

Conformational Properties of the Calix[4]naphthalenes*

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Abstract. The base-catalyzed condensation of 1-naphthol and formaldehyde in refluxing dimethylformamide affords three isomeric cyclic tetramers which are conformationally flexible over a wide temperature range. Their tetrabenzoate esters however show restricted flexibility. Variable-temperature NMR and low-temperature COSY is used to analyze the conformational preferences of these calix[4]naphthalenes.

Key words: 1-Naphthol, formaldehyde, calix[4]arenes, calix[4]naphthalenes, NMR, conformational analysis.

1. Introduction

It has been 50 years since Zincke and Ziegler assigned cyclic tetrameric structures to substances obtained from the base-induced reaction of *p*-substituted phenols with formaldehyde [1], substances which we have since come to know as the calixarenes. However, it has taken almost 50 years since their assignment for the first report to appear, in 1993, of cyclic tetrameric structures from the base-induced reaction of formaldehyde with the naphthalene analogue of phenol, 1-naphthol [2].

The naphthols are more reactive than phenols and resemble resorcinol rather than phenol in many of their reactions [3]. The complexity of the reaction of 1-naphthol with formaldehyde is well known [4] and it has been assumed that cross-linked polymers are formed since reaction can occur at both C-2 and C-4, the positions which are respectively *ortho* and *para* to the hydroxyl group. In 1907 Breslauer and Pictet [5] reported obtaining an amorphous product having empirical formula $C_{23}H_{16}O_3$ from the reaction of 1-naphthol with formaldehyde in the presence of potassium carbonate. Abel [6] reported obtaining a "brown, brittle, alkali-soluble resin" on heating 1-naphthol with formaldehyde in 50% acetic acid containing a small quantity of hydrochloric acid. By way of contrast, 2-naphthol reacts mainly at C-1, and as a result, condenses with formaldehyde under either

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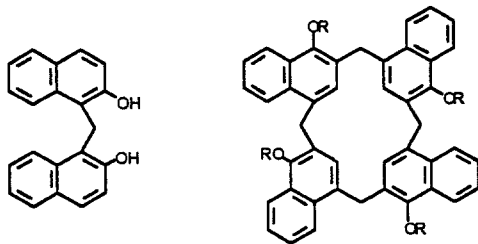
base [7] or acid [8] catalysis to readily afford a well-defined, single product, *bis*-(2-hydroxy-1-naphthyl)-methane, **I**.

When we reinvestigated the base-induced reaction of 1-naphthol with formaldehyde we isolated and identified three isomeric tetrameric compounds [2] which we named "calix[4]naphthalenes" by analogy with the calix[4]arenes and calix[4]resorcinarenes. However, unlike the latter which are derived from *p*-substituted phenols and resorcinol respectively, several different isomers can theoretically exist for the calix[4]naphthalenes. Additionally, the conformations that are possible for some of these isomers are further complicated due to the dissymmetry that is introduced by the naphthalene rings. In this contribution we will describe some properties of this new class of compounds.

2. Results and Discussion

When a solution containing purified 1-naphthol, formaldehyde and potassium carbonate was heated in DMF under reflux for 30 h, a crude product was obtained that thin-layer chromatography indicated to be a complex mixture. The $^1\text{H-NMR}$ spectrum of this crude product however had surprisingly clearly-defined features. In particular, the signals in the 4.0–4.8 ppm region resembled those usually seen for the methylene bridge protons of the various conformers of calixarene derivatives [9, 10]. The limited solubility of the crude product in the usual organic solvents prohibited purification by conventional chromatographic techniques. However, fractional crystallization of the crude reaction mixture afforded three crystalline products. Mass spectra indicated that these are isomeric tetramers, each having a molecular ion peak at $m/z = 624$.

If ring A of the naphthalene ring only is considered, there are four isomers that are possible for cyclic tetramers which can be formed from the condensation of 1-naphthol with formaldehyde. These are depicted as **II–V**. Using symmetry considerations alone, the number of $^{13}\text{C-NMR}$ resonance signals that would be expected for **II** would be eleven, for **III** the number would be twelve, and for **IV** the number would be twenty three. Isomer **V**, the least symmetrical of the isomers, would be expected to show forty four carbon signals.



I

II : R = H
IX : R = Bz

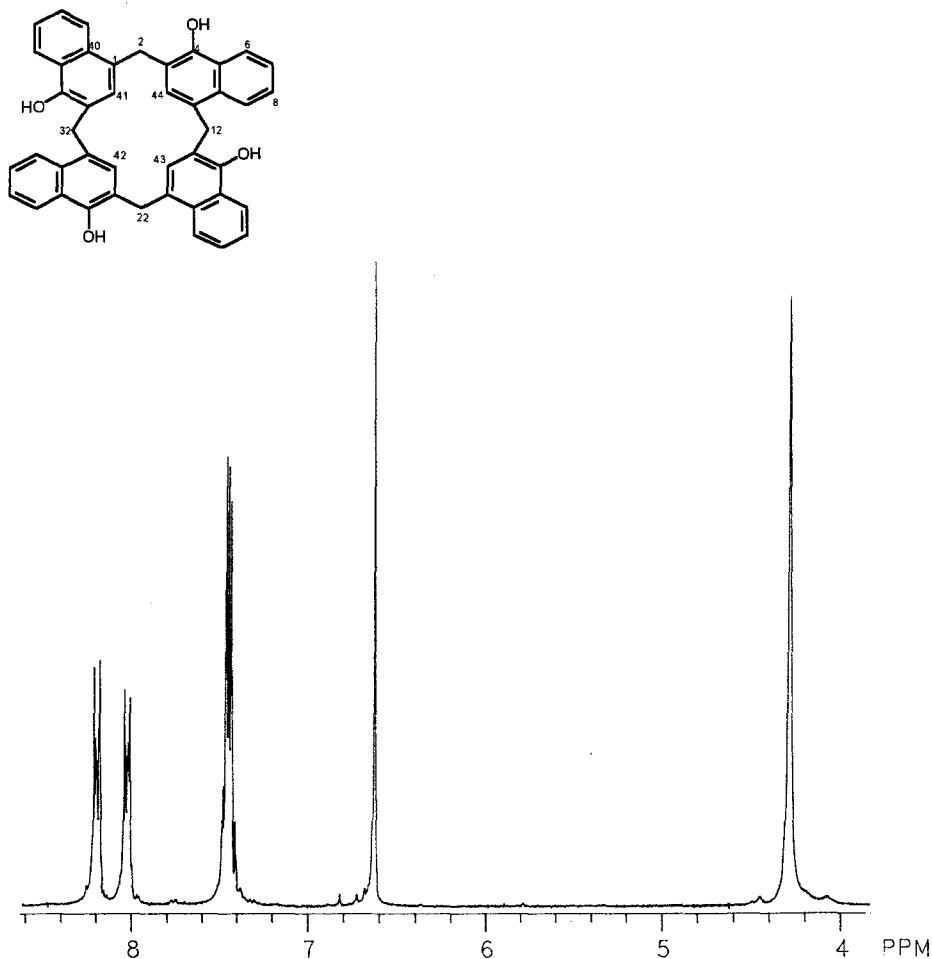


Fig. 1. 300 MHz ¹H-NMR spectrum of II.

field aromatic signals as two (two-proton) singlets of equal intensity at 6.83 and 6.72 ppm for the intra-annular protons. The methylene protons appear as three singlets, at 4.40, 4.29 and 4.08 ppm with relative intensities in the ratio of 1 : 2 : 1, respectively. In addition to these data, the HETCOR, NOED spectra and MS data (for a more detailed assignment, see [2]) are consistent for structure **IV** which possesses a plane of symmetry through the C-20 and C-40 methylene groups and which is perpendicular to the macrocyclic ring. This isomer is also conformationally flexible at ambient temperature.

The third isomer, and the one which was the most difficult to isolate, was recrystallized from diethyl ether. Its ¹³C-NMR (DMSO-*d*₆) spectrum shows only forty two signals, with some obvious overlapping in the group of signals which are centred around 124.5 ppm. The APT-¹³C-NMR spectrum clearly indicates twenty

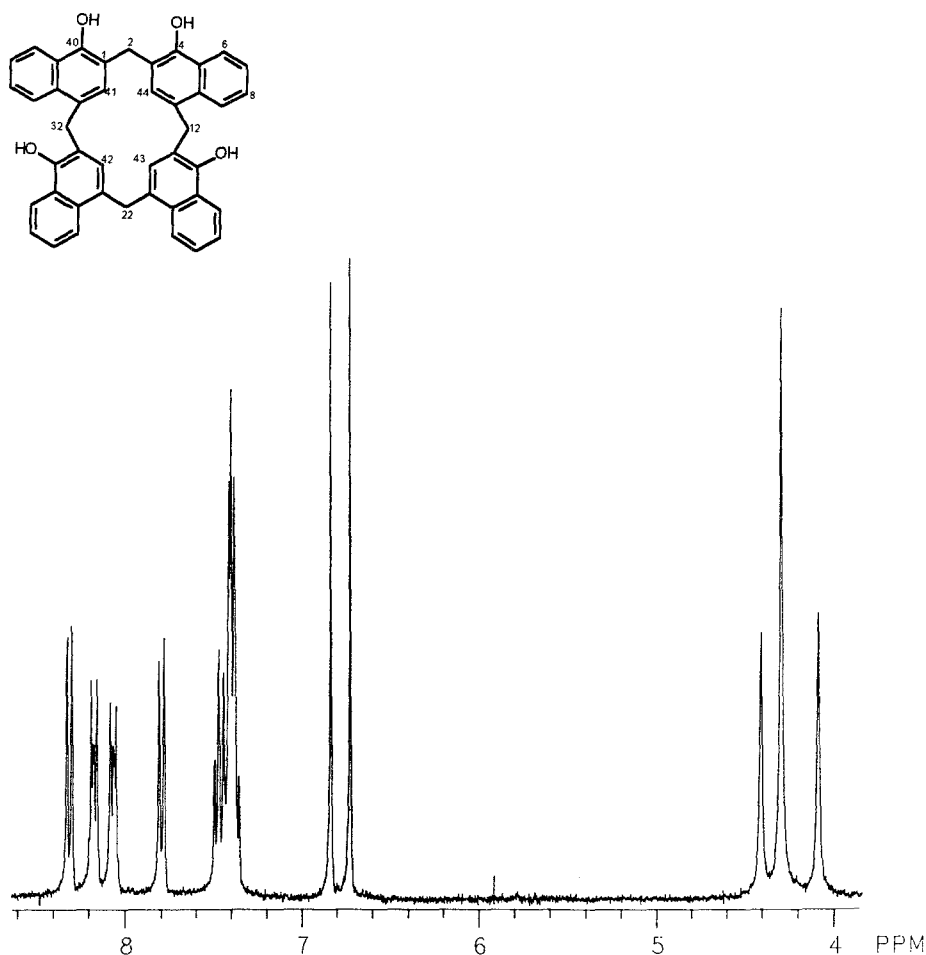


Fig. 2. 300 MHz $^1\text{H-NMR}$ spectrum of IV.

quaternary aromatic carbon signals; twenty methine aromatic carbon signals, of which the same group of signals centred at 124.45 ppm was not clearly resolved; and, four aliphatic methylene carbon signals. The $^1\text{H-NMR}$ spectrum (Figure 3) shows four relatively high-field aromatic (one-proton) singlets of equal intensities, at 6.80, 6.70, 6.66 and 6.64 ppm for the four intra-annular protons. The methylene protons appear as four two-proton singlets of equal intensities, at 4.45, 4.32, 4.21 and 4.09 ppm. These data together with the HETCOR, NOED spectra and MS data (see [2]) were also consistent for structure V which does not possess any symmetry. This isomer is also conformationally flexible at ambient temperature.

When the $^1\text{H-NMR}$ spectra of these three isomers are superimposed, it is obvious that they are the major components of the crude reaction product. In the crude reaction product the ratio of the three isomers can be estimated from integration of

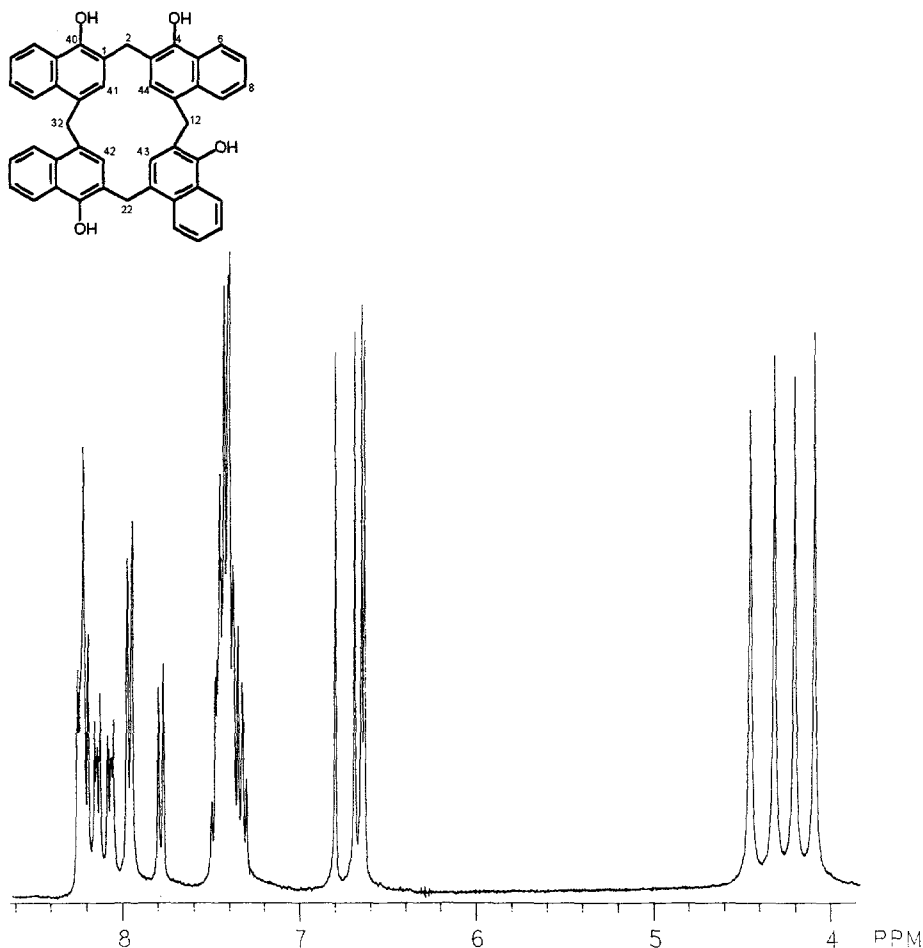
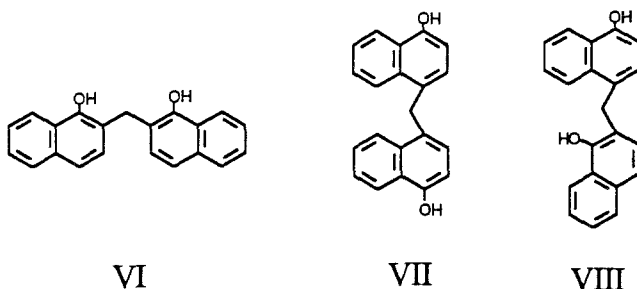


Fig. 3. 300 MHz $^1\text{H-NMR}$ spectrum of **V**.

the intra-annular aromatic signals in the range 6.5–6.9 ppm. The ratio of isomers **II** : **IV** : **V** can be estimated to be approximately 1.0 : 2.2 : 3.0. The total isolated yield (unoptimized) of the three isomers was only 25%, with the ratios of the respective isomers being 1.0 : 1.6 : 0.5. We have been unable to isolate, nor is there any evidence from the $^1\text{H-NMR}$ spectra for any significant amount of the fourth potential isomer, **III**.

There are three potential intermediate *bis*-(1-hydroxynaphthyl)methanes which could be produced that could lead to the formation of cyclic tetramers. They are the *ortho,ortho*-coupled product **VI**, the *para,para*-coupled product **VII**, and the *ortho,para*-coupled product, **VIII**. The following analysis assumes that dimerization of some of these intermediates can account for the formation of the calix[4]naphthalenes that were observed. Dimerization of **VIII** with two equivalents

of formaldehyde would lead to the formation of both **II** and **IV**, but not of **III** or **V**. Dimerization of **VI**, dimerization of **VII** and cross-condensation of **VI** and **VII** with formaldehyde would all lead to the formation of the tetramer **III** which is not observed. However, the formation of **V** indicates that **VIII** could have condensed with formaldehyde and either **VI** or **VII**. Interestingly, the only calix[4]naphthalene derived from a similar reaction of 1,8-naphthalenesulfone with formaldehyde shows twelve carbon signals in its ^{13}C -NMR spectrum [9] and is analogous to **III**.



All three calix[4]arenes are conformationally flexible from ambient temperature down to -50°C , as evidenced by the sharp signals observed for the all of the methylene bridge and intra-annular protons (Figures 1–3). This is not the case when the corresponding tetrabenzoates were similarly analyzed. Using standard procedures, **IX**, **X** and **XI** were prepared from **II**, **IV** and **V** respectively. Each tetrabenzoate showed a molecular ion peak at $m/z = 1040$ by positive FAB mass spectrometry. The ambient ^1H -NMR spectra of each of the tetrabenzoates are characterized by the apparent almost total absence of the intra-annular signals in the 6.0–7.0 ppm region. The methylene protons appear as broad signals. Variable-temperature NMR experiments performed on each of the tetrabenzoates reveal many well-defined signals at the lower temperatures (see Figures 4d–6d). Only at approximately 100°C do the ^1H -NMR spectra resemble the ambient spectra of **II**, **IV** and **V** depicted above, with the intra-annular and methylene protons appearing as singlets.

Figure 4 shows the ^1H -NMR (CD_2Cl_2) spectra of **IX** taken at (a) ambient temperature, (b) 0°C , (c) -20°C , and (d) -50°C . At -50°C conformational freezing is apparent by the presence of well-defined signals in the 4.0–5.0 ppm and 5.8–8.4 ppm ranges.

Figure 5 shows the ^1H -NMR (CD_3Cl) spectra of **X** taken at (a) 50°C , (b) ambient temperature, (c) 0°C , (d) -20°C , and (e) -50°C . Conformational freezing is also apparent at -50°C by the presence of well-defined signals.

In order to interpret the low-temperature spectra, COSY determinations were conducted at -50°C . COSY of **IX** confirmed that the (singlet) signals at 7.14, 7.08, 5.86 and 5.83 ppm (see Figure 4d) are due to the intra-annular protons on C41–44. A conformer which would result in the intra-annular protons being observed as four singlets is a ‘partial cone’ conformer which is analogous to those

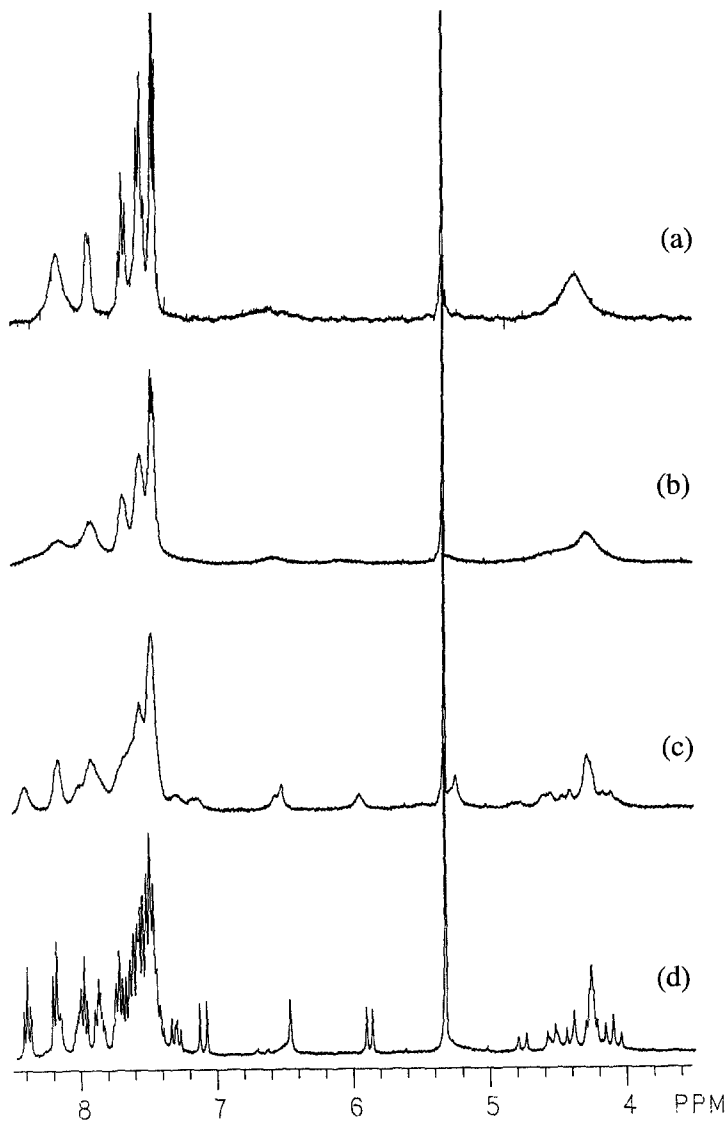


Fig. 4. 300 MHz ^1H -NMR spectra of IX at: (a) $+20^\circ\text{C}$, (b) 0°C , (c) -20°C , and (d) -50°C .

partial cone conformers observed with the calix[4]arenes [10, 11], rather than a 'flattened partial-cone' type of conformer seen with the calix[4]resorcinarenes [12]. This is confirmed by the COSY spectrum shown in Figure 6 which shows eight pairs of doublets due to the methylene geminal protons. However, at least one other conformer (25–30%) is present as evidenced by the large unresolved signal (singlet?) centred at 4.25 ppm and the corresponding aromatic intra-annular signal which appears as a singlet at 6.45 ppm. At this stage it is not possible to assign these latter signals specifically to any of the other three possible conformers

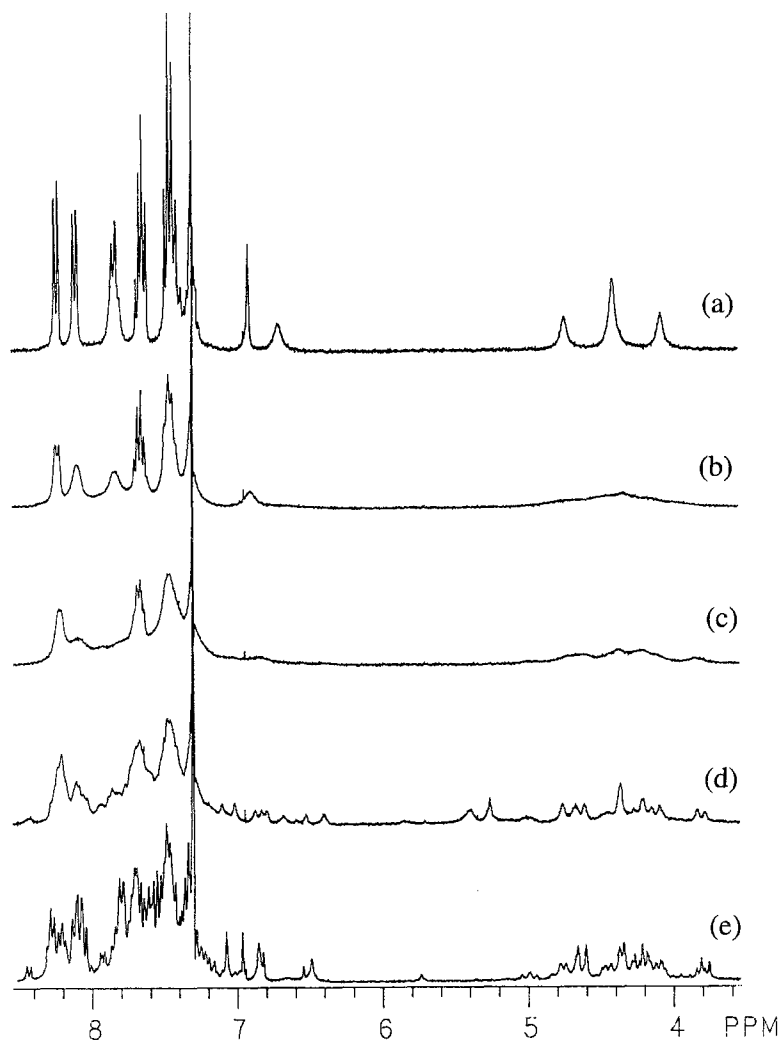


Fig. 5. 300 MHz ^1H -NMR spectra of **X** at: (a) $+50^\circ\text{C}$ (b) $+20^\circ\text{C}$, (c) 0°C , (d) -20°C , and (e) -50°C .

(cone, 1,3-alternate or 1,2-alternate, all of which are analogous to those observed with the calix[4]arenes) as all could be predicted to have a singlet for all four intra-annular protons. Molecular modeling calculations using Alchemy III [13] confirm that the partial cone is the lowest energy conformer and suggest that the 1,2-alternate would be the next higher energy conformer, followed by the cone and 1,3-alternate conformers. However, the energy differences between these conformations that these calculations reveal do not appear to be meaningful as they are much higher than would be expected considering the relative amounts of the two major conformers that are evident at -50°C .

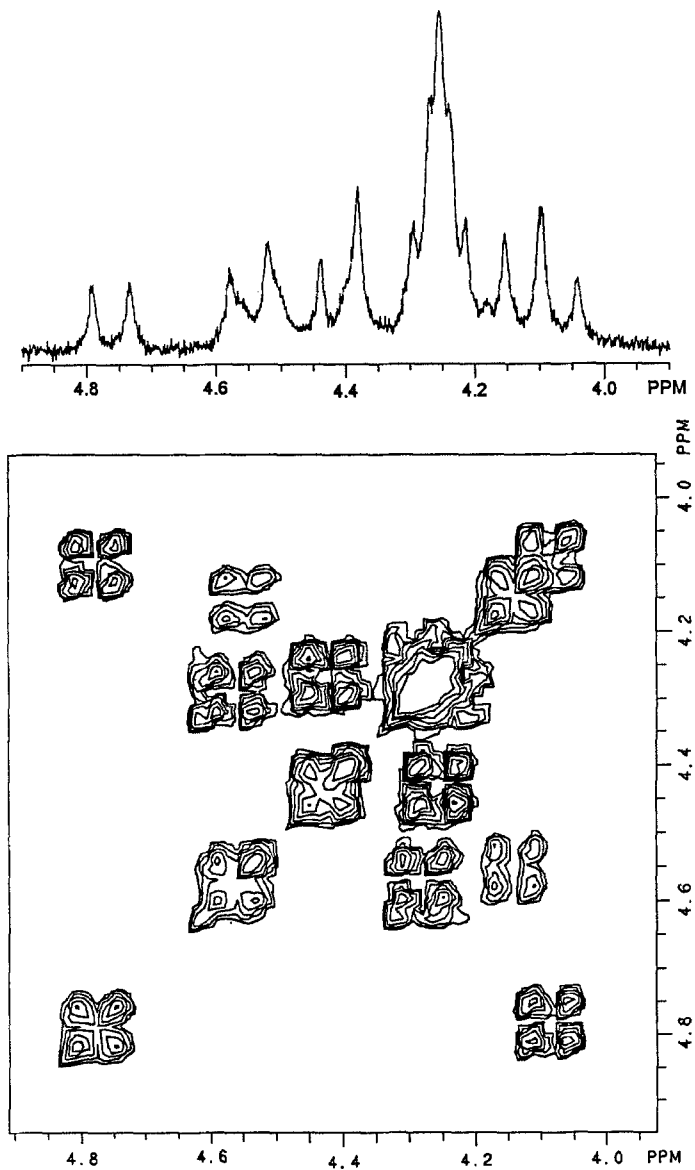


Fig. 6. 300 MHz COSY spectrum (-50°C) of methylene protons in **IX**.

The -50°C COSY spectrum of **X** is considerably more complex than that of **IX**. At least eighteen pairs of doublets and up to four singlets can be discerned in the methylene proton region (Figure 7). At least six signals (singlets) due to the intra-annular protons can also be discerned, albeit with difficulty. As with **IX** a partial-cone conformer could account for eight pairs of doublets; a 1,2-alternate (unsymmetrical) conformer could account for an additional six pairs of doublets; and a 1,2-alternate (symmetrical) conformer could account for an additional four

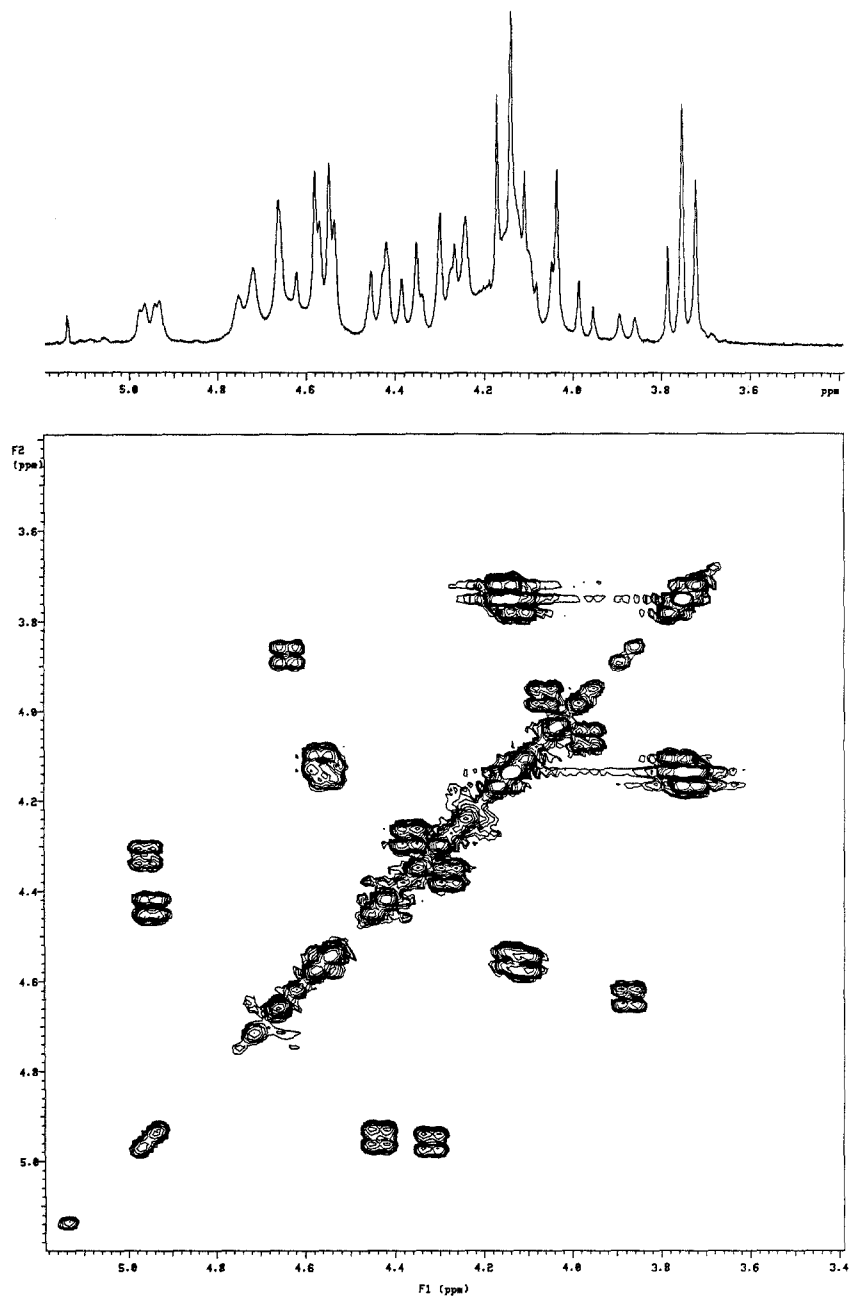


Fig. 7. 500 MHz COSY spectrum (-50°C) of methylene protons in **X**.

pairs of doublets and two singlets. Similar molecular modeling calculations also indicate that as with **IX**, the partial cone is the lowest energy conformer for **X** as

well. The -50°C COSY spectrum of **XI** is the most complex of the three and has not yet been fully assigned.

The well-resolved $^1\text{H-NMR}$ signals observed for both the naphthalene ring and the methylene bridge protons of the three calix[4]naphthalenes **II**, **IV** and **V** indicate that there is rapid conformational interconversion in these molecules at ambient temperatures. The corresponding $^1\text{H-NMR}$ signals of the respective tetrabenzoates **IX**, **X** and **XI** indicate restricted conformational mobility as a result of steric crowding due to the presence of the bulky benzoate groups. However, at ambient temperatures there is no evidence for single conformer formation as noted for example by Jaime *et al.* [14] for their calixarene derivatives.

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References

1. A. Zincke and E. Ziegler: *Ber.* **77**, 264 (1944).
2. P. E. Georghiou and Z. Li: *Tetrahedron Lett.* **34**, 2887 (1993).
3. N. Donaldson: *The Chemistry and Technology of Naphthalene Compounds*, Edward Arnold Publishers Ltd., London (1958).
4. J. F. Walker: *Formaldehyde*, American Chemical Society Monograph Series, No. 159, Reinhold Publishing Corp., New York (1964).
5. J. Breslauer and A. Pictet: *Ber.* **40**, 3785 (1907).
6. J. Abel: *Ber.* **25**, 3477 (1892).
7. O. Manasse: *Ber.* **27**, 2409 (1894).
8. H. Hosaeus: *Ber.* **25**, 3213 (1892).
9. P. E. Georghiou and Z. Li: *unpublished results*.
10. C. D. Gutsche: in *Calixarenes*, J. F. Stoddard (Ed.), Monographs in Supramolecular Chemistry Vol. 1, Royal Society of Chemistry, Cambridge (1989).
11. C. D. Gutsche: in *Calixarenes: A Versatile Class of Macrocyclic Compounds*, J. Vicens, V. Böhmer (Eds.), Topics in Inclusion Science, Kluwer Academic Publishers, Dordrecht (1991).
12. A. G. S. Högberg: *J. Am. Chem. Soc.* **102**, 6046 (1980).
13. *Alchemy III. 3D Molecular Modeling Software*, Tripos Associates Inc., St. Louis, Missouri (1992).
14. C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, and C. Sanchez: *J. Org. Chem.* **56**, 3372 (1991).