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Filled-Orbital Repulsion; A New Factor in π-Facial Selectivity of Diels-Alder Reactions.

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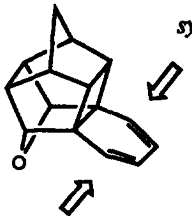
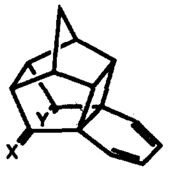
Abstract: *Dimethyl acetylenedicarboxylate and N-phenyl-1,2,4-triazolinedione add to ether 1 from the more sterically congested face of the diene syn to the cyclobutane ring. The interaction of the ether oxygen lone pair with the dienophile acetylenic π-orbital or azo n-orbitals orthogonal to the forming σ-bonds is important in determining the observed facial selection.*

The regio- and stereo- chemistry of Diels-Alder reactions are well understood. Facial selectivity remains a matter of controversy.[1] In order to test the hypothesis that lone pair interactions can be important in determining facial selectivity[2] we now report selected addition reactions with the cage ether 1. This compound is designed[3] to position a lone pair of the ether oxygen centrally so as to interact with the π-orbital of an acetylenic dienophile or n-orbitals of an azo dienophile which are orthogonal to forming σ-bonds when reaction occurs from the face of the diene bearing the ether oxygen. If this electronic effect is important acetylenic and azo dienophiles should react from the cyclobutane face and alkene dienophiles from the opposite and less hindered face.

1

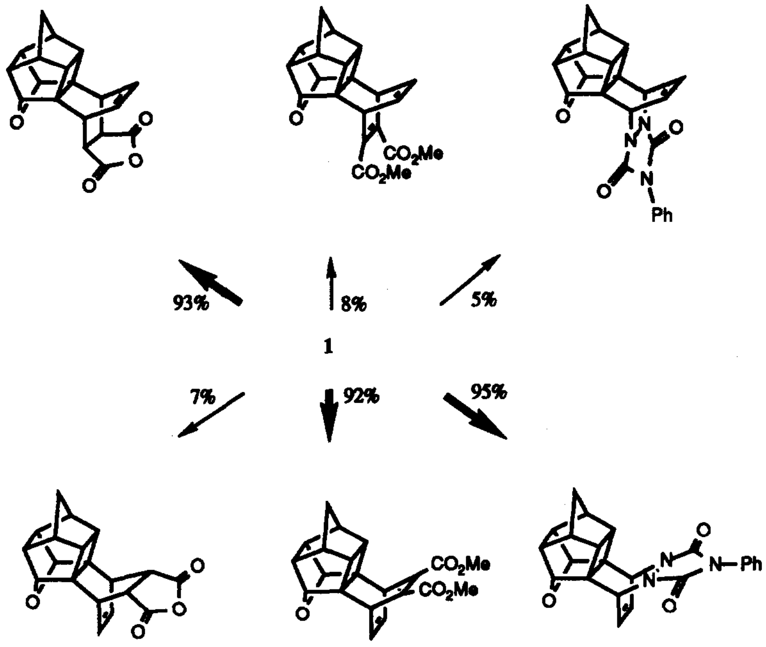


Reaction of maleic anhydride (MA), well established as a representative alkene dienophile, with 1 occurs preferentially[4] from the *anti* face (96:4, *anti*:*syn*). This is consistent with the reactions of alkenes with the cage dienes 2a-c where the *anti*-face of the molecule is considered to be less



2
a, X = Y = O
b, X = O, Y = CH_2
c, X = Y = CH_2

hindered. In parallel with experiment, molecular mechanics transition state calculations[4] for the reaction of **1** with MA predict that reaction will occur from the *anti* face of the diene (93:7, *anti*:*syn*). Similar calculations for the addition of dimethyl acetylenedicarboxylate (DMAD) predict a 78:22; *anti*:*syn* ratio and this conflicts with experiment (8:92).[5] Since the molecular mechanics calculations do not take into account through space stereoelectronic interactions the difference between experiment and calculation could be explained by an interaction of the lone pair of the ether oxygen with the π-orbital of the acetylene that is orthogonal to the forming σ-bonds. This interaction would disfavour addition *syn* to the ether oxygen. N-Phenyl-1,2,4-triazolinedione (PTAD)[6] like DMAD adds with *syn* specificity (5:95)[7] suggesting that the nitrogen lone pairs interact in a similar way with the ether oxygen.



To further characterise the nature of the interaction between lone pair electrons and acetylenic dienophiles, semi-empirical molecular orbital calculations were performed for the addition to **1** of acetylene[8] as a model for DMAD.[9] The AM1 calculated activation enthalpies for *syn* and *anti* face addition (172.5 and 174.1 kJ mol^{-1} respectively) reflect qualitatively the facial preference observed with DMAD. The calculated wavefunctions of the reacting species at their transition state geometries, but at infinite separation, show that distortion to the transition state geometry causes the energy of the filled orthogonal π-HOMO of acetylene to rise to the same extent (44 kJ mol^{-1}) for reaction from each face. When the distorted fragments are positioned at the transition state geometry the subsequent orbital interaction is facially dependent. The transition state for *anti* addition is destablized by a greater increase in energy (43 kJ mol^{-1}) of the π-orbital of acetylene which is orthogonal to the forming σ-bonds than that for *syn* face addition (14 kJ mol^{-1}). The magnitude of the interaction rationalizes the failure of the molecular mechanics based transition state model to predict the selectivity observed in the addition of DMAD and demonstrates unequivocally that interaction of a suitably positioned lone pair with electron density of a dienophile orthogonal to the forming σ-bonds is a factor in determining facial selectivity. This conclusion is supported by further experimental results which will be published in a full paper.[11]

REFERENCES AND NOTES:

1. Watson, W.H., 'Stereochemistry and Reactivity of Systems Containing π Electrons', Verlag Chemie International, Deerfield Beach, Florida, **1983**, 41-75. Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* **1990**, *112*, 1136. Tucker, J.A.; Houk, K.N.; Trost, B.M. *J. Am. Chem. Soc.* **1990**, *112*, 5465. Paquette, L.A.; Vanucci, C.; Rogers, R.D. *J. Am. Chem. Soc.* **1989**, *111*, 5792. Fisher, M.J.; Hehre, W.J.; Kahn, S.D.; Overman, L.E. *J. Am. Chem. Soc.* **1988**, *110*, 4625. Brown, F.K.; Houk, K.N.; Burnell, D.J.; Valenta, Z. *J. Org. Chem*, **1987**, *52*, 3050. Kahn, S.D.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 663. Brown, F.K.; Houk, K.N. *J. Am. Chem. Soc.* **1985**, *107*, 1971. Böhm, M.C.; Carr, R.V.C.; Gleiter, R.; Paquette, L.A. *J. Am. Chem. Soc.* **1980**, *102*, 7218. Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1991**, *113*, 7630.

2. Addition of alkene dienophiles to **2a** (Coxon, J.M.; O'Connell, M.J.; Steel, P.J. *J. Org. Chem.*, **1987**, *52*, 4726) and **2b,c** (Coxon, J.M.; Maclagan, R.G.A.R.; McDonald, D.Q.; Steel, P.J. *J. Org. Chem.* **1991**, *56*, 2542) occurs predominantly *anti* to the cyclobutane group while significant quantities of products of *syn* face addition are observed for acetylene and azo dienophiles. While alkene addition is consistent with transition state calculations which take into account steric and torsional interactions and with Ψ_1/HOMO dienophile antibonding interactions for **2a,b** addition, azo and acetylene dienophiles cannot be rationalized by either method. For reactions of **2a,b** the interaction of the filled orbitals of the carbonyl(s) and in particular the oxygen lone pairs, with the incoming acetylenic dienophile, DMAD, or PTAD, has been postulated by us to disfavor addition from the carbonyl face.

3. The cage ether 13-oxaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]hexadeca-4,6-diene (**1**) was prepared by reduction of the monotosylhydrazone of diketone **2a** and involves the intermediacy of a tosylhydrazine. Coxon, J.M.; Fong, S.T.; O'Connell M.J.; Steel, P.J. *Tetrahedron Letters*, **1991**, *32*, 7115.

4. The Diels-Alder reactions were carried out in refluxing benzene except for those of PTAD where the reaction was carried out in dichloromethane at 0-5°C. Product ratios were determined by analysis of 300 MHz ^{1}H NMR spectra of the crude reaction mixtures. The addition products were isolated for identification purposes and were separately shown to be stable to the reaction conditions. The structural assignments are supported by nOe experiments. *anti* MA adduct: 7,16-dioxanonacyclo[11.5.2.$1^{4,10}$.$0^{2,6}$.$0^{2,12}$.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$.$0^{14,18}$]heneicosa-19-ene-15,17-dione,

mp 236-237°C; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 10.6 Hz, H21b); 1.89 (d, J = 10.6 Hz, H21a); 2.14 (m, H3,H11); 2.40 (m, H4,H10); 2.76 (m, H5,H9); 3.19 (m, H14,H18); 3.26 (m, H1,H13); 4.51 (m, H6,H8); 6.42 (m, H19,H20). *syn* MA adduct: 7,16-dioxanonacyclo-$[11.5.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}.0^{14,18}]$heneicosa-19-ene-15,17-dione. This adduct was not obtained free of the major isomer. The following ^{1}H NMR data were extracted from a spectrum of a mixture with the major isomer and support the assignment by comparison with analogues: δ 1.60 (d, J = 10.7 Hz, H21b); 1.92 (d, J = 10.6 Hz, H21a); 2.16 (m, H3,H11); 2.48 (m, H4,H10); 2.67 (m, H5,H9); 3.32 (m, H14,H18); 3.48 (m, H1,H13); 4.24 (m, H6,H8).

5. The transition state models for acetylene and alkene dienophiles are described in reference 2 and details for these systems will be reported in a full paper.

6. *syn*-DMAD adduct: 7-oxa-14,15-bis(methoxycarbonyl)octacyclo-$[11.2.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}]$octadeca-14,16-diene, mp 98-99°C; ^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 10.5 Hz, H18b); 1.88 (d, J = 10.4 Hz, H18a); 2.20 (m, H3,H11); 2.29 (m, H4,H10); 2.67 (m, H5,H9); 3.80 (s, OCH_3); 4.03 (m, H1,H13); 4.32 (m, H6,H8); 6.29 (m, H16,H17). *anti*-DMAD adduct: 7-oxa-14,15-bis(methoxycarbonyl)octacyclo-$[11.2.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}]$octadeca-14,16-diene: ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 10.4 Hz, H18b); 1.87 (d, J = 10.4 Hz, H18a); 2.05 (m, H3,H11); 2.28 (br s, $W_{h/2}$ = 8 Hz, H4,H10); 2.62 (br s, $W_{h/2}$ = 10 Hz, H5,H9); 3.75 (s, OCH_3); 4.00 (m, H1,H13); 4.36 (m, H6,H8); 6.50 (m, H16,H17).

7. *anti*-PTAD adduct: 16-phenyl-14,16,18-triaza-7-oxanonacyclo-$[11.5.2.1^{4,10}.0^{2,6}.0^{3,11}.0^{5,9}.0^{8,12}.0^{14,18}]$heneicosa-19-ene-15,17-dione: mp 256- 257°C; ^{1}H NMR ($CDCl_3$) δ 1.74 (d, J = 10.6 Hz, H21b); 2.03 (d, J = 10.6 Hz, H21a); 2.46 (br s, H4,H10); 2.81 (m, H5,H9); 2.91 (m, H3,H11); 4.45 (m, H6,H18); 5.09 (m, H1,H13); 6.39 (m, H19,H20); 7.36, 7.45 (m, phenyl). *syn*-PTAD adduct: The following ^{1}H NMR data were extracted from a spectrum of an enriched mixture with the major isomer; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, J = 10.4 Hz, H21b); 1.92 (d, J = 10.4 Hz, H21a); 2.25 (m, H4,H10); 4.80 (m, H6,H18 or H1,H13); 6.71 (m, H19,H20).

8. The mechanism of PTAD addition is uncertain and the relative orientation of the dienophile and diene at the transition state remains undetermined. Jensen, F.; Foote, C.S. *J. Am. Chem. Soc.*, **1987**, *109*, 6376. Coxon, J.M.; D.Q.McDonald. *Tetrahedron Letters*. **1992**, *33*, 3673.

9. The use of acetylene as a model is necessitated since inclusion of the rotationally flexible methoxycarbonyl groups makes location of the transition states difficult. The factors operative in determining facial selectivity in DMAD should be apparent with the acetylene model. *Ab initio* calculations of such large systems are impracticable.

10. The transition states were located by minimizing the gradient norm (C_s symmetry imposed) of a starting geometry based on the AM1 transition state for the reaction of acetylene and 1,3-cyclohexadiene.

11. Further support for this interpretation is provided by a recent report describing the Diels-Alder reactions of a related hydrocarbon in which the ether oxygen of 1 is replaced by a methylene group. For all dienophiles studied the reaction occurred preferentially from the same face. Fessner, W-D.; Grund, C.; Prinzbach, H. *Tetrahedron Letters*. **1991**, *32*, 5935.

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