Highly *Syn* π-Facial Preference in the Diels-Alder Reactions of 1,2,3,4,5-Pentamethylcyclopentadienes Having Carboxy, Ethoxycarbonyl, and Cyano Substituents at 5-Positions

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Diels-Alder reactions of 1,2,3,4,5-pentamethylcyclopentadienes having carboxy, alkoxycarbonyl, and cyano substituents at 5-positions with *N*-phenymaleimide preferentially afforded the corresponding *syn*-attack products with the ratio of *syn*/*anti* = 80 : 20 to 100 : 0, while the diene having 5-hydroxymethyl moiety gave the *anti*-attack product exclusively.

It was well known that the Diels-Alder reactions of the cyclopentadienes having hydroxy,[1] acetoxy,[2] fluoro,[3] and chloro[4] moieties at the 5-positions exclusively afforded the *syn*-attack products regardless of the repulsive interactions between the substituents and dienophiles. The selectivity[5] was attributable to the nonequivalent extension of the frontier molecular orbital (FMO) and was predicted on the basis of the orbital mixing rule.[6,7]

These success prompted us to investigate the reactions of the new class of the cyclopentadienes **1** (X= CO_2H, CO_2Et, and C≡N). The orbital mixing rule predicts *syn* π-facial selectivity in the reaction of **1**, since the FMO is expected to extend and to distort inwardly on the *syn* side of X due to the π-σ mixing through the π-orbital on X (Figure1: $\Psi_{(FMO)} = \pi - \pi_X + \sigma$: where $\varepsilon_\pi > \varepsilon_{\pi X}$).[8]

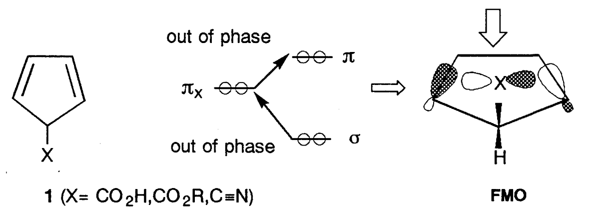
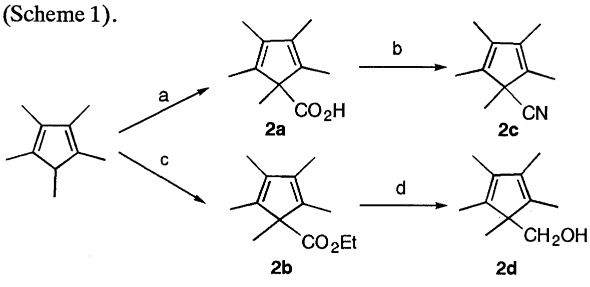


Figure 1. Prediction of the selectivity in the Diels-Alder reactions of the cyclopentadienes **1**.

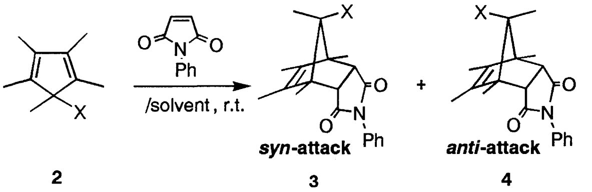
The prediction was confirmed by experiments. To avoid potential complication from [1,5] sigmatropic rearrangement of 5-positioned hydrogen, the 1,2,3,4,5-pentamethylcyclopentadienes **2a-d** (X= CO_2H, CO_2Et,[9] C≡N,[10] and CH_2OH[9]) were prepared (Scheme 1).



a) n-BuLi, THF, 25 °C, 0.5h; CO_2, -60 °C to 25°C, 55%;b) PCl_5, ether, 25 °C, 12h; NH_4OH, THF, 25°C, 75%, then TsCl, py; 25 °C, 18h, 61%; c) n-BuLi, THF, 25 °C, 0.5h; $ClCO_2Et$, reflux, 2h, 44%; d) $LiAlH_4$, ether, 0 °C, 12h, 48%(from cyclopentadiene without separation of **2b**).

Scheme 1.

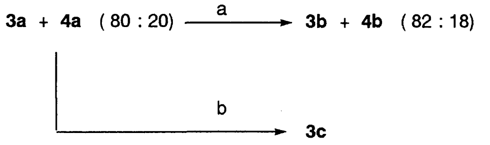
Table 1. Diels-Alder reactions of the cyclopentadienes **2** with *N*-Phenylmaleimide



2 **3** **4**

Diene 2	X=	Solv.	Products	Yield[a] / %	Selectivity *syn* : *anti*	Prediction
2a	CO_2H	CCl_4	**3a, 4a**[b]	98	80 : 20	*syn*
		Toluene		98	78 : 22	
		THF		91	86 : 14	
		Pyridine		99	85 : 15	
		MeOH		89	85 : 15	
2b	CO_2Et	CCl_4	**3b, 4b**	72	83 : 17	*syn*
2c	C≡N	CCl_4	**3c**	89	100 : 0	*syn*
2d	CH_2OH	CCl_4	**4d**	84	0 :100	—

[a] Yields and ratios of products were determined on the basis of ^{1}H-NMR (internal standard : Anisole). [b] See Ref 11.



a) PCl_5, Ether, then EtOH, pyridine, 25 °C, 95%; b) PCl_5, Ether, then aq NH_4OH, THF; The *syn* product was separated and dehydrated by TsCl, Pyridine, 31%.

Scheme 2. Confirmation of the stereochemistry of the products.

The reactions of the dienes **2a-d** with *N*-phenylmaleimide (NPM) were carried out at room temperature in carbon tetrachloride (or various solvents for **2a**). The predictions based on the mixing rule and the experimental results were summarized in Table 1. The stereochemistry of the products were determined on the basis of the NOE differential spectroscopy and by chemical transformation as illustrated in scheme 2.

Syn π-facial preference observed in the reactions of the dienes **2a-c** was well consistent with the simple prediction. Participation of the hydrogen bonding between the carboxy moiety and NPM was ruled out, since the selectivity was independent on the solvents. The steric repulsion between the 5-substituents and NPM at *syn* attack transition states should be effectively defeated by electronic factors. *Anti* π-facial selectivity in the reaction of the hydroxymethyl diene **2d** showed a striking contrast to the results of the reaction of **2a-c**. The *anti* selectivity in the reaction of **2d** was attributable to the steric repulsion between the dienophile and hydroxymethyl substituents.[12]

These results are the first prediction and observation of *syn* π-facial preference in the Diels-Alder reactions of the new class of the cyclopentadienes having the substituents X in 5-positions (X= CO_2H, CO_2Et, and C≡N).

Studies on the scope and limitation of the reactions and theoretical study on the selectivity are now in progress.

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8 a) The diene **1** (X= C≡CH) is also expected to react at the *syn*-face,[8b] since $\varepsilon_\pi > \varepsilon_{\pi X}$. b) Computation of the facial selectivity in the Diels Alder reactions of **1** (X= C≡CH and C≡N) was very recently reported: R. A. Poirier, C. C. Pye, J. D. Xidos, and D. J. Burnell, *J. Org. Chem.*, **60**, 2328 (1995).

9 **2b** and **2d** were prepared by the modified methods of L. deVries: L. deVries, *J. Org. Chem.*, **25**, 1838 (1960).

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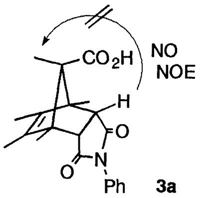
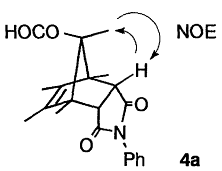
11 The spectra of key compounds; **3a:** mp 201.5-202.5 °C,^1H NMR($CDCl_3$): δ 7.44-7.04 (5H, Ph, m), 3.42 (2H, 2CH, s), 1.63 (6H, $2CH_3$, s), 1.58 (6H, $2CH_3$, s), 1.07 (3H, CH_3, s); ^{13}C NMR($CDCl_3$): δ 179.58, 176.14, 134.51, 131.87, 129.14, 128.49, 126.54, 72.70, 59.30, 50.95, 13.13, 12.36, and 11.53; MS (CI) *m/z* 354(M+1, 100.0), 181(27.5), 137 (36.5). Anal. Found: C, 71.27; H, 6.57; N, 3.98%. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.51; N, 3.97%. **4a:** mp 244.0-245.0 °C, ^1H NMR($CDCl_3$): δ 7.44-7.05 (5H, Ph, m), 3.04 (2H, 2CH, s), 1.65 (6H, $2CH_3$, s), 1.59 (6H, $2CH_3$, s), 1.12(3H,CH_3,s); ^{13}C NMR($CDCl_3$): δ 178.93, 175.98, 137.14, 131.91, 129.15, 128.53, 126.53, 73.53, 59.09, 50.31, 13.54, 13.25, and 11.44; MS (CI): *m/z* 354 (M+1, 100), 308(15.8), 181 (38.3), 137 (40.6); Anal. Found: C, 71.22; H, 7.22; N, 3.10%. Calcd for $C_{26}H_{31}NO_5$: C, 71.40; H, 7.09 ; N, 3.20% (After conversion to the corresponding tetrahydropyranyl ester).



3a



4a

12 Diels-Alder reaction of 5-hydroxymethyl-5-methylcyclopentadiene was reported; L. A. Paquette, C. Vanucci, and R. D. Rogers, *J. Am. Chem. Soc.*, **111**, 5792 (1989).