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X-ray structures of 1:1 complexes of (L)-menthol with β-cyclodextrin and permethylated β-cyclodextrin

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Inclusion complexes of (L)-menthol with β-cyclodextrin and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB) have been crystallised and their structures determined by single crystal X-ray diffraction methods. The menthol-β-cyclodextrin complex crystallises in the monoclinic system, space group $P2_1$, Z = 4, D_x = 1.380 g cm^{-3}, a = 15.342(3) Å, b = 32.54(2) Å, c = 15.324(3) Å and β = 102.44(2)°. The structure was solved by isomorphous replacement and was refined to a final R-value of 0.108 for 5469 observed reflections. This is a dimeric β-cyclodextrin complex which packs in screw channel mode and the guest is oriented differently in the two crystallographically independent host molecules. The menthol-TRIMEB complex crystallises in the orthorhombic system, space group $P2_12_12_1$, Z = 4, D_x = 1.256 g cm^{-3}, a = 11.060(3) Å, b = 26.138(6) Å and c = 29.669(6) Å. The structure was solved by direct methods and refined to a final R-value of 0.105 for 4387 observed reflections. In contrast to what was found for the menthol-β-cyclodextrin complex, the hydroxyl group of the menthol molecule is located within the cavity of the TRIMEB molecule, and although the crystal packing is different from that observed in other TRIMEB complexes, the host adopts a similar conformation.

INTRODUCTION

(L)-menthol ((1α,2β,5α)-5-methyl-2-(1-methylethyl)-cyclohexanol) has long been known to form inclusion complexes with the cyclodextrins.[1] More recently, a patent was taken out for the preparation of a menthol-β-cyclodextrin inclusion complex for use as an inhalant in the treatment of respiratory ailments.[2] There are only a few studies for which the nature of inclusion of the same guest in different β-cyclodextrin hosts has been elucidated.[3–7] We report here the preparation and X-ray structures of inclusion complexes of (L)-menthol with β-cyclodextrin and with heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB).

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RESULTS AND DISCUSSION

Carbon and hydrogen microanalysis

The results of the microanalyses are given in Table 1, together with the calculated values for 1:1 ratios of the respective host to guest. The calculated values for the complexes include water molecules of crystallisation based on weight losses obtained by thermogravimetric analysis. Detailed thermoanalytical data for these complexes, as well as the menthol complex with heptakis(2,6-di-O-methyl)-β-cyclodextrin, will be published elsewhere.[8]

Crystal and molecular structures

Figure 1 shows the numbering scheme for the guest. Numbering schemes for the host molecules are the same as those in the (R)-fenoprofen-β-cyclodextrin complex[9] and the p-iodophenol-TRIMEB complex.[10]

Figure 2 shows a stereodiagram of the (L)-menthol-β-cyclodextrin complex in which the glucose residues in the two independent host molecules have been labelled. All seven glucose residues of each cyclodextrin molecule are in the $^4C_1$ chair conformation. Atom O(246) is disordered over two sites with site occupancies of 0.6

TABLE 1 C, H elemental analysis results.

	Calculated		Experimental	
	C	H	C	H
Menthol:β-CD:H_2O (2:2:29)	40.23	7.73	40.49	7.50
Menthol:TRIMEB:H_2O (1:1:2)	54.06	8.45	54.32	8.41

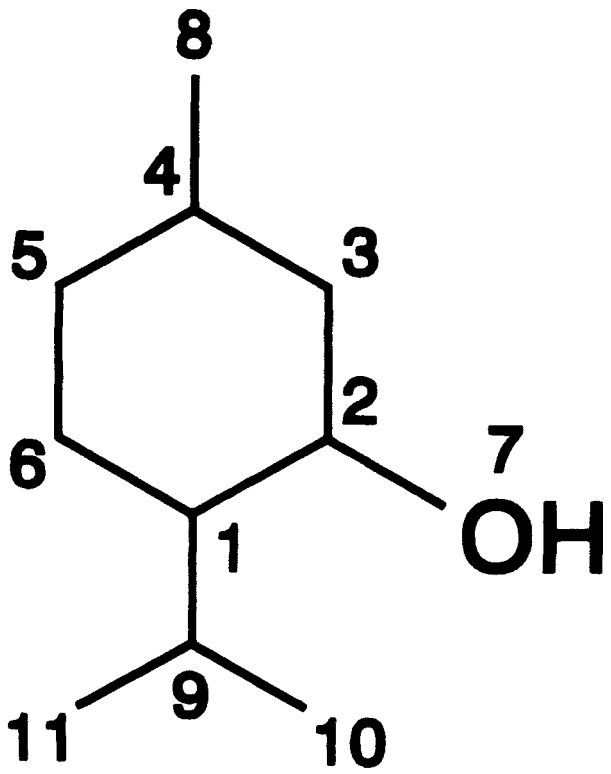

Figure 1 Numbering scheme for the guest.

and 0.4. The C(6)—O(6) bonds are all in the (−)-*gauche* conformation,[11] except in G2 of cyclodextrin 1 and G4 in cyclodextrin 2, where they are in the (+)-*gauche* conformation.

As is the case in the majority of β-cyclodextrin complexes, two host molecules form a head-to-head dimer stabilised by hydrogen bonding.[12] The guest molecules are oriented differently in the cavities of the two crystallographically independent cyclodextrin molecules comprising the dimer. This type of head-to-tail orientation of guest molecules has also been observed in the phenobarbital, racemic fenoprofen and (S)-fenoprofen complexes with β-cyclodextrin.[9,13,14] Both menthol molecules have their hydroxyl and isopropyl substituents protruding from, and their methyl substituents buried in, the cavities of their respective host molecules. However, one protrudes from the primary hydroxyl side and the other from the secondary hydroxyl side of its host (Fig 2). This results in the unusual situation where the hydroxyl group of a guest molecule is found at the interface of the cyclodextrin dimer. Furthermore, this hydroxyl group is not within hydrogen bonding distance of the cyclodextrin secondary hydroxyl groups or any of the water molecules. The hydroxyl group of the other menthol molecule is within hydrogen bonding distance of a water molecule. The guest molecules are therefore held in the cyclodextrin cavities by hydrophobic forces alone.

Thermogravimetric analysis of the complex gave a weight loss which corresponds to approximately 29 water molecules per dimer complex unit.[8] In addition, the C, H microanalysis results are within 0.3% of the calculated values for a 2:2:29 menthol:β-cyclodextrin:water complex and the measured density of the complex, 1.37(1) g cm^{-3}, gives 27.73 ± 1.25 water molecules per 2:2 menthol:β-cyclodextrin complex unit. Only 22.5 of the 29 water molecules were placed owing to extensive disorder. Sixteen of these were ordered and the remaining 6.5 water molecules were disordered over 11 sites. No water molecules were found to occupy positions within the hydrophobic cavity, even at the dimeric interface. A statistical analysis of high-resolution neutron crystal structures of cyclodextrin complexes by Steiner and Saenger[15] has shown that all O...O contact distances of 3.0 Å and less (table of values deposited) are actually associated with hydrogen bonds. Figure 3 is a stereo packing diagram which shows how the complex packs in screw channel mode[12] along the b-axis.

Figure 4 shows a stereodiagram of the (L)-menthol-TRIMEB complex. All seven methylglucose moieties of the TRIMEB molecule are in the $^4C_1$ chair conformation. Atom C(8G2) is disordered over two sites with site occupancies of 0.6 and 0.4. Bond lengths are within the e.s.d.s of those reported for other cyclodextrin complexes, except for O(2G1)–C(7G1) and C(5G4)–C(6G4)

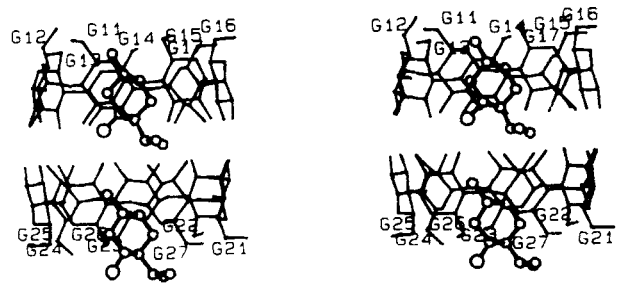

Figure 2 Stereodiagram of the (L)-menthol-β-cyclodextrin complex. Water molecules have been omitted.

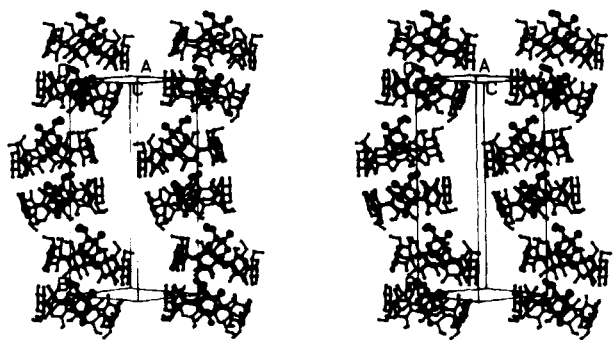

Figure 3 Stereo packing diagram of the (L)-menthol-β-cyclodextrin complex viewed perpendicular to the b-axis. Water molecules have been omitted.

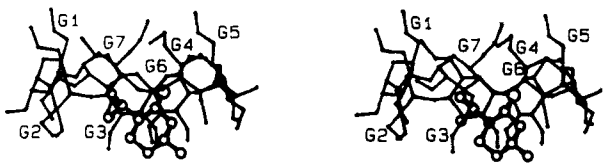

Figure 4 Stereodiagram of the (L)-menthol-TRIMEB complex. Water molecules have been omitted.

(1.31(1) and 1.68(2) Å, respectively). This is probably due to residual disorder which was not modelled. The C(6)–O(6) bonds are in the (−)-*gauche* conformation, except in G4 and G5, where they have the (+)-*gauche* conformation. All O(6)–C(9) bonds are *trans* to the corresponding C(5)–C(6) bonds, except in G4 and G6, where the relationship is *gauche*. As usual, the TRIMEB molecule is cup-shaped with the O(6)–C(9) groups of G1, G2, G4, G5 and G7 almost completely closing off the O(6) side of the TRIMEB molecule.

In contrast to the inclusion of menthol by β-cyclodextrin, the menthol molecule here has its hydroxyl and isopropyl substituents buried in the cup-shaped TRIMEB cavity with its methyl substituent protruding from the O(2), O(3) face. The hydroxyl group is not within hydrogen bonding distance of any of the O(4) atoms of the TRIMEB molecule. The fact that this group is found buried in the cavity, instead of protruding from the O(2), O(3) face of the host (where it could form a hydrogen bond with an O(2) or O(3) atom) is further evidence that the extent of hydrophobic host-guest interactions is sufficient for complex stabilisation with menthol as guest.

Thermogravimetric analysis gave a weight loss which corresponds to two water molecules per 1:1 complex unit.[8] These water molecules were located in the X-ray analysis and although their temperature factors were rather high, were refined with full site occupancy as there were no indications for any alternative positions. The water molecules are situated at the periphery of the cyclodextrin molecule and fill the intermolecular space between complex units. Close O...O contacts for these water molecules and parameters for a C-H...O(1W) hydrogen bond are given in Table 2.[16]

The conformation of the TRIMEB molecule is stabilised by six intramolecular C-H...O hydrogen bonds,[17] five of the type $C(6G_n)$-H...$O(5G_{n-1})$. We have previously found that these hydrogen bonds also exist in the (S)-naproxen-TRIMEB complex and in TRIMEB monohydrate.[18,19] Calculation of the $C(6G_n)$...$O(5G_{n-1})$ distances in other TRIMEB complexes shows that five of them are less than 3.4 Å. Table 2 also lists these interactions. Figure 5 shows a stereo packing diagram for the (L)-menthol-TRIMEB complex. Complex units stack in head-to-tail mode, forming what appear to be continuous channels along the a-axis. However, a space-filling diagram of the host shows that the O(6)–C(9) methoxy groups almost completely block off the O(6) side of the molecule and therefore the packing is more accurately described as cage-type packing. This packing arrangement is different from those observed thus far in TRIMEB complexes. All but one of the complexes published to date pack in 'screw channel' mode along the b-axis.[4,10,18,20,21] The exception to these is the m-iodophenol (MIP) complex, where the axis of the TRIMEB molecule makes an angle of 26.2° with the b-axis, resulting in a cage-type packing arrangement.[21] One of the methylglucose residues of the host in this complex is in the $^0S_2$ twist boat conformation, but apart from this, the authors found that the TRIMEB conformation was very similar to that in the 4-biphenylacetic acid complex.[21] In the present complex, the a-axis direction corresponds with the direction of the b-axes in all the other complexes. Because the cell length a is much shorter than the cell length b in the other complexes, only one cyclodextrin molecule is accommodated per unit cell in this direction. This means that the columns of complex units along this axis are related by

TABLE 2 O...O contacts less than 3.0 Å and C-H...O hydrogen bonds in the menthol-TRIMEB complex.

O	O	Distance (Å)	Symmetry operation		
O(1W)	O(3G5)	2.71(2)	−x + 1,	y + 1/2,	−z + 1/2
O(1W)	O(2W)	2.93(3)	x − 1,	y,	z
O(2W)	O(3G2)	2.62(2)	x + 1/2,	−y − 1/2,	−z
O(2W)	O(6G2)	2.87(2)	x + 1,	y + 1,	z

			Distance (Å)		Angle (°)
C H	O	C...O	C-H	H...O	C-H...O
C(1G2)–H(1G2)	O(1W) (a)	3.18(3)	0.98	2.43	132.8
C(6G1)–H(612)	O(5G7)	3.17(2)	0.97	2.36	140.3
C(6G2)–H(622)	O(5G1)	3.17(2)	0.97	2.41	133.9
C(6G3)–H(632)	O(5G2)	3.22(1)	0.97	2.58	122.9
C(6G5)–H(651)	O(5G4)	3.16(1)	0.97	2.28	149.7
C(6G6)–H(662)	O(5G5)	3.12(1)	0.97	2.42	128.7
C(1G6)–H(1G6)	O(3G7)	3.06(2)	0.98	2.39	125.3
	(a)	x, y − 1,	z		

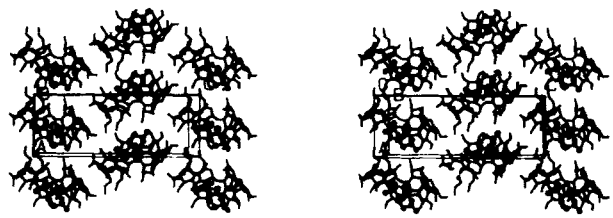

Figure 5 Stereo packing diagram of the (L)-menthol-TRIMEB complex viewed down the b-axis. Water molecules have been omitted. Molecules related by the twofold screw axis parallel to the a-axis have also been omitted for clarity.

a unit cell translation rather than by a two-fold screw axis as in the other complexes.

Despite the reported occurrence of three different packing arrangements and a range of very different guests, the TRIMEB molecule has a remarkably similar conformation in all of these complexes, the major differences lying in the different conformations of the O(6)–C(9) methoxy groups which determine the relative extent to which the O(6) side of the molecule is closed off. The comparison of the tilt-angles of the methylglucose residues in the three different packing arrangements shows the similarity in the conformations of the TRIMEB molecule (Table 3).

The conformation of the TRIMEB molecule observed in its inclusion complexes thus appears to be a preferred one which is independent of guest or crystal packing, although the latter two factors could induce small local conformational differences. It therefore seems reasonable to conclude that the C(6G_n)-H...O(5G_{n-1}) hydrogen bonding, which invariably occurs in TRIMEB complexes, plays an important role in stabilising the conformation of this host molecule in the solid state, in much the same way as the O(2)...O(3) hydrogen bonding does in the parent cyclodextrin.

The conformation of the TRIMEB molecule in TRIMEB monohydrate is much more distorted than in its complexes (one methylglucose residue adopting a $^1C_4$ conformation), yet the overall trend in the tilt angles is comparable with those in the complexes (Table 3). We have attributed this distorted conformation, characterised by very large tilt angles, to an attempt to minimise the hydrophobic cavity size in the absence of a guest molecule in order to achieve more efficient packing.[19] It is possible that an additional factor causing such large tilt angles is the maintenance of the C(6G_n)-H...O(5G_{n-1}) hydrogen bonding.

In conclusion, the variety of orientations adopted by the (L)-menthol molecule in the cavities of the host molecules, as well as the unusually passive role of the guest hydroxyl group, emphasise the true clathrate nature of the title complexes.

TABLE 3 Tilt angles (°) for the methylglucose residues in the three different packing arrangements of TRIMEB complexes and in TRIMEB monohydrate.

	PIP[a]	MIP[b]	MENTH[c]	TRIMEB[d]
G1	28.6 ± 1.5	27.7	26.5	38.0
G2	17.3 ± 1.9	13.3	10.2	21.0
G3	−12.1 ± 1.1	−6.1	−7.4	−4.6
G4	43.6 ± 0.4	45.2	47.7	72.9
G5	35.3 ± 0.9	28.3	25.1	57.3
G6	−14.5 ± 0.7	−13.6	−9.3	−24.5
G7	39.4 ± 3.1	51.7	46.5	24.7

[a]p-iodophenol-TRIMEB complex. The values quoted are the averages with mean deviations for this complex together with four isomorphous complexes.[4,10,18,21]
[b]m-iodophenol-TRIMEB complex.[21]
[c]menthol-TRIMEB complex
[d]TRIMEB monohydrate.[19]

EXPERIMENTAL

Materials

β-cyclodextrin (Sigma, U.S.A), TRIMEB (Cyclolab, Hungary) and (L)-menthol (Sigma, U.S.A.) were used as received.

Preparation of the complexes

Crystals of the menthol-β-cyclodextrin complex, which are colourless and prismatic, were grown by stirring β-cyclodextrin and menthol in a 1:1.8 molar ratio in distilled water at approximately 60°C and leaving at room temperature for 7–14 days. Crystals of the menthol-TRIMEB complex crystallised as colourless needles at approximately 40°C by slow evaporation over 10 weeks of an aqueous solution made by stirring TRIMEB and menthol in a 1:1 molar ratio in distilled water at room temperature.

Carbon and hydrogen microanalysis

C,H elemental analyses were performed in duplicate on a Carlo Erba Elemental Analyser Model 1106.

Crystal structure solutions

Menthol-β-cyclodextrin complex

Crystals of this species were very unstable, developing cracks immediately on removal from mother liquor. A single crystal of dimensions 0.35 × 0.45 × 0.55 mm was mounted in a Lindemann capillary which had been filled with quick-setting cyanoacrylate glue. Intensity data were collected at room temperature (298K) on an Enraf-Nonius CAD-4 diffractometer using MoKα radiation (λ = 0.71069 Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range 16° ≤ θ ≤ 17°. A final intensity acceptance limit of 20σ at 20°/min in ω was used with a maximum recording time of 40s per reflection. Data were collected by the ω-2θ scan technique to $(\sin\theta/\lambda)_{max}$ = 0.595 $Å^{-1}$. Three standard reflections (6 −15 6; −2 −15

10; −1 −26 −1), which were monitored every hour, showed an 8% decrease in intensity during data collection and a linear decay correction was applied. Orientation control was performed every 200 reflections and data were corrected for Lp effects. The structure was solved using published co-ordinates for the non-hydrogen cyclodextrin atoms (excluding the primary hydroxyl oxygen atoms) of the isomorphous (R)-fenoprofen-β-cyclodextrin complex.[9] The y-coordinate of atom C(111) was fixed and a difference Fourier synthesis after refinement by full-matrix least-squares techniques[22] revealed the remaining non-hydrogen atoms of the host. All the non-hydrogen atoms of the two guest molecules were located in subsequent difference Fourier maps during refinement by the block-diagonal least-squares method. Subsequent refinement yielded abnormal bond lengths and angles for the guest molecules and therefore the two menthol molecules were refined as rigid bodies with C—C = 1.54, C—O = 1.44, C...C = 2.52 and C...O = 2.43 Å (σ = 0.01 Å). At this stage, the temperature factors of the guest atoms which had previously been refined were fixed, with those higher than 0.20 Å^2 being fixed at 0.20 Å^2. Water molecules were then located and the site occupancies of those with either abnormally high temperature factors or closer than 2.6 Å from other water molecules were refined. All hydrogen atoms attached to carbon atoms of both host molecules were inserted at idealised positions with C—H = 1.00 Å. The hydrogen atoms of each independent host molecule were assigned common fixed isotropic temperature factors.

Menthol-TRIMEB complex

Data were collected at −25° C (248 K) from a crystal of dimensions 0.5 × 0.5 × 0.5 mm, mounted without mother liquor in a Lindemann capillary, on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.71069 Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range 16° ≤ θ ≤ 17°. Intensity data were collected by the ω-scan technique to $(\sin\theta/\lambda)_{max}$ = 0.595 Å^{-1} and to ensure accurate measurement of weak reflections, a pre-scan acceptance parameter of zero was chosen to force their final intensity scans up to a maximum time of 100s per reflection. Three standard reflections (2,9,20;8,8,4;7,11,6), which were monitored every 3 hours, showed no significant decrease in intensity during data collection. Orientation control was performed every 200 reflections and data were corrected for Lp effects. The structure was solved by direct methods using program SHELX86.[23] Most of the non-hydrogen atoms of the host and all of the non-hydrogen atoms of the guest were located in the resultant E-map. After refinement by full-matrix least-squares techniques,[24] a difference Fourier map revealed the remaining non-hydrogen atoms of the host. Two water molecules were located in subsequent difference Fourier maps. Hydrogen atoms linked to carbons of both host and guest were inserted at idealised positions with C—H = 1.00 Å, provided that the relevant carbon atom was not disordered. Abnormally high temperature factors for several of the O(6)—C(9) groups indicated disorder. However, attempts at modelling disorder for these groups did not result in any significant improvement and therefore only one position with full site occupancy for each of these atoms was retained. Anisotropic temperature factors were then assigned to all the non-hydrogen atoms, excluding those which were disordered and those for which anisotropic refinement resulted in unsatisfactory thermal parameters. The hydrogen atoms of each methylglucose residue and those of the guest molecule were assigned common variable isotropic temperature factors. The hydrogen atoms of the water molecules and of the hydroxyl group of the menthol molecule were not located.

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REFERENCES

1 Bavley, A. and Robb, E. W. **Chemical Abstracts 1962**, **57**, 17091.
2 Koczka, G.; Hung, A. **Chemical Abstracts 1992**, **117**, 448.
3 Uekama, K.; Hirayama, F.; Imai, T.; Otagiti, M.; Harata, K. **Chem. Pharm. Bull. 1983**, **31**, 3363.
4 Harata, K.; Uekama, K.; Imai, T.; Hirayama, F.; Otagiri, M. **J. Incl. Phenom. 1988**, **6**, 443.
5 Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. **J. Incl. Phenom. 1984**, **1**, 279.
6 Harata, K.; Hirayama, F.; Uekama, K.; Tsoucaris, G. **Chem. Lett. 1988**, 1585.
7 Harata, K. **Bull. Chem. Soc. Jpn. 1988**, **61**, 1939.
8 Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R., in preparation.
9 Hamilton J. A. and Chen L. **J. Am. Chem. Soc. 1988**, **110**, 4379.
10 Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. **Bull. Chem. Soc. Jpn. 1983**, **56**, 1732.
11 Saenger, W. **Inclusion Compounds**, Volume 2, Chapter 8, London, Academic Press, edited by J. L. Atwood, J. E. D. Davies and D. D. MacNicol, **1984**.
12 Mentzafos, D.; Mavridis, I. M.; Le Bas, G.; Tsoucaris, G. **Acta Crystallog. 1991**, **B47**, 746.
13 Nakanishi, I.; Fujiwara, T.; Tomita, K. **Acta Crystallog. A 1984**, C78.
14 Hamilton, J. A.; Chen, L. **J. Am. Chem. Soc. 1988**, **110**, 5833.
15 Steiner, T.; Saenger, W. **Carb. Res. 1994**, **259**, 1.
16 Steiner, T.; Saenger, W. **J. Am. Chem. Soc. 1993**, **115**, 4540.
17 Steiner, T.; Saenger, W. **J. Am. Chem. Soc. 1992**, **114**, 10146.
18 Caira, M. R.; Griffith V. J.; Nassimbeni, L.R.; Van Oudtshoorn, B. **J. Incl. Phenom.**, **20**, 277, **1995**.

19 Caira, M. R.; Griffith V. J.; Nassimbeni, L.R.; Van Oudtshoorn, B. **J. Chem. Soc. Perkin Trans. 2 1994**, 2071.
20 Mentzafos, D.; Mavridis, I. M.; Schenk, H. **Carb. Res. 1994, 253**, 39.
21 Harata, K.; Hirayama, F.; Arima, H.; Uekama, K.; Miyaji, T. **J. Chem. Soc. Perkin Trans 2 1992**, 1159.
22 Sheldrick, G. M. **SHELX76**, Program for crystal structure determination, Univ. of Cambridge, England, **1976**.
23 Sheldrick, G. M. **Crystallographic Computing**, ed. G. M. Sheldrick, C. Kruger and R. Goddard, Oxford University Press, vol. 3, 175, **1985**.
24 Sheldrick, G. M. **J. Appl. Cryst.**, in preparation, **1993**.