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REVERSE-ELECTRON-DEMAND DIELS-ALDER DIENOPHILE π-FACE SELECTIVITY VIA CONFORMATION DEPENDENT TRANSMISSION OF π–σ–π ELECTRONIC INTERACTIONS.

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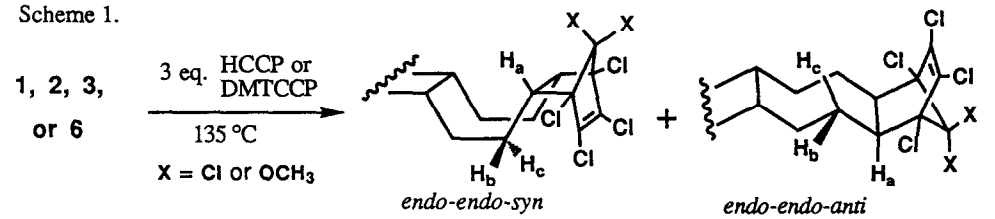
Summary: Reverse-electron-demand Diels-Alder reactions of a series of remotely substituted cyclooctenes with hexachlorocyclopentadiene and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopenta-2,4-diene indicate that dienophile π-face selectivity results from conformation dependent transmission of π–σ–π electronic interactions.

Paquette and others have attributed Diels-Alder diene π-face selectivity to σ–π electronic interactions[1] and Gugelchuk has reported long-range electronic control of Diels-Alder diene π-face stereoselection.[2] Hoffman, Gleiter, and Paddon-Row have reported evidence for conformation dependent transmission of π–σ–π electronic interactions.[3,4] These related studies and the lack of other satisfactory explanations for the diastereoselectivity observed in the preceding paper led us to test for remote electronic effects on reverse-electron-demand Diels-Alder reactions with a series of structurally similar dienophiles. The results provide evidence that conformation dependent transmission of π–σ–π electronic interactions mediate reverse-electron-demand Diels-Alder dienophile π-face selectivity.

A series of remotely substituted cycloctenes[5,6,7,8] (Scheme 1; Table 1) react with hexachlorocyclopentadiene (HCCP) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopenta-2,4-diene (DMTCCP). The reaction conditions (neat in diene at 135 °C) are under kinetic control since the diadducts do not interconvert at 250 °C. Diels-Alder reaction of the flexible cyclooctenes lock in either a syn (boat) or anti (chair) eight-membered ring stereochemistry and determines the dienophile π-face selectivity.

Scheme 1.

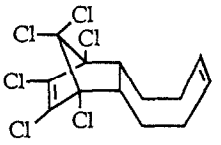
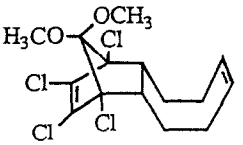
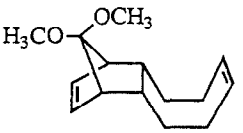
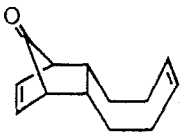
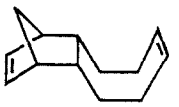
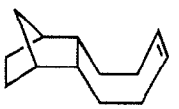


endo-endo-syn *endo-endo-anti*

The syn:anti ratios were determined by integration of diagnostic ^{1}H NMR chemical shift differences in H_a and H_b and the methoxyl groups when present. The stereochemistry of the adducts, **1a**, **1b**, **2a**, and **2b**, reported in the preceding paper combined with the ^{1}H NMR assignments of H_a, H_b, and H_c allows unambiguous stereochemical assignments for the unsymmetric pentacyclic products. The heptacyclic product stereochemistry is determined by methoxyl and H_a or H_a integrations alone for **4a**:**4b** and **5a**:**5b**.[9] The ^{1}H NMR assignment of H_a and the methoxyls is based on the powerful NOE observed between the proximate methoxyl groups of **2a** and **2b**

with H_a. The assignment of H_b and H_c is based on coupling differences with H_a. The near anti geometry of H_a with H_c is expected to produce a large coupling constant compared to the near 90 ° torsion angle of H_a with H_b.

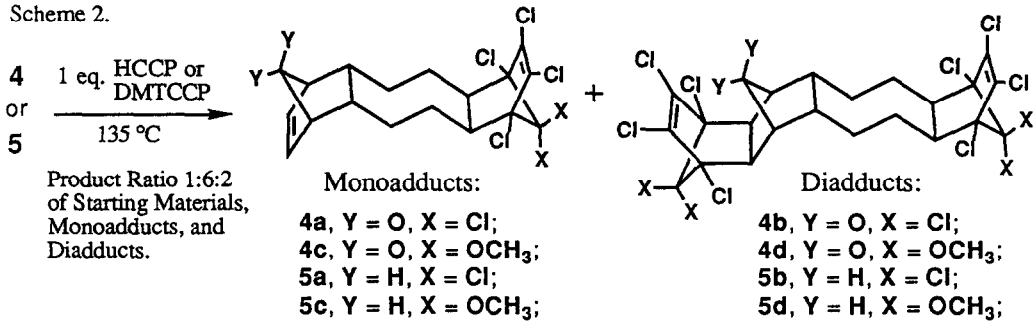
Table 1. Syn:anti ratios and isolated yields for reaction of a series cyclooctenes with electron deficient diene.

Compound Number	Dienophile[a]	HCCP adducts syn:anti ratio	DMTCCP adducts syn:anti ratio
1		**1a:1b** 1:4 combined yield 95%	**1c:1d** 1:4 combined yield 82%
2		**1c:1d** 1:4 combined yield 74%	**2a:2b** 1:4 combined yield 88%
3		**3a:3b** 1:12 80% yield of **3b**	**3c:3d** 1:12 82% yield of **3d**
4		**4a:4b**[b] 1:≥20 anti isomer[c] 65% yield of **4a** 19% yield of **4b**	**4c:4d**[b] 1:≥20 anti isomer[c] 57% yield of **4c** 18% yield of **4d**
5		**5a:5b**[b] 1:≥20 anti isomer[c] 56% yield of **5a** 12% yield of **5b**	**5c:5d**[b] 1:≥20 anti isomer[c] 46% yield of **5c** 9% yield of **5d**
6		**6a:6b** 1:2.5 78% combined yield	**6c:6d** 1:2.5 72% combined yield

[a]The cyclooctenes are fluxional at room temperature, but the boat conformer is slightly favored over the chair conformer. [b]See scheme 2. [c]Syn isomer not detected by NMR; diadduct forms exclusively with excess diene.

The dienes, **1**, **2**, and **3**, undergo highly selective cycloaddition at the cyclooctenyl double bond. Whereas, **4** or **5** are less selective and react with excess electron deficient diene (3 h at 135 °C) to produce predominantly heptacyclic diadducts with the anti geometry (**4b**, **4d**, **5b**, and **5d** in Scheme 2). The lesser steric shielding of the norbornenyl double bond of these cyclooctenes is probably responsible for this dual reactivity. When **4** or **5** reacts with 1 eq. of diene, a 1:6:2 ratio of reactant:monoadduct:diadduct forms (Scheme 2). We see no evidence for the other monoadduct or any syn products. Presumably, the cyclooctenyl double bond of **4** and **5** reacts more rapidly than the norbornenyl double bond.

Scheme 2.



The cyclooctenes show no diastereoselectivity differences in reactions with HCCP and DMTCCP. But, the donating ability of remote double bonds in the cyclooctenes correlate with anti dienophile π-face selectivity. The dramatic selectivity change for **5** compared to **6** graphically illustrates the norbornenyl double bond is influencing π-face selectivity. The chlorinated double bond of **1** and **2** is expected to donate poorly and it is only slightly more anti selective than **6** with no remote double bond donating site. The norbornenyl double bond in **3**, **4**, and **5** is a better donor and those dienophiles display enhanced anti selectivity.

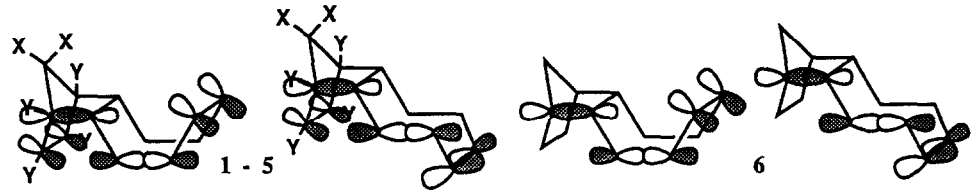


Figure 1. Possible π-σ-π electronic interactions for **1** - **5** and σ-π electronic interactions in **6**.

These cyclooctenyl systems provide a conformationally flexible framework that becomes relatively rigid following cycloaddition. The adduct eight-membered ring stereochemistry is readily determined and yields the π-face selectivity of these reactions. The results provide evidence that trans π-σ-π electronic interactions are more effective than cis interactions in stabilizing reverse-electron-demand Diels-Alder transition states.

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References and Notes

1. (a) J. C. Gallucci, T. M. Kravetz, K. E. Green, L. A. Paquette, J. Am. Chem. Soc. 107 (1985) 6592-6598; (b) Paquette, L. A. In *Stereochemistry and Reactivity of Pi Systems*; Watson, W. H., Ed.; Verlag Chemie International: Deerfield Beach, Fl, 1983; pp 41-73; (c) Gleiter, R.; Böhm, M. C. *ibid*; *idem*; pp 105-146; (d) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328-334.
2. Gugelchuk, M.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 246-253.
3. Theory: (a) Hoffman, R. *Acc. Chem. Res.* **1971**, *4*, 1-9; (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 696-701; (c) Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245-251.
4. Experiment: (a) Grimme, W.; Schumachers, L.; Gleiter, R.; Gubernator, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 113-115; (b) Paquette, L. A.; Doecke, C. W.; Klein, G. *J. Am. Chem. Soc.* **1979**, *101*, 7599-7604; (c) Kroon, J.; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *ibid* **1990**, *112*, 4868-4873.
5. Cyclooctenes **1**, **2**, **3**, and **4** have been reported; see ref.6. Reduction of **4** with sodium in ethanol gives a 64% yield of **5**; see ref. 7. Selective reduction of the norbornenyl double bond of **5** with P2-nickel catalyst gives a 42% yield of **6**; see ref. 8. The Diels-Alder reactions were performed neat with a 1:3 ratio of cyclooctene:diene at 135 °C for 3 h. NMR scale experiments without isolation were used to determine anti:syn ratios. The isolated adducts do not isomerize at 250 °C. All compounds gave satisfactory spectroscopic data. Spectroscopic data for **1a**, **1b**, **2a**, and **2b** can be found in the preceding paper.
6. **1**: Sporka, K.; Ruzicka, V.; Horak, Z. *Chem. Prum.* **1979**, *29*, 526-528; **2**: Akhtar, I. A.; Fray, G. I.; Yarrow, J. M. *J. Chem. Soc. (C)* **1968**, 812-815; **3** and **4**: Eaton, P. E.; Sidhu, R. S.; Langford, G. E.; Cullison, D. A.; Pietruszewski, C. L. *Tetrahedron* **1981**, *25*, 4479-4493.
7. Procedure: Lap, B. V.; Paddon-Row, M. N. *J. Org. Chem.* **1979**, *26*, 4979-4981; **5**: bp 90-95°C 0.1 mm Hg. ^{1}H NMR ($CDCl_3$) δ 6.08 (t, 2H), 5.73 (t, 2H), 2.64 (t, 2H), 2.36-2.28 (m, 2H), 2.10-1.90 (m, 2H), 1.84-1.69 (m, 2H), 1.45-1.26 (m, 2H), 1.35 (d,2H), 0.92-0.76 (m, 2H); ^{13}C NMR ($CDCl_3$) 135.8, 132.1, 50.5, 50.0, 44.7, 31.4, 26.2 ppm; HR-MS, $C_{13}H_{18}$ Calcd. 174.1407, Obsd. 174.1418; FT-IR: 3059.2, 3016.5, 2955, 2932.6, 2863.5, 1652.8, 1475.7, 1463, 1437.1, 1339.4, 1253.3, 1165.7 cm^{-1}.
8. Procedure: Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *12*, 2226-2230; Prep TLC ($AgNO_3$ impregnated silica gel) hexane elution was to isolate **6**: ^{1}H NMR ($CDCl_3$) δ 5.75 (t, 2H), 2.39-2.21 (m, 2H), 2.08-1.91 (m, 4H), 1.86-1.53 (m, 4H), 1.51-1.32 (m, 4H), 1.32-1.18 (m, 4H); ^{13}C NMR ($CDCl_3$) 131.8, 44.2, 42.7, 40.6, 28.6, 26.1, 22.2 ppm; HR-MS: $C_{13}H_{20}$ Calcd. 176.1562, Obsd. 176.1577; FT-IR: 3016.4, 2938.5, 2874.6, 2841.7, 2360.9, 2342.7, 1476.8, 1463.4 cm^{-1}.
9. Recently completed X-ray structures of **1d**, **3b**, **4b**, **5c**, and **6b** confirm ^{1}H NMR stereochemical assignments.

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