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Characterization of Crystalline Complexes between Heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin and Various Alkanes or Alkenes ($5 \leq C \leq 10$) *

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Abstract

Crystallization, at room temperature under normal pressure, of heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB) in the presence of various hydrocarbons (*n*-pentane, *n*-hexane, cyclohexane, methylcyclohexane, (RS)-α-pinene, (S)-α-pinene and (R)-α-pinene) gave two series of isomorphous crystalline phases: Ua (metastable) and Ub (stable). In this study, the molar guest/host ratio is defined as the variable x. On the one hand, the experiments carried out in solution at high supersaturations led to the Ua phase, with $x < 1$ for linear alkanes (non-stoichiometric and efflorescent phases) and $x = 1$ for cyclic guests. On the other hand, by slow evaporation, the Ub phase obtained with cyclic components was stoichiometric ($x = 1$) and non-efflorescent; whereas the Ub phase with *n*-pentane and *n*-hexane as guests displayed efflorescent character and was non-stoichiometric ($x \approx 0.15$). Temperature-resolved X-ray powder diffraction allowed the irreversible transition from Ua to Ub to be observed. Following this thermal process and whatever the nature of the cyclic guest molecule, Ub was non-stoichiometric ($x \approx 0.7$ for methylcyclohexane); thus, x was significantly lower than that of the mother phase Ua with $x = 1$. This suggests a destructive-reconstructive solid-solid transition. The crystal structure solved at 120K of Ub obtained from solution, with methylcyclohexane, reveals that the guest molecule is totally buried within the cavity. The methylcyclohexane mean plane, defined by the C(2), C(3), C(5) and C(6) atoms, is 45° away from the pseudo seven-fold axis of the macrocycle. The methylcyclohexane molecule is disordered within the cavity, and its possible conformations were *twisted chair and twisted boat*. These results differ from the conformations reported by Rontoyianni *et al.*, *J. Incl. Phenom.* **32**, 415–428 (1998) for the structure of the same complex solved at 293K. Molecular simulations of *n*-alkane (C(5) and C(6)) movements along the *a* axis showed that the Ub phase structure can easily undergo a partial release of this linear alkane, due to the presence of channels in this structure. Comparison between solid state conformations observed for the TRIMEB molecule in its complexes does not support the notion of 'induced fit' in the inclusion process.

Introduction

Cyclodextrins have been extensively studied as molecular hosts for a variety of molecules. They are commonly used in many fields such as the pharmaceutical, food, cosmetic, and pesticide industries as well as in analytical chemistry [1]. Among the cyclodextrins, permethylated-β-cyclodextrin (TRIMEB hereafter) is known for its non-polar cavity and ability to bind organic molecules, both in solution [2, 3] and in the crystalline state [4, 5]. The shape and the internal diameter of the TRIMEB cavity as well as the size of the guest molecule, (i.e., the possibility of a good fit) are of primary importance in the formation of complexes. The present report is devoted to the characterization of host-guest crystalline complexes between the TRIMEB molecule and different alkanes or alkenes and to a better understanding of the inclusion mechanisms.

Experimental

Preparation of complexes

Native cyclodextrin was supplied by Roquette (Lestrem-France) under the reference βCD-633403. The permethylation was achieved according to the Schurig *et al.* procedure [6].

The degree of permethylation was checked by mass spectrometry (FAB^+, matrix magic bullet) and NMR: [MH^+] (m/z 1429), ^1H NMR (200 MHz, ppm, $CDCl_3$): 3.341 (s, 3H, OMe-6); 3.461 (s, 3H, OMe-2); 3.602 (s, 3H, OMe-3); 5.086 (d, 1H, H-1).

* Crystallographic data related to this article are deposited at The Cambridge Crystallographic Data Centre under reference 112114.

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In order to avoid a mixture of guest molecules included within the TRIMEB cavity, a combined preparation-purification process, specific for each guest molecule, was carried out. Complexes were purified by three consecutive recrystallizations of the TRIMEB molecule in a dichloromethane/alkane (*n*-pentane, *n*-hexane, cyclohexane and methylcyclohexane (MCH hereafter)) or alkene ((RS)-α-pinene, (S)-α-pinene and (R)-α-pinene) mixture (1/9, v/v) by slow evaporation at room temperature under atmospheric pressure (a few days for cyclic guests and weeks for *n*-alkane and (R)-α-pinene). This procedure led to the Ub phase.

Ua crystalline phases were obtained from Ub by the following procedure: (i) dissolution in CH_2Cl_2, (ii) precipitation by means of swift addition of alkanes or alkenes to the homogeneous solution.

The TRIMEB purity was monitored by HPLC using the Schomburg *et al.* procedure [7].

Analytical methods

Static headspace coupled with gas chromatography

In order to identify the guest molecule and to obtain a quantitative determination of the guest [8], a few milligrams of complex were placed in a sealed vial thermostated at 180 °C for 30 minutes until equilibrium was reached. An *aliquot* of the gas phase was transferred to an analytical column and analyzed using appropriate gas chromatographic conditions (10 minutes at 35 °C and an increase of temperature by steps of 5 °C per minute up to 160 °C). The quantitative method used in this work was Multiple Headspace Extraction with an external standard method for matrix effect elimination.

In this work, the guest/host molar ratio is expressed as x.

Water coulometric titration: Karl Fischer method

An automated apparatus (Metrohm 684 KF Coulometer) connected to a programmed oven was used. Water was released from samples under a constant flow of dry gas. In the absence of samples, the drift of this instrumentation was below 10 μg of water/min and the accuracy of a determination of 100 μg of water in a sample is $\pm$ 4%.

X-ray powder diffraction

X-ray powder diffraction (XRPD hereafter) patterns were recorded on a Siemens D5005 diffractometer (Cu Kα). Measurement control and data processing were carried out using the software package Diffract Plus (v 5.0) [9]. The scan step was 0.04° or 0.02°(2θ) and the 2θ range was 5°–25° with, respectively, a step time of 4s or 10s. Temperature-resolved XRPD were recorded in a TTK450 Anton Paar chamber, regulated via a specific program included in the Diffract Plus package. The temperature was given to within $\pm$ 0.15 °C.

Table 1. Crystal data and structure refinement for the TRIMEB/MCH complex

Formula	$C_{63}H_{112}O_{35}$, C_7H_{14}
Molecular weight	1527.7 g/mol
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a	11.043(4) Å
b	25.333(4) Å
c	29.132(2) Å
V	8150 (3) Å^3
Z	4
Calculated density	1.244 g/cm^3
F(000)	3304
μ(MoKα)	0.99 cm^{-1}
Temperature	120(2) K
Crystal size	0.36 × 0.28 × 0.25 mm
Radiation λ Kα	MoKα λ = 0.71073
Theta range for data collection	1.07 to 24.96 deg
Scan	$\omega/2\theta$
Refinement method	Full-matrix least-squares on F^2
T_{max} per reflection	60 s
Intensity variation of standards	0.4%
Index ranges	$0 \leq h \leq 12$, $0 \leq k \leq 30$, $0 \leq 1 \leq 34$
Reflections collected/unique	7786/7786
Data/restraints/parameters	7786/0/437
Final R (isotropic) [I > 2sigma(I)]	0.106
Rw (isotropic)	0.2031
Max and min residual electron density	0.631 and −0.442 e.Å^{-3}

Single crystal X-ray structure analysis and molecular modeling

Single crystals of complexes were obtained according to the procedure described in the preparation of complexes. A suitable single crystal of the TRIMEB/MCH complex was selected. The absence of mother liquor inclusion was carefully checked before intensity measurements. The crystal data of the TRIMEB/MCH complex were collected on an Enraf-Nonius CAD4 automatic diffractometer. Table 1 summarizes the crystallographic parameters, experimental conditions (120K) for data collection and refinement of the structure. All the calculations were performed on a Silicon Graphics Indy R4600 computer with the MolEN package (Enraf-Nonius, 1990 [10]) and SHELXL 93 [11]. All the hydrogen atoms have been located by calculation. Two molecular modeling software programs, SYBYL (v 6.3) [12] and CERIUS^2 (v 3.5) [13] implemented on a Silicon graphics (O_2) workstation were used.

Results and discussion

Study by XRPD of host–guest complexes in the solid state

Characterization of the Ub phase

Figure 1 depicts the XRPD patterns of the Ub phase with *n*-pentane, *n*-hexane, cyclohexane, methylcyclohexane, (RS)-α-pinene, and (S)-α-pinene obtained as described in the experimental section. Whatever the guest considered, the most intense peaks have been used to calculate (DICVOL91 program included in CERIUS^2 software [13]) the crystallographic parameters of the Ub phase.

Table 2 collects the crystallographic parameters at room temperature from XRPD pattern indexing and the x guest/host molar ratios of Ub phases after storage for several months at 20 °C under normal pressure. All crystallographic parameters are similar, whatever the guest included; nevertheless it appears that only cyclic alkanes or alkenes form stable stoichiometric host/guest complexes ($x = 1$). The use of a linear alkane leads to a non-stoichiometric complex ($x \approx 0.15$). This is consistent with the efflorescent character (destruction of the crystal) observed soon after the separation of the crystals from their mother liquor. A similar behavior has been reported for TRIMEB/*n*-alkanes phases with $6 \leq C \leq 16$ [14]. Periodic measurements of the composition have shown that the departure from the stoichiometry is due to a progressive release of linear alkane molecules. For the TRIMEB/*n*-pentane and TRIMEB/*n*-hexane complexes, it was not possible to assign some peaks of low intensities, nevertheless Ub phases were in large excess. The XRPD of the TRIMEB/(R)-α-pinene complex (not represented on Figure 1) shows a poor crystallinity but is isomorphous with the Ub phase.

In close-to-equilibrium conditions, crystallization of the TRIMEB/(RS)-α-pinene complex does not induce any chiral discrimination in the solid phase. Interestingly, a variation of the crystallization rate and crystallinity between complexes involving the guest molecules (R)-α-pinene, (S)-α-pinene and (RS)-α-pinene, can be observed.

Karl Fischer coulometric titrations performed on every complex revealed no significant quantities of water and showed no sign of hygroscopicity up to 70% of relative humidity at 20 °C.

All these results show that a systematic molar ratio $x = 1$ is observed for cyclic alkanes or alkenes prepared by crystallization from a solution. In contrast for the TRIMEB/*n*-alkane complexes the molar ratio x is consistent with a large departure from the stoichiometry resulting from the efflorescent character.

Characterization of the Ua phase

As described in the experimental section another TRIMEB/alkane or alkene series of isomorphous phases (Ua) was obtained. Figure 2 presents XRPD patterns of the Ua and Ub phases obtained with MCH. The crystallinity of the Ua phase is poorer than that of the Ub phase; this can explain why several attempts at unit cell determination and peak assignment for the Ua phases have failed.

Thermal behavior and stability

Starting from one of the Ua phases, temperature-resolved XRPD experiments have shown, as early as 80 °C (Figure 3), an irreversible transition from this Ua phase to the corresponding stable Ub phase.

A significant departure from 1/1 stoichiometry was observed ($x \approx 0.7$ of MCH instead of $x = 1$ for the Ua phase) in the composition of the resulting Ub phase. Therefore, the mechanism is likely to be of the destructive-reconstructive type. A similar transition appeared for the other complexes. This is in accordance with the higher stability of the Ub phase, regardless of the guest molecules tested in this study. Therefore, non-stoichiometric Ub phases can be prepared from Ua phases even if the guest molecule contains at least one ring.

Crystal structure of the TRlMEB/MCH complex and molecular modeling

A preliminary X-ray crystal structure determination was carried out at room temperature. The TRIMEB macrocycle was unambiguously located within the unit-cell but the electron density attributed to MCH carbon atoms, located inside the cyclodextrin cavity, was not clearly defined. Further investigations at 120K showed a slight densification of the electronic density peaks within the cavity. Nevertheless some doubts exist concerning the position and the conformation of the MCH molecule.

The poor accuracy for the MCH molecule led us to use molecular modeling tools to improve both the location and the geometry of the MCH. Partial charges were evaluated according to the Gasteiger-Marsili algorithm [15] and Charge Equilibration algorithm [16] with, respectively, SYBYL (v 6.4) [12] and CERIUS^2 (v 3.5) [13] software programs. The force fields used were Tripos and Dreiding 2.21. Initial atomic coordinates located inside the cavity were taken from the crystal structure. These coordinates were extracted from the main peaks observed in the Fourier map. The peak assignment from this map revealed one carbon atom in excess compared to the molecular formula of the guest molecule. This led us to postulate two different conformations (*chair* and *boat*) for the guest molecule. During the computation of energy minimization, the TRIMEB molecule was defined as a frozen aggregate with no degree of freedom in accordance with the well-defined atomic positions obtained from the crystal structure. These calculations gave two possible conformations: slightly *twisted chair* and slightly *twisted boat*. Starting from the two new sets of coordinates, further refinements were performed using a variable ratio between the guest conformations, without significant improvement of the isotropic R factor. Therefore, in addition to these two major conformations, many other slightly different conformations might exist within the cavity.

Whatever the selected set of final atomic coordinates, it appears that the TRIMEB/MCH complex exhibits a complete inclusion of the guest molecule within the macrocyclic cavity. Moreover, the seven methylglucose residues are in the $^4C_1$ chair conformation.

During the course of this study, the same structure has been reported at 293K [17]. The following features are observed between the two structures:

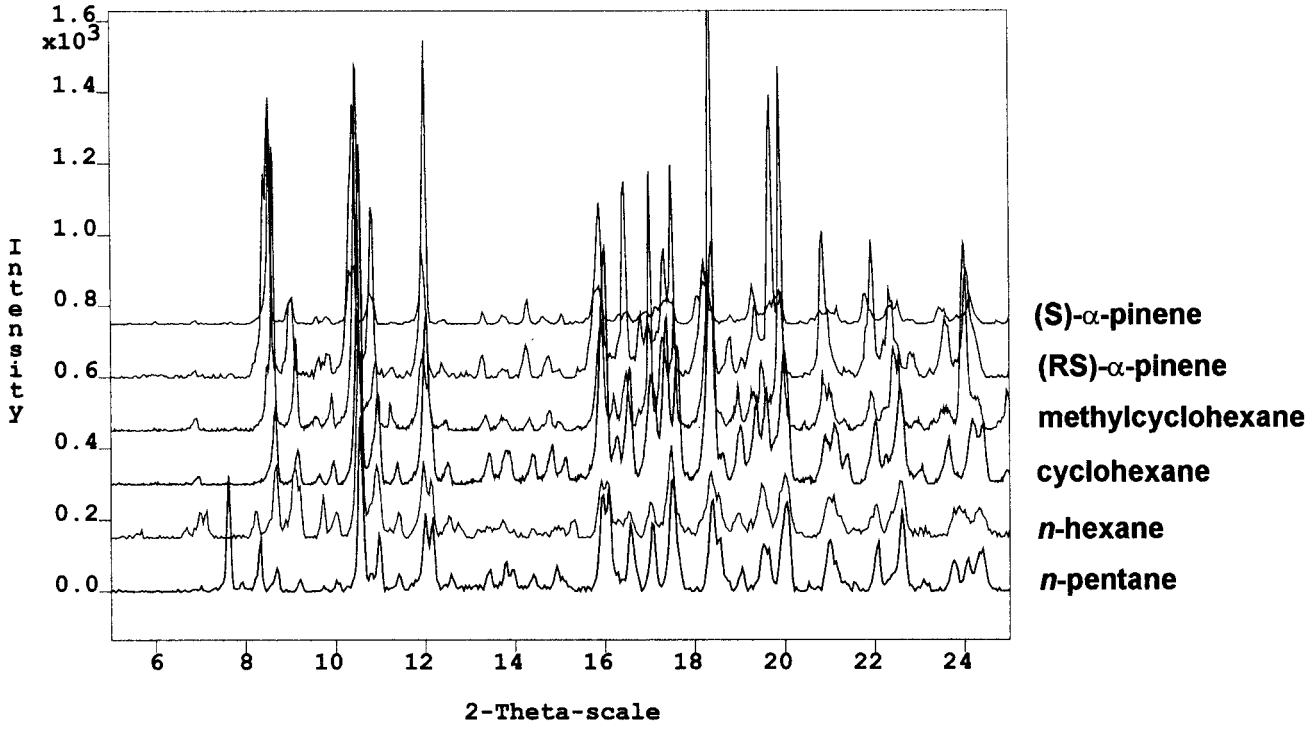

Figure 1. X-ray powder diffraction patterns of *n*-pentane, *n*-hexane, cyclohexane, methylcyclohexane, (RS)-α-pinene, and (S)-α-pinene.

Table 2. Crystallographic parameters from XRPD patterns at 293K and guest/host molar ratios determination of the Ub phase with the *n*-pentane, *n*-hexane, cyclohexane, methylcyclohexane, (RS)-α-pinene, and (S)-α-pinene.

Guest molecule	X	Crystallographic parameters (at room temperature, volumes are given at ± 100 Å^3)				M(15)
n-pentane	0.13–0.18	a = 11.11(6)Å	b = 25.6(1)Å	c = 29.2(1)Å	V = 8305Å^3	12
n-hexane	0.13–0.18	a = 11.09(6)Å	b = 25.8(1)Å	c = 29.2(1)Å	V = 8355Å^3	12
cyclohexane	1	a = 11.13(6)Å	b = 25.6(1)Å	c = 29.4(1)Å	V = 8377Å^3	14.7
methylcyclohexane	1	a = 11.18(6)Å	b = 25.7(1)Å	c = 29.3(1)Å	V = 8418Å^3	13.5
(RS)-α-pinene	1	a = 11.36(6)Å	b = 25.7(1)Å	c = 29.6(1)Å	V = 8642Å^3	10.9
(S)-α-pinene	1	a = 11.34(6)Å	b = 25.7(1)Å	c = 29.6(1)Å	V = 8626Å^3	11.5

- Small variations are observed in the unit cell dimensions in accordance with the difference in data collection temperatures.
- The macrocycle shapes (Figure 4), except for the methoxy groups, are very similar. Tilt angles are defined as the dihedral angles between the O(4) atom mean plane and the planes containing the C(4n), O(4n), C(1n) and O(4(n + 1)) atoms of the Gn glucosidic unit. The differences observed in tilt angle values at 120K and in [17] are less than 0.2°. Moreover, the Root Mean Square calculated with Sybyl software [12] (except for the methoxy groups and the guest molecule) is RMS = 0.016 for these two structures. Some minor discrepancies could result more from different interpretations in the fuzzy electronic density than from actual differences.
- At 120K no disorder is observed for the O(66) and C(96) atoms. In contrast, the O(63) atom is disordered over two positions *a* and *b* whatever the temperature. The C(93) atom exhibits a high-temperature agitation factor at 120K and two close positions at 293K.
- Two major differences appear in the number and the location of the MCH carbon atoms (Figures 5a and 5b):
  - From the structure measured at 293K, the authors [17] describe two independent *chair* conformations for MCH (Figure 5b), with the methyl group in the equatorial position, disordered over two positions (site occupancy factors 0.48 and 0.52).
  - The number of carbon atom positions, deduced from the electronic density map of the structure at 120K, is quite different (8 carbon atoms instead of 14 at 293K) and cannot support two chair conformations. As discussed earlier, these atomic positions might be interpreted by the existence of two MCH conformations (*twisted chair and twisted boat* with a possible site-occupancy factor, Figure 5a). This disorder cannot be derived from a simple dynamic conversion of the *twisted chair* into the *twisted boat* form as the same methyl equatorial position exists for both conformations. A static disorder can therefore be postulated.

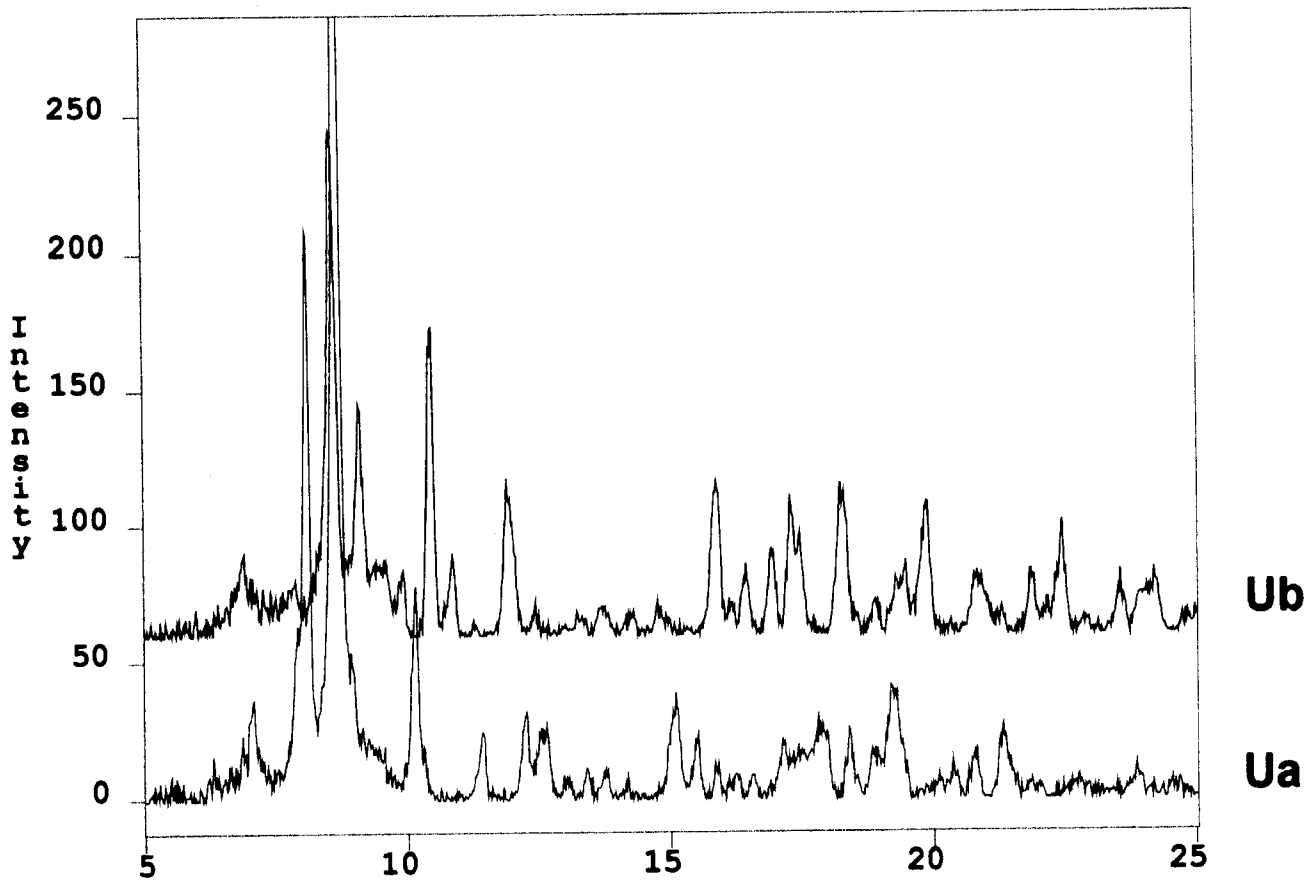

Figure 2. X-ray powder diffraction patterns of Ua and Ub phases of TRIMEB/MCH.

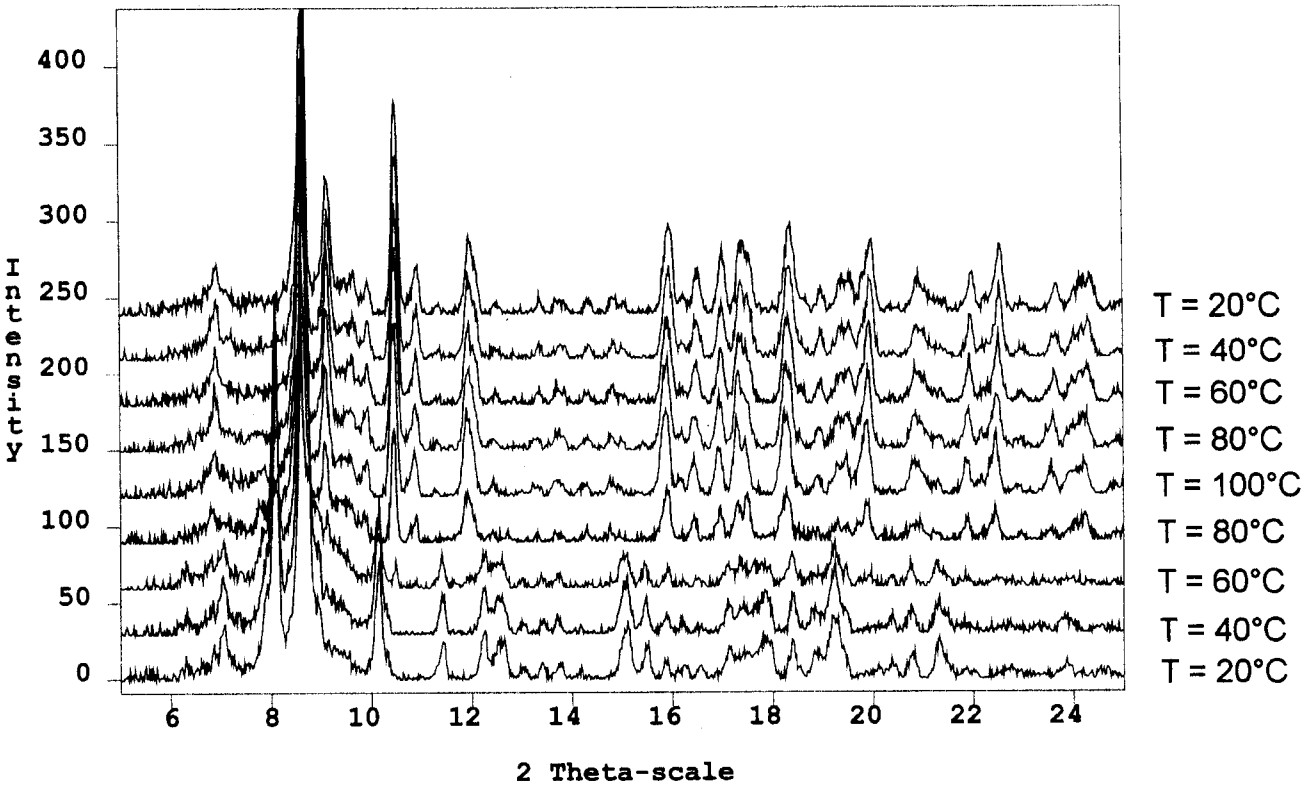

Figure 3. X-ray powder diffraction patterns of the Ua phase after temperature-resolved XPRD experiments from the TRIMEB/MCH complex.

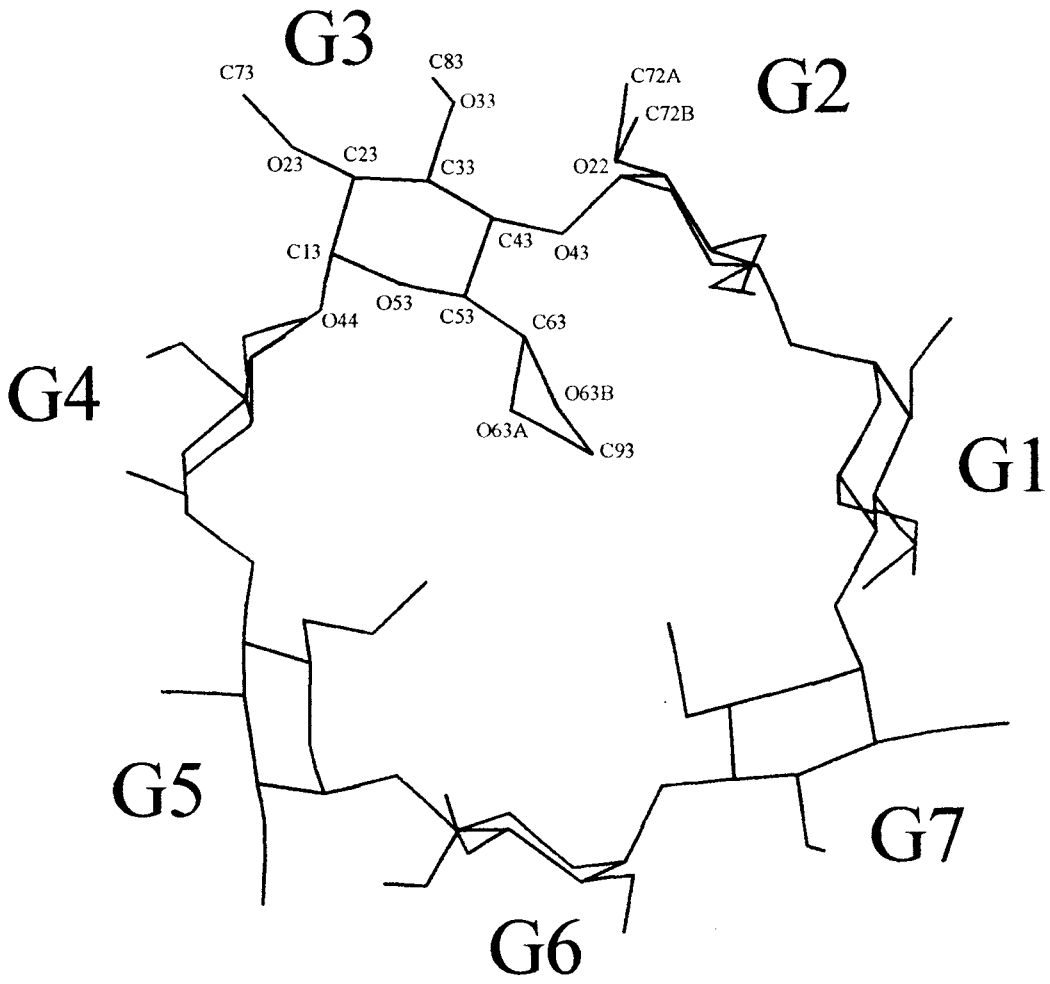

Figure 4. Atomic numbering scheme of a TRIMEB molecule in the TRIMEB/MCH complex. Guest molecule and hydrogen atoms are omitted.

Table 3. Tilt angles (°) of the complexes of TRIMEB

	Type of packing		Tilt angles (°)						
Guest		Refcode	G1	G2	G3	G4	G5	G6	G7
p-iodophenol [20]	Uc	CAMPIP	30.4	16.7	−12.7	43.0	34.9	−16.3	42.4
(S)-ibuprofen [21]	Uc	RONWOG	28.3	18.8	−11.2	41.9	33.3	−14.2	36.4
(S)-naproxen [22]	Uc	ZIFQOU	26.9	20.7	−9.3	44.3	34.5	−14.4	34.4
(S)-flurbiprofen [23]	Uc	COYXET20	26.5	18.6	−12.3	43.3	34.5	−14.3	36.6
(R)-flurbiprofen [23]	Uc	COYXAP10	30.2	14.5	−12.5	43.8	36.4	−12.9	42.2
4-biphenylacetic acid [24]	Uc	PAFSOE	28.2	15.8	−14.0	43.4	36.6	−14.5	41.3
ethyl laurate [25]	Uc	PINMAA	31.9	12.8	−14.0	37.9	35.8	−13.8	38.7
m-iodophenol [24]**	Uc	GELKEN10	27.8	13.2	6.0	46.6	28.3	−13.6	51.7
H_2O [26]		HEZWAK	37.9	21.0	−4.6	72.9	57.3	−24.5	24.7
L-menthol [19]*	Ub		26.5	10.2	7.4	47.7	25.1	−9.3	46.5
mehylcylohexane [17]†	Ub	[17]	15.7	6.0	51.7	8.9	24.8	8.4	40.1
methylcylohexane	Ub	This work	15.7	7.2	52.4	7.2	25.2	7.6	39.4
(R)12Hdi [18]	Ub	[18]	16.1	7.2	51.3	7.3	25.7	7.7	38.7

*Fractional coordinates transmitted by the authors, value published by Caira *et al.* [19] is −7.4 for G3.
**Value published by Harata *et al.* [24] is −6.0 for G3.
†Values published by Mentzafos *et al.* for the TRIMEB/ethyl laurate [25] are +33, +14, +13, +31, +27, +17 and +30.

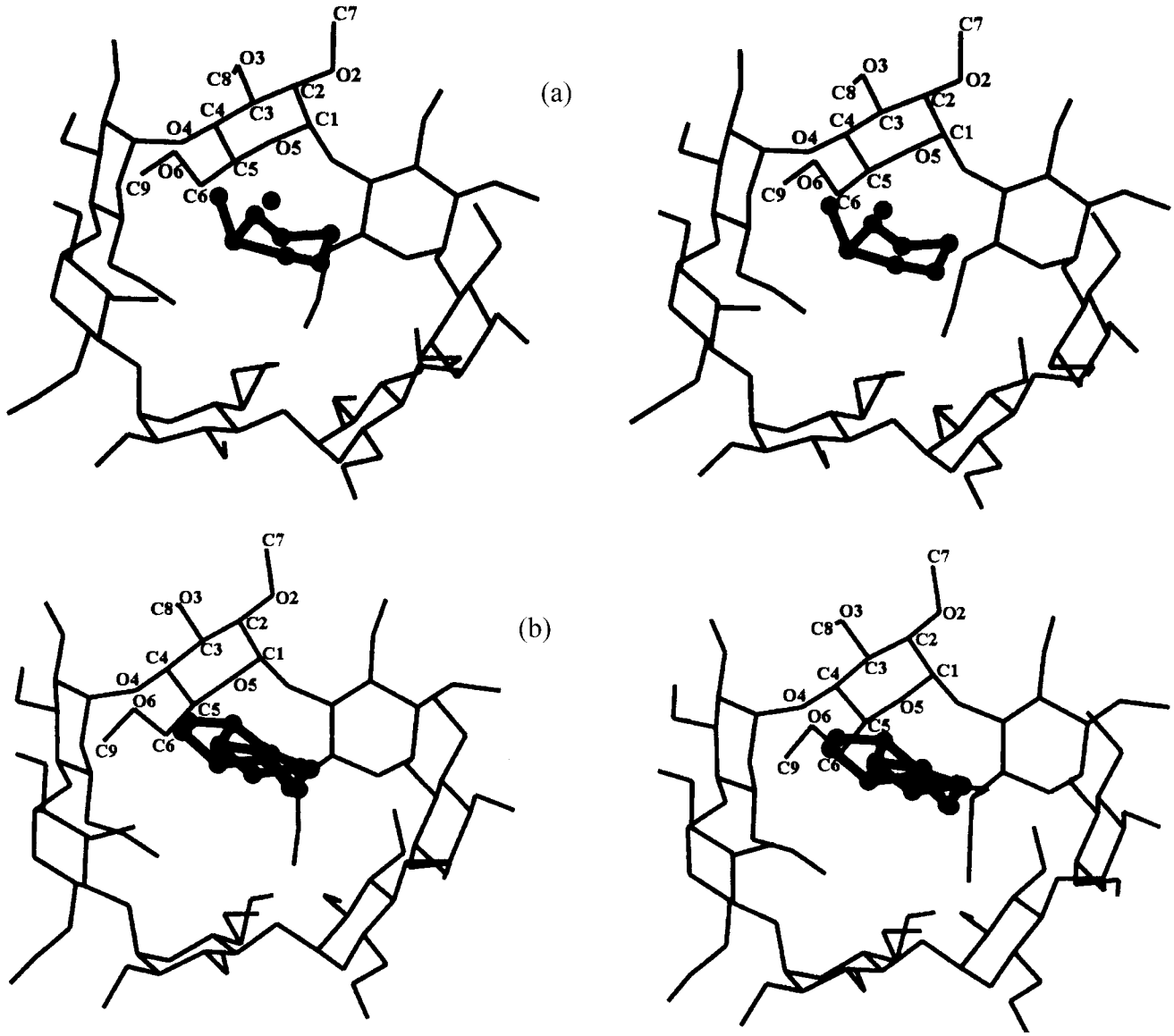

Figure 5. Stereo view of the TRIMEB/MCH complex from data measurement at 120K (a) and at 293K (b) [17].

Since the TRIMEB/MCH and TRIMEB/*n*-pentane structures are isomorphous, a molecular modeling study was performed using the TRIMEB/MCH data and replacing the MCH molecule by *n*-pentane. Figure 6 shows the stereo packing of the TRIMEB without MCH viewed down the *a* axis. The host molecule arrangement appears to form continuous channels along the *a* axis. Assuming that primary methoxy groups have sufficient degrees of freedom to open the bottom of the bowl shaped macrocycle (especially O(63)–C(93)), it appears that linear alkanes (n = 5, 6) are small and flexible enough to allow (modeled with CERIUS^2 software) 'zigzag' displacement along this channel. In contrast, displacements inside the channels cannot occur for cycloalkane or cycloalkene molecules because of steric hindrance.

The modeling results are consistent with the efflorescent character of the Ub phase with linear guest molecules only. The residual *n*-alkane molecules could be active partners in the cohesion of the crystal lattice by means of displacements along the channels.

Comparison of some isomorphous crystals of TRIMEB complexes

As a complement to this study, a recent structural determination on a single crystal of the TRIMEB/(R)-5-ethyl-1,3,5-trimethyl-hydantoin (TRIMEB/(R)12Hdi) complex has been achieved in our laboratory [18]. This structure is isomorphous (a = 11.190(5), b = 26.080(5), c = 29.187(5) Å and spacegroup $P2_12_12_1$) to the Ub phase. Another isomorphous crystal structure was reported for TRIMEB/L-menthol [19] with the following parameters (a = 11.060(3), b = 26.138(6), c = 29.669(6) Å and space group $P2_12_12_1$). In these three structures, the guest is totally engulfed inside the cavity. Eight other isomorphous TRIMEB complexes [20–25] (Uc phases hereafter) present another packing along the *b* axis. Among these complexes, the authors of TRlMEB/*m*-

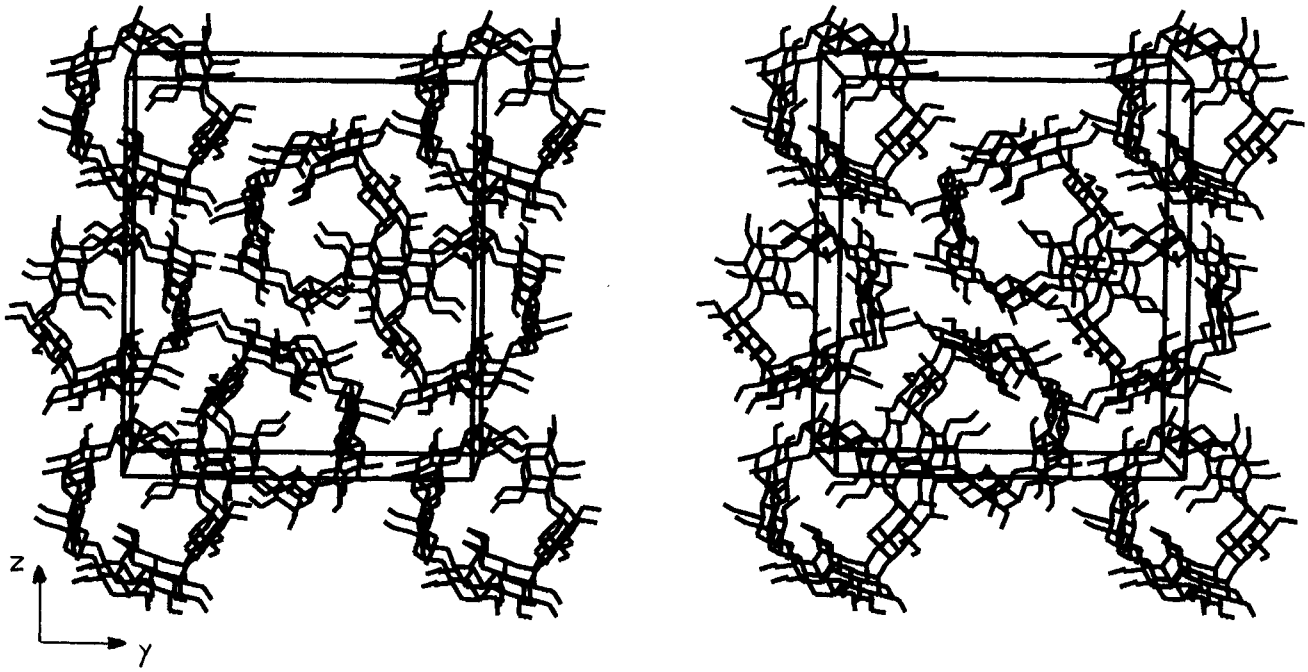

Figure 6. Stereo diagram of the TRIMEB/MCH packing. Guest and hydrogen atoms are omitted for clarity.

iodophenol [24] reported a skew-boat conformation for the G5 methylglucose unit This particular conformation may relieve steric hindrance between this particular host and some methyl groups. TRIMEB monohydrate has a particular packing and one glucose unit is in the $^1C_4$ conformation. Table 3 summarizes the tilt angles of TRIMEB for all the complexes recalculated from data deposited in the Cambridge Structural Database System [27]. In contrast to what is stated by Mentzafos *et al.* [25], two negative tilt angles were found for G3 and G6 units in the TRIMEB/ethyl laurate complex.

The TRIMEB/MCH and TRIMEB/(R)l2Hdi tilt angles are very similar and different from those of TRIMEB/L-menthol. The authors of the TRIMEB/L-menthol crystal structure postulate that the set of tilt angles observed seems to be independent of the nature of the guest and the crystal packing. They attribute this most stable conformation to hydrogen bonding between C(6n)-H and O(5($n-1$)). This conclusion was reconsidered for tilt angles observed for the TRIMEB/MCH complex [17]; the authors claim that TRIMEB exhibits 'induced-fit' in this case. Nevertheless the similarities among the tilt angles observed for Ub and Uc (Table 3) do not support this conclusion.

In our opinion, despite a small number of TRIMEB/Guest structures with $0.1 \leq x \leq 1$ already published, it appears that, in the solid state:

- All stable complexes (except TRIMEB monohydrate) can be classified into two main stable types of packing defined by two sets of unit cells (Ub and Uc phases). TRIMEB complexes crystallizing as a Ua phase belong to a third, different, unstable arrangement.
- In a similar way, all known TRIMEB conformations can be split into two main families of tilt-angles. These fixed schemes of tilt angles are not connected to the nature of the guest and the packing mode Ub or Uc (see TRIMEB/L-menthol). Therefore, the set of TRIMEB tilt angles might be in relation with a limited number of conformations stabilized by weak hydrogen bonds (C(6n)-H and O(5($n-1$))). This hypothesis is supported by the existence of six close contacts (C(6n)-H – unambiguously located – and O(5($n-1$))) with C$\cdots$O distances ranging from 3.06 to 3.22 Å for the TRIMEB/L-menthol complex. In the same way Rontoyianni *et al.* [17] describe six equivalent close contacts in the range 3.13–3.69 Å. At 120K and within the margin of uncertainty, the same weak intramolecular contacts are observed.
- Thus in the solid state, the TRIMEB conformation results from the best fit with the guest molecule, but among a limited number of stable conformations of the macrocycle. As a piece of evidence, whereas the guest molecules are quite different, the great similarities between the TRIMEB/MCH and TRIMEB/(R)12Hdi tilt angles show no evidence of the so called 'induced fit' in the strict acceptance of the term.

  New examples are required to assess these trends, especially polymorphic forms of the same host/guest association with $0 \leq x \leq 1$.

Conclusion

n-Pentane, *n*-hexane, cyclohexane, methylcyclohexane, (RS)-α-pinene, (R)-α-pinene and (S)-α-pinene give two series of isomorphous host-guest crystalline complexes with the TRIMEB molecule (Ub stable phases and Ua metastable phases). The structure of one Ub phase (TRIMEB/MCH) was solved at 120K. Inside the cavity two disordered MCH conformations, *twisted chair* and *twisted boat*, are proposed. In the Ub phases, TRIMEB/MCH complexes are stacked in a head to tail mode forming channels along the a axis.

This packing arrangement is consistent with the efflorescent character of the TRIMEB/*n*-alkane complexes. A comparison with other TRIMEB/guest structures already published seems to indicate that there is no systematic 'induced fit' because in the solid state only a limited number of TRIMEB conformations are available for host/guest association.

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