Determination of the Preferred Conformation of a Macrocyclic Bis(bibenzyl) by Nuclear Magnetic Resonance Spectroscopy and Molecular Mechanics Calculations

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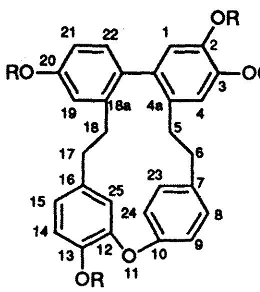
The highly resolved ^1H NMR spectrum of an intermediate **2** in the synthesis of the macrocyclic bis(bibenzyl) plagiochin C **1** allows its conformation to be studied by DIFNOE experiments supported by molecular mechanics calculations and calculation of coupling constants.

In recent years we have been engaged in the synthesis of macrocyclic bis(bibenzyls),[1] typical constituents of liverwort species. The last intermediate in the synthesis of plagiochin C **1**[1] (a constituent of *Plagiochila acanthophylla*),[2] is the tribenzylether **2** that gives a fascinating, highly resolved ^1H NMR spectrum at 400 MHz inspiring us to carry out the detailed assignment of this spectrum and exploit it to gain information about the conformation of this compound as well as about its ring system in general. Earlier works on this class of natural compounds, including some X-ray studies, were only aimed at the elucidation of their constitution and did not concern their conformation in solution.[3]



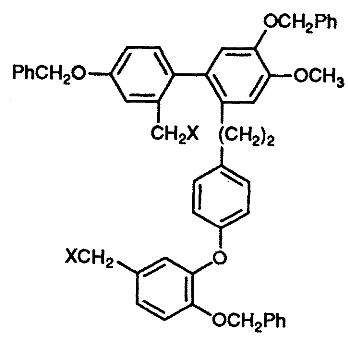
1; R = H
2; R = CH₂Ph

Table 1 Assignment of the 400 MHz proton NMR signals for compound **2**

Proton	Chemical shift/δ	Multiplicity	Coupling constant/Hz
H-1	6.56	s	
H-4	7.135	s	
H-5_A	3.0–	m	
H-5_B	3.12		
H-6_A	2.90	m	
H-6_B	3.12	m	
H-8,23	6.88	symm. m	
H-9,24	6.695	symm. m	
H-14	6.805	d	8.2
H-15	6.64	dd	8.2, 2.1
H-17_A	2.50	m	
H-17_B	1.93	m	
H-18_A	2.78	m	
H-18_B	2.64	m	
H-19	6.62	d	2.6
H-21	6.74	dd	8.4, 2.6
H-22	6.925	d	8.4
H-25	5.206	d	2.1
2-OCH_{2A}	4.985	d	12.5
2-OCH_{2B}	5.165	d	12.5
13-OCH_2	5.22	s	
20-OCH_2	4.95	s	
3-OCH_3	4.03	s	
C_6H_5	7.14–7.54	m	

Results and Discussion

^1H NMR data for **2** are shown in Table 1. Assignment of the aromatic proton signals in **2** was mainly based on the splitting patterns and analogy with congeners and corroborated by decoupling experiments. Protons of the ethylene bridges, as well as the protons of methoxy and benzyloxy methylene groups couple with aromatic protons in *ortho* positions causing line broadening, which may be eliminated by decoupling. A noteable feature of the spectrum is the splitting of the methylene signal of the 2-OCH_2Ph group to an AB-quartet. The reason for this diastereotopy is ambiguous. It could be attributed to slow exchange between enantiomeric ring conformers or to hindered rotation of the benzyl group. Since in the acyclic precursors of **2** *i.e.* in **3** (X = OH or Br) not only the above mentioned methylene signal but also that of one of the CH_2X groups appears as an AB-quartet, splitting of methylene signals should be attributed to hindered rotation around the Ar–Ar′ bond. This is in accordance with the observation that the CH_2 signal of 2,2′-bis(acetoxymethyl)biphenyl appears as an AB-quartet at room temperature[4] ($\Delta G^\ddagger$ = 13 kcal mol^{-1}).† According to our own calculations the lower rotational barrier of 2′-ethyl-2-hydroxymethylbiphenyl, a close model for **3** (X = OH), is 15 kcal mol^{-1}.



3; (X = OH, Br)

† 1 cal = 4.184 J.

Table 2 Trivial names, ring size, calculated rotational barriers, splitting pattern of the *p*-disubstituted benzene ring and chemical shift of the 'inside proton' in various cyclic bis(bibenzyls)

Trivial name	Ring size	Rotational barrier/ kcal mol^{-1}	Splitting pattern at 293 K	δ	Ref.
Plagiochin C	16	65	ABCD	5.21	1
Riccardin A	18	28	coalescence	5.37	9
Marchantin H	18	24	AA'BB'	5.55	10
Riccardin B	18	20	AB quartett	5.98	9
Pakyonol	20	17	AB quartett	6.19	11

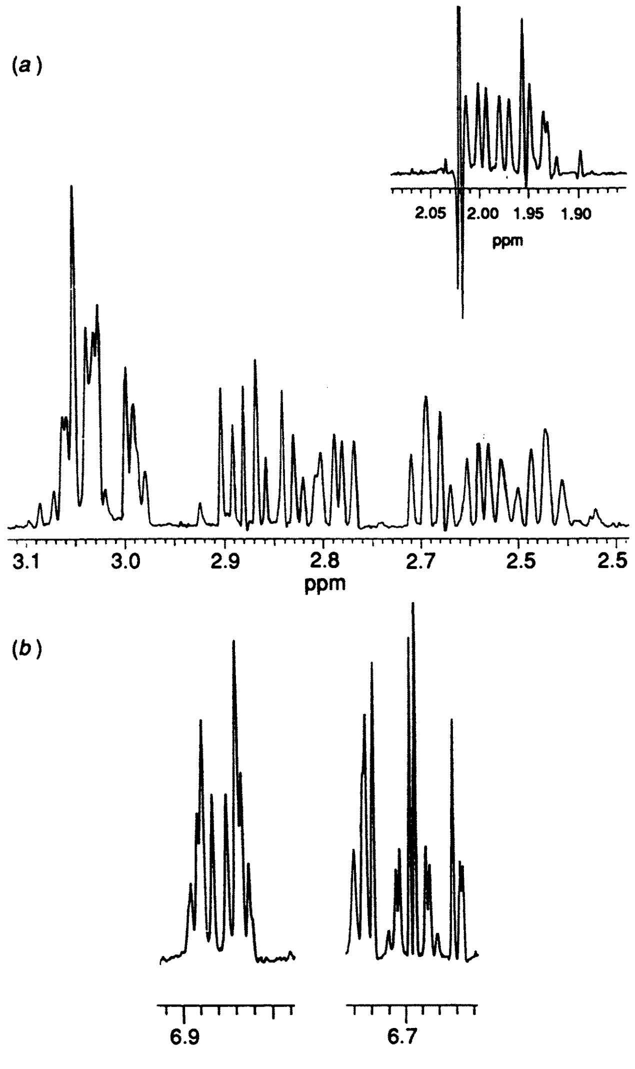


Fig. 1 Signals for (*a*) the bridge protons and (*b*) for protons of the *p*-disubstituted benzene ring of compound **2**

Resolution of the bridge CH_2 signals indicate the existence of a stable conformation of the ring system, while the ABCD-type splitting of the signals for the *p*-disubstituted benzene ring calls for a hindered rotation of this ring (Fig. 1).

Unfortunately variable temperature studies in the range of −70 to +110 °C did not provide additional information, since no temperature-dependent changes in line shape were observed.

For the demonstration of hindered rotation the rotational barrier of the *p*-disubstituted benzene ring was calculated using the rigid rotor approximation based on nonbonded interactions and found to be 65 kcal mol^{-1}. This suggests that the system is probably unsuited for variable temperature NMR studies. For comparison the rotational barriers of the *p*-disubstituted benzene ring in some other cyclic bis(bibenzyls), for which NMR data were available,[9-11] were calculated and compiled in Table 2. Hindered rotation should be caused by the unfavourable steric interactions between the inside proton (H-25 in **2**) and H-9/H-24. This steric hindrance becomes evident when looking at the calculated van der Waals surface (Fig. 2) and the significant diamagnetic shift of the H-25 signal effected by the *p*-disubstituted benzene ring. This effect is characteristic of the whole class of cyclic bis(bibenzyls) and can be, in our opinion, correlated with the height of the rotational barrier of this group, which in turn, depends on ring size (Table 2).

Table 3 Positive nuclear Overhauser effects between protons in compound **2**

Selective saturation at	Intensity enchancement at
H-1	H-17$_B$, H-22
H-4	H-8, 23, H-5
H-22	H-6$_B$, H-1
H-25	H-17$_A$, H-9, 24
H-8, 23	C6-H_2, H-4, OCH_3
3-OCH_3	H-8, 23

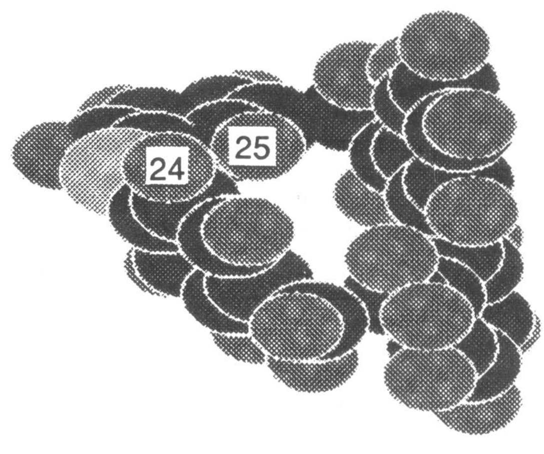


Fig. 2 The calculated van der Waals surface of **2A**, the minimum energy conformer of **2**. For the sake of clarity substituents were stripped and van der Waals radii were scaled down by a factor of 0.75.

Differential NOE (DIFNOE) experiments revealed a wealth of interactions which are compiled in Table 3. When evaluating the distances between protons using a Dreiding model it became clear that all of the observed NOE interactions could be interpreted by a single conformation. To gain more exact data molecular mechanics calculations[5] were carried out and a conformational energy map was prepared. The ω_1 and ω_2 dihedral angles [C(16)–C(17)–C(18)–C(18a) and C(4a)–C(5)–C(6)–C(7), respectively] were driven in steps of 10° in the 360° space. The potential energy map indicated three minimum energy conformations, **2A**, **2B** and **2C** (Fig. 3). Note that the most favoured conformation is **2A** shown in Fig. 2 (ω_1 = 236°, ω_2 = −61° and E_{steric} = 156.1 kcal mol^{-1}), while **2B** and **2C** represent local minima ($\omega_1 = 43°$, $\omega_2 = -38°$, $E_{steric} = 160.9$ kcal mol^{-1} and $\omega_1 = 317°$, $\omega_2 = -92°$, $E_{steric} = 159.2$ kcal mol^{-1} respectively). Owing to their high relative steric energy the less stable conformers cannot be observed by NMR spectroscopy. Distances between relevant pairs of atoms in conformer **2A** are compatible with DIFNOE data, as shown by the above calculations (Table 4). The predominance of conformer **2A** was further confirmed by calculating the expected vicinal coupling constants of the bridge protons using a program based on a refined Karplus equation.[6] Calculated and observed coupling constants are shown in Table 5. The expected geminal coupling constants were also calculated[7] and compared with the experimental values (Table 6). With regard to the π-contribution to the geminal coupling constant[8] good correlation was found between calculated and experimental values.

The preferred conformation of **2** was further analysed in terms of the mobility of the cyclic structure by carrying out of molecular dynamics (MD) calculations on **2A** at 300 and 600 K. In this way, along with the already known minimum, a set of relative minima were generated. The superposition of these conformations can be seen in Fig. 4. Apparently distortions of the macrocyclic ring are rather limited. Deviation of the dihedral angles by a few degrees is possible, but the macrocyclic ring system retains its shape.

A final proof for the rigidity of the ring system was provided by recording the spectrum of **2** in the presence of the optically active shift reagent tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). OMe, H-21 and H-22 signals were clearly split to two signals of equal intensity indicating the presence of two enantiomeric conformations with a rate of interconversion slow on the NMR time scale.

Table 4 Calculated distances between bridge protons and some characteristic aromatic protons in conformer **2A** (in Angstrom)

	H-5$_A$	H-5$_B$	H-6$_A$	H-6$_B$
H-1	4.86	5.31	—	—
H-4	2.66	3.62	2.14	3.60
H-22	2.05	2.45	4.66	4.27
	H-17$_A$	H-17$_B$	H-18$_A$	H-18$_B$
H-1	—	—	2.20	2.16
H-19	2.66	2.19	2.85	3.62
H-25	2.48	3.66	2.64	4.04

Table 5 Calculated and observed vicinal coupling constants of the bridge protons H-17$_A$, H-17$_B$, H-18$_A$ and H-18$_B$

Protons	Coupling constant/Hz Observed	Calculated	Calculated dihedral angle
H-17$_A$, H-18$_A$	5.2	5.4	128°
H-17$_B$, H-18$_A$	8.7	8.3	33°
H-17$_A$, H-18$_B$	6.5	6.7	134°
H-17$_B$, H-18$_B$	5.5	5.6	129°

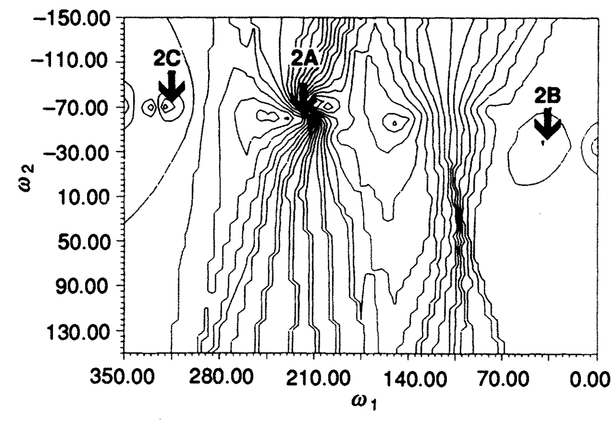


Fig. 3 Contour map of calculated conformational energies of **2** as a function of the rotational angle ω_1 and ω_2. Energy range from 0 to 20 kcal mol^{-1} (relative to the minimum), contoured lines drawn at 2 kcal mol^{-1} intervals. Minima are indicated by arrows.

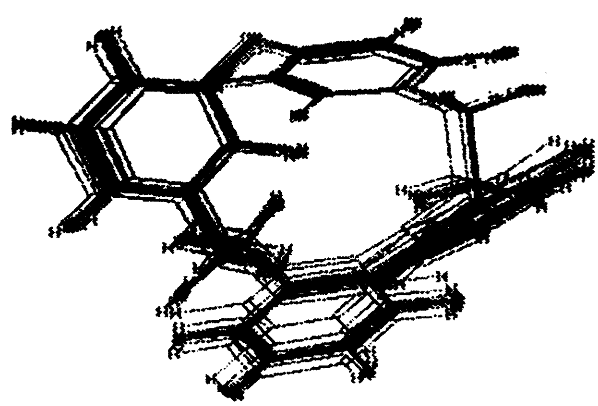


Fig. 4 Superposition of some different conformations of **2A** obtained by molecular dynamics simulation at 300 K

Experimental

^1H NMR spectra were recorded for **2** in $CDCl_3$ on a Varian VXR-400 spectrometer at 400 MHz, the chemical shifts were measured relative to tetramethylsilane as internal standard (0.0 ppm). Assignment of signals was accomplished by conventional techniques, typically double resonance and DIFNOE at a sample temperature of 293 K. The error margin of the coupling constant was 0.1 Hz. Calculations of the theoretical coupling constants for related dihedral angles of vicinal protons of conformer **2A** were carried out using the generalised Karplus equation of the Altona program.[6]

Molecular mechanics calculations were carried out on an IBM 80486 computer using the MM2/MMP2/MMX program.[5] The conformational energy map was generated by driving dihedral angles ω_1 and ω_2 [C(16)–C(17)–C(18)–C(18a) and C(4a)–C(5)–C(6)–C(7), respectively] in the 360° space by steps of 10°. The steric energy was minimised within 0.0009 kcal mol^{-1} at each step, the average of the accumulated movements was 0.000 07 Å $atom^{-1}$, the maximal movement was 0.000 34 Å $atom^{-1}$ in the last step of minimisation.

Table 6 Calculated and observed geminal coupling constants of the bridge protons H-17$_A$, H-17$_B$ and H-18$_A$, H-18$_B$

Protons	Observed coupling constant/Hz	Calculated HCH bond angle (coupling constant/Hz)	π-Contribution (coupling constant/Hz)	Coupling constant/Hz
H-17$_A$, H-17$_B$	18	109° (18)	125° (0.3)	18.3
H-18$_B$, H-18$_B$	16.5	106° (14)	14° (2.7)	16.7

Molecular dynamics simulation was performed with a time step of 5 ps over a range of 400 ps at 300 K and 600 K. The first 50 ps were taken for the equilibration of the system.

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