Molecular Structure of the Double Diels–Alder Cycloadduct of 2-Pyrone and Cycloocta-1,5-diene. Very Close Intramolecular H/H Contact and Some Comments

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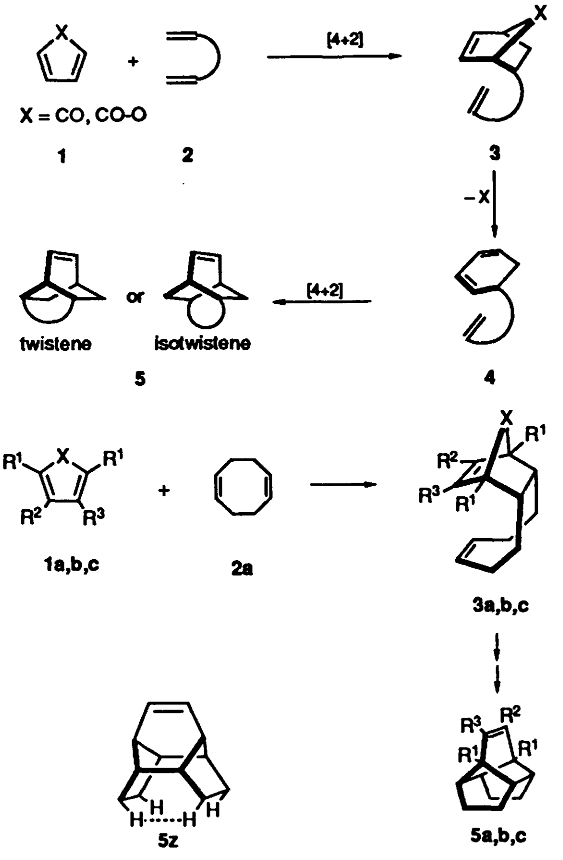
The molecular structure of the double Diels–Alder adduct (DDA) of 5-methoxycarbonyl-2-pyrone and 1,5-cyclooctadiene has been clarified by single crystal X-ray analysis on the phenylurethane of the hydroxymethyl derivative obtained from LiAlH$_4$ reduction of the DDA adduct. The X-ray analysis indicates that the DDA adduct has very close non-bonded H/H contacts of *ca.* 1.94 Å. The observed data are compared with those derived from the MM- and MO-optimized structures.

In previous papers,[1] we reported that 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienones (**1a**), 2-oxo-1,3-bis(ethoxycarbonyl)-2*H*-cyclopenta[*a*]acenaphthylene (**1b**) and 5-methoxycarbonyl-2-pyrone (methyl coumalate) (**1c**) reacted with 1,5-cyclooctadiene (**2a**) to give double Diels–Alder (DDA) adducts (**5**), *i.e.* tetracyclo[6.4.0.0^{4,12}.0^{5,9}]dodec-10-ene, *via* three-step sequential pericyclic reactions (intermolecular cycloaddition ⟶ decarbonylation ⟶ intramolecular cycloaddition). The cage **5** has attracted much attention because of its interesting structural features, the remarkably accelerated intramolecular DA reaction[2] of the precursor (**4**) and the stability of the DDA adduct.



1a: X = CO, R^1 = CO$_2$Me, R^2 = R^3 = Ph
1b: X = CO, R^1 = CO$_2$Et, R^2 + R^3 = naphthyl
1c: X = CO-O, R^1 = R^2 = H, R^3 = CO$_2$Me

Scheme 1

Molecular mechanics (MM2) calculations on the parent skeleton[2] (**5z**) of the DDA adduct of **1a** and 1,5-cyclooctadiene (**2a**) suggested that **5z** has a moderate strain energy (*ca.* 40 kcal mol^{-1})[1a,2] with the presence of very close intramolecular H···H contacts (2.06 Å).† Taking into consideration the known tendency[3a] of the MM method to overestimate such close non-bonded distances by about 0.1 Å, we estimated the actual value to be *ca.* 1.96 Å.

In order to obtain detailed information on the molecular structure of **5c**, we have determined the structure of the DDA adduct by means of a single-crystal X-ray analysis.

Experimental

Melting point is uncorrected. ^{1}H NMR spectra were taken with Hitachi R-600 and JEOL GX-400 spectrometers for *ca.* 10% (w/v) solution with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed as δ values and the coupling constants (J) are expressed in Hz. IR spectra were recorded on a Hitachi 270–30 infrared spectrophotometer. Mass spectra (MS) were taken with a JEOL JMS-DX303HF double-focussing spectrometer operating at an ionization potential of 75 eV.

All calculations were performed on a FACOM M-780 computer at the Kumamoto University Information Processing Center and a Fujitsu S-4/2 work station. Graphical analysis of the MO and X-ray data were performed on a FACOM G-150 work station and a Fujitsu FM R-60HD personal computer.

DDA Adduct (**5c**) *of Methyl Coumalate* (**1c**) *and* 1,5-*Cyclooctadiene* (**2a**).—The DDA adduct (**5c**) was prepared according to the previously reported method.[1a]

Formation of Hydroxymethyl Derivative (**6c**) *by* LiAlH$_4$ *Reduction of* **5c**.—The DDA adduct **5c** (1.0 g, 4.6 mmol) was added to a solution containing LiAlH$_4$ (87 mg, 2.3 mmol) in diethyl ether (20 cm^3) and stirred for 2.5 h. The ether solution was treated with water to decompose excess LiAlH$_4$ and then with HCl solution. The ether layer was separated and washed with NaHCO$_3$ solution and dried over anhydrous MgSO$_4$. The ether was evaporated off. The residue was purified by chromatography on silica gel (CHCl$_3$–AcOEt, 10:1) to give **6c** as a colourless oil (630 mg, 72%); δ_H(400 MHz; CDCl$_3$) 6.08 (1 H, ddd, $J_{7,13}$ 1.47, $J_{11,12}$ 6.39, $J_{5,7}$ 1.83, C$_{11}$-H), 4.20 (2 H, d, $J_{11,13}$ 1.47, C$_{13}$-H), 2.22 (1 H, dd $J_{11,12}$ 6.59, $J_{4,12}$ and $J_{1,12}$ 2.56, C$_{12}$-H), 2.19 (1 H, d, $J_{9,11}$ 1.83, C$_9$-H), 1.65–1.77 (8 H, m, C$_4$-H, C$_1$-H, C$_8$-H and C$_3$-H, C$_2$-H or C$_6$-H, C$_7$-H), 1.46–1.54 (4 H, m, C$_3$-H, C$_2$-H or C$_6$-H, C$_7$-H). The product was sufficiently pure for further synthetic purposes.

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† 1 cal = 4.184 J

Table 1 Interatomic distances (Å) and their estimated standard deviations of 7c

Atom–Atom	Distance	Atom–Atom	Distance
C(1)–C(2)	1.539(8)	C(1)–C(8)	1.552(8)
C(1)–C(12)	1.556(8)	C(2)–C(3)	1.539(10)
C(3)–C(4)	1.548(7)	C(4)–C(5)	1.551(8)
C(4)–C(12)	1.554(7)	C(5)–C(6)	1.536(7)
C(5)–C(9)	1.549(7)	C(6)–C(7)	1.545(7)
C(7)–C(8)	1.525(7)	C(8)–C(9)	1.544(6)
C(9)–C(10)	1.486(6)	C(10)–C(11)	1.306(8)
C(10)–C(13)	1.486(7)	C(11)–C(12)	1.485(7)
C(13)–O(14)	1.454(5)	O(14)–C(15)	1.328(5)
C(15)–O(16)	1.209(6)	C(15)–N(17)	1.347(6)
N(17)–C(18)	1.422(6)	C(18)–C(19)	1.376(6)
C(18)–C(20)	1.398(6)	C(19)–C(21)	1.372(8)
C(20)–C(18)	1.398(6)	C(20)–C(22)	1.378(7)
C(21)–C(23)	1.370(8)	C(22)–C(23)	1.372(7)

Table 2 Bond angles (°) and their estimated standard deviation of 7c

Atom–Atom–Atom	Angle	Atom–Atom–Atom	Angle
C(2)–C(1)–C(8)	116.6(5)	C(2)–C(1)–C(12)	99.4(5)
C(8)–C(1)–C(12)	107.9(4)	C(1)–C(2)–C(3)	104.9(4)
C(2)–C(3)–C(4)	104.7(5)	C(3)–C(4)–C(5)	116.0(5)
C(3)–C(4)–C(12)	100.0(4)	C(5)–C(4)–C(12)	108.6(5)
C(4)–C(5)–C(6)	116.1(4)	C(4)–C(5)–C(9)	108.7(4)
C(6)–C(5)–C(9)	99.4(4)	C(5)–C(6)–C(7)	104.4(4)
C(6)–C(7)–C(8)	104.8(4)	C(1)–C(8)–C(7)	116.2(4)
C(1)–C(8)–C(9)	109.3(4)	C(7)–C(8)–C(9)	100.1(3)
C(5)–C(9)–C(8)	96.9(3)	C(5)–C(9)–C(10)	113.3(4)
C(8)–C(9)–C(10)	113.5(3)	C(9)–C(10)–C(11)	114.1(4)
C(9)–C(10)–C(13)	120.6(5)	C(11)–C(10)–C(13)	125.3(5)
C(10)–C(11)–C(12)	115.1(5)	C(1)–C(12)–C(4)	96.9(4)
C(4)–C(12)–C(11)	113.1(4)	C(1)–C(12)–C(11)	113.4(5)
C(10)–C(13)–O(14)	107.3(4)	C(13)–O(14)–C(15)	116.3(3)
O(14)–C(15)–O(16)	123.2(4)	O(14)–C(15)–N(17)	113.8(4)
O(16)–C(15)–N(17)	123.0(4)	C(15)–N(17)–C(18)	132.0(3)
N(17)–C(18)–C(19)	116.4(4)	N(17)–C(18)–C(20)	123.5(4)
C(19)–C(18)–C(20)	120.0(4)	C(18)–C(19)–C(21)	120.2(4)
C(18)–C(20)–C(22)	118.1(4)	C(19)–C(21)–C(23)	120.7(5)
C(20)–C(22)–C(23)	122.0(5)	C(21)–C(23)–C(22)	119.0(5)

Formation of Phenylurethane Derivative **7c**.—Phenylisocyanate (0.25 g, 2 mmol) was added to a mixture of **6c** (0.3 g, 1.6 mmol) and a small amount of pyridine with ice cooling under Ar atmosphere and shaken. The resulting oil was purified by chromatography on silica gel (benzene–hexane, 3:1). The solid was recrystallized from ethanol to give **7c** as colourless prisms (0.17 g, 35%), m.p. 111–113 °C; δ_H(400 MHz, $CDCl_3$) 7.98 (2 H, m, aromatic H), 7.41 (2 H, m, aromatic H), 6.25 (1 H, dd, $J_{11,12}$ 6.59, $J_{5,7}$ 1.83, C_{11}-H), 4.88 (2 H, d, $J_{11,13}$ 1.10, C_{13}-H), 2.25 (2 H, m, C_5-H, C_{7a}-H), 1.69–1.83 (8 H, m, C_4-H, C_1-H, C_8-H C_5-H and C_3-H, C_2-H or C_6-H, C_7-H), 1.46–1.54 (4 H, m, C_3-H, C_2-H or C_6-H, C_7-H).

X-Ray Crystallography.—The single crystals were prepared by slow evaporation of an acetone–ethanol solution at room temperature.

Crystal data. $C_{20}H_{23}O_2N$ (**7c**) $M = 309.4$, triclinic, $a = 10.409(11)$ Å, $b = 10.405(12)$ Å, $c = 8.326(8)$ Å, $\alpha = 90.92(10)°$, $\beta = 101.45(9)°$, $\gamma = 111.55(8)°$, $V = 818(2)$ Å^3, $D_m = 1.255$ g cm ^{3} (by flotation in aq. KI), $D_c = 1.257$ g cm^{-3}, $Z = 2$, Mo-Kα radiation (40 kV–20 mA), $\lambda = 0.7107$ Å.

The cell constants were determined from a least-squares procedure using the value of the Bragg angles of 20 reflections measured on a RIGAKU AFC-6 four-circle autodiffractometer equipped with a graphite monochromated Mo-Kα source, interfaced to a PANAFACOM U-1200 minicomputer.

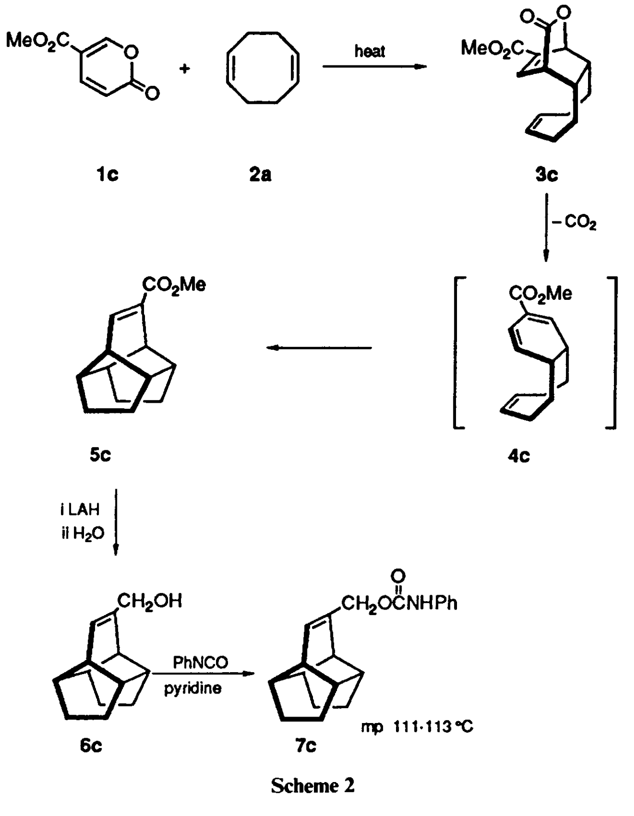
The space group $P\bar{1}$ (*No. 2*) was selected from the number of molecules per unit cell ($Z = 2$) and was later confirmed in the course of the structure refinement. Intensity data were collected in the range $2\theta < 55°$ using the ω–2θ scan technique. The variable scan rate was adopted. Three reflections were monitored after every measurement of 100 reflections. Of the 2593 independent reflections, 1636 were treated as observed ($F_o > 3\sigma F$, $F_o > 15.0$). The intensities were corrected for Lorentz and polarization effects, but no correction was applied for absorption.

Structure solution and refinement. All reflections involving F_{unobs} were used for calculation of normalized structure factors. The structure was solved by the direct method using the MULTAN78[4] series of programs. An E map calculated with 381 signed E's ($E > 1.2$), which gave a combined figure of merit of 2.7025, revealed the positions of all the expected non-hydrogen atoms. Refinements were carried out by the block-diagonal least-squares method.[5] Six cycles of isotropic refinement and six cycles of anisotropic refinement led to an R index of 11.54. All the hydrogen atoms were located in calculated positions. Subsequent refinement of all positional parameters, anisotropic temperature factors for the non-hydrogen atoms, and isotropic temperature factors for the hydrogen atoms led to a final R value of 0.065. In final refinements, the following weights were used for the observed reflections: $w = 1.0$ for $F_o < 5.0$, $w = 25/F_o^2$ for $F_o > 5.0$.

All structure-solving programs were from the Kumamoto University Information Processing Center with the Universal Crystallographic Computation Program System (UNICS III).[5]

Results and Discussion

The DDA adduct (**5c**) of **1c** and 1,5-cyclooctadiene (**2a**) was prepared according to the previously reported method[1a] and converted to the hydroxymethyl compound (**6c**) by lithium alminum hydride (LAH) reduction followed by derivatization to the phenylurethane derivative (**7c**). The final atomic parameters, together with their standard deviations and



Scheme 2

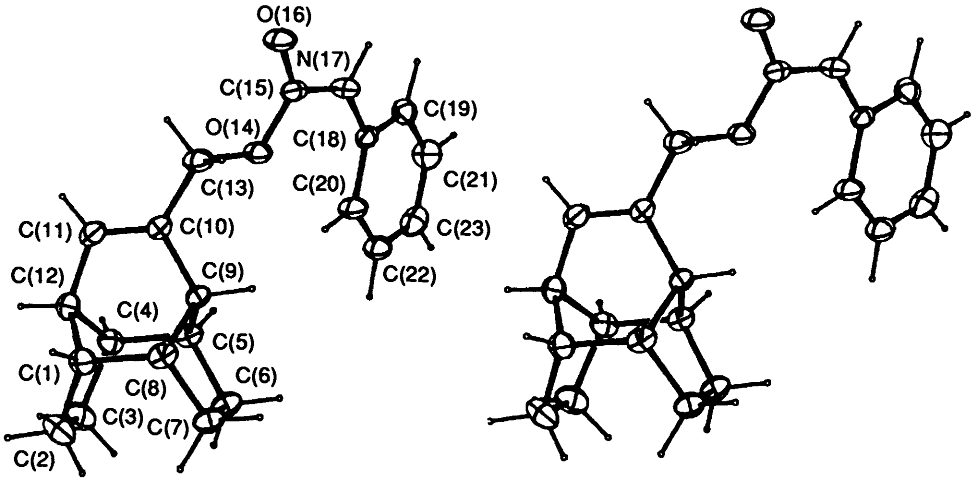
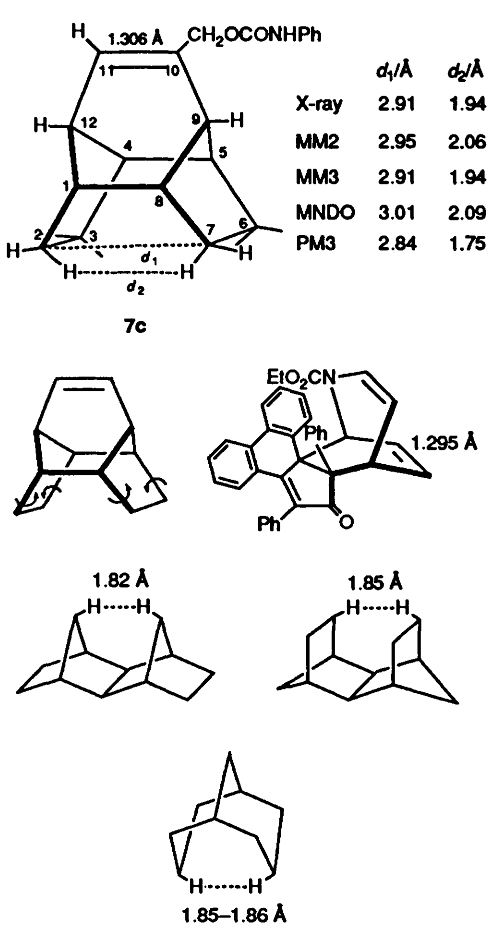


Fig. 1 Stereoscopic view of **7c**



	d_1/Å	d_2/Å
X-ray	2.91	1.94
MM2	2.95	2.06
MM3	2.91	1.94
MNDO	3.01	2.09
PM3	2.84	1.75

Fig. 2 Short H/H contact of **7c**

anisotropic temperature factors have been deposited at the Cambridge Crystallographic Data Centre.* The temperature factors of the protons in question [C(2)-H, C(3)-H, C(6)-H and C(7)-H] are in the range 5.0–9.5.

The computer-generated stereo-pair drawing[6] of **7c** with the numbering system for atoms is depicted in Fig. 1. The atomic distances and angles are listed in Tables 1 and 2.

As can be seen in Table 1, the bond lengths of the framework of **7c** are within normal values for C_{sp^3}–C_{sp^3} bonds except the C(10)–C(11) double bond. In contrast, the interatomic angles are considerably distorted, indicating that the molecular strain is mainly localized at the bond angles. The five-membered ring is strained considerably. In the absence of strain, internal bond angles at C(1), C(2) and C(12) would be *ca.* 108°, but these are reduced to 99.4, 104.9 and 96.9, respectively.

The C(10)–C(11) bond length [1.306(8) Å] is short in comparison with normal C_{sp^2}–C_{sp^2} bonds (1.34 Å) and comparable to that of cyclopropene (1.300 Å) or allene (1.308 Å).[7] The proton nuclear magnetic resonance (^{1}H NMR) spectrum of the hydroxymethyl derivative (**6c**) showed that the olefinic proton resonates at 6.08 ppm which is at considerably lower field than those of structurally similar alkenes (*e.g.* substituted allyl alcohols). This bond shortening is probably due to an increase of s character of the double bond whose π-orbitals interact with the strained σ-bonds of the adjacent carbon atoms. A similarly short double bond [1.295(11) Å] has been observed in the [4 + 2]π cycloadduct of *N*-ethoxycarbonylazepine (4π) and phencyclone (2π), in which the bridged double bond is affected by the large ring strain of the rigid bicyclo[3.2.2]nonyl system.[8]

In **7c**, the non-bonded distances of C(2)–H ··· H–C(7) and C(3)–H ··· H–C(6) are found to be 1.89 ± 0.09 and 1.98 ± 0.09 Å, respectively, in which the C–H bond lengths lie in the range between 0.97 ± 0.05 and 1.03 ± 0.04 Å. The latter value [C(3)–H ··· H–C(6)] is considered to involve considerable error judged from the C(4)–C(3)–H angle (106.6 ± 3.7°). Taking into account the fact that the C(2) ··· C(7) [C(3) ··· C(6)] distance [2.907 (2.913) Å] is comparable to the MM3 value (2.913 Å) and the X-ray C–H bond lengths are observed to be very short (the ideal C–H bond lengths are 1.09–1.10 Å), we can expect that the distances in question are somewhat shorter than 2.0 Å.

Owing to the presence of the short H/H contact, the C(2)–C(1)–C(8) and C(1)–C(8)–C(7) angles undergo an opening of the internal angles from the tetrahedral angle of 109.5 to 116.2–116.6°. This steric repulsion is also reflected in the angles C(3)–C(2) ··· C(7) [88.4(4)°], C(2)–C(3) ··· C(6) [91.8(4)°], C(2) ··· C(7)–C(6) [91.4(4)°] and C(3) ··· C(6)–C(7) [88.5(4)°]. This fact suggests that **5c** is transformed into a slightly twisted structure by the effect of the short H/H contacts (see Fig. 2).

The MM2-calculated strain energy of the DDA adduct (**5z**) is 41.8 kcal mol^{-1},[1b] considerably higher than that of the DDA adduct from 1,5-hexadiene (**2b**) and cyclopentadienone. At first,

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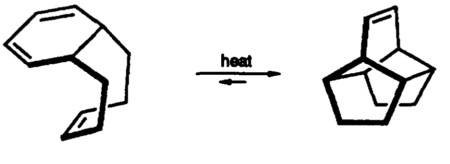
* For details of the deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

Table 3 Comparison of X-ray structural data of **7c** with those calculated by MM2, MM3, MNDO and PM3 for **5z**

Structural Data	**7c**	**5z**				
	X-Ray	MM2	MM3	MNDO	AM1	PM3
Nonbanded distance (Å)						
C(2) ··· C(7)	2.913(10)	2.949	2.913	3.008	2.856	2.836
C(3) ··· C(6)	2.907(10)					
Short H/H contact (Å)						
C(2)–H ··· H–C(7)	1.890(85)	2.057	1.936	2.093	1.848	1.746
C(3)–H ··· H–C(6)	1.982(85)					
C–H (inner)	0.996	1.112	1.108	1.106	1.112	1.108

we thought that the adduct might easily undergo a retro-Diels–Alder reaction to give the cyclohexadiene derivative **4**, owing to its strain energy. Contrary to this expectation, however, the retro DA reaction could not be observed on heating. On the basis of the MM2-calculated bond lengths, we assumed that the observed stability may be due to the localization of the strain energy at the C(1)–C(8) bond rather than the C(1)–C(12) bond which ought to be cleaved by a retro DA reaction (see Scheme 3). The X-ray structure analysis rules out this assumption: the bond length of C(1)–C(12) (1.556 Å) is approximately equal to that of C(1)–C(8) (1.552 Å), indicating the strain does not localize at the two bonds but delocalizes around angles all over the molecule.



4z **5z**

Scheme 3

With regard to the short H/H contacts in some polycyclic hydrocarbons such as bicyclo[2.2.1]heptane or bicyclo[3.3.1]-nonane,[9] their conformations have been studied to test the reliability of MM calculations. The DDA adducts (**5**) of **1c** and nonconjugated dienes (**2**) seem to be suitable model compounds to measure the reliability of MM and MO calculations.[3] In this connection, we performed typical MM and MO calculations on the DDA adduct **7c**.

The selected bond distances and angles of **7c** and the MM2,[3a,b] MM3,[3c] MNDO[10a] and MNDO-PM3[10b] calculated structures of the parent molecule (**5z**) of **7c** are summarized in Table 3. The MM3-calculated H/H distance is 1.94 Å. However, the MM2 calculation gave 2.06 Å, which is 0.12 Å longer than the MM3 value. The MNDO calculation gave 2.09 Å, whereas the AM1 and PM3 calculations gave 1.848 and 1.746 Å, respectively.

In summary, the present X-ray analysis provides valuable information on cage molecules of type **5**. However, neutron diffraction measurements seem to be desirable to get more precise data for the close non-bonded H/H distances.

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References

1 (*a*) K. Harano, T. Aoki, M. Eto and T. Hisano, *Chem. Pharm. Bull.*, 1990, **38**, 1182. (*b*) K. Harano, K. Uchida, M. Izuma, T. Aoki, M. Eto and T. Hisano, *Chem. Pharm. Bull.*, 1988, **36**, 2312. (*c*) K. Harano, M. Yasuda and K. Kanematsu, *J. Org. Chem.*, 1982, **47**, 3736.

2 Recently, the precursor (bicyclo[6.4.0]dodeca-4,9,11-triene) was synthesized and a kinetic study on the formation reaction of the DDA adduct (A) was reported: W. Grime and G. Wiechers, *Tetrahedron Lett.*, 1987, **28**, 6035.

3 (*a*) E. Osawa and H. Musso, *Topics in Stereochemistry: Application of Molecular Mechanics Calculations to Organic Chemistry*, ed. N. L. Allinger, E. L. Eliel and S. H. Wilen, Interscience Publication, New York, 1982, vol. 13, pp. 117–193. (*b*) For MM2, see: N. L. Allinger, *J. Am. Chem. Soc.*, 1963, **85**, 2870; N. L. Allinger and Y. H. Yuh, *QCPE* (*Quantum Chemistry Program Exchange*), 1980, **12**, 395. (*c*) For MM3, see: N. L. Allinger, Y. H. Yuh and J.-H. Lii, *J. Am. Chem. Soc.*, 1989, **111**, 8551; J.-H. Lii and N. L. Allinger, *J. Am. Chem. Soc.*, 1989, **111**, 8566; 8576.

4 P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, *MULTAN78, A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data*, University of York, England, 1978.

5 T. Sakurai and K. Kobayashi, *Rikagaku Kenkyusho Hookoku*, 1979, **55**, 69: S. Kawano, *Koho, Center Kyushu Univ.*, 1983, **16**, 113.

6 C. K. Johnson, *ORTEP*, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965. The program was locally modified for generation of the graphic data for use of a Fujitsu personal computer equipped with a X–Y Plotter.

7 R. C. Bingham, M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.*, 1975, **97**, 1294 and references cited therein.

8 M. Yasuda, K. Harano and K. Kanematsu, *J. Org. Chem.*, 1980, **45**, 2368.

9 For example, see ref. 2, pp. 131–136.

10 (*a*) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899; 4907; M. J. S. Dewar and J. J. P. Stewart, *Quantum Chemistry Program Exchange* (*QCPE*), *Program No. 464*, Indiana University, 1984. (*b*) J. J. P. Stewart, *Comput. Chem.*, 1989, **10**, 221.

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