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De novo designed contrasteric Diels–Alder reactions of 5-(2-oxazolynyl)-1,2,3,4,5-pentamethylcyclopentadiene

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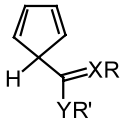
Abstract—5-(2-Oxazolynyl)cyclopentadiene was designed on the basis of the orbital mixing rule to react with dienophiles with highly contrasteric manner in Diels–Alder reactions. The design was validated by the synthesis and reactions of the corresponding pentamethyl derivative, 5-(2-oxazolynyl)-1,2,3,4,5-pentamethylcyclopentadiene, to afford the products with the ratios of *syn*/*anti*= 89–93/11–7. © 2003 Elsevier Science Ltd. All rights reserved.

The origin of the π-facial selectivity in the Diels–Alder reactions of 5-substituted cyclopentadienes is one of the fundamental problems in organic chemistry.[1] Anh proposed that, in the reactions of 5-acetoxycyclopentadiene, the stabilization interaction between the LUMO of a dienophile and n-orbital of the substituent at the *syn* attack transition state is the origin of the *syn* π-facial selectivity.[2] However recently such an interaction was pointed out to destabilize the system since the LUMO and the n-orbital should be out of phase.[1a,b] Hehre et al. suggested that the approach of a dienophile to a diene would occur at the *syn* side of the substituent having lone pairs because of electrostatic interaction,[3] although there were some arguments against the theory.[4a,b] Cieplak effects[1c] was proposed as the origin of the selectivity by Fallis et al.;[5] however, semi-empirical calculations reported by Werstiuk and Ma[6] and us[7] provided no support for the proposal. Burnell et al. recently reported that the selectivity was primarily due to steric hindrance between a dienophile and 5-positioned substituent on the basis of theoretical calculations.[8]

We have been investigating the reactions of 5-substituted cyclopentadienes as the simplest dienes having unsymmetrical π-plane.[7,10] We have proposed that deformation of the frontier molecular orbitals (FMO) of the dienes is the major contributor to the selectivity. The deformation is predictable on the basis of orbital mixing rule.[7,9,10b] Recently, the rule was applied to the reactions of the dienes having carbon substituents of various π-systems such as formyl, *N*-hydroxyiminomethyl, vinyl, alkoxycarbonyl, carboxyl and carbamoyl at 5-positions. The rule successfully predicted the selectivities that are highly dependent on the natures of the substituent orbitals.[10d–g]

These successes prompted us to show an extensive application of the theory by designing new cyclopentadiene **1** to react in contrasteric fashion overwhelming the steric hindrance due to the substituent. As the first candidate of **1**, we will show herein the de novo design of 5-(2-oxazolynyl)cyclopentadiene **2** and the synthesis and reactions of its pentamethyl derivative **3**.



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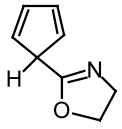

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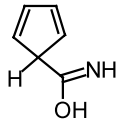

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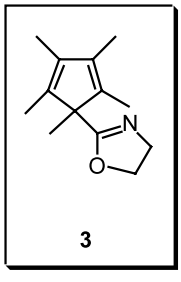

3

Keywords: cyclopentadienes; Diels–Alder reactions; molecular design; stereocontrol; substituent effects.

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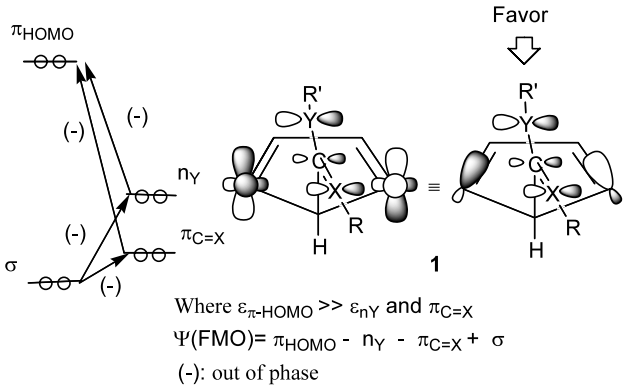


Figure 1. The necessary condition for the deformation of the FMO of CpC(=XR)YR′ **1** to favor contrasteric reactions.

The diene **2** was singled out for the following reasons: (i) The FMO of the diene **1** is comprised of four molecular orbitals, namely, π-HOMO of the diene, σ-orbitals of carbon framework, n-orbital of Y, and π-orbital of C=X (hereinafter referred to as π_{HOMO}, σ, n_Y, and $\pi_{C=X}$, respectively). The diene **1** has to fulfill the requirement of orbital energy relationship of $\varepsilon_{\pi HOMO} \gg \varepsilon_{nYo}$, $\varepsilon_{\pi C=X}$, as illustrated in Figure 1. Under such a condition, the FMO mainly consists of π_{HOMO}, to which the component orbitals of the substituent, n_Y and $\pi_{C=X}$, combine so as to be out of phase with π_{HOMO}. Mixing of σ of carbon framework takes place through the interaction with both of the component orbitals resulted in the nonsymmetrical deformation of FMO to favor the contrasteric reactions, since σ should be out of phase with the mediated orbitals ($\Psi(FMO) = \pi_{HOMO} - n_Y - \pi_{C=X} + \sigma$). The diene **2** obviously fulfills the requirement since π_{HOMO} lies much higher than n_O and $\pi_{C=N}$. (ii) 2-Oxazolynyl moiety is a bulky substituent (2-oxazolynyl≫methyl>hydrgen). (iii) Easy procedure for the transformation of chlorocarbonyl moiety to 2-oxazolynyl moiety was reported.[11]

It is also noteworthy that novel selectivity control by simple modification at the substituent will be exemplified by the reaction of **2**, since 5-carbamoyl-1,2,3,4,5-pentamethyl-cyclopentadiene reacted with dienophiles with *anti* π-facial selectivity.[10g]

The designed deformation of FMO was evaluated briefly by ab initio molecular orbital calculations. The molecular geometry of the model diene **2′** was optimized at the RHF/6-31G* level of the theory and the FMO was calculated at the same level of the theory. Figure 2 illustrates the FMO of **2′** of the equilibrium structure (*Cs*).[12,13] It is clearly shown in the contour map of the sections of $x = 0.880$ Å that both of the substituent orbitals, n_O and $\pi_{C=NH}$, combine with π_{HOMO} so as to be out of phase with π_{HOMO} as predicted in Figure 1. The tilting of the FMO inwardly at

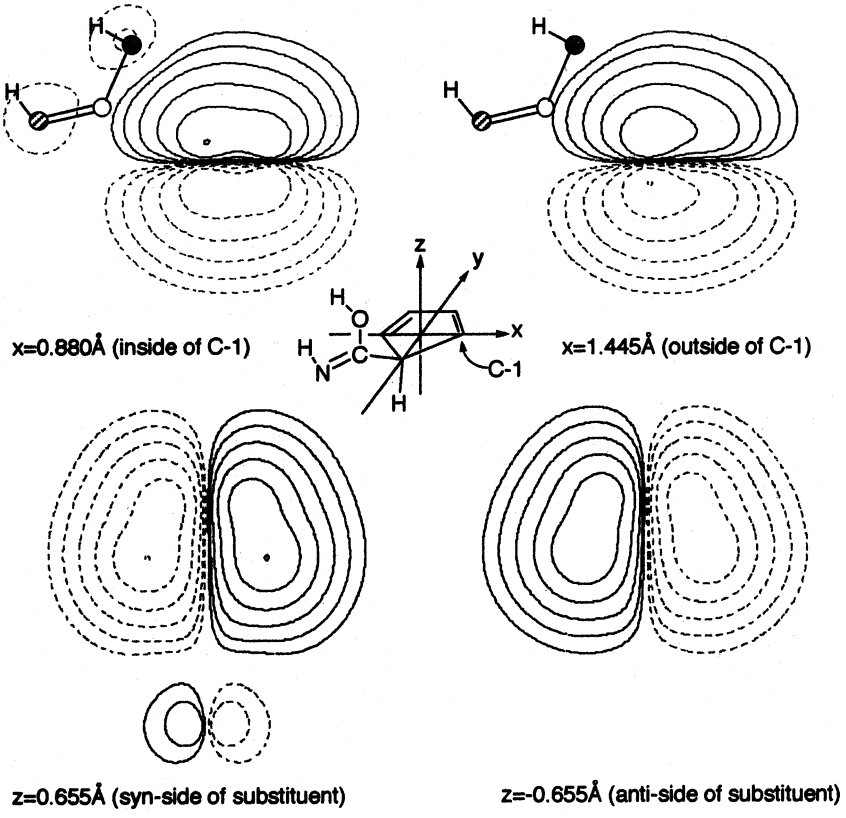
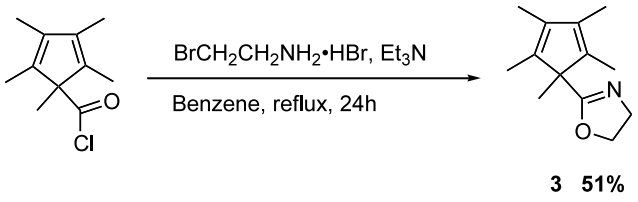


Figure 2. Contour maps of the sections ($x = 0.880, 1.445$, and $z = \pm 0.655$ Å) of the FMO of the model diene **2′** at the RHF/6-31G* level (*Cs*). The Cp ring is in the *xy* plane and C-1 and C-4 carbons are on the *x* axis at the space coordinates (Å) of (1.176. 0. 0) and (−1.176. 0. 0), respectively. The absolute value of the largest contour line is 5.0×10^{-3} AU . The heights of adjacent contours differ by a factor of 2. Atoms in substituents: clear circle = C, shaded circle = O, striped circle = N.



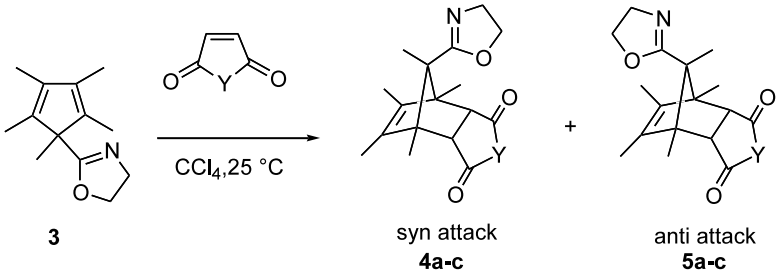
Scheme 1. Preparation of **3**.

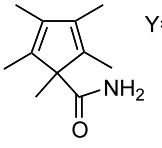
the *syn* side of the substituent is confirmed from the contour maps of the sections of $x=0.880$ and 1.445 Å. The contours of the highest absolute value appeared at the *syn* side in the map of $x=0.880$ Å (inside of C1), while at the *anti* side of the substituent in the map of $x=1.445$ Å (outside of C1). The extension of the FMO at the *syn* side of substituent is also clearly shown by the maps of the sections of $z=\pm0.655$ Å. The highest contours appeared in the map of $z=0.655$ Å (*syn* side), not in the map of $z=-0.655$ Å (*anti* side). The deformation of the FMO was also well consistent with the theory.[14]

Encouraged by these results, the prediction was validated experimentally. To avoid complication due to [1,5]-hydrogen rearrangement, the corresponding 1,2,3,4,5-pentamethylcyclo-pentadiene derivative **3** was prepared from 5-chlorocarbonyl-1,2,3,4,5-pentamethylcyclo-pentadiene[15] by the procedure of Kashima et al,[11] in a 51% yield (Scheme 1).[16]

The reactions of **3** with *N*-methylmaleimide, *N*-phenylmaleimide and maleic anhydride in carbon tetrachloride at 25°C proceeded quantitatively with highly contrasteric manner to give the corresponding adducts in the *syn*/*anti* ratios of 89/11, 92/8, and 93/7, respectively (Table 1).[17] The selectivity in the reactions of **3** showed sharp contrast to the *anti* π-facial selectivity in the reaction of 5-carbamoyl-1,2,3,4,5-pentamethylcyclopentadiene,[10g,18] of which substituent is smaller than that of **3**.

Table 1. Diels–Alder reactions of **3** with dienophiles



Entry	Dienophile	products	syn : anti (**4**/**5**)[a,b,c]
1	Y= NCH_3	**4a, 5a**	89 : 11
2	Y= NPh	**4b, 5b**	92 : 8
3	Y= O	**4c, 5c**	93 : 7
cf.[d]			
	Y= NPh	**4d**[e], **5d**[e]	26 : 74

[a]All products gave correct elemental analyses or highresolution mass spectra. [b]The ratios were determined from 400 MHz ^{1}H-NMR spectra of the crude mixture. [c]The ^{1}H-NMR spectra showed that the reactions proceeded quantitatively. [d]See ref. 10g and 18. [e]Carbamoyl instead of 2-oxazolynyl.

Acknowledgements

Further investigation and application of the selectivity control by this concept is now in progress.

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16. Mp 61.4–62.7°C (colorless solid from hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, CH_3), 1.76 (s, 6H, $2CH_3$), 1.80 (s, 6H, $2CH_3$), 3.81 (t, J=9.4 Hz, 2H, CH_2), 4.15 (t, J=9.4 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 11.3, 19.1, 54.2, 57.5, 67.5, 136.0, 138.3, 169.9, HRMS calcd for $C_{13}H_{19}NO$ 205.1467; found 205.1459.
17. Selected spectral data; **4a**: mp 200.0–201.0°C (colorless solid from AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3H, CH_3), 1.56 (s, 6H, $2CH_3$), 1.62 (s, 6H, $2CH_3$), 3.49 (s, 2H, 2CH), 3.84 (t, J=9.5 Hz, 2H, CH_2), 4.15 (t, J=9.5 Hz, 2H, CH_2), 7.04–7.43 (m, 5H, aromatic). **4a** displayed no NOE between the methyne protons at δ 3.49 and the methyl protons at δ 0.98; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 12.4, 13.3, 51.2, 54.4, 60.0, 66.1, 68.1, 126.6, 128.3, 129.0, 132.1, 134.6, 168.7,176.6. Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.98; H, 6.94; N, 7.40. Found: C, 72.97; H, 7.00; N, 7.37. **5a**: mp 192.8–193.6°C (colorless solid from hexane–AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H, CH_3), 1.59 (s, 6H, $2CH_3$), 1.61 (s, 6H, $2CH_3$), 3.06 (s, 2H, 2CH), 3.73 (t, J=9.5 Hz, 2H, CH_2), 4.05 (t, J=9.5 Hz, 2H, CH_2), 7.05–7.44 (m, 5H, aromatic). **5a** displayed NOE between the methyne protons at δ 3.06 and the methyl protons at δ 1.09; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 13.4, 14.7, 50.8, 54.3, 59.8, 66.2, 69.0, 126.6, 128.4, 129.1, 132.1, 136.2, 169.2, 176.3. Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.98; H, 6.94; N, 7.40. Found: C, 72.70; H, 6.86; N, 7.38.
18. *anti* π-Facial selectivity in the reactions of 5-carbamoyl-1,2,3,4,5-pentamethyl-cyclopentadiene was predicted and substantiated in our preceding paper.[10g] The energy relationship of the component orbitals of the FMO of the diene is $\varepsilon_{\pi HOMO}$, $\varepsilon_{nNH2} \gg \varepsilon_{\pi C=O}$.