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HOW IMPORTANT IS SECONDARY OVERLAP IN DETERMINING THE REGIOSELECTIVITY OF DIELS-ALDER REACTIONS?

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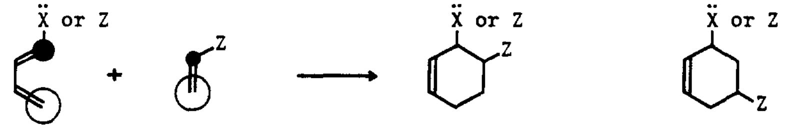
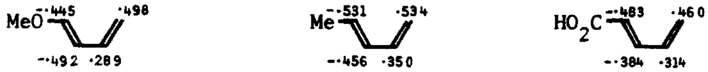
In most Diels-Alder reactions, 1-substituted dienes react with unsymmetrical dienophiles to give 'ortho' adducts (**1**) as major products, whether the 1-substituent is electron-donating ($\ddot{X}$) or electron-withdrawing (Z). Frontier orbital theory has been very successful in explaining this kind of regioselectivity: in its simplest form it matches the coefficients on C-1 and C-4 in the HOMO of the diene to the coefficients on C-1 and C-2 in the LUMO of the dienophile.[1]



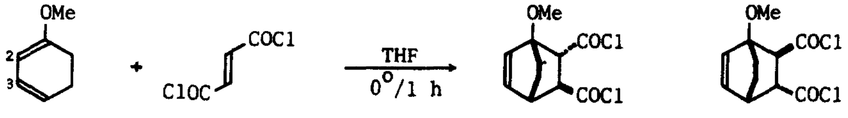
(**1**) major (**2**) minor

However, calculations on 1-substituted dienes often show only a small difference between the coefficients on C-1 and C-4 in cases where the regioselectivity is, nevertheless, quite high. The same calculations generally show a much larger difference between the coefficients on C-2 and C-3. With this in mind, Alston suggested[2] that perhaps regioselectivity in such cases is principally determined, through secondary overlap, by the difference in the coefficients on C-2 and C-3. We now report the results of two experiments which seem to show that this is not a large effect, but that it can be a noticeable one.

HOMO's:[3]



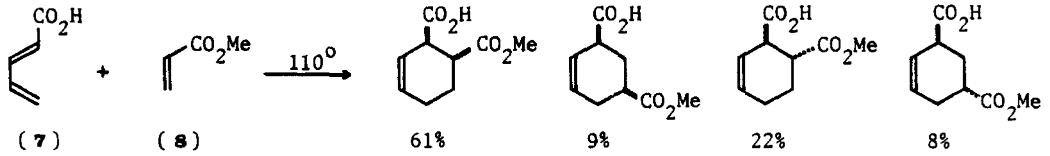
In the first, we investigated the Diels-Alder reaction between 1-methoxycyclohexa-1,3-diene (**3**) and fumaroyl chloride (**4**), in which two adducts (**5**) and (**6**) are formed.[4] The



(**3**) (**4**) (**5**) 28%[5] (**6**) 72%[5]

transition state leading to the minor adduct (**5**) benefits from secondary overlap between the p orbital on C-2 of the diene and the p orbital on the carbon atom of the *endo* carbonyl group, and the transition state leading to the major adduct (**6**) benefits from secondary overlap between the p orbital on C-3 and the p orbital on the carbon atom of the *endo* carbonyl group. Since the p orbital on C-2 has the larger coefficient in the HOMO, the former ought to have been the major product. Since it was not, we conclude that secondary overlap is a small effect, and that some other factor, not yet identified, tips the balance the other way.

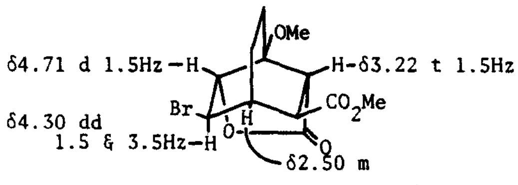
In the second, we looked more closely at the regioselectivity of the Diels-Alder reaction between *trans*-penta-2,4-dienoic acid (**7**) and methyl acrylate (**8**).[6] If the coefficients on C-2 and C-3 are to be the principal directing effect, the proportion of 'ortho' adduct should be much greater for the *endo* than for the *exo* adducts. This is the direction in which the effect is observed: the ratio of 'ortho' to 'meta' adducts is 61:9 for the *endo* pair, and 22:8 for the *exo* pair. Nevertheless the regioselectivity in the formation of the *exo* adducts is still clearly in favour of the 'ortho' isomer, and this cannot be a result of secondary overlap. If all other factors were equal, these numbers indicate that the regioselectivity for the *endo* adducts is determined almost equally by secondary and by primary overlap.



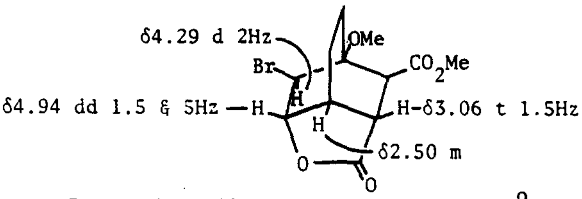
(**7**) (**8**)

REFERENCES AND NOTES

1. K. N. Houk, *Accounts Chem. Res.*, **8**, 361 (1975); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976, Chapter 4.
2. P. V. Alston, R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38**, 4075 (1973).
3. Coefficients from: P. V. Alston and R. M. Ottenbrite, *J. Org. Chem.*, **40**, 1111 (1975); other calculations[7] show C-4 of a Z-substituted diene to have slightly the larger coefficient.
4. The structures of the two adducts were determined by separating their methyl esters[5] (silica gel-CCl_4- EtOAc) and then converting each to the bromolactones (**9**) and (**10**)(Br_2-$CHCl_3$-r.t.). These had definitive NMR spectra, the salient features of which are shown:



From minor adduct: (**9**) m.p. 93-94°



From major adduct: (**10**) m.p. 140-143°

(**9**): irradiation at 3.22 caused the d at 4.71 to collapse to s, and irradiation at 2.50 caused the dd at 4.30 to collapse to d 1.5Hz. (**10**): irradiation at 3.06 caused the dd at 4.94 to collapse to a d 5Hz, and irradiation at 2.50 caused the dd at 4.94 to collapse to a d 1.5Hz.
5. Estimated (±3%) by g.l.c. of the methyl esters. The conditions in which the methyl esters were formed (1M NaOMe-r.t.-45 min) had no effect on the ratio. The direct reaction between (**3**) and dimethyl fumarate (reflux-xylene-90 h) gave the same esters in the same ratio. The proportion in which (**5**) and (**6**) were formed did not change as the reaction proceeded.
6. The experimental details are reported in L. E. Overman, G. F. Taylor, K. N. Houk, and L. N. Domelsmith, *J. Amer. Chem. Soc.*, in press.
7. K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Amer. Chem. Soc.*, **95**, 7287, (1973).