[2+4] and [6+4] Type Cycloaddition Reactions of 1-Ethoxycarbonyl-1*H*-azepine and 1-Ethoxycarbonyl-1*H*-1,2-diazepine with 3,4,5,6-Tetrachloro-1,2-benzoquinone

Katsuhiro Saito,* Toshio Mukai,† and Shigenori Iida†
Department of Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466
†Department of Chemistry, Faculty of Science, Tohoku University, Aoba, Aramaki, Sendai 980
(Received March 14, 1986)

The reaction of 1-ethoxycarbonyl-1*H*-azepine with 3,4,5,6-tetrachloro-1,2-benzoquinone at room temperature gave a [6+4]-type cycloadduct as the major product and two kinds of [2+4]-type cycloadducts. In this reaction the diketone moiety of the benzoquinone derivative was used as the 4π component to form ether linkages. The [6+4]-type cycloadduct became rearranged to one of the [2+4]-type cycloadducts by heating at 90 °C. The same reaction, but using 1-ethoxycarbonyl-1*H*-1,2-diazepine, afforded two kinds of [2+4]-type cycloadducts. An electronic attraction between the oxygen atoms of the benzoquinone derivative and the carbons in the 2 and 7-positions of the azepine derivative is considered to be one of the driving force of the [6+4]-type cycloaddition reaction. The [2+4]-type cycloadducts are regarded to be formed via inverse electron demand Diels-Alder reactions.

Unsaturated heterocyclic compounds have attracted the attention of chemists from the viewpoint of their synthetic utility and an elucidation of their electronic nature. Five-membered unsaturated heterocyclic compounds such as furan, pyrrole, or thiophene derivatives are known to have aromaticity due to the contributions of lone-pair electrons of the heteroatoms to construct a 6 π-electron aromatic structure.[1] On the other hand, seven-membered unsaturated heterocyclic compounds such as oxepine, azepine, or diazepine derivatives are olefinic compounds because of a lack of the above-type contribution.[2] The five-membered unsaturated heterocyclic compounds proceed substitution and addition reactions,[3] but the seven-membered unsaturated heterocyclic compounds proceed mainly valence isomerization[4] and addition reactions[5] as olefinic compounds.[3]

While a lot of details have been published in connection with the reactions of five-membered unsaturated heterocyclic compounds,[3] reports concerning the addition reactions of seven-membered unsaturated heterocyclic compounds are relatively few in number. One of the reasons is considered to be the instability of these seven-membered unsaturated heterocyclic compounds; and also, the stable derivatives of these heterocyclic compounds are limited to only a few kinds.[4,5]

Azepine and diazepine derivatives are known to react with olefins possessing electron-withdrawing groups to give [2+4], [4+2], and [4+6]-types of cycloadducts.[5] The reaction positions of azepine and diazepines in a [2+4]-type cycloaddition is limited to their 4 and 5 positions; the yields of a [4+6]-type cycloaddition reaction is low. Exceptional cases are the dimerization reactions.[5a,b,c] The authors have investigated addition reactions of azepine and diazepine derivatives with variable olefins and organosilane compounds.[5i,j,k] Also studied were the addition reactions of azepine and diazepine derivatives with 3,4,5,6-tetrachlo-1,2-benzoquinone (**3**), typical of the class of dienes displaying a reverse electron demand in Diels-Alder reactions.[6] The cycloaddition reactions proceeded not through the olefinic part but through the diketone moiety of **3** to give [2+4]- and [6+4]-type cycloadduts forming the ether linkages. Here, we wish to report on the results of these reactions.

Result

1-Ethoxycarbonyl-1*H*-azepine (**1**) was allowed to react with one molar equivalent of 3,4,5,6-tetrachloro-1,2-benzoquinone (**3**) in benzene at room temperature for 70 min to give three kinds of colorles crystals **4**, **5**, and **6** in the yields of 46, 16, and 8%, respectively. The same reaction, but using 1-ethoxycarbonyl-1*H*-1,2-diazepine (**2**) at room temperature for 3.5 h, afforded two kinds of colorless crystals **7** and **8** in yields of 10 and 4%, respectively, along with an intractable black oily material. Products **5** and **6** were stable during heating and recovered completely even after being heated at 180° C for 24 h in benzene in a sealed tube. On the other hand, product **4** rearranged to **6** in a 63% yield upon being heated at 90° C for 4 h in benzene. Products **7** and **8** did not changed at all upon being heated at 130° C for 15 h in benzene in a sealed tube, but turned to black intractable materials upon heating at 180 °C for 10 h.

Reaction of **1** with 1,2-naphthoquinone (**9**) at room temperature for 4 d resulted in a quantitative recovery of **1**. Reactions of **1** and **9** at elevated temperatures of 70 and 110° C for 5 d gave the recovery of **1** in 30 and 0% yields, respectively, along with balck intractable materials. The same reaction of **2** with **9** gave almost the same results as the above.

The structures of the products were deduced on the basis of their spectral properties as follows. The elemental analyses and the molecular-ion peaks in the mass spectra showed that all of the products were 1:1 addition products of **1** or **2** with **3**. The fact that the IR spectra of these products showed no absorption of carbonyl group, except those due to the ester groups, indicates that **1** and **2** reacted with **3** at its oxygen atoms to form the ether linkages.

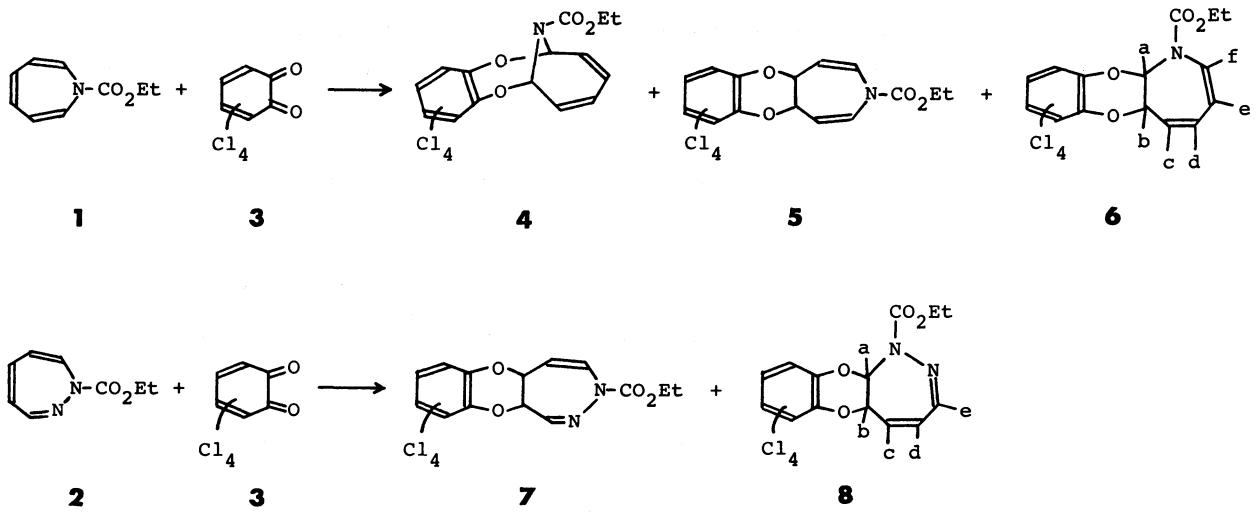


Fig. 1.

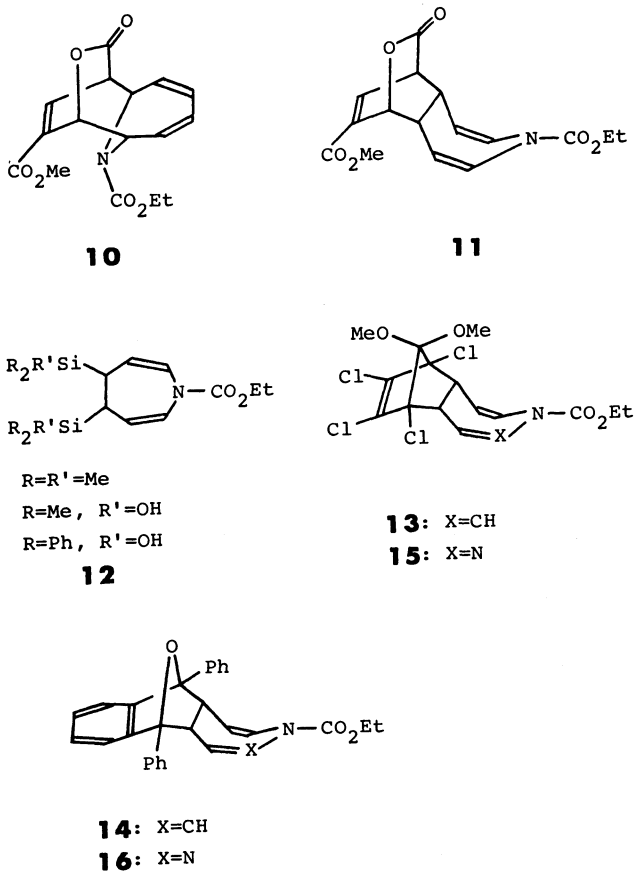


Fig. 2.

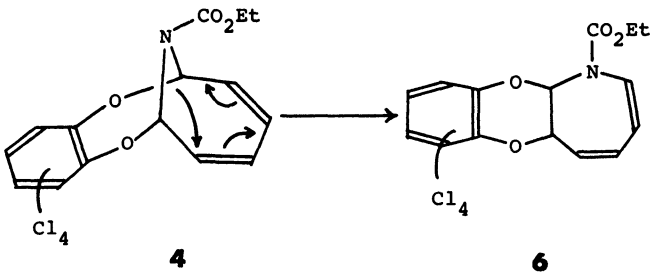
The structures of **4** and **5** were determined mainly on the basis of their NMR spectral properties, which show that these adducts are symmetric compounds. This suggests that the 2 and 7 positions or the 4 and 5 positions of **1** were involved in these reactions. The chemical shift (δ=6.04) and the broad singlet nature of the olefinic protons of **4** closely resembled those features of the olefinic protons of the skeletary analogous compound (**10**)[5i,j] and the azepine dimers. Similarly, the chemical shift (δ=7.06) and the coupling constant (9.0 Hz) of the olefinic protons of **5** had a likeness to those parameters of a similar compound (**10**,[5i,j] **11**,[5i,j] **12**,[5k] **13**,[5i,j,l] **14**[5f,m]). The broad singlet peak at δ 4.97 of **5** was considered to contain absorptions due to the other two olefinic protons and the two methine protons. On the basis of this spectroscopic data, the structures of **4** and **5** were determined as shown in the figure. The electronegativity of the oxygen atoms accounts for the observed lower field resonance of the bridgehead protons of **4** and **5** compared to **10**, **11**, **12**, **13**, and **14**.

The structure of **6** was assigned mainly on the basis of its NMR spectral properties, employing the double-resonance technique. The two continued methine protons (H_a, H_b) and four olefinic protons (H_c–H_f) and the coupling constants between these olefinic protons suggested that **6** contains a seven-membered ring.[5k,7] Dreiding models demonstrate that the diheadral angle between H_a and H_b should be approximately 60° for a cis-configuration and 170° for a trans-configuration. The small coupling constant between H_a and H_b (ca. 2 Hz) indicates that **6** is a cis-adduct of **1** with **3**.[7] The structure of **6** was confirmed by the formation of **6** from **4**, since the transformation of **4** to **6** can be quite reasonably attributed to a thermally allowed 1,5-carbon migration.[8]

The structures of **7** and **8** were also determined mainly on the basis of their NMR spectral properties and were confirmed by a comparison of these data with those of analogous compounds such as **15**,[5i,j] **16**,[5i,j] and **6**. The low field shift of the bridgehead protons of **7** and **8** in their NMR spectra compared to **15** and **16** can be explained using the same reason as that proposed for **5** and **6**.

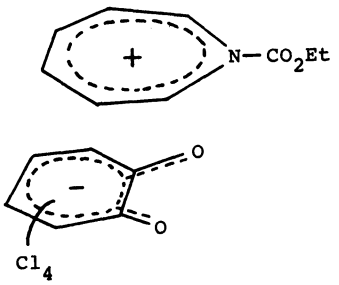
Discussion

Adduct **6** can be regarded as a secondary product, thermally derived from **4**. However, the fact that the



4 6

Fig. 3.



17

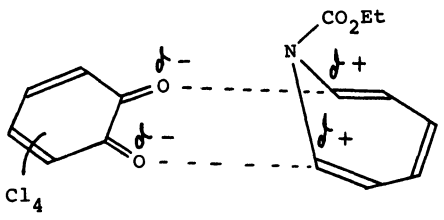
Fig. 4.

addition reaction of **1** with **3** proceeded at room temperature and that the isomerization of **4** to **6** required prolonged heating, seem to prove that **6** was the primary product of a [2+4]-type cycloaddition reaction of **1** with **3**.

The major adduct **4** was formed via a [6+4]-type cycloaddition of **1** with **3**. As previously mentioned, azepine derivatives are known to proceed a [6+4]-type addition reactions in low yields.[5] Furthermore, to our knowledge, no example can be found for [6+4]-type cycloadditions, in which **3** reacts as a **4** π-component. The possibility of a participation of a charge-transfer complex such as **17** can be proposed. The above possibility seems to be negated by the fact that no absorption due to a charge-transfer complex could not be observed in the UV spectrum of a mixture of **1** and **3**.

The major formation of the [6+4]-type cycloaddition product can be regarded as the result of an elctronic attraction between the oxygen atoms of **3** and the carbon atoms in the 2 and 7 positions of **1** as shown in Fig. 5.[8] It is well-known that oxygen atoms of carbonyl groups are negatively charged and a molecular orbital calculation has shown that the azepine has the lowest electron density at the carbons in the 2 and 7 positions.[9]

The adducts **5**, **6**, **7**, and **8** are considered to be formed via reverse electron demand [4+2]-type cycloaddition reactions,[8] in which the HOMO of **1** or **2** interact with the LUMO of **3**. The low energy level of the LUMO of **3** promotes an interaction with the HOMO of **1** or **2**; as a result, it stimulates the addition reactions.[10]



18

Fig. 5.

Experimental

All melting points were uncorrected. NMR spectra were measured with a Varian HA-100 or Hitachi R-20B spectrometer with tetramethylsilane as an internal standard. UV and IR spectra were measured with Hitachi 220A and DS-701G spectrometers, respectively. Mass spectra were measured with a Hitachi M-52 spectrometer. Wako Gel C-200 and Wako Gel B5F were used for column and thin-layer chromatography, respectively.

Reaction of 1 with 3. A mixture of **1** (1650 mg, 10 mmol) and **3** (2460 mg, 10 mmol) in benzene (10 ml) was stirred at room temperature for 70 min. After evaporating of the solvent, the crystals **4** (1860 mg, 46%) were separated by filtration and the filtrate was chromatographed on silica gel to give crystals **5** (637 mg, 16%) and crystals **6** (315 mg, 8%) in this order by the use of pet ether–benzene (2:3). The crystals were recrystallized from cyclohexane to give pure crystals.

4: Mp 156—157°C. Found: C, 43.55; H, 2.67; N, 3.27%. Calcd for $C_{15}H_{11}O_4NCl_4$: C, 43.82; H, 2.70; N, 3.41%. Mass *m/z* (rel intensity): 411 (M^+, 9), 165 (100), 92 (82). IR (KBr): 3030, 2980, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.29 (t, CH_3, J=7.0 Hz), 4.20 (d, CH_2, J=7.0 Hz), 6.04 (bs, 4H), 6.83 (d, 2H, J=4.5 Hz).

5: Mp 165—166°C. Found: C, 43.78; H, 2.54; N, 3.40%. Calcd for $C_{15}H_{11}O_4NCl_4$: C, 43.82; H, 2.70; N, 3.41%. Mass *m/z* (rel intensity): 411 (M^+, 1), 165 (31), 152 (98), 80 (100). IR (KBr): 3030, 2980, 1735 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.36 (t, CH_3, J=7.0 Hz), 4.30 (q, CH_2, J=7.0 Hz), 4.97 (bs, 4H), 7.06 (d, 2H, J=9.0 Hz).

6: Mp 200—202°C. Found: C, 43.93; H, 2.62; N, 3.31%. Calcd for $C_{15}H_{11}O_4NCl_4$: C, 43.82; H, 2.70, N, 3.41%. Mass *m/z* (rel intensity): 411 (M^+, 8), 165 (100), 152 (48), 92 (84). IR (KBr): 3030, 2980, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.36 (t, CH_3, J=7.0 Hz), 4.31 (q, CH_2, J=7.0 Hz), 5.11 (narrow m, H_b), 5.28 (dd, H_e, J_{de}=7.5, J_{ef}=8.6 Hz), 5.39 (bd, H_c, J_{bc}= 2.1, J_{cd}=11.9 Hz), 5.91 (ddd, H_d, J_{cd}=11.9, J_{de}=7.5, J_{bd}=2.1 Hz), 6.63 (narrow m, H_a), 6.87 (d, H_f, J_{ef}=8.6 Hz).

Reaction of 2 with 3. A mixture of **2** (1660 mg, 10 mmol) and **3** (2460 mg, 10 mmol) in benzene (10 ml) was stirred at room temperature for 3.5 h. After evaporating of the solvent, the residue was chromatographed on silica gel to give crystals of **7** (415 mg, 10%) and **8** (165 mg, 4%), in this order, by the use of benzene–ether (4:1). The crystals were recrystallized from benzene to give pure crystals.

7: Mp 183—184°C. Found: C, 40.67; H, 2.56; N, 6.73%. Calcd for $C_{14}H_{10}O_4N_2Cl_4$: C, 40, 81; H, 2.45; N, 6.80%. Mass *m/z* (rel intensity): 412 (M^+, 11), 166 (65), 107 (50), 94 (100), 81 (71). IR (KBr): 3030, 2980, 1740 cm^{-1}. ^1H NMR ($CDCl_3$)

δ=1.40 (t, CH_3, J=7.0 Hz), 4.40 (q, CH_2, J=7.0 Hz), 4.93 (ddd, H_c, J_{ac}=2.5, J_{ac}=2.1, J_{cd}=6.5 Hz), 5.22 (dd, H_b, J_{ab}=2.5, J_{bc}=3.1 Hz), 5.30 (dd, H_d, J_{cd}=6.5, J_{de}=10.3 Hz), 7.07 (dd, H_a, J_{ab}=2.5, J_{ac}=2.5 Hz), 7.49 (d, H_e, J_{de}=10.3 Hz).

8: Mp 209—211 °C. Found: C, 41.03; H, 2.41; N, 6.86%. Calcd for $C_{14}H_{10}O_4N_2Cl_4$: C, 40.81; H, 2.41; N, 6.80%. Mass m/z (rel intensity): 412 (M^+, 14), 166 (50), 107 (44), 94 (83), 81 (100). IR (KBr): 3030, 2980, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.41 (t, CH_3, J=7.0 Hz), 4.45 (q, CH_2, J=7.0 Hz), 5.08 (narrow m, H_b, J_{bc}=2.1 Hz), 5.90 (ddd, H_d, J_{dc}=11.2, J_{db}=2.0, J_{de}=5.5 Hz), 5.98 (dd, H_c, J_{cb}=2.0, J_{cd}=11.2, J_{ce}=2.0 Hz), 6.88 (narrow m, H_a), 7.25 (dd, J_{de}=5.5, J_{ec}=2.0 Hz).

Thermal Rearrangement of 4 to Form 6. A solution of **4** (40 mg) in benzene-d_6 (0.3 ml) was heated at 90 °C for 4 h and subjected to preparative thin layer chromatography on silica gel using pet ether–benzene 1:1 as a developing solvent to give crystals **6** (R_f=0.65, 25 mg, 63%).

The authors are indebted to Honorable Professor Tadashi Sasaki of Nagoya University for his kind suggestions.

References

1) D. S. Sappenfield and M. Kreevoy, *Tetrahedron*, **19**, 157 (1963); D. T. Clark, *ibid.*, **24**, 3285 and 4689 (1968): G. M. Marino, *J. Heterocycl. Chem.*, **9**, 817 (1972); T. J. Barton, R. W. Roth, and J. G. Verkade, *J. Am. Chem. Soc.*, **94**, 8854 (1972); R. M. Acheson, "An Introduction to the Heterocyclic Compounds," John Willey & Sons, Inc., New York (1976), Chap. 3.

2) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Willey & Sons, Inc., New York (1961), Chap. 10; M. Cook, Jr., A. R. Katritzky, and P. Linda, *Adv. Heterocyclic Chem.*, **17**, 255 (1974).

3) A. P. Terent'ev, L. I. Belen'kii, and L. A. Yanovskaya, *Chem. Abstr.*, **49**, 12327d (1955); F. A. Annet, *Tetrahedron Lett.*, **1962**, 1219; A. W. McCulloch, D. G. Smith, and A. G. MacInnes, *Can. J. Chem.*, **51**, 4125 (1973); A. R. Butler and A. P. Sanderson, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1214; R. Helder and H, Wynberg, *Tetrahedron Lett.*, **1972**, 605; D. D. Callander. P. L. Coe, and J. C. Tatlow, *J. Chem. Soc., Chem. Commun.*, **1966**, 143; A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, **26**, 5101 (1970); V. Bocchi, L. Chierici, and G. P. Gardini, *ibid.*, **26**, 4073 (1970); M. G. Barlow, R. N. Hazeldine, and R. Hubbrad, *J. Chem. Soc., Chem. Commun.*, **1969**, 301; R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.*, **48**, 1472 (1970).

4) J. A. Moore, W. J. Freeman, R. C. Gearhart, and H. B. Yokelson, *J. Org. Chem.*, **43**, 787 (1978); J. M. Holovka and P. D. Gardner, *J. Am. Chem. Soc.*, **89**, 6390 (1967); H. Hofmann, and P. Hofmann, *Tetrahedron Lett.*, **1971**, 4055; L. A. Paquette and D. E. Kuhla, *J. Org. Chem.* **34**, 2885 (1969); R. A. Odum and B. Shmall, *J. Chem. Soc., Chem. Commun.*, **1969**, 1299; E. Lerner, R. A. Odum, and B. Schmall., *ibid.*, **1973**, 327; J. Streith, J. P. Luttringer, M. Nastasi, *J. Org. Chem.*, **36**, 2962 (1971).

5) a) K. Hafner and J. Mondt, *Angew. Chem. Int. Ed. Engl.*, **5**, 839 (1966); b) A. L. Johnson and H. E. Simmons, *J. Am. Chem. Soc.*, **88**, 2591 (1966); c) L. A. Paquette and J. H. Barrett, *ibid.*, **88**, 2590 (1966); d) E. Vogel, W. A. Boll, and H. Gunther, *Tetrahedron Lett.*, **1965**, 609; e) W. H. Rastetter, *J. Am. Chem. Soc.*, **97**, 210 (1975); f) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and C. M. Leichter, *J. Org. Chem.*, **34**, 2888 (1969); g) A. G. Annastassiou, E. Reichmanis, S. J. Girgenti, M. S. Ridder, *ibid.*, **43**, 315 (1978); h) J. M. Photis, *J. Heterocycl. Chem.*, **8**, 729 (1971); i) S. Iida, T. Mukai, and K. Saito, *Heterocycles*, **11**, 401 (1978); j) K. Saito, S. Iida, and T. Mukai, *Bull. Chem. Soc. Jpn.*, **57**, 3483 (1984); k) K. Saito, S. Kojima, T. Okudaira, and K. Takahashi, *ibid.*, **56**, 175 (1983); l) T. Imagawa, N. Sueda, and M. Kawanishi, *Tetrahedron*, **30**, 2227 (1974); m) J. R. Wiseman and B. P. Chong, *Tetrahedron Lett.*, **1969**, 1619; n) K. Harano, T. Ban, M. Yasuda, and K. Kanematsu, *ibid.*, **1979**, 1599; o) M. Yasuda, H. Harano, and K. Kanematsu, *J. Org. Chem.*, **45**, 4455 (1980); p) U. Gockel, U. Hartmannsgruber, A. Steigel, and J. Sauer, *Tetrahedron Lett.*, **21**, 599 (1980); q) W. S. Murphy and K. P. Raman, *ibid.*, **21**, 319 (1980).

6) S. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967); E. E. Numann, W. S. Wilson, and R. N. Warrener, *Tetrahedron Lett.*, **1972**, 175; R. Allmann, T. Debaerdemaeker, W. Friedrichsen, H. J. Jurgens, and M. Betz, *Tetrahedron*, **32**, 147 (1976); R. N. Warrener, E. E. Numann, and M. N. Paddon-Row, *Tetrahedron Lett.*, **1976**, 2355; W. Pritschins and W. Grimme, *ibid.*, **1979**, 4545; E. Buldt, T. Debaerdemaeker, and W. Friedrichsen, *Tetrahedron*, **36**, 267 (1980).

7) O. L. Chapman, *J. Am. Chem. Soc.*, **85**, 2014 (1963); M. Karplus, *ibid.*, **85**, 2870 (1963).

8) R. B. Woodward and R. Hoffman, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

9) R. W. Shmidt, *Helv. Chim. Acta*, **45**, 1982 (1962).

10) The energy level of the LUMO of **9** is considered to be higher than that of **3**. The bigger energy difference between the HOMO of **1** and the LUMO of **9** (ΔE_2) comparing to that between the HOMO of **1** and the LUMO of **3** (ΔE_1) explains the inertness of **9** to **1**. The same explanation can be applied to the [6+4] type cycloaddition reaction as shown below.

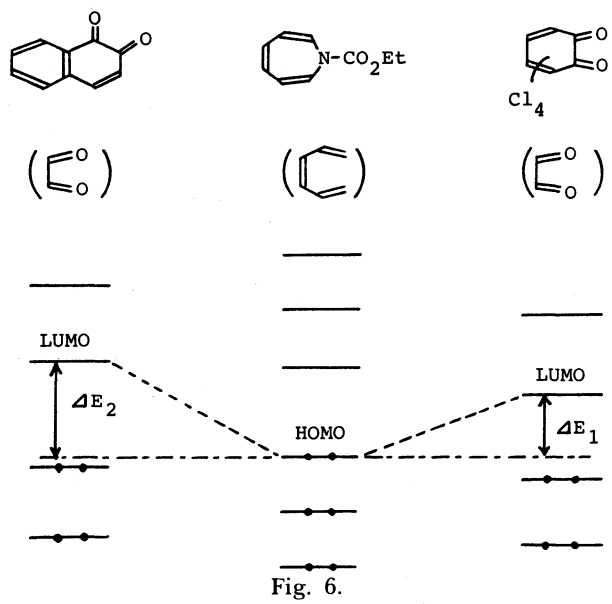


Fig. 6.