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Structural Characterization of L-proline and Morpholine Appended Chiral Calix[4]resorcinarene Molecules

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Abstract. Calix[4]resorcinarenes serve as host molecules for small guest molecules. Recently calixarenes have been appended to chiral molecules in an attempt to promote chiral recognition. To take advantage of both cavity host and chiral substituent properties the position of the chiral moiety is important. We report the synthesis and structural characterization of two calix[4]resorcinarene based molecules that have helical chirality in the solid state. The calix[4]resorcinarene **1** has chiral L-proline ethyl ester substituents positioned perpendicular to the cavity whereas the calix[4]resorcinarene **2** has morpholines positioned parallel to the cavity which extend the depth of the cavity. Compound **1** is one of the first compounds to show the position of chiral centers with respect to the calixarene cavity. ^{1}H and ^{13}C NMR spectroscopy indicate that the helical chirality of **2** is retained at low temperature in nonpolar solvents.

Key words: calix[4]resorcinarene, L-proline and morpholine appended, structural characterization

Supplementary Data: Abstract and tables of bond lengths, bond angles, observed and calculated structure factors and crystal packing diagrams of **1** and **2** have been deposited with the British Library at Boston Spa, Wetherby, West Yorkshire, U.K. as Supplementary Publication No. SUP 82250 (29 pages).

1. Introduction

Calixarenes have or form cavities that interact and create sites for the inclusion of guest molecules[1]. The host properties of calixarenes continue to draw research interest due to potential application within the technologies of guest-host systems [2], sensors [3], catalysts [4], and separations [5]. It was of great interest to learn that calixarenes can be used for chiral molecular recognition as had been previously demonstrated for cyclic ethers and cyclodextrins [6]. Unlike cyclodextrins, for calixarenes to have chiral properties they must be functionalized with chiral molecules or form conformational chirality due to the helical [7] or asymmetric arrangement of substituent groups [8]. Recent interest aimed at promoting chiral

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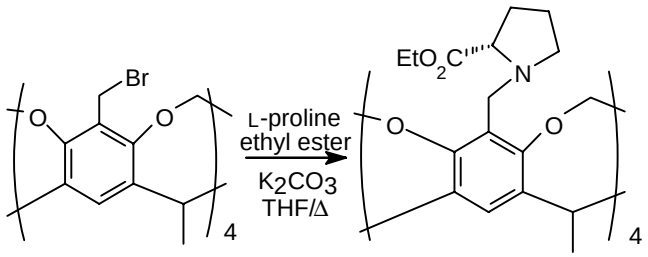
recognition has focused on appending calixarene systems with groups possessing chiral centers [9]. For nonchiral substituent groups to promote chiral recognition, helical chirality must be retained under the reaction conditions, while calixarenes with chiral substituents may still achieve chiral recognition even when their helical chirality is lost. However, their effectiveness as chiral hosts may be strongly influenced by the proximity of the substituent group to the cavity. Herein, we report two calix[4]resorcinarene molecules, both of which display helical chirality and one of which has attached chiral substituents. The solid-state structures of these two molecules implicate forces that promote the arrangement of appended substituents in a helical chiral manner. Also, the proximity of chiral substituents to the calixarene cavity is displayed. Furthermore, the solution state structures (deduced from ^{1}H and ^{13}C NMR experiments) demonstrate that retention of helical chirality is dependent upon both temperature and solvent effects.

2. Experimental

2.1. GENERAL METHODS

All commercial reagents were used as supplied, THF was distilled from sodium-benzophenone. ^{1}H and ^{13}C-{^{1}H} NMR spectra were obtained using a Varian 500 MHz spectrometer operating at 500 and 125 MHz respectively; chemical shifts were recorded in ppm (downfield positive) and coupling constants in Hz. Chemical shift assignments were made with the help of COSY and HETCOR pulse sequences. Mass spectra were determined on a JOEL SX 102A instrument (FAB) with 1-thioglycerol as the matrix and a Bruker APEX 47e Fourier Transform Ion Cyclotron Resonance instrument (ESI). Elemental analyses were performed by M-H-W Labs, Phoenix, AZ. Optical rotation measurements were taken on a Perkin-Elmer 241 Polarimeter.

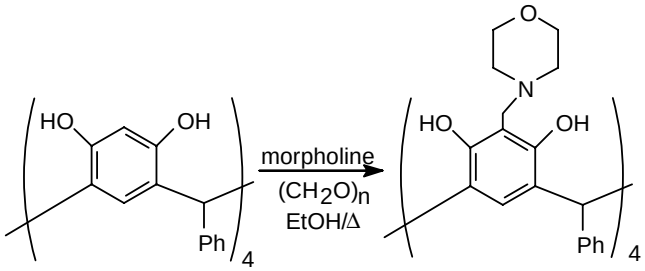


3 **1**

*1,21,23,25-Tetramethyl-7,11,15,28-tetrakis(N-(*L*-proline ethyl ester)methyl)-2,20:3,19-dimetheno-1H,21H,23H,25H-bis[1,3]dioxocino[5,4-i:5′,4′-I′]benso[1,2-d:5,4-d′]bis[1,3]benzodioxocin* (**1**).

Potassium carbonate (1.50 g, 0.0217 mol) was added to a stirred solution of cavitand **3** [10] (0.5 g, 1.04 mmol) and L-proline ethyl ester (0.30 g, 2.08 mmol) in

freshly distilled THF (150 mL) and the mixture heated under reflux (12 h). On cooling to room temperature, insoluble impurities and residual potassium carbonate were removed by filtration and the solution evaporated (under reduced pressure) to a viscous yellow oil. The addition of diethyl ether afforded a brown solid which was removed by filtration through a celite pad and discarded. The diethyl ether was evaporated and the resulting yellow solid was crystallized from a CH_3CN-CH_2Cl_2 mixture affording **1** as pale yellow crystals (0.22 g, 18%). mp (decomp.): 173–175 °C. $[\alpha]_D^{20} = -66.3$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 4 H, C_6H), 5.79 (d, 4 H, J = 7.0, outer OCH_2O), 5.00 (q, 4 H, J = 7.5, $CHCH_3$), 4.16 (d, 4 H, J = 7.0, inner OCH_2O), 4.00 (m, 8 H, $CO_2CH_2CH_3$), 3.60 (AB system, 8 H, benzylic CH_2), 3.15 (AB system, 4 H, proline αCH), 2.99 (t, 4 H, J = 7.25, proline δCH), 2.40 (q, 4 H, J = 7.5, proline δCH), 2.08, 1.87 (br m, 8 H, proline βCH_2), 1.78, 1.64 (br m, 8 H, proline γCH_2), 1.74 (d, 12 H, J = 7.5, $CHCH_3$), 0.83 (br t, 12 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 174.2 ($CO_2CH_2CH_3$), 154.1 and 153.8 (C_6H *C*1 and *C*3), 139.0, and 138.9 (C_6H *C*4 and *C*6), 123.5 (C_6H *C*2), 119.5 (C_6H *C*5), 99.5 (OCH_2O), 64.4 (proline αC), 60.4 ($CO_2CH_2CH_3$), 53.4 (proline δC), 46.3 (benzylic CH_2), 31.4 ($CHCH_3$), 29.5 (proline βC), 22.9 (proline γC), 16.4 ($CHCH_3$), 13.8 ($CO_2CH_2CH_3$); MS (FAB)*m/z*: 1212 (M^+, 100%). Anal. Calcd for $C_{68}H_{84}N_4O_{16}\cdot CH_3CN\cdot H_2O$: C, 66.1; H, 7.00; N, 5.51. Found: C, 66.4; H, 6.78; N, 5.50.



2

2,8,14,20-Tetraphenyl-5,11,17,23-tetrakis(N-(morpholine)methyl)pentacyclo [19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24 - octol (**2**).

Paraformaldehyde (0.3 g) and morpholine (0.78 g, 8.9 mmol) were added to a stirred suspension of *C*-phenylcalix[4]resorcinarene [11] (1.0 g, 1.26 mmol) in EtOH (250 mL). The resultant mixture was heated under reflux (12 h), cooled to room temperature and the orange precipitate thus formed, removed by filtration and recrystallized from DMF-EtOH (1.27 g, 85%). Recrystallization from a DMF-CH_3OH mixture afforded X-ray quality crystals. mp: >250 °C. ^{1}H NMR (DMSO-d_6) δ 9.34 (br s, 8 H, O*H*), 6.94 (m, 12 H, C_6H_5), 6.70 (m, 8 H, C_6H_5), 6.13 (s, 4 H, C_6H), 5.68 (s, 4 H, C_6H_5CH), 3.57 (s, 8 H, benzyl CH_2), 3.52 (br s, 16 H, morpholine CH_2OCH_2), 2.35 (br s, 16 H, morpholine CH_2NCH_2); ^{13}C NMR (DMSO-d_6) δ 151.8 (C_6H *C*1 and *C*3), 145.1 (C_6H_5 *C* 1), 129.3 (C_6H *C* 5), 128.5

(C_6H_5 2C), 127.2, 124.6 (C_6H_5 3C), 121.5 (C_6H *C* 4 and *C* 6), 107.3 (C_6H *C* 2), 66.0 (morpholine *C* H_2O*C* H_2), 54.5 (benzyl *C* H_2), 52.3 (morpholine *C* H_2N*C* H_2), 40.8 (Ph*C*H); MS (ESI with acetic acid) *m/z*: 1189 (MH^+). Anal. Calcd for $C_{72}H_{76}N_{[}4]O_{12}(CH_3)_2NC(O)HC_2H_5OH$: C, 70.4; H, 6.92; N, 5.40. Found: C, 70.6; H, 7.08; N, 5.74. (Solvent verified by ^{1}H NMR.)

2.2. CRYSTAL STRUCTURE ANALYSIS OF **1** AND **2**

All X-ray data were obtained using a Siemens R3m/V automated diffractometer with Mo, Kα radiation (λ = 0.71073 Å). Programs used for solving, refining, and displaying these structures are contained in the SHELXTL-PLUS program package [12].

2.3. STRUCTURE DETERMINATIONS OF **1** AND **2**

The lattice parameters and orientation matrix for each crystal were obtained using a least-squares procedure with an appropriate number (48, 9.74° $\leq 2\theta \leq$ 25.95° for **1** and 21, 7.04° $\leq 2\theta \leq$ 18.60° for **2**) of carefully centered reflections. The lattice parameters for **2** were obtained using a smaller but better quality crystal than that which was used for data collections. Crystal data and experimental details are included in Table I. Atomic coordinates and isotropic displacement coefficients for **1** and **2** are listed in Tables II and III respectively. Both structures were solved using direct methods. Compound **1** lies about a 2-fold axis while **2** lies about a 4-fold axis. Because of the relatively small number of observed data compared to the number of parameters in **1**, all nonhydrogen atoms of that compound were refined isotropically. Positions for hydrogen atoms bonded to the carbons of the bowl and the proline rings of **1** were calculated. There were large uncertainties in the positions of the atoms of the ester groups and so positions of the hydrogen atoms bonded to the last two carbons of the esters were not calculated. In the refinement, the bond lengths between atoms in the proline groups were constrained to reasonable values. All hydrogen atoms included in the refinement of **1** were refined using a riding model. The terminal carbon atom on each ester group is disordered, but it was possible to resolve the disorder for C(44). An acetonitrile molecule located on the two fold axis was found in the difference map. The disorder of the atoms of the proline ester groups and the inability to refine the nonhydrogen atoms of the structure anisotropically are principle causes of the large R value of **1** [13].

The nonhydrogen atoms of **2** were refined anisotropically. Positions for the hydrogen atoms bonded to carbon atoms of **2** were calculated while positions of hydrogen atoms bonded to the oxygen atoms were located in difference maps. It was possible to locate a methanol molecule and two water molecules in the asymmetric unit of **2**. One of the water molecules was disordered. Isotropic thermal parameters were assigned to all the hydrogen atoms which were refined using a riding model.

Table I. Crystal data and experimental details for **1** and **2**

	1	**2**
Formula	$C_{68}H_{84}N_4O_{16}\cdot CH_3CN$	$C_{72}H_{76}N_4O_{12}\cdot CH_3OH\cdot 2H_2O$
Formula weight	1254.4	1257.4
F (000)	1340	2680
Crystal size, mm	$0.35 \times 0.45 \times 0.6$	$0.24 \times 0.35 \times 0.45$
μ, mm^{-1}	0.085	0.083
Temperature, °C	20	20
Crystal system	Monoclinic	Tetragonal
Space group	I2	P4/ncc
a, Å	21.705(9)	16.321(3)
b, Å	8.341(3)	
c, Å	19.237(11)	26.274(7)
β, °	90.02	
V, $Å^3$	3483	7028
Z	2	4
ρ, kg/m^3	1.20	1.19
Max $2\theta°$	50.0	40.0
Unique data	3304 (R_{int} = 2.29%)	2321(R_{int} = 3.29%)
Observed data	1719 ($F > 6.0\sigma(F)$)	1015 ($F > 4.0\sigma(F)$)
R	15.1%	9.82%
Data/parameter	9.3 : 1	4.8 : 1
Largest peak, Δmap, $eÅ^{-3}$	0.64	0.58
Largest hole, Δmap, $eÅ^{-3}$	−0.55	−0.42
Index range	$-25 \le h \le 25$, $0 \le k \le 9$, $0 \le l \le 22$	$-12 \le h \le 0$, $-17 \le k \le 0$, $-2 \le l \le 28$

3. Results and Discussion

To create a host molecule to recognize chiral molecules, **1**, a calix[4]resorcinarene based molecule with four L-proline ethyl esters appended to its upper rim was synthesized. The addition of L-proline ethyl ester to a stirred THF solution of brominated cavitand (**3**) and K_2CO_3 afforded **1** (Equation 1). X-ray crystallographic characterization of **1** shows the L-proline substituents to be positioned around the outer edge of the host cavity in a clockwise helical conformation like the petals of an open flower (Figure 1). Compound **1** is one of the first calixarene molecules with chiral substituents to be crystallographically characterized [14]. The anticlockwise helical conformation is not present (**1** crystallized in a chiral space group), nor are the conformations with the L-prolines positioned up and parallel with the cavity. Evidently, the presence of the four chiral substituents allows one of the two helical forms greater stability and hence facilitates crystallization of one helical diastereomer from solution. Investigation of CPK models did not reveal why energetically **1** favors crystallizing as the clockwise and not the anticlockwise helical diastereomer. Furthermore, the crystal packing diagram of **1**, which shows

Table II. Atomic coordinates ($\times 10^4$) and isotropic displacement coefficients (Å $\times$ 10^3) for **1**

Atom	x	y	z	U(iso)
C(1)	9950(9)	2704	3080(10)	43(5)
C(2)	9998(10)	4595(37)	3132(12)	50(6)
C(3)	9409(8)	5238(36)	3459(9)	33(5)
C(4)	9173(9)	6722(36)	3240(10)	33(5)
C(5)	8684(8)	7428(37)	3580(9)	32(4)
C(6)	8402(9)	6665(36)	4117(10)	33(5)
O(7)	7892(6)	7354(33)	4437(7)	46(4)
C(8)	7979(10)	8243(37)	5019(10)	44(6)
O(9)	7919(6)	7371(32)	5655(7)	45(4)
C(10)	8454(10)	6706(38)	5931(11)	45(6)
C(11)	8739(9)	7494(41)	6482(10)	42(5)
C(12)	9227(9)	6713(36)	6789(8)	40(5)
O(13)	9496(5)	7462(31)	7362(6)	40(3)
C(14)	10037(8)	8371(38)	7276(11)	52(6)
O(15)	10578(6)	7427(32)	7349(7)	44(3)
C(16)	9459(7)	5212(35)	6558(8)	24(4)
C(17)	9164(8)	4548(34)	5982(8)	24(4)
C(18)	8649(7)	5160(34)	5663(8)	19(4)
C(19)	8334(10)	4499(38)	5043(11)	45(6)
C(20)	8364(10)	2645(39)	5046(11)	53(6)
C(21)	8633(9)	5198(37)	4380(10)	39(5)
C(22)	9150(7)	4506(34)	4027(8)	18(4)
C(23)	8441(8)	9124(34)	3312(9)	30(5)
N(24)	7959(8)	9099(34)	2773(9)	45(5)
C(25)	7386(13)	8433(51)	2987(14)	93(10)
C(26)	7071(13)	8438(54)	2252(14)	99(10)
C(27)	7516(14)	8202(60)	1626(16)	131(14)
C(28)	8080(11)	8253(43)	2159(13)	74(8)
C(29)	8535(16)	9011(48)	1728(20)	145(16)
O(30)	8820(11)	10306(41)	1791(12)	128(9)
O(31)	8580(20)	8057(59)	1132(21)	255(19)
C(32)	9037(21)	8786(71)	680(34)	235(27)
C(33)[a]	8900	8613	−55	448(63)
C(34)	8517(10)	9235(39)	6732(11)	50(6)
N(35)	8059(8)	9217(35)	7278(9)	55(5)
C(36)	8296(10)	8874(47)	7955(12)	76(8)
C(37)	7672(9)	8855(51)	8351(12)	99(10)
C(38)	7114(10)	8484(44)	7880(11)	68(7)
C(39)	7475(11)	8468(42)	7185(11)	59(7)
C(40)	7106(16)	8953(54)	6720(17)	102(11)

Table II. Continued

Atom	x	y	z	U(iso)
O(41)	7143(11)	10218(43)	6261(12)	123(8)
O(42)	6545(13)	8199(45)	6563(13)	139(9)
C(43)	6164(21)	8671(68)	5954(23)	146(15)
C(44a)[b]	5646(39)	7573(117)	5975(54)	178(39)
C(44b)[b]	5631(50)	8756(265)	6408(71)	319(88)
C(51)	10000	7616(47)	5000	36(7)
C(52)	10000	9305(98)	5000	134(21)
N (53)	10000	10593(102)	000	196(27)

[a] Because the position of this terminal atom of the ester chain was so uncertain, C(33) was allowed to ride on C(32) in the final refinement. Its position was obtained from the difference map.
[b] Lower case letters indicate disordered atoms.

the molecules residing directly above and below each other, does not indicate any close intermolecular interactions which could enforce one helical conformation. Thus, we attribute formation of one helical diastereomer to the chirality of the proline substituent and plan to investigate whether such a preference is maintained when the proline is replaced by noncyclic amino acids.

An acetonitrile molecule from the solvent of crystallization resides in the bowl shaped cavity. The methyl group of the acetonitrile is positioned down into the cavity and shows a favorable C-H—π aryl interaction with a C_{methyl}-centroid distance of 3.57 Å and a $C_{N,methyl}$ -C_{methyl}-centroid angle of 112.6° [15].

In contrast to **1**, the morpholine substituents on the *C*-phenylcalix[4]resorcinarene **2**, are all aligned upward and parallel with the calixarene cavity (Figure 2). Compound **2** is formed by addition of morpholine and paraformaldehyde to an ethanol suspension of *C*-phenylcalix[4]resorcinarene (Equation 2). Compound **2** crystallizes as a racemic mixture of the clockwise and anticlockwise helical enantiomers as evidenced by the centrosymmetric space group [7]. The helical chirality of **2** appears to be a consequence of the network of hydrogen bonds that exist between phenoxy oxygen and amino nitrogen atoms (O-H $\cdots$ N distance of 1.33 Å, angle 163°). The hydrogen atom is shared almost equally by the oxygen and nitrogen atoms (O$\cdots$N distance of 2.58 Å). These hydrogen bonds stabilize the morpholine moieties above the calixarene rim and parallel to the cavity [16]. An additional set of hydrogen bonds between phenoxy oxygen atoms (O-H $\cdots$ O distance of 1.76 Å, angle 132°) encircle the upper rim of the bowl and promote cavity stability. The hydrogen bonding capability of **2** does not exist in **1** due to methylene linkages between the oxygens on the phenyl rings of **1**. Consequently, the proline moieties of **1** are not stabilized parallel to

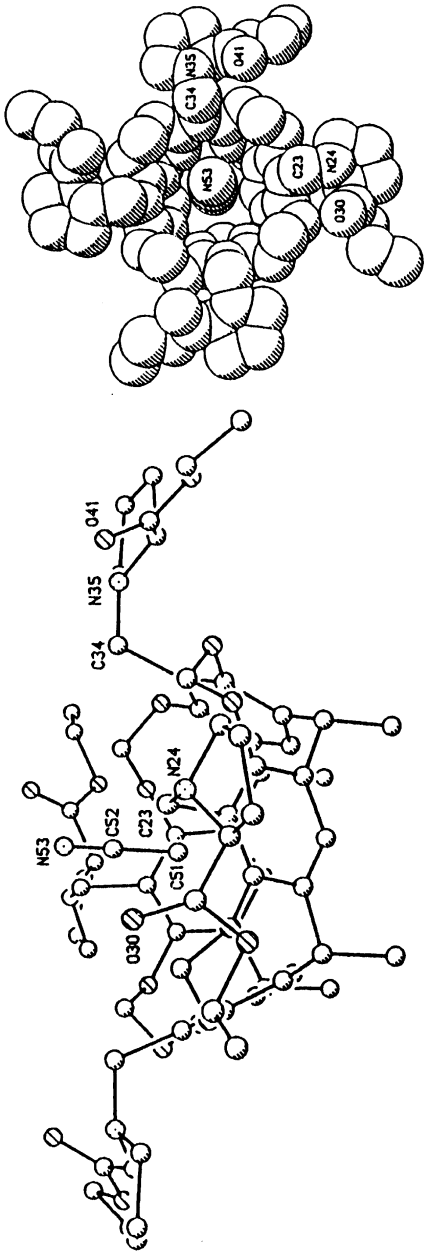


Figure 1. Side and top (space filling) views of the molecular structure of **1** showing the prolines positioned perpendicular to the calix[4]resorcinarene cavity in a clockwise arrangement and the acetonitrile molecule positioned in the cavity.

Table III. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients (Å $\times 10^3$) for **2**

Atom	x	y	z	U(eq)
O(1)	3242(11)	−558(13)	2895(5)	147(9)
C(2)	3276(13)	42(14)	3252(8)	138(12)
C(3)	2524(12)	143(11)	3557(5)	93(8)
N(4)	2342(7)	−581(8)	3823(4)	68(5)
C(5)	2297(10)	−1257(12)	3467(6)	114(9)
C(6)	3064(13)	−1269(16)	3142(8)	141(13)
C(7)	1611(9)	−481(10)	4144(6)	89(7)
C(8)	1764(7)	17(7)	4622(4)	41(4)
C(9)	1142(7)	495(7)	4809(4)	40(4)
O(9)	408(5)	471(5)	4563(3)	55(3)
C(10)	1251(6)	957(6)	5257(4)	34(4)
C(11)	546(6)	1450(7)	5494(4)	35(4)
C(12)	483(7)	1387(7)	6067(4)	40(4)
C(13)	706(8)	668(8)	6324(4)	54(5)
C(14)	599(10)	575(9)	6839(4)	65(6)
C(15)	221(10)	1184(11)	7120(6)	84(7)
C(16)	−18(9)	1905(10)	6870(5)	72(6)
C(17)	101(8)	1996(8)	6362(5)	54(5)
C(18)	512(6)	2316(7)	5271(4)	34(4)
C(19)	12(7)	2472(8)	4857(4)	41(4)
O(19)	−473(5)	1862(5)	4669(3)	66(4)
C(20)	2043(6)	963(6)	5468(4)	35(4)
C(30)	2500	2500	1702(14)	157(17)
O(31)	2500	2500	2253(8)	140(9)
O(32)	7500	2500	240(10)	196(26)
O(33)	7500	7500	647(15)	335(26)

* Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

the calixarene cavity and are allowed to position themselves perpendicular to the cavity. Although a methanol molecule and two water molecules are associated with a molecule of **2**, they were not found within the cavity. The molecular packing diagram of **2** reveals columns of molecules with each column having its morpholine moieties facing the same direction but in the opposite direction to adjacent columns of molecules.

After observing the different solid state conformations for **1** and **2** we questioned whether these static conformations are retained in solution. Broad reso-

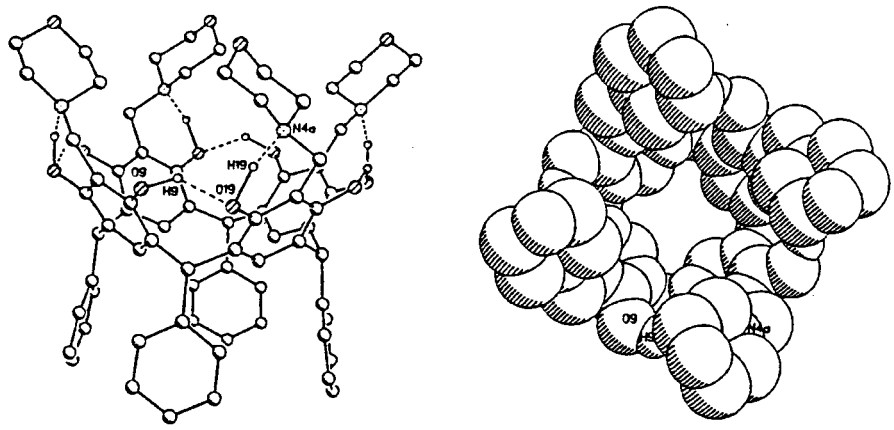


Figure 2. Side and top (space filling) views of the molecular structure of **2** showing the morpholines positioned parallel to the calix[4]resorcinarene cavity and bound by a network of hydrogen bonds. (Methanol and water molecules removed for clarity.)

nances were observed for the methylene hydrogens of the morpholine and benzyl groups in the ^{1}H NMR spectra of **2** in $CDCl_3$ and C_6D_6 at 20 °C. This was in contrast to the sharper and more defined signals observed in the ^{1}H NMR spectrum of **2** in DMSO-d_6. Upon cooling **2** in $CDCl_3$ to −30 °C, the broad resonance for the benzylic hydrogens became an AB system. Similarly, the signals attributed to the four morpholine ring methylene hydrogens alpha to the nitrogen, resolved into four distinct doublets. This increase in spectral clarity suggests the morpholine moiety is no longer freely rotating and the hydrogen atoms on the morpholine ring are in different environments. Also upon cooling, the broad signal attributed to the resorcinol hydrogen (OH) resolved into two sharp singlets. This is evidence that free rotation of the morpholine moiety occurs in polar solvents like DMSO and hindered rotation occurs in nonpolar solvents like $CHCl_3$ and benzene, while a locked conformation exists in non polar solvents at low temperature. The low temperature solution NMR spectra of **2** are consistent with the static conformation observed in the solid state and that **2**, under certain conditions, may retain helical chirality in solution.

Due to the inherent chirality of **1**, hindered rotation of the proline moiety about the benzylic carbon cannot easily be determined. Indeed, one helical diastereomer of **1** may predominate in solution but this is difficult to discern, due to the chirality of the proline moiety which causes the benzyl and other hydrogens to be chemically inequivalent. The benzyl hydrogens maintained an AB coupling pattern at high temperature (70 °C, toluene-d_8; 105 °C, DMSO-d_6). However, there are spectral changes upon heating and cooling. The broad peaks observed at 20 °C for the methyl and methylene hydrogens of the ethyl ester substituent ($CDCl_3$, toluene-d_8, and DMSO-d_6) were resolved into multiplets. Upon cooling **1** in $CDCl_3$ or toluene-d_8 to −50 °C, the methyl and methylene peaks broadened and moved downfield by

0.5 ppm from their position at 20 °C. Thus, at low temperature the ethyl substituent of the ester group resides in an environment of less electron shielding.

The synthesis and structural characterization of **1** demonstrates that calixarene molecules may be easily functionalized with amino acids which do not merely extend the physical size of the cavity but provide a secondary structure and shape which is expected to enhance the selectivity of host-guest interactions. Compound **2** illustrates how helical chirality exists in the solid state and at low temperatures in solution. This implies that solvent and temperature must be considered to achieve effective chiral recognition with calixarenes which posses chirality by virtue of a suitable arrangement of achiral groups. Studies on the chiral recognition properties of these molecules have been initiated.

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