Conformational Analysis by the Ring Current Method. The Structure of 2,2,13,13-Tetramethyl[4.4]metacyclophane

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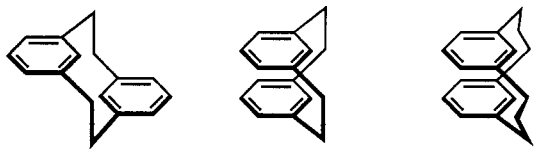
Abstract: The conformational analysis of 2,2,13,13-tetramethyl[4.4]metacyclophane (**4**) using X-ray crystallographic analysis, molecular mechanics calculations, and the ring current method is presented. Compound **4** shows a characteristic temperature-dependent chemical shift behavior in its ^{1}H-NMR spectrum. Three conformers are found to play an important role in the conformational dynamic process. The method for analysis employed consists of three stages, generation of plausible structures by two programs (MMRS and MM3), estimation of the chemical shift of aromatic protons in these structures by the ring current effect, and selection of the most plausible structures by comparison of the observed and calculated chemical shifts. The C_s symmetric structure found in the crystal is the main contributor in solution below −80 °C. Above this temperature another structure is found to be predominant, in which the conformation of one of the bridging chains is different from that in the C_s symmetric structure.

The conformational analysis of medium and large ring compounds is not straightforward because these compounds are flexible with many conformational possibilities. However, the conformation of macrocycles is known to play a decisive role for the successful prediction of the stereochemical outcome of some reactions of these compounds.[1] Hence, it is desirable to develop an efficient method for the conformational analysis of macrocyclic compounds. Conformations of macrocycles have been analyzed mainly by NMR spectroscopy by taking advantage of the torsional dependent ^3J coupling constant[2] and distance-dependent NOE.[3] Freezing a conformational equilibrium has been employed extensively; however, there are still experimental difficulties to freeze all the equilibria in some highly flexible molecules. Moreover, difficulty still remains in cases which do not show well-separated signal patterns or have a small number of hydrogens with a great many allowed conformers. The conformational behavior of highly flexible [*m.m*]cyclophanes is such a case. Analysis of the conformational behavior of such compounds is still a challenging problem.

The stereochemical aspects of mobile [*m.m*]metacyclophanes have been of synthetic and theoretical interest for over two decades.[4] Mainly two conformational versions, syn and anti, are known for the compounds having short bridging chains (m = 2,[5] **1** and **2**; m = 3,[6] **3**). The conformational equilibrium between



1 **2** **3**

syn and anti is completely shifted in favor of the anti form in [2.2]metacyclophanes. Unfavorable torsional strain (Pitzer strain) in the bridging chains has been suggested to be the principal cause of the enthalpy difference between the two.[7] The conformational equilibrium is completely shifted to the opposite side in [3.3]metacyclophanes.[8] When the bridges consist of four atoms, a planar conformer has been suggested.[9] As a result of the higher flexibility of the bridging chain than that of the smaller congeners,

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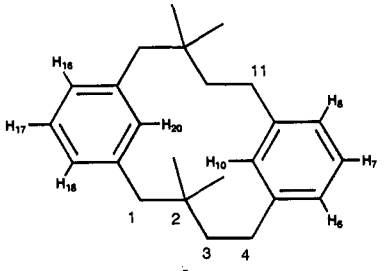
conformational studies of [4.4]metacyclophanes are rather limited.[10]

Here we present a useful and highly reliable method for the conformational analysis of flexible molecules by the combination of molecular mechanics calculations and chemical shift simulations of some hydrogens. Simulation of the chemical shift can be achieved by use of the calculation of secondary induced magnetic fields due to the aromatic ring current. We now apply the method to the conformational study of 2,2,13,13-tetramethyl-[4.4]metacyclophane (**4**), in which at least three conformers play important roles, and succeed in predicting the structures of the main contributors in the conformational dynamic equilibrium.



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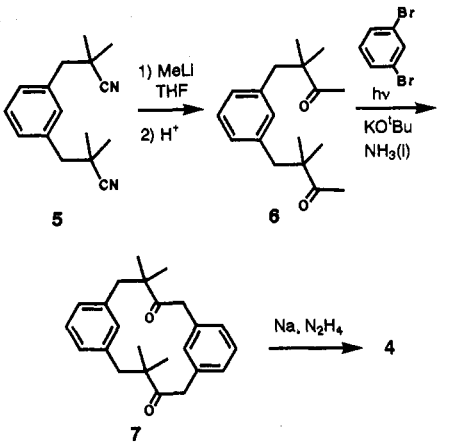
Results and Discussion

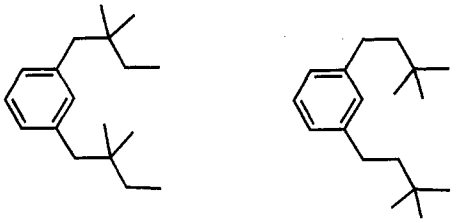
Synthesis of 4. We have selected the photoinduced $S_{RN}1$ reaction[11] as the key step for the synthesis of the title compound, since the overall yields in the wide variety of synthetic methods so far developed for large-membered [*m.m*]cyclophanes are generally not satisfactory because they involved multistep reaction sequences.[12] We have reported previously a facile one-step preparation of C_2 symmetric [*m.m*]metacyclophanes utilizing the $S_{RN}1$ reaction of ω-(*m*-bromophenyl)-3,3-dimethylalkane-2-one.[13]

In the synthesis of the C_s symmetric cyclophane **4**, the precursor is diketone **6**, which is easily prepared by conventional methods. By starting from 1,3-bis(bromomethyl)benzene, the precursor for the cyclization was prepared as shown in Scheme 1. This was then subjected to the photoinduced $S_{RN}1$ reaction with 1,3-dibromobenzene in the presence of KO^{t}Bu in liquid ammonia. The crude products were purified by silica gel column chromatography to give [4.4]metacyclophanedione (**7**) in 18% yield. Treatment of the dione with anhydrous hydrazine in diethylene glycol gave the desired hydrocarbon in 32% yield.

Scheme 1



Dynamic NMR Spectroscopy. In the case of short-bridged [*m.m*]metacyclophanes, the ^{1}H-NMR chemical shift of the internal aryl hydrogens can be a useful probe for assignment of structure. The magnetic anisotropy due to the facing benzene ring causes the internal aryl hydrogen to exhibit a large upfield shift when the two aromatic rings are situated anti. This same hydrogen stays in the usual aromatic chemical shift region if the two aromatic rings are arranged in a syn fashion.[14] This rather simple criterion of the structure could not be applied to **4** because the two internal aryl hydrogens, H_{10} and H_{20}, show completely opposite shift directions when they are compared with the corresponding hydrogens of the reference compounds, 1,3-bis-(2,2-dimethylbutyl)benzene (**8**) and 1,3-bis(3,3-dimethylbutyl)-benzene (**9**), respectively. While H_{10} remains in the usual



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aromatic chemical shift region, H_{20} shows an extensive upfield shift at room temperature. In order to understand the conflicting shift behavior of the two hydrogens, variable-temperature ^{1}H-NMR spectra were examined over the temperature range 30 to −110 °C. On lowering the temperature, changes occur in the aromatic proton region. The behavior of one of the inner aryl hydrogens (H_{20}) is especially characteristic. The signal shifts to higher magnetic field with concomitant gradual broadening when the temperature is lowered. It almost disappears at around −60 °C. Below this temperature, it appears as a broad signal at higher magnetic field. It sharpens again with further temperature decrease. The chemical shift moves almost linearly to higher magnetic field, and at −110 °C, the chemical shift difference is 2.62 ppm from that of the reference compound. This characteristic temperature-dependent signal behavior cannot be explained by either a dynamic process of a single conformer to its mirror image or a temperature-dependent change of the probabilities of the equilibrating two conformers. Hence, more than three mutually interconverting structures are necessary.

The other aromatic hydrogens do not show a well-separated signal pattern even at room temperature. Broadening of these signals at low temperature prevented unequivocal assignment of the individual hydrogens. In order to assign the chemical shifts

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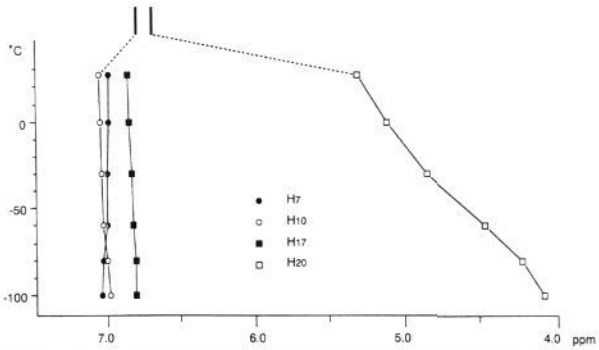

Figure 1. Temperature-dependent chemical shift of the aromatic hydrogens of **4** in CS_2. Thick vertical bars represent the chemical shifts of the inner aryl hydrogens of reference compounds **8** and **9**.

of the aromatic protons at any temperature, the 6,8,16,18-tetradeuterio derivative was prepared. This simplified the signal splitting pattern. The other internal aryl hydrogen (H_{10}) shows a downfield shift from that of the reference compound. The chemical shifts of the other two hydrogens can be assigned at all temperatures. Figure 1 shows a schematic presentation of the temperature-dependent chemical shifts of the four aromatic hydrogens.[15]

The analysis of the conformational behavior of the molecule requires determination of the preferred structures and energetics of the dynamic equilibrium between them. The method for the analysis which we employed consists of three stages: generation of plausible structures by molecular mechanics calculations, estimation of the chemical shift of aromatic protons in these structures by the ring current effect, and selection of the most plausible conformations by comparison of the observed and calculated chemical shifts. The effect of the secondary induced magnetic field due to a benzenoid aromatic ring can be used to estimate the chemical shift. We have recently shown that the effect of the induced magnetic field on the aromatic protons can be used to predict the correct chemical shifts and it can be used to estimate the relative arrangement of two benzene rings in a [4.4]metacyclophane.[16]

Molecular Mechanics Calculation. Molecular mechanics calculations for **4** were performed to obtain the structures of the most probable conformers. By use of our MMRS[17] and the MM3[18] programs, the former of which generates all the plausible initial structures,[19] a large number of conformers were obtained. The most probable conformers were selected on the basis of their steric energies.

(15) The characteristic temperature-dependent signal behavior is also seen in various solvents. The upfield shift values of the H_{20} from that of the reference compound **8** at −80 °C are as follows: 2.40 ppm (in CS_2), 2.24 ppm (in CD_3OD), 2.09 ppm (in CD_3COCD_3). Further results of the induced shifts at various temperatures are available and are described in the supplementary material.

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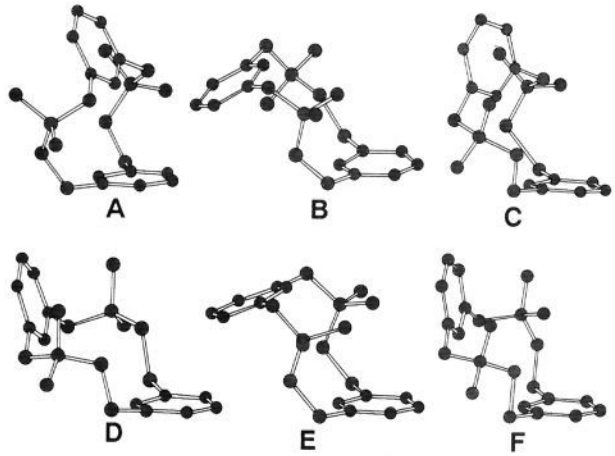

Figure 2. *Structures of the calculated conformers of* ***4****.*

Table 1. Calculated Thermodynamic Parameters of the Six Calculated Conformers of **4**

conformer	steric energy[a]	enthalpy[a]	entropy[b]	free energy[a]
A	31.38	353.198	154.585	307.107
B	32.04	353.480	155.386	307.150
C	32.72	354.067	156.965	307.266
D	32.99	354.073	156.513	307.408
E	33.19	354.745	152.895	309.158
F	33.36	354.793	155.425	308.452

[a] These values are in kcal mol^{-1} (at 298 K). [b] These values are in cal mol^{-1} K^{-1}.

Table 2. Structural Characteristics of the Six Calculated Conformers of **4**

conformer	inclination angle (deg)	transverse displacement[a] (Å)	longitudinal displacement[a] (Å)
A	121	1.53	4.46
B	−158	4.95	3.27
C	98	2.40	4.62
D	109	4.86	3.33
E	−157	4.49	3.24
F	103	3.98	4.03

[a] The values are the displacement of the center of the upper benzene ring with respect to that of the lower benzene ring.

There are six conformers within 2.7 kcal of the steric energy for the most stable conformers (Figure 2). They are characterized by the arrangement of two benzene rings, which is defined by the inclination angle and the transverse and longitudinal disposition of the upper benzene ring with respect to the lower. In Tables 1 and 2, the calculated thermodynamic parameters and structural characteristics of these conformers are listed. There are four anticlinal (A, C, D, and F) and two antiperiplanar conformers (B and E).[20] Three conformers (A, D, and E) have actual C_s symmetry. Both conformers A and C have rather small transverse movements of the upper ring and close to a perpendicular arrangement of the two aromatic rings. Hence, the inner aryl hydrogens of the upper ring (H_{20}) of both conformers should have upfield shift values due to the secondary induced magnetic field effect of the lower benzene ring. In structure A, H_{20} projects into the π cloud of the facing aromatic ring and it should show a significant upfield shift.

Calculation of the Ring Current Induced Shift. *The induced* shift values for the aromatic hydrogens in these conformers were estimated. Several ring current models have been used to estimate the local anisotropic contribution to chemical shift for a hydrogen at any point, whether in or out of the aromatic ring. McGlinchey et al. have claimed that the incremental shifts for hydrogens in

(20) The lowest steric energy conformer having a synclinal structure has a higher energy than conformer A by 6.3 kcal.

Table 3. Calculated Induced Shifts[a] (ppm) of the Four Aromatic Hydrogens of the Six Calculated Conformers of 4

conformer	H_7	H_{10}	H_{17}	H_{20}
A	0.163	-0.234	-0.149	-3.716
B	-0.045	-0.984	0.074	-0.274
C	0.033	0.341	-0.118	-0.975
D	-0.056	0.261	-0.021	0.440
E	-0.057	-1.152	0.076	-0.429
F	-0.060	0.438	-0.084	0.278

[a] A minus sign denotes an upfield shift.

the bridging chain of [n]paracyclophanes follow the Waugh–Fessenden[21] and Johnson–Bovey[22] classified ring current model but that the loop separation originally invoked was unnecessary.[23] Hence, we calculated the ring current effect using the line current approximation.[24] In Table 3 are listed the induced shift values for the four aromatic hydrogens caused by the diamagnetic ring current due to the opposite benzene ring in the molecule. H_{20} of conformer A shows an extremely large upfield shift (3.72 ppm). Conformers A, C, F, and D have anticlinal arrangements of the two benzene rings. The transverse displacements of H_{20} from the facing benzene rings increase and the induced shift values decrease in this order. Though the conformers B and E have antiperiplanar arrangement of the two aromatic rings, the inner aryl hydrogen does not show a significant upfield shift since the transverse separation of the two benzenes is rather large.

Probability of the Conformers. Since the conformational dynamic processes in this molecule are rapid, the observed chemical shifts should be the weighted average of the several conformers within the equilibrium. We have compared the observed and calculated induced shift values for the four aromatic hydrogens by changing the probability of each candidate. The probability of the six conformers, the calculated induced shift of the four hydrogens, and the agreement factor (R) are summarized in Table 4. The observed induced shifts are shown for comparison.

The R factor at 27 °C is very small, indicating a good agreement of the observed and calculated induced shifts. As the temperature is lowered, the R factor increases gradually. At -100 °C, it is 8.9% but agreement of the observed and calculated values is still acceptable. The conformers A and C play an important role in the conformational equilibrium. Although at higher temperatures the latter conformer is predominant, the situation is reversed below -80 °C and the ratio at -100 °C is 56:39. The probability of the F conformer is small, but it is not negligible. Since the contributions of the other conformers (B, D, and E) are always zero or 1%, except at room temperature, these conformers can be neglected. This analysis thus identifies the three important conformers.

Simulation of the characteristic NMR signal behavior for H_{20} was then achieved using these three conformers. By employing the probability of each conformer obtained from the previous calculation and the assumed rates of interconversion between the three, the observed characteristic signal behavior of H_{20} can be reproduced successfully (Figure 3). At room temperature, the rates of interconversion between all three conformers are rapid. Although the interconversion rates between conformers A and F (k_{A-F}) and between C and F (k_{C-F}) diminish rapidly with the temperature decrease, the rate between conformers A and C is still fast even at the lowest temperature. The fast rate of k_{A-C} is understandable when we compare the two structures. The conformation of one bridging chain of the C conformer is identical with that of conformer A. Examination of a molecular model indicates that conformer A is easily converted to conformer C by two continuous corner flapping motions[19b] for C_2 and C_3. The energy barrier to this motion should be small because of the small movement of atoms within the bridge.

Using the probability of the two main conformers, we can calculate the free energy difference at each temperature. Regression analysis of free energy versus temperature gives thermodynamic parameters for these two conformers. The enthalpy difference between the two is 1.5 ± 0.1 kcal/mol, and the entropy difference is 7.7 ± 0.5 cal/(mol·K). These values are both larger than those estimated with MM3 calculations.

Figure 4 shows the ORTEP drawing of compound **4**. The structure found in the crystal is identical with the predicted major conformer below -80 °C in solution. Comparison of the observed and calculated torsion angles for the 14-membered carbocycle suggests that the structure predicted by MM3 is favored.

It is worth noting the effect of the alkyl substituent within the bridging chains. The conformational behavior of compound **4** with regard to temperature variation is totally different from that of the C_2 symmetric congener **10**. While multiple conformers play an important role in the former, only one anticlinal conformer is present with no detectable amount of other conformers at a wide range of temperatures in the latter.[16] Molecular mechanics calculations for **10** support this view since the MM3 steric energy difference between the most stable anticlinal conformer and the second most stable conformer is 3.3 kcal/mol. The two aromatic rings in **4** are not chemically equivalent to each other as they are in **10**. Thus, a much larger number of conformers is possible in **4** than in **10** since the geometrical constraint imposed by symmetry on the two aromatic rings in **4** is smaller than in **10**.

A single predominant conformer also is predicted for the compound without the alkyl substituent[25] by our molecular mechanics technique. In this case a highly symmetric (C_{2h}) antiperiplanar conformer is predominant. The MM3 steric energy difference between the most stable conformer and the second most stable is 3.6 kcal/mol, suggesting no chemical shift variation of the aromatic hydrogens with temperature change. It is thus found that the alkyl substituents play an important role in the conformational behavior of the [4.4]metacyclophanes.

Conclusions

The title compound shows a characteristic temperature-dependent chemical shift behavior in its ^{1}H-NMR spectra. The three conformers of **4** which play an important role in the conformational dynamic process can be identified from this signal behavior. The C_s symmetric structure found in the crystal is the main contributor in solution below -80 °C. At higher temperatures, the other conformer, in which the conformation of only one bridging chain is different from that in the C_s symmetric structure, is predominant. In this investigation, we have shown that the conformational analysis of an extremely flexible molecule can be achieved. The method consists of the creation of plausible conformers by molecular mechanics calculations, estimation of the proton chemical shifts of these conformers, and selection of the most probable ones by comparison of the observed and calculated chemical shifts, the latter of which is a weighted average of that in the selected conformers. We conclude that the method can be employed as a general method for the analysis of a multiple conformational problem.

Since there is an increasing interest for determining the precise structure of macrocycles containing multi-aromatic rings such as calixarenes, crown ethers, cryptands, and cavitands, this type of approach should have a wide applicability for this purpose.

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Table 4. Calculated and Observed Induced Shifts of the Aromatic Hydrogens and Probabilities of the Six Conformers of **4**

	induced shift (ppm)														
	H_7		H_{10}		H_{17}		H_{20}			probability (%)					
temp (°C)	calcd	obsd	calcd	obsd	calcd	obsd	calcd	obsd	*R* factor	A	B	C	D	E	F
27	0.044	0.017	0.244	0.246	−0.116	−0.108	−1.286	−1.286	2.3	18	0	68	4	0	10
0	0.056	0.024	0.219	0.242	−0.122	−0.121	−1.501	−1.490	3.6	22	0	72	1	0	5
−30	0.068	0.031	0.167	0.233	−0.125	−0.139	−1.748	−1.763	6.1	31	0	63	1	0	5
−60	0.087	0.044	0.085	0.217	−0.130	−0.155	−2.144	−2.152	8.1	45	0	50	1	0	4
−80	0.100	0.051	0.041	0.202	−0.133	−0.166	−2.386	−2.401	9.1	50	0	45	1	0	4
−100	0.108	0.058	0.007	0.181	−0.135	−0.175	−2.551	−2.550	8.9	56	0	39	1	0	4

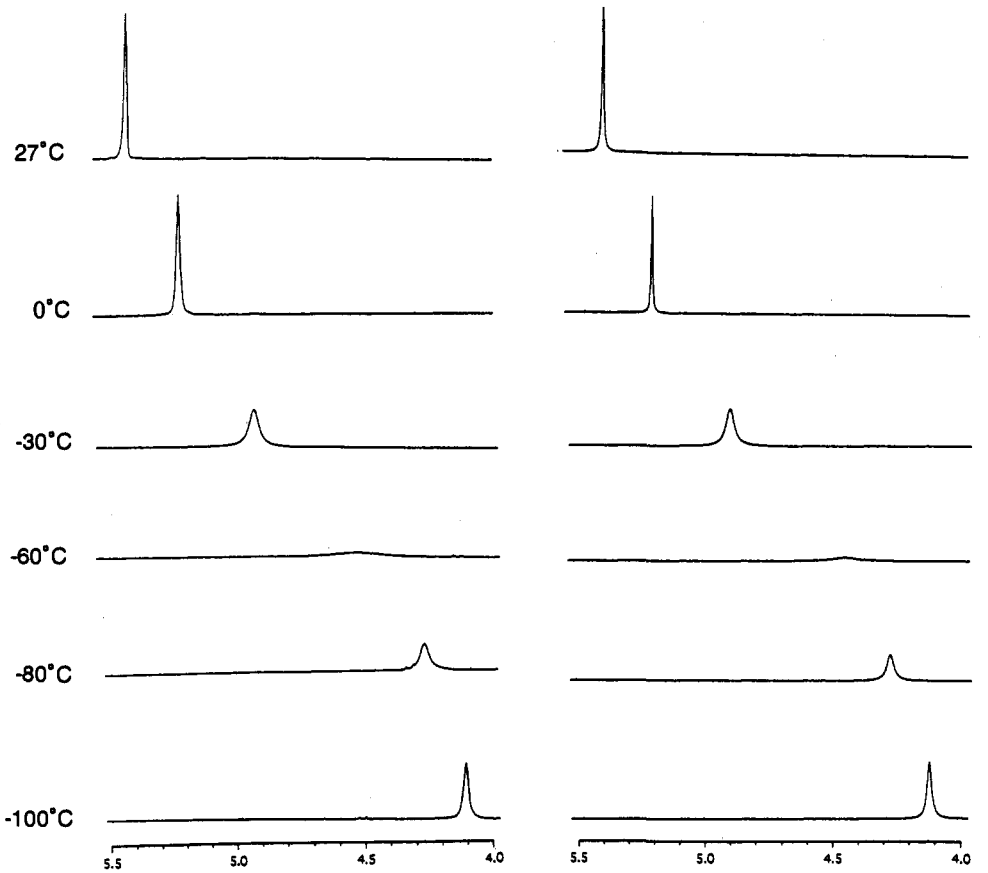

Figure 3. Observed (left) and simulated (right) spectra of the inner aryl hydrogen (H_{20}) of **4** at various temperatures.

Further studies on the conformational analysis of a wide variety of multi-aromatic compounds are now in progress in our laboratory.

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 on JEOL-GX270 (270 MHz) and JEOL-EX400 (400 MHz) spectrometers in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in δ (ppm downfield from Me_4Si). IR spectra were recorded on a Hitachi 260-10 spectrometer. Mass spectra are recorded on a Hitachi-M80B. All melting points are uncorrected. Column chromatography was performed using Merck silica gel (70–230 mesh).

1,3-Bis(2-methyl-2-cyanopropyl)benzene (5). To an ice-cooled solution of LDA in THF (40 mL), prepared from 5.6 mL (40 mmol) of diisopropylamine and 20 mL of 1.5 M *n*-butyllithium was added isobutyronitrile (2.5 mL, 21 mmol). After 10 min of stirring, 1,3-bis(bromomethyl)benzene (3.078 g, 11.7 mmol) was added. The mixture was stirred at 0–5 °C for 10 min, poured into dilute hydrochloric acid, and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using benzene as the eluent to give **5** (2.628 g, 93%) as colorless prisms: mp 60–62 °C; ^{1}H-NMR (400 MHz) 1.36 (s, 12H), 2.82 (s, 4H), 7.18

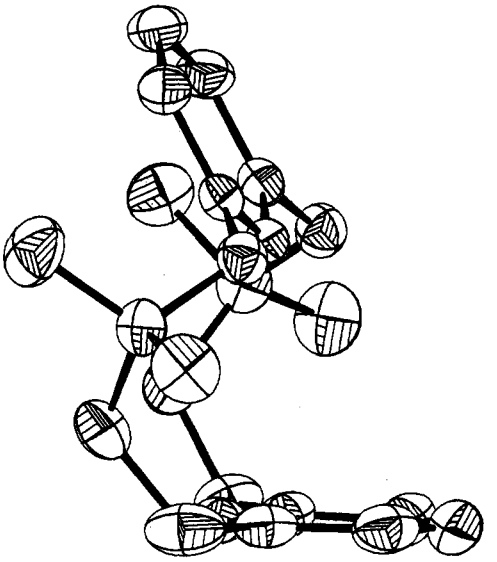

Figure 4. ORTEP drawing of **4**.

(bs, 1H), 7.22 (bd, J = 7.5 Hz, 2H), 7.32 (bt, J = 7.5 Hz, 1H); ^{13}C-NMR (100 MHz) 26.4, 33.5, 46.4, 124.6, 128.3, 129.1, 132.0, 135.8; IR (KBr) 2240 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.71; H, 8.69; N, 11.43.

1,3-Bis(2-methyl-2-cyanopropyl)benzene-*4,6-d*$_2$ (*5-4,6-d*$_2$). To a solution of 4,6-dibromo-*m*-xylene (3.0 g, 11 mmol) in dry THF (60 mL) was added *n*-butyllithium in hexane (11 mL, 17 mmol) at −78 °C. After 5 min of stirring, the solution was quenched by MeOD (2.5 mL) and extracted with CH_2Cl_2. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was passed through a short silica gel column using hexane as the eluent to give a colorless oil (1.5 g): ^{1}H-NMR (60 MHz) 2.25 (s, 3H), 2.31 (s, 3H), 6.93 (s, 1H), 7.29 (s, 1H).

The same procedure was repeated on the above oil (1.5 g) to give *m*-xylene-*3,6-d*$_2$ as a colorless oil (783 mg, 62% by two steps): ^{1}H__NMR (60 MHz) 1.39 (s, 6H), 6.95 (s, 1H), 7.10 (s, 1H).

To a solution of *m*-xylene-*3,6-d*$_2$ (500 mg, 4.6 mmol) in dry CCl_4 was added *N*-bromosuccinimide (1.64 g, 9.3 mmol) and catalytic amount of benzoyl peroxide. The mixture was refluxed for 8 h, cooled to room temperature, and filtered. The filtrate was concentrated and chromatographed on silica gel using hexane as the eluent to afford 1,3-bis(bromomethyl)benzene-*4,6-d*$_2$ as colorless prisms (from hexane, 1.41 g, 31%): ^{1}H-NMR (60 MHz) 4.45 (s, 4H), 7.23 (s, 1H), 7.32 (s,1H).

1,3-Bis(bromomethyl)benzene-*4,6-d*$_2$ was treated by the same procedure described in the preparation of **5** to give **5-*4,6-d*$_2$**. The ^{1}H-NMR spectrum is the same as that of **5** except for the aromatic region: ^{1}H-NMR (400 MHz) 7.18 (s, 1H), 7.32 (s, 1H); MS m/z 242 (68%, d_2), 241 (32%, d_1), 240 (0%, d_0).

1,3-Bis(2,2-dimethyl-3-oxobutyl)benzene (6). To a solution of **5** (485 mg, 2.02 mmol) in dry ether (10 mL) was added a solution of methyllithium in ether (0.68 M, 10 mL, 6.8 mmol) at 0–5 °C. After 10 min of stirring at the same temperature, 10% hydrochloric acid was added. Stirring was continued for 2 h at ambient temperature, and the mixture was extracted with ether. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel using 7:3 hexane–EtOAc as the eluent to give **6** (554 mg, 97%) as a colorless oil: ^{1}H-NMR (400 MHz) 1.11 (s, 12H), 2.12 (s, 6H), 2.77 (s, 4H), 6.82 (bs, 1H), 6.94 (bd, J = 7.7 Hz, 2H), 7.15 (bt, J = 7.7 Hz, 1H); ^{13}C-NMR (100 MHz) 24.2, 26.0, 45.1, 48.6, 127.6, 128.2, 132.1, 137.4, 213.7; IR (neat) 1709 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.95; H, 9.81.

1,3-Bis(2,2-dimethyl-3-oxobutyl)benzene-*4,6-d*$_2$ (*6-4,6-d*$_2$). *6-4,6-d*$_2$ was prepared from **5-*4,6-d*$_2$** by the same procedure described above. ^{1}H-NMR spectrum is the same as that of **6** except for the aromatic region: ^{1}H-NMR (400 MHz) 6.82 (s, 1H), 7.15 (s, 1H); MS m/z 276 (68%, d_2), 275 (32%, d_1), 274 (0%, d_0).

3,3,12,12-Tetramethyl[4.4]metacyclophane-2,13-dione (7). To a solution of **6** (79 mg, 0.29 mmol) and *m*-dibromobenzene (0.04 mL, 0.33 mmol) in 8 mL of *tert*-butylamine and 70 mL of liquid NH_3 was added potassium *tert*-butoxide (20 mg, 1.8 mmol). The mixture was placed in a Pyrex Dewar flask equipped with a dry-ice condenser and irradiated with a medium pressure mercury lamp for 15 min. After the solution was poured into ammonium chloride, the ammonia was allowed to evaporate. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Chromatography of the oily residue on silica gel using 7:3 hexane–EtOAc as the eluent afforded **7** (18.4 mg, 18%) as colorless prisms: mp 80–81 °C; ^{1}H-NMR (400 MHz) 1.25 (s, 12H), 2.78 (s, 4H), 3.56 (s, 4H), 6.12 (s, 1H), 6.69 (s, 1H), 6.93 (d, J = 7.5 Hz, 2H), 7.04–7.10 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H); ^{13}C-NMR (100 MHz) 26.3, 45.4, 46.0, 49.7, 127.4, 127.6, 128.6, 128.9, 129.0, 131.8, 134.0, 138.1, 212.1; IR ($CHCl_3$) 1700 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.53; H, 8.07.

1,3-Dibromobenzene-*4,6-d*$_2$. To a solution of 4,6-diiodo-1,3-dibromobenzene[26] (5.0 g, 10.2 mmol) in dry THF (70 mL) was added an ether solution of EtMgBr (48 mL, 57 mmol) at −40 °C. The mixture was stirred for 30 min at the same temperature, quenched by MeOD (5.85 g, 18 mmol), and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was passed through a short silica gel column using hexane as the eluent to give 1,3-dibromobenzene-*4,6-d*$_2$ as a colorless oil (1.64 g, 68%): ^{1}H-NMR (60 MHz) 7.10 (bs, 1H), 7.65 (s, 1H).

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3,3,12,12-Tetramethyl[4.4]metacyclophane-2,13-dione-*6,8,16,18-d*$_4$ (*7-6,8,16,18-d*$_4$). ***7-6,8,16,18-d*$_4$** was prepared from **6-*4,6-d*$_2$** and 4,6-dideuterio-1,3-dibromobenzene by the same procedure described in the preparation of **7**. The ^{1}H-NMR spectrum is the same as that of **7** except for the aromatic region: ^{1}H-NMR (270 MHz) 6.12 (s, 1H), 6.69 (s, 1H), 7.09 (s, 1H), 7.15 (s, 1H).

2,2,13,13-Tetramethyl[4.4]metacyclophane (4). To a solution of **7** (72 mg, 12 mmol) in dry diethylene glycol (10 mL) was added sodium (277 mg, 12 mmol) and anhydrous hydrazine (2 mL). The mixture was heated at 180 °C for 3 h, then at 230 °C for 9.5 h, and cooled to room temperature. After dilution with brine, the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane as the eluent to provide **4** as colorless prisms (21.3 mg, 32 %): mp 69–71 °C; ^{1}H-NMR (400 MHz) 1.01 (s, 12H), 1.48 (t, J = 6.6 Hz, 4H), 2.36 (s, 4H), 2.70 (t, J = 6.6 Hz, 4H), 5.72 (s, 1H), 6.92 (bd, J = 7.7 Hz, 2H), 7.03–7.05 (m, 3H), 7.14 (t, J = 7.7 Hz, 1H), 7.23 (s, 1H); ^{1}H-NMR (400 MHz, CS_2) 0.99 (s, 12H), 1.46 (m, 4H), 2.28 (s, 4H), 2.66 (t, J = 6.6 Hz, 4H), 5.54 (s, 1H), 6.81 (dd, J = 1.5, 7.3 Hz, 2H), 6.92 (d, J = 7.3 Hz, 1H), 6.96 (dd, J = 1.5, 8.1 Hz, 2H), 7.05 (dd, J = 6.6, 8.1 Hz, 1H), 7.14 (s, 1H); ^{13}C-NMR (100 MHz) 29.5, 30.8, 35.5, 40.3, 45.7, 126.0, 126.3, 128.0, 128.2, 131.0, 134.2, 138.4, 144.3. Anal. Calcd for $C_{24}H_{32}$: C, 89.94; H, 10.06. Found: C, 90.25; H, 10.44.

2,2,13,13-Tetramethyl[4.4]metacyclophane-*7,9,16,18-d*$_4$ (*4-7,9,16,18-d*$_4$). ***4-7,9,16,18-d*$_4$** was prepared from **7-*6,8,16,18-d*$_4$** by the same procedure described above. The ^{1}H-NMR spectrum is the same as that of **4** except for the aromatic region: ^{1}H-NMR (270 MHz, CS_2) 5.44 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.08 (s, 1H); MS m/z 324 (58%, d_4), 323 (32%, d_3), 322 (8%, d_2), 321 (1%, d_1), 320 (0%, d_0).

1,3-Bis(2,2-dimethylbutyl)benzene (8). A mixture of **6** (197 mg, 0.72 mmol), hydrazine monohydrate (2 mL), and KOH (180 mg) in diethylene glycol (10 mL) was heated under reflux at 160 °C for 6.5 h and then at 180 °C for 13 h, during which time the excess hydrazine was distilled off. After cooling, the mixture was diluted with brine and extracted with EtOAc. The organic extract was washed with brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane as the eluent to give **8** (88 mg, 50%) as a colorless oil: ^{1}H NMR (270 MHz, CS_2) 0.79 (s, 12H), 0.86 (t, J = 7.3 Hz, 6H), 1.12 (q, J = 7.3 Hz, 4H), 2.38 (s, 4H), 6.73 (s, 1H), 6.81 (d, J = 7.3 Hz, 2H), 7.00 (t, J = 7.3 Hz, 1H). Anal. Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.38; H, 12.67.

1,3-Bis(3,3-dimethylbutyl)benzene (9). A mixture of pinacolon (1.0 mL, 8.0 mmol), *m*-dibromobenzene (0.12 mL, 1.0 mmol), and potassium *tert*-butoxide (627 mg, 6.0 mmol) in 2 mL of *tert*-butylamine and 30 mL of liquid NH_3 was irradiated for 15 min. After the solution was poured into ammonium chloride, the ammonia was allowed to evaporate. The residue was diluted with brine and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from hexane to afford 1,3-bis-(3,3-dimethyl-2-oxobutyl)benzene (98 mg, 36%) as colorless needles: mp 86–87 °C; IR (KBr) 1698 cm^{-1}; ^{1}H-NMR (270 MHz, CS_2) 1.12 (s, 18H), 3.68 (s, 4H), 6.84 (s, 1H), 6.90 (d, J = 7.8 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.73; H, 9.79.

A mixture of the above diketone (35 mg, 0.13 mmol), hydrazine monohydrate (2 mL), and KOH (150 mg) in diethylene glycol (15 mL) was heated under reflux at 160 °C for 2.5 h and then at 220 °C for 10 h. After cooling, the mixture was diluted with brine and extracted with AcOEt. The organic extract was washed with brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane as the eluent to give **9** (21 mg, 67%) as a colorless powder: mp 34–35 °C; ^{1}H-NMR (270 MHz, CS_2) 0.95 (s, 18H), 1.40–1.46 (m, 4H), 2.24–2.48 (m, 4H), 6.82 (d, J = 7.3 Hz, 2H), 6.83 (s, 1H), 7.00 (t, J = 7.3 Hz, 1H). Anal. Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.39; H, 12.18.

Single-Crystal X-ray Diffraction Analysis of 4. The crystal data for **4** are as follows: monoclinic, space group $P2_1/a$ with a = 15.366(2) Å, b = 12.428(3) Å, c = 10.824(2) Å, β = 104.46(1)°, V = 2001.6(7) Å^3, and Z = 4. The empirical formula is $C_{24}H_{32}$, the molecular weight is 320.52, and the calculated density is 1.064 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 4585 total unique reflections, 2842 were considered observed at the level of $|F_o| > 3.0\sigma|F_o|$.

Data were corrected for Lorentz and polarization effects by the usual way but not for absorption as the linear absorption coefficient is too small [λ(Mo Kα) = 2.3 cm^{-1}]. The structure was solved by direct methods (SHELXS). 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 24 anisotropic non-hydrogen atoms and 32 isotropic hydrogens have converged to a conventional *R* factor of 0.063. All the calculations were done on a HITAC M-200H computer of Hiroshima University using the structure analysis program system UNICS3.[27] Further results of the crystallographic experiment are available in the supplementary material.

Ring Current Calculation. In this model, the induced magnetic field is a sum of the contribution from each edge of the current flowing polygon, and so, it is necessary to estimate the magnitude of the line current experimentally. Using rigid [2.2]cyclophanes (meta- and para-) as the reference compounds, we adjusted the magnitude of the line current for the benzene hexagon to reproduce the induced shift value of the facing aromatic hydrogens. Extra correction for nonplanar benzene rings must be taken into account because these cyclophanes have boat-shaped benzenes due to their inherent skeletal strain. We obtained a best fit value of the line current and reproduced the induced shift of the arene hydrogens of these cyclophanes quite satisfactorily. Using the value obtained for the line current, we estimated the magnitude of the induced shift of the aromatic hydrogens for each conformer of **4**.

Estimation of the Probability of Conformers. We have compared the observed and calculated induced shift values for the four aromatic hydrogens and evaluated the discrepancy factor *R* defined by

$$R = (\sum_i |\Delta\delta H^i_{obsd} - \Delta\delta H^i_{calcd}|)/(\sum_i |\Delta\delta H^i_{obsd}|)$$

where $\Delta\delta H^i_{obsd}$ and $\Delta\delta H^i_{calcd}$ are the observed and calculated induced shifts of H^i. The latter can be defined by

$$\Delta\delta H^i_{calcd} = \sum_j \Delta\delta H^i_j w_j$$

where $\Delta\delta H^i_j$ is the predicted induced shift value of H^i (Table 3) and w_j is the probability of the *j*th conformer. The probability of each conformer was systematically changed by the increment of 1% until the minimum *R* value was obtained. When the width of the *R* factor was expanded by the amount of 1.0% from the minimum value, a large number of sets of the probability of the conformers are obtained. At 0 °C, for example, 71 sets are possible. The deviations of the probabilities for each conformer are as follow: A, 15–27%; B, 0%; C, 55–82%; D, 0–5%; E, 0–1%; F, 0–18%. The probability of each conformer was then estimated by the weighted average of its histogram. This procedure was repeated at every temperature except at −80 and −100 °C. At these temperatures, the conformer F was frozen out from the conformational dynamic equilibrium (see Dynamic NMR Simulation), and hence, extra corrections of this freezing were applied.

Computer Simulations. Theoretical spectra were obtained on a personal computer using a modified version of the DNMR2,[28] a spectral simulation program of exchange-broadened NMR line shape. The temperature dependence of the H_{20} signal was analyzed as a one-spin three-site system. The probabilitiy of each conformer (A, C, and F) was used from the value listed in Table 4. We assumed the following parameters at each temperature for the rate of interconversion between the three conformers: k_{A-F}, k_{A-C}, and k_{C-F}; 1×10^5 (cps), 5×10^5, and 1×10^5 (27 °C); 5×10^4, 5×10^5, and 5×10^4 (0 °C); 1×10^4, 5×10^5, and 1×10^4 (−30 °C); 2×10^3, 2×10^5, and 2×10^3 (−60 °C); 1×10^2, 2×10^5, and 1×10^2 (−80 °C); 1×10^0, 2×10^5, and 1×10^0 (−100 °C).

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Supplementary Material Available: Tables of NMR data in various solvents, final atomic coordinates, thermal parameters, bond distances, and bond angles for **4** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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