Stereoselectivity of Diels-Alder Reactions of 6,7-Dioxabicyclo[3.2.2]-nona-3,8-dien-2-one and 6,7-Diethoxycarbonyl-6,7-diazabicyclo[3.2.2]nona-3,8-dien-2-one

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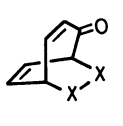
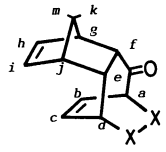
Synopsis. A Diels-Alder reaction of 6,7-dioxabicyclo[3.2.2]-nona-3,8-dien-2-one (**2**) with cyclopentadiene gave the *cis-endo*-[4+2] adduct and the *trans-endo*-[4+2] adduct. Their yields were improved when the reaction was carried out under high-pressure conditions. The reaction of 6,7-diethoxycarbonyl-6,7-diazabicyclo[3.2.2]nona-3,8-dien-2-one (**3**) gave the *cis-endo*-[4+2] adduct. Reactions of **2** and **3** with isobenzofuran and its 1,3-diphenyl derivative gave the thermodynamically-controlled *exo*-[4+2] adducts.

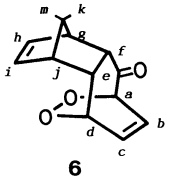
Several years ago, we investigated the Diels-Alder reaction[1] of bicyclo[3.2.2]nona-3,6-dien-2-one (**1**),[2] to give stereospecific *cis-endo*-adducts[3] from several dienes. The bicyclic enone, **1**, is an interesting dienophile, whose structure possesses an ideal arrangement of a vinylene group having an intramolecular homoconjugation with the enone,[4] to evaluate the secondary stereoelectronic effect in the Diels-Alder reaction. An HMO calculation supported the results.[1] In this connection, it will be worthwhile to check the Diels-Alder reaction of the heterocyclic analogs of **1** as dienophiles. Herein, we wish to describe the reaction of 6,7-dioxabicyclo[3.2.2]nona-3,8-dien-2-one (**2**)[5] and 6,7-diethoxycarbonyl-6,7-diazabicyclo[3.2.2]nona-3,8-dien-2-one (**3**),[6] dioxa and diaza analogs of **1**, with dienes.



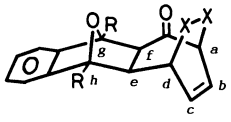
1 X=CH_2
2 X=O
3 X=NCO_2Et



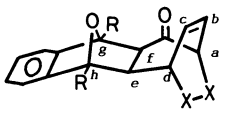
5 X=O
12 X=NCO_2Et



6



8 X=O, R=H
11 X=O, R=Ph
14 X=NCO_2Et, R=H



9 X=O, R=H
13 X=NCO_2Et, R=H
15 X=NCO_2Et, R=Ph

Heating of **2** in benzene with cyclopentadiene (**4**) and a catalytic amount of *p*-toluenesulfonic acid (TsOH) formed two products (**5** and **6**). Silica-gel column chromatography led to an isolation, from the less polar eluent, of colorless needles (**5**) in 2% yield. Its ^1H NMR spectrum revealed a broad vinylic proton signal at a somewhat higher field than expected, δ=5.93 (2H, m), ascribable for the norbornene part. In addition, mutually coupled two-proton signals appeared at 6.50 (dd, J=9, 7 Hz, Hc) and 5.77 (dd, J=9, 7 Hz, Hb). The coupling constant of the methine protons, J_{ej}=3 Hz, showed that the stereochemistry was an *endo*-attack to the enone part. These findings indicated that the stereochemistry of **5** is same to that of the Diels-Alder adducts of **1** with **4** and some cyclic dienes.[1] Subsequent elution afforded colorless needles (**6**) in 3% yield. Its NMR signals of vinylic protons revealed different stereochemistry with **5**; the characteristic signals ascribable to the norbornene part were at 6.06 and 6.35 as each dd; the other signals at 6.29 and 6.83 were those of the dioxacyclohexene moiety. Yet, the coupling constants of the methine protons, J_{ej}=3 Hz and J_{fg}=4 Hz, had the same magnitude as **5** and confirmed the *endo*-orientation. Thus, **6** is *trans-endo*-adduct.

Similarly, **2** with isobenzofuran (**7**),[7] afforded two products (**8**, 41% yield, and **9**, 18% yield) which were deduced to be both *exo*-adducts from a different magnitude of the spin-spin couplings; J_{eh}=J_{fg}=0 Hz for both **8** and **9**. A comparison of the chemical shifts ascribable to H_e and H_f determined the rest of the stereochemistry as depicted; **5** and **9** showed signals at a lower field than **6** and **8**. Moreover, the reaction of **2** with 1,3-diphenylisobenzofuran (**10**) also only yielded a *trans-exo*-adduct (**11**) in 31% yield.

These observations indicated: i) in the reaction of **2** with **4**, the secondary effect of the orbital interaction was still operative for an exclusive *endo*-adducts formation, ii) the secondary effect of the lone-pair electrons of dioxy oxygens is capable of determining the stereochemistry of the adducts to the same extent as the π-orbital of the vinylene group,[8] and iii) an exclusive formation of the thermodynamically stable *exo*-adducts from **7** is attributable to a facile cycloreversion of the kinetically controlled *proto*-adducts under the reaction conditions. The Diels-Alder adducts of furans fall into a category.[9]

When a reaction of **2** with **4** was carried out under high-pressure conditions, the yields were improved to a great extent; the best result was 45% for **5** and 38% for **6** (Table 1).

It is evident that the improved formation of **5** and **6** under high-pressure conditions showed them to be the kinetically controlled products; an inhibition of the *retro*-Diels-Alder process should favor a retention of the *proto*-adducts. It should be noted that a reaction of **2** and **4** under atmospheric pressure produced **5** and **6** only in the presence of TsOH at 80 °C. However, due to the instability of **2** under acidic conditions, an accel-

Table 1. The Reaction of **2** and **4** under Various Conditions

Runs	Solv.	Conditions Press./bar	Temp/°C	Consumption/% Additive	**2**	Yield/% **5**	**6**
1	Benzene	1	80	TsOH	79	2	3
2	Cumene	2500	40	TsOH	66	36	28
3	Cumene	2500	40		64	45	38
4	Acetone	2000	40		49	27	8

eration of the product formation was compensated by the decomposition of **2**. This may be attributable to the lower yields for **5** and **6** with TsOH than without TsOH at 2500 bar.

In cases of reactions of **3**, the nitrogen analogs of **2**, a similar secondary orbital effect should also play a role in the stereochemistry of the adducts; however, at the same time, the inversion of unshared electron pairs of nitrogen and a steric hindrance due to bulky ethoxycarbonyl groups on the hydrazo linkage should minimize the effect of the secondary interaction. The reaction of **3** with **4** yielded a *cis-endo*-adduct (**12**, 96% yield) as the product only identified. The improved yield was due to the stability of the bicyclic dienophile under the conditions. The reaction of **3** with **7** gave two products, *cis-exo*-adduct (**13**, 54% yield) and *trans-exo*-adduct (**14**, 31% yield), while that of **3** with **10** gave the sole product, *cis-exo*-adduct (**15**, 46% yield).

In conclusion, the reactions of **2** and **3** with **4** verified the operation of an attractive secondary interaction between the dioxy group or the hydrazo group as well as the vinylene group and the diene chromophore of **4**, and the absence of a *trans-endo*-adduct from **3**, should be interpreted as a steric effect rather than a lack of the secondary orbital interaction. However, this could not be extended to the reactions with **7** and **10**, since the furans are known to preferably give the thermodynamically controlled cycloadducts.[9]

Experimental

Elemental analyses were performed at the Research Institute of Industrial Science, Kyushu University. The NMR spectra were measured by a JEOL FX 100 Spectrometer in a $CDCl_3$ solution, unless otherwise specified, and the chemical shifts were expressed in δ units (internal Me_4Si). The mass spectra were measured by a JEOL 01SG-2 Spectrometer. The IR spectra were taken either as KBr disks or as liquid films inserted between NaCl plates using a Jasco IR-A 102 Spectrometer.

Reaction of 2 and 4. **a)** A benzene solution (10 cm^3) of **2** (1.01 g) and **4** (5 cm^3) containing TsOH (200 mg) was refluxed for 1.5 h. The mixture was chromatographed on a silica-gel column to give colorless needles, mp 119—121 °C, 29 mg (2%), **5** [Found: M.W., 204.0786. Calcd for $C_{12}H_{12}O_3$: 204.0784. ^1H NMR δ=1.36 (d, J=8.5 Hz, Hm), 1.55 (dt, J=8.5, 2 Hz, Hk), 2.85 (m, Hj), 3.08 (dtd, J=11, 3, 1.5 Hz, He), 3.4 (m, Hf and Hg), 4.67 (dt, J=7, 3 Hz, Hd), 4.93 (dd, J=7, 2 Hz, Ha), 5.77 (dd, J=9, 7 Hz, Hb), 5.93 (m, Hh and Hi), and 6.50 (dd, J=9, 7 Hz, Hc). ^{13}C NMR δ=43.8, 44.8, 45.8, 49.0, 54.6, 80.4, 84.2, 118.4, 132.7, 134.8, 136.6, and 200.3. IR ν: 1700 cm^{-1}], and colorless needles, mp 104—105.5 °C, 37.2 mg (3%), **6** [Found: M.W., 204.0786. ^1H NMR δ=1.34 (dtt, J=8.5, 1.5, 0.5 Hz, Hm), 1.52 (dt, J=8.5, 2 Hz, Hk), 2.55 (dt, J=9.5, 3 Hz, He), 2.98 (m, Hj), 3.12 (dd, J=9.5, 4 Hz, Hf), 3.34 (m, Hg), 4.57 (ddd, J=7, 2, 1 Hz, Ha), 4.73 (dddt, J=7, 3, 2, 1 Hz, Hd), 6.06 (dd, J=5.5, 2.5 Hz, Hh), 6.29 (ddd, J=9, 7, 1 Hz, Hb), 6.35 (dd, J=5.5, 3 Hz, Hi), and 6.83 (ddd, J=9, 7, 1 Hz, Hc). ^{13}C NMR δ=45.2, 46.5, 48.4, 49.4, 51.1, 78.5, 83.4, 123.0, 132.9, 136.0, 136.5, and 204.3. IR ν: 1700 cm^{-1}], together with the recovered **2**, 207.3 mg (21%).

b) A cumene solution (3 cm^3) of **2** (ca. 0.5 mmol) and **4** (ca. 10 mmol), with or without TsOH (21 mg), was heated at 40 °C by means of the pressure vessel under the pressure as indicated in Table 1, for ca. 10 h. The mixture was chromatographed to obtain the products **5** and **6**, and the recovered **2**.

c) An acetone solution (3 cm^3) of **2** (102.6 mg) and **4** (551 mg) was similarly heated by use of the pressure vessel under 2000 bar at 40 °C for 10 h. The results are compiled in Table 1.

Reaction of 2 and 7. A CH_2Cl_2 solution (2 cm^3) of **2** (112.5 mg) was added at −70 °C to **7**, generated in situ by the pyrolysis of dihydro derivative of benzyne-furan adduct.[10] The mixture was kept at 4 °C for 2 d, and chromatographed on a silica-gel column to give colorless needles, mp 144—147 °C, 75.5 mg (41%), **8** [Found: C, 70.27; H, 4.65%. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.73%. ^1H NMR δ=2.22 (dd, J=9, 4 Hz, He), 2.80 (d, J=9 Hz, Hf), 4.90 (ddd, J=7, 2, 1 Hz, Ha), 5.07 (ddd, J=7, 4, 2.5 Hz, Hd), 5.46 (s, Hh), 5.54 (s, Hg), 6.35 (ddd, J=9, 7, 1 Hz, Hb), 6.82 (ddd, J=9, 7, 1 Hz, Hc), and 7.1—7.4 (4H, m). ^{13}C NMR δ=46.2, 52.8, 78.4, 81.8, 83.6, 84.3, 119.0, 119.8, 123.0, 127.2, 127.4, 135.4, 144.8, 146.0, and 200.9. IR ν: 1695 cm^{-1}], and colorless needles, mp 137—140 °C, 34.1 mg (18%), **9** [Found: C, 70.45; H, 4.65%. ^1H NMR δ=2.69 (dd, J=8, 3 Hz, He), 2.92 (d, J=8 Hz, Hf), 5.0—5.15 (m, Ha and Hd), 5.16 (s, Hh), 5.70 (s, Hg), 6.23 (dd, J=9.5, 8 Hz, Hb), 6.87 (dd, J=9.5, 8 Hz, Hc), and 7.1—7.4 (4H, m). ^{13}C NMR δ=44.7, 54.7, 79.8, 80.9 (2C), 83.8, 119.0, 120.0, 121.4, 127.4, 127.5, 135.2, 143.9, 145.3, and 199.2. IR ν: 1710 cm^{-1}], together with the recovered **2**, 12.6 mg (11%).

Reaction of 2 and 10. A CH_2Cl_2 solution (2 cm^3) of **2** (102.2 mg) and **10**[11] (298.5 mg) was refluxed for 14 h. The mixture was then chromatographed on a silica-gel column to give colorless crystals, mp 139—141 °C, 94 mg (31%), **11** [Found: M.W., 408.1362. Calcd for $C_{27}H_{20}O_4$: 408.1360. ^1H NMR δ=3.30 (dd, J=8, 3 Hz, He), 3.48 (dd, J=8, 1 Hz, Hf), 4.55 (ddt, J=7, 2, 1 Hz, Ha), 4.76 (dddd, J=7, 3, 2, 1 Hz, Hd), 5.99 (ddd, J=9, 7, 1 Hz, Hb), 6.39 (ddd, J=9, 7, 1 Hz, Hc), and 7.1—7.8 (14H, m). ^{13}C NMR δ=48.9, 59.7, 79.2, 83.7, 88.9, 90.3, 118.7, 119.3, 119.7, 125.6 (2C), 126.8 (2C), 127.3, 127.7 (2C), 127.8 (2C), 128.6, 129.3 (2C), 135.1, 135.3, 136.5, 145.5, 148.7, and 195.0. IR ν: 1700 cm^{-1}].

Reaction of 3 and 4. A toluene solution (5 cm^3) of **3** (367.5 mg), and **4** (5.5 cm^3), TsOH (59 mg) was refluxed for 10 h. Silica-gel column chromatography of the mixture yielded colorless needles, mp 146.5—149.5 °C, 344.6 mg (96%), **12** [Found: C, 62.61; H, 6.41; N, 8.06%. Calcd for $C_{18}H_{22}O_5N_2$: C, 62.40; H, 6.41; N, 8.09%. ^1H NMR δ=1.25 (3H, t, J=7 Hz), 1.30 (3H, t, J=7 Hz), 1.15—1.4 (m, Hm, underneath the t), 1.48 (dt, J=8.5, 2 Hz, Hk), 2.75 (dt, J=9, 2.5 Hz, He), 2.8—2.9 (m, Hj, underneath the dd), 2.96 (dd, J=9, 3 Hz, Hf), 3.38 (m, Hg), 4.18 (2H, q, J=7 Hz), 4.25 (2H, q, J=7 Hz), 4.83 (2H, dm, J=7 Hz, Ha and Hd), 5.50 (ddd, J=9, 7, 3 Hz, Hb), 5.94 (2H, t, J=2 Hz, Hh and Hi), and 6.40 (ddd, J=9, 7, 1.5 Hz,

Hc). IR ν: 1700 cm^{-1}] together with the recovered **3**, 76.5 mg (21%).

Reaction of 3 and 7. A CH_2Cl_2 solution (2 cm^3) of **3** (293.6 mg) was added to similarly generated **7**. The mixture was then chromatographed on silica-gel column to give a colorless oil, 173 mg (54%), **13** [Found: M.W., 398.1477. Calcd for $C_{22}H_{22}O_2N_2$: 398.1476. ^1H NMR δ=1.18 (3H, t, J=7 Hz), 1.26 (3H, t, J=7 Hz), 2.49 (m, He and Hf), 4.17 (2H, q, J=7 Hz), 4.20 (2H, q, J=7 Hz), 4.98 (d, J=7 Hz, Ha), 5.26 (s, Hh), 5.29 (dm, J=6 Hz, Hd), 5.74 (s, Hg), 5.97 (dd, J=9, 7 Hz, Hb), 6.78 (dd, J=9, 6 Hz, Hc), and 7.1—7.4 (4H, m). IR ν: 1705 cm^{-1}], and a colorless oil, 100.2 mg (31%), **14** [Found: M. W., 398.1479. ^1H NMR δ=1.1—1.4 (6H, m), 2.30 (dd, J=8.5, 5.5 Hz, He), 2.75 (dd, J=8.5, 1.5 Hz, Hf), 4.0—4.4 (4H, m), 4.94 (dd, J=7, 2 Hz, Ha), 5.2—5.4 (m, Hd), 5.32 (s, Hh), 5.39 (s, Hg), 6.12 (ddd, J=9, 7, 1.5 Hz, Hb), 6.69 (dd, J=9, 6.5 Hz, Hc) and 7.1—7.4 (4H, m). IR ν: 1710 cm^{-1}] together with the recovered **3**, 66.5 mg (23%).

Reaction of 3 and 10. Similarly, a toluene solution (4 cm^3) of **3** (101.8 mg) and **10** (100.2 mg) was refluxed for 4 h. The mixture was then chromatographed on a silica-gel column to give colorless crystals, mp 182—184 °C, 63.6 mg (46%), **15** [Found: C, 71.74; H, 5.56; N, 5.57%. $C_{33}H_{30}O_6N_2$: C, 71.97; H, 5.50; N, 5.09%. ^1H NMR δ=1.14 (3H, t, J=7 Hz), 1.20 (3H, t, J=7 Hz), 3.09 (dd, J=8, 2 Hz, He), 3.20 (dd, J=8, 0.5 Hz, Hf), 3.9—4.2 (4H, m), 4.66 (d, J=7 Hz, Ha), 5.03 (ddd, J=6, 2, 1 Hz, Hd), 5.72 (ddd, J=9, 7, 1 Hz, Hb), 6.27 (ddd, J=9, 6, 1 Hz, Hc), and 7.1—7.8 (14H, m). ^{13}C NMR δ=14.2, 14.5, 48.4, 57.2, 62.8, 63.1, 63.5, 78.4, 89.4, 90.1, 119.2, 119.5, 120.0, 125.7, 126.8 (2C), 127.2, 127.6 (3C), 128.5 (3C), 129.2 (2C), 135.9, 136.7, 137.1, 145.9, 148.3, 155.4, 157.4, and 191.4. IR ν: 1710 cm^{-1}] together with the recovered **3**, 32 mg (31%).

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