

SOLID STATE STRUCTURE AND SOLUTION CONFORMATION OF A MACROBICYCLIC CYCLOPHANE

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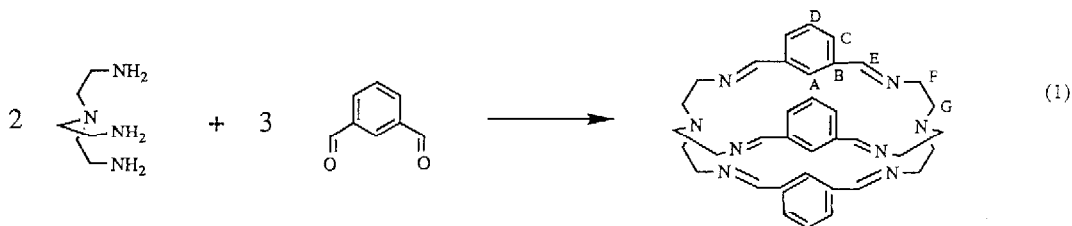
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X-ray crystallographic structure determination of the macrobicyclc cyclophane L¹ reveals a compact structure involving close edge-to-face approach of aromatic rings; ¹H nmr shows that this is also the solution conformation.

Much interest currently attaches to the synthesis and structural characterisation of cyclophane molecules⁽¹⁾ suitable for use as hosts for selective complexation of organic and inorganic guests. One objective of this work, ie the preparation of water-soluble hosts with apolar binding sites, might be more effectively achieved in macrobicyclc "cryptophanes" than in the macrocyclic hosts where so much valuable work has already been done⁽²⁾; however such "cryptophane" syntheses tend to be demanding.

We have recently⁽³⁾ described a facile route to the synthesis (via Schiff-base condensation: Eqn. 1) of a family of macrobicyclcs containing aromatic or heterocyclic rings which have potential value as cryptands. The crystal structures of some of these molecules^(4,5) and their disilver cryptates^(6,7) have subsequently been elucidated; however, although L¹ was the first of the series to be isolated as the free macrobicyclc, its structure has until now resisted solution.



In comparison with other [2+3] tren*/dicarbonyl condensation products, L¹ has several exceptional properties:

- (i) It is isolated in high yield (≈75%) without the use of metal ion as template.

* tren = tris(2 aminoethyl)amine

- (ii) It is reluctant to encapsulate metal ions, showing no tendency to coordinate such apparently suitable small stereochemically non-demanding ions as Zn^{2+} , Pb^{2+} and Ba^{2+} which are coordinated by the other macrobicyclic ligands. Cu^{2+} encapsulation results in ligand modification (10).
- (iii) Although, in common with other members of the series, L^1 displays fluxionality in the room temperature 1H nmr spectrum, the dynamic process is more highly activated for L^1 , the spectrum being just below coalescence at ambient.
- (iv) The 1H nmr spectrum of the aromatic protons is unusual, displaying H_A resonance at exceptionally high and H_C at abnormally low field.

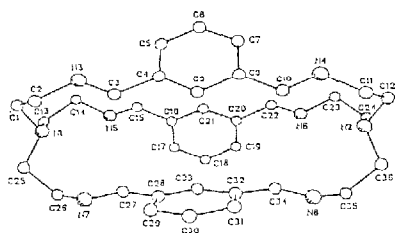
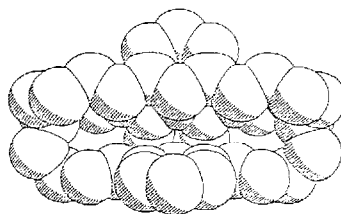


Fig. 1 Structure of L^1 (a) showing the numbering scheme



(b) the space-filling model.

The structural and nmr investigations which follow reveal the origin of these singularities. The structure of the macrobicyclic is shown in Fig 1^{a(11)}. There is a non-crystallographic mirror plane through C(9), C(21) and C(33), a 3-fold non-crystallographic axis running through N(1) and N(2) and the methylene carbons are eclipsed as shown in Fig. 2. The N(1)---N(2) distance is 10.677 Å and adjacent imine nitrogens are separated by ~4.35-4.40 Å. There is no evidence of any intermolecular interactions or of H-bonded water as found in other members of the series. The aromatic rings are triangularly disposed in such a fashion that each C_A is 3.6 Å from the mean plane of the adjacent ring. This configuration appears to provide good steric protection for the 'cavity', but in fact, as Fig. 1^b shows, there is little free space inside the molecule. A sphere of no more than 1.46 Å radius could be accommodated within the triangular framework delineated by the three aromatic rings and such an atom would be perforce bonded to three aromatic carbons. In addition the imine donors are directed outwards away from the cavity.

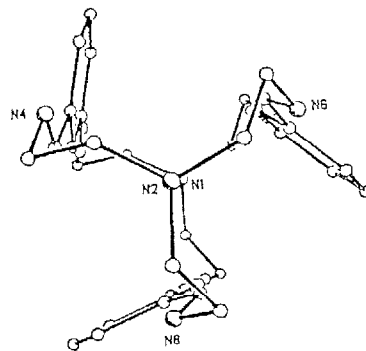


Fig 2 L^1 viewed down the N-N bridgehead axis

The observed fluxionality (Table I) of the 1H nmr spectrum suggested the possibility of alternative conformations in solution. However the fluxionality was confined to the methylene signals, both imine and aromatic resonances remaining sharp down to -70 °C in CD_2Cl_2 . Below coalescence each methylene signal freezes out into a triplet and a pair of poorly resolved doublets. This pattern was interpreted in terms of an $aa'bb'$ system with $J_{ax-ax'} = J_{eq-ax} \approx 11$ Hz and a smaller coupling $J_{eq-eq'} = J_{eq-ax'} \approx 2-3$ Hz. Thus, steric constraints in the molecule appear to prevent interconversion of axial and equatorial sites at temperatures below ambient. The appearance of H_A at unusually high field presents further evidence of crowding in the solution conformation, while NOE experiments clearly indicate (from the exceptionally large enhancement of one of these signals upon irradiation of the other) the close approach of imino- and H_A protons. Furthermore, irradiation into H_E generates preferential enhancement of the $H_F(ax)$ signal, providing conclusive evidence that the solid state configuration of Figs 1 and 2 is also the dominant (if not exclusive) conformation in solution. There is indeed no evidence that free rotation around the C_E-C_B bond, tentatively (and probably erroneously) suggested⁽⁴⁾ as the origin of fluxionality in a related

macrobicycle, is occurring in the absence of metal at temperatures below 30 °C. None the less,⁽¹⁰⁾ treatment of an alcoholic solution of L¹ with AgCF₃SO₃ at 25 °C results in the incorporation of two silver ions as the disilver cryptate, showing that the presence of metal ion significantly lowers the activation energy of this conformational change.

TABLE 1 ¹H nmr spectra^a of L¹ and L²

Compd.	T/K	Spectrum	A	C	D	E	F	G
L ¹	298	¹ H(360MHz)	5.33(s)	8.19(d)	7.52(tr)	7.58(s)	3.72,3.29(br,s)	2.89,2.70(br,s)
L ¹	203	¹ H(400MHz)	5.14(s)	8.14(d)	7.52(tr)	7.49(s)	3.75(q) ^b 3.19(tr)	2.87(tr)2.62(q)
L ¹	203	NOE ¹ H(400MHz)	12.9 ^g	2.8 ^g ^e	c	c	1.5 ^g	4.7 ^g
L ¹	203	NOE ¹ H(400MHz)	c	1.7 ^g		7.5 ^g		
L ²	298	¹ H(360MHz)	7.09(s)	7.20(m) ^f	7.20(m) ^f	3.62(s)	2.59(m)	2.45(m)
L ²	298	NOE ¹ H(400MHz)	10.9 ^g	5 ^g		c	2.6 ^g	0.08 ^g

spectra recorded in CD₂Cl₂ solvent.

a ppm from TMS (s) = singlet, (d) = doublet, (tr) = triplet, (q) = quartet, (m) = multiplet, (br) = broad
 b poorly resolved c irradiation into this signal e partly due to accidental irradiation of H_D f unassignable multiplet
 g % NOE enhancement

In contrast to L¹, the octaamino derivative L² (= L¹ + 12H) derived from L¹ by BH₃ reduction of all 6 imino functions shows no evidence of fluxional behaviour in the ¹H nmr spectrum above -70 °C, or of abnormal chemical shifts deriving from close approach of aromatic rings. The increased flexibility of L² implicit in these results suggests that its host properties are superior to those of L¹. Accordingly, we are now investigating the ability of L² to encapsulate metal cations or small non-polar guests.

The incorporation of a larger rigid aromatic section to ensure a larger cavity and demonstrate more fully the potential of these new cryptophane ligands is now our high priority objective.

Acknowledgements

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References and Notes

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(12) CRYSTAL DATA: $C_{36}H_{42}N_8$, colourless, crystal dimensions $0.44 \times 0.40 \times 0.26 \text{ mm}^3$, rhombohedral (hexagonal axes), $a = 30.284(7)$, $c = 18.450(6) \text{ \AA}$, $U = 14654(9) \text{ \AA}^3$, space group $R\bar{3}$, $Z = 18$, $F(000) = 5651$. Using ω scans at scan rate $5.86^\circ \text{ min}^{-1}$, 5126 unique reflections were collected in the range $4 < 2\theta < 48^\circ$: 2536 having $1 < 3\sigma(1)$ were used in the structural analysis. Data were collected at 150 K on a Nicolet R3m four-circle diffractometer. The cell parameters were determined by least-squares refinement of 25 accurately centered reflections in the range $7 < 2\theta < 34^\circ$. Automatic routines for unit cell determination indicated a cubic cell ($a = 21.40 \text{ \AA}$), however the least-squares refinement was poor ($U = 9805(20) \text{ \AA}^3$). Investigation of sets of reflections which should be equivalent under cubic symmetry showed only one genuine three-fold axis. Crystal stability was monitored by recording three check reflections every 100 reflections and no significant variations were observed. The data were corrected by Lorentz and polarisation effects but not for absorption.

The structure was solved by direct methods using the program TREF⁽⁸⁾ which revealed the positions of all the non-hydrogen atoms. Hydrogen atoms were inserted at calculated positions using a riding model with a common thermal parameter. The non-hydrogen atoms were refined with anisotropic thermal parameters and the refinement converged with $R = 0.052$ $wR = 0.056$. The function minimised was $\sum w (|F_O| - |F_C|)^2$ where $w = [\sigma^2(F_O) + 0.00041 F_O^2]^{-1}$. The final difference map showed no features greater than $\pm 0.25 \text{ e \AA}^{-3}$. Programs used for data reduction and structure refinement are contained in the SHELXTL (Version 4.0) package⁽⁹⁾, the direct methods program TREF is part of the SHELXS-86 package⁽⁸⁾.

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