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High-Pressure Diels-Alder Reaction of N-Phenylmaleimide with Tropone and Tropolone. Pressure Acceleration of Thermal Acyloin Rearrangement

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The high-pressure (to 10000 bar) Diels-Alder reaction of tropolone with *N*-phenylmaleimide showed a pressure acceleration to afford *exo*-and *endo*-Diels-Alder adducts at much lower temperatures. The *endo*-adduct was isomerized to *exo*-adduct under high-pressure conditons to indicate negative activation volume for this molecular rearrangement. The high-pressure Diels-Alder reaction of tropone and *N*-phenymaleimide also smoothly gave the *endo*-adduct as the major product together with the hitherto undetected *exo*-adduct.

Synthetic utility of the Diels-Alder adducts of tropones is recently a focus of attention; we reported[1] an improved synthesis of homobarrelenones (**A**)[2] by means of the high-pressure Diels-Alder reaction of tropones to 2,3-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]-heptadiene and subsequent fragmentation, and further photochemical isomerization of **A** to functionalized dihydroindenones.[3] Moveover, an intermediate ketene from 2-methoxytropone resulted in a formation of cyclopropane-ring-fused tricyclic derivatives, which would be otherwise difficult to prepare, due to the polarized character of the enolic double bond.[3] We now investigated the high-pressure Diels-Alder reaction of *N*-phenylmaleimide (**1**) with tropone (**2**)[4] and tropolone (**3**) to furnish *endo*- and *exo*-4-phenyl-4-azatricyclo[5.3.2.$0^{2,6}$]-dodeca-9,11-diene-3, 5, 8-triones.

Results and Discussion

Thermal High-Pressure Cycloaddition. Following the literature,[4] **1** and **2** were refluxed in toluene for 10 h. Collection of the resultant crystalline mass furnished *endo*-4-phenyl-4-azatricyclo[5.3.2.$0^{2,6}$]dodeca-9,11-diene-3,5,8-trione (**4**),[4] in 93% yield. However, from the filtrate obtained after evaporation of the solvent was isomeric *exo*-4-phenyl-4-azatricyclc[5.3.2.$0^{2,6}$]dodeca-9,11-diene-3,5,8-trione (**5**), in 7% yield, which was not detected by original investigators. Anyway, combined yield of **4** and **5** was quantitative. However, under 10000 bar (1 bar=10^5 Pa) at 20℃ for 100 h, the reaction proceeded to give only **4** in 95% yield. The ^{1}H and ^{13}C NMR spectra of **4** and **5** were consistent to the structures.

On the other hand, the reaction of **1** and **3** by refluxing in a toluene solution failed to give any reaction product; the starting materials were recovered quantitatively. By an aid of raising the temperature, the reaction became feasible: at 135℃ in xylene for 50 h, the con-

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version was reached to 68% with a ratio of two isomeric adducts (**6**:**7**) being 35:65.

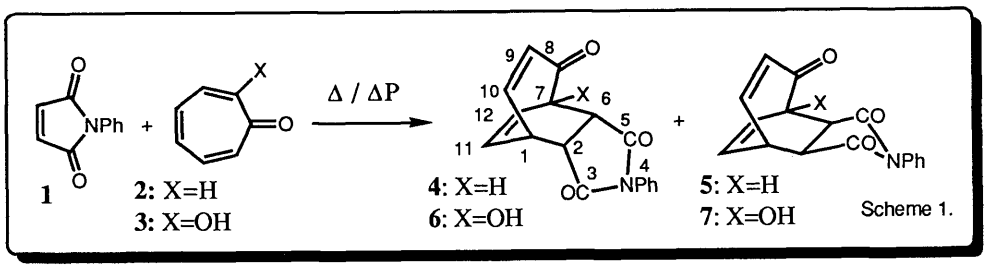
As expected, the reaction was much faster under high-pressure conditions; under 10000 bar at 25℃, the reaction finished within 120 h to give 20% of **6** and 80% of **7**. On the basis of the ^{1}H NMR spectral analysis, **6** was identified to be *endo*-7-hydroxy-4-phenyl-4-azatricyclo[5.3.2.0^{2,6}]dodeca-9,11-diene-3,5,8-trione, and **7**, *exo*-7-hydroxy-4-phenyl-4-azatricyclo-[5.3.2.0^{2,6}]dodeca-9,11-diene-3,5,8-trione.

However, when the reaction was performed at 120℃, the single product isolated in quantitative yield was **7**. In other words, the high-pressure conditions favored a formation of the *exo*-adduct from **1** and **3**. This is rather surprising, since, in general, kinetically-controlled products in Diels-Alder reaction are *endo*-adducts, and under the high-pressure conditions thermodynamically-controlled products are disfavored by a suppression of the *retro*-Diels-Alder process. Therefore, a different factor is responsible for the present formation of the *exo*-adduct, **7**, under the high-pressure conditions.[5]

As the different product selectivities were observed between the reactions with **2** and **3**, the C-2 hydroxy function of **3** must be playing a role. In this respect, we have already observed a thermal acyloin rearrangement of the Diels-Alder adducts obtained from **3** and maleic anhydride.[6] To verify the occurrence of this rearrangement with **6** and **7**, we have independently carried out their mutual conversion.

Table 1. Yields of Diels-Alder Adducts under Various Conditions.

	Conditions	Conversion/%	Products (Yields/%)
2	110℃, 10h, 10^5 Pa/toluene	100	**4** (93) **5** (7)
	20℃, 70h, 10^9 Pa/toluene	95	**4** (100) **5** (—)
	100℃, 10h, 10^9 Pa/toluene	100	**4** (100) **5** (—)
3	110℃, 3h, 10^5 Pa/toluene	0	
	135℃, 50h, 10^5 Pa/xylene	68	**6** (35) **7** (65)
	25℃, 10h, 10^9 Pa/toluene	100	**6** (—) **7** (100)
	120℃, 20h, 10^9 Pa/toluene	100	**6** (20) **7** (80)



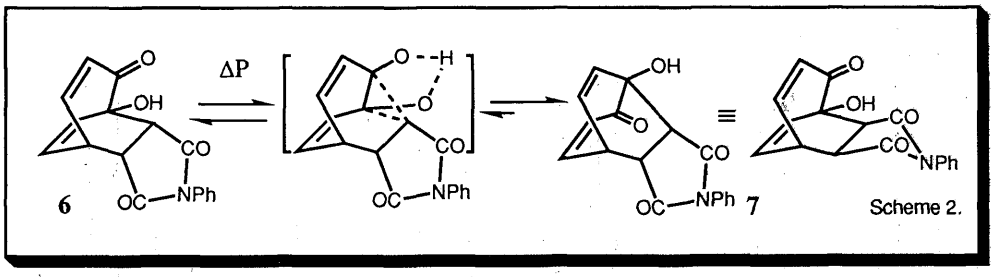
Scheme 1.

(Scheme 1)

Indeed, after reflux of toluene solution of **7** under 1 bar for 30 h, the resultant mixture was shown to contain 38% of **6** and 62% of **7**. In paralled, similar thermal treatment of **7**

for 15 h caused a partial isomerization to a mixiture of **6** and **7** in 26 : 74. Noteworthy is that the temperature of the isomerization was below ca. 25℃ than those for the Diels-Alder reaction, and the absence of **3** in the mixture eliminated the occurrence of a cycloreversion process. Therefore, the isomerization occurred via a different route having lower activation energy than the cycloaddition-cycloreversion pathway. This means that the exclusive formation of **7** under 10000 bar at 120℃ must be a result of the pressure-acceleration.

Recently, we have analyzed high-pressure kinetics of [1, 5][7] and [1, 9][8] sigmatropies of the seven-membered ring compounds to establish the negative activation volumes for these processes. The present observation, pressure acceleration of the rearrangement, in non-polar solvent should also be interpreted as concerted sigmatropic process.



(Scheme 2)

Usually, the thermal exo-endo isomerizations of Diels-Alder adducts were performed at high temperatures, and it is difficult to obtain the one isomer in a good selectivity. The exclusive formation of *exo*-adducts by facilitation of the sigmatropy under the high-pressure conditions is therefore a great synthetic value.

Experimental

Elemental analyses were performed by Mrs. M. Miyazawa of this Insitute, Kyushu University. The mps were measured with a Yanagimoto Micro mp apparatus and are not corrected. The NMR spectra were measured by JEOX FX 100 and GSX 270H specified, and the chemical shifts expressed were in δ untis. 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 spectrometer. The stationary phase for the column chromatography was Wakogel C-300 and the elution solvents were mixtures of hexane and ethyl acetate.

High-Pressure Diels-Alder Reaction of and 2. **a)** A toluene solution (2 cm^3) of **1** (207 mg), **2** (106 mg), and hydroquinone (20 mg) was placed in a pressure vessel and was kept at 100℃ under 10000 bar for 10 h. The resultant precipitates thus formed were then recrystallized from EtOAc to give **4** [colorless srystals, mp 236—236.5℃ (*lit.*[4] 234—236℃), 279 mg; 100%. Found: C, 73.11; H, 4.11; N, 5.29%. Calcd for $C_{17}H_{13}O_3N$: C, 73.11; , 4.69; N, 5.02%. ^{1}H NMR δ[10] = 3.45 (1H, dd, J=8.8, 1.8 Hz), 3.60 (1H, dd, J=8.8, 2.2 Hz), 3.95 (1H, dddm, J=8.8, 7.0, 1.8 Hz), 4.12 (1H, dtm, J=7.3, 2.2 Hz), 5.91

(1H, ddd, J=11.0, 2.2, 0.7 Hz), 6.23 (1H, dd, J=8.1, 7.3 Hz), 6.58 (1H, ddd, J=8.1, 7.0, 1.1 Hz), 7.23 (1H, dd, J=11.0, 8.8 Hz), 7.2−7.7 (2H, m), and 7.35-7.5 (3H, m). MS m/z (%): 279 (M^+, 40), 251 (37), 131 (30), 104 (100), 78 (16). IR (KBr) 3030, 2966, 1706, 1498, 1385, 1189, 826, 757, and 691 cm^{-1}. UV λ_{max}^{MeOH} =218 nm (ε =14900) and 252 (3800)], and previously undetected *exo*-adduct **5** [colorless crystals, mp 192−193℃. ^1H NMR δ =3.43 (1H, dd, J=9.5, 5.5 Hz), 3.59 (1H, dd, J=9.5, 6.6 Hz), 4.02 (1H, dddm, J=8.4, 7.3, 5.5 Hz), 4.17 (1H, dddd, J=7.3, 6.6, 2.2, 0.7 Hz), 5.95 (1H, ddd, J=11.0, 2.0, 0.7 Hz), 6.33 (1H, ddd, J=8.4, 7.3, 0.7 Hz), 6.71 (1H, ddd, J=8.4, 7.3, 0.7 Hz), 7.00 (1H, dd, J=11.0, 8.4 Hz), 7.15−7.2 (2H, m), and 7.35−7.5 (3H, m)],

b) Similarly, a toluene solution (2 cm^3) of **1** (207 mg), **2** (106 mg), and hydroquinone (20 mg) was placed in a pressure vessel and was kept at 25℃ under 10000 bar for 70 h. The resultant precipitates were recrystallized from EtOAc to give **4** (275 mg; 95%).

High-Pressure Diels-Alder Reaction of and 3. **a)** A toluene solution (4 cm^3) of **1** (346 mg) and **3** (122 mg) was kept at 120℃ under 10000 bar for 12 h. The resultant precipitates thus formed were then recrystallized from EtOAc to give the *exo*-adduct, **7** [colorless crystals, mp 205−206℃, 295 mg; 100%. Found: C, 69.16; H, 4.50; N, 4.50%. ^1H NMR δ =3.63 (1H, dd, J=9.5, 5.1 Hz), 3.72 (1H, d, J=9.5 Hz), 4.13 (1H, ddd, J=8.4, 7.3, 5.1 Hz), 4.97 (1H, s), 6.03 (1H, dd, J=8.8, 0.7 Hz), 6.13 (1H, dd, J=11.4, 0.7 Hz), 6.70 (1H, dd, J=8.8, 7.3 Hz), 7.16 (2H, m), 7.28 (1H, dd, J=11.4, 8.4 Hz), and 7.38−7.50 (3H, m). MS m/z (%): 295 (M^+, 61), 267 (54), 174 (33), 173 (62), 148 (36), 120 (100), 94 (80), 91 (35), 77 (30), 65 (35), and 39 (26). UV λ_{max}^{MeOH} =216 nm (ε =13900, sh), 257 (2600, sh), 281 (1200), and 327 (600)].

b) A toluene solution (4 cm^3) of **1** (346 mg) and **3** (122 mg) was kept at 20℃ under 10000 bar for 100 h. The mixture was heated in vacuo to remove the solvent, and residue was chromatographed on a silica-gel column to give the *endo*-adduct, **6** [colorless crystals, mp 176−177℃. 59 mg; 20%. Found: C, 69.23; H, 4.74; N, 4.53%. Calcd for $C_{17}H_{13}O_4N$: C, 69.14; H, 4.44; N, 4.74%. ^1H NMR δ =3.20 (1H, dd, J=8.8, 0.7 Hz), 3.51 (1H, dd, J=8.8, 0.7 Hz), 3.51 (1H, dd, J=8.8, 2.2 Hz), 4.09 (1H, dddm, J=8.8, 7.0, 2.0 Hz), 4.97 (1H, s), 6.10 (1H, d, J=8.8 Hz), 6.13 (1H, d, J=11.0 Hz), 6.51 (1H, dd, J=8.8, 7.0 Hz), 7.24 (2H, m), 7.36 (1H, dd, J=11.0, 8.8 Hz), and 7.40−7.50 (3H, m). MS m/z (%): 295 (M^+, 74), 267 (56), 174 (32), 173 (70), 148 (33), 147 (28), 120 (100), 94 (79), 91 (35), 77 (28), 65 (36), and 39 (29). IR ν: 3408, 3066, 2962, 1714, 1668, 1497, 1383, 1187, 1120, 739, and 694 cm^{-1}. UV λ_{max}^{MeOH} =216 nm (ε =13300, sh), 258 (2300, sh), 280 (1100), and 325 (500)], and **7** (245 mg; 80%).

Diels-Alder Reaction of 1 with under Atmospheric Pressure. **a)** A toluene solution (4 cm^3) of **1** (138 mg) and **3** (80 mg) was refluxed for 3 h. No reaction occurred and the starting materials, **1** (60 mg; 75%) and **3** (130 mg), were recovered.

b) A xylene solution (10 cm^3) of **1** (260 mg) and **3** (122 mg) was refluxed for 50 h. The mixture was heated in vacuo to remove the solvent and the residue was separated by thin-layer chromatography (silica-gel) and high-pressure liquid chromatography to give **6** (70 mg; 24%) and **7** (130 mg; 44%).

Thermal Equilibration of and 7. **a)** A toluene solution (5 cm^3) of **7** (80 mg) was refluxed for 30 h. The mixture was then heated in vacuo to remove the solvent and the re-

sidue was analyzed with high-pressure liquid chromatography to show **6**:**7**=43:57. The high-pressure liquid chromatogram showed none of **3**, which should be formed by cycloreversion, if occurred.

b) Similarly, a toluene solution (5 cm^3) of **6** (15 mg) was refluxed for 15 h. The mixture was then heated in vacuo to remove the solvent and the residue (15 mg) was analyzed with high-pressure liquid chromatography to show **6**:**7**=26:74. The high-pressure liquid chromatogram confirmed again absence of **3**.

High-Pressure Isomerization of 6 to 7. A toluene solution (2 cm^3) of **6** (30 mg) was heated at 120℃ under 10000 bar for 10 h. The mixture was then heated in vacuo to remove the solvent, the residue (30 mg) isolated was shown to be solely **7**.

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