Pergamon

Tetrahedron 54 (1998) 13495–13504

TETRAHEDRON

Conformational Analysis of Dioxa[2.2]orthocyclophanes

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Received 26 June 1998; accepted 1 September 1998

Abstract Conformations of dioxa[2.2]orthocyclophanes (5,8-dihydro-1,4-dibenzo[b,f]di - oxocine) were examined by theoretical calculations and X-ray crystallographic analysis. In the crystalline state a twist boat form was observed, which is identical to the structure predicted both by molecular mechanics and molecular orbital calculations. By contrast, an unique screw conformation was observed in a cyclophane having two dioxa[2.2]orthocyclophane units within the molecule in the crystalline state.

Keywords: Cyclophanes; Conformation; Molecular mechanics; X-ray crystal structure

Introduction

Determination of significantly populating conformers in flexible molecules such as medium size ring compounds is of long standing interest.1) Although x-ray crystallography is one of the most important methods to determine the precise structure in the crystalline state, the structure obtained by this method does not always correspond to the global energy minimum conformer in solution because of the effect of crystal packing forces. ^{1}H-NMR spectroscopy has thus been extensively utilized not only for the determination of the most preferred conformation but also to analyze the conformational behavior of such compounds. Incorporation of some unsaturated bonds into a ring reduces its flexibility to some extent, hence many works have been reported on the conformational analysis of unsaturated medium size ring compounds.2) The structures of 1,5-cyclooctadiene, the basic skeleton of the [2.2]orthocyclophane, have been determined both crystallographically and in solution.3) In the parent [2.2]orthocyclophane **1**, (5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene) three conformers, chair, boat or twist boat, and screw forms were predicted by molecular mechanics calculations (Fig. 1).4) The presence of the chair form was confirmed in the crystalline state.5) ^{1}H-NMR spectroscopic analysis disclosed the coexistence of the chair and boat forms in solution. The NMR spectrum at low temperature showed the presence of the two sets of methylene proton signals, one as a singlet and the other in an AA'BB' system; the latter signals were assigned as arising from the rigid chair conformation. Similar conformers were reported in [2.2](5,6)-indanophane **2**6) and some heteroaromatic derivatives **3** - **5**.7)

PII: S0040-4020(98)00830-8

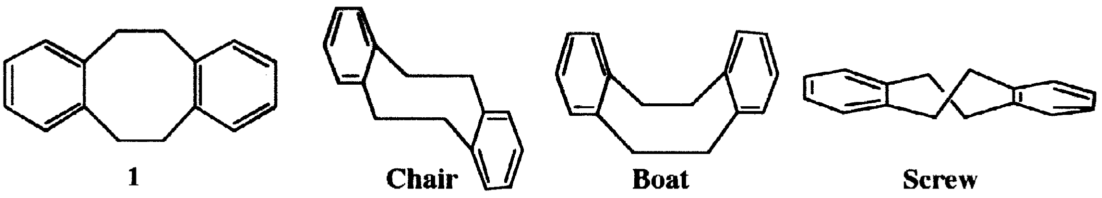
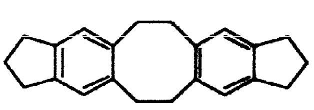


Figure 1. Three stable conformations of **1**

Introduction of some bulky substituents and/or hetero atom(s) into the ethano bridge(s) of **1** influences the relative stability of these conformations. Distorted boat forms of **6**[8] and **7**[9] were found in the crystalline state. In the case of hetero-atom containing compounds, p-π type conjugation between the aromatic ring and the bridging heteroatom(s) should play an important role in determining the preferred conformation. Thus, the conformational behavior of a number of derivatives containing amide,[10] ester,[11] or thioester[12] moieties in their bridge(s) was examined. Although the relative stabilities and the energy barrier for the interconversion of the conformers were influenced by the introduction of the heteroatoms in the bridges, the basic structures were not significantly altered in these compounds. While the structures of some aza[13] and thia[14] derivatives were elucidated, that of a simple oxa derivative was not examined satisfactorily.[15] In this paper, we report the conformational behavior of **8** and its related compounds **9** and **10**.

Results and Discussions

Synthesis



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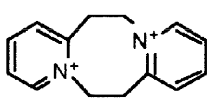

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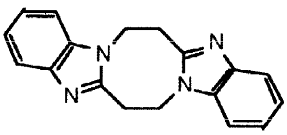

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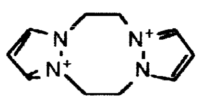

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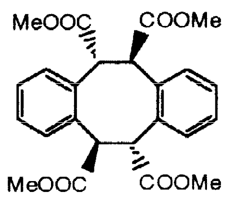

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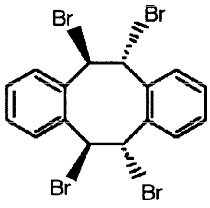

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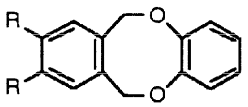
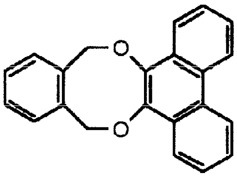


8a:R=H

b:R=



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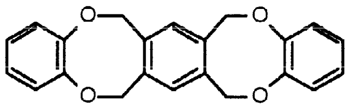

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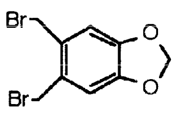

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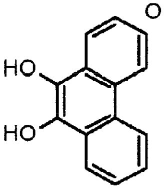

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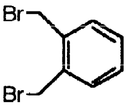

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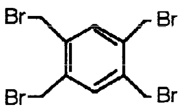

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To simplify the ^{1}H-NMR spectrum, compound **8b** having a tetra-substituted benzene ring was chosen in this study. Compound **8b** was synthesized from catecol and bis(bromomethyl)benzene derivative **11** by treatment with Cs_2CO_2 in acetone. Compound **9** was prepared from 9,10-dihydroxyphenanthrene **12** and bis(bromomethyl)benzene **13** in acetone with Cs_2CO_3 as a base. Compound **10** having the two units of the dioxa[2.2]orthocyclophane within the molecule was prepared by the coupling of 1,2,4,5-tetrakis(bromomethyl)benzene **14** with catecol.

NMR spectra

From a molecular modeling consideration, there are also three structures, chair, boat or twist boat, and screw forms in both **8** and **9**. We could not identify the preferred structure of these compounds only by the NMR spectroscopy. In the ^{1}H-NMR spectrum, both **8** and **9** gave a respective singlet signal due to the bridge methylene protons (Ar-CH_2-O-Ar) at room temperature, suggesting a rapid conformational dynamic process which makes the intrinsically non-equivalent two geminal protons of the methylene equivalent. The conformational interconversion which causes equivalence of the geminal sites of the methylene protons must be an enantiomeric one. The singlet nature of the methylene protons suggested that the conformational interconversion is quite fast at room temperature. The singlet signal did not change even at -90 °C, implying that the conformational interconversion processes could not be frozen at this low temperature because of the extremely low energy barrier for the interconversion processes.

Theoretical Calculations

In order to obtain the precise structure of **8a** and to know the details of the dynamic conformational interconversion processes, theoretical calculations both by the molecular mechanics and molecular orbital methods were carried out. Because the searching process for all the possible conformers is time consuming, molecular mechanics calculations were applied. Using the low mode conformational search algorithms16) in the modeling software system, MacroModel17) V6.0 with MM3* force field, three structures of **8a**, twist boat, screw, and chair forms were found within 5.0 kcal/mol of the steric energy (Fig. 2).

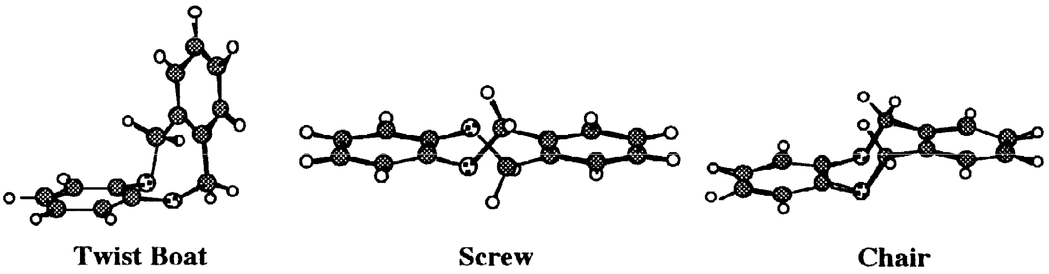

Figure 2. Three conformers of **8a**.

The most stable structure is the twist boat form in which the two benzene rings are nearly perpendicular with each other. The screw and the chair forms are higher in the steric energy by 1.37 and 2.85 kcal/mol, respectively. No stable conformer other than these three was found even if we expand the energy window to 10 kcal/mol. These three structures were optimized also by molecular orbital calculations with semiempirical PM3 and *ab initio* method (RHF/3-21G and Becke3LYP/6-31G*//RHF/3-21G).

Table 1. Relative energy (kcal/mol) of three conformers of **8**

Method	T-Boat	Screw	Chair
MM3*	0.0	1.4	2.9
PM3	0.0	0.8	1.1
3-21G	0.0	0.2	5.6
DFT[a]	0.6	0.0	3.3

a) Becke3LYP/6-31G*//RHF/3-21G

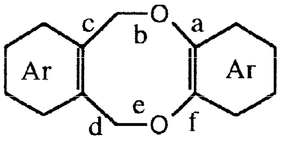

Table 2. Torsion angles (°) in dihydrodioxocine skeleton

	calcd.				obsd. (X-ray)		
	MM3*	PM3	3-21G	DFT[a]	**8b**	**9**	**10**
T-Boat							
a	24.9	22.2	28.9	28.7	33.3(3)	31.4(1)	
b	62.8	62.4	60.7	58.9	51.6(3)	54.9(1)	
c	-99.9	-96.5	-98.7	-98.9	-101.2(4)	-97.2(1)	
d	18.7	19.3	24.1	26.1	31.0(3)	26.4(1)	
e	61.1	60.6	57.0	53.2	48.8(3)	54.1(1)	
f	-90.6	-88.4	-87.6	-86.1	-92.5(4)	-87.1(1)	
Screw							
a	48.6	50.3	47.2	47.8			49.9(8)
b	-113.4	-110.7	-117.6	-115.7			-117.6(5)
c	51.4	56.2	55.9	56.8			56.3(7)
d	51.4	56.2	55.9	56.8			53.9(7)
e	-113.4	-110.7	-117.6	-115.7			-115.1(5)
f	48.6	50.3	47.2	47.6			48.9(8)
Chair							
a	-74.3	-74.8	-72.6	-70.3			
b	110.2	107.8	109.7	110.2			
c	-75.8	-73.1	-74.0	-76.5			

a) Becke3LYP/6-31G*//RHF/3-21G

Although the relative stability between the three forms is dependent on the method of calculation (Table 1), the structures obtained by these methods are almost identical with each other (Table 2). Three of the methods used predicted that the twist boat form is the most stable structure and the screw and chair forms follow in this order. In contrast, Beckel3LYP/6-31G*//RHF/3-21G predicted the reverse order in the stability of the first and second forms. All the methods agreed that the chair form has the highest conformational energy among the three.

Conformational Dynamic Processs

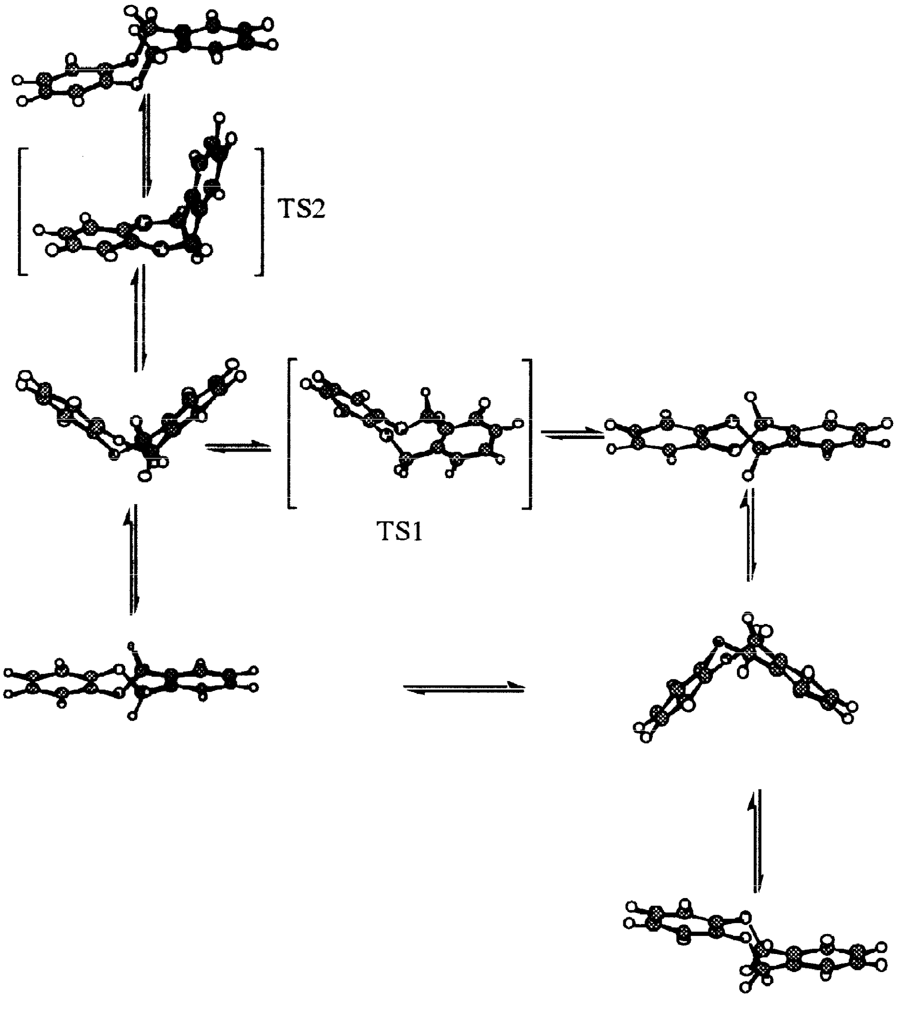

Figure 3. Conformational dynamic process of **8**

It is known that the mechanisms of the conformational interconversion processes in [2.2]orthocyclophane **1** involves the rotation of the aromatic rings with respect to one another and a bridge bond rotation.4) The former, the aromatic ring flipping mechanism, can convert the rigid chair to the twist boat form and the latter a pseudorotational process, interconverts the twist boat and screw forms. The pseudorotational process was known to be facile ($\Delta G^{\neq}$ = 7.5 kcal/mol) in the NMR time scale because no severe steric repulsion nor large bond angle expansion was assumed during the interconversion process. The activation energy of the aromatic ring flipping process is higher (10.2 kcal/mol) than the pseudorotational process. Since we could not obtain any information of the conformational interconversion processes of **8b** from a low temperature NMR study, the conformational dynamic processes of **8a** was analyzed by semi-empirical molecular orbital calculation using the torsional drive method. The transition state (TS1)18) within the interconversion process of the twist boat and screw forms is close to the screw form in energy. The activation energy from the twist boat is very small (1.1 kcal/mol) and hence, the pseudorotational process is extremely facile and almost barrier free. By contrast, the activation energy of the ring flipping process (TS2) was predicted to be higher (7.2 kcal/mol). Hence, the most stable twist boat form can interconvert to its mirror image only by the pseudorotational process *via* screw forms (Fig. 3). The high energy chair forms do not always contribute to the conformational dynamic process of **8a**.

X-ray crystallographic study

The ORTEP drawings of **8b**, **9**, and **10** are shown in Figure 4. The structure found in the crystalline state of **8b** and **9** is the twist boat form as was predicted by the theoretical calculations. There are two independent molecules in an asymmetric unit of the crystal cell of **9**. They have almost identical structures with each other. The two aromatic rings of both **8b** and **9** have nearly perpendicular arrangement, respectively. Similar twist boat forms of the [2.2]orthocyclophane skeleton were observed in some heavily substituted compounds (**6**8) and **7**9)) or bicyclic systems such as dibenzo[3.3.1]19) and [4.2.1]rings,20) however, it is rather rare in compounds containing no substituent on the 8-membered ring system of the [2.2]orthocyclophane skeleton.

The structure of the 8-membered dihydrodioxocine skeleton in **10** is the screw form. The dihedral angles between the aromatic rings (center-terminal) within the molecule is 48.7 °. To our knowledge, this is the first example of the screw form found in the crystalline state. The structures of the dioxa[2.2]orthocyclohane skeleton observed in the crystalline state are the twisted boat and screw forms. Of course, subtle effects due to crystal packing forces may change a mainly populated structure in solution to a different conformer in the crystal, however, the energy difference between the two structures should not be so large in the present case because both structures were observed in the crystalline state. Hence, it is not so unreasonable to consider from the results of the X-ray crystallographic analysis that the two structures, twist boat and screw, are energetically very close to each other in solution. This was further supported by the theoretical calculations.

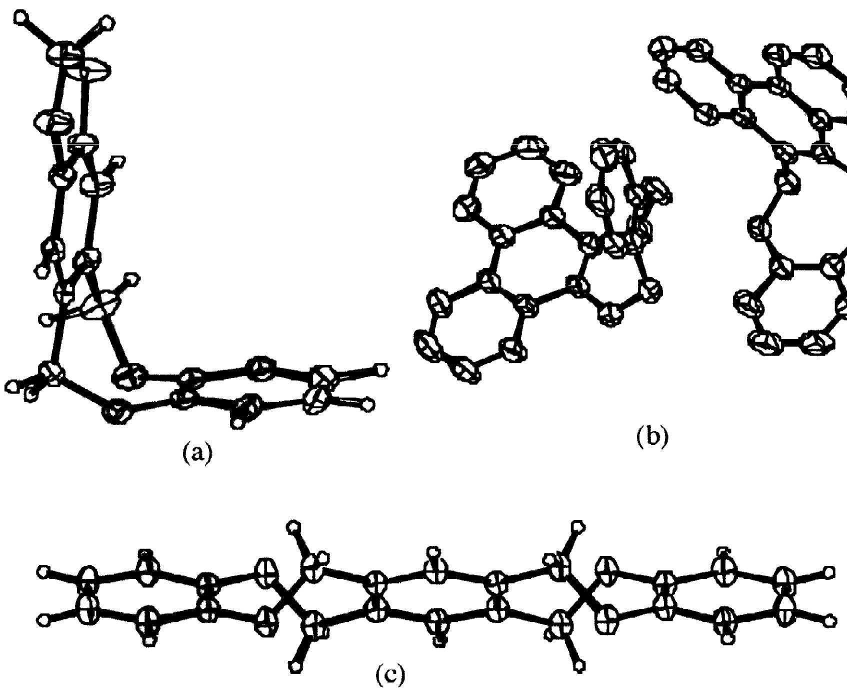

Figure 4. ORTEP drawing of **8b** (a), **9** (b), and **10** (c).

Conclusion

From the analyses of the X-ray crystallography and theoretical calculations, we can conclude that the twist boat and screw forms in the dioxa[2.2]orthocyclophane are the two most important conformers in solution and they are interconverting between each other quite rapidly even at low temperature (-90 °C).

Experimental

Preparation of 8b

A mixture of 4,5-methylenedioxy-1,2-bis(bromomethyl)benzene **11**21) (200mg, 0.649mmol) and catecol (72mg, 0.654mmol) in 20ml of acetone was added dropwise to a suspension of cesium carbonate (530mg, 1.63mmol) in 20ml of acetone at refluxed temperature. The mixture was refluxed for 2 hours and was filtered. The solvent was removed by evaporation, residue was purified by silicagel column chromatography (10% Ethylacetate/Hexanes) to afford 50mg (30% yield) of **8a**; colorless prisms, mp 125-126°C. ^{1}HNMR (270MHz CDCl$_3$) δ 6.96 (bs, 4H), 6.63 (s, 2H), 5.90 (s, 2H), 5.32 (s, 4H); ^{13}CNMR (270MHz CDCl$_3$) δ 149.090, 147.524, 129.395, 123.657, 121.930, 109.370, 101.348, 74.555; MS m/z (M$^+$) 256. Anal. Calcd for C$_{15}$H$_{12}$O$_4$ C, 70.31; H, 4.72 Found C,70.29; H, 4.62.

Preparation of 9

A mixture of phenanthrenequinone (1.7g, 8.317mmol) and a catalytic amount of palladium-carbon in 20ml of THF was stirred under H$_2$ for one day at room temperature. The reaction mixture was filtered under Ar and the filtrate was added dropwise to a mixture of 1,2-bis(bromomethyl)benzene **13** (1.8g, 8.17mmol) and cesium carbonate (6g, 18.4mmol) in 100ml of acetone at refluxed temperature. The mixture was refluxed for 5 hours and was filtered. The solvent was removed by evaporation and the residual yellow solid (2.6g) was chromatographed by silicagel (3% Ethylacetate/Hexane) to afford 0.46g (22% yield) of **9** ; colorless prisms, mp 191-192°C. ^{1}HNMR (270MHz, $CDCl_3$) δ8.56-8.56 (m, 2H), 8.30-8.27 (m, 2H), 7.64-7.53 (m, 4H), 7.26 (s, 4H), 5.70 (s, 4H); ^{13}CNMR (270MHz $CDCl_3$) δ140.457, 135.843, 128.906, 128.768, 128.508, 126.705, 125.437, 122.458, 121.969, 75.441; MS m/z (M^+) 312. Anal. Calcd for $C_{22}H_{16}O_2$ C, 84.59; H, 5.16 Found C, 84.61; H, 5.16.

Preparation of 10

A mixture of 1,2,4,5-tetrakis(bromomethyl)benzene **14** (100mg, 0.224mmol) and catecol (54mg, 0.49mmol) in 50ml of acetone was added dropwise to a suspension of cesium carbonate (200mg, 0.59mmol) in 50ml of acetone at refluxed temperature. And the mixture was refluxed for 30 minutes and was filtered. The solvent was removed by evaporation, residue was purified by silicagel column chromatography ($CHCl_3$) and then by GPC ($CHCl_3$) to afford 10mg (13% yield) of **10**; colorless prisms, mp 299-303°C. ^{1}HNMR (270MHz $CDCl_3$) δ 7.01 (s, 2H), 7.00-6.89 (m, 8H), 5.35 (s, 8H); ^{13}CNMR (270MHz $CDCl_3$) δ 149.686, 136.026, 129.677, 123.711, 121.915, 74.708; MS m/z (M^+) 346. Anal. Calcd for $C_{32}H_{18}O_4$ C, 76.29; H, 5.24 Found C, 76.18; H, 5.29.

X-Ray Diffraction Analysis of 8b.

The crystal data for **8b** are as follows; Monoclinic, space group $P2_1/a$ with a = 12.877 (5), b = 8.793 (2), c = 10.860 (2) Å, β = 93.90 (2) °, V = 1226.8 (6) Å^3, and Z = 4. The empirical formula is $C_{15}H_{12}O_4$, molecular ^{W}eight is 256.26, and calculated density is 1.33 g•cm-3. The three-dimensional intensity data were collected by the use of graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å}) on a Rigaku AFC-4 automatic four-circle diffractometer up to a maximum 2θ of 110°. Of 2089 total unique reflections, 1580 were considered observed at the level of |Fo| > 2.0 σ|Fo|. The structure was solved by the direct method (Sir97)$^{22)}$. All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were found from the difference fourier map and included in the further calculations. Full matrix least squares refinements with anisotropic 19 non-hydrogen atoms and 12 isotropic hydrogens converged to a conventional R factor of 0.054.

X-Ray Diffraction Analysis of 9.

The crystal data for **9** are as follows; Monoclinic, space group $P2_1/n$ with a = 10.504 (1), b = 10.620 (1), c = 28.486 (2) Å, β = 95.566 (3) °, V = 3162.7 (2) Å^3, and Z = 8. The empirical formula is $C_{22}H_{16}O_2$, molecular weight is 312.37, and calculated density is 1.31 g•cm-3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) on a Mac Science imaging plate diffractometer. Of 6599 total unique reflections, 5368 were considered observed at the level of |Fo| > 2.0 σ |Fo|. The structure was solved by the direct method (Sir97). All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were found from the difference fourier map and included in the further calculations. Full matrix least squares refinements with anisotropic 48 non-hydrogen atoms and 32 isotropic hydrogens converged to a conventional R factor of 0.063.

X-Ray Diffraction Analysis of 10.

The crystal data for **3** are as follows; Monoclinic, space group $P2_1/a$ with a = 9.474 (2), b = 6.388 (1), c = 13.510 (3) Å, β = 90.84 (2) °, V = 817.6 (3) $Å^3$, and Z = 2. The empirical formula is $C_{22}H_{18}O_4$, molecular weight is 346.38, and calculated density is 1.41 g•cm-3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å) on a Mac Science MXC3 automatic four-circle diffractometer up to a maximum 2θ of 120°. Of 1315 total unique reflections, 1240 were considered observed at the level of |Fo| > 3.0 σ|Fo|. The structure was solved by the direct method (Sir97). All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were found from the difference fourier map and included in the further calculations. Full matrix least squares refinements with anisotropic 13 non-hydrogen atoms and 9 isotropic hydrogens converged to a conventional R factor of 0.063.

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