Clathrates and Molecular Inclusion Phenomena

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1 Introduction

In recent years a rapidly growing interest in inclusion phenomena has been focused in two major directions. In the first, the binding or complexation of guest species by unimolecular hosts *in solution* has received much attention, and excellent recent reviews have appeared for two particularly important classes of host, the naturally-occurring cyclodextrins[1-3] and compounds of the synthetic 'crown' type.[4] The second equally fascinating aspect of 'host and guest chemistry' relates to the study of *crystalline* multimolecular inclusion compounds,[5-21] which may be sub-classified as the true clathrate type[22] in which the guest molecules are imprisoned in discrete closed cavities or cages; the channel type[23] in which the guest species are accommodated in continuous canals running

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[1] See for example D. W. Griffiths and M. L. Bender, *Adv. in Catalysis*, 1973, **23**, 209.

[2] F. Cramer and H. Hettler, *Naturwiss*, 1967, **54**, 625.

[3] J. A. Thoma and L. Stewart in 'Starch: Chemistry and Technology', ed. R. L. Whistler and E. F. Paschall, Academic Press, New York, 1965, Vol. 1, p..209.

[4] See for example D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 1975, **43**, 327; G. W. Gokel and H. D. Durst, *Synthesis*, 1976, 168; D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803; C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16; J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74**, 351; see also R. J. Hayward, M. Htay, and O. Meth-Cohn, *Chem. and Ind.*, 1977, 373.

[5] S. G. Frank, *J. Pharm. Sci.*, 1975, **64**, 1585.

[6] 'Non-Stoichiometric Compounds', ed. L. Mandelcorn, Academic Press, New York, 1964.

[7] M. Hagan, 'Clathrate Inclusion Compounds', Reinhold, New York, 1962.

[8] F. Cramer, 'Einschlussverbindungen', Springer-Verlag, Berlin, 1954.

[9] V. M. Bhatnagar, 'Clathrate Compounds', Chemical Publishing Co., New York, 1970.

[10] G. Zilberstein, *Bull. Soc. chim. France*, 1951, **18**, D33.

[11] W. Schlenk, *Fortschr. Chem. Forsch.*, 1951, **2**, 92.

[12] F. Cramer, *Angew. Chem.*, 1952, **64**, 437.

[13] H. M. Powell, *J. Chem. Soc.*, 1954, 2658.

[14] G. Montel, *Bull. Soc. chim. France*, 1955, 1013.

[15] F. D. Cramer, *Rev. Pure Appl. Chem.*, 1955, **5**, 143.

[16] H. M. Powell, *Rec. Trav. chim.*, 1956, **75**, 885.

[17] F. Cramer, *Angew. Chem.*, 1956, **68**, 115.

[18] L. Mandelcorn, *Chem. Rev.*, 1959, **59**, 827.

[19] J. F. Brown, *Sci. Amer.*, 1962, **207**, 82.

[20] C. Asselineau and J. Asselineau, *Ann. Chim.*, 1964, **9**, 461.

[21] C. Solacolu and I. Solacolu, *Stud. Cert. Chem.*, 1973, **21**, 1307.

[22] See for example H. M. Powell, in 'Non-Stoichiometric Compounds', ed. L. Mandelcorn, Academic Press, New York, 1964, p. 438.

[23] See for example L. C. Fetterly, in 'Non-Stoichiometric Compounds', ed. L. Mandelcorn, Academic Press, New York, 1964, 491.

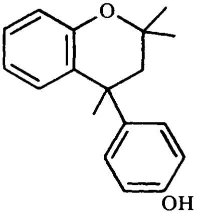
through the crystal; and the layer type[24] where the guest component is situated between bands of host structure. Familiar examples of these types are the β-hydroquinone clathrates,[7,22] the channel inclusion compounds formed by urea and thiourea,[23] and the layer or intercalation compounds formed by graphite.[24] In the extremely important inorganic zeolites,[25] one has an intermediate class possessing cavities interconnected by channels.

The present review is mainly concerned with organic multimolecular inclusion compounds, particularly those of the true clathrate or cage type,[22] and points for detailed consideration are (i) work directed towards the design and synthesis of new clathrate host materials; (ii) recent structural information which has become available on selected clathrates, and the nature of host–guest interactions in such systems; (iii) studies of the properties of guest molecules when actually present within clathrare cavities. In Section 6 a brief account of very recent work on the cyclodextrins is also given. The present review intends to be illustrative rather than comprehensive, and hopes to stimulate further work in the field. Not all of the above main points are encountered for each clathrate or family of clathrates chosen.

2 Dianin's Compound and Related Molecules

These molecules are considered first since they are particularly well suited to illustrating the main themes of the present review.

A. Structure and Properties of the Parent Host.—The parent, 4-*p*-hydroxyphenyl-2,2,4-trimethylchroman (1), widely known as Dianin's compound was first prepared[26] by the Russian chemist A. P. Dianin in 1914. He reported the remarkable ability of (1) to retain tightly certain organic solvents. Subsequently this compound has been shown to be capable of including a wide range of guest



(1)

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[24] See for example F. R. Gamble and T. H. Geballe in, 'Treatise on Solid State Chemistry', Vol. 3, Crystalline and Noncrystalline Solids, ed. N. B. Hannay, Plenum Press, New York, 1976, p. 89; H. Selig, M. Rabinovitz, I. Agranat, and Chun-Hsu Lin, *J. Amer. Chem. Soc.*, 1976, **98**, 1601.

[25] See for example, R. M. Barrer, in 'Non-Stoichiometric Compounds', ed. L. Mandelcorn, Academic Press, New York, 1964, 309; K. Seff, *Accounts Chem. Res.*, 1976, **9**, 121.

[26] A. P. Dianin, *J. Russe. Phys. Chem. Soc.*, 1914, **46**, 1310; for later syntheses see G. G. Kondrateva, *Metody Polsich. Khim. Reaktivov Prep.*, 1969, **20**, 199 (*Chem. Abs.*, 1972, **76**, 113 017); D. B. G. Jaquiss, Ger. Offen. 2 335 854, 1974 (*Chem. Abs.*, 1974, **81**, 26 162).

species, *e.g.* argon,[27] sulphur dioxide,[28] ammonia,[28] benzene,[29] decalin,[29] and di-t-butylnitroxide.[30] The structure of (1) was unambiguously established in the mid-fifties by Baker and co-workers,[28,29] who also prepared[28] over fifty adducts. At this time also Powell and Wetters,[31] on the basis of space group, unit cell dimensions, and crystal packing considerations, suggested a true cage structure for the adducts, and the unsolvated form. Some decade and a half later, detailed *X*-ray studies confirmed the cage structure for the ethanol,[32] chloroform,[32] n-heptanol[33] complexes, and for the unsolvated crystal.[34] Figure 1 shows a view normal to the *c*-axis for the unsolvated form,[34] which is isomorphous with the

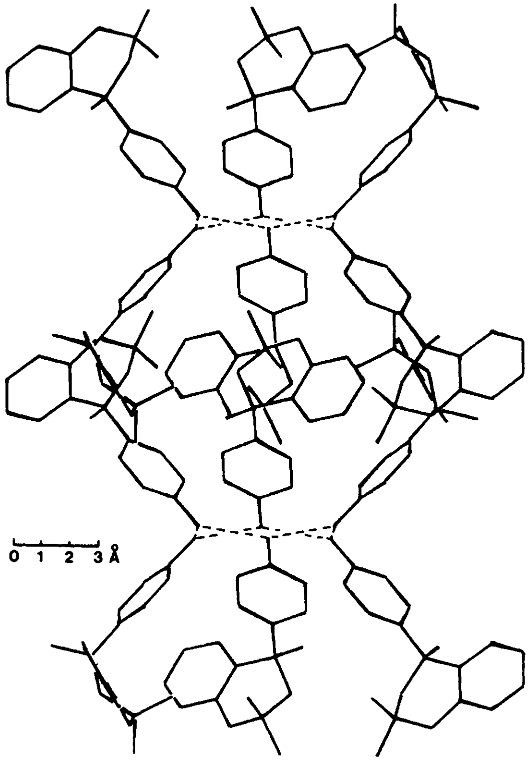

Figure 1 *A view normal to the* c*-axis of the unsolvated form of Dianin's Compound* (1), *the cage formed between sextet units being unoccupied in this case*

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[27] W. Baker and J. F. W. McOmie, *Chem. and Ind.*, 1955, 256.

[28] W. Baker, A. J. Floyd, J. F. W. McOmie, G. Pope, A. S. Weaving, and J. H. Wild, *J. Chem. Soc.*, 1956, 2010.

[29] W. Baker, J. F. W. McOmie, and A. S. Weaving, *J. Chem. Soc.*, 1956, 2018.

[30] A. A. McConnell, D. D. MacNicol, and A. L. Porte, *J. Chem. Soc. (A)*, 1971, 3516.

[31] H. M. Powell and B. D. P. Wetters, *Chem. and Ind.*, 1955, 256.

[32] J. L. Flippen, J. Karle, and I. L. Karle, *J. Amer. Chem. Soc.*, 1970, **92**, 3749.

[33] J. L. Flippen and J. Karle, *J. Phys. Chem.*, 1971, **75**, 3566.

[34] H. H. Mills, D. D. MacNicol, and F. B. Wilson, unpublished results.

adducts of (1) [see Table which also gives a comparison of crystal data for compounds (2), (4)—(8), (10), and (12)—(15)]. The basic feature of the structure is the linking of the hydroxy groups of six molecules by a network of hydrogen bonds such that the oxygen atoms form a distorted hexagon, with alternate molecules of opposite configuration lying on opposite sides of its plane. Two such groups are stacked along the *c*-axis such that their bulkier parts interlock forming a cage. The cage has an hour-glass shape of length equal to the *c*-spacing, 10.94 Å (for the unsolvated crystal). All guest molecules in the above studies[32,33] exhibit disorder; in the case of n-heptanol a *gauche* conformation has been assigned on the basis of cavity length considerations.[33] For smaller guest species such as ethanol or acetone, two molecules are accommodated per cage,[28] corresponding to a host to guest ratio of 3:1, while for larger guests such as benzene or *p*-xylene each cage is singly occupied, the ratio then being 6:1.

Several physical and spectroscopic studies have been directed towards elucidating the environment experienced by guest molecules in the well-defined cavities formed by Dianin's compound. Detailed studies of molecular motion of guest molecules have been carried out employing dielectric relaxation measurements,[35a,36] and e.p.r.[30] and n.m.r. spectroscopy:[37] barriers to internal rotation of 2.1 kcal mol^{-1} for acetonitrile[35b] and 2.3 kcal mol^{-1} for the di-t-butylnitroxide radical[30] in the cage of (1) have been reported.

An interesting study[38] by Kispert and Pearson demonstrated that (1) could serve as a matrix for studying free radicals. These workers *X*-irradiated the 1,2-dibromo-1,1-difluoroethane clathrate of (1) at 77 K and observed the $Br_2^{\cdot -}$ radical by e.p.r. spectroscopy, the radical being located as lying parallel to the *c*-axis.

I.r. studies of guest molecules in (1) have been reported,[39] and a novel suggestion[40] is the use of (1) as a suitable host for the observation of transitions between two rotational sublevels of the same vibrational state, in small organic (guest) molecules.

Very recently Barrer and Shanson have described[41] the ready sorption of gases such as Ar, Kr, Xe, and CH_4, when (1) is suitably agitated.

B. Structural Modification of Dianin's Compound.—The first deliberate attempt to modify (1) was reported by Baker and co-workers[28] in 1956. They successfully prepared the phenolic crystalline homologue (3) which possesses an extra methyl group adjacent to the hydroxy function. Compound (3), however, exhibited no

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[35] (*a*) M. Davies and K. Williams, *Trans. Faraday Soc.*, 1968, **64**, 529; (*b*) P. Dansas, and P. Sixou, *Mol. Phys.*, 1976, **31**, 1319; *cf.*, *idem.*, *ibid.*, 1297.

[36] J. S. Cook, R. G. Heydon, and H. K. Welsh, *J.C.S. Faraday II*, 1974, 1591.

[37] P. Gregoire and J. Meinnel, *Compt. rend.*, 1971, **272**, *C* 347.

[38] L. K. Kispert and J. Pearson, *J. Phys. Chem.*, 1972, **76**, 133; for related studies employing γ-irradiation see A. P. Kuleshov, V. I. Trofimov and I. I. Chkeidze, *Khim. Vys. Energ.*, 1973, **7**, 82 (*Chem. Abs.*, 1973, **79**, 25 604); A. P. Kuleshov and V. I. Trofimov, *Khim. Vys. Energ.*, 1973, **7**, 143 (*Chem. Abs.*, 1973, **78**, 146 926).

[39] M. Davies and W. C. Child, *Spectrochim. Acta*, 1965, **21**, 1195.

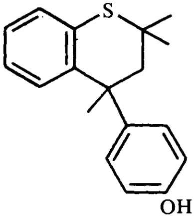
[40] E. W. Aslaksen, *Phys. Letters A*, 1972, **40**, 47.

[41] R. M. Barrer and V. H. Shanson, *J.C.S. Chem. Comm*, 1976, 333.

Table *A comparison of crystal data for Dianin's compound* (1) *and related molecules*

Compound	*Space Group*	*Lattice Parameters**	*Guest*	*Mole Ratio Host:Guest*	*Ref.*
(1)	$R\bar{3}$	$a = 26.97, c = 10.99$ Å	Ethanol	3:1†	*a*
	$R\bar{3}$	$a = 27.12, c = 11.02$ Å	Chloroform	6:1	*a*
	$R\bar{3}$	$a = 27.12, c = 11.02$ Å	n-Heptanol	6:1	*b*
	$R\bar{3}$	$a = 26.94, c = 10.94$ Å	None		*c*
(2)	$R\bar{3}$	$a = 27.81, c = 10.90$ Å	Ethanol	3:1	*d*
	$R\bar{3}$	$a = 27.91, c = 10.99$ Å	2,2,5-Trimethylhex-3-yn-2-ol	6:1	*e*
	$R\bar{3}$	$a = 28.00, c = 11.08$ Å	Di-t-butylacetylene	6:1	*f*
(6)	$R\bar{3}$	$a = 29.22, c = 10.82$ Å	Cyclopentane	6:1	*g*
(7)	$P2_12_12_1$	$a = 11.78, b = 16.50, c = 8.48$ Å	‡		*h*
(8)	$R\bar{3}$	$a = 33.63, c = 8.24$ Å	Cyclo-octane	4.5:1	*i*
(4)	$P2_1/c$	$a = 14.25, b = 6.52, c = 18.67$ Å, $\beta = 113.0°$	‡		*g*
(5)	$P2_1/n$	$a = 12.91, b = 12.11, c = 9.79$ Å, $\beta = 90.3°$	‡		*g*
(10)	$R\bar{3}$	$a = 26.94, c = 10.80$ Å	Carbon tetrachloride	6:1	*j*
(12)	$P\bar{4}2_1c$	$a = b = 12.64, c = 17.25$ Å	‡		*k*
(13)	$P2_12_12_1$	$a = 10.60, b = 13.30, c = 10.08$ Å	‡		*l*, *f*
(14)	$P2_12_12_1$	$a = 10.42, b = 13.69, c = 10.37$ Å	‡		*m*, *g*
(15)	$P2_12_12_1$	$a = 10.66, b = 13.55, c = 10.50$ Å	§		*m*, *g*
	$R\bar{3}$	$a = 27.06, c = 12.07$ Å	Carbon tetrachloride	3:1	*m*, *n*

* For $R\bar{3}$, the values of a and c given are referred to a hexagonal unit cell containing 18 host molecules ($\alpha = \beta = 90°$, $\gamma = 120°$); for other space groups unspecified angles are 90°. † Ratio from ref. 28. ‡ No inclusion behaviour found to date. § for unsolvated form obtained by recrystallization from cyclohexane. [a] J. L. Flippen, J. Karle, and I. L. Karle, *J. Amer. Chem. Soc.*, 1970, **92,** 3749. [b] J. L. Flippen and J. Karle, *J. Phys. Chem.*, 1971, **75,** 3566. [c] H. H. Mills, D. D. MacNicol, and F. B. Wilson, unpublished results. [d] D. D. MacNicol, H. H. Mills, and F. B. Wilson, *Chem. Comm.*, 1969, 1332. [e] D D. MacNicol and F. B. Wilson, *Chem. Comm.*, 1971, 786. [f] A. D. U. Hardy and D. D. MacNicol, unpublished results. [g] A. D. U. Hardy, D. D. MacNicol and J. J. McKendrick, unpublished results. [h] A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J.C.S. Perkin II*, 1977, 1145. [i] D. D. MacNicol, A. D. U. Hardy, and J. J. McKendrick, *Nature*, 1975, **256,** 343. [j] A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J.C.S. Chem. Comm.*, 1976, 355. [k] J. H. Gall, A. D. U. Hardy, and D. D. MacNicol, in preparation. [l] Crystals (ref. 56) kindly provided by Professor J. Jacques. [m] A. D. U. Hardy, D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *Tetrahedron Letters*, 1975, 4711. [n] A. D. U. Hardy, D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *J.C.S. Chem. Comm.*, 1977, 292.



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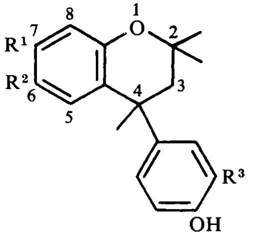

(3) $R^1 = R^2 = H$; $R^3 = Me$
(4) $R^1 = R^3 = H$; $R^2 = Me$
(5) $R^2 = R^3 = H$; $R^1 = Me$

inclusion behaviour. Subsequent systematic studies have not only led to the discovery of new clathrates, but also to those with much altered cage geometry in certain cases. These modifications are now considered under convenient sub-headings.

Replacement of the Heteroatom. The synthesis[42] of the thiachroman analogue of (1), compound (2), yielded a new general clathrate host. Indeed (2) appears to be the earliest example of a versatile organic clathrate host, of established[43] closed-cage type, which was deliberately prepared.[44] Thioether (2) shares the wide range of inclusion ability of (1), reflecting similar cavity geometry.[43] A particularly interesting guest[45] is the acetylenic alcohol, $Me_3CC{\equiv}CCMe_2OH$, for here a detailed *X*-ray study shows that *all* guest molecules adopt a staggered conformation (with a statistical disorder of OH and Me groups to conform with the imposed $\bar{3}$ symmetry of the cavity). As shown in Figure 2, the acetylenic unit of the guest molecule is collinear with the *c*-axis, the triple bond fitting neatly into the waist of the cavity, leaving a tetrahedral unit in the upper and lower halves of the cavity. Similar results[46] have also been obtained for the more symmetrical di-t-butylacetylene as guest in (2). The corresponding selena-ether,[47a] 4-*p*-hydroxyphenyl-2,2,4-trimethylselenachroman exhibits inclusion properties, a property not shared by the sulphone,[47a] 4-*p*-hydroxyphenyl-2,2,4-trimethylthiachroman 1,1-dioxide. Employing (2) as host, the *intramolecular* group rotation of the formyl group of benzaldehyde has been studied by far i.r. spectroscopy: the increased rotation barrier of 6.0 kcal mol^{-1} for PhCHO in (2) compared with 4.9 kcal mol^{-1} for the vapour is in keeping with a significant interaction between the guest and the cage wall.[47b]

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[42] D. D. MacNicol, *Chem. Comm.*, 1969, 836.

[43] D. D. MacNicol, H. H. Mills, and F. B. Wilson, *Chem. Comm.*, 1969, 1332.

[44] Previously (see ref. 65) an analogue of Dianin's compound possessing an additional OH group *meta* to the hydroxy function of (1) had been prepared and found to form adducts: the detailed nature of these complexes is, however, unknown.

[45] D. D. MacNicol and F. B. Wilson, *Chem. Comm.*, 1971, 786.

[46] (*a*) A. D. U. Hardy and D. D. MacNicol, unpublished results; (*b*) A. D. U. Hardy. D. D. MacNicol, and D. R. Wilson, in preparation.

[47] (*a*) B. S. Middleditch and D. D. MacNicol, *Org. Mass. Spectrometry*, 1976, **11**, 212; (*b*) D. D. MacNicol, *J.C.S. Chem Comm.*, 1973, 621.

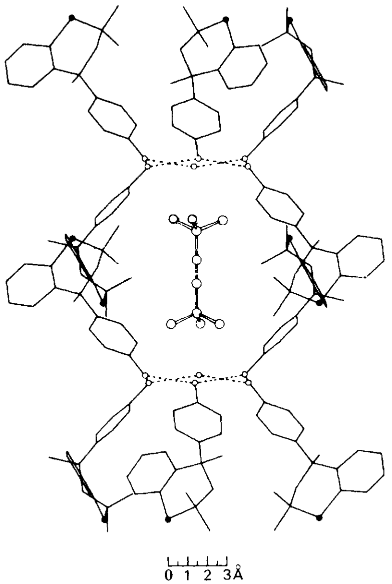

Figure 2 *A view normal to the* c-*axis of the* 2,5,5-*trimethylhex*-3-*yn*-2-*ol clathrate of* (2), *the guest molecule being shown in the cavity. Two molecules of* (2), *which lie directly above and below the cavity as viewed in this direction, have been excluded apart from their hydroxy-oxygen atoms*

(Reproduced from *Chem. Comm.*, 1971, 786)

Substitution of the Ring Skeleton of Compounds (1) *and* (2). The columns, part of which are shown in Figures 1 and 2, are infinite in extent and are surrounded by six identical columns related by three-fold screw axes which run parallel to the *c*-axis. Since the carbon atoms C-5, C-6, C-7, and C-8 of the aromatic ring of the chroman or thiachroman are situated on the 'outside' of columns, modification at these positions may be expected to affect intercolumn packing. Not unexpectedly, fusion of an additional bulky benzene ring to give (9) leads to severe column disruption with elimination of inclusion properties.[48] On the other hand, introduction of methyl groups in the 6-, 7-, and 8-position of the thia-analogue of (1), to give (6), (7), and (8) respectively, produces an interesting spectrum of behaviour.[48] Of these only (7) exhibits no inclusion behaviour, and in this crystal one finds infinite chains of molecules linked head-to-tail by OH · · · S hydrogen bonds, such that no voids are left for solvent inclusion.[49] The most remarkable case is, however, (8) where a major change in cavity shape has been achieved.[50] As shown in Figure 3, the hour-glass shaped cavity of (2) has been converted into the 'chinese-lantern' contour of (8). This change in cavity geometry is reflected in modification of selective clathration properties.[48]

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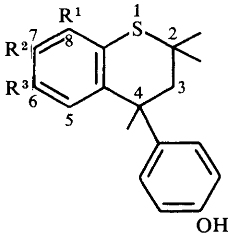
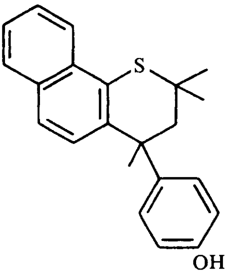
[48] A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J.C.S. Chem. Comm.*, 1974, 972.
[49] A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J.C.S. Perkin II*, 1977, 1145.
[50] D. D. MacNicol, A. D. U. Hardy, and J. J. McKendrick, *Nature*, 1975, **256**, 343.





(6) $R^1 = R^2 = H$; $R^3 = Me$
(7) $R^1 = R^3 = H$; $R^2 = Me$
(8) $R^2 = R^3 = H$; $R^1 = Me$

(9)

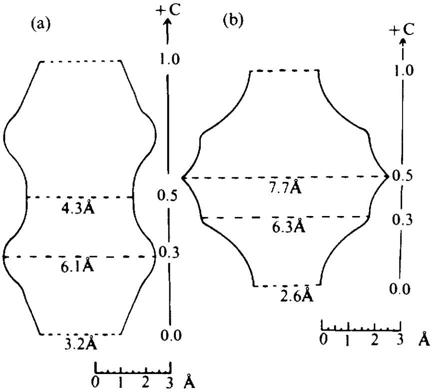


Figure 3 *Section through the van der Waals' surface of the cavity A, for* (2); *B, for* (8), *representing the space available for guest accommodation*
(Reproduced by permission from *Nature*, 1975, **256,** 343)

Interestingly, the 6- and 7-methyl homologues of Dianin's compound itself, (4) and (5) form monoclinic crystals (see Table) without inclusion of solvent.[51]

Modification of the Substitution Pattern at C-2 and C-4 of Dianin's Compound and its Optical Resolution. The hour-glass cavity contour of (1) owes its central constriction to six inward-pointing methyl groups,[32] one from each of six molecules of (1); the methyl group involved is the one *syn* to the *p*-hydroxyphenyl substituent. A new clathrate host (10), which corresponds to specific removal of this methyl group has been recently reported, and its modified cage geometry described.[52] Figure 4 (a) shows the hour-glass cage shape of (1), and the curved broken lines represent the effect of *formal* replacement of the *syn* methyl by an appropriately placed hydrogen atom: the similarity between this predicted

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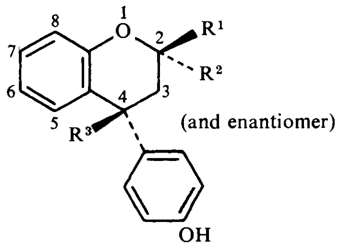
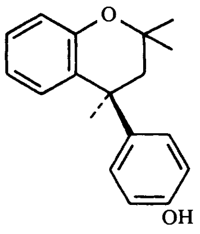
[51] A. D. U. Hardy, D. D. MacNicol, and J. J. McKendrick, unpublished results.
[52] A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J.C.S. Chem. Comm.*, 1976, 355.



(10) $R^2 = H$; $R^1 = R^3 = Me$
(11) $R^1 = H$; $R^2 = R^3 = Me$
(12) $R^3 = H$; $R^1 = R^2 = Me$



(13) *S*(−)—Dianin's compound

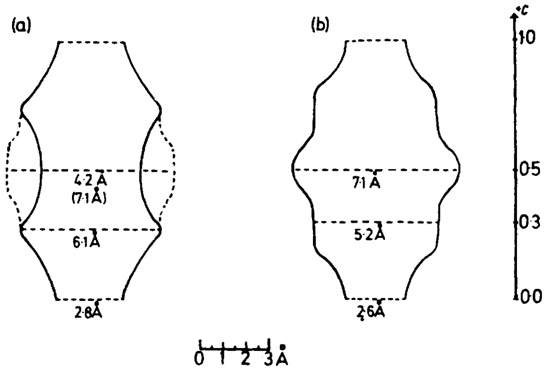


Figure 4 *Section through the van der Waals' surface of the cavity for:* (a) *Dianin's Compound* (1) *as chloroform clathrate, replotted from data of ref.* 32, *the curved broken lines represent the effect of formal removal of the waist methyl groups* (*see text*)*;* (b) *compound* (10) *as* CCl_4 *clathrate*

(Reproduced from *J.C.S. Chem. Comm.*, 1976, 355)

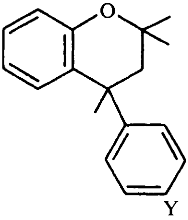
contour and that actually found experimentally by *X*-ray methods, Figure 4 (b), is most striking. Removal of the methyl group on C-2 *anti* to the *p*-hydroxyphenyl substituent also yields[53] a new host (11), though interestingly compound (12) which lacks the 4-methyl group crystallizes unsolvated in the tetragonal crystal system[54] with infinite chains of molecules linked head-to-tail by (ether) O · · · HO hydrogen bonds.

In Dianin's compound the centrosymmetric cage is made up of three molecules of one configuration and three of the opposite configuration. Inquiring into the outcome[55] of having only *one* enantiomer present in which any cage formed would necessarily be chiral, Brienne and Jacques,[56] have recently resolved (1) thereby obtaining *S*(−)-Dianin's compound (13), which has the absolute

[53] A. Collet and J. Jacques, *J.C.S. Chem. Comm.*, 1976, 708.
[54] J. H. Gall, A. D. U. Hardy, and D. D. MacNicol, in preparation.
[55] S. H. Wilen, *Topics in Stereochemistry*, 1971, **6**, 128.
[56] B. J. Brienne and J. Jacques, *Tetrahedron Letters*, 1975, 2349.

configuration shown.[57] No inclusion compound formation has been found for (13) with either chiral or achiral guests.[56]

Changes in the Hydrogen-bonding Functionality of (1). In view of the key role of the hydrogen-bonded hexamers which form the floor and roof of each cavity in (1) it is of great interest to determine whether another hydrogen-bond-forming group might be capable of replacing the OH group without eliminating the clathrate forming ability. While the amine (14), recently prepared[58] from (1) does not include solvent, it is noteworthy that this compound undergoes spontaneous resolution on crystallization, the crystals being isomorphous with resolved Dianin's compound (13) (see Table). The corresponding thiol (15) is particularly interesting, undergoing spontaneous resolution from cyclohexane,[58] but forming a clathrate[58,59] with carbon tetrachloride which is isomorphous with the clathrates of (1). A view of the hydrogen-bonded hexameric host unit of (15) is shown in Figure 5, the SH · · · S hydrogen bond is 3.75 Å in length. These sextets are stacked on top of one another analogously to (1), cages being formed between units, in this case however, the top and bottom of a cage are formed by hexagons of sulphur atoms, 12.07 Å apart. The related amine and thiol corresponding to (2), 4-*p*-aminophenyl-2,2,4-trimethylthiachroman, and 4-*p*-mercaptophenyl-2,2,4-trimethylthiachroman, have also been synthesized, but these compounds crystallize without inclusion of solvent.[60]



(14) Y = NH_2
(15) Y = SH

*2-Phenyl-*3-p-(2,2,4-*trimethylchroman*-4-*yl*)*phenylquinazolin*-4(3H)-*one* (16) *and its sulphur analogue* (17). The wide-ranging inclusion behaviour of compound (16) was discovered[61] when it was characterized as a synthetic intermediate in the conversion of Dianin's compound (1) into amine (14). This host is extremely versatile, stable adducts being formed with a very wide range of solvents:[61,62]

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[57] A. Collet and J. Jacques, *Israel J Chem.*, 1976/77, **15**, 82.

[58] A. D. U. Hardy, D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *Tetrahedron Letters*, 1975, 4711.

[59] A. D. U. Hardy, D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *J.C.S. Chem. Comm.*, 1977, 292.

[60] D. D. MacNicol and D. R. Wilson, unpublished results.

[61] A. D. U. Hardy, D. D. MacNicol, and D. R. Wilson, *J.C.S. Chem. Comm.*, 1974,783.

[62] C. J. Gilmore, A. D. U. Hardy, D. D. MacNicol, and D. R. Wilson, *J.C.S. Perkin II*, 1977, 1427.

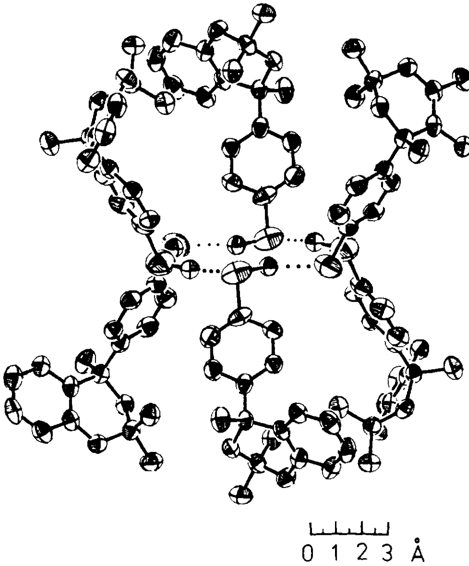
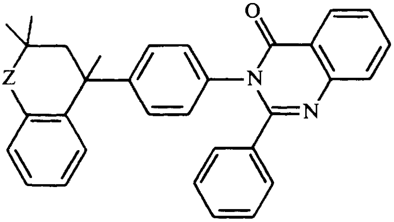


Figure 5 *A general view of the hydrogen-bonded hexameric host unit of thiol* (15) *in the* CCl_4 *clathrate*
(Reproduced from *J.C.S. Chem. Comm.*, 1977, 292)



(16) Z = O
(17) Z = S

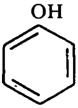
important classes of guest are cycloalkanes, cyclic ethers and ketones, alcohols, and aromatic molecules. A very recent[62] *X*-ray analysis of the methylcyclohexane adduct, showed it to be of the true clathrate type, with two methylcyclohexane guest molecules accommodated in a large closed cage. Compound (17) a thia-analogue of (16), has also been prepared[62] and found to exhibit inclusion properties. In these cases, hydrogen-bonding between host molecules is not involved, the host structures being consolidated by van der Waals' forces alone.

C. Applications of Dianin's Compound and Related Systems.—An early potential use of (1) involved its SF_6 clathrate as a convenient means of storage and controlled release of SF_6, a gas of considerable use in the electrical industry.[63,64] Johnson[65] has employed amine complexes of (1) as polymerizing agents in the preparation of epoxy and urethane resins, and the $(CF_3SO_2)_2CH_2$ clathrate acts as a latent curing catalyst in cationic polymerization,[66] while the diethylamine clathrate can be used[67] as a developer for the production of heat sensitive copying sheets. Host (1) exhibits useful selective clathration properties allowing efficient separation of certain hydrocarbon mixtures.[68] It has also been proposed[69] that the highly toxic organo-mercurial dimethylmercury, may be handled with comparative safety in the form of its clathrate with thiachroman host (2).

3 Hydroquinone, Phenol and Substituted Phenols, and Other Hydroxy-aromatic Hosts

A. Hydroquinone.—The inclusion compounds formed by quinol or hydroquinone (18), referred to as β-hydroquinone clathrates,[70] are of central importance in inclusion chemistry. Indeed the true cage structure of these, established by the pioneering *X*-ray studies of Powell and co-workers,[71] led to the introduction of the name *clathrate compound.*[72] Various aspects of these clathrates have been reviewed including structural considerations,[7,22,73] thermodynamic proper-


(18)


(19)

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[63] L. Mandelcorn, N. N. Goldberg, and R. E. Hoff, *J. Amer. Chem. Soc.*, 1960, **82**, 3297.
[64] L. Mandelcorn, R. W. Auxier, and C. W. Lewis, U.S P. 2 949 424, 1960 (*Chem. Abs.*, 1961, **55**, 11 364).
[65] C. K. Johnson, Fr.P. 1 530 511, 1968 (*Chem. Abs.*, 1969, **71**, 13 717).
[66] J. E. Kropp, M. G. Allen, and G. W. B. Warren, Ger. Offen. 2 012 103 (*Chem. Abs.*, 1971, **74**, 43 074).
[67] W. R. Lawton, Belg.P. 632 833, 1963 (*Chem. Abs.*, 1964, **61**, 3 851).
[68] A. Goldup and G. W. Smith, *Separation Sci.*, 1971, **6**, 791; D. H. Desty, A. Goldup, and D. G. Barnard-Smith, B.P. 973 306, 1964 (*Chem. Abs.*, 1965, **62**, 2655).
[69] R. J. Cross, J. J. McKendrick, and D. D. MacNicol, *Nature*, 1973, **245**, 146.
[70] A form known as α-hydroquinone is obtained when (18) is recrystallized from solvents which are not included.
[71] D. E. Palin and H. M. Powell, *J. Chem. Soc.*, 1947, 208; D. E. Palin and H. M. Powell, *Nature*, 1945, **156**, 334; S. C. Wallwork and H. M. Powell, *J. Chem. Soc.*, 1956, 4855; H. M. Powell, *J. Chem. Soc.*, 1950, 298, 300, 468; D. E. Palin and H. M. Powell, *J. Chem. Soc.*, 1948, 571, 815.
[72] H. M. Powell, *J. Chem. Soc.*, 1948, 61.
[73] W. C. Child, jun., *Quart. Rev.*, 1964, **18**, 321.

ties,[9,73] i.r. and Raman spectra,[74] and the motion of guest molecules.[75] In a recent *X*-ray study[76a] Mak and co-workers have accurately defined the β-hydroquinone host lattice by studying the H_2S clathrate which has space group $R\bar{3}$, and stoicheiometry 3 $C_6H_4(OH)_2,xH_2S$ with $x = 0.768$ (if each cage was occupied by H_2S x would be unity). Figure 6 shows a stereodrawing of the centrosymmetric cage, the guest molecule being denoted (S). The floor and roof of the cavity are formed by hexagons of hydrogen-bonded oxygen atoms which are nearly, but not exactly, planar; molecules point alternately up and down from each hexagon, cages being left between hexagons. The cavity is roughly spherical with a free diameter of *ca.* 4.8 Å. As previously described by Powell,[22,71] the upper and lower parts of the cavity belong to two identical but displaced three-dimensional interlocking networks.

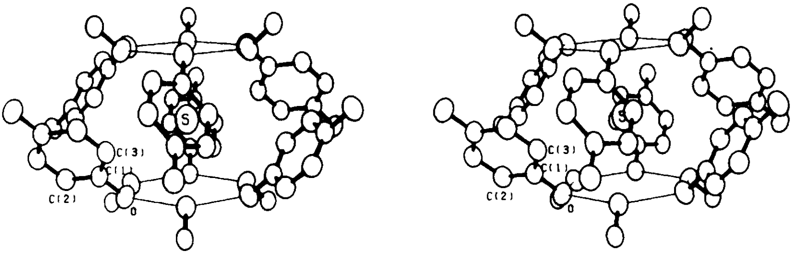

Figure 6 *Stereo drawing showing the hydrogen sulphide guest molecule* (S) *trapped inside a β-hydroquinone cage. For clarity all hydrogen atoms have been omitted*
(Reproduced from *J.C.S. Perkin II*, 1976, 1169)

The space group $R\bar{3}$ is not universally encountered in the clathrates of hydroquinone, the space group *R*3 having been found in the recent *X*-ray and neutron diffraction study[77] of the HCl clathrate, in which the guest molecule resides in a cavity which is trigonal but no longer centrosymmetric. The lowering of symmetry has been attributed[77] to a large number of weak OH · · · Cl--H · · ·OH interactions which orient the HCl guest molecule within the quinol cavity. A further lowering of symmetry to the space group *P*3 is found[76b] when the relatively long guest molecule acetonitrile is included in hydroquinone. There are now three types of clathrate cavity and all these have the shape of prolate spheroids. The three symmetry-independent Me C≡N molecules fit snugly into the cages with one guest molecule aligned in the opposite sense to the other two.

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[74] D. C. McKean in 'Vibrational Spectroscopy of Trapped Species', ed. H. E. Hallam, Wiley, London, 1973, Ch. 8; i.r. and Raman studies are also currently being reviewed *cf.* J. E. D. Davies, in 'Molecular Spectroscopy', ed. J. Sheridan, D. A. Long, and R. F. Barrow, (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 5, Chapter 2.

[75] C. A. Fyfe in 'Molecular Complexes' Vol. 1, ed. R. Foster, Elek Science, London, 1971, Ch. 5.

[76] (*a*) T. C. W. Mak, J. S. Tse, C. Tse, K. Lee, and Y. Chong, *J.C.S. Perkin II*, 1976, 1169; (*b*) T. C. W. Mak, personal communication.

[77] J. C. A. Boeyens and J. A. Pretorius, *Acta Cryst.*, 1977, **B33**, 2120.

Other recent studies on β-hydroquinone clathrates are concerned with i.r. and Raman spectra,[78] *X*-ray photoelectron spectroscopy,[79] thermal decomposition,[80] e.p.r. spectra of *X*-irradiated adducts,[81] n.m.r. spectra,[82] the Mössbauer effect[83] for Kr and Xe complexes, and dielectric relaxation measurements.[35]

B. Phenol and Simple Substituted Phenols.—Phenol itself (19) forms clathrates[7,84,85] in which a basic feature of the host structure is the linking of the OH groups of six phenol molecules by hydrogen bonds such that the oxygen atoms form a hexagon, alternate phenyl groups pointing above and below this hexagon. These sextets are arranged in the rhombohedral lattice, space group $R\bar{3}$, such that two types of centrosymmetric cage are formed,[84] one large (effective length about 15 Å and 4—4.5 Å in free diameter) and one small with a free diameter of *ca.* 4.5 Å. Both cages are capable of including suitably sized guest molecules, and limiting compositions have been considered.[7,18]

Recent studies have been described for the inclusion of noble gases or other volatile species in phenol,[86,87] *p*-fluorophenol,[86,88] *m*-fluorophenol,[89] *o*-fluorophenol,[90] *p*-chlorophenol,[86,91] *p*-cresol,[86,92] and *p*-bromo-,ethyl-,t-butyl-, and phenyl-phenols.[86] In the interesting paper by Barrer and Shanson,[86] the separation of mixtures by clathration in phenol and *p*-cresol is also described.

C. Other More Complex Hydroxy-aromatic Hosts.—The naturally occurring compound guayacanin (20) forms an interesting inclusion compound with

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[78] K. D. Cleaver and J. E. D. Davies, *J. Mol. Structure*, 1977, **36**, 61; and references therein.

[79] R. G. Copperthwaite, *J.C.S. Chem. Comm.*, 1976, 707.

[80] H. G. McAdie, *Canad. J. Chem.*, 1966, **44**, 1373.

[81] H. Ohigashi and Y. Kurita, *J. Magn. Resonance*, 1969, **1**, 464.

[82] E. Hunt and H. Meyer, *J. Chem. Phys.*, 1964, **41**, 353; P. Gregoire, J. Gallier, and J. Meinnel, *J. Chim. Phys.*, 1973, **70**, 1247; J. Gallier, *Chem. Phys. Letters*, 1975, **30**, 306.

[83] Y. Hazoni, P. Hillman, M. Pasternak, and S. Ruby, *Physics Letters*, 1962, **2**, 337; G. J. Perlow, C. E. Johnson, and M. R. Perlow in 'Noble Gas Compounds', ed. H. H. Hyman, University of Chicago Press, 1963, p. 279.

[84] M. V. Stackelberg, A. Hoverath, and Ch. Scheringer, *Z. Elektrochem.*, 1958, **62**, 123.

[85] B. A. Nikitin, *Compt. rend. U.S.S.R.*, 1940, **29**, 571.

[86] R. M. Barrer and V. H. Shanson, *J.C.S. Faraday I*, 1976, 2348.

[87] P. H. Lahr and H. L. Williams, *J. Phys. Chem.*, 1959, **63**, 1432.

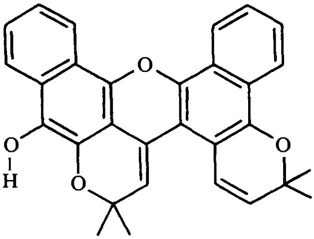
[88] J. E. Mock, J. E. Myers, and E. A. Trabant, *Ind. and Eng. Chem.*, 1961, **53**, 1007; Y. N. Kazankin, F. I. Kazankina, A. A. Palladiev, and A. M. Trofimov, *Doklady Akad. Nauk S.S.S.R.*, 1972, **205**, 1128 (*Chem. Abs.*, 1972, **77**, 172 102); Y. N. Kazankin, F. I. Kazankina, A. A. Palladiev, and A. M. Trofimov, *J. Gen. Chem.* (*U.S.S.R.*), 1973, **43**, 2650; M. F. Pushlenkov and V. A. Ignatov, *J. Gen. Chem.* (*U.S.S.R*), 1974, **44**, 2347; Y. N. Kazankin, F. I. Kazankina, A. A. Palladiev, and A. M. Trofimov, U.S.S.R. P. 411 062, 1974 (*Chem. Abs.*, 1974, **80**, 119 701).

[89] Y. N. Kazankin, A. A. Palladiev, and A. M. Trofimov, *J. Gen. Chem.* (*U.S.S.R.*), 1973, **43**, 2648.

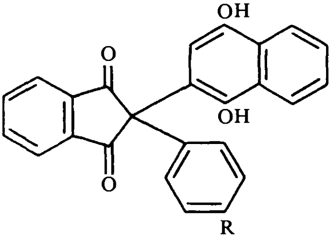
[90] Y. N. Kazankin, A. A. Palladiev, and A. M. Trofimov, *J. Gen. Chem.* (*U.S.S.R.*), 1972, **42**, 2363.

[91] B. A. Nikitin and E. M. Ioffe, *Doklady Akad. Nauk S.S.S.R.*, 1952, **85**, 809 (*Chem. Abs.*, 1953, **47**, 394).

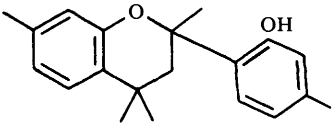
[92] A. M. Trofimov and Y. N. Kazankin, *Radiokhimiya*, 1965, **7**, 288 (*Chem. Abs.*, 1966, **64**, 2999); A. M. Trofimov and Y. N. Kazankin, *Radiokhimiya*, 1966, **8**, 720 (*Chem. Abs.*, 1967, **66**, 61 399); A. M. Trofimov and Y. N. Kazankin, *Radiokhimiya*, 1968, **10**, 445 (*Chem. Abs.*, 1968, **69**, 92 527); for studies on dimethyl and trimethyl phenols see also E. Terres and K. Thewalt, *Brenstoff-Chem.*, 1957, **38**, 257 (*Chem. Abs.*, 1958, **52**, 1948).



(20)



(21) a; R = H
b; R = Cl



(22)

acetone,[93] the trigonal crystals have space group $R\bar{3}$, with a host to guest ratio of 3:1. Clusters of six molecules, analogous to those found in Dianin's compound (1), for example, are linked by a network of hydrogen bonds involving the OH group, such that a hexagon of oxygen atoms is formed. Two acetone guest molecules are situated between adjacent sextets positioned along the *c*-axis.

Although the detailed nature of the adducts is not yet known, noteworthy inclusion behaviour has been reported[94] for compounds of the 2-(2-arylindan-1, 3-dion-2-yl)-1,4-napthohydroquinone type (21), hosts (21a) and (21b) trapping a particularly wide range of guest species. A recent e.p.r. study concerns[95] the 2,2,6,6-tetramethyl-4-piperidinol-l-oxyl radical, trapped by the flavan (22) which also traps many ethers, ketones, and amines.[96] The exact structure of these complexes is, however, apparently unknown.

4 Inclusion Compounds of the Hexa-host Type

A recently proposed[97] strategy has led to the synthesis of inclusion hosts not

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[93] R. Y. Wong, K. J. Palmer, G. D. Manners, and L. Jurd, *Acta Cryst.*, 1976, **B32**, 2396.

[94] L. P. Zalukaev, L. G. Barsukova, *Vysokomol. Soedineniya, Ser A*, 1973, **15**, 2185 (*Chem. Abs.*, 1974, **81**, 14 490); L. P. Zalukaev and L. G. Barsukova, *Zhur. obshchei Khim.*, 1972, **42**, 610 (*Chem. Abs.*, 1972, **77**, 101 263).

[95] W. Smith and L. D. Kispert, *J.C.S. Faraday II*, 1977, 152.

[96] W. Baker, R. F. Curtis, and M. G. Edwards, *J. Chem. Soc.*, 1951, 83; for related hosts (and applications) see also for example W. Baker, R. F. Curtis, and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 1774; W. Baker, D. F. Downing, A. E. Hewitt-Symonds, and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 3796; M. P. V. Boarland, J. F. W. McOmie, and R. N. Timms, *J. Chem. Soc.*, 1952, 4691; W. Baker, J. F. W. McOmie and J. H. Wild, *J. Chem. Soc.*, 1957, 3060; T. Ohta and S. Togano, Japan. Kokai, 75 131 533 (*Chem. Abs.*, 1976, **84**, 114 208); K. Yamada and N. Sugiyama, *Bull. Chem. Soc. Japan*, 1965, **38**, 2057, 2061; and *ref.* 67.

[97] D. D. MacNicol and D. R. Wilson, *J.C.S. Chem. Comm.*, 1976, 494.

directly related to any known host. The idea involved is based in the analogy between the hydrogen-bonded hexamer unit present in the clathrates of Dianin's compound and other hosts (Sections 2 and 3), and a hexa-substituted benzene (see Figure 7). The temporary unit (A) which is subject to collapse as the group R is varied is replaced by the permanent consolidated structure (B), it having been noted[97] that unit (A) corresponds to (B) both in terms of overall geometric aspects and 'hexamer' dimensions (*cf.* distances *d* and *d'* in Figure 7, where Z denotes a general atom or group directly attached to the central benzene ring). Following the idea that suitable hexa-substituted benzenes might have an increased chance of crystallizing to form non-close-packed structures, compounds with general formula (23) have been synthesized.[97,98] All of the compounds

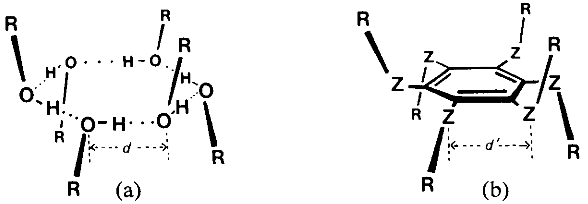
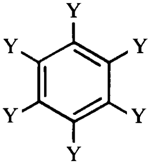


Figure 7 *Comparison of* (a), *hydrogen-bonded hexamer unit with* (b), *hexa-substituted benzene analogue*
(Reproduced from *J.C.S. Chem. Comm.*, 1976, 494)



(23) a; Y = SPh
b; Y = CH_2OPh
c; Y = CH_2SPh
d; Y = CH_2SCH_2Ph
e; Y = $CH_2SC_6H_4Bu^t$-*p*
f; Y = $CH_2SeC_6H_4Bu^t$-*p*
g; Y = $CH_2SC_6H_4$(1-adamantyl)-*p*
h; Y = CH_2S-(2-naphthyl)

(23a—h) exhibit inclusion ability, and (23e) for example, forms adducts with toluene, cycloheptane, cyclo-octane, phenyl acetylene, bromoform, and iodobenzene, with a host to guest ratio of 1:2 in each case. In some cases remarkable guest selectivity is found, 95% *o*-xylene and 5% *p*-xylene being included by host (23e) when it is recrystallized from an equimolar mixture of these solvents.[98] In the case of the CCl_4 adduct of hexaphenylthiobenzene (23a), the crystals are trigonal with space group $R\bar{3}$ and a true clathrate structure is found:[99] two CCl_4 guest molecules fit snugly into a cavity of effective length *ca.* 17 Å, and these are oriented such that a C—Cl bond of each is collinear with the *c*-axis of the crystal.

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[98] D. D. MacNicol and D. R. Wilson, *Chem. and Ind.*, 1977, 84; for other recent work on selective inclusion see D. H. Brown, R. J. Cross, and D. D. MacNicol, *Chem. and Ind.*, 1977, 766, and references therein; K. Takemoto, *Kagaku Kogaku*, 1977, **41**, 184 (a review) (*Chem. Abs.*, 1977, **87**, 7929).

[99] D. D. MacNicol, A. D. U. Hardy, and D. R. Wilson, *Nature*, 1977, **266**, 611.

A very recent *X*-ray study has shown[46b] that, in contrast to the trigonal CCl_4 clathrate of (23a) described above, the crystals of the adduct of (23d) with 1,4-dioxan are monoclinic with space group $P2_1/c$; the chair-shaped dioxan guest molecules being located on crystallographic centres of symmetry.

5 Hosts with Structures Possessing Trigonal Symmetry

Trigonal symmetry is a feature apparent in the molecular structure of several important hosts (including the hexa-hosts in Section 4) forming multimolecular inclusion compounds in which the surrounding lattice is consolidated by van der Waals' attractive forces, but not by hydrogen bonding. The individual host molecule does not always attain exact crystallographic three-fold symmetry, however, although trigonal (or hexagonal) *lattice* symmetry is often encountered.[100] Recent *X*-ray studies have elucidated the structures of channel type adducts of triphenyl methane[101] (24), perhydrotriphenylene[102] (25), tris(*o*-phenylenedioxy) cyclotriphosphazene[103] (26) and related compounds[104,105] and the unsolvated,[106–108] channel-,[106] and cage-type[106,107] forms of tri-*o*-thymotide[22,106] (27). In all the crystal modifications of (27) a propeller conformation is found for the host molecule with the three carbonyl oxygen atoms lying on the same side of the twelve-membered ring, although in no case is exact molecular C_3 symmetry present. In 1954 Baker and co-workers[109] reported results of a study of compounds related to (27), but none of the compounds synthesized gave crystalline inclusion compounds. Interestingly however, *N,N′,N″*-tribenzyltrianthranilide has recently been found[110] to form a 1:1 complex with ethanol. N.m.r. studies of cycloveratril (28) have established that it has a crown conformation.[111]

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[100] See for example S. A. Puckett, I. C. Paul, and D. Y. Curtin, *J.C.S. Perkin II*, 1976, 1873 (Table 3).

[101] A. Allemand and R. Gerdil, *Acta Cryst.*, 1975, **A31**, S130.

[102] G. Allegra, M. Farina, A. Immirzi, A. Colombo, U. Rossi, R. Broggi, and G. Natta, *J. Chem. Soc.* (*B*), 1967, 1020; G. Allegra, M. Farina, A. Colombo, G. Casagrande-Tettamanti, U. Rossi, and G. Natta, *ibid.*, 1967, 1028; A. Immirzi and G. Allegra, *Atti. Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1967, **43,** 181; see also for example, Z. Ciecierska-Tworek, G. B. Birrell, and O. H. Griffith, *J. Phys. Chem.*, 1972, **76,** 1008; and refs. therein.

[103] H. R. Allcock, R. W. Allen, E. C. Bissell, L. A. Smeltz, and M. Teeter, *J. Amer. Chem. Soc.*, 1976, **98,** 5120.

[104] H. R. Allcock and M. T. Stein, *J. Amer. Chem. Soc.*, 1974, **96,** 49 [tris(2,3-naphthylenedioxy)cyclotriphosphazene].

[105] H. R. Allcock, M. T. Stein, and E. C. Bissell, *J. Amer. Chem. Soc.*, 1974, **96,** 4795 [tris(1,8-naphthylenedioxy)cyclotriphosphazene].

[106] D. J. Williams and D. Lawton, *Tetrahedron Letters*, 1975, 111.

[107] S. Brunie, A. Navaza, G. Tsoucaris, J. P. Declercq, and G. Germain, *Acta Cryst.*, 1977, **B33,** 2645.

[108] S. Brunie and G. Tsoucaris, *Cryst. Struct. Comm.*, 1974, **3,** 481.

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[110] W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, and A. G. Fenige, *Angew. Chem. Internat. Edn.*, 1976, **15,** 223; *cf.* D. J. Williams, *J.C.S. Chem. Comm.*, 1977, 170.

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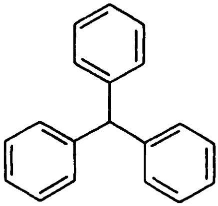

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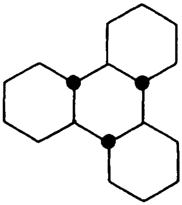

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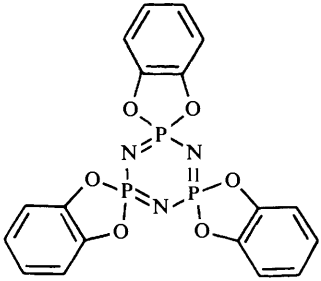

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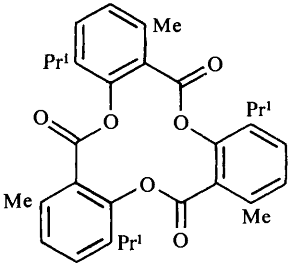

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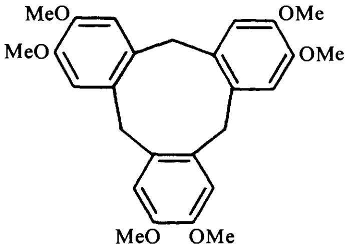

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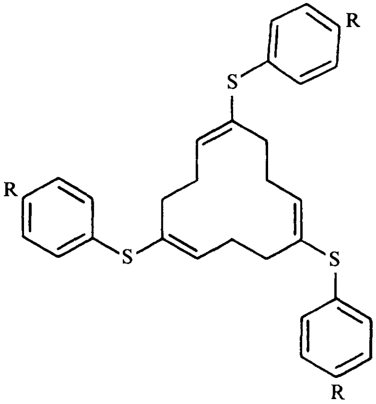
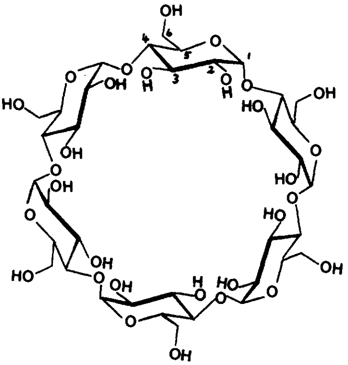


(29) a; R = H
b; R = Me

Compounds (29a) and (29b) have recently been synthesized,[112] trigonal symmetry having been taken into account in their design. Both these hosts tightly retain volatile guest species, for example (29b) forms inclusion compounds with cyclopentane, t-butyl acetylene, and 2,2- and 2,3-dimethylbutanes, the host to guest ratio being 2:1 in each case.

6 Cyclodextrins and Related Molecules

These molecules, which have attracted much attention as enzyme active-site models, are considered very briefly here since several excellent reviews are available.[1–3,5,113] The cyclodextrins (cycloamyloses) are torus-shaped molecules made up of different numbers of α-1,4-linked D-glucopyranose units, α and β-cyclodextrin (α and β-CD), (30) and (31) comprising 6 and 7 units respectively. In contrast to systems discussed earlier, host–guest chemistry is found both in the solid state and in solution. One may also note that the OH groups on C-2, C-3, and C-6 are available as points of structural modification without danger of eliminating the central void availabe for guest accommodation. Numerous *X*-ray studies[114] of α-CD with various guests reveal that both cage-type and channel-type crystalline inclusion compounds are formed. Much work has been done on the binding of guests to the cyclodextrins in aqueous solution, though complexation has also been found for β-CD in non-aqueous solvents.[115] Points arousing much current interest are the geometry of the complexes formed[116] and the factors responsible for complexation[116,117] in aqueous solutions. In extremely



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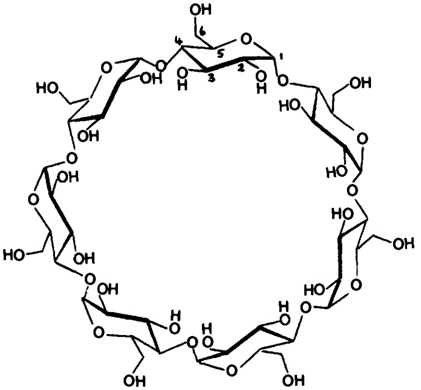

(31)

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[112] D. D. MacNicol and S. Swanson, *Tetrahedron Letters*, 1977, 2969.

[113] D. French, *Adv. Carbohydrate Chem.*, 1957, **12**, 189.

[114] K. Harata, *Bull. Chem. Soc. Japan*, 1977, **50**, 1416; and references therein.

[115] B. Siegel and R. Breslow, *J. Amer. Chem. Soc.*, 1975, **97**, 6869.

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elegant n.m.r. studies[118a,b] involving the nuclear Overhauser effect between host and guest, Bergeron and co-workers have shown that sodium *p*-nitrophenolate penetrates the α-CD cavity to only a limited extent, but is more deeply embedded in the larger β-CD void. In an important study of the molecular dynamics of α-CD complexes by ^2H and ^{13}C relaxation, Behr and Lehn[119] point out the importance of the *dynamic rigidity* of the complex, defined by the coupling between the molecular motions of its component parts. Solution complexation[120] has also been studied by e.p.r.[121] and u.v. spectroscopy,[122] and by c.d.[123,124a] measurements. Microcalorimetric[124b] measurements have also proved valuable, and a recent study[124c] of the interaction of α-CD with a series of small, chiral benzene derivatives has revealed a small, but distinct chiral discrimination for the binding of certain optical isomers, for example, the D and L forms of phenylalanine, the results being consistent with those from a parallel competitive spectral inhibition technique. An equilibrium and kinetic investigation of complexes of β-CD with several small inorganic anions has also been recently described.[125] Stopped-flow spectrophotometry has been employed[126] to study the kinetics of binding of Cu^{II} to α- and β-CD, and an e.p.r. investigation[127] of the complexation of isotopically pure Cu^{II} to these hosts shows two distinct magnetic environments for the copper.

A large number of mono-substituted cyclodextrins have been prepared in connection with enzyme model studies.[1,2,128] In recent work directed towards even more sophisticated enzyme models,[129] a number of specifically bifunc-

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[118] (*a*) R. Bergeron and R. Rowan, *Bioorg. Chem.*, 1976, **5**, 425; (*b*) R. Bergeron and M. A. Channing, *Bioorg. Chem.*, 1976, **5**, 437; (*c*) *cf.* D. J. Wood, F. E. Hruska, and W. Saenger, *J. Amer. Chem. Soc.*, 1977, **99**, 1735; (*d*) for other n.m.r. studies see also ref. 122.

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[120] See also references cited in refs. 119 and 118*c*.

[121] N. M. Atherton and S. J. Strach, *J.C.S. Faraday I*, 1975, **71**, 357; J. Martinie, J. Michon, and A. Rassat, *J. Amer. Chem. Soc.*, 1975, **97**, 1818; N. M. Atherton and S. J. Strach, *J. Magn. Resonance*, 1975, **17**, 134.

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[124] (*a*) K. Takeo and T. Kuge, *Stärke*, 1972, **24**, 331; (*b*) E. A. Lewis and L. D. Hansen, *J.C.S. Perkin II*, 1973, 2081; (*c*) A. Cooper and D. D. MacNicol, *J.C.S. Perkin II*, in press.

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[126] K. Mochida and Y. Matsui, *Chem. Letters*, 1976, 963; and refs. therein.

[127] A. A. McConnell and D. D. MacNicol, unpublished results.

[128] Y. Matsui, T. Yokoi, and K. Mochida, *Chem. Letters*, 1976, 1037; C. van Hooidonk, D. C. de Korte, and M. A. C. Reuland-Meereboer, *Rec. Trav. chim.*, 1977, **96**, 25; and references therein; Y. Iwakura, K. Uno, F. Toda, S. Onozuka, K. Hattori, and M. L. Bender, *J. Amer. Chem. Soc.*, 1975, **97**, 4432; *cf.* also Y. Murakami, Y. Aoyama, and K. Dobashi, *J.C.S. Perkin II*, 1977, 24; and references therein.

[129] I. Tabushi, K. Shimokawa, and K. Fujita, *Tetrahedron Letters*, 1977, 1527; and references therein.

tionalized[129,130] and multifunctionalized[131] cyclodextrins have been prepared. Tabushi and co-workers,[130] studying phosphorescence spectra of complexes of β-CD modified with a 'capping' benzophenone chromophore, have found highly effective and structurally specific triplet energy transfer between excited host and ground state guest molecules. In an extension of earlier work[132] on the remarkable regio-specific chlorination of anisole by HOCl in the presence of α-CD (and β-CD) in aqueous solution, Breslow and co-workers[133] report an even higher specificity employing dodecamethyl-α-CD (all OH groups on C-2 and C-6 methylated), the product being greater than 99% *p*-chloroanisole. This reflects more effective guest binding by the modified α-CD and shows that the C-3 hydroxy (as hypochlorite for Cl transfer) is capable of catalytic function, while not ruling out the possible role of other OH groups in α-CD itself.

The parent α- and β-cyclodextrins have recently found use as chiral n.m.r. shift reagents.[134] For example, in the presence of β-CD in D_2O, ^{19}F n.m.r. spectra of the A_3B_3 type (proton noise decoupled) have been observed for $PhC(CF_3)_2OH$, the induced non-equivalence between CF_3 groups arising from guest accommodation in the optically-active void of the host. Typical spectra for this substrate are shown in Figure 8, dissolved salts such as LiCl increasing the induced chemical shift.

Cyclodextrins and their inclusion compounds have found amazingly diverse uses. In a recent study,[135] β-CD was found to greatly enhance and stabilize the fluorescence intensity of dansyl amino acids, allowing improved detection and determination of these compounds by t.l.c. α-CD is an efficient separating agent for *o*-, *m*-, and *p*-cymene: from an approximately 1:1:1 mixture 97% pure *p*-cymene was obtained by steam distillation of the crystalline adduct.[136] The nitroglycerine inclusion compound of β-CD can be used as an explosive,[137] and the chloropicrin adduct is effective as a bactericide and insecticide.[138] The complex of methyl parathion with β-CD has useful and persistent activity against

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[130] I. Tabushi, K. Fujita, and L. C. Yuan, *Tetrahedron Letters*, 1977, 2503.

[131] R. J. Bergeron, M. P. Meeley, and Y. Machida, *Bioorg. Chem.*, 1976, **5**, 121; K. Tsujihara, H. Kurita, and M. Kawazu, *Bull. Chem. Soc. Japan*, 1977, **50**, 1567; and references therein.

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[133] R. Breslow, H. Kohn, and B. Siegel, *Tetrahedron Letters*, 1976, 1645.

[134] D. D. MacNicol and D. S. Rycroft, *Tetrahedron Letters*, 1977, 2173; *cf.* D. D. MacNicol, *Tetrahedron Letters*, 1975, 3325.

[135] T. Kinoshita, F. Iinuma, K. Atsumi, Y. Kanada, and A. Tsuji, *Chem. Pharm. Bull.*, 1975, **23**, 1166; for other chromatographic applications see also D. M. Sand and H. Schlenk, *Analyt. Chem.*, 1961, **33**, 1624; H. Schlenk, J. L. Gellerman, J. A. Tillotson, and H. K. Mangold, *J. Amer. Oil Chemists' Soq.*, 1957, **34**, 377.

[136] Y. Suzuki, T. Maki, and K. Mineta, Japan. Kokai, 75 96 530 (*Chem. Abs.*, 1975, **83**, 205 896).

[137] E. Akito, Y. Nakajima, and M. Horioka, Japan. Kokai, 75 129 520 (*Chem. Abs.*, 1976, **84**, 58 617).

[138] Y. Suzuki, H. Iwasaki, and F. Kamimoto, Japan. Kokai, 75 89 306 (*Chem. Abs.*, 1976, **84**, 16 737).

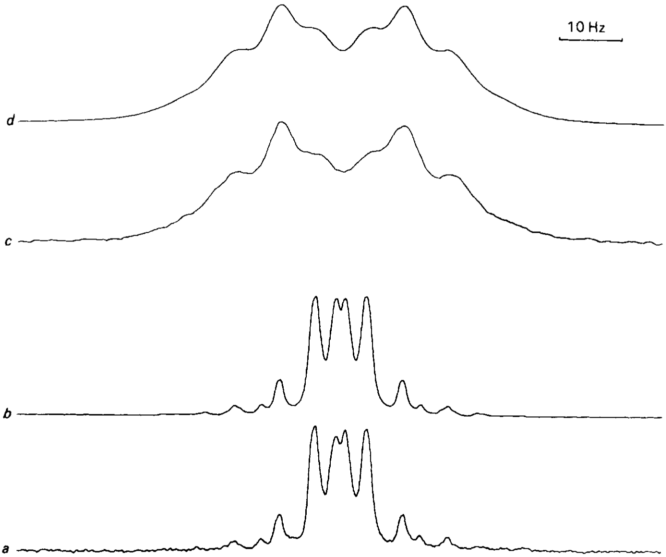

Figure 8 *Proton noise-decoupled* ^{19}F n.m.r. *spectra of* $(CF_3)_2C(OH)Ph$ *in the presence of* β-CD *in* D_2O *showing induced chemical shift non-equivalence. Spectrum a,* 0.01M-β-CD *and* 0.006M-*substrate at* 50°C; *b, simulated* A_3B_3 *spectrum with* ν (A-B) = 13.8 Hz, *J* (A-B) = 8.9 Hz, *and linewidth* = 1.2 Hz; *c, spectrum for* 0.01M-β-CD, 0.01M *substrate, and* 11M-LiCl *at* 25 °C; *d, as b but with* ν (A-B) = 26.0 Hz, *J* (AB) = 8.0 Hz, *and linewidth* = 6.5 Hz

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cotton insects,[139] whereas clathrates of various pyrethroids prove more effective against cockroaches than the guest compounds in their free state.[140] The cyclohexylamine complex of β-CD is useful in rust prevention,[141] and the CO_2 clathrate of α-CD can serve as a baking powder.[142]

The cavities of the cyclodextrins also afford protection to hydroperoxides,[143] coenzyme A,[144] and fatty acids for example, the latter being preserved against oxidation even in a pure oxygen atmosphere.[145]

Currently much of the great interest in the cyclodextrins arises from their

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[139] I. Yamamoto, K. Ohsawa, F. W. Plapp, jun., *Nippon Noyaku Gakkaishi*, 1977, **2**, 41 (*Chem. Abs.*, 1977, **87**, 113 013); see also I. Yamamoto, A. Shima, and N. Saito, Japan. Kokai, 76 95 135 (*Chem. Abs.*, 1977, **86**, 12 714).

[140] A. Mifune, Y. Katsuda, and T. Yoneda, Ger. Offen. 2 357 826, 1974 (*Chem. Abs.*, 1975, **82**, 39 586).

[141] T. Hiroshi and K. Miwa, Japan. Kokai, 76 108 641 (*Chem. Abs.*, 1977, **86**, 31 101).

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[144] T. Oguma, Y. Saito, and T. Kobayashi, Japan. Kokai, 75 142 790 (*Chem. Abs.*, 1976, **84**, 117 800).

[145] J Szejtli and E. Banky-Elod, *Stärke*, 1975, **27**, 368 (*Chem. Abs.*, 1976, **84**, 32 918).

pharmaceutical applications,[5,146] *e.g.*, stable clathrates of l-butyl-l-nitrosourea, a useful anti-tumour agent are formed with α- and β-CD.[147] Significantly, the inclusion compound of flufenamic acid is water soluble unlike the drug itself.[148] The silver-sulphadiazine-β-CD complex[149] is effective in treating burns and infected wounds. Prostaglandin E_2 is greatly stabilized by formation of the α- and β-CD inclusion compounds,[150] and a β-CD complex of a bufadienolide derivative has been found to be more stable, less toxic, and more effective than the free reagent.[151]

Finally, in a recent paper Tabushi and co-workers described[152] a novel one-step preparation of vitamin K_1 or K_2 analogues by cyclodextrin inclusion catalysis.

7 Concluding Remarks

A striking highlight of the literature of the past decade on inclusion chemistry has been the careful design and synthesis of new host materials. The emergence of crown[4] compounds, modified cyclodextrins, and other hosts,[153] is of enormous importance with respect to solution behaviour. New crystalline multimolecular hosts have also been synthesized despite the tendency of the vast majority of organic molecular crystals to be efficiently close packed. Successful tactics here have been the judicious modification of known hosts, and the use of analogy which has led to the discovery of the hexa-hosts. At the present time chemical intuition is still very much to the fore, though with recent developments in crystal packing theory, and the availability of increasingly powerful computer programs for the calculation of potential energy minima in organic crystals, one may predict the possibility of complete void design in the foreseeable future.

We would like to thank Dr. A. D. U. Hardy for reading and making helpful comments on the manuscript.

[146] See for example, S. Tanaka, K. Uekama, and K. Ikeda, *Chem. Pharm. Bull.*, 1976, **24**, 2825; and refs. therein.

[147] T. Nagai and Y. Murata, Japan. Kokai, 73 75 526 (*Chem. Abs.*, 1974, **80**, 71 050).

[148] T. Nagai, Japan. Kokai, 75 116 617 (*Chem. Abs.*, 1976, **84**, 111 654).

[149] H. Trommsdorff, Fr. Demande 2 209 582, 1974 (*Chem. Abs.*, 1975, **82**, 144 957).

[150] M. Hayashi and I. Takatsuki, Ger. Offen. 2 128 674, 1971 (*Chem. Abs.*, 1972, **76**, 59 978).

[151] S. Ohno, Japan. Kokai, 75 160 416 (*Chem. Abs.*, 1976, **84**, 126 774).

[152] I. Tabushi, K. Fujita, and H. Kawakubo, *J. Amer. Chem. Soc.*, 1977, **99**, 6456.

[153] I. Tabushi, Y. Kuroda, and Y. Kimura, *Tetrahedron Letters*, 1976, 3327; I. Tabushi, H. Sasaki, and Y. Kuroda, *J. Amer. Chem. Soc.*, 1976, **98**, 5727.