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TOPOGRAPHY OF CYCLODEXTRIN INCLUSION COMPLEXES

PART I CLASSIFICATION OF CRYSTALLOGRAPHIC DATA OF α-CYCLODEXTRIN INCLUSION COMPLEXES

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ABSTRACT

The crystallographic and stoichiometric data obtained for 17 different inclusion complexes of α-cyclodextrin are reported The cell dimensions and space-group symmetries reflect the packing arrangement of the torus-shaped host molecules and are largely determined by the size and ionic character of the guest molecules

In the series acetic acid, propionic acid, butyric acid, valeric acid, the first three complexes with α-cyclodextrin crystallize in a cage-type structure with space group $P2_12_12_1$, which is characteristic for small, non-ionic guest molecules The valeric acid molecule seems to be too long to be accommodated in a cage structure, thus, the α-cyclodextrin molecules are arranged such that a structure consisting of parallel channels is formed This packing is typical for the inclusion of long, thin, or ionic guest molecules A third class of complexes with structures differing from the two described was also observed

A correlation exists between the type of inclusion complex and the volume required for a complex molecule 1200–~1400 Å^3 for molecular guests, and 1400–1500 Å^3 for ionic guests

INTRODUCTION

The degradation of starch by *Bacillus macerans* amylase yields[1 2] cyclic intermediates consisting of six to ten α-(1→4)-linked D-glucose residues A molecular model and overall dimensions of the smallest member of this family of compounds, α-cyclodextrin (cyclohexa-amylose) with the glucose residues in the *C1*(D) chair conformation[3] is depicted in Fig 1

The cyclodextrins form a large number of inclusion complexes with such dissimilar compounds as benzene derivatives, azo dyes, carboxylic acids, alcohols,

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halogens, polyhalide ions, and the rare gases[1 2 4] Potentiometric, spectral, and reaction-kinetic data on various guest compounds have led to the conclusion that adduct formation in solution is due to the annular structures of the cyclodextrin molecules, which provide space in their interior for the binding of guest molecules of appropriate sizes[1 5–7]

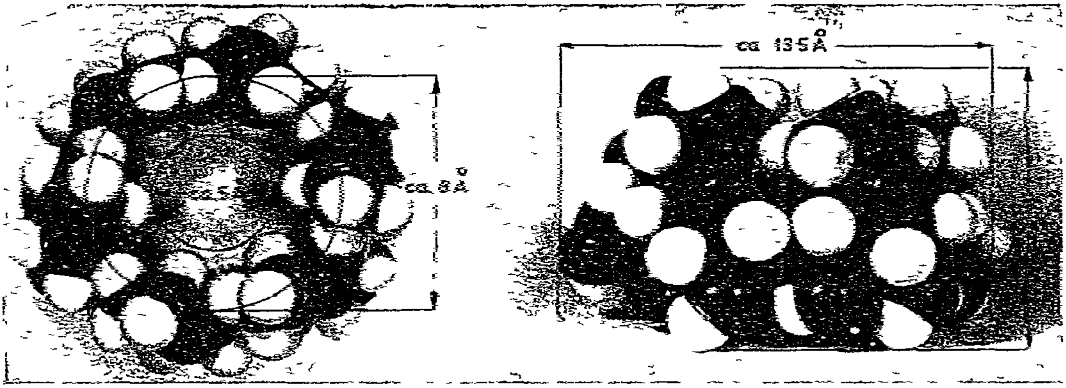

Fig 1 The dimensions (Å) of α-cyclodextrin

The earlier structural data on crystalline cyclodextrin inclusion compounds have largely been summarized by Senti and Erlander[8], and studies of crystalline β-cyclodextrin adducts have been reported[9] The structure of the α-cyclodextrin–iodine complex has been proposed on the basis of an incomplete X-ray study, this structure and the structure of the α-cyclodextrin–1-propanol adduct have been completed in detail by the authors of this paper and will be published elsewhere Hybl *et al*[3] and Manor and Saenger[10] have reported structural analyses of the adducts of α-cyclodextrin with potassium acetate and water, respectively

We now report on the crystallographic data of 17 inclusion complexes of α-cyclodextrin

EXPERIMENTAL

Crystals of the inclusion compounds were grown, following the procedure of Cramer and Henglein[11], from aqueous solutions of α-cyclodextrin mixed with amounts of guest substances in excess of 1 1 molar ratios Attemps to obtain adducts of bromotoluene, nitrotoluene, and pentachlorophenol from preparations containing these materials dissolved in supernatant ether layers produced crystals having diffraction patterns and densities that were almost identical with those of the ether adduct It was therefore concluded that the inclusion of these substances, if it occurred at all, was of the nature of random substitutions, in the predominantly ether-containing adduct On the other hand, crystals of the iodine and 1-butanol adducts could be grown by this procedure In order to prevent decomposition, it was found expedient to store the crystals in their mother liquors

The crystal densities were measured by flotation of the crystals in hexane–methyl iodide mixtures, using relatively large, transparent samples freed from surface liquid by absorbent paper There were no perceptible changes in the crystal densities due to loss of the guest components into the organic mixtures during these measurements The crystals for the X-ray measurements were encased in polystyrene films and thus stabilized Crystals of the iodine adduct underwent radiation damage, but not to a degree that would affect the results of the preliminary X-ray study The space-group symmetries were determined from Weissenberg and precession photographs Data for unit-cell dimensions were either measured by using a diffractometer or obtained from Weissenberg photographs calibrated with aluminium powder diffraction lines

RESULTS

The crystallographic and stoichiometric data for the 16 inclusion complexes which have been examined, and one data set obtained from literature, are given in Table I, where the structures are subdivided into groups, according to their diffraction symmetry (or pseudosymmetry) and unit-cell dimensions The values of the lattice constants are, in most instances, the results from least-squares refinements on sets of 20 data for which the observation to parameter ratios exceed 6 1 In parentheses are listed the standard deviations obtained by this procedure[12] The uncertainty limits on the density values are probable errors as estimated from several independent measurements The entries of column 6 (volume per inclusion complex unit) were obtained by dividing the unit-cell volume by the number of complex molecules per unit cell, column 5 The experimental molecular weights listed in column 7 apply to the formula units of the hydrated α-cyclodextrin or its adduct The hydration numbers of column 8 are determined by difference from these values and molecular weights of the 1 1 adducts (or the 1 2/2 adduct for Methyl Orange)

DISCUSSION

Class I cage structures

The structures of Class I with orthorhombic space-group $P2_12_12_1$ have complex frameworks for which models have been postulated[13] from the guest distribution determined in the adduct of reported composition $(C_6H_{10}O_5)_6$ I_2 $14H_2O$ In this packing arrangement, now resolved in detail for the 1-propanol, iodine, and water adducts[10 14] listed in Table I, the cylindrical openings within the α-cyclodextrin molecules are blocked on open ends by contiguous molecules, thereby forming cylindrical enclosures or cages in the host structure (Fig *2a*), which is held together by an intricate hydrogen-bonding scheme As seen from Table I, and especially in the series acetic acid, propionic acid, butyric acid, valeric acid, this host structure becomes unstable, to structures of Class I, for guest molecules exceeding a critical length consistent with the expectation[8] that the axial dimension of the cage limits

TABLE I

CRYSTALLOGRAPHIC DATA OF α-CYCLODEXTRIN INCLUSION COMPLEXES, CLASSIFIED ACCORDING TO CRYSTAL SYMMETRIES AND UNIT-CELL DIMENSIONS

Guest molecule	*Space groups*		*Cell constants (Å)*	*Observed density (g·cm⁻³)*	*Number of molecules per unit cell*	*Volume per inclusion complex unit (Å³)*	*Mol. wt. of the complex from X-ray data*	*Hydration number for 1:1 complex*
Class I[a]								
Water (1)	$P2_12_12_1$	*a* *b* *c*	14.846(3) 34.00 (1) 9.51 (4)	1.492(1)	4	1200	1078	5.8
Iodine (2)	$P2_12_12_1$	*a* *b* *c*	14.240(4) 36.014(6) 9.558(6)	1.704(calc.)	4	1220	1309	4.0
1-Propanol (3)	$P2_12_12_1$	*a* *b* *c*	14.292(4) 37.515(7) 9.393(3)	1.468(2)	4	1257	1113	4.5(4.8)
Acetic acid (4)	$P2_12_12_1$	*a* *b* *c*	14.34 (1) 37.62 (1) 9.427(5)	1.483(2)	4	1272	1136	5.7
Propionic acid (5)	$P2_12_12_1$	*a* *b* *c*	14.37 (1) 37.91 (2) 9.46 (1)		4	1288		
Butyric acid (6)	$P2_12_12_1$	*a* *b* *c*	14.29 (1) 38.11 (1) 9.45 (1)	1.470(2)	4	1287	1139	4.3
1-Butanol (7)	$P2_12_12_1$	*a* *b* *c*	14.382(3) 37.99 (1) 9.44 (1)	1.476(2)	4	1289	1146	5.5
Class IIA								
Methyl Orange (8)	$P2_12_12_1$	*a* *b* *c*	22.10 (3) 16.39 (3) 8.29 (3)	1.499(2)	2	1500	1356	12.2
Potassium acetate (9) (1.54 guest per α cyclodextrin)[b]	$P2_12_12$	*a* *b* *c*	21.89 16.54 8.30	1.434	2	1500	1298	9.7

Sodium hexanoate (**10**)	$P2_12_12_1$	*a* 21 94 (2) *b* 16 53 (1) *c* 16 56 (5)	1 446(2)	4	1503	1308	10 9
Class IIB							
Diethyl ether	P1	*a* 13 949(5) α 91 3 (3) *b* 13 870(5) β 85 5 (1) *c* 15 669(8) γ 120 29 (2)	1 430	2	1303	1121	4 1
1-Octanol (**11**) Laue	Hexagonal (6/mm)	*a* 13 86 (3) *c* 15 63 (3)	1 409(2)	2	1300	1102	
Valeric acid (**12**) Laue	Hexagonal (6/mm)	*a* 13 85 (3) *c* 15 62 (3)	1,409(2)	2	1298	1101	1 4
3-Methyl-1-butanol (**13**)	$P2_1$	*a* 23 64 (5) *b* 13 95 (3) β 95 0 (2) *c* 16 64 (1)	1 445(2)	4	1368	1189	7 1
Barium iodide-iodine (**14**)	P622	*a* 13 71 *c* 17 04	1 675(5)	2	1387	1400	
Class III							
Potassium iodide-iodine (**15**)	$P6_222$	*a* 15 89 *c* 39 94	1 686(4)	6	1457	1477	
Sodium perchlorate (**16**)	C2	*a* 19 87 (1) *b* 33 71 (3) β 106 86 (4) *c* 27 79 (2)	1 515(2)	12	1483	1355	14 4

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[a] Further data were presented in Ref 13

	a	*b*	*c*
Iodine	14 38 Å	36 07 Å	9 43 Å
1-Propanol	14 24	37 30	9 43
Ethanol	14 31	37 46	9 43

[b] These data were taken from Ref 3

	a	*b*	*c*
Methanol	13 94 Å	36 83 Å	9 47 Å
Water } from two	15 1	33 8	9 6
Water } different batches	14 78	33.96	9 51

the straight-chain guests to C_4 or lower members The salt adducts with anions small enough to fit into these cages, *viz*, potassium acetate and sodium perchlorate adducts, also form structures of other types, probably because of the more-favourable sites for cation coordination existing in those frameworks

The frameworks of Class I are not strictly isomorphous, as has been previously noted in the series comprising the iodine, methanol, ethanol and 1-propanol adducts[13] These small differences in packing of α-cyclodextrin molecules are accompanied by changes in the number of water molecules engaged in the host structures Thus, in the iodine adduct, there are four water molecules per cyclodextrin molecule, whereas the 1-propanol adduct contains five water sites, of which two are statistically occupied, giving the hydration number of 4 8 (Table I) On the other hand, the enclosures appear to be fully occupied, each with one guest molecule Likewise, for other complexes of this class, one might expect 1 1 adducts with 4–6 water molecules per cyclodextrin molecule, with the simple hydrate being a special case in which two water molecules fill the enclosure[10] The hydration number of 14 previously formulated[13] for the iodine adduct greatly exceeds the expectation values imposed on the stoichiometry by the structure and accordingly is probably erroneous

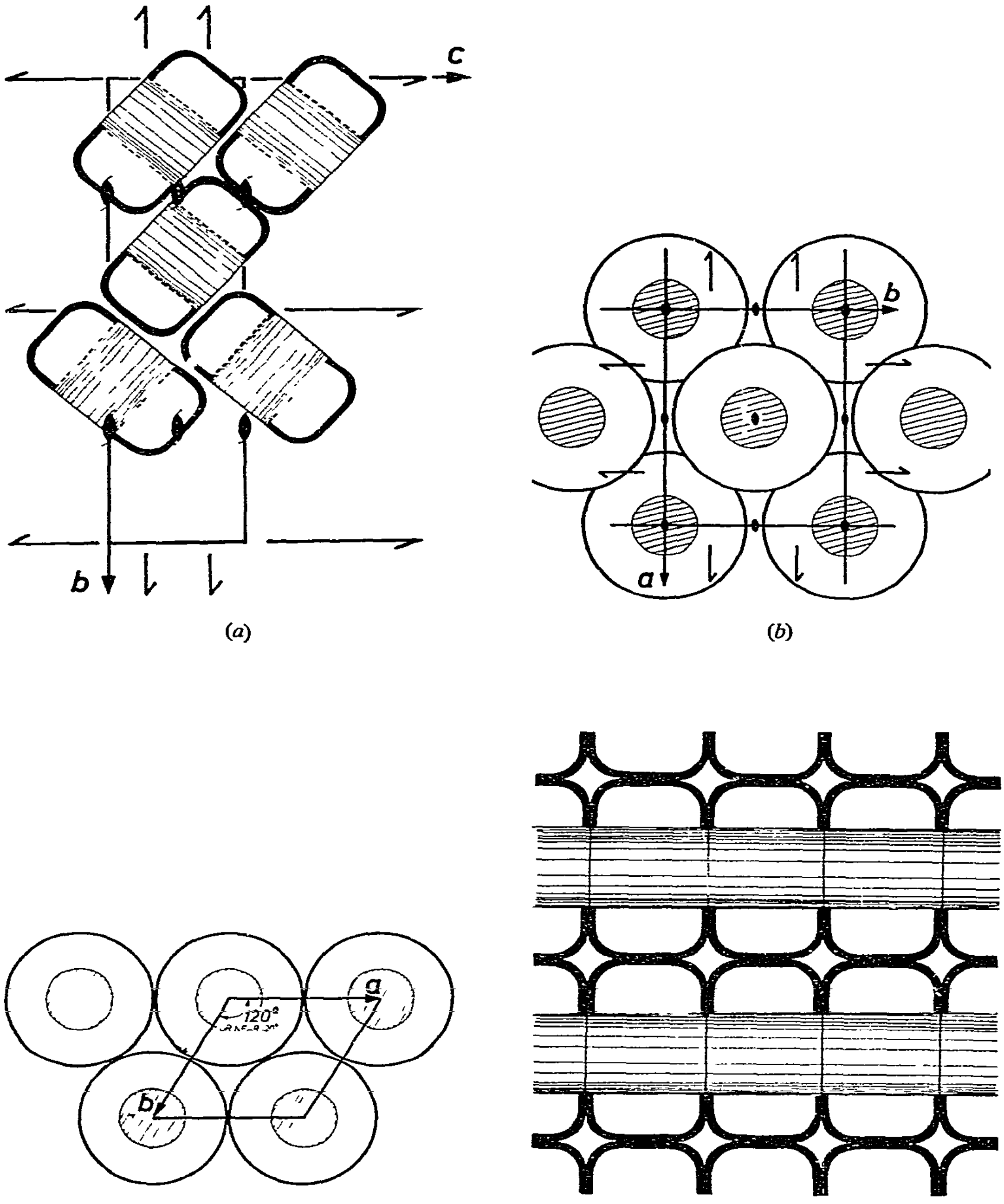
Class II channel structures

The adducts of Class IIA are isostructural in their host frameworks with the α-cyclodextrin–potassium acetate complex[3] In this framework, the cyclodextrin rings pack coaxially to form continuous channels which run along the *c* direction (Figs 2*b* and 2*d*), the anions are distributed through the channels in complex patterns of disorder, while the cations are located in external cavities formed by oxygen atoms

Statistical disorder of the anionic guest must also occur in the Methyl Orange adduct, as the diffraction patterns show no evidence of a superlattice although the maximum dimension of the anion is approximately twice the expected periodic length of the channel In the sodium hexanoate adduct, on the other hand, the anions appear to be ordered, as the channel arrays have a periodicity twice that of the molecular dimensions of α-cyclodextrin

That the frameworks of Class IIA depart significantly from hexagonal closest packing of colinear cylinders appears to be due to the accommodation of ionic guests between channels of the structures, inasmuch as the crystals of adducts of molecular guests (Class IIB) have lattices of dimensions and symmetry consistent with the high intrinsic regularity and simplicity of this arrangement (Figs 2*c* and 2*d*)

Thus, the dimensions of *a* and *c* (~13 9 and ~16 Å) given in Table I (class IIB) correspond to the expected diameter and double height of α-cyclodextrin toruses (Fig 1) in van der Waals contact in hexagonal frameworks The hypersymmetry of this arrangement is remarkably pronounced on diffraction patterns of the triclinic ether adduct and to a lesser extent on patterns of the 3-methylbutan-1-ol adduct While the 1-octanol, valeric acid, and barium iodide–iodine adducts achieve hexagonal symmetry, their diffraction patterns show diffuse streaking in the *c* direction superimposed on sharp reflections which define subcells having the dimensions given



(*a*) (*b*)

(*c*) (*d*)

Fig 2 The packing scheme of α-cyclodextrin adducts (*a*) Class I with small molecular guests, looking along the crystallographic *a*-axis, α-cyclodextrin molecules are seen from the side, similar to Fig 1, right hand (*b*) Class IIA with ionic guests, looking along the channel axis (*c*) Class IIB with large molecular guests, looking along the channel axis (*d*) Side view of class IIA, B channel structures in Table I In view of this streaking and the existence of the apparently ordered ether structure of lower symmetry, it seems probable that, in these structures, the guests are disordered along channels, while the symmetric, cyclodextrin host-molecules are ordered in the main framework The crystal structure of the barium iodide–iodine adduct has been determined from the Patterson function The orientation of the two α-cyclodextrin toruses could not be derived with certainty as the iodine atoms appear disordered along the hexagonal axis[15]

Class III, other structures

The α-cyclodextrin–potassium iodide–iodine complex crystallizes in a hexagonal space-group but, as is obvious from the cell constants, the packing must be different from that observed for Class II structures It was established[15] from a Patterson synthesis that the α-cyclodextrin molecules are again arranged co-linearly in a channel-type structure However, the channels do not run parallel to each other and to the hexagonal crystallographic axis but are perpendicular to this axis This type of packing is also indicated by streak formation in the hkO equator due to a disorder of the iodine atoms along the α-cyclodextrin channels

The crystallographic data of the sodium perchlorate adduct seem to indicate a structure different from any host framework hitherto studied, but bear some relation to the data observed for the α-cyclodextrin–potassium acetate complex The unit-cell axial dimensions of the sodium perchlorate adduct $a = 19\ 87$, $b = 33\ 71$, $c = 27\ 79$ Å, can be considered to be multiples of the cell constants obtained for the α-cyclodextrin–potassium acetate complex, $1 \times 21\ 89$, $2 \times 16\ 54$, $3 \times 8\ 30$ Å

The volume per inclusion complex unit

The volumes per inclusion complex unit given in column 6 of Table I and in Fig 3 represent a measure for the volume required by one α-cyclodextrin molecule plus the surrounding molecules of water of hydration It is interesting to note that these figures vary from one crystal class to another and thus reflect the different packing patterns

In class I structures, the volume per inclusion complex unit increases from 1200 Å^3, the lowest entry in column 6, Table I, until it reaches a plateau at ~ 1290 Å^3 That the water inclusion complex requires the smallest volume also becomes obvious from its detailed X-ray structural analysis[10], the α-cyclodextrin molecule is no longer toroidal, but distorted such that the void becomes smaller in order to achieve van der Waal's contact with the enclosed two water molecules When however, the guest molecule, due to its dimensions or due to its ionic character, requires an adduct volume exceeding ~ 1290 Å^3, the crystal structure changes to class II or III

The volume per inclusion complex unit is constant (1500 Å^3) for class IIA adducts This indicates that the host framework for these adducts is very similar, probably more strictly isomorphous than in the other structure classes of Table I, the accommodation of the ionic guests of different dimensions within the α-cyclodextrin channel and of the different monovalent cations outside the channels[3]

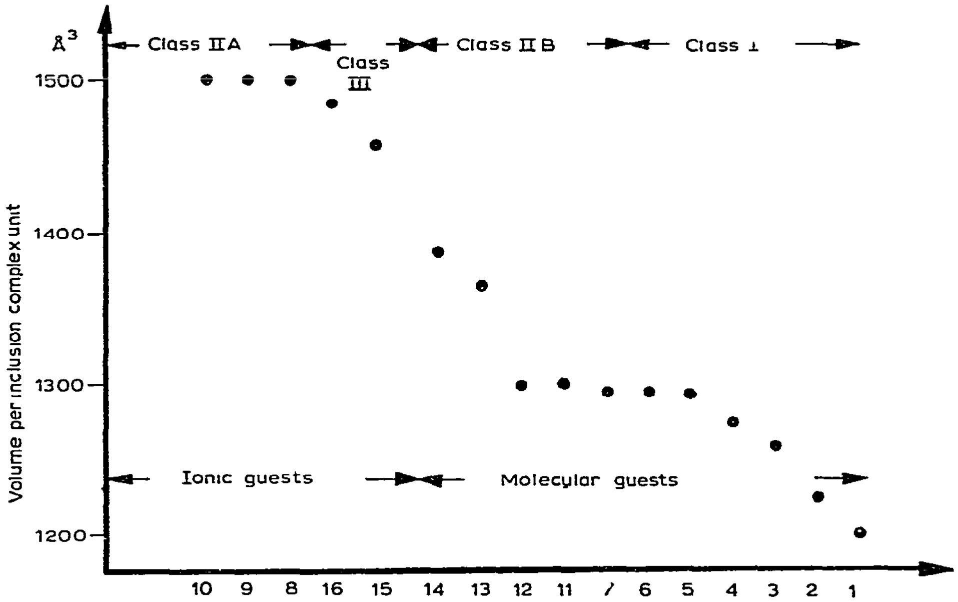


Fig 3 Representation of the "volumes per inclusion complex unit" for the α-cyclodextrin adducts listed in Table I

seems to bear little influence on the packing of the α-cyclodextrin molecules in the orthorhombic unit-cells of $P2_12_12_1$ or $P2_12_12$ symmetry

In class IIB, the volume per inclusion complex for the molecular guests ranges from ~1300–1387 Å^3 In this structural class, the molecular guests are arranged inside the α-cyclodextrin channels, the α-cyclodextrin molecules are packed in a similar scheme but in different (triclinic, monoclinic, and hexagonal) space groups, giving a natural explanation for the variance in the volumes per inclusion-complex unit.

The crystal packing patterns observed for class III with ionic guests are different from the patterns observed for class IIA structures However, the volumes per inclusion complex unit (1457 and 1483 Å^3) are comparable to that (1500 Å^3) recorded for class IIA structures This might indicate that, in the class III adducts, the cations are located "outside" the α-cyclodextrin molecules, as was found[3] for the class IIA potassium acetate complex

It appears to be a structural law that α-cyclodextrin adducts with small molecular guests crystallize in class I structures with 1200–1290 Å^3 per inclusion complex unit, with larger molecular guests, class IIB structures with up to about 1400 Å^3 per inclusion complex unit are obtained The adducts with ionic guests crystallize in class III and class IIA structure types requiring ~1400–1500 Å^3 per inclusion complex unit

CONCLUSIONS

The structure-determining factor in the crystalline materials listed in Table I is the association between guest and α-cyclodextrin molecules with the requirements of inclusion playing the dominant role, the host frameworks comprising α-cyclodextrin molecules and water molecules associated by hydrogen-bonding account for the gross dimensions and intrinsic symmetry properties of the lattices, as do the frameworks in other inclusion or clathrate compounds[16,17] The adducts of molecular compounds, depending on the maximum dimension of the guests, fall into two structural classes crystals of orthorhombic space-groups $P2_12_12_1$ formed by molecules of dimensions smaller or equal to a C_4 chain (Class I, cage structures) and crystals of hexagonal or pseudohexagonal space-groups formed by guest molecules of greater dimensions (Class IIB; channel structures) The structures of ionic (salt) adducts likewise form two structures the channel structures of orthorhombic $P2_12_12$ or $P2_12_12_1$ symmetry (Class IIA) are related to those of the larger molecular nonionic guests (Class IIB); the structures of Class III are different from those of Classes I and II, although the channel structure is preserved in the potassium iodide–iodine adduct and might be present in the sodium perchlorate complex if cell dimensions are taken as sole criterion.

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