HIGH-PRESSURE CYCLOADDITION REACTIONS BETWEEN METHYL 2*H*-CYCLOHEPTA[*b*]FURAN-2-ONE-3-CARBOXYLATE AND ETHOXYETHENE. PRESSURE EFFECT ON THE [8+2] AND [4+2] CYCLOADDITIONS†

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Abstract — The high-pressure cycloaddition reaction between methyl 2*H*-cyclohepta[*b*]furan-2-one-3-carboxylate and ethoxyethene gave the [4+2] adducts as kinetically-controlled products. Heating the [4+2] adduct under 10,000 bar in the presence of the deuterated methyl 2*H*-cyclohepta[*b*]furan-2-one-3-carboxylate caused the *retro*-Diels-Alder reaction. However, formaion of no azulene derivative was observed and no deuterium atom was incorporated into the recovered adduct.

Recently, we have shown the exclusive formation of the [4+2] adducts during the cycloaddition of 2*H*-cyclohepta[*b*]furan-2-one derivatives (**1**) to dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**2**).[1] This was contrasting to the results reported for the reactions of **1** with enamines[2] and alkoxyethenes,[3] which are regarded as versatile methods of azulene syntheses, i.e., [8+2] cycloaddition followed by decarboxylative elimination.

It is reasonable to assume that the exclusive formation of [4+2] adducts from **1** and **2** is attributable to the intervention of subsequent rearrangement to the [8+2] cycloadducts. While such isomerization in the highly-polar molecules might be assisted by anchimeric effect of the nitrogen or oxygen atoms of enamines or alkoxyethenes, such assistance is not expected with the adducts from **1** and **2**.

It is true that the [8+2] cycloaddition is observed only with the highly-polar cycloaddends such as enamines,[2] alkoxyethenes,[3] or fulvenes.[4] In a contrast, the [4+2] cycloaddition is detected only in the reactions with fulvene and with alkoxyethenes other than with **2**.

However, it is also true that the azulene derivatives were obtained from all of the [4+2] adducts of **1** and alkoxyethenes. This seems to indicate the cycloreversion-cycloaddition mechanism for the generation of the azulene precursors. This point should be solved by an aid of high-pressure cycloaddition of **1** and ethoxyethene (**3**). From molecular orbital considerations taking into account of superjacent and subjacent orbitals, [4+2] adducts were kinetically-controlled products.[1] In connection to these points, we studied the cycloaddition reactions

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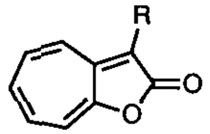
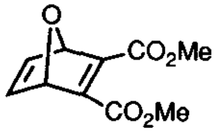
†Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.



1a R = CO_2Me
1b R = H
1c R = CN



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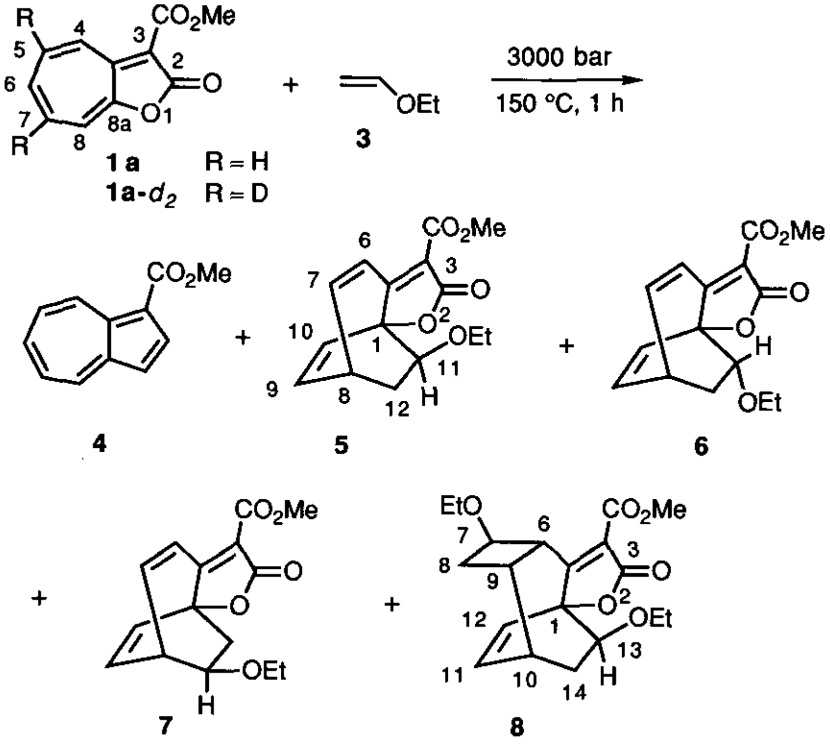


between methyl 2*H*-cyclohepta[*b*]furan-2-one-3-carboxylate (**1a**) and **3** under high-pressure conditions, where a formation of a kinetically-controlled product is expected to be predominant. Herein, we describe our findings.

RESULTS AND DISCUSSION

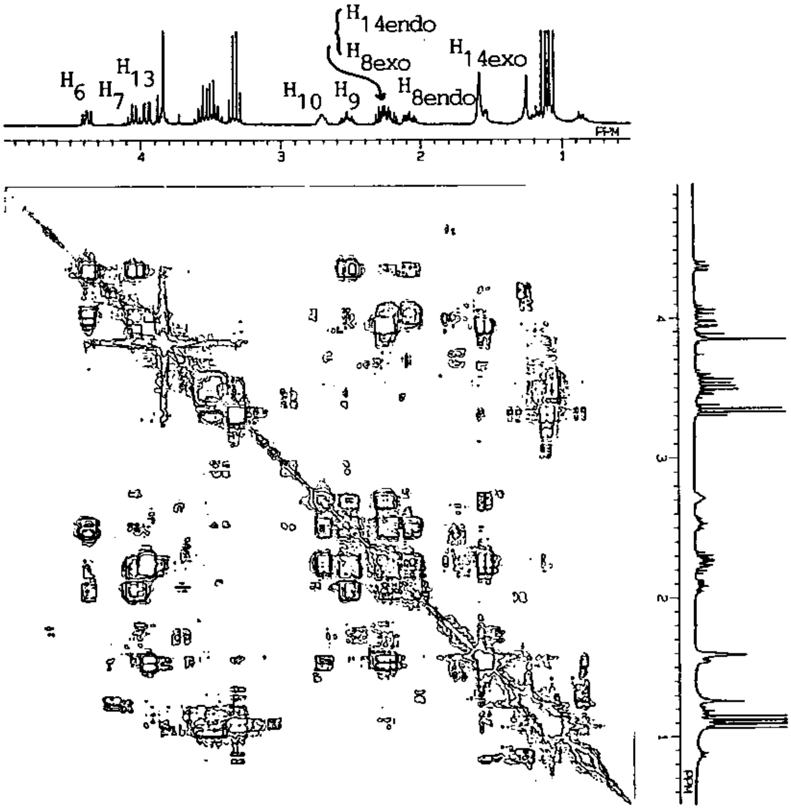
Cycloaddition Reaction of 1a and 3. Heating of a chlorobenzene solution of **1a** and **3** at 150 °C under 3,000 bar gave five products (**4**-**8**), which can be isolated via silica-gel column chromatography and high-pressure liquid chromatography (hplc). A blue-violet compound (**4**) was identical with 1-methoxycarbonylazulene.[5] Products (**5**-**7**) were 1:1-adducts and product (**8**) was a 1:2 adduct between **1a** and **3**. Their structures were elucidated by the spectral data.

The ^{1}H-nmr spectra of 1:1 adducts showed four olefinic protons, two methine protons, and two methylene protons. The splitting patterns indicated that the adducts had the [4+2] structure, derived from the reaction at C-6 and C-8a of **1a**. The methylene protons of **5** and **6** had three kinds of coupling constants, whereas those of **7** had two kinds of coupling constants. These results indicated that **7** had an ethoxyl group at C-12 and the others at C-11. The chemical shift (δ 3.84) of H-8 of **7**, which is lower than those (δ 3.41 and δ 3.43) of **5** and **6**, supported the above conclusion.

The orientation of the ethoxyl group of **7** was determined to be exo from the observation of the coupling constant (4.0 Hz) between H-12 at δ 3.95 and H-8. The chemical shift of *exo*-H-12 is higher than that of *endo*-H-12 in **5**, while that of *exo*-H-12 is lower than that of *endo*-H-12 in **6**. Since it has been observed that in the [4+2] adducts between troponoids and **3**, the protons faced to an ethoxyl group appeared at a higher field,[6] the structures of **5** and **6** were deduced as shown. The coupling constants between the methylene protons and the methine proton attached to the carbon bearing the ethoxyl group supported the above conclusion; the coupling constants (9.5 Hz in **5** and 8.5 Hz in **6**) between the cis protons are larger than those (2.9 Hz in **5** and **6**) of the trans protons.[6]

Next, product (**8**) showed two olefinic protons around δ 6.1-6.4. Since a signal below δ 7.0 of a [4+2] adduct disappeared, the second addition of **3** occurred at C-6-C-7 double bond of **5**. Further informations of the structure of **8** were obtained from the ^{1}H-nmr spectral comparisons with **5**; one of the ethoxyl groups was at C-13 since the nuclear Overhauser effects between H-9 and *exo*-H-14 and between H-11 and both *endo*-H-8 and H-7 and the H-H COSY experiment determined the orientation of the cyclobutane ring as depicted (Figure 1).

Thus, a characterization of **8** which is superficially derived from **5** is worth to mention. Should a Michael-type attack of **3** occur initially at C-5 position of **1a**, the subsequent cyclization of a dipolar intermediate should result in the four-membered ring formation, since its second transoid nature of the 4π-moiety precludes the Diels-Alder process. Second step of Diels-Alder reaction of **3** to the 1:1-adduct should be very fast. *Anti*-geometry of the cyclobutane ring to the ethoxyethano bridge is consistent to this sequence of the reaction.



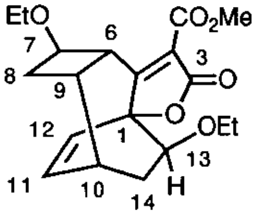


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Figure 1. The H-H COSY Spectrum of **8**.

Table 1. Pressure Effect on the Product Yield

Press. / bar	Temp. / °C	Time / h	Solvent	Additive	Yield			[8+2]/[4+2]
					4	**5-7**	**8**	
1	160	40	Toluene	-	74	21	-	3.6
3,000	150	10	CB[a]	HQ[b]	39	28	1.1	1.39
5,000	150	10	CB	-	28	24	3.2	1.03
5,000	150	10	CB	HQ	33	31	5.0	0.92
10,000	150	10	CB	HQ	25	26	4.0	0.83
10,000	150	1	CB	HQ	33	24	5.8	1.10

a; Chlorobenzene. b; Hydroquinone.

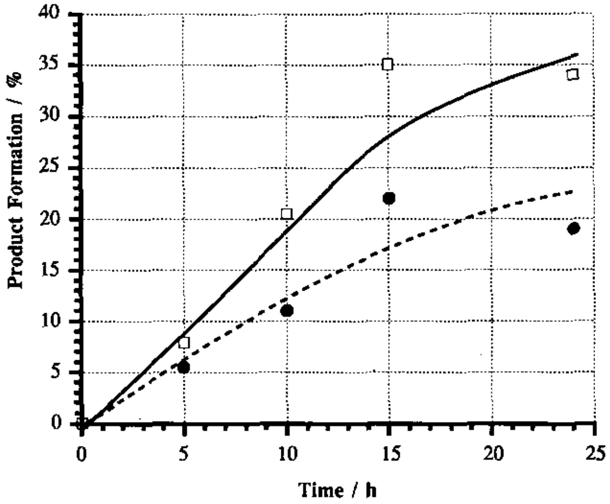

Figure 2. Time Course of Diels-Alder Reaction of **1a** with **3**. (The solid line is the formation of azulene (**4**) and the dotted line is that of the [4+2] adducts (**5-7**) and the 1:2 adduct (**8**).)

Pressure Effect. In order to elucidate the pressure effect on the product distribution, the cycloaddition reaction of **1a** with **3** was performed under certain range of high-pressure conditions. The results are summarized in Table 1 together with that under 1 bar.[3] The ratio of [8+2]/[4+2] adducts decreased by increasing the pressure. The time-course of the reaction under 10,000 bar at 100 °C was shown in Figure 2. From the early stage of the reaction, the amount of [4+2] adduct exceeded that of [8+2] adduct (azulene).[7]

When the [4+2] adduct (**5**) was heated at 150 °C under 10,000 bar in the presence of **1a**-d_2, no azulene was detected and the amount of **1a**-d_0 in the recovered **1a** increased. The formation of **1a** indicated that the *retro*-Diels-Alder reaction of **5** occurred even under 10,000 bar. These results clearly eliminated that the intramolecular path from **5** to the [8+2] adduct and both adducts formed independently from **1a** and **3**. The fact, no deuterium atom incorporation in the recovered [4+2] adduct, was due to the polymerization of **3** prior to the cycloaddition with **1a** since it was known that azulene was detectable only in the reaction of **5** in the presence of excess **3**.

Conclusion. The finding described above clearly showed that between two processes, [4+2] and [8+2] additions, the former is kinetically favorable, but only the latter could be converted to an azulene derivative by the irreversible elimination process. This result was consistent with the prediction from the molecular orbital consideration.[1,8]

EXPERIMENTAL

Elemental analyses were performed by Mrs. M. Miyazawa of this Institute, Kyushu University. The mps were measured with a Yanagimoto Micro mp apparatus and are not corrected. The nmr spectra were measured by JEOL FX 100 and GSX 270H spectrometers in $CDCl_3$, unless otherwise specified, and the chemical shifts expressed were in δ units. Mass spectra were measured with a JEOL 01SG-2 spectrometer. The ir spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily materials using a JASCO IR-A 102 spectrophotometer. The uv spectra were measured by the use of Hitachi U-3200 and U-3410 spectrophotometers. The stationary phase for the column chromatography was Wakogel C-300 and the elution solvents were mixtures of hexane and ethyl acetate.

Reaction of 1a with 3 under high-pressure conditions. A chlorobenzene solution (3.2 ml) of **1a** (70 mg, 0.34 mmol) and **3** (160 mg, 2.2 mmol) was heated at 150 °C for 10 h under 3,000 bar in the presence of hydroquinone (3 mg). The solvent was removed under reduced pressure and the residue was purified on silica gel column chromatography (EtOAc:hexane=1:5) and hplc (EtOAc:hexane=1:1) to give 22.9 mg (39%) of **4**, 24.6 mg (28%) of a mixture of **5-8** (**5**:**6**:**7**:**8**=42:33:24:1), and 5.5 mg of recovered **1a**.

4: Blue-violet crystals, mp 57-59 °C (lit.,[5] violet needles, mp 56-57 °C); ^{1}H-nmr δ=3.96 (3H, s), 7.30 (1H, d, J=4.4 Hz), 7.45 (1H, t, J=9.9 Hz), 7.55 (1H, t, J=9.9 Hz), 7.81 (1H, br t, J=9.9 Hz), 8.37 (1H, d, J=4.4 Hz), 8.46 (1H, dd, J=9.9, 0.7 Hz), and 9.65 (1H, dd, J=9.9, 0.7 Hz); ^{13}C-nmr δ=51.1, 116.7, 117.6, 126.7, 127.7, 137.8, 138.2, 139.0, 140.2, 140.7, 144.7, and 165.9. **5**: A colorless oil; ^{1}H-nmr δ=1.09 (3H, t, J=7.0 Hz), 1.66 (1H, ddd, J=13.6, 2.9, 1.5 Hz), 2.28 (1H, ddd, J=13.6, 9.5, 5.5 Hz), 3.41 (1H, dddm, J=8.8, 7.3, 5.5 Hz), 3.55 (2H, m), 3.89 (3H, s), 4.14 (1H, dd, J=9.5, 2.9 Hz), 6.08 (1H, dd, J=8.8, 1.1 Hz), 6.36 (1H, dd, J=8.8, 7.3 Hz), 6.97 (1H, dd, J=10.6, 8.8 Hz), and 7.26 (1H, dd, J=10.6, 0.7 Hz); ^{13}C-nmr δ=15.4, 30.6, 36.3, 52.1, 67.8, 78.5, 90.2, 113.5, 121.8, 130.0, 134.0, 150.1, 161.9, 166.6, and 168.8; ir 2974, 2952, 2876, 1769, 1714, 1623, 1109, 1076, and 1044 cm^{-1}; uv (MeOH) 289.2 nm (ε 10400) and 404 (300 sh). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 6.22. **6**: A colorless oil; ^{1}H-nmr δ=1.18 (3H, t, J=7.0 Hz), 1.82 (1H, ddd, J=13.9, 5.9, 2.9 Hz), 2.36 (1H, ddd, J=13.9, 8.5, 1.4 Hz), 3.43 (1H, tdd, J=8.8, 5.9, 1.4 Hz), 3.53 (1H, dq, J=9.5, 7.0 Hz), 3.70 (1H, ddd, J=8.5, 2.9, 1.5 Hz), 3.89 (1H, dq, J=9.5, 7.0 Hz), 3.89 (3H, s), 6.15 (1H, dd, J=8.8, 1.5 Hz), 6.45 (1H, t, J=8.8 Hz), 6.96 (1H, dd, J=10.6, 8.8 Hz), and 7.14 (1H, d, J=10.6 Hz); ^{13}C-nmr δ=15.5, 34.7, 35.0, 52.3, 67.7, 75.0, 81.0, 89.1, 112.8, 129.1, 132.8, 151.5, 162.0, 166.4, and 168.2; ir 2974, 2952, 2876, 1770, 1714, 1619, 1101, 1073, and 1040 cm^{-1}; uv (MeOH) 286.8 nm (ε 9300) and 400 (700 sh). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.06; H, 6.23. **7**: A colorless oil; ^{1}H-nmr δ=1.16 (3H, t, J=6.8 Hz), 1.76 (1H, dd, J=13.5, 4.0 Hz), 2.77 (1H, dd, J=13.5, 9.5 Hz), 3.4-3.6 (2H, m), 3.84 (1H, ddd, J=8.3, 7.5, 4.0 Hz), 3.88 (3H, s), 3.95 (1H, dt, J=9.5, 4.0 Hz), 6.14 (1H, d, J=8.7 Hz), 6.24 (1H, dd, J=8.7, 7.5 Hz), 6.78 (1H, dd, J=10.7, 8.3 Hz), and 7.41 (1H, d, J=10.7 Hz); ^{13}C-nmr δ=15.3, 38.5, 41.9, 52.1, 64.6, 75.0, 85.1, 110.9, 122.1, 131.0, 132.6, 147.5, 162.0, 168.3, and 170.2; ir 2970, 2876, 1772, 1715, 1621, 1078, and 1034 cm^{-1}; UV(MeOH) 292.8 nm (ε 12700) and 403 (500 sh). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.17; H, 6.07. **8**: Colorless crystals, mp 58-60 °C; ^{1}H-nmr δ=1.09 (3H, t, *J*=6.9 Hz), 1.12 (3H, t, *J*=6.9 Hz), 1.57 (1H, br dd, *J*=14.1, 3.2 Hz), 2.08 (1H, ddd, *J*=7.5, 3.4, 1.5 Hz), 2.24 (1H, dd, *J*=9.9, 7.5 Hz), 2.27 (1H, ddd, *J*=14.1, 10.1, 4.0 Hz), 2.53 (1H, tt, *J*=9.9, 3.4 Hz), 2.71 (1H, br ddd, *J*=7.3, 4.0, 3.4 Hz), 3.34 (2H, q, *J*=6.9 Hz), 3.49 (1H, dq, *J*=9.7, 6.9 Hz), 3.56 (1H, dq, *J*=9.7, 6.9 Hz), 3.84 (3H, s), 3.96 (1H, dd, *J*=10.1, 3.2 Hz), 4.05 (1H, q, *J*=7.5 Hz), 4.38 (1H, ddd, *J*=9.9, 7.5, 1.7 Hz), 6.12 (1H, d, *J*=9.3 Hz), and 6.42 (1H, dd, *J*=9.3, 7.3 Hz); ^{13}C-nmr δ=15.3, 15.4, 32.1, 33.2, 33.5, 36.5, 43.3, 51.9, 64.4, 67.4, 79.7, 80.4, 88.4, 116.6, 130.0, 135.1, 161.6, 168.6, and 174.5; ir 2970, 2930, 1779, 1732, 1260, 1103, and 1040 cm^{-1}; uv (MeOH) 237.2 nm (ε 7200). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.12; H, 7.53. Found: *m/z* 343.1584 (M$^+$). Calcd for $C_{19}H_{24}O_6$: 384.1571 (M).

Preparation of 1a-*d*$_2$ A methanol solution (2 ml) of 3,5,7-trideuterium-2-chlorotropone[9] (50.5 mg, 0.35 mmol), dimethyl malonate (69 mg, 0.52 mmol), and NaOMe (22.6 mg, 0.42 mmol) was stirred at room temperature for 140 min. The reaction was quenched with water. The reaction mixture was neutralized with 2N HCl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed (CH_2Cl_2:hexane=12:1) to give **1a-*d*$_2$** (40.7 mg, 69%).

1a-*d*$_2$: Yellow crystals, mp 173-174 °C; ^{1}H-nmr δ=3.94 (3H, s), 7.38 (1H, s), 7.51 (1H, s), and 8.86 (1H, s); ms *m/z* 206:207:208:209=2.7:18.9:77.1:1.3. Found: m/z 206.0569 (M$^+$). Calcd for $C_{11}H_6D_2O_4$: 206.0548 (M).

Thermolysis of 5 in the Presence of 1a-*d*$_2$ A chlorobenzene solution (1.2 ml) of **5** (13.1 mg, 0.047 mmol) and **1a-*d*$_2$** (9.4 mg, 0.046 mmol) was heated at 150 °C for 10 h under 10,000 bar. The solvent was evaporated and the residue was chromatographed (EtOAc:hexane=1:2) on a silica gel column to recover 8.9 mg of **5** and 11.1 mg of a mixture of **1a-*d*$_0$**, **1a-*d*$_1$**, and **1a-*d*$_2$** (m/z 206:207:208=21.2:10.7:68.1).

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