Synthesis and Conformational Analysis of 3,3,12,12-Tetramethy[4.4]paracyclophane-2,13-dione

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Three [4.4]paracyclophanes (**2**–**4**) were synthesized by radical cyclization using the photoinduced $S_{RN}1$ reaction. The structure of the most stable conformer of **4** was ascertained by means of X-ray crystallographic analysis, molecular mechanics calculations, and variable-temperature NMR spectra. The energy barriers to rotation of the two benzene rings in these compounds were obtained from an analysis of the temperature-dependent signals due to the 1,3-dioxolene and aromatic ring protons. Molecular mechanics calculations predicted three stable conformers for **4**. Actually, three sets of signals were observed in its low-temperature ^{1}H NMR spectrum. An experimental technique was used in which crystals were dissolved in precooled solvent. In this manner, NMR signals were recorded due to the single conformer found in its crystalline state, which are identical to the major set of signals present in the original spectrum. The structures due to the other two sets of signals of **4** can be successfully assigned by comparison of the low temperature ^{1}H NMR spectra of the two compounds (**2** and **3**). The interconversion pathways among these conformers were characterized.

Introduction

Determination of significantly populating conformers in extremely flexible molecules such as macrocyclic compounds is a matter of long standing interest. Spectroscopic methods have been extensively used for conformational analysis. X-ray analysis is also one of the most important methods to determine the precise geometry in a crystal; however, the structure obtained by this method is often not the true global minimum energy structure because of the effect of packing forces. Hence, the NMR signals in solution do not always correspond to the structure in the crystalline state. Moreover, conformational dynamic equilibrium operating in solution often complicates the spectroscopy. The analysis of conformational behavior of macrocyclic compounds is thus not straightforward. If all the conformational dynamic processes could be significantly slowed down at low temperature, NMR signals due to the single conformer found in its crystalline state could be available by simple dissolution of a crystalline compound into precooled solvent.[1] The conformational behavior of [*m.m*]-paracyclophanes might offer a good example to test whether or not such an interesting technique is applicable.

The stereochemical aspects of mobile cyclophanes have been of particular synthetic and theoretical interest for well over three decades.[2] Although [*m.m*]metacyclophanes have been extensively investigated,[3] studies on paracyclophanes are rather limited. Within the paracyclophane series, interest has been focused on the rather shorter bridged compounds,[4] so that few investigations on the structural aspects of [4.4]paracyclophanes have been reported.

Syntheses of [4.4]paracyclophanes have been accomplished by several groups. Using the acyloin condensation as a key cyclization step, Cram and co-workers pioneered their synthesis.[5] A ring expansion approach from shorter bridged congeners has also been a method of choice.[6] Misumi reported syntheses involving thermal SO_2 extrusion from the disulfone obtained by the oxidation of dithia[5.5]paracyclophanes.[7] Reductive ring cleavage of cyclobutane in 1,2-ethano[2.4]paracyclophanes, which are obtained by intramolecular [2 + 2]photocycloaddition of 1,4-bis(*p*-vinylphenyl)butanes, has been shown to have extensive applicability for the synthesis of a wide variety of [4.4]paracyclophanes.[8]

Conformational dynamic processes in mobile [*m.n*]-paracyclophanes involve the rotation of aromatic rings with respect to one another and the flipping of bridging

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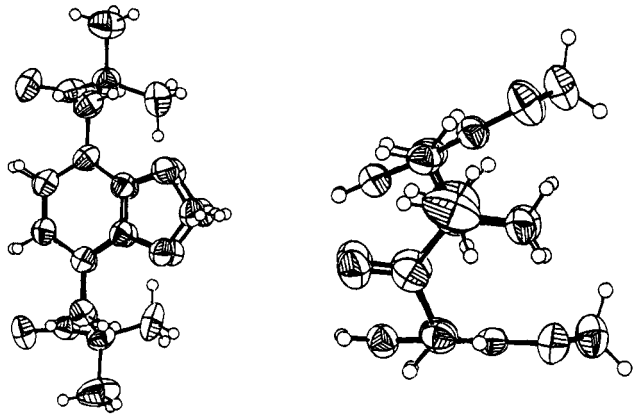


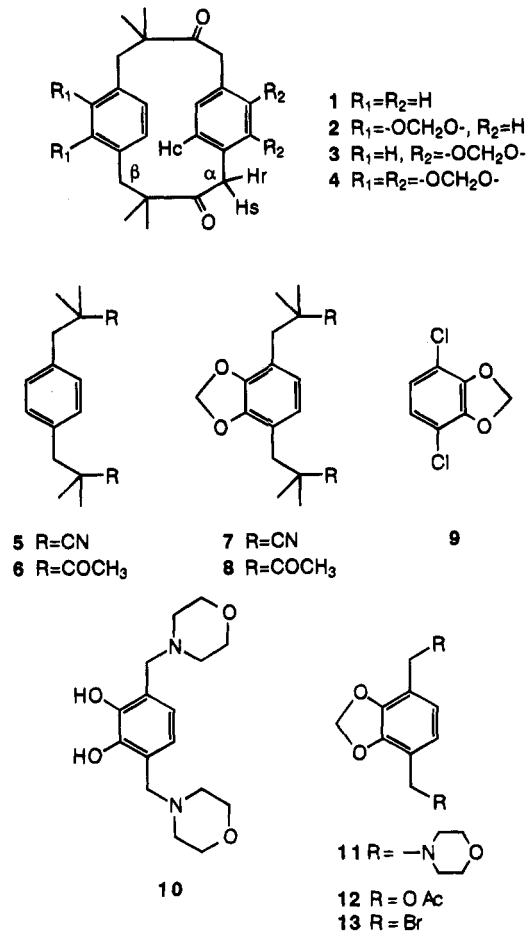
Figure 1. ORTEP drawing of **4**; (a) the top and (b) the side views.

chains.[9] The rate and activation parameters for such processes are known to be amenable to variable-temperature NMR study. A rather high activation energy (~33 kcal/mol) for the rotation of the benzene rings has been reported in [3.4]paracyclophane.[10] Significant reduction of the activation energy (~15 kcal/mol) has been found in [4.4]paracyclophane.[10c,11] In contrast, no extensive investigation has been reported for the analysis of the conformational dynamic process of the bridging chains. The main reason for this is the lack of a suitable derivative which has the proper substituents within its bridging chains to give a well separated NMR pattern. We introduced an α,α′-dimethyl carbonyl group within the bridging chain for that purpose.

Results and Discussion

Synthesis of [4.4]Paracyclophanes. As part of our synthetic approach in the use of radical cyclizations for macrocycles containing aromatic rings, we have utilized a photoinduced double $S_{RN}1$ reaction.[12] Photoirradiation of diketones **6** and **8**, which are derived from their respective precursors **5** and **7** with *p*-dihalobenzenes in the presence of excess *t*-BuOK in liquid ammonia, gave 3,3,12,12-tetramethyl[4.4]paracyclophane-2,13-diones (**1**–**4**) in 5–10% yield. The low yield of this reaction might reflect the steric congestion associated with [4.4]paracyclophanes.[13]

X-Ray Crystallography. The ORTEP drawing of **4** is shown in Figure 1. The structure found in the crystal is essentially C_s symmetric. The two benzene rings of **4** are planar but tilted from each other by an angle of 30°. The aromatic rings of [4.4]paracyclophanes carrying no substituent on their bridging chains are usually parallel to each other but twisted to some extent about an axis perpendicular and common to both rings.[14] The tilting of the aromatic rings should thus arise from the asymmetric substitution of the bridging chains of **4**. While the lower benzene ring has an almost perpendicular arrangement with respect to the orientation defined by the interconnective bridges, the upper benzene ring tilts 60° away from perpendicularity. The shortest transannular contact between the arene carbons of the two benzene rings is 3.3 Å, a value approximately equal to the normal π–π stacking distance. Severe steric repulsion between the two π-electron systems is likely to be absent. The two carbonyl groups are almost parallel to each other. The two dioxolene rings are bent toward each other to some extent.



Molecular Mechanics Calculations. In order to obtain information about the structure and conformational energies of the [4.4]paracyclophanediones in solution, molecular mechanics calculations were carried out. Such calculations represent a reliable and fast way to determine molecular geometries.[15] There are several force fields for which extensive applications have been

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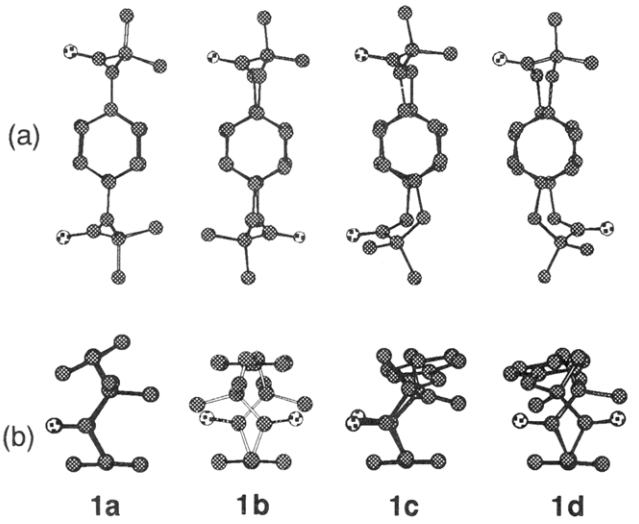


Figure 2. (a) Top and (b) side views of the calculated conformers for **1**.

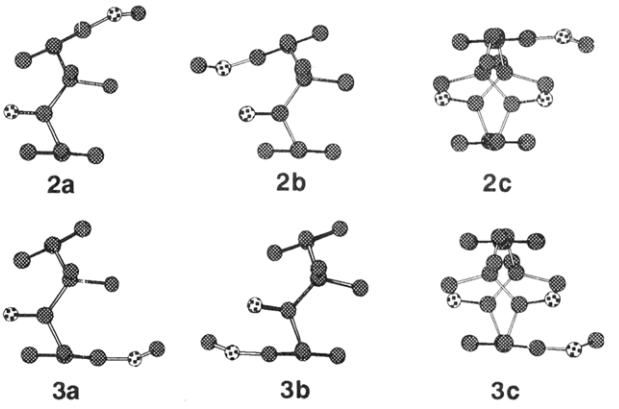
Table 1. Steric Energies[a] for Conformers of the [4.4]Paracyclophanes 1–4 from the MM3 Calculations

	conformers					
compd	a	b	c	d	e	f
1	29.56	31.49	33.11	33.43		
2	33.05	34.19	35.34			
3	32.68	34.15	35.21			
4	36.13	37.67	37.32	39.47	38.93	39.08

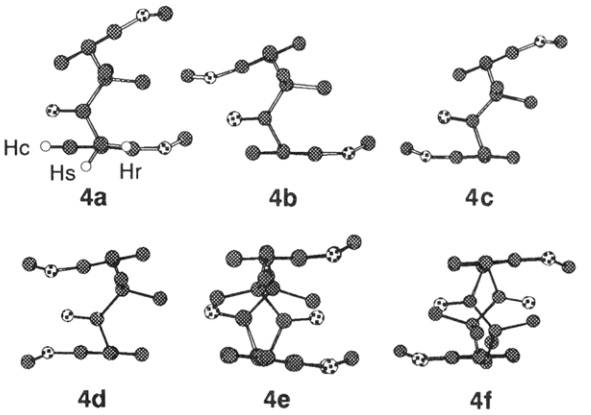
[a] In kcal/mol.

reported.[16] MM3 is one of the most reliable force fields currently in use worldwide.[17] Through use of the MM3 and our MMRS[18] programs, the latter of which generates all the plausible initial geometries[19] for a flexible cyclic molecule, four structures of **1** (Figure 2) were obtained within 4.0 kcal/mol of the steric energy from the most stable conformer (Table 1). The calculations also disclosed that the geometry of the most stable conformer (**1a**) is identical to the basic structure of **4** found in the crystal. The observed tilting angles of the two benzene rings of **4** are well reproduced. The second structure (**1b**) is C_2 symmetric and hence its two benzene rings are parallel to each other. Both the third (**1c**) and the fourth (**1d**) conformers have similar steric energies and a near eclipsing arrangement around the second and third carbon atoms for one of their bridging chains. As a result of this unfavorable arrangement, these two conformers have steric energies higher than **1a** by more than 3.5 kcal/mol, suggesting a negligible population of these structures at equilibrium.

Two symmetric structures for **1**, C_s and C_2, were thus suggested to be the most plausible conformers in solution. The introduction of a dioxolene ring onto one of the benzene rings gave three structures. Conformers **2a** and **2b** are derived from the C_s form and conformer **2c** from the C_2 structure. The MM3 steric energies of these three structures increase in the order of **2a**, **2b**, and **2c**. Compound **3** also has three low energy conformers (**3a**, **3b**, and **3c**). The structural and energetic features found in **2** were also noted in these three conformers.



On the other hand, six structures are possible when two dioxolene units are introduced into compound **1**. Four conformers (**4a**–**d**) are derivable from the C_s structure and two (**4e** and **4f**) from the C_2 symmetric one. The most stable structure (**4a**) is predicted to be identical to that observed in the crystal. Severe steric repulsion between the two facing 1,3-dioxolene units in **4d** is suggested by its high steric energy and the significant deviation of the tilting angle between the two benzene rings from the most stable one. Out-of-plane bending for the methylene carbons of the two 1,3-dioxolenes away from each other is additional evidence of the significant steric repulsion in this conformer. Both of the structures that come from the C_2 symmetric conformer have rather high steric energies.



Dynamic NMR Spectroscopy. In order to determine the conformational behavior of the [4.4]paracyclophanes in solution, the structures of the conformers and the interconversion pathway between them warrant consideration. Conformational dynamic processes in these molecules involve the rotation of aromatic rings with respect to each other and the flipping of bridging chains. ^{1}H NMR measurement of **3** over the temperature range of 180 to −90 °C was carried out in order to analyze the dynamics. The rotation of the two benzene rings was found to be very slow or frozen at room temperature because there are two sets of two singlets due to the methylene protons in the 1,3-dioxolene ring and to the upper benzene protons in the hexachlorobutadiene solution. Upon heating, the aromatic and aliphatic protons broaden and then coalesce to a broad singlet and eventually to a sharp singlet at higher temperature. The

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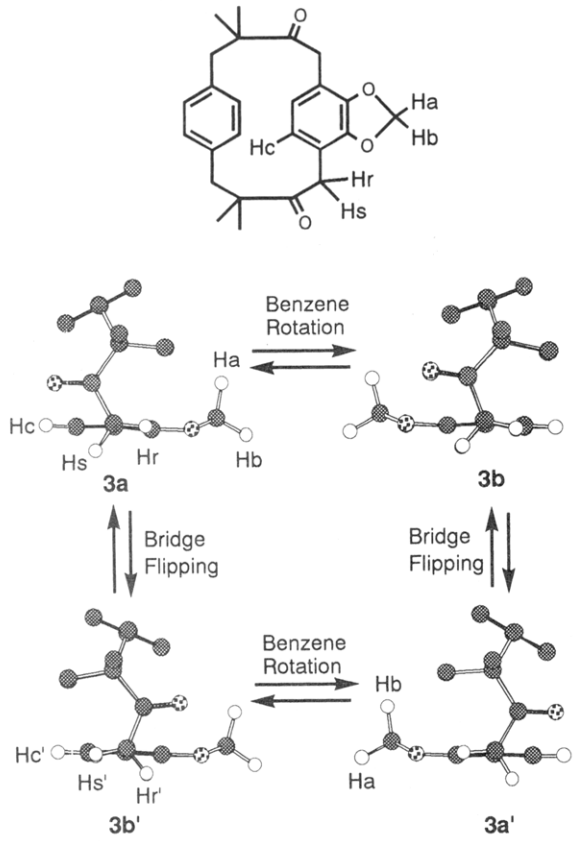

Figure 3. Conformational interconversion processes of **3**.

Table 2. Free Energies of Activation[a] with the Coalescence Temperatures (T_c)[b] to Rotation of the Benzene Rings in the [4.4]Paracyclophanes 2–4

compound	ring A[c] (T_c)	ring B[c] (T_c)
2	17.7 (353)	–
3	17.1 (353)	21.3 (413)
4	18.3 (353)	22.7 (433)

[a] In kcal/mol. [b] In K. [c] Rings A and B indicate the upper and the lower benzene rings of **2**–**4**, respectively.

activation energies to the rotation of the aromatic rings were thus estimated by the coalescence method.

The dioxolene methylene protons Ha and Hb cannot be equivalent on the basis of simple rotation of the lower benzene if the conformation of the bridging chains is fixed as shown in Figure 3. Flipping of the bridging chains changes **3b** into the mirror image of **3a**. Two successive motions, the rotation of the benzene and the flipping of the bridges, cause interconversion between **3a** and **3a′** and the magnetic environment of Ha and Hb are equivalent. Hence, the sharp singlets of the methylene protons suggested that the two dynamic processes, the rotation of the benzene ring and the flipping of the bridging chains, both occur rapidly at high temperature. For compound **3**, the activation energy barrier to the rotation of the benzene ring closer to the *gem*-dimethyl group is smaller than that of the other benzene ring. Table 2 summarizes the activation energy to rotation of the benzene rings in the [4.4]paracyclophanes. The general feature of the activation energy found in **3** is also observed in **4**.

The rate and activation parameters for the bridge flipping process is amenable to low temperature ^{1}H NMR study. The two sets of AB splitting patterns due to the α- and β-methylene protons of **2** became broad when the

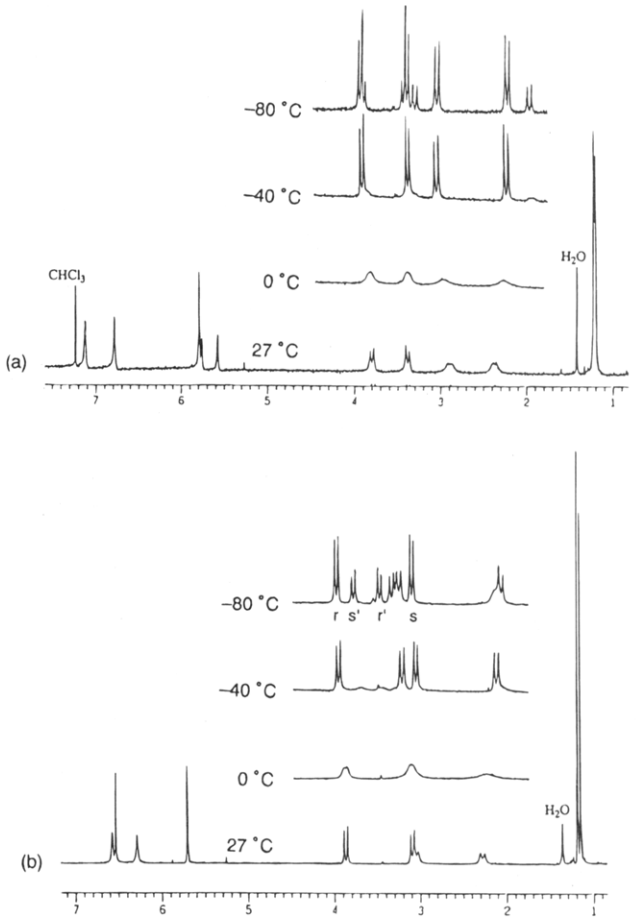

Figure 4. Variable temperature ^{1}H NMR spectra of (a) **2** and (b) **3** in $CDCl_3$–CS_2 (1:1).

temperature was lowered [Figure 4(a)]. They broadened further and each signal split into two sets of doublets of unequal intensity below −40 °C. The signals became somewhat sharp but the splitting pattern remain unchanged with further cooling. At −80 °C, the intensity ratio of the minor and major signals is 1 to 3. These two set of signals can be assigned to the two C_s symmetric structures, respectively, because the other possible structure, which derived from the C_2 symmetric form, should exhibit four sets of AB splitting patterns of equal intensities.

Similar signal behavior was also observed in **3** for both the α- and β-methylene protons [Figure 4(b)]. At −80 °C, two sets of signals due to the α-methylene protons were observed at δ 3.76 and 3.45 (each d), and δ 3.95 and 3.08 (each d), whose intensity ratio is 1:2. These two sets of signals were also assigned to the two C_s symmetric structures. In the minor conformer, NOE was observed between the aromatic proton of the dioxolene-carrying benzene ring (δ 6.38) and the lower field doublet of the AB pattern of the α-methylene signals (δ 3.76). In **3b′**, one of the lower methylene protons (Hs′) is in-plane of the dioxolene-carrying benzene ring, and is very close to the aromatic proton (Hc′) and suffers the deshielding effect of the benzene ring (Figure 3). Hence, the lower field doublet of the AB pattern of the minor conformer can be assigned to the Hs′ for **3b′**. A magnetization transfer experiment at this temperature disclosed that the Hs′ in the minor conformer (**3b′**) is directly correlated to the higher magnetic field doublet (δ 3.08) of the AB pattern of the α-methylene signals of the major conformer **3a**. This experiment disclosed that the main conformer

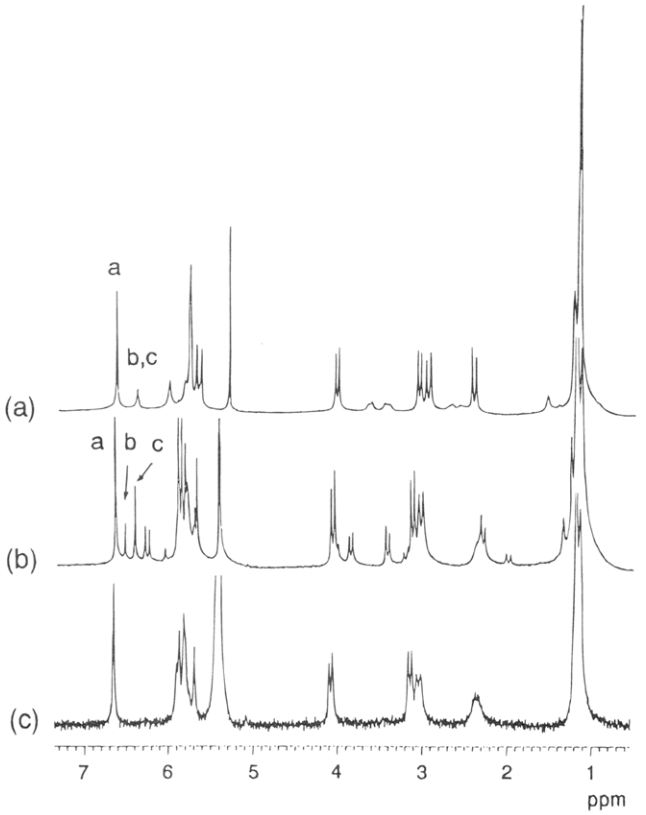

Figure 5. Temperature dependent ^1H NMR spectra of **4** in CD_2Cl_2; (a) 27 °C, (b) −80 °C, and (c) dissolution at −80 °C.

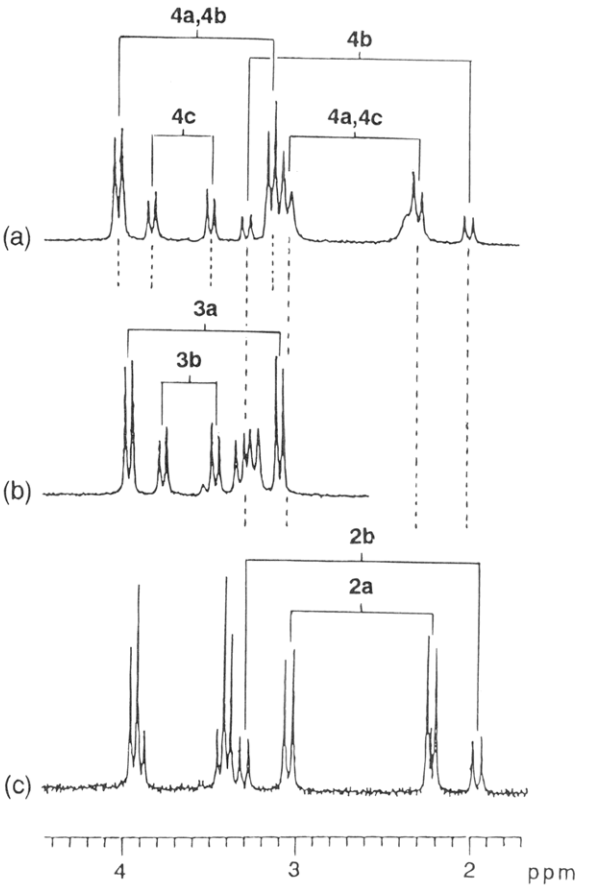

Figure 6. Comparison of the chemical shift of methylene signals of **2**−**4** in $CDCl_3$−CS_2 (1:1); (a) **4**, (b) **3** (signals above 3 ppm are omitted for clarity), and (c) **2**.

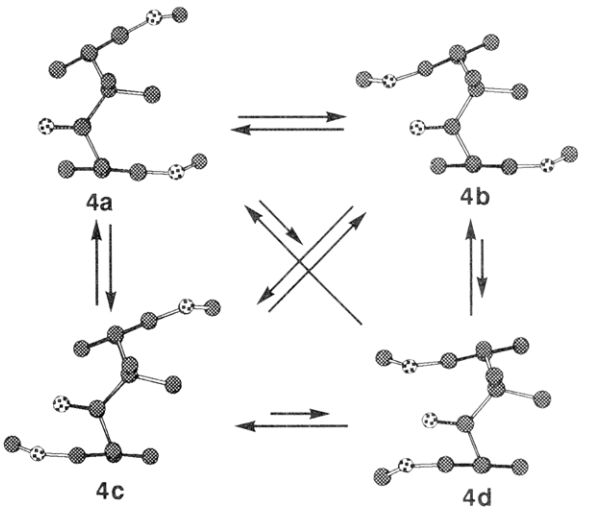

Figure 7. Conformational interconversion of **4**.

is identical to the most stable calculated structure **3a** and the minor one is identical to the second conformer, and that the conformational interconversion between the two occurs as a result of the bridge flippings even at the low temperature within the NMR time scale.

Noteworthy is reversal of the chemical shift value of the α-methylene signals between **3a** and **3b**. Due to the tilting of the bridge bonds, there are two different positions for the methylene protons with respect to the lower benzene ring. One is in and the other is out of the benzene plane. In the major conformer **3a**, the proton Hr syn to the dioxolene ring is in the plane, while the corresponding proton Hr′ of the minor conformer is out of the benzene plane. The in-plane proton should be deshielded by the magnetic anisotropy effect of the benzene ring[20] to a greater extent than the out-of-plane proton. The extra deshielding effect of the C−O bond[21] in the dioxolene shifted Hr further downfield. The larger chemical shift difference between the two α-methylene protons in the major conformer compared to that of the minor one is more supporting evidence for the assignment of the conformers.

Contrary to the signal behavior of these two compounds (**2** and **3**), there are already two sets of signals of the aromatic proton Hc at δ 6.64 and 6.37 in **4** at room temperature; one is sharp and intense and the other is broad and weak (Figure 5). Broad signals are indicative of some low energy conformational dynamic processes operating even at room temperature. The set of broad signals became broader when the temperature was lowered and eventually resolved into two sets of sharp signals of unequal intensities at −80 °C. In contrast the set of sharp and intense signals did not show any temperature dependence due to cooling. At −80 °C, three sets of signals of the aromatic proton Hc at δ 6.65, 6.55, and 6.43, with an intensity ratio of 4:1:2, were then observed. Judging from the molecular mechanics calculations, we thought these signals might be assigned to the three conformers of the low steric energies. The two sets of signals, which showed temperature dependence,

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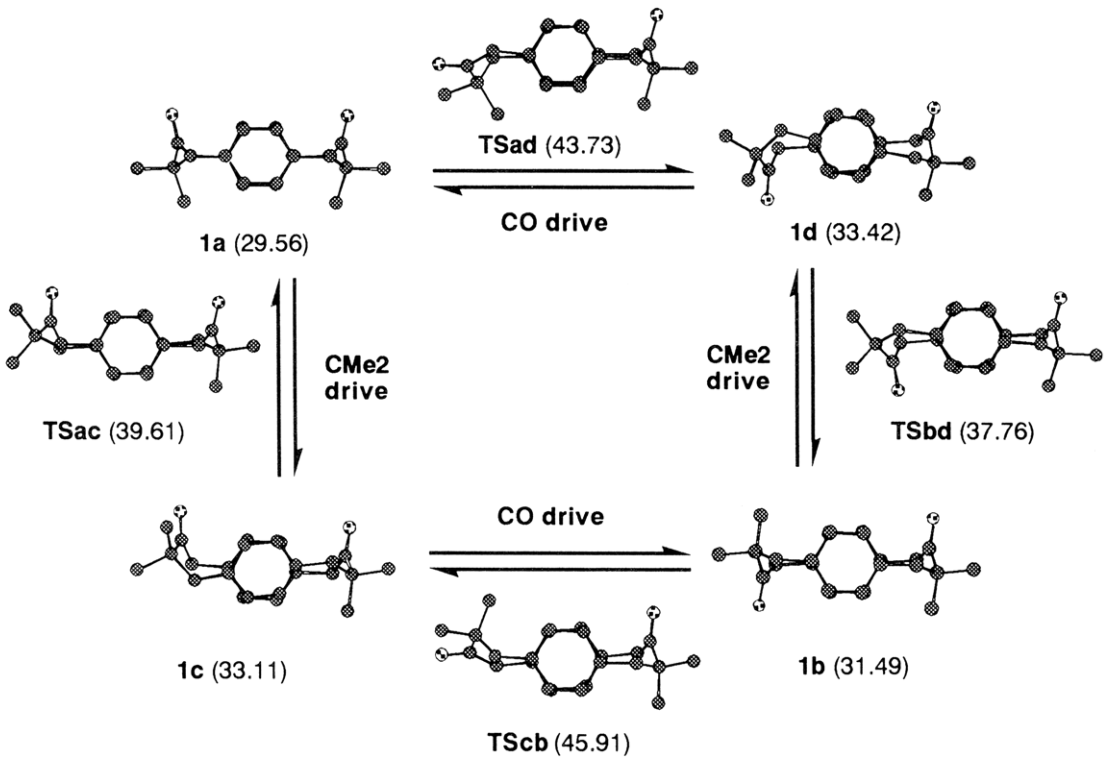

Figure 8. Conformational dynamic processes for **1** (steric energy/kcal mol^{-1} in parentheses).

should be attributable to **4b** and **4c** because they can be interconverted by flipping of the bridging chains. The activation energy for this interconversion can be estimated as ca. 12 kcal/mol from the coalescence temperature.

Of course, the interconversion between **4a** and **4d** is theoretically possible due to flipping; however, since the latter conformer is highly strained, it should have a negligible population. Hence, the temperature independence of the signals can be explained by the single conformer for the most stable one without any detectable contribution of **4d**.

Conclusive evidence for the assignment of the sharp and intense signals can be obtained by simple dissolution of the crystals of **4** into precooled solvent to −80 °C (Figure 5). The NMR spectrum obtained by this method is identical to that of the major and temperature-independent signals at the same temperature. Since the conformer found in the crystalline state is identical to the lowest steric energy structure **4a**, the signal obtained by this method can be clearly assigned to the conformer of the crystalline state. The assignment of the high field signal due to one of the α-methylene protons Hs (δ 3.14) of **4a** was confirmed by NOE signal enhancement between the aromatic proton Hc (δ 6.66). The other proton Hr (δ 4.08), which is syn and in-plane with the dioxolene ring, resonates downfield. The chemical shift criterion of the methylene proton shown in **3** is valid in this case. Since the local environment of the bottom part of **4a** is identical to that of **3a**, the chemical shift of these α-methylene protons are very close to each other. The local environment of the upper part of **4a** is again identical to that of **2a**. Comparison of the two chemical shifts of the β-methylene protons of **4a** with those of the frozen signal sets of **2** disclosed that the major conformer of **2** is identical to the predicted most stable conformer (**2a**) (Figure 6).

The two other sets of the α- and β-methylene signals (**4b** and **4c**) at the low temperature can be assigned by comparison of the signals of frozen conformers of the compounds **2** and **3**. Since the combination of the local environment of the bottom part of **3b** and the upper part of **2a** makes **4c**, the chemical shift of these α- and β-methylene protons disclosed that the second populating conformer should be **4c**. Similar treatment confirmed that the third conformer is **4b**. There is no signal assignable to the **4d** suggesting the validity of the MM3 results.

Dynamic Conformational Process of 4. The conformational dynamic processes for **4** are summarized in Figure 7. These four conformers are interconvertible with one another by rotating the two benzene rings. The barriers to this ring rotation are both higher than the reference compound having no substituent on the bridging chain. The rotational energy barrier of the benzene ring closer to the carbonyl groups is higher than that of the other.

Interconversion between conformers **4a** and **4d** and between **4b** and **4c** are also attained by flipping of the bridging chains. These processes require less energy than the benzene ring rotation. MM3 calculation was carried out for **1** to locate the transition states of the bridge flipping process (Figure 8). Starting from **1a**, the flipping of the quaternary carbon bearing *gem*-dimethyl group in one of the bridges leads to the near eclipsing conformation (**1c**) via a transition state (**TSac**). Subsequent flipping of the carbonyl group from the eclipsing conformer leads to the C_2 symmetric structure **1b**. The transition state (**TScb**) of the latter process has higher steric energy than the former. Another possible pathway for the same interconversion is first flipping of the carbonyl via a transition state (**TSad**) to **1d** and subsequent flipping to **1b** through **TSbd**. In the second pathway, the first step requires higher energy than the

second. The steric energy of the **TSad** is smaller than **TScd** by 2.2 kcal/mol, suggesting the second pathway through **1d** is more probable than the first one. Flipping of the other bridge of **1b** completed the conversion of **1a** to its mirror image. The calculated activation parameters for the interconversion process at 298 K are obtained ($\Delta H^{\ddagger} = 13.84$ kcal/mol, $\Delta S^{\ddagger} = -2.28$ cal/mol deg, and $\Delta G^{\ddagger} = 14.52$ kcal/mol).

Conclusions

The conformational dynamic processes for [4.4]paracyclophanes were analyzed by molecular mechanics calculations and X-ray crystallographic and dynamic NMR studies. We presented here an interesting example in which simple dissolution of a crystalline compound in precooled solvent can give an NMR signal due to the single conformer found in its crystalline state. In contrast, cooling the solution prepared at room temperature gave complicated signals due to the multiconformers of the compound. We conclude the method we employed can be useful for the analysis of a multiple conformational problem.

Experimental Section

Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. Ether and THF were distilled under nitrogen from sodium–benzophenone. All anhydrous reactions were performed under a dry nitrogen atmosphere.

^{1}H and ^{13}C NMR spectra were recorded at 270 and 68 MHz in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in δ (ppm downfield from Me_4Si). All melting points are uncorrected. Column chromatography was performed using Merck silica gel (70–230 mesh). The organic extracts were dried over anhydrous Na_2SO_4.

1,4-Bis(2-cyano-2-methylpropyl)benzene (5). To a solution of LDA, prepared from diisopropylamine (6.0 mL, 43 mmol) and *n*-butyllithium (1.5 N, 32 mL, 48 mmol) in dry THF (500 mL), was added isobutyronitrile (4.0 mL, 40 mmol) at 0–5 °C. After 30 min of stirring, a solution of 1,4-bis(bromomethyl)benzene (3.87 g, 14.1 mmol) in THF (80 mL) was added at the same temperature. The mixture was stirred for 2 h, treated with dilute HCl, and concentrated. The residue was extracted with ethyl acetate, and the organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (elution with CH_2Cl_2) to give 3.21 g (94%) of **5** as colorless prisms: mp 154–156 °C (from hexane); ^{1}H NMR 1.35 (s, 12 H), 2.81 (s, 4 H), 7.25 (s, 4 H); ^{13}C NMR 26.5, 33.5, 46.3, 124.7, 130.2, 134.8; IR (KBr) 2230 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.69; H, 8.45; N, 11.66.

1,4-Bis(2-cyano-2-methylpropyl)-2,3-(methylenedioxy)benzene (7). A solution of 3,6-bis(morphorinomethyl)catechol (**10**)[22] (11.51 g, 37.3 mmol) and NaOH (9.83 g, 0.24 mol) in DMSO (450 mL) and CH_2Cl_2 (200 mL) was heated at 110–115 °C (bath temperature) for 4 h under nitrogen. After the solution was cooled, **10** (10.83 g, 33.6 mmol) and NaOH (5.2 g, 0.13 mol) were added. The mixture was refluxed further for 10 h, diluted with 700 mL of water, and extracted with ethyl acetate. The organic layers was washed with water, dried, and evaporated *in vacuo*. Chromatography on alumina (Merck Act. II, elution with hexane and then $CHCl_3$) afforded 21.25 g (90%) of 2,3-(methylenedioxy)-1,4-bis(morphorinomethyl)benzene (**11**) as pale yellow prisms: mp 76–77 °C; ^{1}H NMR (60 MHz) 2.34–2.67 (m, 8 H), 3.53 (s, 4 H), 3.62–3.93 (m, 8 H), 5.99 (s, 2 H), 6.83 (s, 2 H).

A solution of **11** (6.10 g, 19.0 mmol) in Ac_2O (40 mL) was refluxed for 72 h. Concentration and chromatography on silica gel (elution with hexane–benzene) afforded 3.56 g (70%) of 1,4-bis(acetoxymethyl)-2,3-(methylenedioxy)benzene (**12**) as pale yellow powder: mp 68.5–71 °C; ^{1}H NMR (60 MHz) 2.14 (s, 6 H), 6.06 (s, 2 H), 6.88 (s, 2 H).

To a solution of **12** (4.06 g, 13.8 mmol) in CH_2Cl_2 (40 mL) was added a solution of 30% HBr in AcOH (20 mL). The solution was stirred overnight at ambient temperature, diluted with water (50 mL), and extracted with $CHCl_3$. The organic layers were washed successively with aqueous $NaHCO_3$ and brine, dried, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (elution with hexane and then with $CHCl_3$) to give 4.52 g (85%) of 1,4-bis(bromomethyl)-2,3-(methylenedioxy)benzene (**13**) as colorless needles: mp 161–162 °C; ^{1}H NMR (60 MHz) 4.43 (s, 4 H), 6.07 (s, 2 H), 6.80 (s, 2 H).

The compound **7** was prepared from **13** (3.00 g, 9.75 mmol) according to the procedure described for **5**. Chromatography on silica gel (50 g, elution with CH_2Cl_2) gave 2.71 g (97%) of **7** as colorless prisms: mp 93–95 °C (hexane); ^{1}H NMR 1.39 (s, 12 H), 2.82 (s, 4 H), 5.92 (s, 2 H), 6.79 (s, 2 H); ^{13}C NMR 26.4, 33.6, 39.7, 100.5, 116.5, 124.0, 124.7, 146.2; IR (KBr) 2230 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_2N_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.08; H, 7.30; N, 9.63.

1,4-Bis(2,2-dimethyl-3-oxobutyl)benzene (6). To a solution of **5** (990 mg, 4.12 mmol) in THF (250 mL) was added a solution of methyllithium in ether (1.0 M, 25 mL, 25 mmol) at −30 °C. After 100 min of stirring at 0–5 °C, 10% hydrochloric acid was added. The mixture was stirred overnight at ambient temperature and extracted with ethyl acetate. The organic extract was washed successively with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, dried, and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel (elution with hexane and then with $CHCl_3$) to give 554 mg (97%) of **6** as colorless needles: mp 86.5–87 °C (from hexane); ^{1}H NMR 1.11 (s, 12 H), 2.10 (s, 6 H), 2.77 (s, 4 H), 6.98 (s, 4 H); ^{13}C NMR 24.3, 26.0, 44.9, 48.6, 129.8, 135.8, 213.8; IR (KBr) 1700 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.72; H, 9.82.

1,4-Bis(2,2-dimethyl-3-oxobutyl)-2,3-(methylenedioxy)benzene (8) was prepared from **7** (1.78 g, 6.25 mmol) according to the procedure described for **6**. Chromatography on silica gel (elution with hexane and then $CHCl_3$) gave 1.83 g (91%) of **8** as colorless needles: mp 76–77 °C (from hexane); ^{1}H NMR 1.13 (s, 12 H), 2.16 (s, 6 H), 2.76 (s, 4 H), 5.83 (s, 2 H), 6.48 (s, 2 H); ^{13}C NMR 24.5, 26.1, 38.7, 49.2, 100.3, 118.2, 124.3, 146.1, 213.9; IR (KBr) 1690 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.96; H, 8.51. Found: C, 71.67; H, 8.23.

1,4-Dichloro-2,3-(methylenedioxy)benzene (9). To a solution of 3,6-dichlorocatechol[23] (1.88 g, 10.5 mmol) in DMSO (140 mL) and CH_2Cl_2 (50 mL) was added NaOH (2.62 g, 65.5 mmol), and the mixture was stirred at 110–120 °C (bath tempereture) for 6.5 h. After the mixture was cooled, water (200 mL) was added and the mixture was extracted with ethyl acetate. The organic extract was washed with water and with brine, dried, and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel (elution with hexane and then with benzene) to give 1.78 g (89%) of **9** as a colorless powder: mp 108–109 °C (from hexane–CH_2Cl_2); ^{1}H NMR (60 MHz) 6.06 (s, 2 H), 6.74 (s, 2 H). Anal. Calcd for $C_7H_4Cl_2O_2$: C, 44.01; H, 2.09. Found: C, 44.07; H, 2.00.

General Procedure for the Synthesis of [4.4]Paracyclophanediones. The reaction was carried out in a Pyrex dewar flask equipped with a dry ice condenser. To a solution of 0.5 mmol of bismethyl ketone (e.g., **6** or **8**) and 0.4 mmol of *p*-dihalobenzene (e.g., **9**) in a mixture of *t*-BuNH$_2$ (10 mL) and liquid NH_3 (100 mL) was added 2 mmol of *t*-BuOK. The mixture was irradiated with a mercury lamp for 15 min at −33 °C. To this mixture was added 10 g of NH_4Cl, followed by allowing ammonia to evaporate. The residue was treated with 10% HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated *in vacuo*.

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The crude product was chromatographed (SiO_2, 5% EtOAc–hexane) to give [4.4]paracyclophane (**1–4**).

3,3,12,12-Tetramethyl[4.4]paracyclophane-2,13-dione (1) was prepared according to general procedure from **6** (118 mg, 0.43 mmol), *p*-dibromobenzene (79 mg, 0.34 mmol), *t*-BuOK (197 mg, 1.75 mmol), *t*-$BuNH_2$ (10 mL), and liquid NH_3 (90 mL). Workup and chromatography on silica gel (elution with 5% EtOAc–hexane) gave 12 mg (10%) of **1** as colorless powder: mp 175–177 °C (from EtOH); ^1H NMR (90 MHz) 1.14 (s, 12 H), 2.52 (bs, 4 H), 3.41 (bs, 4 H), 6.24 (s, 4 H), 6.73 (bs, 4 H); ^{13}C NMR 24.4, 29.7, 45.77, 45.85, 50.3, 129.6, 129.7 129.9, 130.1, 135.5, 211.8; IR (KBr) 1690 cm^{-1}. HRMS *m/z* 348.2100 (M^+), calcd for $C_{24}H_{28}O_2$ 348.2089.

6,7-(Methylenedioxy)-3,3,12,12-tetramethyl[4.4]paracyclophane-2,13-dione (2) was prepared according to general procedure from **8** (508 mg, 1.60 mmol), *p*-dibromobenzene (359 mg, 1.52 mmol), *t*-BuOK (962 mg, 8.57 mmol), *t*-$BuNH_2$ (50 mL), and liquid NH_3 (450 mL). Workup and chromatography on silica gel (elution with 10% EtOAc–hexane) gave 42 mg (7%) of **2** as colorless needles: mp 192–194 °C; ^1H NMR 1.25 (s, 6 H), 1.26 (s, 6 H), 2.45 (bs, 2 H), 2.89 (bs, 2 H), 3.44 (bd, J = 10 Hz, 2 H), 3.84 (bd, J = 10 Hz, 2 H), 5.62 (s, 1 H), 5.81 (s, 1 H), 5.86 (s, 2 H), 6.85 (s, 2 H), 7.17 (s, 2 H); ^{13}C NMR 24.2, 28.6, 39.0, 45.8, 50.8, 99.5, 118.0, 124.3, 129.7, 130.0, 130.2, 212.0; IR (KBr) 1685 cm^{-1}. Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.20. Found: C, 76.26; H, 7.38.

16,17-Methylenedioxy-3,3,12,12-tetramethyl[4.4]paracyclophane-2,13-dione (3) was prepared according to general procedure from **6** (502 mg, 1.82 mmol), **9** (301 mg, 1.56 mmol), *t*-BuOK (982 mg, 8.75 mmol), *t*-$BuNH_2$ (50 mL), and liquid NH_3 (450 mL). Chromatography on silica gel (elution with 10% EtOAc–hexane) gave 19 mg (3%) of **3** as colorless needles: mp 218–220 °C; ^1H NMR 1.20 (s, 6 H), 1.23 (s, 6 H), 2.41 (bd, J = 11 Hz, 2 H), 3.04 (bd, J = 11 Hz, 2 H), 3.20 (d, J = 11 Hz, 2 H), 3.91 (d, J = 11 Hz, 2 H), 5.76 (s, 1 H), 5.78 (s, 1 H), 6.40 (s, 2 H), 6.59 (s, 2 H), 6.66 (s, 2 H); ^{13}C NMR 24.8, 28.1, 38.8, 45.7, 49.5, 100.1, 111.2, 123.6, 128.6, 129.9, 135.6, 211.4; IR (KBr) 1690 cm^{-1}. Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.20. Found: C, 76.80; H, 7.17.

6,7:16,17-Bis(methylenedioxy)-3,3,12,12-tetramethyl[4.4]paracyclophane-2,13-dione (4) was prepared according to general procedure from **8** (501 mg, 1.60 mmol), **9** (264 mg, 1.38 mmol), *t*-BuOK (960 mg, 8.56 mmol), *t*-$BuNH_2$ (50 mL), and liquid NH_3 (450 mL). Chromatography on silica gel (elution with 10% EtOAc–hexane) gave 34 mg (5%) of **4** as colorless prisms: mp 223.5–225 °C; ^1H NMR (major conformer) 1.21 (bs, 12 H), 2.46 (d, J = 14 Hz, 2 H), 3.01 (d, J = 14 Hz, 2 H), 3.12 (d, J = 11 Hz, 2 H), 4.05 (d, J = 11 Hz, 2 H), 5.64 (s 1 H), 5.74 or 5.77 (s, 1 H), 5.83 (s, 2 H), 6.08 (bs, 1 H), 6.44 (bs, 1 H), 6.70 (s, 2 H); ^{13}C NMR 23.2, 28.3, 38.1, 38.7, 50.0, 99.4, 99.9, 111.6, 118.2, 123.7, 123.9, 212.0; IR (KBr) 1690 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.61; H, 6.38.

Single-Crystal X-ray Diffraction Analysis of 4. The crystal data for **4** are as follows: Triclinic; space group $P\bar{1}$ with a = 9.939 (5), b = 15.118 (7), c = 7.902 (3) Å, α = 95.95 (3)°, β = 94.31 (3)°, γ = 71.24 (4)°, V = 1117.1 (9) Å^3, and Z = 2. The empirical formula is $C_{26}H_{28}O_6$, molecular weight is 436.50, and calculated density is 1.296 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 Syntex R3 automatic four-circle diffractometer up to a maximum 2θ of 55.0°. Of 5116 total unique reflections, 3302 were considered observed at the level of $|F_o| > 3.0\sigma|F_o|$. Data were corrected for Lorentz and polarization effect by the usual way but not for absorption, as linear absorption coefficient is small enough [λ(Mo Kα) = 2.3 cm^{-1}]. The structure was solved by the direct method (Monte Carlo-Multan).[24] 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 32 non-hydrogen atoms and 28 isotropic hydrogens have converged to a conventional R factor of 0.072. All the calculations were carried out on a Titan-750 computer using the program system Crystan-G.[25] Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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