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THE REGIOSELECTIVITY OF THE DIELS-ALDER REACTION BETWEEN A DIENE WITH AN ELECTRON-DONATING SUBSTITUENT AND A DIENOPHILE WITH AN ELECTRON-DONATING SUBSTITUENT A TEST CASE FOR FRONTIER ORBITAL THEORY

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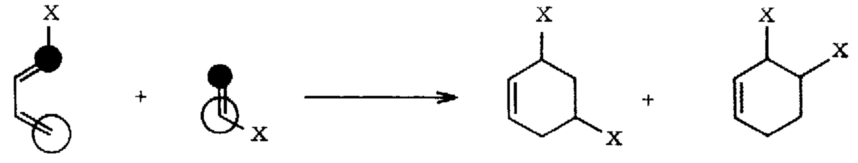
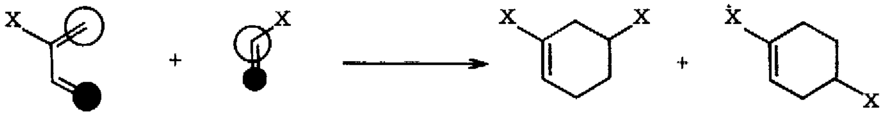
Frontier orbital theory has been used to explain the regioselectivity of many Diels-Alder reactions and of other cycloadditions.[1,2] In the most useful account of this subject, Houk[2] has classified substituents into three classes C-, Z- and X-, these are, respectively, simple conjugated substituents (C = vinyl, phenyl etc), conjugated and electron-withdrawing substituents (Z = COR, CN, NO_2 etc) and electron-donating substituents (X = NMe_2, OMe, Me etc.). Most of the eighteen possible combinations of 1- or 2-C-, Z- or X-substituted dienes reacting with C-, Z- or X-substituted dienophiles are known, and almost all of the known reactions show regioselectivity in accordance with frontier orbital theory. The common pattern is for "ortho" adducts to be favoured with 1-substituted dienes and for "para" adducts to be favoured with 2-substituted dienes, and this is what is expected for sixteen of the eighteen possible combinations. The two exceptions are the reactions of 1- or 2-X-substituted dienes reacting with an X-substituted dienophile, for both of which the theory predicts that the "meta" adducts (**1** and **3**) *should be favoured. As it happens, these two types of Diels-Alder reaction* are virtually unknown,[3] and therefore the discovery of what regioselectivity they would show will serve as a test of the predictive power of frontier orbital theory. A theory has been put forward, it suggested a corroborative experiment and we have now carried out that experiment. It is a particularly significant experiment, because the only other theory that has successfully accounted for the regioselectivity of Diels-Alder reactions - the diradical theory[4] - makes the opposite prediction.

The problem is to persuade X-substituted dienes to react at all with X-substituted dienophiles. We have solved this problem by using the very reactive dienes[5] (**6** and **10**) as our 1- and (vinylogous) 2-substituted dienes, and these are readily available in low concentration when the corresponding benzcyclobutenes (**5** and **9**) are heated. The adducts we obtained show that, although there is little regioselectivity, the "meta" adducts are the major products in each case.[6] The preferred formation of the "meta" adduct (**7**) in the case of the diene (**6**) might have been a steric effect and is therefore inevitably an ambiguous result The results with the other diene (**10**), however, are plainly not steric in origin. Furthermore, simple arrow-pushing (or the drawing of canonical forms) does not explain why the major adducts are the "meta" ones, and neither does the theory which invokes the formation of the most stable possible diradical intermediate. Frontier orbital theory clearly provides the best simple explanation of these observations.

THE PREDICTION



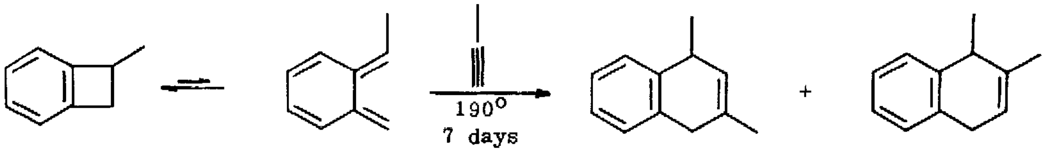
(1) major **(2)** minor



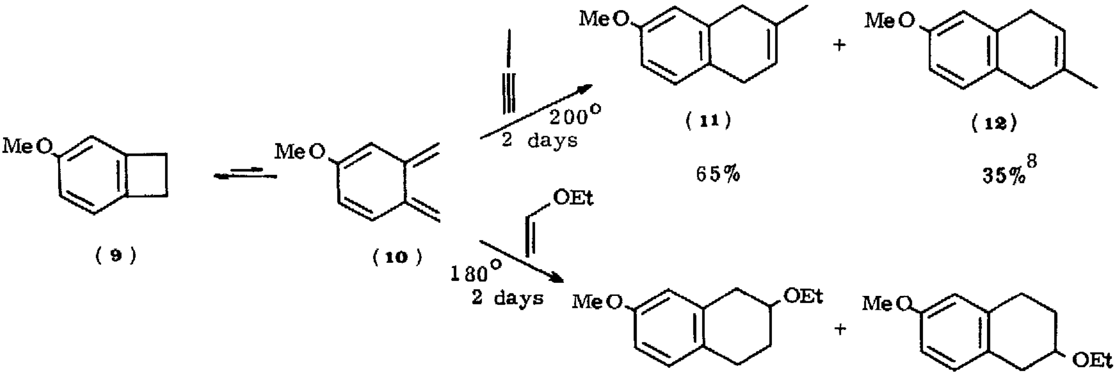
(3) major **(4)** minor

(X = NMe_2, OMe, Me etc.)

THE OBSERVATIONS



(5) (6) (7) 65% (8) 35%[7]



(9) (10) (11) 65% (12) 35%[8] (13) 61% (14) 39%[9]

FOOTNOTES AND REFERENCES

1. W. C. Herndon, Chem. Rev., 72, 157 (1972), O. Eisenstein, J.-M. Lefour and N. T. Anh, Chem. Comm., 969 (1971), R. Sustmann, Pure Appl. Chem., 40, 569 (1975), K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and J. K. George, J. Amer. Chem. Soc., 95, 7287 (1973), K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, ibid., 7301, N. D. Epiotis, ibid, 5624, J. Bastide, N. E. Ghandour and O. Henri-Rousseau, Bull. Soc. chim. France, 2290 and 2294 (1973), J. Bastide and O. Henri-Rousseau, ibid., 1037 (1974), P. V. Alston and R. M. Ottenbrite, J. Org. Chem., 40, 1111 (1975).

2. K. N. Houk, J. Amer. Chem. Soc., 95, 4092 (1973).

3. Vinyl acetate reacts with 1,5,5-trimethylcyclopentadiene to give more epibornyl acetate than bornyl acetate,[10] but this reaction was done before accurate analysis was easy, and the result could have been steric in origin. The reactions of vinyl acetate with methylcyclopentadiene[11] show little regioselectivity.

4. R. A. Firestone, J. Org. Chem., 37, 2181 (1972), see also, T. Kametani, Y. Kato, T. Honda and K. Fukumoto, J. Chem Soc. Perkin I, 2001 (1975).

5. By using "very reactive dienes" we have, of course, found ourselves studying relatively exothermic reactions. Frontier orbital theory is likely to be particularly successful with exothermic reactions, because, in such reactions, the transition state resembles the starting materials more than the products.

6. The reactions were carried out in sealed tubes, using 100 mg of the benzcyclobutene[12] and approximately 2 ml of the dienophile. Yields were essentially quantitative.

7. The mixture of **7** and **8** was oxidised in 70% yield using 1 equivalent of DDQ in benzene at room temperature for 30 min. The NMR spectrum of the mixture obtained from this oxidation was compared with that of a mixture of authentic 1,2- and 1,3-dimethylnaphthalenes. The C-methyl signals were well separated in C_6D_6 solution, those of 1,2-dimethylnaphthalene appearing at δ 2.18 and 2.28, and those of 1,3-dimethylnaphthalene at 2.22 and 2.39. Simple integration of the four signals gave an estimate of the proportion of the two isomers accurate to ±5%. Both dimethylnaphthalenes were stable to DDQ under the reaction conditions, and both dimethylnaphthalenes were consumed at very similar rates under somewhat more vigorous conditions.

8. The mixture of **11** and **12** was oxidised in 96% yield using 1 equivalent of DDQ in benzene at room temperature for 1 min. It could also be oxidised in comparable yield simply by stirring a solution in benzene in the air at room temperature for 5 days. The NMR spectra of the mixtures obtained from these oxidations were compared with those of a mixture of authentic 2-methoxy-7-methylnaphthalene and 2-methoxy-6-methylnaphthalene.[13] The methoxy and methyl signals of the latter were 0.01 ppm upfield from those of the former. The proportion of the two isomers was estimated by comparison of the appearance of these just-resolved signals in the oxidation mixture with the appearance of the signals in mixtures of the authentic compounds. The results are probably accurate to ±5%. Propylene was also used as a dienophile with both dienes. There appeared to be little regioselectivity with **6**, but we were unable to analyse the mixture of products accurately enough to give any kind of number. The regioselectivity with **10** was only 52 48 in favour of the "meta" adduct, as judged by the 220MHz NMR spectrum and comparison with the authentic compounds prepared from the known 6- and 7-methoxy-2-tetralones.[14]

9. The mixture of **13** and **14** was analysed by comparison of its ^{13}C NMR spectrum in $CDCl_3$ with the spectrum of the authentic compounds prepared from the known 6- and 7-methoxy-2-tetralones.[14] Calibration of the spectra was done using carefully weighed out mixtures of the authentic materials and comparing peak heights with weight. (Within experimental error, the peak height was proportional to weight.) The signals used were, for **13**, three peaks 40.03, 32.67 and 30.47 ppm downfield from TMS, and, for **14**, the corresponding peaks at 38.92, 32.46 and 31.64. This is our most accurate measurement, the standard deviation is ±3%.

10. K. Alder and E. E. Windemith, *Annalen*, *543*, 41 (1940).

11. H. Krieger and S.-E. Masar, *Suomen Kem.*, *43B*, 318 (1970).

12. The benzcyclobutene (**5**) was prepared by the method of M. P. Cava and M. J. Mitchell, *J. Org. Chem.*, *27*, 631 (1962). The benzcyclobutene (**9**) was prepared by methylation of the known phenol. The phenol was prepared by modification of the method of J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, *21*, 2281 (1965).

13. T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2564 (1956), R. N. Shreve and F. F Lloyd, *Ind. Eng. Chem.*, *42*, 811 (1950). We thank Dr. Halsall for the sample of 2-hydroxy-7-methylnaphthalene.

14. J. J. Sims, L. H. Selman and M. Cadogan, *Org. Synth.*, 51, 109 (1971), H. Cassebaum, *Chem. Ber.*, 90, 2876 (1957).