

## Reactivity Enhanced Selectivity. Dienophile Dependent $\pi$ -Facial Selectivity in the Diels-Alder Reactions of 5-Substituted 1,3-Cyclopentadienes

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Against a frequently held view in organic chemistry, it was proposed that the selectivity is enhanced by the reactivity in a certain class of reactions. The reactivity-enhanced selectivity (RES) theory was experimentally confirmed by the  $\pi$ -facial selectivities in the Diels-Alder reactions of 5-phenylthiocyclopentadiene dependent on the reactivities of dienophiles.

For many years it was an accepted principle in organic chemistry that the lower the selectivity the greater the reactivity.<sup>1</sup> Against this frequently held view, we here propose that the selectivity is enhanced by the reactivity in a certain class of reactions. The theory of the reactivity-enhanced selectivity (RES) is confirmed by the observed dependence of the  $\pi$ -facial selectivities of 5-substituted cyclopentadienes on the reactivities of dienophiles.

The stabilization energy SE due to the frontier orbital interaction is directly proportional to the square of the overlap integral ( $s^2$ ) and inversely proportional to the orbital energy separation  $\Delta\epsilon$ :  $SE = Ks^2/\Delta\epsilon$ . The reactivity (or SE) increases as the orbital energy gap decreases (see the curve A in Figure 1). Suppose another reaction path B where the orbital overlap is smaller than that on the path A. The reaction prefers the path A to B (see the curve A above B at any point  $\Delta\epsilon$ ). With the decrease in  $\Delta\epsilon$ , the hyperbolic curve A ascends to a greater extent than the curve B since the overlap  $s$  is greater on the path A. This increases the separation  $\Delta SE$  between the curves A and B ( $\Delta E_\alpha > \Delta E_\beta$  where  $\Delta\epsilon_\alpha < \Delta\epsilon_\beta$ ), resulting in the enhanced preference of the path A to B. This leads to the RES theory that the selectivity is enhanced by the reactivity.

The RES theory suggests an interesting possibility that the selectivity should be reversed with the change in the reactivity when the overlap-favored reaction (path A) is retarded by another

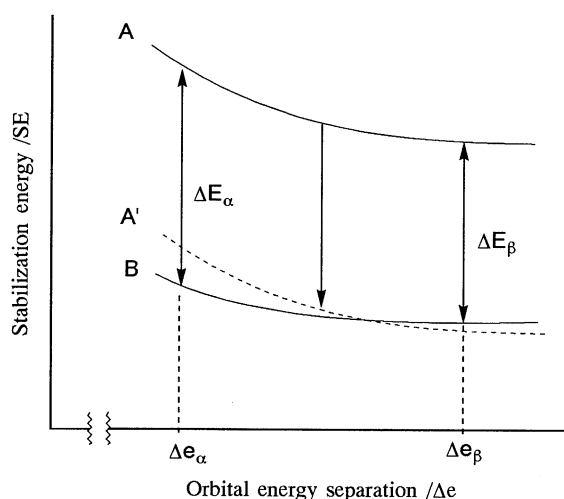
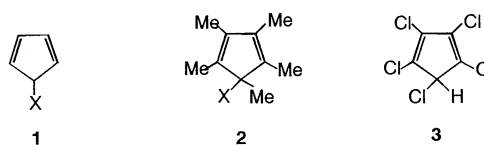


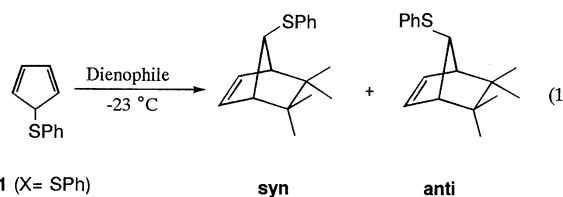
Figure 1. Stabilization energy (SE) by the frontier orbital interaction ( $\Delta\epsilon$ : energy separation).

factor, e.g., steric hindrance, etc. The retarded reaction path is represented by the dotted curve A' below A, which possibly intersects with the curve B. This implies that the overlap-disfavored path B is preferred on the right-hand side of the intersection, or on the low reactivity side. The overlap favored reaction A' is accelerated by the reactivity to occur faster than the path B on the left-hand side of the intersection, or on the high reactivity side.

There is much current interest in the  $\pi$ -facial selectivities of the Diels-Alder reactions.<sup>2</sup> We previously proposed that the  $\pi$ -facial selectivity was successfully predicted by the orbital mixing rule.<sup>3</sup> The direction of the nonequivalent extension or the distortion of the frontier orbitals of the cyclopentadienes **1** depend on the 5-substituents,<sup>4</sup> in agreement with the  $\pi$ -facial selectivities in the Diels-Alder reactions.<sup>5</sup>







The frontier orbital of 5-phenylthiocyclopentadiene (**1**: X= PhS) is distorted at the reaction centers, C(1) and C(4), to overlap with that of a dienophile more effectively at the anti face.<sup>4</sup> The curves A and B correspond to the reactions at the anti and syn faces, respectively. The anti-selectivity is predicted by the RES theory to be enhanced with the reactivity of the dienophiles. The reactions of the diene **1** (X= PhS) with some dienophiles (Eq. 1) were investigated. The reactivity of the dienophiles increases in the



order of maleic anhydride < N-phenylmaleimide < 4-phenyl-1,2,4-triazoline-3,5-dione < tetracyanoethylene.<sup>6</sup> The selectivity (Table 1) changed from the slight preference of the anti-attack (less reactive dienophile) to the exclusive anti-attack (more reactive dienophile). The selectivity-reactivity relationship confirmed the predictions.<sup>7,8</sup>

Evidence is available<sup>9,10</sup> for the reactivity reversed selectivity. The frontier orbitals of 5-chloro substituted cyclopentadienes are distorted to facilitate the syn-attack of dienophiles in the Diels-Alder reactions.<sup>3</sup> However, the overlap favored path A is hindered by the 5-substituent to some extent (the path A'). The  $\pi$ -facial selectivity is possibly reversed with the reactivity of dienophiles. The reactions of pentachlorocyclopentadiene **3** with less reactive dienophiles such as styrene and propylene occur at

**Table 1.**  $\pi$ -Facial Selectivities in the Diels-Alder Reactions of 5-Phenylthiocyclopentadiene <sup>a</sup>

Dienophile	reactivity <sup>b</sup>	syn / anti <sup>c</sup>
	55600	45 : 55 <sup>d</sup>
	70500	30 : 70 <sup>e</sup>
	16000000	14 : 86 <sup>f</sup>
	430000000	0 : 100 <sup>g</sup>

<sup>a</sup>The diene **1** (1.00 mmol) was treated with the dienophiles (1.00 mmol) in dichloromethane/carbon tetrachloride = 1 : 3 (20 mL) at -23 °C under N<sub>2</sub>. <sup>b</sup>See Ref.6. <sup>c</sup>Determined by <sup>1</sup>H-NMR. <sup>d</sup>Yield: 56%(NMR). <sup>e</sup>Isolated yield: 27%(syn), 42%(anti). <sup>f</sup>Isolated yield: 6%(syn), 67% (anti). <sup>g</sup>Isolated yield 38%(anti), Solvent: dichloromethane/carbon tetrachloride = 2:3 (25 mL).

the anti face predominantly (on the right-hand side of the intersection of the curves A' and B). The reactions with vinyl acetate, bromide and chloride give almost equal amounts of the syn and anti products (around the intersection). More reactive dienophiles such as maleic anhydride, acrylonitrile, and methyl acrylate undergo the syn-attack (on the left-hand side).

It is also noteworthy that Lewis acid catalysts are expected to enhance the selectivity. The reactions of **3** with maleic anhydride, acrylonitrile, and methyl acrylate were reported to show higher syn-selectivity in the presence of aluminum chloride (AlCl<sub>3</sub>).<sup>10</sup> The dienophiles are activated by the complexation with the Lewis acid.

In conclusion we theoretically proposed and experimentally confirmed the RES theory that selectivity is enhanced by reactivity. Further investigation is now in progress.

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## References and Notes

- 1 J. March, "Advanced Organic Chemistry," John Wiley & Sons, Inc, New York (1992), p 199.
- 2 For recent reviews, see: M. Ishida and S. Inagaki, *J. Synth. Org. Chem. Jpn.*, **52**, 649 (1994); A. G. Fallis and Y. Lu, in "Advances in Cycloaddition," JAI Press (1993), Vol. 3, p 1.
- 3 S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4054 (1976).
- 4 M. Ishida, Y. Beniya, S. Inagaki, and S. Kato, *J. Am. Chem. Soc.*, **112**, 8980 (1990); M. Ishida, T. Aoyama, Y. Beniya, S. Yamabe, S. Kato, and S. Inagaki, *Bull. Chem. Soc. Jpn.*, **66**, 3430 (1993).
- 5 M. Ishida, T. Aoyama, and S. Kato, *Chem. Lett.*, **1989**, 663.
- 6 The relative reactivity of N-phenyltriazoline-2,4-dione was estimated from the competitive reaction with N-phenylmaleimide. The reaction of cyclopentadiene (0.18 mmol) with a mixture of N-phenyltriazoline-2,4-dione (0.4 mmol) and N-phenylmaleimide (40 mmol) in dioxane at 25 °C gave the corresponding adducts with the ratio of 69 : 31. For the other dienophiles, see : J. Sauer, H. Wuest and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).
- 7 The reactions of 5-(methylthio)pentamethylcyclopentadiene (**2**: X= SCH<sub>3</sub>) with maleic anhydride, N-phenylmaleimide and tetracyanoethylene (TCNE) were reported by Fallis et al<sup>8b</sup> to give the products with the ratio of syn/anti = 10 : 90, 7 : 93, and 0 : 100, respectively. These results are also consistent with the RES theory though the change in the selectivity is slight.
- 8 (a) The observed diene-dependent selectivities are compatible with the RES theory. The pentamethyl diene **2** (X= SR) shows higher anti-selectivity than the mother diene **1** (X= PhS), regardless of the repulsive interaction with the methyl group at the 5-position. For example, the diene **2** (X= PhS) reacted with maleic anhydride to give the products with the ratio of syn/anti= 3 : 97,<sup>8b</sup> in contrast to the ratio of 45 : 55 in the reaction of **1**. The diene **2** is more reactive than **1** because the five methyls elevate the HOMO energy. The anti  $\pi$ -facial selectivity of **2** is enhanced. However, the possibility cannot be ruled out that the HOMO of **2** is more distorted than **1** to favor the anti-attack. (b) J. B. Macaulay and A. G. Fallis, *J. Am. Chem. Soc.*, **112**, 1136 (1990).
- 9 K. L. Williamson, Y. L. Hsu, R. Lacko, and C. H. Youn, *J. Am. Chem. Soc.*, **91**, 6129 (1969).
- 10 K. L. Williamson and Y. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).