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Contrasteric Diels–Alder reactions of 5-methyl-5-phenylcyclopentadiene

Masaru Ishida *, Makoto Itakura, Hiroshi Tashiro

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan

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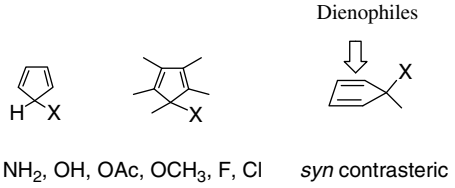
Abstract

The frontier molecular orbital of 5-phenylcyclopentadiene was predicted on the basis of the orbital mixing rule to deform to favor the Diels–Alder reaction in a *syn* contrasteric manner. The prediction was substantiated experimentally by the reactions of 5-methyl-5-phenylcyclopentadiene with dienophiles to afford the *syn* attack products, exclusively.

Keywords: Cyclopentadienes; Diels–Alder reactions; Frontier molecular orbital; Facial selectivities; Substituent effects

Control of the π-facial selectivity in the Diels–Alder reactions of 5-substituted cyclopentadienes has been one of the most fundamental subjects of organic chemistry.[1] The dienes can react at either face. *anti* π-Facial selectivity with respect to the substituents has been attributed to steric hindrance due to the substituents at the *syn* attack transition states. The reactions of 5-alkylcyclopentadienes were typical examples.[2] However, the cyclopentadienes having smaller heteroatom substituents such as amino,[3a] acetoxy,[3b] hydroxyl,[3a,c] methoxy,[3a,d] fluoro,[3e] and chloro[3a,f–h] moieties at the 5-positions were found to react with dienophiles in a *syn* contrasteric manner (see Scheme 1).

There had been proposed some stereoelectronic phenomena due to heteroatoms in substituents as the origin of the selectivity. These include beneficial interaction of the antisymmetric oxygen orbital with the LUMO of dienophiles by Anh for 5-acetoxycyclopentadiene,[4a] electrostatic interaction of electrophilic dienophiles with the more nucleophilic diene face, *syn* to 'a lone-pair-containing substituent', by Kahn and Hehre,[4b] transition state hyperconjugative stabilization (Cieplak-effect) by Macaulay and Fallis,[3a,5] and the frontier orbital deformation by Inagaki and Fukui.[6] This latter proposed that unsymmetrical deformation of the frontier molecular orbital (FMO) of the dienes with respect to the π-plane is the major contributor to the selectivity. The orbital mixing rule can predict the deformation. On the basis of the orbital mixing rule, we successfully predicted and designed the π-facial selectivity in the reactions of various cyclopentadiene having various substituents such as SR, SeR, TeR, COOR, COOH, $CONH_2$, CHO, CH=NOH, $CH{=}CH_2$, and 2-oxazolynyl moiety at the 5-position.[5a,7a–h] The next task is to avoid the factors due to the heteroatoms in the substituents. In this Letter we will show the extensive application of the theory by designing a heteroatom-free 5-substituted cyclopentadiene, which reacted in a contrasteric fashion, overwhelming the steric hindrance due to the substituent.



Scheme 1.

* Corresponding author. Tel.: +81 58 293 2613; fax: +81 58 230 1893.
E-mail address: m_ishida@gifu-u.ac.jp (M. Ishida).

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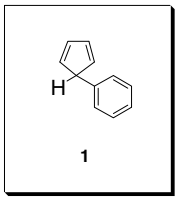


As the first candidate of such a diene, 5-phenylcyclopentadiene **1** was selected, since the phenyl moiety of diene **1** can mediate orbital mixing through its degenerated $\pi_{\text{Ph-HOMO}}$'s almost independently on the conformation around the phenyl moiety. The deformation of the FMO is predicted as follows. When the phenyl moiety lies in the plane of symmetry perpendicular to the cyclopentadiene π-plane (hereinafter referred to as a bisected conformation, $\mathbf{1_b}$), the symmetric $\pi_{\text{Ph-HOMO(S)}}$ mediates the mixing. The π_{HOMO} of the diene combines with the low-lying $\pi_{\text{Ph-HOMO(S)}}$ out of phase and mixes the low-lying σ-orbital of carbon framework out of phase with the $\pi_{\text{Ph-HOMO(S)}}$. As the result, the mixing of the π_{HOMO} and the σ-system of the diene is perturbed by the low-lying $\pi_{\text{Ph-HOMO(S)}}$ in such a way that both diene orbitals contribute to the FMO in an out of phase manner relative to mediated orbital $\pi_{\text{Ph-HOMO(S)}}$. The FMO extends and distorts inwardly to favor the reaction on the *syn* side of the phenyl moiety (Fig. 1a: Ψ (FMO) = $\pi_{\text{HOMO}} - \pi_{\text{Ph-HOMO(S)}} + \sigma$). When

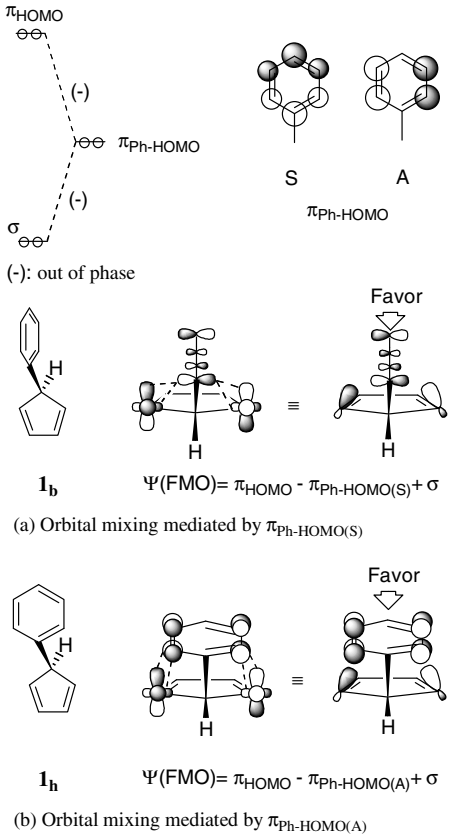


Fig. 1. Deformation of the FMO of 5-phenylcyclopentadiene.

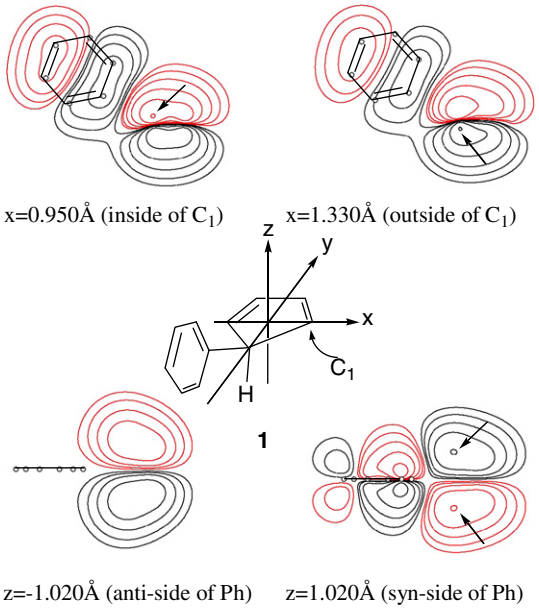


Fig. 2. Contour maps of the sections ($x = 0.950, 1.330$, and $z = \pm 1.020$ Å) of the FMO of diene $\mathbf{1_b}$ at the RHF/6-31G* level (C_s). The C_p ring and the phenyl moiety are in xy and yz planes, respectively. C_1 and C_4 carbons are on the x-axis at the space coordinates (Å) of (1.174, 0 0) and (−1.174 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 2.0.

the phenyl moiety rotates by 90° around C_5–$C_{1'}$ bond from the bisected conformation (hereinafter referred to a horizontal conformation $\mathbf{1_h}$), the asymmetric $\pi_{\text{Ph-HOMO(A)}}$ similarly mediates the mixing (Fig. 1b: Ψ(FMO) = $\pi_{\text{HOMO}} - \pi_{\text{Ph-HOMO(A)}} + \sigma$).

The prediction was briefly examined by ab initio molecular orbital calculation at the RHF/6-31G* level.[8] The bisected conformer $\mathbf{1_b}$ was fully optimized to be a C_s symmetric structure as the global minimum. The nonequivalency of the FMO was confirmed based on contour maps (Fig. 2).[9] Small contours of the highest absolute value appeared in the map of the section of $x = 0.950$ Å (inside of C_1) and $X = 1.330$ Å (outside of C_1) at *syn* and *anti* sides of phenyl moiety, respectively. The highest contours of the sections of $z = \pm 1.020$ Å appeared at the *syn* side of the phenyl moiety but not in the *anti* side. The FMO of $\mathbf{1_b}$ does distort inwardly and extends at the *syn* side of the phenyl moiety.

The molecular geometry of the horizontal conformer $\mathbf{1_h}$ was similarly optimized by fixing the phenyl moiety to lie in an orthogonal plane with respect to the plane of symmetry perpendicular to the cyclopentadiene. Conformer $\mathbf{1_h}$ is the transition state for rotation of the phenyl moiety around the C_5–$C_{1'}$ bond and less stable than $\mathbf{1_b}$ by 3.4 kcal/mol. The contour maps of the FMO showed small contours of the highest absolute value in the maps of the section of $x = -0.905$ and 1.420 Å and $z = 1.121$ Å at the *syn* side of the phenyl moiety, but not in the map of the section of $z = -1.121$ Å (Fig. 3). The FMO dose extent at the *syn* side of phenyl moiety, although distortion is not clearly confirmed.[10]

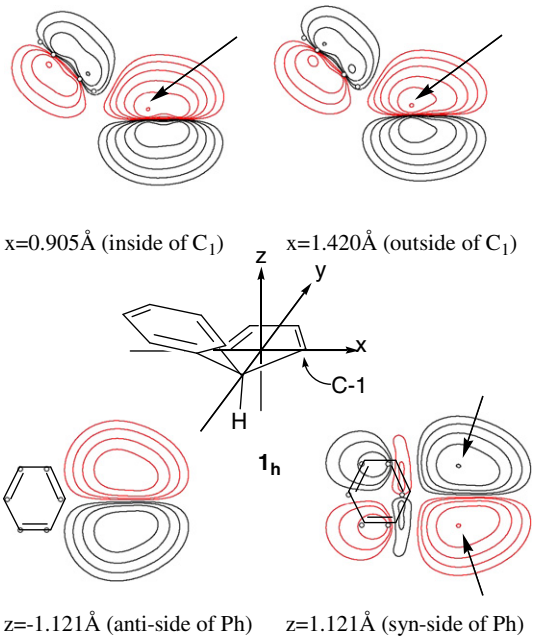
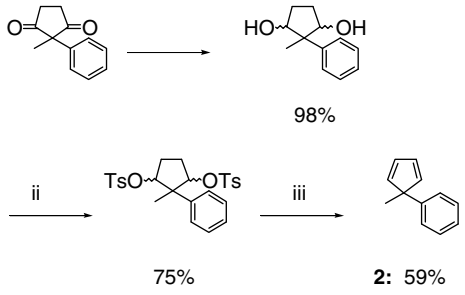


Fig. 3. Contour maps of the sections ($x = 0.905$, 1.420, and $z = \pm 1.121$ Å) of the FMO of the fixed conformer $\mathbf{1_h}$ at the RHF/6-31G* level (C_s). The C_p ring is in xy plane. C_1 and C_4 carbons are on the x-axis at the space coordinates (Å) of (1.173, 0, 0) and (−1.173, 0, 0), respectively. The absolute value of the largest contour line is 5.0×10^{-3} AU. The heights of adjacent contours differ by a factor 2.0.

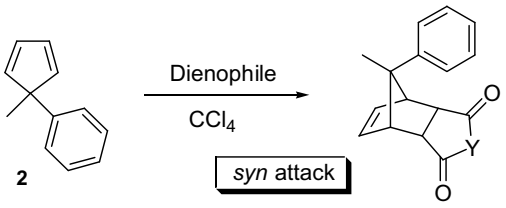


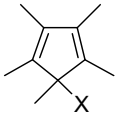
Scheme 2. Preparation of 5-methyl-5-phenylcyclopentadiene **2**. Reagents: (i) $NaBH_4$/MeOH; (ii) TsCl, DMAP/pyridine; (iii) DBU/toluene.

Encouraged by these calculations, the prediction was examined experimentally. To avoid complication due to [1,5] hydrogen rearrangement, 5-methyl-5-phenylcyclopentadiene **2**[11,12] was prepared from 2-methyl-2-phenylcyclopentane-1,3-dione[13] in 43% total yield (Scheme 2).

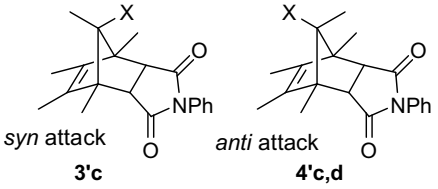
The reactions of diene **2** with dienophiles *N*-phenylmaleimide (PMI) and maleic anhydride (MA) were performed at 25 °C in carbon tetrachloride (0.5 M) under nitrogen atmosphere. The reactions were followed by TLC. After completion of the reactions, the solvent was removed and the residues were subjected to ^{1}H NMR to show exclusive formation of *syn* attack products, **3a** and **3b**, respectively (Table 1).[14,15] These results are in contrast with the *anti* π-facial selectivity observed in the reactions of the cyclopentadiene derivatives having smaller substituents such as vinyl and formyl moieties at the 5-positions.[7f,16]

Table 1
Diels–Alder reactions of **2** with dienophiles



Diene	Dienophile	Products	Selectivity[a] *syn*/*anti*
2	PMI	**3a** (Y = NPh)	100:0
	MA	**3b** (Y = O)	100:0
	PMI	**3′c**, **4′c** (X=CH=CH$_2$)	34:66[b,c]
	PMI	**4′d** (X=CH=O)	0:100[b,d]

[a] The reactions proceeded quantitatively.

[b]


[c] See Ref. 7f.

[d] See Refs. 7f and 16.

In conclusion, orbital effects designed on the basis of the orbital mixing rule can overcome the steric effects due to substituents.[17] Further applications of the reactions designed by this concept are now in progress.

Acknowledgments

We thank Professor Satoshi Inagaki for fruitful discussions and helpful suggestions. We also thank Professor Hiroaki Wasada for helpful suggestions and for providing the software for drawing contour maps.

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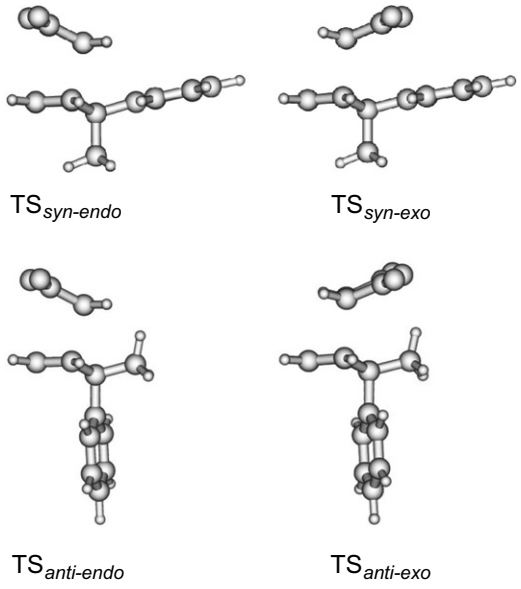
14. *Selected spectroscopic data*: Compound **3a**: mp 181.3–182.6 °C (colorless solid from hexane–AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H, Me), 3.37–3.39 (m, 2H, CH), 3.74 (s, 2H, CH), 6.36 (t, $J = 2.0$ Hz, 2H, CH=CH), 7.08–7.48 (m, 10H, Ph). Compound **3a** displayed 3.3% of NOE between the methyl protons at δ 1.26 and the CH=CH protons at δ 6.36. No NOE was observed between the methyl protons at δ 1.26 and the methyne protons at δ 3.37–3.39. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 45.1, 51.9, 71.3, 125.6, 126.6, 126.8, 128.6, 129.1, 131.8, 133.6, 145.0, 177.1; HRMS calcd for $C_{22}H_{19}NO_2$ 329.1416; found 329.1407. Compound **3b**: mp 134.6–135.6 °C (colorless solid from hexane–AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, Me), 3.49–3.51 (m, 2H, CH), 3.72 (s, 2H, CH), 6.41 (t, $J = 2.0$ Hz, 2H, CH), 7.20–7.39 (m, 5H, Ph). Compound **3b** displayed 4.7% of NOE between the methyl protons at δ 1.24 and the CH=CH protons at δ 6.41. No NOE was observed between the methyl protons at δ 1.24 and the methyne protons at δ 3.49–3.51. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 46.5, 52.4, 72.1, 125.3, 127.0, 129.3, 134.6, 144.4, 171.6; HRMS calcd for $C_{16}H_{14}O_3$ 254.0943; found 254.0946.
15. Following the suggestion made by one reviewer, the transition states for the reaction between diene **2** and maleic anhydride were calculated at the RHF/6-31G* level. The results were confirmed by IRC calculations at the same level. The *syn* attack transition states $TS_{syn\text{-}endo}$ and $TS_{syn\text{-}exo}$ are C_s-symmetric. The phenyl moieties of *syn* attack transition states are in horizontal conformation similar to $\mathbf{1_h}$. The *anti* attack transition states $TS_{anti\text{-}endo}$ and $TS_{anti\text{-}exo}$ are C_1-symmetric. Relative energies of $TS_{syn\text{-}endo}$, $TS_{syn\text{-}exo}$, $TS_{anti\text{-}endo}$, and $TS_{anti\text{-}exo}$ were 0.0, 9.3, 4.2, and 14.4 kcal/mol, respectively. These results are well consistent with the observation.



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17. π–π Interaction between a dienophile and the phenyl moiety of diene **2** was suggested as a possible explanation for the observed selectivity by one reviewer. This explanation seemed to be less likely since the interaction destabilizes *syn* attack transition states due to the out of phase relationship between $\pi^*_{\text{dienophile}}$ and $\pi_{\text{Ph-HOMO(A)}}$. The interaction can be the origin of the selectivity of 5-aryl-5-phenylcyclopentadiene to favor the reactions on the *anti* side of more electron rich aromatic system.[12a] The selectivity is consistent with the approach of reactants to avoid the interaction between $\pi^*_{\text{dienophile}}$ and $\pi_{\text{Ph-HOMO(A)'}}$ of more electron rich aromatic system.