Communications to the Editor

Conformational Analysis by Ring Current Method. The Structure of 2,2,12,12-Tetramethyl[4.4]metacyclophane

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High stereoselectivity of intermolecular reactions of macrocycles is usually controlled by their conformations.[1] The conformational analysis of large-membered ring compounds, however, is not straightforward because these molecules are believed to be flexible with many conformational options. We present here a new and efficient method for predicting the conformation of macrocycles containing aromatic rings. It utilizes the calculation of secondary induced magnetic field due to an aromatic ring current.

Conformations of macrocycles have been analyzed mainly by NMR spectroscopy by taking advantage of the torsional dependent ^3J coupling constant[2] and NOE.[3] However, ^3J coupling is invalid if there is an intervention of a quaternary center or of divalent heteroatoms. NOE is also not practical if the two spin centers are more than 4.5 Å apart. On the other hand, it is known that the effect of a diamagnetic ring current[4] of arenes extends to longer distances (~6 Å). We applied this effect for the conformational analysis of macrocycles containing two benzene rings. Relative arrangement of the two benzenes can be obtained by the chemical shift differences of the benzene protons from those of the reference compound, arising from the influence of the secondary induced magnetic field due to the other benzene in the molecule.

[4.4]Metacyclophanes are selected for the application of this method since they have a flexible 14-membered ring, and the conformational analysis of them is rather limited.[5,6] The incremental shift of benzene protons ($\Delta\delta H_{ar}$) was calculated by the classical ring current model. Since the Johnson–Bovey's type separated current loops method[4b,7] is known to be inappropriate for the evaluation of the chemical shift of out-of-plane protons,[8] the line current method[9] has been used.

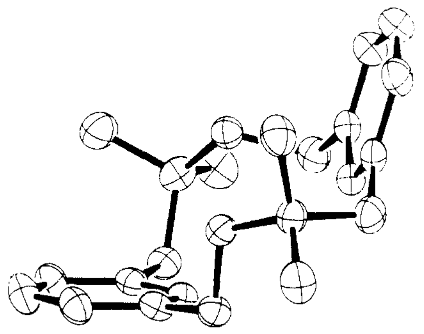


Figure 1. ORTEP drawing of 1.

Table I. Observed and Calculated Induced Shifts ($\Delta\delta$) for [4.4]Phane 1[a]

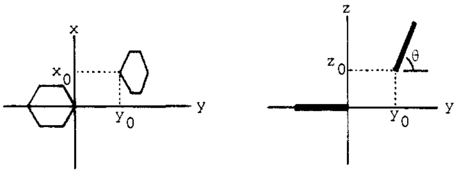
	$\Delta\delta$ (ppm)	
	obsd	calcd
H_6, H_{16}	+0.064	+0.063
H_7, H_{17}	+0.028	+0.061
H_8, H_{18}	+0.025	+0.024
H_{10}, H_{20}	−0.527	−0.529

[a] + denotes upfield shift from the reference compound: 1-(2,2-dimethylbutyl)-3-(3,3-dimethylbutyl)benzene.

Table II. Relative Arrangement of the Two Benzenes for 1

	obsd[a]	calcd[b]
x_0[c]	1.04 Å	1.00 Å
y_0	2.61 Å	2.55 Å
z_0	2.23 Å	2.02 Å
θ	82°	76°

[a] Obtained from the X-ray analysis. [b] Obtained from the ring current method. [c] The axes of coordinates are chosen as shown below.



We have compared the observed and calculated induced shift values for protons of two benzenes placed on certain positions and evaluated the discrepancy factor *R* defined by

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

The position and the orientation of one benzene ring is changed until the minimum *R* value is obtained. Application of this method for 2,2,12,12-tetramethyl[4.4]metacyclophane (**1**)[10] afforded the minimum *R* value of 5.8% (Table I). The relative arrangement of the two benzene rings thus obtained (Table II) is almost completely identical with that found in its crystalline state (Figure 1).[11]

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(10) Compound **1** is prepared with our newly developed photoinduced double $S_{RN}1$ reaction as a key reaction (Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1987**, *28*, 91). See also Supplementary Material.

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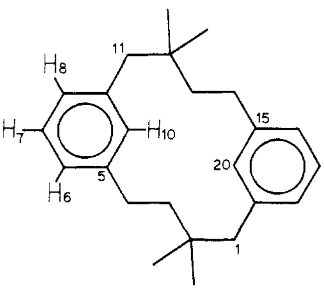

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The observed induced shifts are explained satisfactorily by the single anticlinal[12] conformation which is very close to the one observed in the crystalline state. However, it is difficult to exclude the possibility that the weighted average of several different conformers is very close to this structure. To address this point, NMR spectra of **1** at lower temperature are examined. As the temperature is lowered, a sharp methyl singlet becomes broad and resolves to two singlets at −100 °C, indicating that some dynamic process is slowed down at this temperature. On the other hand, the signals due to the aromatic protons remain unchanged, and no minor signal could be detected even at the lowest temperature (−100 °C). The behavior of these NMR signals is consistent with the hypothesis that only one anticlinal conformer is present in **1** and that it interconverts to its mirror image by a flipping of the two benzene rings. The negligible population of conformers other than this conformer is further supported by molecular mechanics calculations.[13]

Since there is an increasing interest for determining the precise three-dimensional geometry of macrocycles consisting of polyaromatic rings such as calixarenes, crown ethers, cryptands, and cavitands, this type of calculation might have wide applicability for this purpose. Further studies on the conformational analysis of polyaromatic crown ethers and calixarenes are currently in progress in our laboratory.

Supplementary Material Available: Information listing calculations of the ring current induced shift values of benzene protons, preparation of **1** and the reference compound, and molecular mechanics calculations, figures representing torsion angles, low-temperature ^{1}H NMR spectra, and perspective drawings of the calculated structures of **1**, and tables listing observed and calculated induced shifts for [2.2]cyclophanes and high-energy conformers **1b–1d** and *R* factors, fractional coordinates, isotropic temperature factors, anisotropic thermal parameters, and bond distances and angles for **1** (19 pages). Ordering information is given on any current masthead page.

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[11] The crystals of **1** belong to a monoclinic system with cell dimensions $a = 10.794$ (3) Å, $b = 20.127$ (4) Å, $c = 9.832$ (2) Å, $\beta = 110.01$ (2)°, and $V = 2008.5$ (8) Å^3. The space group is $P2_1/c$, $Z = 4$. The empirical formula is $C_{24}H_{32}$, molecular weight is 320.50, and calculated density is 1.060 g/cm^3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Rigaku AFC-5 automatic four-circle diffractometer up to a maximum 2θ of 55.0°. Of 3249 total unique reflections, 1844 were considered observed at the leve of $|F_o| > 4.0\sigma|F_o|$. Data were corrected for Lorentz and polarization effect by the usual way but not for absorption as the linear absorption coefficient is small enough [λ(Mo Kα) = 2.3 cm^{-1}]. The structure was solved by the direct method (MULTAN78). All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were included in the calculated positions (C–H 1.08 Å). Block-diagonal least-squares refinements with 24 anisotropic non-hydrogen atoms and 32 isotropic hydrogens have converged to a conventional *R* factor of 0.082. All the calculations were done on a HITAC M-200H computer of the Hiroshima University with a structure analysis program system UNICS3 [Sakurai T.; Kobayashi, K. *Rep. Inst. Phys. Chem. Res.* **1979**, *56*, 69]. Further results of the crystallographic experiment are available as Supplementary Material.

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Orientation Dependence of ^{2}H NMR Spin–Lattice Relaxation Rates for Cholesterol in Macroscopically Oriented Multibilayers[†]

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Establishing the time scales and amplitudes of molecular motions in the anisotropic environment of lipid bilayers is a task well suited to NMR, since it provides a window precisely in the range where the frequencies of most molecular motions in lipid bilayers are concentrated (10^0–10^{10} Hz).[1] In this regard, ^{2}H NMR continues to play a leading role in studies of dynamic disorder and molecular mobility in these systems.[2a–e] A potentially valuable source of information on molecular dynamics in lipid bilayers can be provided by measurements of the dependence of the ^{2}H spin–lattice relaxation times on the angle between the bilayer normal (director) and the magnetic field (T_1 anisotropy). Such measurements not only put constraints on models of membrane dynamics but also facilitate the identification of the most significant relaxation pathways for ^{2}H nuclei in such systems.[3a–d] Measurements of the T_1 anisotropy for labeled cholesterol in oriented DPPC multibilayers, presented in this note, serve a 2-fold purpose: they allow us to test the validity of a simple model for cholesterol motion and to demonstrate the utility of oriented systems for studies of molecular dynamics.

In the absence of orientational averaging,[4] anisotropic T_1 behavior can be observed in the partially relaxed line shapes of unoriented dispersions.[3b,d] A distinct advantage of oriented systems is that they circumvent the orientational averaging effects of rapid lateral diffusion over the curved liposomal surfaces, a physical process which would thwart any attempt to observe anisotropic spin–lattice relaxation.[4,5] In addition, the enhanced sensitivity and resolution afforded by oriented samples obviously permit a more rapid and straightforward measurement of T_1 anisotropies, particularly when there are overlapping powder patterns in the unoriented spectrum, as is the case for the labeled cholesterol of this study. The fused rings of cholesterol present a rigid moiety whose molecular motion will relax ^{2}H nuclei at different sites at rates modulated *only* by the respective angles (Θ_i) between the C–^{2}H bonds and the motional averaging axis. We exploit this fact to test a simple model for cholesterol dynamics in lipid bilayers, since a correct description of this system should simultaneously predict the angular-dependent relaxation profiles for *all* labeled sites on the steroid ring system.

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[5] Note that orientational averaging by rapid lateral diffusion is a *sufficient*, but not a *necessary* condition, to explain the angular independence of T_1 in the L_α phase of disaturated lecithins.[3c]

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