Tetrahedron Letters, Vol.32, No.28, pp 3289-3292, 1991 Printed in Great Britain

## TANDEM REVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS OF 1,5-CYCLOOCTADIENE.

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Summary: Hexachlorocyclopentadiene and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopenta-2,4-diene react with 1,5-cyclooctadiene to produce a 1:4 syn to anti mixture of diadducts in good yield. The stereochemistry of the diastereomers is examined using X-ray and molecular mechanics calculations are used to explore some of the potential causes for the observed diastereoselectivity.

Tandem reverse-electron-demand Diels-Alder reactions of multifunctional dienophiles have not been widely exploited for synthesis.<sup>1</sup> This approach potentially allows the transformation of "unactivated" olefins into cyclopentadienes as outlined below for 1,5-cyclooctadiene (COD). The conformations imposed on the eightmembered ring following cycloaddition and the  $\pi$ -face selectivity of the second Diels-Alder reaction are the subjects of this report. The subsequent paper focuses on the remote control of the cycloaddition diastereoselectivity, which is probably transmitted via conformation dependent  $\pi$ - $\sigma$ - $\pi$  electronic interactions.



COD reacts with excess hexachlorocyclopentadiene (HCCP) or 5,5-dimethoxy-1,2,3,4tetrachlorocyclopenta-2,4-diene<sup>2</sup> (DMTCCP) to produce 95 or 88% isolated yields, respectively, of mixtures of two stereoisomeric diadducts.<sup>3</sup>



Only the *endo*, *endo*-Diels-Alder isomers are produced and perspective drawings of the single crystal Xray structures are shown in figure 1. The steric bulk of the norbornenyl ring fusion ensures mainly the 1,2- and 4,5-diequatorial stereochemistry. The rigidity of the norbornenyl rings induce near-zero torsion angles in the eight-membered ring at the fused sites: -0.8 (3) and 1.1 (3)° for  $1;^4 \pm 0.7$  (4) and  $\pm 0.5$  (4)° for the two independent, centrosymmetric molecules of  $2;^5$  -2.8 (9) and -6.8 (10)°; 4.2 (8) and 9.3 (10)° for the two independent molecules of 3;<sup>6</sup> and  $\pm 1.8$  (3)° for 4.<sup>7</sup> The torsion angles at C2-C3-C4-C5 and C1-C8-C7-C6 for 1 are 2.3 (4) and 0.7 (3)°; these values are nearly ideal (zero) for the boat conformation.<sup>8</sup> In contrast, the analogous values for 3 are 29.0 (9) and 26.5 (15)°; -31.4 (13) and -30.6(10)°, indicating a twist-boat conformation. The torsion angles about the C-C bonds comprising the arms of the chair (C5-C8-C9'-C6' for 2) are  $\pm 117.9$  (3) and  $\pm 118.4$  (3)°; analogous values for 4 are  $\pm 119.0$  (2)°. These values are near ideal ( $\pm 116.8$ ) for the chair conformation.<sup>8</sup>



Figure 1. Three dimensional structures of 1, 2, 3, and 4.

What controls the diastereoselectivity of the second Diels-Alder reaction? The cycloaddition reaction conditions are under kinetic control since the diadducts are stable to interconversion at 250 °C. The second Diels-Alder reaction locks in the stereochemistry of the intermediate monoadducts, but the monoadducts,  $5^{10}$  and 6,<sup>11</sup> are flexible at room temperature according to  $^{13}$ C NMR. Macromodel<sup>9</sup> molecular mechanics calculations indicate that neither reactant conformationally preferences or product stability correlate with the observed selectivity. Twist boat (TB) 5 is favored over twist chair (TC) 5 by 3.0 kJ mol<sup>-1</sup> and TB 6 is favored over TC 6 by 0.9 kJ mol<sup>-1</sup>. Thus in accord with the Curtin-Hammett principle, monoadduct conformational preferences do not account for the diastereoselectivity of the second cycloaddition. The exchange of the chlorines for the methoxyl

groups reverses the relative stabilities of the diadduct products. TB 1 is less stable than TC 2 by 8.4 kJ mol<sup>-1</sup>, but, TB 3 is more stable than TC 4 by 11.1 kJ mol<sup>-1</sup>. In addition, PCModel<sup>12</sup> calculations of the diastereometric diadduct transition states predict a slight syn selectivity, showing that steric interactions do not account for the diastereoselectivity.



The 1:4 syn:anti dienophile  $\pi$ -face selectivity observed above does not correlate with reactant conformational preferences, product stability, or TS steric interactions. The subsequent paper shows that electronic modification of structurally similar cyclooctenes significantly affects the  $\pi$ -face selectivity of these Diels-Alder reactions.

Acknowledgement. The financial support of the Louisiana Educational Quality Support Fund through grant LEQSF-(1987-90)-A-5 is gratefully acknowledged. Also, we thank Nabeel B. Nabulsi for help with the PCModel calculations and Prof. Richard D. Gandour for helpful discussions.

## **References and Notes**

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- 3. General Experimental Procedure: Reactions were run neat with a 1:4 ratio of COD:diene at 135 °C for 3 h. The resulting paste is filtered and washed with a minimal amount of ether affording a fine white powder (anti isomer) and from the ether solution, the syn isomer is isolated. NMR scale experiments without isolation were used to determine anti:syn ratios. The isolated diadducts do not isomerize at 250 °C.
- 4. 1: mp >320°C (subl.); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.00 (dd, 4H), 2.06 (d, 4H), 1.48 (d, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 131.2, 82.9, 46.3, 29.8, 20.7 ppm; FT-IR: 2970.2, 1604.3, 1168.2, 1006.7, 917.9 cm<sup>-1</sup>; HR-MS: C<sub>18</sub>H<sub>12</sub><sup>35</sup>Cl<sub>10</sub><sup>37</sup>Cl<sub>2</sub> Calcd. 651.7142; Obsd. 651.7142; C<sub>18</sub>H<sub>12</sub><sup>35</sup>Cl<sub>9</sub><sup>37</sup>Cl<sub>3</sub> Calcd. 653.7112; Obsd. 653.7111. (a) Crystals of 1 suitable for X-ray diffraction were grown by partial evaporation of a 1:1:1 (by volume) mixture of xylenes-toluene-hexane. Crystal data: C<sub>18</sub>H<sub>12</sub>Cl<sub>12</sub>, ca. 0.45 x 0.50 x 0.50 mm, monoclinic, space group P2<sub>1</sub>/c, a = 8.4091(14), b =11.7929(13), c = 24.270(4) Å,  $\beta$  = 93.26(2)°, T = 22 °C, V = 2402.9(11) Å<sup>3</sup>, Mo K\alpha radiation,  $\lambda$  = 0.71073 Å (CAD-diffractometer),  $\mu$  = 14.0 cm<sup>-1</sup>,  $\rho_{calcd}$  = 1.807 g cm<sup>-3</sup>, Z = 4, FW = 653.7, 1° <  $\theta$  <30°, absorption corrections by psi scans. The structure was solved by direct methods and refined by full-matrix least squares to residuals of *R* = 0.040,

Rw = 0.047, GOF = 2.327 for 5028 unique reflections with  $I \ge 3\sigma(I)$  and 320 variables, including isotropic refinement of all hydrogen atoms. (b) Further details of the crystal structure investigations are available on request from the the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, GB-Cambridge CB21EW (UK), on quoting the full journal citation.

- 5. 2: mp >360°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.87 (dd, 4H), 2.24 (d, 4H), 0.87 (d, 4H) <sup>13</sup>C NMR (CDCl<sub>3</sub>) 130.8, 82.7, 51.4, 29.8, 22.9 ppm; FT-IR: 2941.1, 1601.5, 1463.3, 1283.3, 1168.2, 1001.5, 911.7 cm<sup>-1</sup>; HR-MS: C<sub>18</sub>H<sub>12</sub><sup>35</sup>Cl<sub>10</sub><sup>37</sup>Cl<sub>2</sub> Calcd. 651.714206; Obsd. 651.7142; C<sub>18</sub>H<sub>12</sub><sup>35</sup>Cl<sub>9</sub><sup>37</sup>Cl<sub>3</sub> Calcd. 653.711253; Obsd. 653.7111. (a) Crystals of 2 suitable for X-ray diffraction were grown by slow cooling of xylenes. Crystal data: C<sub>18</sub>H<sub>12</sub>Cl<sub>12</sub>, ca. 0.14 x 0.15 x 0.45 mm, monoclinic, space group  $P2_1/c$ , a = 13.421(2), b = 12.3928(13), c = 14.602(2) Å,  $\beta$  = 98.518(11)°, T = 23 °C, V = 2401.8(10) Å<sup>3</sup>, Mo Kα radiation,  $\lambda$  = 0.71073 Å (CAD-diffractometer),  $\mu$  = 14.0 cm<sup>-1</sup>,  $\rho_{calcd}$  = 1.808 g cm<sup>-3</sup>, Z = 4, FW = 653.7, 1° <  $\theta$  <27.5°, absorption corrections by psi scans. The structure was solved and refined as for 1; R = 0.035, Rw = 0.036, GOF = 1.416 for 3275 data and 319 variables. See 4(b).
- 6. 3: mp 219-222 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.66 (s, 3H), 3.56 (s, 3H), 2.85 (d, 4H), 1.94 (d, 4H), 1.38 (dd, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 129.04, 111.62, 79.35, 52.82, 51.83, 46.64, 19.96 ppm; FT-IR: 2950.1, 2844.4, 1604.3, 1451.4, 1198.5, 1174.6, 1107.9, 983.6 cm<sup>-1</sup> HR-MS: [M<sup>+</sup>-Cl]: C<sub>22</sub>H<sub>24</sub><sup>35</sup>Cl<sub>7</sub>O<sub>4</sub> Calcd: 596.9494, Obsd: 596.9504; C<sub>22</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub><sup>37</sup>ClO<sub>4</sub> Calcd: 598.9467, Obsd: 598.9475; C<sub>22</sub>H<sub>24</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>Cl<sub>2</sub>O<sub>4</sub> Calcd: 600.9439, Obsd: 600.9451; (a) Crystals of **3** suitable for X-ray diffraction were grown by slow cooling of xylenes. Crystal data: C<sub>22</sub>H<sub>24</sub>Cl<sub>8</sub>O<sub>4</sub>, ca. 0.08 x 0.18 x 0.23 mm, monoclinic, space group P2<sub>1</sub>, a = 8.1616(12), b = 14.387(3), c = 23.281(3) Å,  $\beta$  = 96.460(11)°, T = 26 °C, V = 2716.3(8) Å<sup>3</sup>, Cu K\alpha radiation,  $\lambda$  = 1.54184 Å (CAD-diffractometer),  $\mu$  = 80.2 cm<sup>-1</sup>,  $\rho_{calcd}$  = 1.555 g cm<sup>-3</sup>, Z = 4, FW = 636.1, 2° <  $\theta$  < 75°, absorption corrections by psi scans. Two independent molecules in the unit cell. The structure was solved and refined as for 1, except that H atoms were not refined; *R* = 0.066, *Rw* = 0.055, GOF = 2.044 for 3887 unique reflections with  $I \ge 1\sigma(I)$  and 613 variables. The mirror image structure yielded *R* = 0.069, *Rw* = 0.058, GOF = 2.142. See 4(b).
- 4: mp 356-358°C (dec.); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.58 (s, 6H), 3.52 (s, 6H), 2.67 (d, 4H), 2.10 (d, 4H), 0.80 (dd, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 128.6, 111.3, 79.1, 52.7, 51.9, 51.6, 21.9 ppm; FT-IR: 2982.3, 2949.9, 2909.4, 2845, 1606.8, 1471.1, 1289.2, 1197, 1110.2, 993, 953.4 cm<sup>-1</sup>; HRMS: [M<sup>+</sup>-Cl]: C<sub>22</sub>H<sub>24</sub><sup>35</sup>Cl<sub>7</sub>O<sub>4</sub> Calcd: 596.9501, Obsd: 596.9489; C<sub>22</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub><sup>37</sup>ClO<sub>4</sub> Calcd: 598.9465, Obsd: 598.9465. For details of this structure; Garcia, J. G.; Fronczek, F. R.; McLaughlin, M. L. Acta Cryst. 1991, C47, in press.
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- 12. Default parameters for the Diels-Alder transition states were used from PCModel V2.

(Received in USA 25 January 1991)