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Stereoselection of sterically unbiased Diels–Alder dienes with spiro conjugation

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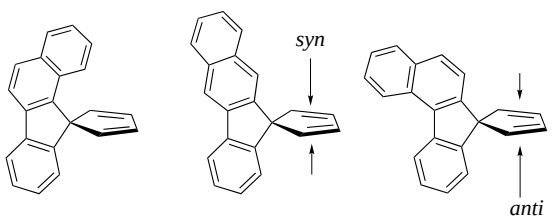
Abstract—1,3-Cyclopentadienes bearing a fluorene in spiro geometry are nonsterically biased dienes, which can be used to probe the facial selectivities of Diels–Alder reactions. *Anti* preference of spiro dienes (**2** and **3**) bearing 2- and 4-nitro and 2-methoxy substituents as Diels–Alder dienes is in striking contrast to facial preference of the related open-chain 5,5-diphenyl-cyclo-1,3-pentadienes.

Although there have been many experimental and theoretical studies on the behavior of facially perturbed dienes in Diels–Alder reactions, the number of sterically unbiased dienes available to probe the factors that determine the facial selectivity is limited.[1,2] In most cases, the steric effect controls selectivity. Facial selectivities of certain dienes have been accounted for in terms of hyperconjugative,[3–6] electrostatic,[7,8] torsional[9,10] or orbital effects.[11–15] The general applicability and predictive value of these proposed explanations are not obvious at present.[1,2] A recent review by Mehta on stereoselection in Diels–Alder reactions of disymmetric 1,3-dienes highlighted the lack of consistent understanding of the observed facial selectivities.[2]



Scheme 1.

We previously studied the facial selectivities of benzo[*a*]- (**a**), benzo[*b*]- (**b**) and benzo[*c*]fluorenes (**c**) bearing a diene group (**1**) in spiro geometry; these compounds are the three possible combinatorial isomers wherein the direction of fusion of the naphthalene is different.[16] The π reaction centers of the diene groups are subject to spiro-conjugation[17] with the planar aromatic π system. With respect to the π faces of the relevant reaction centers, the first aromatic system (**1a**) is sterically biased (i.e. sterically unsymmetrical), while the latter two systems (**1b**,**c**) are assumed to be free from steric bias. These dienes react as Diels–Alder dienes with several dienophiles (maleic anhydride (MA), *N*-phenylmaleimide (PMI) and *N*-phenyl-1,3,5-triazoline-2,4-dione (PTD)). The diene (**1b**) bearing benzo[*b*]fluorene favored *syn* addition of the dienophiles (*syn*:*anti*=62:38 (for maleic anhydride)) with respect to the naphthalene ring, whereas the diene **1c** (benzo[*c*]fluorene) showed a reverse *anti* preference for the additions (*syn*:*anti*=28:72 (for maleic anhydride)). Thus, the direction of fusion of the aromatic ring changes the facial preference (Scheme 1).

In order to study the effect of perturbation arising from spiro-conjugation on the chemical reactivities, in particular the facial selectivities, we have synthesized sterically unbiased dienes (**2** and **3**) based on fluorenes in spiro geometry (Scheme 2). These dienes react as Diels–Alder dienes with several dienophiles (maleic anhydride (MA), *N*-phenylmaleimide (PMI), *N*-phenyl-1,3,5-triazoline-2,4-dione (PTD) and *N*-methyl-1,3,5-triazoline-2,4-dione (MTD)). The different reaction conditions and yields in the case of the parent unsubstituted diene

Keywords: spiro compounds; Diels–Alder reactions; facial selectivities; diastereoselection; 1,3-cyclopentadienes.

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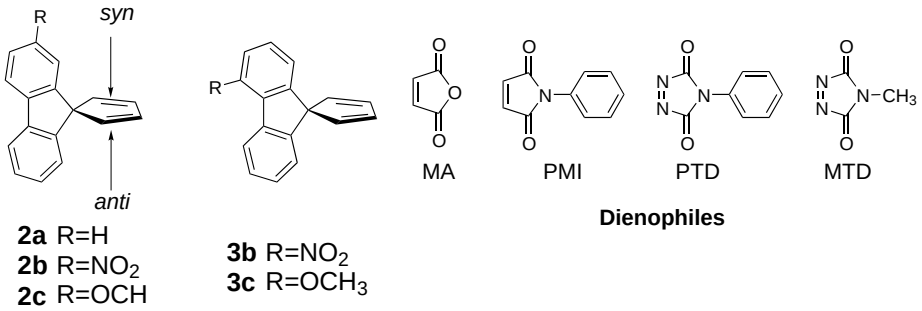


Scheme 2.

2a suggest that the relative reactivities of the dienophiles are in the order PTD ≈ MTD ≫ PMI>MA, this order being consistent with the established reactivity (Table 1).[19] *Endo* isomers of the adducts were exclusively formed, as was confirmed by a single-crystal structural determination of the adduct of **1a** and PTD (data not shown).

A single-crystal structure determination of the 2-nitro-substituted diene **2b** revealed a near-isosteric environment of the diene and fluorene faces, both being bisected (Fig. 1).[18] We detected facial selectivities of these sterically unbiased dienes (**2b**, **2c**, **3b** and **3c**) (Table 1).

In the cases of the 2-nitro-substituted (**2b**) and 4-nitro-substituted dienes (**3b**), *anti* addition of the dieneophiles with respect to the nitro substituent was favored. *Endo* isomers of the adducts were exclusively formed, as was confirmed by a single-crystal structural determination of the *anti*- and *syn*-adducts of **2b** with PMI (Fig. 2).[19] The latter adduct can include dichloromethane in the crystal state (Fig. 2(b)). The reactions of **2b** and **3b** with PTD and MTD proceed readily even at low temperature (below −43°C), and the facial selectivity (*anti*:*syn*) is as large as 87:13 (**2b** in the case of PTD) and 75:25 (**3b** in the case of MTD). When the reaction of **2b** with PTD was carried out at a higher temperature (0°C), the facial selectivity was reduced (*anti*:*syn* = 76:24), though *anti* preference was retained. The isolated minor adduct (*syn* isomer) of **2b** and PTD was placed in a large excess of PDT in methylene chloride at ambient temperature,

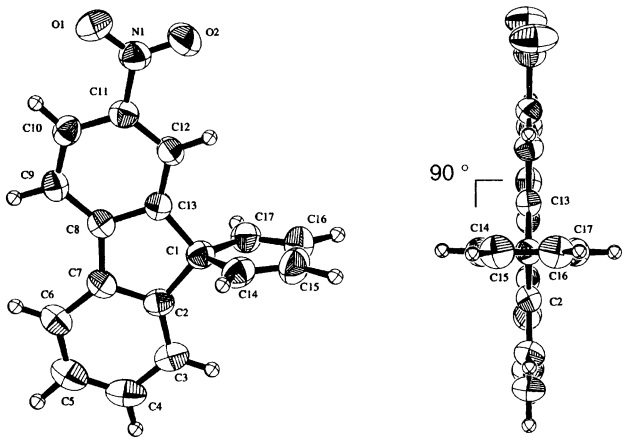


Figure 1. ORTEP diagrams of 2-nitro substituted diene **2b** showing isosteric π faces. Atoms are drawn as 50% probability displacement ellipsoids.

Table 1. Facial selectivities of Diels–Alder dienes

Diene	Dienophile[a]	Temp. (°C)	Time (h)	Yield (%)	*anti*:*syn*[b]
2a	MA	100	96	45[c]	50:50
	PMI	90	96	65	50:50
	PTD	0	2	92	50:50
2b	MA	90	72	51	55:45
	PMI	90	30	70	59:41
	PTD	−48	20 min	98	87:13
	PTD	0	1.5	96	76:24
	MTD	−43	20 min	74	74:26
3b	MA	100	120	64	55:45
	PMI	95	95	41	61:39
	PTD	−46	20 min	96	72:28
	MTD	−44	20 min	89	75:25
2c	PTD	−47	20 min	95	61:39
	MTD	−47	20 min	99	60:40
3c	PTD	−49	20 min	nd[d]	46:54
	MTD	−48	20 min	nd[d]	55:45

[a] MA = maleic anhydride; PMI = *N*-phenylmaleimide; PTD = *N*-phenyl-1,3,5-triazoline-2,4-dione; MTD = *N*-methyl-1,3,5-triazoline-2,4-dione.
[b] Ratios of isomers (except **2a**) are estimated in terms of 400 MHz ^{1}H NMR signal integrations.
[c] 17% recovery.
[d] nd = not determined.

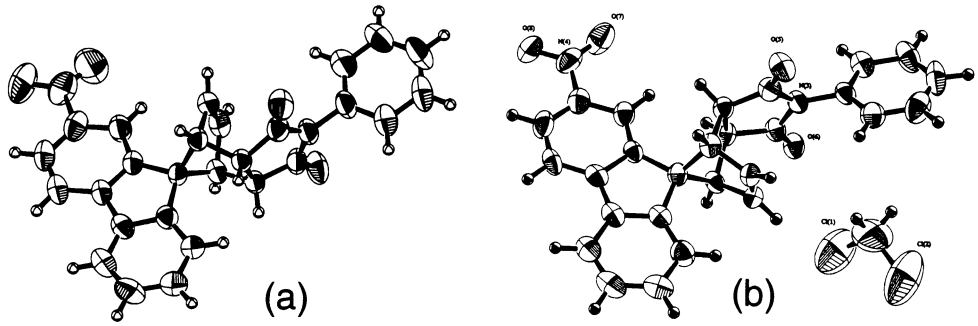
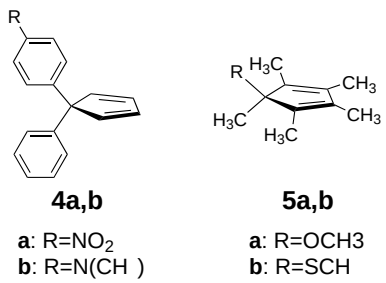


Figure 2. ORTEP diagrams of Diels–Alder adducts of **2b** with *N*-phenylmaleimide (PMI). Atoms are drawn as 50% probability displacement ellipsoids. (a) Major isomer (*anti*-adduct); (b) minor adduct (*syn*-adduct).

and no isomerization to the *anti* adduct was detected, confirming that the distribution of the Diels–Alder adducts was determined kinetically. In the reactions of **2b** with less reactive dienophiles (MA and PMI), which required high reaction temperature and long reaction time, *anti* preference of the addition of PMI was observed, although the magnitude of the facial selectivity decreased, i.e. *anti*:*syn* = 59:41, and in the case of MA the selectivity almost disappeared.[20]

In the case of the 2-methoxy-substituted diene **2c**, *anti* preference of the addition was observed, but the magnitude of the facial selectivity was reduced (*anti*:*syn* = 60:40) even in the reactions of the reactive dienophiles (PTD and MTD). On the other hand, the 4-methoxy-substituted diene **3c** showed no significant facial selectivity in the reactions of the dienophiles, PTD and MTD.[20] This divergent behavior of **2c** and **3c** is in contrast to the similar behaviors of the 2- (**2b**) and 4-nitro substituted dienes (**3b**) in terms of *syn* facial preference.

The related open-chain 5,5-diphenyl-cyclo-1,3-pentadienes **4** behaved differently as Diels–Alder dienes; in the case of the *p*-nitro-substituted **4a**, *syn* attack (with respect to the substituted benzene) was favored, while in the case of the *p*-*N*,*N*-dimethylamino-substituted **4b**, *anti* attack was favored (Scheme 3).[21] The observed preference was accounted for in terms of the Cieplak hyperconjugative model, which is essentially related to the Hammett σ_p values, i.e. the aromatic nitro group is electron-withdrawing and the aromatic amine group is electron-donating.[21]



Scheme 3.

Anti addition with respect to the 5-substituent was observed in the Diels–Alder reaction of 5-(methylthio)-1,2,3,4,5-pentamethylpentadiene **5b** (*anti*:*syn* = 90:10), while 5-methoxy-1,2,3,4,5-pentamethylpentadiene **5a** favored *syn* addition.[12] This *anti* selectivity was interpreted in terms of Cieplak's hyperconjugative stabilization,[3] orbital distortion,[12] and steric effect.[12] Therefore, the present *anti* selectivities of the spiro-fluorene dienes (e.g. **2b** and **3b**), which are vinylogous to the five-substituted 1,3-cyclopentadienes, are genuine examples due to non-steric bias, and probably also due to orbital control (not an electrostatic effect).

The attack is favored on the side of the prevailed antibonding interaction of the diene π orbital of **2b**, **2c** and **3b** (Fig. 3(b)). The orbital phase arrangements of the HOMO of the dienes (for example **2b** and **3b**) were similar to that of the 5-hydroxy-1,3-cyclopentadienes (**5a**) (Fig. 3(a)).[12] In this context, the facial selectivities of **2b** and **3b** can be rationalized in terms of the orbital tilt of the HOMO, arising from σ–π orbital mixing, in a similar manner to the case of 5-hydroxy-1,3-cyclopentadienes (**5a**) (Fig. 3(c)).[12,22]

In summary, the compounds described in this work are excellent probes for examining non-steric facial selectivities in Diels–Alder dienes. This work reveals that the facial selectivities are divergent in the strictly related π-systems, that is, the facial preference of the 5,5-diphenyl-cyclo-1,3-pentadienes (**4**). Systematic comparison of facial selective behavior in sterically unbiased probes will be crucial for construction of a general rationalization model of facial selectivities.

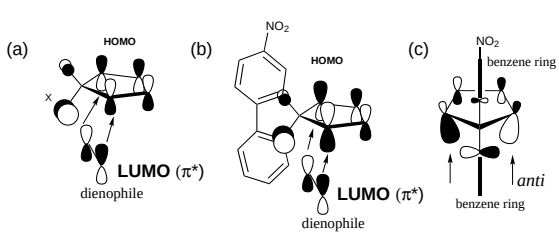


Figure 3. Orbital phase environments.

Acknowledgements

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18. Crystal data of **2b**: MW = 261.28, monoclinic, $P2_1/n$, $a = 10.076(2)$ Å, $b = 11.618(2)$ Å, $c = 11.317(2)$ Å, $\beta = 92.769(2)°$, $V = 1323.2(4)$ Å^3, $Z = 4$, $d_{calcd} = 1.311$ g cm^{-3}, $T = 298$ K, μ(Mo Kα) = 0.87 cm^{-1}, 3213 observed reflections ($I > 3.0\sigma(I)$), 226 variables, $R = 0.043$, $R_w = 0.052$.
19. Crystal data of (**a**): MW = 478.93, triclinic, $P\bar{1}$, $a = 11.153(10)$ Å, $b = 25.48(2)$ Å, $c = 9.136(10)$ Å, $\alpha = 90.05(8)°$, $\beta = 114.18(5)°$, $\gamma = 98.87(5)°$, $V = 2331(4)$ Å^3, $Z = 4$, $d_{calcd} = 1.364$ g cm^{-3}, $T = 298$ K, μ(Mo Kα) = 2.02 cm^{-1}, 4905 observed reflections ($I > 4.0\sigma(I)$), 623 variables, $R = 0.073$, $R_w = 0.086$. Crystal data of (**b**): MW = 476.92, triclinic, P-1, $a = 12.248(4)$ Å, $b = 17.592(4)$ Å, $c = 10.688(2)$ Å, $\alpha = 101.81(2)°$, $\beta = 99.05(2)°$, $\gamma = 87.42(2)°$, $V = 2225.9(10)$ Å^3, $Z = 4$, $d_{calcd} = 1.423$ g cm^{-3}, $T = 298$ K, μ(Cu Kα) = 1.85 cm^{-1}, 3412 observed reflections ($I > 2.0\sigma(I)$), 622 variables $R = 0.060$, $R_w = 0.061$.
20. This result implies that the more reactive the dienophile, the larger the facial selectivity. This is the reverse of the usual relationship between reactivity and selectivity (usually, more reactive, less selective). A similar reverse relationship was previously observed in the Diels–Alder reactions of five-substituted 1,3-cyclopenta-dienes. See: Ishida, M.; Kakita, S.; Inagaki, S. *Chem. Lett.* **1995**, 469–470. See also: Sauer, J.; Wuest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183.
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22. A similar distribution of the orbital coefficients was also found in the case of **2c**. See: Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818–8827.