Importance of Steric Effects in the [4 + 2] Cycloaddition of 5-Substituted Pentamethylcyclopentadienes

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Pentamethylcyclopentadienes with a carbon substituent (X = Pr^i, Et, CH_2OH, CHO) at the C-5 position give *anti* cycloadducts with a variety of dienophiles, which establishes the importance of steric effects in the [4 + 2] cycloaddition of these plane-nonsymmetric dienes.

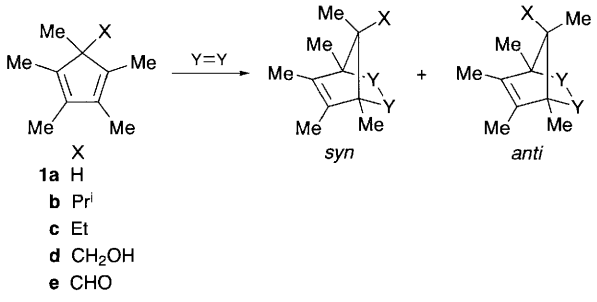
One prominent feature of the Diels–Alder reaction, which makes it such a powerful synthetic tool, is its remarkable regio- and stereo-control.[1] It allows the simultaneous introduction of up to four new stereogenic centres in a one-step operation. For plane-nonsymmetric dienes, the π-facial selectivity of the dienophilic attack constitutes an additional stereochemical feature. In recent years considerable attention has been focused on chiral acyclic[2] and semicyclic dienes,[3] but most experimental [4] and theoretical [5] contributions on π-facial selectivities have been concerned with 5-substituted cyclopentadienes (Scheme 1).

For the latter dienes much work has been conducted to elucidate the extent of diastereoselectivity that can be induced when X represents a heteroatom substituent. Macaulay and Fallis[4g] employed a variety of 5-substituted 1,2,3,4,5-pentamethylcyclopentadienes in the [4 + 2] cycloaddition with standard carbon dienophiles [maleic anhydride (MA) or *N*-phenylmaleimide (NPM)], in which the pentamethyl substitution avoids complications of the facile 1,5-sigmatropic hydrogen atom migrations. It was established that the attack is preferentially (≥ 90 : 10) *syn*‡ for X = OH, OMe, NHAc, NH_2 or Cl, whereas *anti* attack was preferred for X = SH, SR, SOR or SO_2R.

The results were rationalized in terms of the Cieplak model, *i.e.* hyperconjugative stabilization by σ bonds antiperiplanar to the incipient bond.[4g] This qualitative argument was put on a more quantitative basis by Coxon and McDonald,[5g] who performed AM1 calculations on the transition states for *syn* and *anti* attack. An alternative rationalization of the experimental results invokes the orbital mixing rule,[4h,5b,f] *i.e.* a nonequivalent extension of the π HOMO by mixing of the σ orbitals of the carbon framework through interaction with the n orbitals of the C-5 substituent.

Both theoretical models give reasonable mechanistic explanations when X represents a heteroatom substituent, but do not apply when X is a carbon substituent. The application of the Cieplak concept is based on the difference in the σ donor ability of the C–X bond compared to the C–Me σ bond, which is expected to be negligible when X represents a carbon substituent and should be small for X = H. The orbital mixing rule, on the other hand, demands the presence of a free nonbonding electron pair at the X substituent.

We, therefore, were interested in the [4 + 2] cycloaddition of pentamethylcyclopentadienes **1b–e** (Scheme 1) which bear simple carbon substituents at C-5, and their comparison to the parent system **1a**. The absence of stereoelectronic effects due to heteroatom substituents directly attached to the cyclopentadiene moiety should allow evaluation of the importance of steric effects on the stereocontrol in the present reaction.



X
1a H
b Pr^i
c Et
d CH_2OH
e CHO

Scheme 1

The starting dienes were prepared by reaction of pentamethylcyclopentadienyllithium with Pr^{i}I (**1b**, 91%), EtI (**1c**, 87%) and HCO_2Me[6] (**1e**, 67%) at room temperature. Sodium borohydride reduction of the latter gave the alcohol **1d**[7] in 92% yield.

To assess the influence of the dienophile on the π-facial selectivity, in addition to the carbon dienophile maleic anhydride (NPM in the case of **1d**), we employed also the heteroatomic dienophile 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) and the excited-state dienophile singlet oxygen ($^1O_2$). The reactions were run to complete conversion of the starting dienes **1** and in all cases high yields of the corresponding cycloadducts were obtained. The observed diastereoselectivities are summarized in Table 1. The assignment of the *syn*/*anti* stereochemistry was made on the basis of NOE experiments for the respective cycloadducts. Furthermore, the *anti* adduct of the reaction of MTAD with aldehyde **1e** was unequivocally assessed by means of an X-ray analysis (details will be published elsewhere).

All dienophiles used herein showed a moderate *syn* preference in their [4 + 2] cycloaddition with diene **1a** (Table 1). This is in good agreement with previously published data[4e] on the [4 + 2] cycloaddition of this particular substrate with the dienophiles maleic anhydride, NPM, *p*-benzoquinone and 1,4-naphthoquinone. It is attributed to the preferred approach of the dienophile from the sterically less congested *syn* face of the diene.

In accordance with stereocontrol by steric bias, in the reaction of the carbon-substituted dienes **1b–e**, the *anti* adducts were formed exclusively (Table 1), regardless of the nature of the

Table 1 Diastereoisomeric ratios (d.r.) in the [4 + 2] cycloadditions of cyclopentadienes **1a–e**[a]

Diene	X	Major diastereoisomer	Dienophile MA[b]	MTAD[c]	$^1O_2$[d]
1a	H	*syn*	79 : 21[e]	75 : 25	80 : 20
1b	Pr^i	*anti*	≥95 : 5	≥95 : 5	≥95 : 5
1c	Et	*anti*	≥95 : 5	≥95 : 5	≥95 : 5
1d	CHO	*anti*	≥95 : 5	≥95 : 5	≥95 : 5
1e	CH_2OH	*anti*	≥95 : 5[f]	≥95 : 5	≥95 : 5

[a] The d.r. values were estimated by ^1H NMR analysis of the spectra for the crude reaction mixtures (error limit ± 5% of the stated values). All unknown cycloadducts were fully characterized by combustion analyses or iodometry, the latter for the labile singlet oxygen adducts. [b] Maleic anhydride cycloadditions were run in benzene at room temp., only adducts which resulted from *endo* attack were observed (yields ≥90%). [c] Reactions were run in CH_2Cl_2 at 0 °C for 5 min (yields ≥95%). [d] A solution of the respective substrate and a catalytic amount of tetraphenylporphyrin as sensitizer in deuteriochloroform was irradiated for 15 min (30 min for **1d**) by means of two OSRAM Vialox NAV-E (250 W) sodium lamps, while a gentle stream of dry oxygen gas was allowed to pass through the solution [yields (^1H NMR analysis) *ca.* 80% for **1a,b**; ≥90% for **1c,d,e**]. [e] Taken from ref. 4*e*. [f] NPM adduct.

dienophile employed. While this stereochemical outcome is not unexpected for the bulky isopropyl substituent **1b**, the high (≥ 95 : 5) *anti* selectivity for X = Et **1c**, CH_2OH **1d** and CHO **1e** is somewhat surprising, since these substituents exercise only slightly more steric hindrance than the methyl group.

Furthermore, it can be seen that a homoallylic hydroxy functionality, as in alcohol **1d**, plays no beneficial role in directing the incoming dienophile to the *syn* face of the diene. This has already been noted by Paquette *et al.*,[4f] who observed in the [4 + 2] cycloaddition of 5-methyl-5-hydroxymethylcyclopentadiene with NPM good *anti* selectivity (d.r. = 87 : 13). The slight increase for the *anti* adduct (d.r. ≥ 95 : 5) for alcohol **1d** in the present study is consistent with the general trend that highly alkylated and, thus, more electron-rich cyclopentadienes show higher π-facial selectivities compared to their parent systems. The higher reactivity of the pentamethylated dienes suggests an early, substrate-like transition state for the present cycloaddition,[4e] for which the effect of steric bias in the substrate should be enhanced. In accordance with this rationale, the observed d.r. values do not vary with the dienophile, *i.e.* substrate control is decisive for π-facial selectivity. On the other hand, for the less electron-rich 5-methylcyclopenta-1,3-diene a dependence of the d.r. values on the nature of the dienophile has been observed.[4b,e,8]

The present results clearly indicate that steric control alone, *i.e.* non-bonding repulsion of the dienophile, is sufficient to induce high π-facial selectivities for 5-substituted pentamethylcyclopentadienes. Also the *anti* selectivities encountered in the Diels–Alder reaction of the heteroatom-substituted derivatives (X = SR, SOR, SO_2R, SeR, TeR, SiR_3)[4g,h] can be easily explained in terms of steric control without the need to invoke complex stereoelectronic effects. The present results further stress the importance of the rare cases[4a,d,h,5f] for which actually contrasteric π-facial selectivity has been observed. Finally, regardless of mechanistic queries, the present stereochemical information, *i.e.* high *anti* control caused by steric hindrance, should be helpful to the synthetic chemist to make the proper choice of dienes for [4 + 2] cycloadditions.

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Footnotes

† Undergraduate research participant, autumn 1993.

‡ To avoid confusion which may arise from nomenclature or from priority changes when X = H, in harmony with standard practice, the stereochemical labels *syn* and *anti* describe the facial approach relative to X throughout this paper.

References

1 L. Paquette, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, ch. 7.

2 R. Tripathy, R. W. Franck and K. D. Onan, *J. Am. Chem. Soc.*, 1988, **110**, 3257.

3 M. J. Fisher, W. J. Hehre, S. D. Kahn and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 4625.

4 (*a*) S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Am. Chem. Soc.*, 1955, **77**, 4183; (*b*) S. McLean and P. Haynes, *Tetrahedron*, 1965, **21**, 2313; (*c*) R. Breslow, J. M. Hoffman Jr. and C. Perchonock, *Tetrahedron Lett.*, 1973, **38**, 3723; (*d*) D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1980, 739; (*e*) D. J. Burnell and Z. Valenta, *J. Chem. Soc., Chem. Commun.*, 1985, 1247; (*f*) L. A. Paquette, C. Vanucci and R. D. Rogers, *J. Am. Chem. Soc.*, 1989, **111**, 5792; (*g*) J. B. Macaulay and A. G. Fallis, *J. Am. Chem. Soc.*, 1990, **112**, 1136; (*h*) M. Ishida, T. Aoyama, Y. Beniya, S. Yamabe, S. Kato and S. Inagaki, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3430.

5 (*a*) N. T. Anh, *Tetrahedron*, 1973, 3227; (*b*) S. Inagaki, H. Fujimoto and K. Fukui, *J. Am. Chem. Soc.*, 1976, **98**, 4054; (*c*) R. Gleiter and L. A. Paquette, *Acc. Chem. Res.*, 1983, **16**, 328; (*d*) S. D. Kahn and W. J. Hehre, *J. Am. Chem. Soc.*, 1987, **109**, 663; (*e*) F. K. Brown, K. N. Houk, D. J. Burnell and Z. Valenta, *J. Org. Chem.*, 1987, **52**, 3050; (*f*) M. Ishida, Y. Beniya, S. Inagaki and S. Kato, *J. Am. Chem. Soc.*, 1990, **112**, 8980; (*g*) J. M. Coxon and D. Q. McDonald, *Tetrahedron Lett.*, 1992, **33**, 651.

6 F. X. Kohl and P. Jutzi, *Chem. Ber.*, 1987, **120**, 1539.

7 R. J. Bushby and D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1979, 688.

8 W. Adam, H. Walter, G. F. Chen and F. Williams, *J. Am. Chem. Soc.*, 1992, **114**, 3007.