Pergamon

Tetrahedron Letters 42 (2001) 49–51

TETRAHEDRON
LETTERS

Conformational analysis by chemical shift simulation: structure of 1,4,11,14-tetraoxa[4.4]metacyclophane

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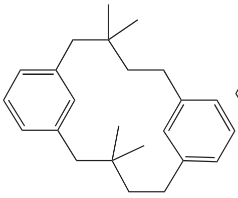
Received 18 September 2000; revised 16 October 2000; accepted 20 October 2000

Abstract—Conformational analysis of 1,4,11,14-tetraoxa[4.4]metacyclophane was carried out using a combination of the molecular mechanics calculation, analysis of the temperature dependent ^{1}H NMR signal change and the chemical shift simulation method. The molecular mechanics calculation with Amber* force-field gave the two structures, one is highly symmetric C_{2v} and the other is C_i symmetric. The latter is identical to the structure found in the crystal. Both of the structures were confirmed by the chemical shift simulation. © 2000 Elsevier Science Ltd. All rights reserved.

While the *syn* and *anti* conformations of metacyclophane are well known and a number of structural studies for short bridged [*m.n*]metacyclophanes ($m,n \leqq 3$) has been performed,[1] those for the higher homologues ($m,n \geqq 4$) are rather limited because they are extremely flexible and were believed to have many conformational options.[2] However, some substituents on the bridging chains reduce the flexibility and restrict its conformational freedom. While the four structures play an important role in the conformational equilibrium of 2,2,13,13-tetramethyl[4.4]metacyclophane (**1**),[3] an isomer, 2,2,12,12-tetramethyl[4.4]metacyclophane (**2**)[4] has only one conformer in solution. It is thus obvious that even a simple substituent such as a methyl group can reduce the conformational freedom if it is situated in the proper position in the bridging chain.

Incorporation of heteroatom(s) into the bridging chain is also known to reduce the conformational freedom of the basic skeleton. An entire planar conformation of 1,4,11,14-tetraoxa[4.4](2,6)pyridinophane (**3**) in which the O–C sp^3 bonds tend to lie in the plane of the pyridine ring was claimed to be the most stable structure.[5] There is much theoretical and experimental evidence that methoxy groups attached to aromatic rings prefer planar conformation.[6] Another well-documented heteroatom effect is the *gauche* attractive effect in the O–C–C–O system;[7,8] however, the O–C–C–O bridging chains of **3** have an anti-periplanar conformation. The unique planar conformation of **3** prompted us to clarify the heteroatom effect of the bridging chain on the structure of the [4.4]metacyclophane. Hence, the conformational analysis of the title compound was carried out using a combination of the molecular mechanics calculation, analysis of the temperature dependent ^{1}H NMR signal change and the chemical shift simulation method.

To assess the conformers of **4**, molecular mechanics calculations were performed using MacroModel V. 6.5.[9] Low Mode search[10] and solvation treatment using GB/SA ($CHCl_3$) was applied to obtain all the possible structures. A total of 96 structures were obtained in the energy window of 10 kcal/mol from the most stable



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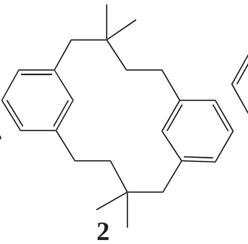

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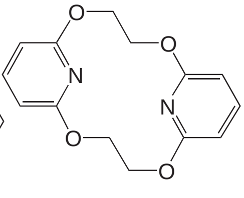

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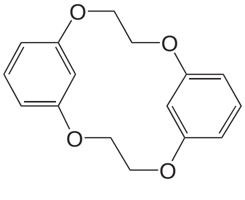

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Keywords: [4.4]metacyclophane; temperature dependent NMR; conformational analysis; molecular modeling; chemical shift simulation.

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PII: S0040-4039(00)01876-1

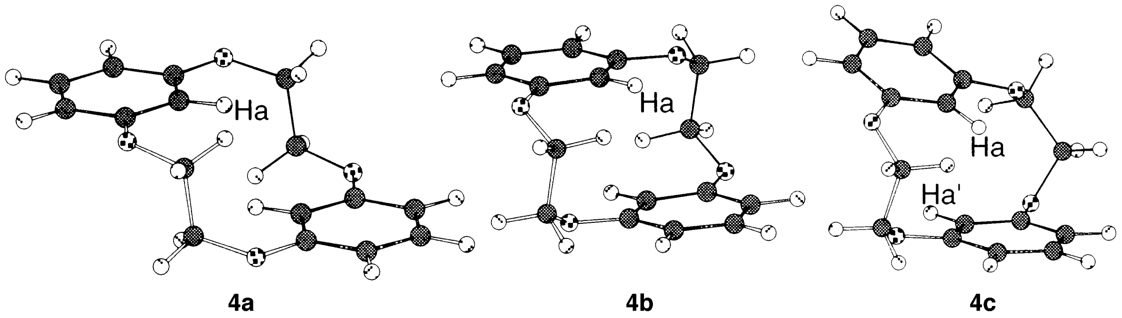

Figure 1. Three conformers of **4**.

Table 1. Calculated incremental shift for inner aryl proton in three conformers

		Calculated $\Delta\delta$ (ppm)[a]		
	Conformer	*a*	*b*	*c*
Ha	Ar[b]	−0.052	−1.583	−2.230
	C–O–C[c]	0.568	0.313	0.329
	Total	0.516	−1.270	−1.901
Ha′	Ar[b]			−0.929
	C–O–C[c]			0.323
	Total			−0.669

[a] A − sign denotes up-field shift.
[b] Due to the facing benzene.
[c] Due to the ether groups.

one. None of the structures has the entire planar conformation as was found in **3**, suggesting a difference in steric bulk between the inner aryl CH of the benzene ring and the N atom of the pyridine ring. Only three structures were energetically important and they are shown in Fig. 1. The lowest energy structure has C_{2v} symmetry (a; relative energy 0.0 kcal/mol) with an anti-periplanar O–C–C–O, the second one has C_i symmetry (b; relative energy 0.129 kcal/mol)[11] with a *gauche* O–C–C-O and the third one is non-symmetric (c; relative energy 1.806 kcal/mol).

Variable temperature ^{1}H NMR spectra of **4** in CD_2Cl_2 disclosed the presence of the two conformers, since the signal of the inner aryl proton of **4** decoalesced at −60°C then split into the two singlets at −90°C. The magnetization transfer experiment disclosed that there is no other signal assignable to the inner aryl proton. These two signals have almost the same intensity. They shifted to the lower and higher magnetic field by 0.47 and 1.10 ppm, respectively, from the chemical shift of the corresponding proton of the reference, 1,3-dimethoxybenzene (**5**).

Our method for the analysis of the conformation[12] is based on the comparison of the theoretical and observed shifts of the protons. The theoretical chemical shift of a proton on a certain conformer can be obtained from the induced chemical shift increment of the proton by a nearby substituent.[13] The calculated incremental shift of the inner aryl proton of each conformer can be estimated by adding the shift increment caused by the facing benzene ring and ether groups[13a] in the molecule. In the process of the estimation of the shift difference of the inner aryl proton from that of the reference compound, the effect of the orientation of the two vicinal ether groups should be taken into account. In the C_{2v} conformer, the inner aryl proton has a total incremental shift of 1.293 ppm due to the four ether groups, which can be divided into two contributions (0.932 ppm from the proximal two ethers and 0.361 ppm from the distal groups). Since **5** has a corresponding incremental shift of 0.725 ppm,[14] the shift difference is 0.568 ppm. Addition of the incremental shift from the facing benzene ring (−0.052 ppm) gave a total of 0.516 ppm in the C_{2v} structure (Table 1). Similarly, the shift difference of the C_i structure was given as −1.270 ppm. Since these theoretical shift values are in good

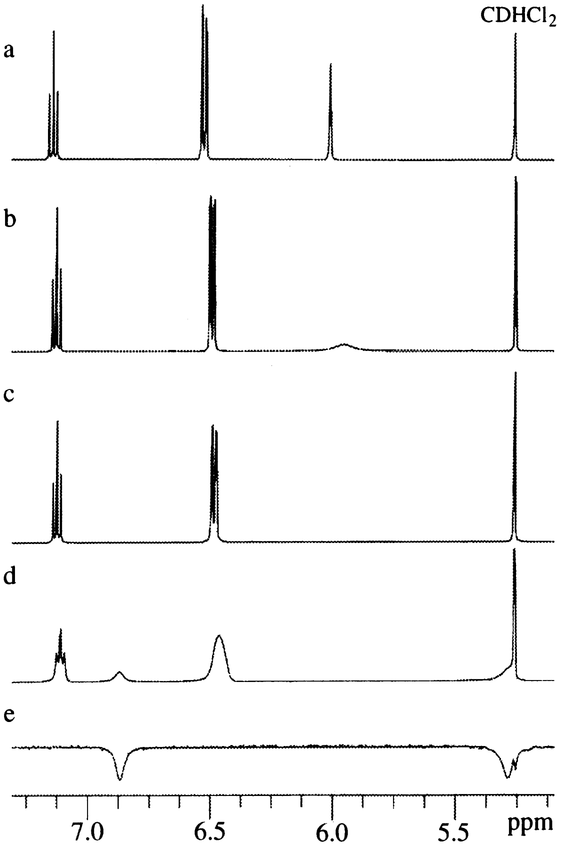

Figure 2. A part of proton NMR spectra at various temperatures, (a) 25°C, (b) −40°C, (c) −60°C, (d) −90°C, (e) magnetization transfer experiment at −90°C.

agreement with the observed ones (0.47 and −1.10 ppm) and the two signals (5.33 and 6.91 ppm) at −90°C were found to be due to the C_i (b) and $C_{2V\ \mathrm{(a)\ structures,}}$ respectively. From this analysis it is found that the two structures a and b play an important role in the conformational equilibrium of **4**. Since these two structures are almost equally populated in solution, both *trans* and *gauche* O–C–C–O are equally found in **4**. The calculated substituent-induced shifts of protons in the closed proximity to the functional group are satisfactory in these cases, suggesting that our shielding parameters for the ether group can be applicable even to such a proton in close proximity to the functional group (Fig. 2).[13a]

Acknowledgements

This work was supported by a Grant-in Aid for Scientific Research (Nos. 10304053 and 12045248) from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.

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14. Almost iso-energetic three conformers, aa, as, and ss, are rapidly equilibrating in **5**. The incremental shift of **5** due to the two in-plane ether groups was calculated to be 0.725 ppm (the weighted average of the three forms aa, 0.56; as, 0.725; ss, 0.89 ppm).