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Studies on 5-8 Fused Ring Compounds. VII. The Conformations of the Eight-Membered Rings in C_6–C_8–C_5 Fused Ring Compounds

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The five cis/trans isomers of C_6–C_8–C_5 fused ring compound, tricyclo[9.4.0.0^{4,8}]pentadecane-2,9-dione were synthesized by photocycloaddition of decalin-1,3-dione to cyclopentene. The conformational analyses were carried out by MM2 and the results were compared with X-ray analyses. The eight-membered rings take predominantly boat-chair forms although those in C_5–C_8–C_5 fused ring compounds exist in various conformations.

The cyclooctane ring is so flexible that there are many possible conformations. Cyclooctane,[1] its simple derivatives,[2] and 1,5-cyclooctanedione,[3,4] were found to be predominantly in boat-chair (BC) form, which is the most stable conformation predicted by the molecular mechanics calculations.[5] In monobromo derivatives of C_5–C_8 fused ring compounds the eight-membered rings also take BC forms.[6] In the preceding papers[7,8] we reported the syntheses of C_5–C_8–C_5 fused ring compounds, tricyclo[9.3.0.0^{4,8}]tetradecane-2, 9-dione, by photocycloaddition. The molecular structures of several geometrical isomers were determined by X-ray crystallography,[8,9] and the steric energies were calculated[8] by molecular mechanics (MM2 force filed).[10] The eight-membered rings of C_5–C_8–C_5 fused ring compounds were found in various conformations, boat-chair (BC), twist-boat-chair (TBC), chair-chair (CC), twist-boat (S_4), and chair (C) forms. In this study C_6–C_8–C_5 fused ring compounds were synthesized and the conformations of the eight-membered rings were compared with those of the corresponding C_5–C_8–C_5 fused ring compounds. Conformations of eight-membered ring in other fused ring systems have been investigated for taxane bridgehead olefin system,[11] and for a compound having rigid norbornenyl rings.[12]

The photocycloaddition of *cis*- and *trans*-decalin-1, 3-dione to cyclopentene in methanol yielded directly C_6–C_8–C_5 fused ring compounds, *cis-cisoid-cis-*, *trans-transoid-cis-*, and *trans-cisoid-cis-*tricyclo[9.4.0.0^{4,8}]-pentadecane-2,9-dione (**1**, **2**, and **3**). The compounds **2** and **3** were isomerized to trans configuration under basic conditions, and yielded **4** and **5**, respectively (Fig. 1). The molecular structures of **1**, **2**, and **3** were determined by X-ray crystallography.[13] Because of the difficulty of preparing single crystals of **4** and **5**, their X-ray studies are incomplete. Figure 2 shows the side views of the molecules, **1**, **2**, and **3**. Their eight-membered rings take familiar BC forms, as in 1,5-cyclooctanedione.[4]

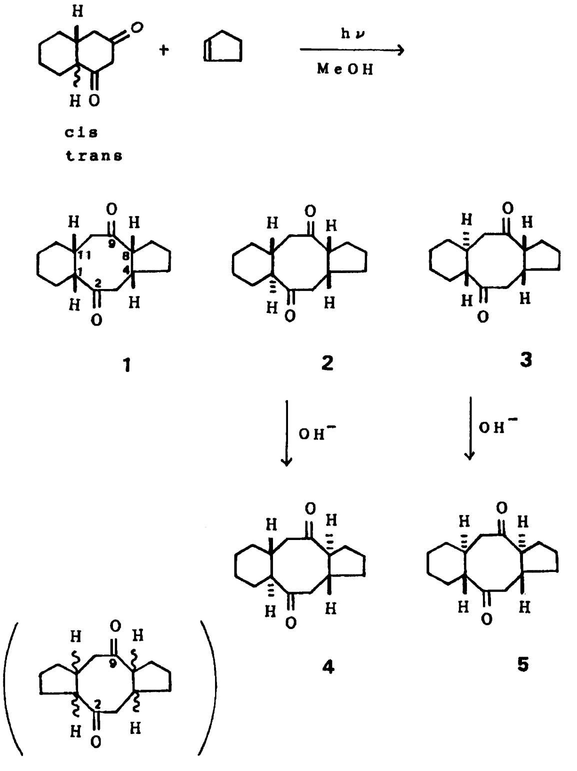

Fig. 1.

Steric energies of these compounds were calculated by MM2 assuming several forms of the eight-membered ring (BC, TBC, CC, S_4, C, twist-chair-chair (TCC), and twist-chair (TC)), and the conformations of lowest energy[14] were compared with the observed structures in crystals. These results were also compared with those of the C_5–C_8–C_5 fused ring compounds.[8] The strain energies for typical conformations of 1,5-cyclooctanedione and C_6–C_8–C_5 fused ring compounds were listed in Table 1. The observed conformations (BC form) of

Table 1. Total Energies of **1**, **2**, **3**, **4**, and **5** by MM2 (kcal mol^{-1})[a)]

Conformations \ Compounds	1,5-Cyclooctanedione[b)]	**1**	**2**	**3**	**4**	**5**
BC[d)]	13.17	32.75[c)]	32.22[c)]	30.33[c)]	30.39[e)]	29.95
TBC	14.04	36.50	30.60	31.56	—[f)]	31.52
TCC	14.43	35.04	32.95	—	30.81	—
CC	14.61	—	—	39.73	—	—
S$_4$	15.73	33.12	31.69	—	33.46	—
TC	17.98	—	—	—	—	—
C	18.5	—	—	—	—	31.78

a) 1 kcal mol^{-1}=4.184 kJ mol^{-1}. b) Ref. 8. c) Observed conformation in crystals. d) BC-3,7 forms except **4**. e) BC-1,5 form. f) — No energy minimum around the starting conformation.

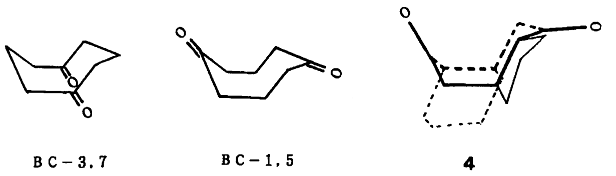

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Chart 1.

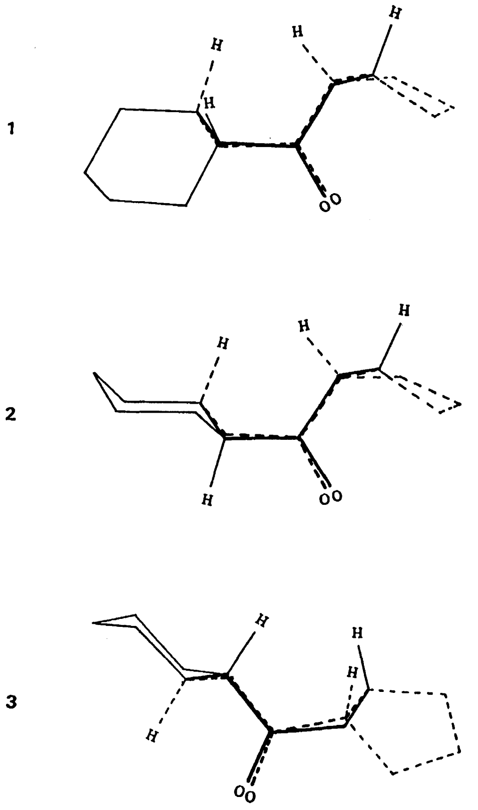


Fig. 2. The side views of the molecules **1**, **2**, and **3** by X-ray analyses. Projections along the C(2)···C(9) vectors.

1 and **3** are consistent with the lowest energy, however for **2** the conformation (TBC form) predicted by MM2 disagrees with that (BC form) obtained by X-ray analysis. Although the crystal structures of **4** and **5** were not determined by X-ray analysis, the MM2 calculations predict that the eight-membered rings take BC form in **4** and **5** (Chart 1). These BC-conformations are BC-3, 7 forms except for **4** which is BC-1,5 form. Molecular model indicates that **4** cannot exist in BC-3,7 form on account of the extreme torsional strain. The observed (X-ray) and calculated lowest energy (MM2) conformations of eight-membered rings in C$_6$–C$_8$–C$_5$ fused ring compounds were summarized in Table 2 with their ring fusions. The conformations in C$_5$–C$_8$–C$_5$ fused ring compounds (**6**, **7**, **8**, **9**, and **10**)[8)] with the same ring fusion as **1**, **2**, **3**, **4**, and **5**, were also shown in Table 2. Though the eight-membered rings in C$_5$–C$_8$–C$_5$ fused ring compounds exist in various conformations: BC, S$_4$, TBC, CC, and C forms, the eight-membered rings in C$_6$–C$_8$–C$_5$ fused ring compounds take predominantly BC forms. The TBC form which was calculated to be the lowest energy conformation for **2** is the second lowest energy conformation for 1,5-cyclooctanedione (Table 1). In C$_5$–C$_8$–C$_5$ fused ring compounds various conformations of the eight-membered ring were observed, because the flexibility of the eight-membered rings is reduced by the five-membered rings attached at two sites. When one of the two five-membered rings of the C$_5$–C$_8$–C$_5$ fused rings is replaced with a six-membered ring, steric strain of the eight-membered ring reduces appreciably, and BC forms become preferred conformation similarly to cyclooctane[1)] and 1,5-cyclooctanedione.[3,4)] The torsion angles at the ring junction in five membered rings of C$_6$–C$_8$–C$_5$ compounds are smaller than those in the six-membered rings. The observed C–C(1)–C(11)–C torsion angles in the six-membered ring of **1**, **2**, and **3** are in the range from 52.1 to 53.7°. Whereas, the C–C(4)–C(8)–C angles in the five-membered ring are 40.1 to 43.2°.

In the BC forms the observed (X-ray) and calculated (MM2) torsion angles for eight-membered rings are compared in Table 3, where the deviation parameter ΔBC[4)] is a measure of fit to the symmetrical BC conformation. The ΔBC values for **1**, **2**, **3**, **4**, and **5** (9.9, 4.2, and 9.3 (X-ray), and 2.1, 1.5, 1.7, 2.3, and 4.4 (MM2)) are fairly smaller than that for **8** (19.9 (X-ray) and 7.8 (MM2)). These results indicate that the eight-membered rings in C$_6$–C$_8$–C$_5$ fused ring compounds are symmetric and less strained than those in the C$_5$–C$_8$–

Table 2. Ring-Fusions and Conformations of Eight-Membered Rings

	C_6–C_8–C_5			C_5–C_8–C_5		
Ring-fusions	Compd	X-Ray	MM2	Compd	X-Ray	MM2
cis-cisoid-cis	**1**	BC	BC	**6**[a)]	S_4	S_4
trans-transoid-cis	**2**	BC	TBC	**7**[a)]	TBC	TBC
trans-cisoid-cis	**3**	BC	BC	**8**[a)]	BC	BC
trans-transoid-trans	**4**	—	BC[b)]	**9**[a)]	—	CC
trans-cisoid-trans	**5**	—	BC	**10**[a)]	C	TBC

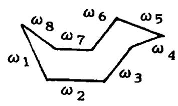
a) Ref. 8. b) BC-1,5 form. The others are BC-3,7 forms.

Table 3. Torsion Angles ω_{1-8} (Observed and Calculated) for Eight-Membered Rings of **1**, **2**, **3**, **4**, **5**, and **8** in BC Forms

		Torsion angles/°								
Compounds		ω_1[a)]	ω_2[a)]	ω_3[a)]	ω_4[a)]	ω_5[a)]	ω_6[a)]	ω_7[a)]	ω_8[a)]	ΔBC(°)[b)]
1	X-Ray	−57.4	−58.5	108.9	−52.8	53.2	−97.8	42.4	69.5	9.9
	MM2	−57.9	−54.3	106.8	−52.2	50.4	−102.8	53.5	59.7	2.1
2	X-Ray	−65.1	−47.1	106.5	−56.5	52.6	−102.0	53.0	62.6	4.2
	MM2	−59.3	−52.3	106.1	−52.9	51.5	−103.0	52.6	60.6	1.5
3	X-Ray	−48.7	−61.4	112.9	−64.3	65.6	−106.6	44.5	61.3	9.3
	MM2	−52.5	−55.8	111.8	−63.6	61.3	−109.8	55.2	54.5	1.7
4[c)]	MM2	−65.7	−46.7	100.6	−69.2	70.6	−100.6	42.1	68.8	2.3
5	MM2	−62.3	−45.0	104.3	−67.9	67.0	−110.3	52.0	58.7	4.4
8[d)]	X-Ray	−47.1	−66.5	110.0	−61.9	70.3	−100.3	29.0	71.1	19.9
	MM2	−52.7	−57.4	109.1	−66.3	69.4	−104.9	42.4	61.4	7.8

a) The positions of the torsion angles ω_{1-8} are shown below.

	1	**2**	**3**	**4**	**5**	**8**
C(10)–C(11)–C(1)–C(2)	ω_1	ω_1	ω_5	ω_3	ω_8	ω_5
C(11)–C(1)–C(2)–C(3)	ω_2	ω_2	ω_6	ω_4	ω_1	ω_6
C(1)–C(2)–C(3)–C(4)	ω_3	ω_3	ω_7	ω_5	ω_2	ω_7
C(2)–C(3)–C(4)–C(8)	ω_4	ω_4	ω_8	ω_6	ω_3	ω_8
C(3)–C(4)–C(8)–C(9)	ω_5	ω_5	ω_1	ω_7	ω_4	ω_1
C(4)–C(8)–C(9)–C(10)	ω_6	ω_6	ω_2	ω_8	ω_5	ω_2
C(8)–C(9)–C(10)–C(11)	ω_7	ω_7	ω_3	ω_1	ω_6	ω_3
C(9)–C(10)–C(11)–C(1)	ω_8	ω_8	ω_4	ω_2	ω_7	ω_4



b) Ref. 4, $\Delta BC=(|\omega_1+\omega_8|+|\omega_2+\omega_7|+|\omega_3+\omega_6|+|\omega_4+\omega_5|)/4$. c) BC-1,5 form. The others are BC-3,7 forms. d) Ref. 8.

C_5 fused ring compounds.

Experimental

The IR spectra were recorded using Horiba FT-200 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-400 (400-MHz) spectrometer in $CDCl_3$ with TMS as the internal standard. The mass spectra were obtained with JOEL JMS-DX300 mass spectrometer.

***cis-cisoid-cis*-Tricyclo[9.4.0.0^{4,8}]pentadecane-2,9-dione (1).** A solution of cis-decalin-1,3-dione[15)] (1.4 g, 8.43 mmol) in methanol (100 ml) and cyclopentene (30 ml, 0.44 mol) was irradiated for 20 h in a Pyrex tube with 100 W high-pressure mercury lamp at 5 °C in a nitrogen atmosphere. After the irradiation, the solvent was removed under reduced pressure. The remaining residue was subjected to column chromatography on silica gel (hexane–ether, 3 : 1). From the second fraction 0.36 g (1.54 mmol, 18.3%) of **1** was obtained. In the other fractions two or three compounds were present and their molecular structures have still not been elucidated.

1: Mp 122—124 °C; IR (Nujol) 1697 and 1684 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ=21.0, 21.7, 22.5, 24.7, 28.0, 30.4, 32.7, 41.0, and 45.9 (CH_2), 31.9, 42.4, 51.8, and 54.6 (CH), 212.4 and 213.6 (C=O); MS, Found: *m/z* 234.1611. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

***trans-transoid-cis-* and *trans-cisoid-cis*-Tricyclo[9.4.0.0^{4,8}]pentadecane-2,9-dione (2 and 3).** A solution of *trans*-decalin-1,3-dione[15)] (2.0 g, 12.0 mmol) in methanol (110 ml) and cyclopentene (35 ml, 0.51 mol) was irradiated for 20 h in a similar manner as above. By the chromatography of crude product, **2** (0.52 g, 2.2 mmol, 18.4%) was obtained from the first fruction, and the second fruction gave **3** (0.53 g, 2.4 mmol, 19.9%). From the further fractions other two isomers (mp, 162—164 °C and 100—102 °C) were obtained and their molecular structures are under investigation.

2: Mp 104—105 °C; IR (Nujol) 1693 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ=23.0, 24.7, 25.9, 26.5, 28.2, 32.3, 34.5, 44.4, and 49.3 (CH_2), 39.0, 42.2, 54.7, and 58.2 (CH), 213.8 and 215.0 (C=O); MS, Found: *m/z* 234.1629. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

3: Mp 163—164 °C; IR (Nujol) 1701, and 1689 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ=22.3, 23.6, 24.9, 25.6, 28.9, 32.4, 34.4, 44.7, and 50.5 (CH_2), 38.1, 40.0, 56.0, and 57.5

(CH), 212.9 and 213.9 (C=O); MS, Found: m/z 234.1617. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

Isomerization of 2 and 3 to 4 and 5. A solution of **2** (0.20 g, 0.85 mmol) in 2% KOH–methanol (5 ml) was left to stand at room temperature for 5 d. The reaction mixture was extracted with ether. The usual work-up of the extracts gave a crystalline residue, **4** (0.16 g, 0.68 mmol, 80%), which was recrystallized from ether–hexane. Similarly **3** (0.20 g) was isomerized to **5** (0.17 g, 85%).

4: Mp 124—125 °C; IR (Nujol) 1701 and 1697 cm^{-1} (C=O); ^{13}CNMR ($CDCl_3$) $\delta=23.1$, 24.8, 25.8, 28.0, 29.9, 33.9, 35.1, 46.9, and 50.5 (CH_2), 42.0, 46.1, 57.7, and 59.2 (CH), 212.3 and 218.5 (C=O); MS, Found: m/z 234.1633. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

5: Mp 147—149 °C; IR (Nujol) 1697 cm^{-1} (C=O); ^{13}CNMR ($CDCl_3$) $\delta=22.6$, 24.8, 25.8, 28.8, 29.1, 33.4, 33.6, 44.8, and 50.2 (CH_2), 36.7, 43.8, 57.1, and 57.6 (CH), 213.4 (C2 and C9, C=O); MS, Found: m/z 234.1625. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

References

1) F. A. L. Anet and J. Krane, *Tetrahedron Lett.*, **1973**, 5029; F. A. L. Anet and V. J. Busus, *J. Am. Chem. Soc.*, **95**, 4424 (1973); S. Merboom, R. C. Howitt, and Z. Luz, *J. Chem. Phys.*, **66**, 4041 (1977); O. V. Dorofeeva, V. S. Mastryukov, N. L. Allinger, and A. Almenningen, *J. Phys. Chem.*, **1985**, 252.

2) M. Dobler, J. D. Dunitz, and A. Mugunoli, *Helv. Chim. Acta*, **49**, 2492 (1966); H. B. Bürgi and J. D. Dunitz, *Helv. Chim. Acta*, **51**, 1514 (1968); J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 1386 (1969); J. V. Egmond and C. Romers, *Tetrahedron*, **25**, 2693 (1969); R. Srinivasan and T. Srikishnan, *Tetrahedron*, **27**, 1009 (1971); M. St. Jacques and R. Prud'homme, *J. Am. Chem. Soc.*, **94**, 6479 (1972); F. A. L. Anet, *Top. Curr. Chem.*, **45**, 169 (1974); T. C. Rounds and H. L. Strauss, *J. Chem. Phys.*, **69**, 268 (1978); P. Groth, *Acta Chem. Scand., Ser. A*, **A35**, 117 (1981); V. V. Kloclkov, P. P. Chernov, A. M. Polozov, V. L. Antonovskii, and A. V. Aganov, *Zh. Org. Khim.*, **24**, 2280 (1988).

3) F. A. L. Anet, M. St. Jacques, P. M. Henrichs, A. K. Cheng, J. Krane, and L. Wrong, *Tetrahedron*, **30**, 1629 (1974).

4) R. W. Miller and A. T. McPhail, *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1527.

5) J. B. Hendrickson, *J. Am Chem. Soc.*, **86**, 4854 (1964); *J. Am. Chem. Soc.*, **89**, 7036 (1967); M. Bixon and S. Lifson, *Tetrahedron*, **23**, 769 (1967); N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Timinski, and F. A. Van-Catledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968); E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973); N. A. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972); P. M. Ivanov and E. Osawa, *J. Comput. Chem.*, **5**, 307 (1984).

6) M. Umehara, H. Takayanagi, H. Ogura, and S. Hishida, *Bull. Chem. Soc. Jpn.*, **51**, 3277 (1978); S. Okumoto, S. Ohba, Y. Saito, T. Ishii, M. Umehara, and S. Hishida, *Acta Crystallogr., Sect. C*, **C43**, 1584 (1987).

7) M. Umehara, S. Hishida, S. Okumoto, S. Ohba, M. Ito, and Y. Saito, *Bull. Chem. Soc. Jpn.*, **60**, 4474 (1987).

8) M. Umehara, S. Hishida, M. Okuda, S. Ohba, M. Ito, and Y. Saito, *Bull. Chem. Soc. Jpn.*, **63**, 2002 (1990).

9) S. Okumoto, S. Ohba, Y. Saito, M. Umehara, and S. Hishida, *Acta Crystallogry., Sect. C*, **C44**, 1275 (1988).

10) N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).

11) C. S. Swindell, T. F. Isaacs, and K. J. Kanes, *Tetrahedron Lett.*, **26**, 289 (1985); E. Osawa, H. Goto, T. Oishi, Y. Ohtsuka, and T. Chuman, *Pure Appl. Chem.*, **61**, 597 (1989); L. A. Paquette, S. W. Elmore, K. D. Combrink, and E. R. Hickey, *Helv. Chim. Acta*, **75**, 1755 (1992).

12) J. G. Garcia, F. R. Fronczek, and M. L. McLaughlin, *Tetrahedron Lett.*, **32**, 3289 (1991).

13) T. Kawata, S. Ohba, M. Umehara, and H. Honnami, *Acta Crystallogr., Sect. C*, **C49**, in press.

14) We believe that we have carefully considered all reasonable low energy conformers but one can never be absolutely sure that the global minima have been found.

15) C. Tamm and R. Albrecht, *Helv. Chim. Acta*, **43**, 768 (1960); C-K. Chuang and Y-L. Tien, *Chem. Ber.*, **69**, 25 (1936); G. A. R. Kong and M. Qudrat-I-Khuda, *J. Chem. Soc.*, **1926**, 3071.