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Orbital control of π-facial selectivity in Diels–Alder reactions of cyclopentadienes having C(=O)YR substituents at the 5-positions

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Abstract—π-Facial selectivity in Diels–Alder reactions of cyclopentadienes having C(=O)YR substituents at the 5-positions was predicted on the basis of the orbital mixing rule and was substantiated experimentally. The selectivity was disclosed to be highly dependent on the relative orbital energy between π_{HOMO} of the diene and n_Y of the substituent. © 2001 Elsevier Science Ltd. All rights reserved.

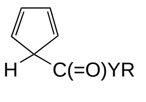
Diels–Alder reaction is one of the most important methods for organic synthesis. Much attention has been paid to disclose the origin of π-facial selectivity in the reactions of dienes having an unsymmetrical π-plane.[1] We have been investigating the reactions of 5-substituted cyclopentadienes as the simplest dienes and proposed that the deformation of frontier molecular orbitals (FMO) of dienes is the major contributor to the selectivity.[2,3] The orbital mixing rule has been successfully applied to predict the deformation. We will predict the π-facial selectivity in the reactions of cyclopentadienes **1** (and **2**) having C(=O)YR substituents at the 5-positions. The prediction will be confirmed by theoretical calculations and by experimental observations.

In the prediction of the FMO of the dienes, the interactions between four molecular orbitals, namely the π-HOMO of the diene, the σ-orbitals of the carbon framework, the n-orbital of Y, and the π-orbital of C=O, were taken into account (hereinafter referred to as π_{HOMO}, σ, n_Y, and $\pi_{C=O}$, respectively).[4]

According to the orbital mixing rule, the deformation of FMO takes place by the mixing of π_{HOMO} and σ through interaction with the substituent orbital n_Y. Participation of the second substituent orbital $\pi_{C=O}$ perturbs this mixing to determine the final deformation with a dependence on the relative orbital energy between π_{HOMO} and n_Y (Fig. 1).

When π_{HOMO} is high, π_{HOMO} mainly contributes to the FMO. π_{HOMO} combines with both of the low-lying substituent orbitals, n_Y and $\pi_{C=O}$, out of phase. The mixing of the low-lying σ to π_{HOMO} takes place in such a way that it is out of phase with n_Y and $\pi_{C=O}$ to give the FMO of the whole diene (since π_{HOMO} lies higher than σ). It is noteworthy that the component orbitals of the C(=O)YR substituent, n_Y and $\pi_{C=O}$, participate in the mixing. Since $\pi_{C=O}$ has the same phase with n_Y, the mixing of σ is enhanced to give FMO, which favors the reaction at the *syn* side of the substituent (case A: $\Psi(FMO) = \pi_{HOMO} - n_Y - \pi_{C=O} + \sigma$). This is the case with dienes **1a**–**d**.

On the other hand, when n_Y lies closely to π_{HOMO}, the interaction between π_{HOMO} and n_Y is strong. Both orbitals contribute considerably to the FMO. The combined orbital, $\pi_{HOMO} - n_Y$, is a component of FMO. The $\pi_{C=O}$ orbital interacts with the n_Y more strongly rather than with the π_{HOMO} due to the spatial proximity. The



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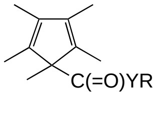

2

a: YR = OH
b: YR = OMe
c: YR = OPh
d: YR = OAr (Ar= 4-MeOC_6H_4)
e: YR = NH_2
f: YR = SMe
g: YR = SMe (C(=S) instead of C(=O))

Keywords: cyclopentadiene; Diels–Alder reactions; orbital effect; stereocontrol; substituent effect.

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phase of $\pi_{C=O}$ is determined by the relation with n_Y rather than π_{HOMO} in such a way that it is out of phase with n_Y (viz. in phase with π_{HOMO}). As a result, $\pi_{C=O}$ is in the opposite phase with n_Y, while the orbitals are in phase with each other in case A. The mixing of σ, caused by the interaction with $\pi_{C=O}$ and n_Y, is diminished by each other. The deformation of FMO is predicted to be reduced (case B: $\Psi(\text{FMO}) = \pi_{HOMO} - n_Y + \pi_{C=O} + \sigma$). In this case, the orbital-phase environment around the reaction centers lower the *syn* π-facial selectivity or results in *anti* π-facial selectivity.[1b,2] The out-of-phase interaction between the n_Y segment of the HOMO of the diene and the LUMO of a dienophile significantly destabilizes the *syn* attack transition states. This is the case with dienes **1e**–**g**, while **1g** has the C(=S)SMe substituent.

The predicted FMO deformation was examined by ab initio molecular orbital calculations. The dienes **1b** and **1f** were chosen as typical examples of dienes of cases A and B, respectively. The molecular geometries of the dienes (*Cs*) were optimized by ab initio molecular orbital calculation at the RHF/6-31G* level (Fig. 2).[5] The contour maps at the sections of $x = 0.500$ Å of **1b** and **1f** clearly indicated the in-phase and out-of-phase relationship between n_Y and $\pi_{C=O}$, respectively.[6] The difference between the maps ($x = 0.891$ Å) is clear. Small contours of the highest value appeared in the map of **1b** (at the *syn* side) but not in the map of **1f**, thus showing that the FMO of **1b** is more effectively deformed than that of **1f**.

The prediction was examined experimentally. To avoid complication due to [1,5]-hydrogen rearrangement, the corresponding pentamethylcyclopentadienes **2a**–**g** were prepared and subjected to reaction with *N*-phenylmaleimide (NPM) in non-polar solvents, such as carbon tetrachloride and/or toluene (Scheme 1). The progress of reaction was followed by TLC. After completion of reaction,[7] the residues were analyzed by ^{1}H NMR to determine the ratios and yields of the products[8] (Table 1).

Consistent with the prediction, reactions of case A dienes **2a**–**d** and case B dienes **2e**–**g** predominantly afforded the corresponding *syn* and *anti* attack products, **3** and **4**, respectively.

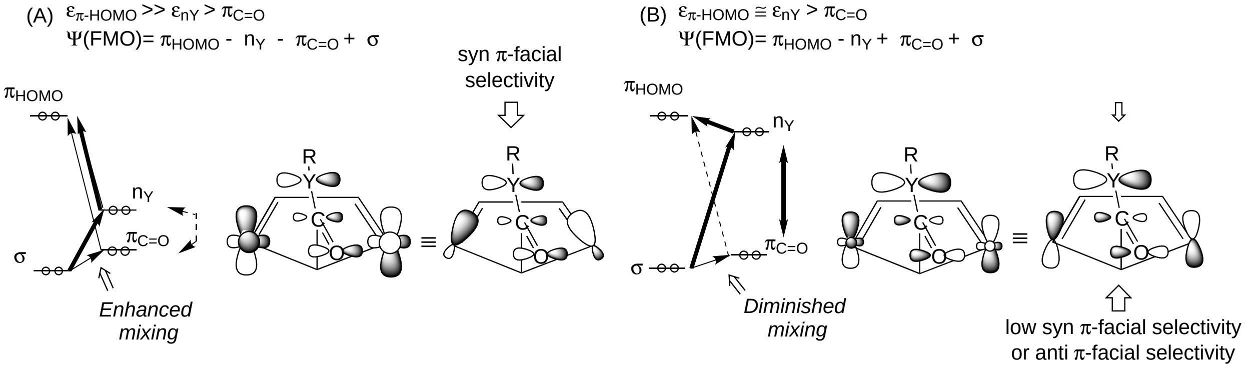
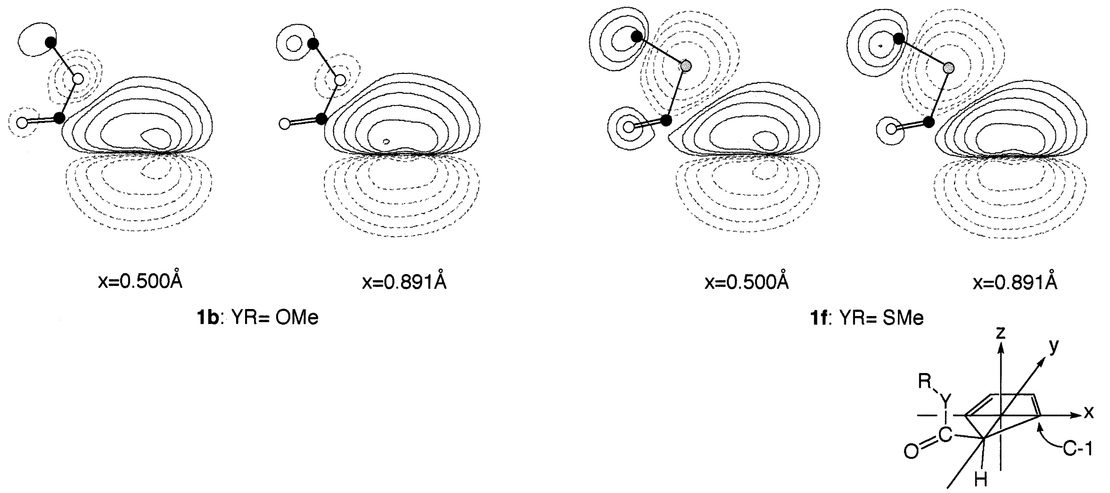


Figure 1. Direction of non-equivalent extension of the FMO of cyclopentadienes having C(=O)YR substituents. Phase relationship: ----, in phase; —, out of phase. Orbital mixing: ⟶ , major interaction; —>, minor interaction (and ---->).

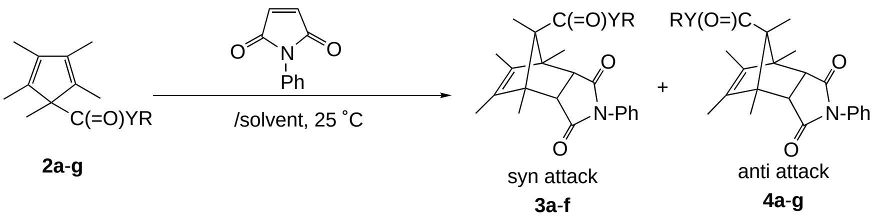

x=0.500Å x=0.891Å

1b: YR= OMe

x=0.500Å x=0.891Å

1f: YR= SMe

Figure 2. Contour maps of the sections ($x = 0.500$ and 0.891 Å) of the FMO of dienes **1b** and **1f** at the RHF/6-31G* level (*Cs*). The Cp ring is in the *xy* plane and C-1 and C-4 carbons are on the *x*-axis at the space coordinates (Å) of (1.177. 0. 0) and (−1.177. 0. 0), respectively. The absolute value of the largest contour line is 5.0×10^{-3} AU. The heights of adjacent contours differ by a factor of two. Atoms in substituents: filled circle, C; open circle, O; shaded circle, S.



Scheme 1. Reactions of **2a**–**g** with NPM. Solvent: CCl_4 and/or toluene.

Table 1. Diels–Alder reactions of the dienes **2a**–**g** with NPM

Diene	YR	*syn*:*anti*[a,b,c] **3**:**4**	Prediction (case)	Diene	YR	*syn*:*anti*[a,b,c] **3**:**4**	Prediction (case)
2a	OH[d]	80:20[e] 78:22[f]	*syn* (A)	**2e**	NH_2	26:74[e] 27:73[f]	Low-*syn* or *anti* (B)
2b	OMe	84:16[f]	*syn* (A)	**2f**	SMe	1:99[f]	Low-*syn* or *anti* (B)
2c	OPh	83:17[e] 84:16[f]	*syn* (A)	**2g**	SMe [C(=S) instead of C(=O)]	0:100[f]	Low-*syn* or anti (B)
2d	OAr (Ar = 4-MeOC_6H_4-)	84:16[e]	*syn* (A)				

[a] All products gave correct elemental analyses or high-resolution mass spectra.

[b] The ratio was determined from 400 MHz (or 270 MHz) ^1H NMR spectra of the crude mixture.

[c] The ^1H NMR spectra showed that the reactions proceeded quantitatively (exception: **2g**, yield 70%).

[d] See Ref.[3e]

[e] Solvent: CCl_4.

[f] Solvent: toluene.

In conclusion, the results open a highly applicable approach to designing orbital control of π-facial selectivity in organic reactions.

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7. The reaction of diene **2g** proceeded very slowly. After 190 h, the reaction gave **4g** in 70% yield.
8. Selected spectroscopic data: Compound **3b**: mp 157.2–157.7°C (colorless solid from hexane–AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H, CH_3), 1.55 (s, 6H, $2CH_3$), 1.61 (s, 6H, $2CH_3$), 3.32 (s, 2H, 2CH), 3.71 (s, 3H, OCH_3), 7.04–7.44 (m, 5H, aromatic); Compound **3b** displayed an NOE between the methyne protons at δ 3.32 and the methoxy protons at δ 3.71; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 12.4, 12.9, 51.0, 51.4, 59.3, 72.9, 126.5, 128.3, 129.0, 131.9, 134.4, 174.5, 176.1; MS (CI) m/z 368 (M^++1); MS (EI) (20 eV) m/z 367 (M^+). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.77; H, 6.76; N, 3.80. Compound **4b**: mp 114.5–115.5°C (colorless solid from hexane–AcOEt); ^1H NMR

(400 MHz, $CDCl_3$) δ 1.07 (s, 3H, CH_3), 1.58 (s, 6H, $2CH_3$), 1.63 (s, 6H, $2CH_3$), 3.04 (s, 2H, 2CH), 3.60 (s, 3H, OCH_3), 7.04–7.44 (m, 5H, aromatic); Compound **4b** displayed an NOE between the methyl protons at δ 1.07 and the methyne protons at δ 3.04; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 13.3, 13.5, 50.3, 51.3, 59.2, 73.8, 126.5, 128.5, 129.1, 131.9, 136.8, 173.9, 176.1; MS (CI) *m*/*z* 368 (M^++1); MS (EI) (20 eV) *m*/*z* 367 (M^+). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.63; H, 6.91; N, 3.69.