major product, and **B′** and **C′** give the minor product.

Cycloadditions occur via conformers which are staggered with respect to the partial bonds.[3] That conformer which has the largest alkyl group (L) anti (opposite to the attacking atom), the medium-sized or alkoxy group (M) inside (on the same side of the attacking atom and directed toward the double bond), and the smallest group, usually H (S), outside (on the same side of the attacking atom and directed away from the double bond), is the most stable, as shown in **A′**. In a series of experiments on 1,3-dipolar cycloadditions of nitrile oxides to chiral dipolarophiles, the main diastereomeric product is "*anti*",[4] which would arise from transition state **A′**.[2,5] The minor "*syn*" diastereomer can form from the conformer **B′**, which has the reversed alignment of S and M. Other conformers, such as **C′**, may also contribute (see below).



A' (*anti*) **B'** (*syn*) **C'** (*syn*)

Figure 1. Model transition structures for the "inside-alkoxy" effect in the reaction of chiral alkenes with nitrile oxides. L, M, S = large, medium (or alkoxy), and small substituents.

Higher level quantum mechanical calculations than were previously available have confirmed and refined the quantitative importance of the "inside-alkoxy" effect. The energies for the three possible staggered conformers were calculated for the cycloaddition of nitrile oxide with allyl alcohol and 1-butene. For allyl alcohol (with the hydroxy group fixed anti-periplanar to prevent hydrogen-bonding) the inside position was slightly preferred over the anti position by 0.2 kcal/mol with MP2/6-31G*//RHF/6-31G*. The outside position is 2.0 kcal/mol higher in energy, due to the electrostatic repulsion between the two oxygen atoms of the forming isoxazoline and the allyl alcohol. For 1-butene only steric interactions are important. For this reason the anti position is preferred by 0.6 kcal/mol over the inside and outside positions. From the summation of these energy differences for the three transition state models in Figure 1, **A′** is favored over **B′** and **C′** by 2.0 and 0.8 kcal/mol, respectively. The energy difference of 0.8 kcal/mol between the transition states leading to the two stereoisomeric products is in accord with the experimentally found diastereomeric ratio of ∼3:2.

In cyclic cases, there is a strong preference for attack of nitrile oxides, OsO_4,[6] and other oxygenated species anti to the alkoxy group; here, the alkoxy group is constrained to be outside or anti, and anti is highly favored. The

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(2) (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880−3882. (b) Raimondi, L.; Wu, Y.-D.; Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4409−4412. (c) This "inside-alkoxy" position is crowded in 1,3-dipolar cycloadditions of *Z*-alkenes, and the conformer with the alkoxy anti and the alkyl outside becomes the most stable.[2b] (d) Schwarz, M. V. Ph.D. Dissertation, University of Würzburg, 1993.

(3) (a) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438−2440. (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166.

(4) "*Anti*" and "*syn*" are not in all cases used according to the IUPAC rules. Instead, it refers to the relative configuration of the medium substituent (M) and the atom, O or C, added to the dipolarophile to form the new stereogenic center. When the carbon chain plus L are drawn in the zig-zag representation, M and the new atom define *anti* or *syn*.

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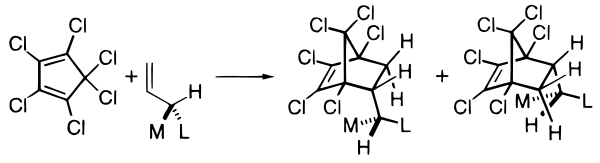
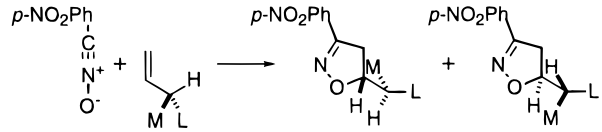
Table 1. Experimental Ratios of Diastereomers for Diels−Alder Reactions of Hexachlorocyclopentadiene, 1, with Chiral Propenes, 2−10.[9] Ratios for the 1,3-Dipolar Cycloaddition of *p*-Nitrobenzonitrile Oxide, 11, Are Given for Comparison[2a,5]





	L	M	2−10 A:B (% yield)	2'−10' A:B
2	Me	OH	60:40[a] (30)	50:50
3	Me	O(*p*-NO_2Ph)	64:36[a] (81)	60:40
4	Me	OPh	66:34[a] (91)	60:40
5	Me	O(*p*-MeOPh)	67:33[a] (83)	66:34
6	Me	OMe	71:29 (79)	64:36
7	C(OMe)Me_2	Me	80:20 (25)	80:20
8	*t*-Bu	Me	81:19 (74)	77:23
9	*t*-Bu	OH	87:13 (56)	35:65
10	*t*-Bu	OMe	100:0[a] (35)	97:3

[a] Structures of major adducts were confirmed by X-ray crystallographic analysis.

model proposed by Kishi for osmylation fits this expectation.[7a] The Vedejs results are also consistent with this model.[7b] When M = OH, transition state **B′** is favored. There is now a hydrogen-bonding attractive interaction between the allylic OH and the nitrile oxide O, which causes **B′** to be the lowest energy conformer.[2a]

Hehre *et al.* also rationalized the diastereofacial selectivity of electrophilic additions to allylic ethers.[8] Their interpretation is based on the electrostatic potentials of the ground states; changes in conformations and the electrostatic potentials in the transition state are assumed to be small, and the selection of the preferred pathway occurs well in advance of the real transition state. Electrophiles prefer to add from the alkene face which is more electron-rich. For allylic ethers, the analysis was made on the basis of the conformational energy profile in the ground state along with the electrostatic potentials for each conformer. For a series of chiral cyclic allyl ethers, however, this approach gives predictions which do not agree with experimental results.

We have undertaken a more general investigation of stereoselectivity in other cycloadditions to chiral allylic ethers and alcohols. Most of the common Diels−Alder dienes do not react readily with alkenes. Electron-deficient dienes are reactive, and experimental studies of the diastereofacial selectivity in inverse electron-demand Diels−Alder reactions of hexachlorocyclopentadiene, **1**, with a series of chiral allylic dienophiles have been performed.[9] Hexachlorocyclopentadiene is an electron-deficient diene whose Diels−Alder reaction rate is accelerated by electron-donating substituents on the dienophile,[10] in contrast to normal Diels−Alder reactions. Therefore, it undergoes relatively facile cycloadditions with propene and derivatives.

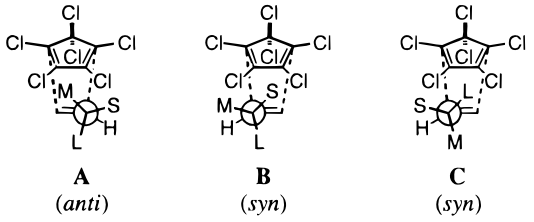


Figure 2. Proposed transition states for the Diels−Alder reaction of hexachlorocyclopentadiene with chiral allylic ethers and alcohols. L, M, S = large, medium (or alkoxy), and small substituents.

Diels−Alder reactions of excess hexachlorocyclopentadiene, **1**, and racemic chiral propene derivatives, including allylic ethers or alcohols, **2**−**10**, afford one or two *endo* adducts, **2A**−**10A** (*anti*) and **2B**−**9B** (*syn*).[11] The results are summarized in Table 1.[9] The *endo* selectivity for Diels−Alder reactions of hexachlorocyclopentadiene results from the steric requirement of the chlorine atoms at C-5.[12] The structures of some cycloadducts were confirmed by X-ray crystallographic analysis.[9,13] The ratios of the corresponding adducts in nitrile oxide cycloadditions, **2A′**/**2B′**−**10A′**/**10B′** (*anti*, *syn*)[2a,5] are also summarized for a comparison.

Anti diastereomers are the major products in all the Diels−Alder reactions. These are believed to be formed from transition state **A** or one of its rotamers (Figure 2). Selectivities ranged from low when L = Me to high when L = *t*-Bu. The transition state models depicted for hexachlorocyclopentadiene in Figure 2 also apply to this electrophilic inverse electron-demand Diels−Alder reaction. The largest alkyl group (L) is favored at the anti position to avoid steric repulsion with the diene, and the alkoxy group (M) or medium-sized group orients inside, minimizing steric and electrostatic repulsion with the outside chlorine atom.

The substituent effects on stereoselectivity are in reasonable agreement with this rationalization. In the case of the cycloaddition to 4,4-dimethyl-3-methoxy-1-pentene (L = *t*-Bu, M = OMe), **10**, only the *anti* diastereomer **10A** is produced. In the cases of **2**−**6**, electrostatic interaction with oxygen plays a more important role than the electronic nature of the aryloxy group or steric effects. The *anti* selectivity is nearly constant even upon variations in the aryloxy group (M = OPhG, with

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(11) A typical reaction was conducted as follows: A mixture of 2-methoxy-3-butene (**6**) (1.30 g, 15.1 mmol) and hexachlorocyclopentadiene (**1**) (8.48 g, 31.1 mmol) and 25 mL of toluene was sealed in a Pyrex tube and heated at 100 ± 3 °C for 6 days. The 300 MHz NMR spectrum showed the diastereomer ratio of 71:19 (±2%). Removal of the solvent under reduced pressure gave two products, separated by silica gel column chromatography eluting with 3% ethyl acetate in hexane to give two diastereomers, **6A** and **6B**, 4.28g (79% yield). Both were purified as colorless oils by Kugelrohr distillation at 93 °C/1.2 mmHg.

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Table 2. Calculated Relative Energies (kcal/mol) for the Transition Structures of Allyl Alcohol and 1-Butene with Cyclopentadiene (CPD), 1-Chlorocyclopentadiene (1-ClCPD), 2-Chlorocyclopentadiene (2-ClCPD), and 1,2-Dichlorocyclopentadiene (1,2-ClCPD)

	position	CPD RHF/6-31G*	1-ClCPD RHF/6-31G*//RHF/6-31G[a]	2-ClCPD RHF/6-31G*//RHF/6-31G[a]	1,2-ClCPD RHF/6-31G*//RHF/6-31G[a]
OH	anti	1.28	0.0	1.32	0.0
	inside	2.72	0.24	2.65	
	outside	0.0	1.10	0.0	1.31
CH_3	anti	0.0	0.0	0.0	
	inside	2.86	2.76	3.13	
	outside	0.76	2.36	0.85	

[a] The forming C···C bond distances were constrained to the values of the parent system without chlorine.

Table 3. Estimated and Calculated Relative Energies (kcal/mol) for the Transition Structures of 3-Buten-2-ol with Cyclopentadiene

	CH_3 position	E_{calcd}	OH position	E_{calcd}	$\Sigma(CH_3 + OH)$ E_{est}	RHF/6-31G*//RHF/6-31G[a] E_{calcd}	RHF/6-31G* E_{calcd}
A (*anti*)	anti	0.0	inside	2.72	2.72	2.31	2.29
	inside	2.86	outside	0.0	2.86	3.27	
	outside	0.76	anti	1.28	2.04	2.50	2.50
B (*syn*)	anti	0.0	outside	0.0	0.0	0.0	0.0
	inside	2.86	anti	1.28	4.14	3.80	
	outside	0.76	inside	2.72	3.48	3.76	

[a] The forming C···C bond distances were constrained to the values of the parent system without chlorine.

G = *p*-NO_2, H, *p*-OMe, and M = OH, OMe) while keeping the alkyl group constant (L = Me). The *anti* selectivity is much smaller with the small alkyl group, L = Me (**2**−**6**), than with the large group, L = *t*-Bu (**8**−**10**).

The homoallylic oxygen in **7** does not introduce additional electrostatic repulsive interactions with the chlorine; thus, in the reaction of 2-methoxy-2,3-dimethyl-4-pentene, **7**, the L group [C(OMe)Me_2] behaves as a bulky alkyl group, and the ratio of the two adducts is almost the same as in the case of the dienophile **8**. When L = *t*-Bu, the selectivity increases in the sequence of M = Me < OH < OMe. This implies that both steric and electrostatic factors are important, but indicates that the electrostatic "inside-alkoxy" effect is important, because there is higher stereoselectivity with OMe than with Me (cf. **8** and **10**). As shown in Table 1, almost all of these experimental results are quite similar to those observed in the 1,3-dipolar cycloadditions of *p*-nitrobenzonitrile oxide (**11**) with the same olefins.

The Diels−Alder reactions with allylic alcohol derivatives, **2** and **9**, give stereoselectivities like those of ethers, in contrast to the reversal of diastereofacial selectivity observed in the cycloadditions of benzonitrile oxides to allylic alcohols. The attractive hydrogen-bonding interaction between the OH group and the oxygen of nitrile oxides is responsible for the *syn* adduct (**9B′**) predominance with allylic alcohols. The results with **2** and **9** show that the attractive hydrogen bonding interaction of OH and chlorine is absent. The electrostatic repulsions between the oxygens of OH and OR and the chlorine operate in Diels−Alder reactions of hexachlorocyclopentadiene; consequently, *anti* stereoselectivity is observed with both ethers and alcohols.

In order to determine which molecular properties influence the relative energies of the transition states, RHF/6-31G* calculations[14] were performed on the *endo* transition structures for the Diels−Alder reactions of cyclopentadiene, 1-chloro, 2-chloro, and 1,2-dichlorocyclopentadiene with allyl alcohol, 1-butene, and 3-buten-2-ol. For the model system reaction of cyclopentadiene with allyl alcohol and 1-butene, all three staggered conformers of the transition structures were fully optimized (Table 2). For allyl alcohol, the outside position of the hydroxy group is preferred by 1.3 kcal/mol over the anti position. This reversal compared to 1-butene is explained by the increase of the dipole moment of the transition structure from 1.3 to 1.6 D and the lowering of electron density in the π-orbital of the alkene due to σ/π polarization of the C−O bond and the double bond. The lower steric demand of the cyclopentadiene and the lack of electronegative atoms in the outer sphere of cyclopentadiene account for the difference as compared to the nitrile oxide system. The higher energy for the inside position is, as with 1-butene, a result of the steric interaction with the cyclopentadiene ring.

An estimate of the relative stabilities of the stereoisomeric transition structures in the reaction of 3-buten-2-ol with cyclopentadiene was made by the summation of these energies (Table 3). The favored conformer with the methyl group in the anti position and the hydroxy group in the outside position, leading to the *syn* product (**B**), is 2.0 kcal/mol lower in energy than the conformer with the two larger substituents exchanged, leading to the diastereomeric *anti* product (**A**). Both 6-31G*//6-31G calculations with fixed distances for the forming bonds (taken from the transition structures of the related 1-butene systems) and 6-31G* full optimizations on the conformers with the lowest energies confirm this trend (Table 3). Note that the relative energies for full optimizations and single points on constrained structures show no significant difference. The preference for the *syn* (**B**) over the *anti* product (**A**) does not, however, agree with the experimental results for hexachlorocyclopentadiene.

Both the chlorine atoms in the 1- and the 2-positions of the cyclopentadiene are near the groups in the outside position at the stereogenic center. Therefore calculations on the transition structures for the reaction of the chloro-

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Table 4. Estimated and Calculated Relative Energies (kcal/mol) for the Transition Structures of 3-Buten-2-ol with 1-Chlorocyclopentadiene

	CH_3 position	E_{calcd}	OH position	E_{calcd}	$\Sigma(CH_3 + OH)$ E_{est}	RHF/6-31G*//RHF/6-31G[a] E_{calcd}	RHF/6-31G* E_{calcd}
A (*anti*)	anti	0.0	inside	0.24	0.24	0.0	0.0
	inside	2.76	outside	1.10	3.86	5.31	
	outside	2.36	anti	0.0	2.36	2.71	
B (*syn*)	anti	0.0	outside	1.10	1.10	1.33	1.41
	inside	2.76	anti	0.0	2.76	2.47	
	outside	2.36	inside	0.24	2.60	3.70	

[a] The forming C···C bond distances were constrained to the values of the parent system without chlorine.

substituted cyclopentadienes with allyl alcohol, 1-butene, and 3-buten-2-ol were conducted. The distances for the forming bonds were constrained at values obtained in the transition structures of the related structures without the chlorine atom. To save computation time and with the justification provided by the results in Tables 3 and 4, 6-31G* single point calculations were conducted on the 6-31G optimized structures (Table 2). For 1-chlorocyclopentadiene, the most important change compared to unsubstituted cyclopentadiene is found for the outside positions both with the methyl group in 1-butene and the hydroxy group in allyl alcohol. This position is destabilized by 1.5 and 3.3 kcal/mol, respectively, in comparison to the situation with the parent cyclopentadiene. This results from the steric interaction for both groups and additional electrostatic repulsion for the hydroxy group. The inside position of the hydroxy group now has a low relative energy, so that the difference between this and the anti position becomes very small. Again, the dipole moment for the anti position (2.4 D) is significantly greater than for the inside position (1.6 D). Also, the σ/π polarization leads to a decrease of the electron density in the π-orbital of the double bond. Since the chlorine atom makes the diene electron-demanding, this lowering of electron density in both π-systems destabilizes the transition structure.

Summing the relative conformational energies of methyl and hydroxy groups as described above results in the lowest energy for the transition structure with the methyl group in the anti position and the hydroxy group in the inside position leading to the *anti* product (**A**, Table 4). In the most stable conformer (6-31G*//6-31G) leading to the *syn* product the hydroxy group is moved to the outside position while the methyl group remains anti to the forming bond. RHF/6-31G* full optimizations confirm the relative stabilities. These results are in good agreement with the experimental results showing that the chlorine atoms not only change the electron demand of the diene but also the steric properties.

An additional chlorine atom in the 2-position does not considerably influence the relative energies of the conformers in comparison to the systems without this chlorine atom (Table 2, 2-ClCPD vs CPD and 1,2-ClCPD vs 1-ClCPD). Therefore, the origin of the diastereoselectivity resides in the chlorine atom in the 1-position and is a result of the steric and electrostatic interactions between large substituents in the outside position and the chlorine atom. The inside-alkoxy effect arises mainly from the repulsion of the alkoxy group and the electronegative atoms in the outside sphere, with their lone-pair electrons pointing into this direction, as in the nitrile oxide (3 + 2) cycloaddition and also in the osmium tetraoxide dihydroxylation.[6]

Conclusion. Experimental results show that the pattern of stereoselectivity found with cycloadditions of nitrile oxides to chiral allylic ethers is nearly quantitatively observed in another electrophilic cycloaddition involving hexachlorocyclopentadiene. Ab initio calculations explain these results by an "inside-alkoxy" effect due to electrostatic repulsion of the oxy group in the outside position with the chlorine atom of HCCP in the 1-position.

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Supporting Information Available: Structural data of all calculated geometries; Ortep plot of **10A′**; experimental procedures and spectroscopic data (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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