

Inclusion Compounds – Past, Present, and Future

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1. The Past

1.1. INTRODUCTION

Although one tends to think of the clathrate and inclusion compound story starting in 1947 with the publication of H. M. Powell's papers on the structures and compositions of β -quinol clathrates, the history of the preparation of compounds we now know to be inclusion compounds can be traced back to 1823 when Faraday [1] reported the preparation of the chlorine clathrate hydrate, and even to 1811 if we consider Davy's observations [2] to be a confirmed report.

Amongst other pre-1947 observations of significance are the preparation of graphite intercalates [3] in 1841; the preparation of the β -quinol H_2S clathrate [4] in 1849; the preparation of cyclodextrin inclusion compounds [5] in 1891; the preparation of the nickel cyanide ammonia inclusion with benzene [6] in 1897; the preparation of inclusion compounds of triphenylmethane [7] in 1906; the preparation of the tri-*o*-thymotide benzene inclusion compound [8] in 1909; the preparation of clathrates of Dianin's compound [9] in 1914; the preparation of inclusion compounds of the choleic acids [10] in 1916; the preparation of phenol clathrates [11] in 1935; the preparation of urea inclusion compounds [12] in 1940 and the preparation of amylose inclusion compounds [13] in 1946.

At the time of their preparation, the nature of these compounds was unknown and many of the authors commented on the fact that they seemed to be of variable composition and that in some instances the guest molecule could be removed quite easily from the compound. With hindsight, it does seem remarkable that none of the authors was able to propose a structure for these compounds, and there is at least one instance of an X-ray study being carried out on a β -quinol clathrate with the author failing to detect the presence of the methanol guest molecule [14].

The scene was thus set for the appearance of an inspired crystallographer who was prepared to set aside the prevailing notion that all compounds should be stoichiometric, and propose a structure for these novel compounds. That crystallographer was H. M. Powell who not only proposed a structure for these compounds but also coined a new word '*clathrate*' [15] which has become an accepted part of chemical nomenclature and has gained respectability by being included in the *Oxford English Dictionary*!

In this section of the review we have been fortunate in persuading three people who were very active in the early work on clathrates and inclusion compounds to recount their experiences in working with these novel compounds. Our first contribution is provided by the 'Father' of these compounds, H. M. Powell:

1.2. H. M. POWELL: CLATHRATES

The establishment of clathrate structures could not precede the development of crystal-structure determination to the level of early three-dimensional Fourier treatment of a many-atom problem. The cage-like structure of $Fe_2(CO)_9$ could be determined in 1939 by two-dimensional projection methods because there was no overlap of molecules, nothing and no room for anything in the cage and, owing to symmetry, only 11 independent positional atomic parameters. For the compound $3C_6H_4(OH)_2 \cdot SO_2$, formed by quinol and sulphur dioxide, the structural problem was about the same except that there was a molecule hidden in the cage. In compensation there was, in this case, no difficulty in obtaining data for the three-dimensional analysis that this necessitated. Clathrates ought therefore to have emerged round

about 1939. The structure was delayed. It was known in 1945 and early in 1947 details were published. The β -quinol clathrates were established and named.

To tell, on editorial command, how it came about, to get somewhere near the genesis in which everything inheres, forces me to break a rule by lapses into the first person on a scientific matter. How else could you describe personal involvement in a discovery?

My interest in crystals, like that of every reader, goes back to the first sight of them. There were glittering pyrites in the local coal and sugar on the table – we used a kind called *granulated*, transparent rather than white by reason of crystals, measureable in millimetres, with some oblong facets and visibly different at the two ends. We lived among green fields and hedgerows without surface rock but later and further away, in and around the mountains, I saw rock crystal, the pure source of the word and origin of the science. I had already been suitably instructed against covetousness when I came across a particular cluster of clear quartz cherished under a sideboard by the aged widow of a Welsh quarryman who had risked his life to get it. This gentle lady conveyed to me, at an early age, an even clearer perception of the nature of one of the sins.

A happy school which did no natural science except for those who spent their last two years in its top forms was a suitable next stage. It was from newspapers that I learned about the crucial chemical discovery of hafnium. In the final year I was allowed to go my own way. This included making paper models illustrating crystal symmetry. Encouragement came in the form of a specially purchased spectrometer with which I did my first optical goniometry. The same newspaper sources informed me that the world was then being shown, for the first time, how to determine the crystal structure of rock salt (it was so described because that was what the X-ray spectrometer required). And so to Oxford to read chemistry. By this time crystal structure had become an aim. So little was known about the real dimensions and structures of things represented by unsatisfying chemical formulae. It seemed an obvious way to settle so much disputed chemical constitution. For example, essays used to be written about nitriles and isonitriles and whether the silver cyanide *molecule* (almost everything was perceived in this way) was AgCN or AgNC. I remember later telling N. V. Sidgwick the truth of it.

One tutorial task took up more than a term. It included reading everything in the *Proceedings of the Royal Society* by the Earl of Berkeley and E. G. J. Hartley on osmotic pressures of strong solutions. Substances of sufficient solubility in water were required and one of Hartley's contributions was the synthesis, in *cis* and *trans* forms, of the neutral substance then described as tetramethyl ferrocyanide. One aspect of his work had been disregarded because it was of no relevance to the osmotic problem or to the constitution of ferrocyanides which also engaged his attention. The isomers were separated and purified in the form of solvates. The electronic theory of valency had by this time removed some of the meaningless single dots or empty spaces of the older formulae for coordination compounds but that left the dot that attached the solvating molecule.

I had taken up Crystallography as a Supplementary Subject, working under T. V. Barker. There was no structural work or equipment for it. The main practical exercises were based on optical instruments. Not long afterwards, I was able to help Hartley to complete his ferrocyanide studies by establishing identity or non-identity of products by goniometric methods. Barker, who had worked with Fedorov, used to demonstrate cleavage as an aid to early thought on crystal structure, and discussed packing of polyhedra, pointing out that cleavage octahedra (or tetrahedra) could not be stacked regularly to fill space. I stuck a great many paper octahedra together and contemplated the tetrahedral voids. Eventually Hartley gave me some of his precious materials. Convinced at first that these ferrocyanide complexes could be treated as octahedra which inevitably left some tetrahedral holes when they were

stacked I wished to explain why all my attempts to crystallize one of his isomers *always* gave a solvate. The small solvent molecule would go into a tetrahedral hole. I analysed for solvent and sought to correlate compositions with densities on the assumption of a constant structure with predetermined space for the solvent. This failed and a further blow was success in crystallizing the other isomer free from solvent.

While some of this was going on Barker was appointed full-time Secretary to the University Chest, i.e., the University's chief financial officer. It will pass present belief that up to that time an establishment of some size and importance could manage with a part-time academic such as Barker himself who had occupied the post. One consequence was that I was given a junior appointment to replace Barker's lectures and practical instruction for students of chemistry. For historical and practical reasons this was at first attached to the Department of Mineralogy and Crystallography.

The first task was to start some crystal structure. It was a do-it-yourself period for a number of British crystallographers. X-rays were obtained from gas tubes frequently dismantled for repairs and replacement. There was a vacuum system to be built and maintained. The only available mains supply was 100 volts D. C. In my case this brought a rotary converter of unspeakable parentage, innate delinquency and life-long vicious criminality. But X-rays came out and among the earliest diffraction patterns so obtained was one of a Hartley compound. It was then far beyond the powers of structure analysis but the science developed rapidly to the stage described in the opening paragraph.

During this time, while dealing with more tractable structures I tracked molecular formulae joined by the single dot, the least obtrusive graphic device for concealing the unavoidable ignorance. They had to be manageable and satisfy other conditions. Since 1928 I had known about the benzene compound $\text{Ni}(\text{CN})_2 \cdot \text{NH}_3 \cdot \text{C}_6\text{H}_6$ from a prize, Hofmann's *Lehrbuch der Anorganischen Chemie*, then in a new edition with five of its 750 pages showing how far Crystal Structure had penetrated the subject. He wrote the formula as above but added that one might conclude that strict spatial requirements conditioned the uptake of benzene [or its equivalent] into the 'lückenhafte Komplex $\text{Ni}(\text{CN})_2\text{NH}_3$ ' from which he dropped the dot. Here was the suggestion of voids associated with the other dot, but there were difficulties. Nothing was known structurally about the complex and there were understandable attempts to explain the benzene by including it in the coordination sphere of the metal atom. It was easy enough to make the compound which soon found itself as an exercise in the undergraduate course, but it was a microcrystalline product. I found later that, unknown to the world, many X-ray 'powder' diffraction patterns had been made of it.

So secondary factors determined the course of events. Students, from time to time, in an excess of zeal or through forgetfulness, repeat what Clemm [16] did in 1859. They overdo the reduction of quinone to quinol and end up with the spectacular yellow single crystals of the addition compound with sulphur dioxide. One of these incidents provided a reminder. Then came D. E. Palin who, like Wöhler [4], Clemm [16] and Mylius [17] when they obtained quinol clathrates, was bent on some other urgent purpose. Fortunately it was possible to achieve this by setting him to collect diffraction data for an academic exercise that must otherwise have waited. The compound of quinol and sulphur dioxide was the first choice [18]. A year or two later J. H. Rayner decided, in good time, that he was the one for Hofmann's compound. The problem was to grow a suitable single crystal. It took a lot of systematic variation of conditions and a long time but it was ready when he was. Hofmann's complex was reformulated and the holes for the benzene molecules were found [19]. Materials from other sources began to come in. Professor Wilson Baker, while establishing the structure of tri-*o*-thymotide extended the previous knowledge concerning solvates which, under another

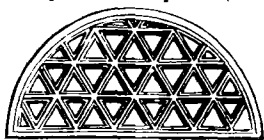
name, it formed [20]. I found with great joy that they were inclusion compounds [21]. Much of the joy concerned a subsidiary matter. Pasteur had always been a hero and every crystal that I ever examined by goniometer or microscope had been scrutinized for signs of enantiomorphism. There were a fair number – natural products like the granulated sugar did not count – but always the enantiomorphism was, like that of quartz, limited to the crystalline state. Ambition to achieve an optical resolution even faintly reflecting the glory of Pasteur's first hand-sorting had not been satisfied. X-ray diffraction had now removed the necessity to get other physical or morphological evidence for enantiomorphism. The first quick diffraction photograph revealed enantiomorphism of the enclosing structure. At once it was planned to resolve this, in the absence of enantiomorphous crystal faces, by observing the sign of the optical activity in the direction of the unique optic axis. Large crystals that could be cut were needed, and what had been learned from T. V. Barker was put into use with the help of his slow coolers, large bomb-like devices that he claimed to have carried to and from Petersburg during the abortive earlier revolutionary period of the century. They were rendered unnecessary by the rapid discovery that the thymotide-benzene compound could easily be grown to centimeter-sized single crystals. One of these was more than enough for a polarimetric confirmation and immediately the procedure was repeated with racemic *sec*-butyl bromide as the solvent. Solution of a single crystal in a passive solvent showed a large optical rotation due to the resolved tri-*o*-thymotide. This rotation decayed rapidly through racemization but left a small permanent rotation due to the selective inclusion of one enantiomorph only of solvent [22]. This seemed a splendid example of sorting molecules by their shapes.

The remaining joy lay in an example of clathrate formation where the enclosing molecules were bound to each other by normal intermolecular forces only, without hydrogen-bonding which is the essence of the quinol compounds or the normal chemical bonding in the extended layers of Hofmann's complex.

The name arose from the events described. In reverse order, something was required to describe an association in which molecular imprisonment was an essential element. Because the perception of enclosure is older than man and much human activity involves it – most manual action, for example – there are widely-spread works of remote ancestry for the idea. Among an international profusion that have the general form of a vowel clutched between

CLATHRA'TUS. Closed or protected by cross-bars of trellis (*clathri*), as explained in the next paragraph. *Plant. Mil.* ii. 4. 25.

CLATHRI. A *trellis* or grating of wood or metal employed to cover over and protect an aperture, such as



a door or window, or to enclose anything generally. (*Hor. A. P.* 473. *Plin. H. N.* viii. 7. *Cato, R. R.* iv. 1. *Columell.* viii. 17. ro.) The example represents the trellis which covered in the lunettes over the stalls (*carceres*) in the circus of Caracalla.

Fig. 1. Entries in *A Dictionary of Roman and Greek Antiquities* (A. Rich, Longmans Green, London, Revised 1884).

some form of KL and a HISS was one happily provided by the school. The mementoes included a dictionary, first published a few years after Clemm made the sulphur dioxide clathrate, concerning the industrial arts and social life of the Greeks and Romans. It gave the meaning of *clathratus* as 'closed or protected by cross bars of trellis'. The *clathri* 'enclose anything generally'. A wood engraving illustrated the trellis which covered the lunettes over the stalls (*carceres*) in the circus of Caracalla (Figure 1). Among international response to the name was instant recall of the birdcage by Slavonic speaking crystallographers. The slavonic world also would understand why the Welsh lady of the quartz cluster would, through *claddfa*, think of enclosure in the burial ground. The other group of Celts have similar words one of which they associate with the use of all the fingers in playing the bagpipes.

It is interesting to note that this nomenclature has recently been extended into the biochemical field with the introduction [23] of the name '*clathrin*' for a protein which can form baskets or cages (Figure 2) which contain particles called vesicles.

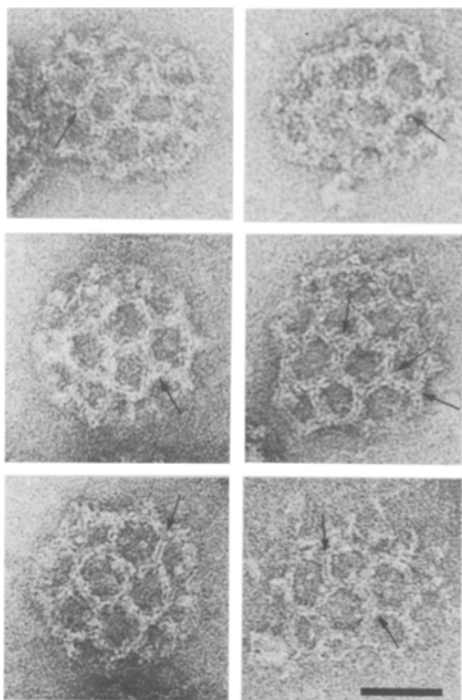


Fig. 2. Large fragments of clathrin cages, negatively stained with uranyl acetate (*J. Cell Biol.* **91**, 793 (1981)).

One paper which inspired much work on the applications of inclusion compounds was the publication by Schaeffer *et al.* [24] describing their studies with Werner ML_4X_2 -type complexes. The following two contributions stem directly from this paper.

1.3. N. O. SMITH: ISOTOPIC FRACTIONATION USING INCLUSION COMPOUNDS

The phenomenon of inclusion had been known for a number of years before the appearance, in 1957, of the important paper by Schaeffer *et al.* [24] of the Union Oil Company of

California, entitled 'Separation of Xylenes, Cymenes, Methylnaphthalenes and other Isomers by Clathration with Inorganic Complexes'. These authors reported the preparation and behavior of a number of Werner hosts of the type ML_4X_2 , where M is a transition metal, L is most commonly a pyridine derivative, and X usually thiocyanate. Although not the first Werner-type host to be reported, the great versatility of this particular kind of substance was impressive, and it was the appearance of this paper which whetted my appetite for further study. The idea of a host such as $Ni(4-Mepy)_4(SCN)_2$ being able to include within its structure guests as widely different in size as benzene and phenanthrene, remarkable in itself, was all the more so when, as the authors demonstrated, it was possible to fractionate *ortho*, *meta*, and *para* isomers. There was also the potential for separating *p*-xylene from ethylbenzene – two isomers with almost the same boiling point. It may be noted parenthetically that the great number of inclusion compounds formed were described as clathrates apparently only on the basis of the analogy between their behavior and that of the host $Ni(NH_3)(CN)_2$, which was already known to form true clathrates with guests such as thiophene and benzene [19].

An understanding of these phenomena required in-depth studies of crystal structure, the nature of the interactions between host and guest, and a more detailed analysis of the selectivity behavior using simpler guest mixtures. With regard to the latter, Schaeffer and his group, with an eye to the utilization of the phenomena for practical applications, had conducted most of their fractionation studies by treating the host with ternary or higher order mixtures of aromatic compounds and comparing the composition of the included material with that of the original mixture. The fact that the solid phase which separated appeared to be a solid solution of clathrates in one another suggested a phase study of the distribution of the guests between liquid solution and solid solution – a variation on a project which I had investigated for ionic substances in water many years earlier [25]. There was also the thermodynamic question of the ideality or non-ideality of the solid solutions – a topic of continuing interest to me [26]. My plan was (1) to find out as much as possible about inclusion compounds of $Ni(4-Mepy)_4(SCN)_2$ (the host which Schaeffer had examined most thoroughly) with only one guest present, and (2) to study the distribution of two guests between solid and liquid phases in an attempt to determine why the ratio of the two guests in the solid solution is different from that in the coexisting liquid.

Our initial studies were with the 1 : 1 compounds of $Ni(4-Mepy)_4(SCN)_2$ with *p*-xylene and with *p*-dichlorobenzene [27]. Powder X-ray diffraction studies showed that although these two compounds may be isomorphous, the crystal lattice was not always the same for different guests. Moreover, the lattice of the inclusion compound, which we called the β form, was different from that for the pure host, which we called the α form. Isothermal phase studies were conducted in the presence of *n*-heptane, and the conditions determined under which the α and β forms were stable. Curiously, the 4-methylpyridine appeared to be able to play a dual role of host ligand and guest. Visible and infrared spectra, and magnetic susceptibilities of the host and its 1 : 1 compounds were taken and interpreted, and enthalpies of formation and heat capacities measured.

Having now gained some familiarity with one-guest inclusion compounds attention was turned to two-guest compounds. Isothermal phase studies at room temperature on ternary systems consisting of $Ni(4-Mepy)_4(SCN)_2$ and two guests were conducted [28] to determine the distribution of the two guests between liquid and solid phase, mentioned above. In the competition between two guests for sites in the host lattice, it was determined that the order of selectivity was *p*-xylene > ethylbenzene > toluene, and *p*-xylene > *p*-dichlorobenzene. In all cases studied these preferences were obtained regardless of the relative quantities of the two guests present. For reasons still not known there was found to be a linear relation between

in R_L and R_S , where R_L and R_S are the mole ratios of the two guests in the coexisting liquid and solid phases. As stated, one of the ultimate goals was to determine why the preferences are in the order found. Various factors such as size, shape, polarity, and polarizability of the guest molecules were clearly properties to be considered.

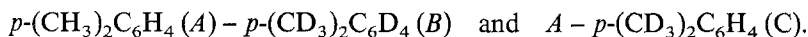
In the meantime, another kind of Werner-type host had been discovered by J. Hanotier and P. de Radtitzky and their associates working for Labofina in Belgium [29]. Their host substances differed from Schaeffer's principally in that the ligands were α -arylalkylamines rather than pyridine derivatives, but they were also very versatile in their ability to include guest molecules. These Belgian workers studied the competitive behavior of their hosts with numerous pairs of guests, and found that the selectivities in a number of examples seemed to be determined by charge-transfer interactions between guest and ligand. The preferences shown by their hosts were different from those shown by $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$.

In 1967 it was my privilege and pleasure to spend a sabbatical working with Professor H. M. Powell, the discoverer of the cage structure shown by many inclusion compounds, and the one who coined the term '*clathrate*'. The time was spent determining the crystal structure [30] of *cis*- $\text{Fe}(\text{CH}_3\text{NC})_4(\text{CN})_2 \cdot 4\text{CHCl}_3$, suspected of being an inclusion compound and, incidentally, notoriously unstable. It developed that one-half of the chloroform was held in cages formed by the ligands on the iron whilst the remaining chloroform was in a loosely held layer from which it could readily escape. The proximity of the hydrogen atoms of the layer chloroform and the nitrogen atoms of the cyanide groups suggested the possibility of a hydrogen bond at those locations. It occurred to me that, because of this, there might be some selectivity shown by this host toward mixtures of CHCl_3 and CDCl_3 . On return to the U. S., I made some attempts along these lines, without success. Nevertheless, the idea of isotope selectivity through inclusion had germinated, and attention was turned to the selectivity that might be shown by $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$ towards a pair of guests which differed only isotopically. These experiments were successful and will be described below. In this way the first fractionations of isotopic molecules by means of inclusion originated.

While this initial work on isotopomers was taking place some progress had been made in understanding more about the structural features of these materials. In 1963, G. A. Jeffrey and co-workers [31] had concluded from single crystal X-ray data that the inclusion compounds of $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$ with nitroethane, methanol, benzene, nitrobenzene, *p*-xylene and *p*-dichlorobenzene are isomorphous, determined that their space group is $I4_1/a$, and found the lattice constants for the tetragonal crystals. Unfortunately, however, their method of preparation led to inclusion compounds in which not all the guest sites were filled. In 1969 Allison and Barrer [32] studied the sorption properties of the analogous cobalt host towards the vapors of many guests, including toluene, ethylbenzene and the xylenes. They were able to obtain the β lattice of the host, without guest present, in a metastable form. The sorption of the guests was found to be reversible and the behavior in general could be described as zeolitic. Three years later, Andreotti *et al.* [33] reported the first detailed crystal structure of the β form of $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$, and de Gil and Kerr [34] used their data to examine the size and shape of the cavities. (It had become apparent [33], incidentally, that the nitrogen of the SCN group is adjacent to the nickel atom, so that the designation 'isothiocyanate' now seemed more appropriate than 'thiocyanate'.) The most enlightening paper, however, from the structural point of view, was the recent one of Lipkowski *et al.* [35] who reported the results of a single crystal X-ray study of the inclusion compounds of $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$ with *p*-xylene, *m*-xylene, and methanol. For the first time, the actual location of *p*-disubstituted benzene guest molecules in the channels had been determined.

We now return to our fractionation studies with pairs of guests in which the members of

any one pair differ only isotopically. Most of our work has been with the guest pairs



Attempts to prepare *C* yielded mixtures of variously deuterated *p*-xylenes, and all our deuterated compounds have since been purchased ready-made. In studying the competition between such pairs of isotopomers our earlier procedure [28] was modified by the use of a co-solvent, usually *n*-pentane, in order to economize on the quantities of deuterated substances needed. The solid host was stirred at room temperature with excess of a mixture of the two isotopic guests in *n*-pentane for a period of days or weeks. At the end of this equilibration period the mole ratios of the two guests, *B/A* or *C/A*, in the liquid and solid phases were determined by mass spectrometry. These ratios were designated R_L and R_S , respectively. The essential result for both guest pairs was that R_L and R_S for any one original composition are different, with $R_L < R_S$, indicating a preference in the solid phase for the deuterated isomer [36]. Furthermore, as shown later [37], R_L is proportional to R_S within experimental error (with R_L being about 10% less than R_S) and the proportionality constant, really a separation factor, is nearly the same for the *B/A* and *C/A* systems, showing that deuteration of the methyl groups is more important in producing the effect than deuteration of the aromatic ring. Similar but less noticeable fractionation occurred with the isotopic naphthalenes. It was found that the fractionation of the *p*-xylenes could be amplified considerably by liquid chromatography [38] in which the pre-treated host was the stationary phase. (The use of host as stationary phase in liquid chromatography for the separation of guests had been first reported in 1960 by Kemula and Sybilska [39] and the procedure subsequently developed by Lipkowski and others of the Polish Academy of Sciences [40].)

I recall many discussions concerning the reasons for the preference for the more deuterated guest. In the first place, do the results represent thermodynamic or kinetic effects? The good linearity of the plots of R_L vs. R_S suggested thermodynamic effects, since lack of attainment of equilibrium would likely give more scatter to the data. Some felt that the more deuterated isomer was preferred because it is slightly smaller than the protiated, and so arrives at the site in the host lattice more readily. If is so, however, would it not be able to leave more readily also? Alternatively, one might expect the lattice constants with deuterated guest in place to be slightly smaller than those with the protiated guest. Thus the former might be energetically slightly more favored. On the other hand, if the smaller of the two guests is favored by the host, why is *p*-xylene (larger) favored over *p*-dichlorobenzene (smaller)?

Such questions were difficult to resolve without a knowledge of the crystal structure of the *p*-xylene inclusion compound. The timely appearance of this structure [35], already referred to, revealed that the *p*-xylene molecules are held in interconnecting spiral channels in such a way that, at every interconnection, four of the methyl groups of four different *p*-xylene molecules are adjacent, and lie at the corners of a tetrahedron. Moreover, the fit of these in the channels appears to be a somewhat loose one. Needless to say, the inclusion nature of the guest-host combination was proven by this work, but the presence of the guest in channels rather than cages indicated that the use of the term 'clathrate' to describe the structure is less appropriate.

If, then, the *p*-xylene molecules are held comparatively loosely, perhaps the slight differences between protiated and deuterated *p*-xylenes have no effect on the guest-host interactions. This led to another hypothesis which may be advanced to account for the observed selectivity: the relative distribution of two guests depends on the ratio of the equilibrium constants for Guest (in inclusion compound) \rightleftharpoons Guest (in liquid) for the two guests, in this case for the protiated and deuterated species. Thus the fugacity of the guest in the liquid phase is also a determining

factor, and if the pure deuterated isomer should have a greater vapor pressure than the pure protiated isomer this alone could account for the observed selectivities if the vapor pressures differ by about 10%. The vapor pressures of *B* and *C* do not appear to have been measured at room temperature (although the normal boiling points are available), but on the basis of the known vapor pressures of pairs like benzene and perdeuterobenzene a difference of roughly 10% between *A* and *B* and between *A* and *C* is entirely reasonable. A corollary to this would seem to be that one should not compare the preferences of a host for one member of a given pair of guests without first correcting for inequality of their vapor pressures. The obvious thing to do is to measure the vapor pressure differences between *A* and *B* and between *A* and *C* at room temperature, and this is being investigated.

The phenomenon of the fractionation of isotopic molecules by means of inclusion has many ramifications, and the wide variety of materials yet to be studied, not to mention possible practical applications, makes the field attractive. For these reasons we are continuing our investigations. It is a pleasure to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the major support of our researches.

1.4. *W. KEMULA*: SOME REMARKS ON THE APPLICATION OF CLATHRATES IN CHROMATOGRAPHY

Today, when Powell's concept of clathrate compounds is more than 30 years old, the idea of using clathration as a selective means for the separation of mixtures of molecules differing in molecular shape and/or size may appear as a rather obvious one. It was not so however during the 1950s when Schaeffer and his coworkers started their experiments on the clathration of aromatic hydrocarbons by Werner ML_4X_2 coordination complexes. The extensive studies performed by the group of Schaeffer in U.S.A. [24] and de Radzitzky in Belgium [29], and later in several other countries demonstrated the wide possibilities and attractiveness of clathration as a separation process. Another result obtained from Schaeffer's study, namely that clathration may take place not only through a dissolution-crystallisation process but even by simply contacting the host compound with the guest was of great interest to us. This observation prompted us to study the chromatographic properties of some Werner type ML_4X_2 complexes as hosts [39].

At that time the separation of isomers, even on an analytical scale, was a difficult problem. The selectivity provided by the ML_4X_2 hosts was just what we needed: molecular shape and size were the factors determining guest affinity to the host lattice. The results we obtained were extremely interesting.

The first attempt to apply clathrate compounds as a separation system in chromatography was made in 1960.

A simple chromato-polarographic apparatus, which was constructed in 1952 [41], consisting of a chromatographic column and a polarographic detector was used. During a previous application of this apparatus using a reversed phase partition system, consisting of rubber swollen with isooctane we obtained excellent results especially in the separation of nitro-aliphatic homologous molecules differing by molecular weight, but it was not very effective in the separation of isomers.

However using the same apparatus but with the rubber replaced by 0.80 g of the clathrate compound $Ni(NCS)_2(4-Mepy)_4 \cdot (4-Mepy)$ contained in a column 6.0 cm in length and 0.6 cm in diameter, we achieved excellent separation [42] of isomers in 1962. For example, four isomers of nitrobutane could be separated, when only 10 cm³ of percolating liquid were used (Figure 3).

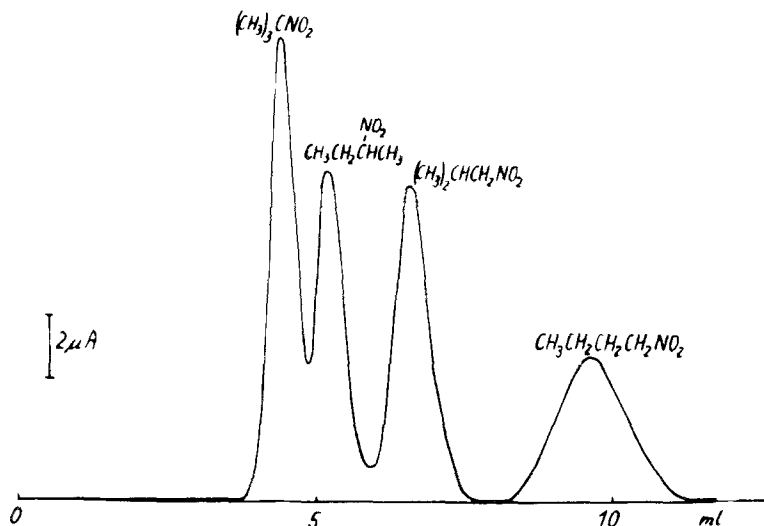


Fig. 3. Elution curve of the nitrobutane isomers (*Acta Chim. Acad. Sci. Hung.* 27, 137 (1961)).

This clathrate system was unable to separate homologues so we devised a mixed separating system, where the reversed phase partition system was combined with the clathrate system. This mixed system had excellent separation properties for the separation of mixtures of homologues and isomers. As an example, I can mention the separation of eight nitroaliphatic C_1 to C_4 species. (Figure 4).

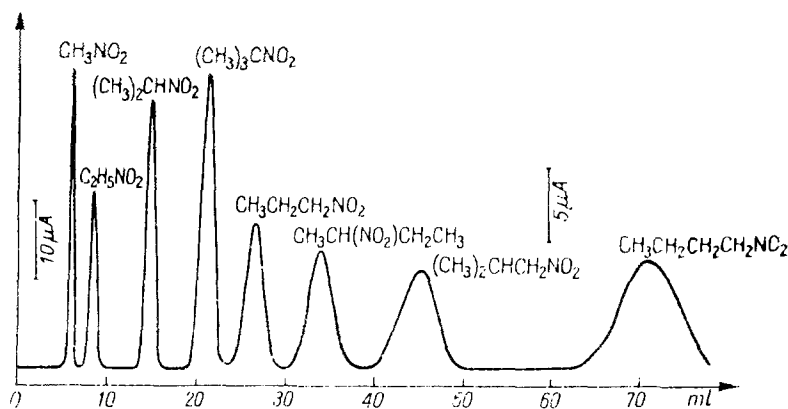


Fig. 4. Separation of eight nitroaliphatic C_1 to C_4 species (*Roczniki Chem.* 38, 861 (1964)).

We have published many results, where other mixtures have been very effectively separated, using our simple chromatopolarographic apparatus. Especially valuable was the electro-analytical polarographic detection, using a dropping mercury electrode.

I illustrate some characteristic examples of chromatographic analyses carried out using Werner clathrates as stationary phases. The most typical are resolutions of *o*-, *m*-, and

p-isomers of disubstituted benzenes (Figure 5). The observed selectivity was always $p \gg m \geq o$. Complex mixtures of dinitrotoluenes could also be analysed (Figure 6).

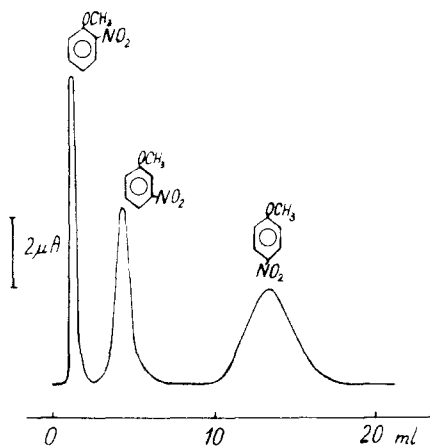


Fig. 5. Elution curve of a mixture of nitroanisoles (*Proc. IV Int. Symp. Chromatography and Electrophoresis*, Presses Academiques Europeennes, Brussels, 1971, p. 212).

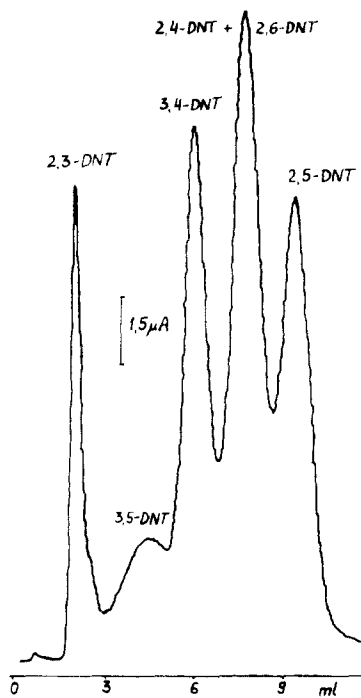


Fig. 6. Elution curve of a mixture of dinitrotoluenes. (*Czechoslovak-Polen Symp. Petro- and Carbochemistry*, Nováky, 1967, 95, Ed. IChO, Warszawa).

The introduction of a new type of electrochemical detector, based on the adsorption of molecules at the electrode surface instead of electrochemical redox reactions [43] resulted in the analyses of electrochemically non-active compounds. An example of the separation and detection of 1-, and 2-methylnaphthalenes is given in Figure 7.

While we were investigating other examples of practical, analytical separations in liquid and gas chromatography using clathrates as the stationary phase, several other competitive analytical techniques were developed and clathrate chromatography is no longer the only technique for the separation of isomers. However, it should be stressed, that the extraordinary selectivity of inclusion processes may still be of fundamental importance in many analytical problems where high selectivity is needed.

It is necessary to understand the physico-chemical basis of inclusion processes before it is possible to predict the selectivity of a given host. Such background must contain structural information, but this was the weakest point for several years.

Thus, about 1970 we started our programme investigating the physicochemical basis of clathration. The scientific cooperation between Prof. Andreetti's group in Parma (Italy) and our team in Warsaw has led to the successful elucidation of the structures [44] of many inclusion compounds formed by $\text{Ni}(4\text{-Mepy})_4(\text{NCS})_2$. This structural information has led to

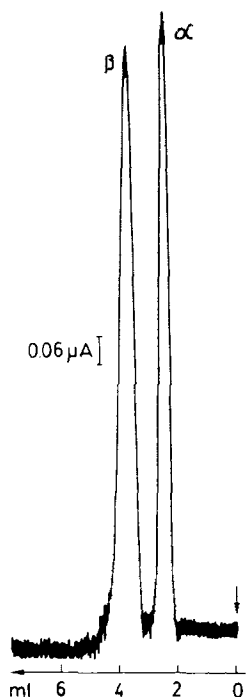


Fig. 7. The chromatographic elution curve of a mixture of 1- and 2-methylnaphthalenes recorded with the AC polarographic method at -1020 mV vs. NCE (*Roczniki Chem.* 45, 268 (1971)).

further analytical developments such as the optimization of chromatographic resolution [45, 46].

Finally, I would like to say that the research carried out in this field has given me much personal scientific satisfaction. Studying the mechanisms of molecular sorption-desorption processes and looking for new clathrating agents is really an exciting and attractive pastime! This is particularly true when we are now able to design analytical separations and related analytical techniques by the selection of an optimal host on the basis of previous physico-chemical studies of the system.

2. The Present

2.1. INTRODUCTION

Figure 8 shows the annual distribution (1948–1981) of the number of abstracts appearing under the 'Clathrates' (1948–1976) and 'Inclusion Compounds' (post 1977) sections in *Chemical Abstracts*. Included in these totals will be studies on clathrates, inclusion compounds and intercalates but not on zeolites since they are abstracted separately. Also excluded will be compounds which have been described in the literature as 'solvates', but there is no doubt that many of these are in fact inclusion compounds [47].

During the compilation of the data required for Figure 8 many interesting and novel applications of inclusion compounds were encountered.

Processes for the purification and desalination of water using clathrate hydrates of

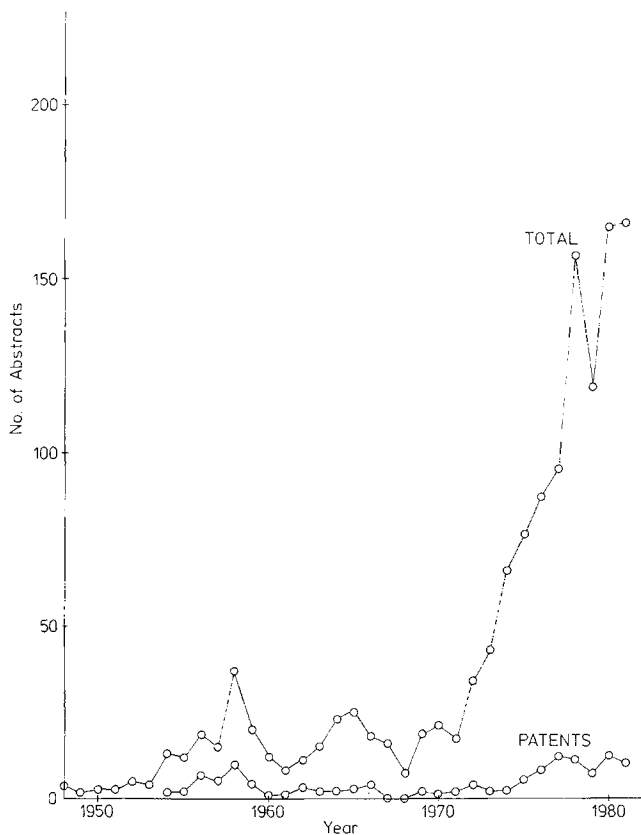


Fig. 8. The annual distribution of abstracts on inclusion compounds.

hydrocarbons and fluorochloromethanes have been proposed [48]. It has also been suggested that clathrate hydrates occur in comets [49], in deposits of natural gas in arctic regions [50], in coal strata [51], and in Saturn's satellite Titan [52].

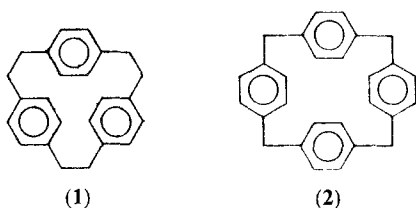
Inclusion compounds of $RCH = CH(CH_2)_{n-1}X$ ($R = \text{alkyl}$; $X = \text{CHO}$ or CH_2OH ; $n = 1$ or 2) in the hosts cyclodextrin, urea and thiourea have been tested as bird repellents with seeded soyabean [53]. The β -cyclodextrin/3-hexen-1-ol inclusion compound was found to be the most effective.

Inclusion compounds of cyclodextrins with fragrant substances such as lavender oil have been added to plastics [54]. The products are claimed to have a long-lasting fragrance.

The inclusion compounds of urea and fatty acids have been found to improve the lathering of non-soap detergent bars [55]. A detergent bar consisting of 3.9% urea, 3% coconut fatty acids, 48.6% sodium acylisethionate, 2% sodium dodecylbenzenesulphonate, 11% sodium soap, 21.7% stearic acid, 8.5% additives, and 5.2% water shows a 50% increase in lather volume compared with a similar bar without the urea.

A rather frightening prospect is the possibility of using inclusion compounds as explosives! [56]. The inclusion compound produced using $\text{Pb}(\text{OH})\text{OC}_6\text{H}_2(\text{NO}_2)_3$ as the host and $\text{Pb}(\text{N}_3)_2$ as the guest in a 4 : 6–13 host : guest ratio turns out to be a sensitive powerful primary explosive, with an instantaneous explosive temperature of 283° . On the other hand it has been found that the β -cyclodextrin inclusion compound of nitroglycerine is extremely stable and cannot be exploded even with an initiator [57].

Peaceful uses of inclusion compounds have also been proposed, such as the proposal to use the thio-Dianin's host as a storage medium for highly toxic compounds such as dimethyl mercury [58]. It has also been proposed that the paracyclophanes (1) and (2) could be used to store hydrogen [59].



A recent interesting application of zeolites is a portable refrigeration system [60] based on the adsorption-desorption cycle shown in Figure 9, and such a refrigerator is being assessed for use in developing countries [61]. Other reported benefits of using zeolites are a 63% yield improvement when growing carrots in zeolite conditioned soils and an increase in body weight when zeolites are added to a pig's diet [62].

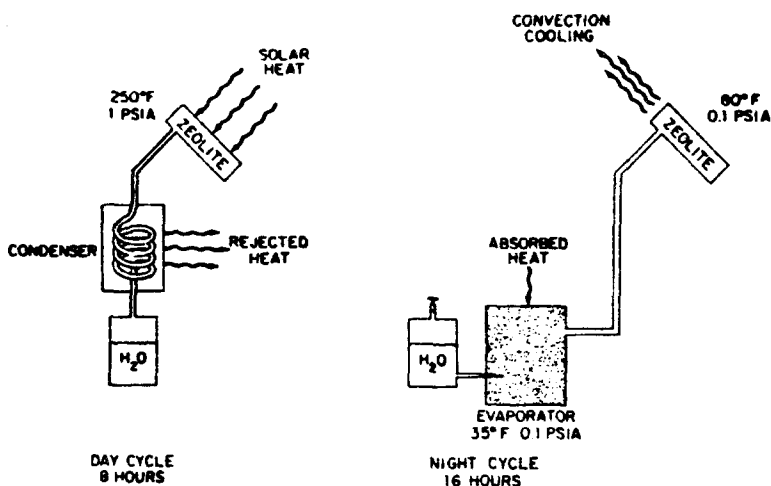


Fig. 9. Zeolite refrigerator system.

Returning now to Figure 8, the rapid increase in the number of publications from 1972 onwards highlights the necessity for the present journal. The increase can be correlated with several factors such as:

2.2. THE DISCOVERY OF THE SIZE SELECTIVITY PROPERTIES OF CROWNS AND CRYPTATES

Two other names, those of C. J. Pedersen and J.-M. Lehn, must now be introduced into the inclusion compound story as persons who not only have made substantial contributions to the development of inclusion chemistry but also introduced two new words of chemical nomenclature, which incidentally have not, as yet, been included in the *Oxford English Dictionary*!

C. J. Pedersen synthesised the first crown ethers [63] and J.-M. Lehn and his coworkers introduced the cryptates [64]. The outstanding property of these ligands is their ability to

complex with metal ions, where the metal ion occupies the void in the centre of the molecule (Figure 10). Since the dimension of the void is governed by the number of atoms forming the cyclic system in the ligand, it has been further found that each ligand generally shows a selectivity for a particular metal ion (Figures 11 and 12) the highest selectivity being shown towards the metal ion whose diameter best matches the diameter of the void.

Subsequent work on crown and cryptate compounds [65] has given rise to an enormous number of compounds which in turn has led to the introduction of new nomenclature so that the literature now abounds with references to coronands (3), cryptands, podands (4), spherands (5), ionophores [66], tweezer molecules [67] (6), hexapus molecules [68] (7), which

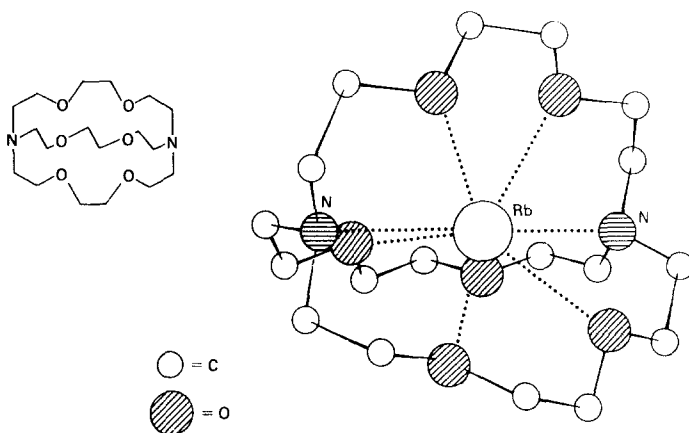


Fig. 10. The structure of the cation in the salt $[\text{RbC}_{18}\text{H}_{36}\text{N}_2\text{O}_6]\text{SCN} \cdot \text{H}_2\text{O}$ (*Chem. Britain* 7, 203 (1971)).

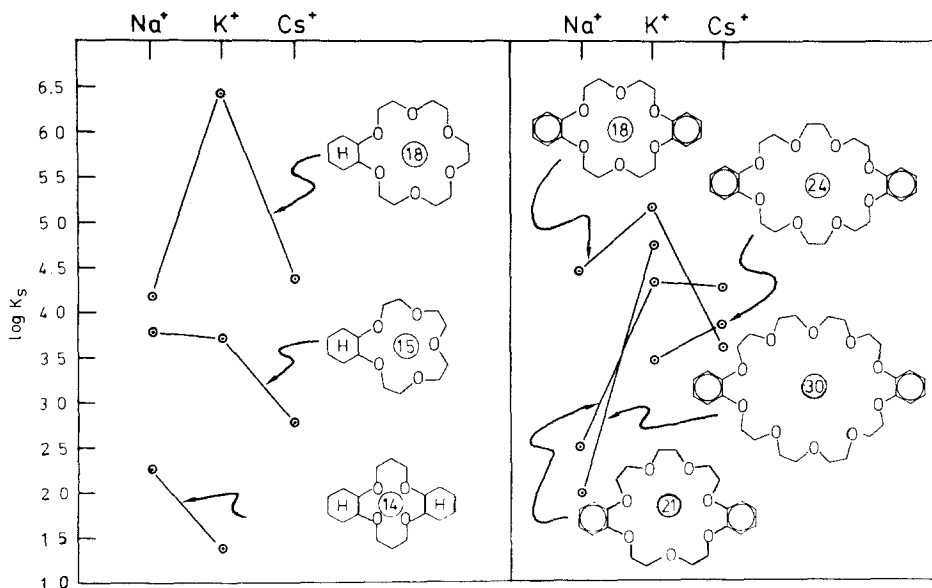
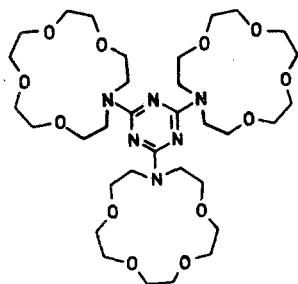
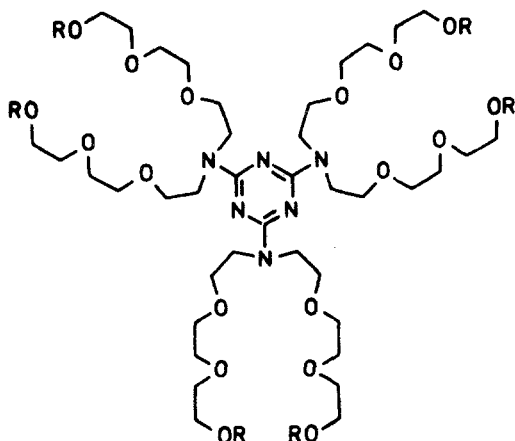


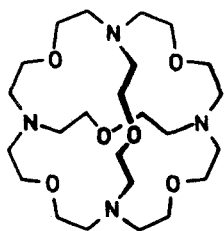
Fig. 11. Stability constants for various crown ether complexes (*Struct. Bonding (Berlin)* 16, 161 (1973)).



(3)



(4)

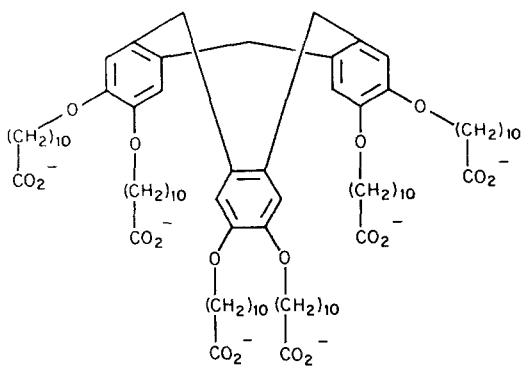


(5)

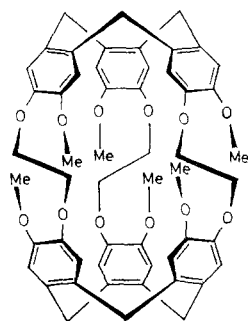


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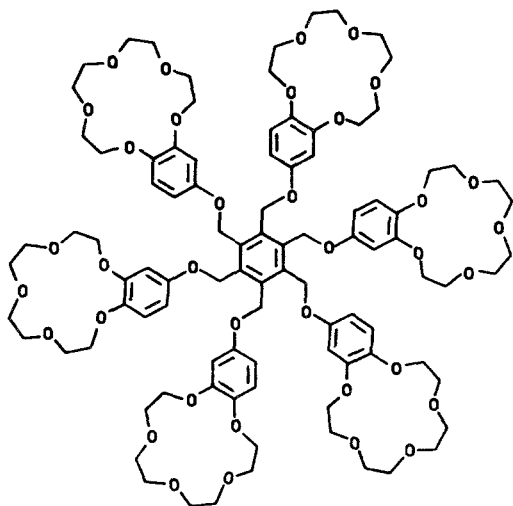
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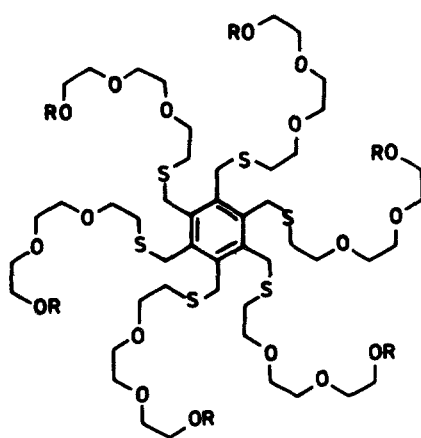
(7)



(8)



(9)



(10)

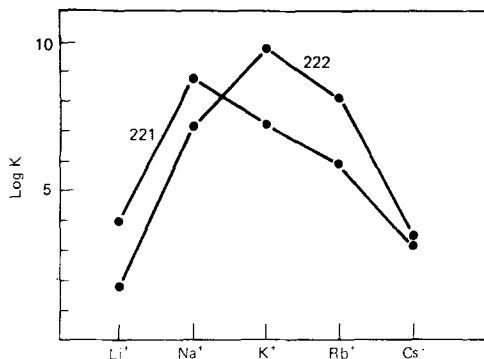
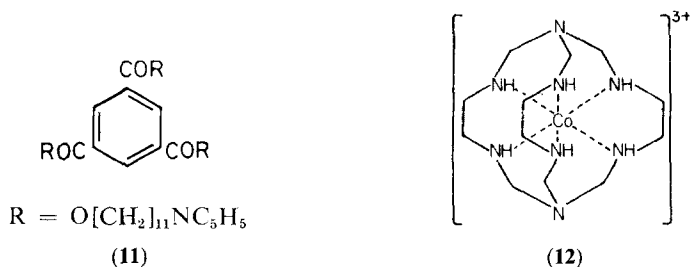


Fig. 12. Stability constants for cryptates – 221 and – 222 versus alkali ion (*J. Am. Chem. Soc.* **97**, 6700 (1975)).

can join to form macrocages [69] (8), octopus molecules (9) and (10), tentacle molecules [70] (11) sepulchrates [71] (12) and even 'Mobius Strip' molecules [72] (Figure 13). This must also be an area of chemistry which appeals to one's artistic tastes!

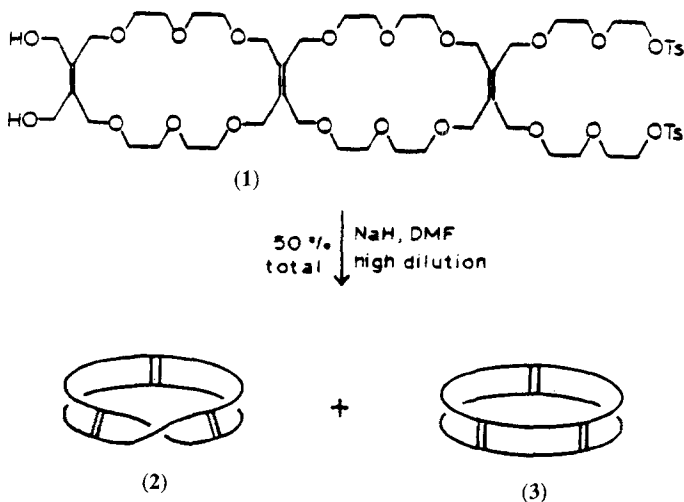


Fig. 13. Synthesis of the Mobius strip molecule (2) (*J. Am. Chem. Soc.* **104**, 3219 (1982)).

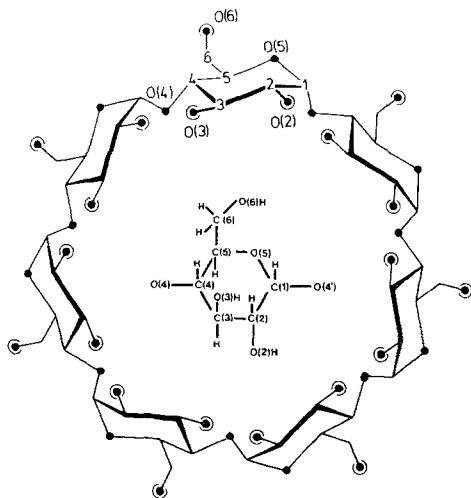


Fig. 14(a). The structure of β -cyclodextrin.

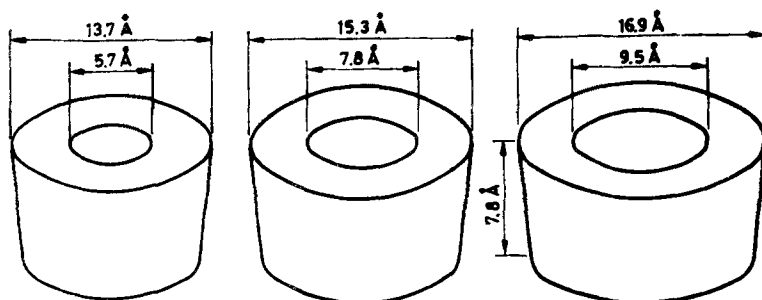


Fig. 14(b). Comparison of the dimensions of α -, β -, and γ -cyclodextrins.

2.3. STUDIES ON CYCLODEXTRIN INCLUSION COMPOUNDS

The cyclodextrins are cyclic oligosaccharides (Figure 14a), the most common ones containing 6(α), 7(β) or 8(γ) glucose units. The diameter of the cavity thus depends on the number of glucose units as shown in Figure 14b, and like the crowns and cryptands they show a selectivity for the guest whose dimensions best match the cavity dimensions. A great deal of work has been carried out on cyclodextrin inclusion compounds [13-15], and this will be discussed in more detail in Section 3.6.

2.4. MODIFICATIONS OF EXISTING HOST LATTICES AND THE SYNTHESSES OF NEW HOST LATTICES

The selectivity of a host lattice can be altered by slight modifications to its chemical structure. The Hofmann-type host lattice serves as an illustration. The structure of the nickel cyanide ammonia inclusion compound with benzene, $\text{Ni}(\text{NH}_3)_2\text{Ni}(\text{CN})_4 \cdot 2\text{C}_6\text{H}_6$, first prepared in 1897 [6], was reported by Powell and Rayner [19] in 1952. The structure (Figure 15) consists of planar layers containing the metal atoms and the cyanide groups with the NH_3 groups

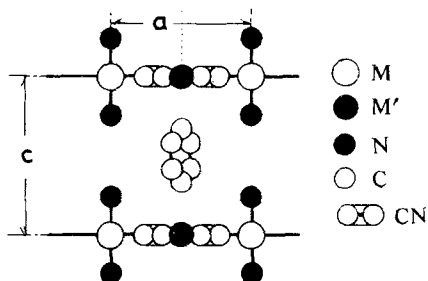


Fig. 15. The structure of a Hofmann inclusion compound $M(NH_3)_2M'(CN)_4 \cdot 2C_6H_6$ (*Inorg. Chim. Acta* **2**, 313 (1968)).

protruding above and below these layers. The ammonia groups then define the void wherein the guest molecule resides. Since the c dimension is essentially fixed the host lattice displays a selectivity towards the length of the molecule, being able to accommodate benzene but not the longer toluene molecule.

Iwamoto and his coworkers [76] have made extensive studies of these host lattices and have been able to introduce several interesting modifications. The ammonia molecules can be replaced by α, ω -diamines such as 1,2-diaminoethane (en) to give a structure (Figure 16) where the diamine bridges the atoms in adjacent layers, giving a compound of stoichiometry $Cd(en)Ni(CN)_4 \cdot 2C_6H_6$. The c dimension in this type of host lattice is smaller than that in the corresponding ammonia containing lattice, thus whilst the latter lattice can accommodate the aniline guest molecule the former cannot.

When 2,4-diaminopropane, $CH_3CH(NH_2)CH_2CH_2NH_2$, (pn) is used as the bridging ligand, the stoichiometry of the compound becomes $Cd(pn)Ni(CN)_4 \cdot 1.5$ Guest, since the terminal methyl groups now occupy one of the voids formerly occupied by the guest molecule (Figure 17).

The final modification is to replace the planar $Ni(CN)_4$ unit with tetrahedral units such as $Hg(CN)_4$ and $Cd(CN)_4$. This modification results in a drastic change in the host lattice structure (Figure 18) since the layers are no longer planar with the result that the structure

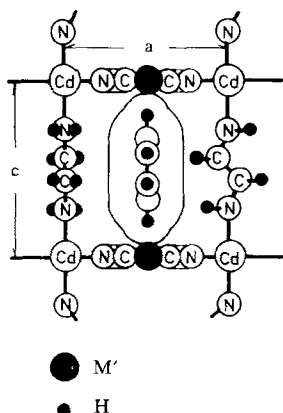


Fig. 16. The structure of $Cd(en)Ni(CN)_4 \cdot 2C_6H_6$ (*Inorg. Chim. Acta* **2**, 269 (1968)).

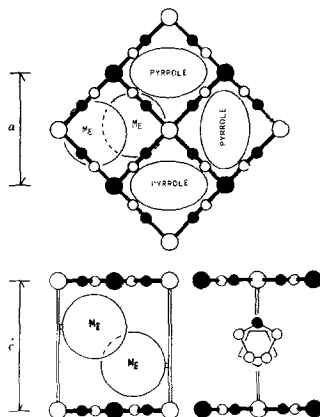


Fig. 17. The structure of $Cd(pn)Ni(CN)_4 \cdot 1.5 C_4H_5N$ (*Isr. J. Chem.* **18**, 240 (1979)).

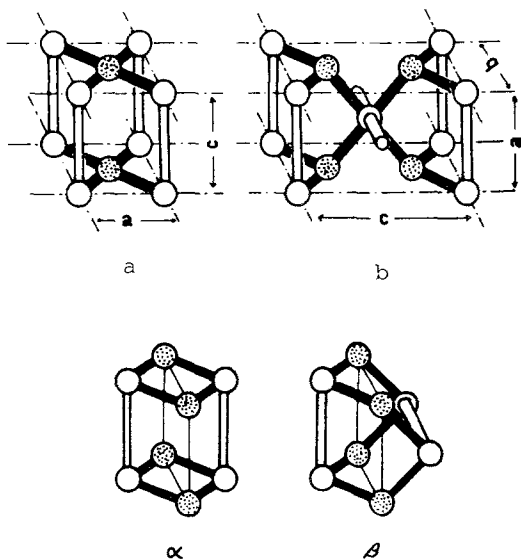


Fig. 18. The structures of (a) Cd(en)Ni(CN)_4 and (b) Cd(en)Cd(CN)_4 , showing the two different types of void in (b) (*Inorg. Chem.* **11**, 2570 (1976)).

now contains two differently shaped voids, a rectangular (α) void and a biprismatic (β) void.

The overall result of the above approach is generally to induce minor changes in the selectivity of the host. The alternative approach is to try and synthesise completely new compounds in the expectation that they would be able to act as host lattices. A precondition of this approach is a good understanding of the nature of inclusion compounds and an appreciation of some of the factors controlling the ability of compounds to act as host lattices.

This approach has been used by MacNicol and his coworkers [77] who noted the similarity between the geometry and dimensions of the hexagonal unit of hydrogen bonded O–H groups which is found in the phenol, quinol and Dianin's compound host lattices with those of a hexasubstituted benzene ring (Figure 19). By choosing suitable substituents it is therefore possible that the hexasubstituted benzenes will act as host lattices. It has indeed been found that compounds with substituents such as SPh, CH_2OPh , CH_2SPh , and $\text{CH}_2\text{SCH}_2\text{Ph}$ can act as host lattices giving the so-called 'hexa-hosts'.

MacNicol has also noted that a feature common to several host lattices is trigonal symmetry

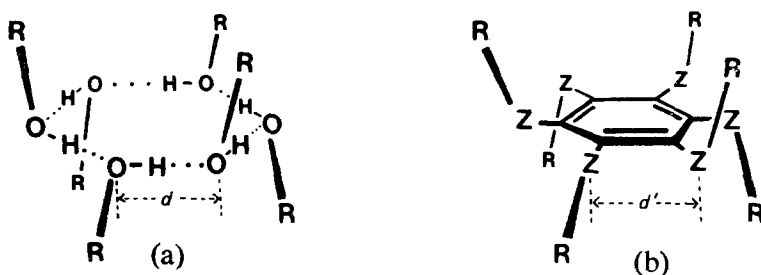
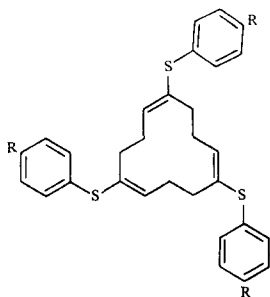


Fig. 19. Comparison of the hydrogen bonded hexagon (a) with a hexa substituted benzene ring (b) (*J. Chem. Soc., Chem. Commun.*, 494 (1972)).



(13)

of either the individual host molecule or of the lattice. Bearing this in mind, compounds (13) were synthesized and it was found that when $R = H$ or CH_3 both molecules do act as host lattices.

2.5. CHROMATOGRAPHIC APPLICATIONS

Professor Kemula has outlined the use of Werner type compounds in chromatography, and has illustrated several separations which can be achieved using very short column lengths of $Ni(4-Mepy)_4(NCS)_2$ (Figures 3–7). Several other host lattices have been used chromatographically, and full details can be found in a recent review [78].

2.6. INDUSTRIAL APPLICATIONS

In recent years there has been considerable interest in the physical properties of inclusion compounds, particularly intercalates, for use in battery systems and in the search for room temperature superconductors. These aspects have been reviewed in depth very recently [79].

3. The Future

3.1. INTRODUCTION

What does the future hold for inclusion compounds, whose extremely diverse geometries are illustrated in Figure 20? It is of course extremely hazardous to attempt to predict the future, but in the euphoria surrounding the launch of a new journal we will grasp the nettle with both hands, and we look forward to reviewing the predictions made here in Volume 21 of the *Journal of Inclusion Phenomena*!

Whilst most of the predictions made here have been arrived at by extrapolating present research work in this area, this approach cannot of course take account of unexpected developments in synthesis or techniques, and it is these unexpected developments which make research work so interesting (and unpredictable!)

One area which causes much confusion is the nomenclature of inclusion compounds as illustrated in Section 2.2. The paper by Drs. Weber and Josel [80] in this issue of the Journal proposes a much needed new system of classification and nomenclature for inclusion compounds.

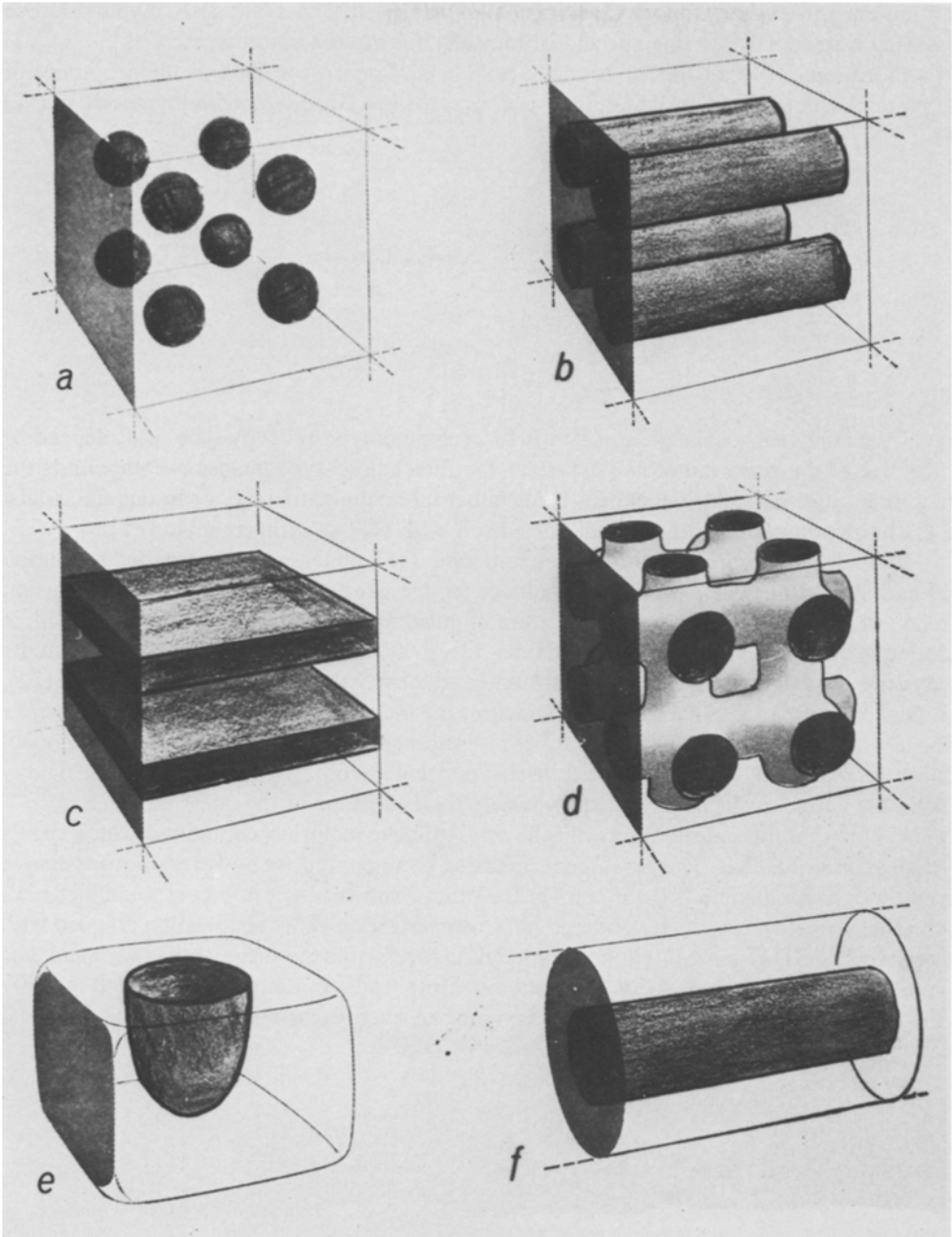


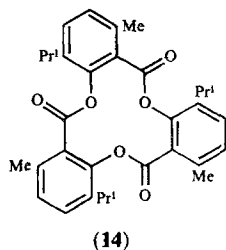
Fig. 20. Some of the possible arrangements of host lattices (*Sci. Amer.*, July 1962).

3.2. THE SYNTHESIS OF HOST LATTICES WITH 'TAILOR MADE' PROPERTIES

Due to the increased understanding of the nature of inclusion compounds and of the factors which govern the selective properties of host lattices, a logical extension of the process outlined in Section 2.4 would be the synthesis of host lattices with 'tailor-made' specificity for isomers,

enantiomers and even isotopomers. It may even be possible to synthesise one host lattice displaying a selectivity for one specific isotopically substituted chiral isomer!

As an example of what the future might hold it is of interest to look at the properties of one particular compound which shows very versatile behaviour, *viz* tri-*o*-thymotide (TOT) (14).



TOT is an unusual host lattice since it will form channel-type or cavity-type voids depending on the size of the guest molecule [21]. Even for the channel-type inclusion compounds the structure is guest molecule dependent being either monoclinic, triclinic, or hexagonal, whilst the clathrate compounds are trigonal and unsolvated TOT is orthorhombic [81].

Additionally, on forming an inclusion compound TOT undergoes spontaneous resolution [22] and should provide a chiral environment for the guest molecule. Thus if an inclusion compound is formed from a racemic mixture of guest, the two guest enantiomers should be included to different extents. Such enantiomer selectivity has been reported for TOT, with the cavity-type host displaying a higher enantiomer selectivity than the channel-type host [82].

A final example of unusual behaviour concerns the inclusion compounds with *cis* and *trans* stilbene and their photolytic behaviour [81]. Although *cis* \rightleftharpoons *trans* photoisomerization of stilbene occurs readily in solution, the restricted molecular mobility of the guest and the rigidity of the host lattice might be expected to modify the behaviour of the guest molecule.

This is found to be the situation with the *trans*-stilbene inclusion compound which shows no change on irradiation. The *cis*-stilbene inclusion compound does however photoisomerize smoothly to *trans*-stilbene (Figure 21). On the other hand the inclusion compounds of both *cis*- and *trans*-methyl cinnamate undergo photoisomerization. This observation coupled with the preference of TOT for *trans*-stilbene rather than for *cis*-stilbene suggests that a coincidence of guest molecule and host cavity symmetry elements leads to a strongly enhanced stability of the inclusion compound as well as providing an element of control over the chemical reactivity of the guest molecule.

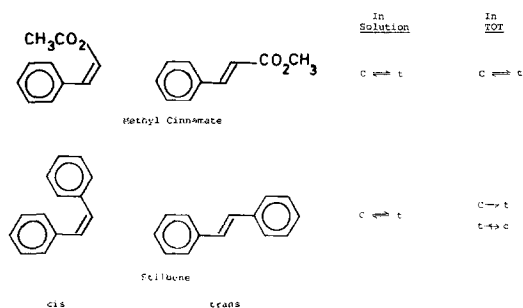


Fig. 21. The photoisomerization reactions of stilbene and methyl cinnamate in solution and as guests in TOT.

3.3. STUDIES OF GUEST MOLECULE REACTIVITY

The study of the reactivities of guest molecules and the way in which this reactivity is governed by the environment of the molecule is a relatively new area of study and one which can be expected to increase in the future as inclusion compounds are more extensively studied as enzyme models [124].

One of the early studies in this area concerned the polymerization of unsaturated molecules in the channels of urea [83] and thiourea [84]. A novel feature of these polymerizations is that many of the monomers were found to give stereo regular polymers according to the scheme shown in Figure 22. Inclusion polymerization has by now been studied in a wide range of host lattices [85].

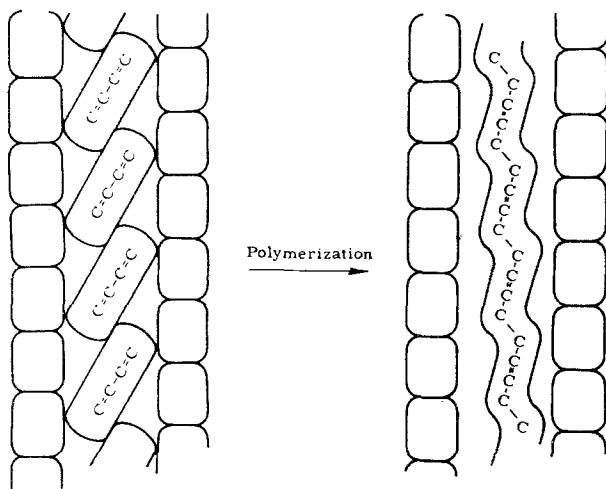
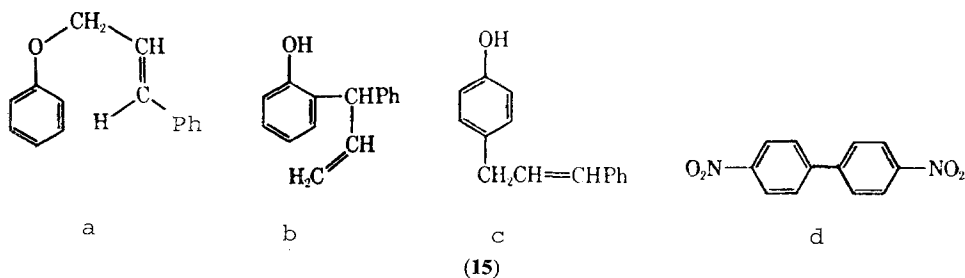


Fig. 22. Polymerization of 2,3-dimethylbutadiene in the thiourea channel (*J. Am. Chem. Soc.* **82**, 5671 (1960)).

The example of the *trans*-stilbene/TOT inclusion compound discussed in Section 3.2 shows that the reactivity of some molecules can be drastically altered on enclosure in a host lattice. Another example is provided by cinnamyl phenyl ether [86] (**15a**). On heating, this molecule (**15a**) undergoes a Claisen rearrangement to give (**15b**) and (**15c**) as the major products. However when (**15a**) is included in the channel of the 4,4'-dinitrophenyl host lattice (**15d**), the constraints imposed by the host lattice are sufficient to inhibit the rearrangement completely.



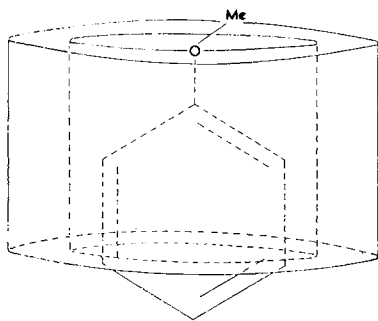


Fig. 23. The anisole α -cyclodextrin inclusion compound.

Molecules included in the cyclodextrin cavity can also display modified reactivity. It is easy to see from Figure 23 why chlorination of anisole in the presence of α -cyclodextrin gives 99% of the *para* product since the *ortho* position is protected by being buried inside the cyclodextrin cavity [87].

Inclusion compounds of deoxycholic acid provide interesting examples of *host-guest* reactions which can be induced thermally or photolytically. On heating the inclusion compound formed with di-*t*-butyldiperoxycarbonate (Figure 24b) at 90 °C for 120 hr or photolysis at 25 °C for two weeks, the guest molecule is completely decomposed and subsequently reacts with the host lattice to give two major products (Figure 24d (15%) and Figure 24c (15%)) and traces of Figure 24e). The interesting aspect of this reaction is that product Figure 24d has been formed by a one-step regiospecific and stereospecific hydroxylation of the host lattice by the decomposition product of the guest molecule [88].

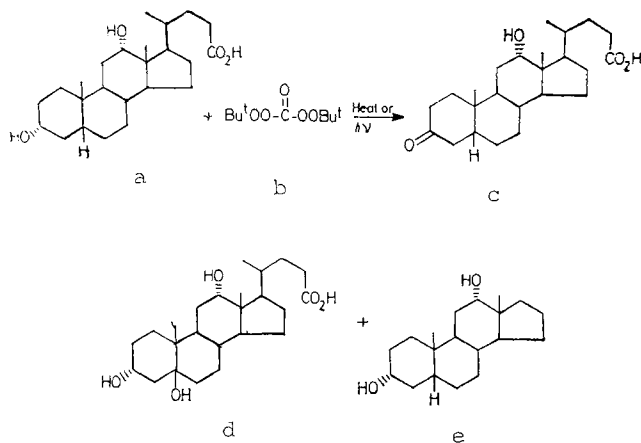


Fig. 24. The host-guest reaction of a deoxycholic acid inclusion compound (*J. Chem. Soc., Chem. Commun.* 864 (1975)).

3.4. USES OF INCLUSION COMPOUNDS AS CHEMICAL REAGENTS

The use of inclusion compounds as chemical reagents is a relatively new application but one which is likely to increase in the future due to the selectivity shown by these reagents.

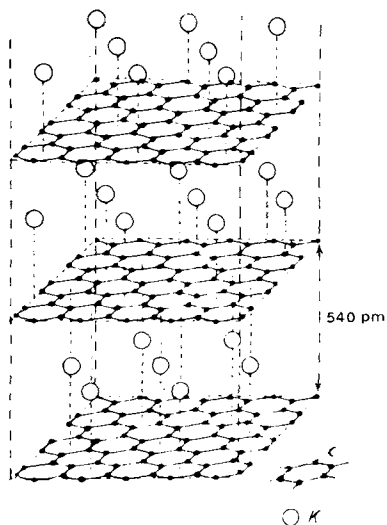


Fig. 25. The structure of C_8K (*Can. J. Chem.* **50**, 3058 (1972)).

The earliest reported work seems to have been on the use of graphite intercalates such as the potassium intercalate C_8K , where the potassium is situated between the layers of hexagonal carbon units (Figure 25). It is therefore not surprising that comparison of the reactivity of an intercalated species with that of the bulk reagent reveals differences in reaction rates because of the necessity for the reacting molecule to diffuse into the graphite structure. The intercalates can also display a selectivity depending on the size of the molecule or the stereochemistry around the reaction centre because of the limitation imposed by the interlayer spacing.

An example is provided by the use of C_8K in reducing camphor to give the *exo* alcohol as the predominant product [89]. This result is quite different from that obtained by reduction with potassium in tetrahydrofuran when the *endo* alcohol is the predominant product. The reason for this difference is shown in Figure 26, where the proposed mechanism involves adsorption at the surface of a C_8K crystallite. Since this adsorption is easier in a position more favourable for the formation of the *exo* alcohol, this isomer becomes the predominant product.

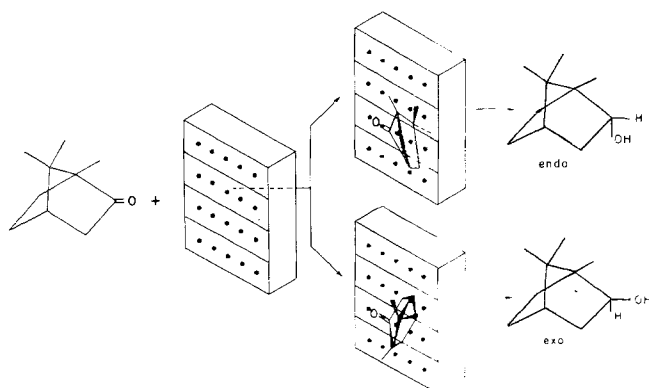


Fig. 26. Stereochemistry of the reduction of camphor with C_8K (*Can. J. Chem.* **50**, 3058 (1972)).

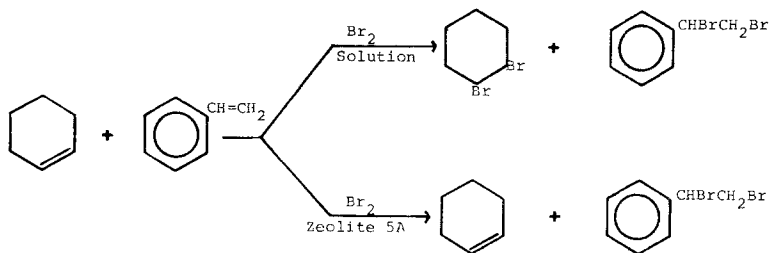


Fig. 27. The bromination reactions of styrene and cyclohexene.

Other uses reported by Lalancette [90] were the oxidation of alcohols using the CrO_3 intercalate, and the use of the AlCl_3 intercalate as a Friedel Crafts catalyst. Further examples of the uses of graphite intercalates can be found in recent reviews [92, 93].

Another example of selectivity concerns the use of Br_2 included in Zeolite 5A as a brominating agent for cyclohexene and styrene [93] (Figure 27). When a mixture of these two compounds was treated with the zeolite reagent the cyclohexene was unaffected whilst the styrene double bond was brominated. Since in homogeneous solution *both* of these compounds are rapidly brominated, the selectivity in the case of the zeolite reagent must be due to the fact that the bromine is accessible to the styrene double bond since it can penetrate into the cavity via the smaller pore opening (Figure 28), whereas the cyclohexene double bond cannot gain access to the bromine.

The sheet silicates have also been found to be effective agents for chemical conversions. Recent examples are the direct addition of intercalated alkenes and acids to give esters [94a], the formation of di-(alk-1-yl)ethers from intercalated primary alcohols [94b], and the elimination of ammonia from molecular pairs of intercalated primary amines generating secondary amines [95]. Several of these reactions give unusual products and the use of sheet silicates for promoting unusual chemical conversions is dealt with in detail in a recent review [96].

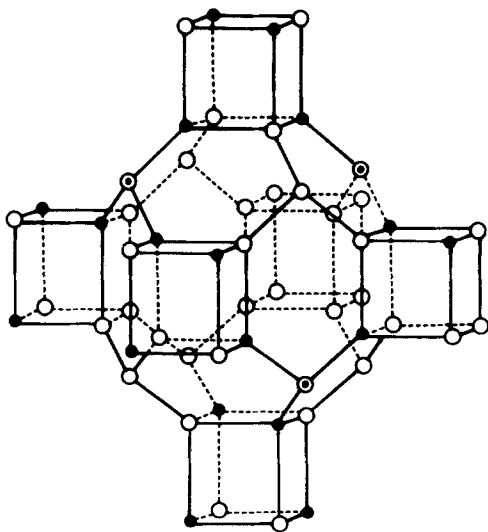
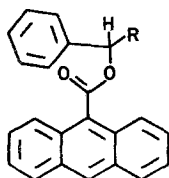


Fig. 28. The basic unit of a zeolite showing the central cavity with the smaller pore openings.

3.5. MEDIA FOR STABILIZING UNSTABLE SPECIES

Although several reports have appeared of unstable species being stabilized in various host lattices, very few of these reports have been concerned with studying the chemical and physical properties of the unstable species. This is surely an area which can be exploited in the future since in many of the cases, these unstable species have configurations which can only be obtained in the host lattice.

Most of the studies have reported the stabilization of thermodynamically disfavoured isomers by host lattices. One of the earliest reports [97] is concerned with a study of the thiourea monohalocyclohexane inclusion compounds, where the host lattice displays a selectivity for the *axial* conformer. This is quite a unique situation since in the gaseous and liquid phases of the monohalocyclohexanes the *equatorial* conformer is the predominant conformer, whilst the solid phase consists of the *equatorial* conformer alone.



- (1); R = Et
 (2); R = Prⁿ
 (16)

The host lattice (16) stabilizes *n*-hexane in an unusual configuration [98] consisting of an extended planar zig-zag chain but with the terminal carbon atom torsional angle being 100° (Figure 29).

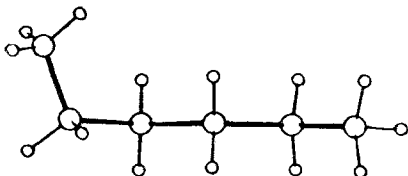


Fig. 29. The unusual conformation of *n*-hexane in the channel formed by host lattice (16) (*J. Chem. Soc., Chem. Commun.* 928 (1977)).

The 'hexa host' molecule (17) has been shown to be a versatile host lattice in stabilizing molecules in unusual configurations. Figure 30 compares the conformation of squalene [99] as a guest molecule (a) with the conformation in the solid state (b) at -110°C . Host (17), also stabilizes 3,3,6,6-tetramethyl-*s*-tetrathiane in the chair conformation (18b) [100] rather than in the twist-boat conformation (18a) which is the favoured conformation in the liquid phase.

The structure II water host lattice has also been found to stabilize guests in unusual conformations. 1,2-dichloroethane is stabilized in a conformation [101] having a dihedral angle of $60 \pm 3^{\circ}$. This conformation is not only very different from that of the *trans* rotamer which is the predominant conformation in the vapour and liquid states, but also different from the conformation of the less abundant *gauche* rotamer which has a dihedral angle of $72 \pm 3^{\circ}$ in the vapour phase.

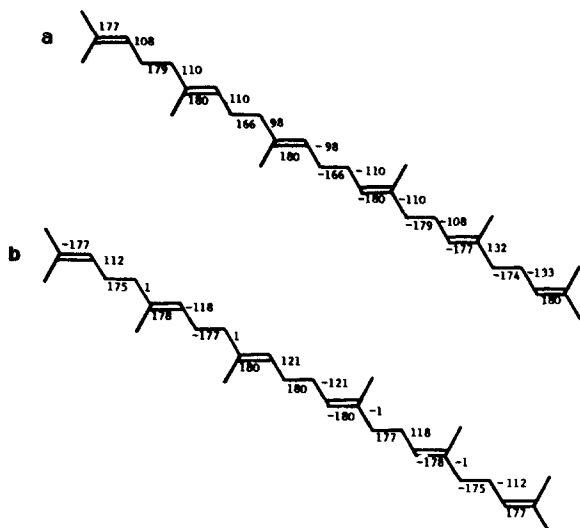
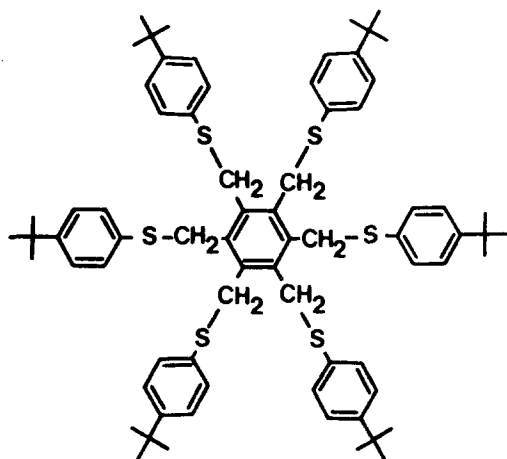
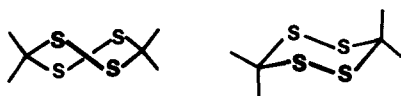


Fig. 30. Comparison of (a) the conformation of squalene as a guest molecule in host (17) with (b) its conformation in the solid state at $-110\text{ }^{\circ}\text{C}$ (*Tetrahedron Lett.* **21**, 1159 (1980)).



(17)



a

b

(18)

n-Butane as a guest in the Structure II host lattice is also thought to exist predominantly in a *gauche* conformation having a dihedral angle value less than that found in the gas phase [102].

A variety of host lattices have been found to stabilize free radicals which can be detected

using ESR spectroscopy. γ -Irradiation of the $\text{Cd(en)M(CN)}_4 \cdot 2\text{C}_6\text{H}_6$ ($\text{M} = \text{Cd, Hg}$) inclusion compounds leads to the formation of the C_6H_7 radical which can be stabilized for a few hours at a temperature as high as 423 K. Since irradiation of $\text{Cd(en)Ni(CN)}_4 \cdot 2\text{C}_6\text{H}_6$ does not lead to the formation of this radical, it seems that the radical is stabilized in the biprismatically shaped (β) void and not in the tetragonally shaped (α) void [103] (See Figure 18).

The influence of the host lattice on the configuration of the guest can be demonstrated by studying the same radical in different host lattices. X-irradiation of methyl-2-nonynoate yields the $\text{CH}_3(\text{CH}_2)_4\dot{\text{C}}\text{H}-\text{C}\equiv\text{C}-\text{CO}_2\text{CH}_3$ (**19**) free radical which has very different ESR spectra when present in the urea and in the perhydropyrene (PHTP) host lattices [104] (Figure 31). Both of these host lattices have a channel structure and the different ESR spectra can be explained by the fact that in the urea channel the radical undergoes a very large amplitude motion about the C_4-C_5 bond (Figure 32), and a much lower amplitude motion in the narrower PHTP channel.

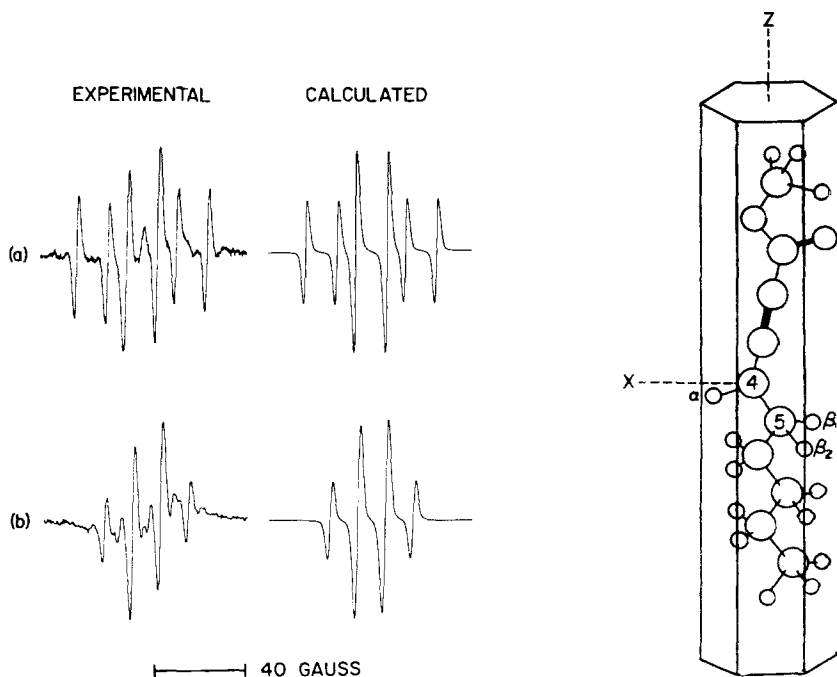


Fig. 31. The room temperature ESR spectra of free radical (**19**) in the urea (a) and PHTP (b) host lattices (*J. Chem. Phys.* **54**, 1630 (1978)).

Fig. 32. The arrangement of (**19**) inside a hexagonal channel (*J. Chem. Phys.* **54**, 1630 (1971)).

Free radicals have also been detected in photolysed samples of clathrate hydrates. Photolysis of the CH_3SH , $\text{C}_2\text{H}_5\text{SH}$ and the H_2S clathrate hydrates have been reported to produce the CH_3S , $\text{C}_2\text{H}_5\text{S}$ and S_2 species [105].

The use of inclusion compounds as sources and reservoirs of unstable species thus resembles the use of the matrix isolation technique. Inclusion compounds do however have the great advantage that they can be used over a very wide temperature range and future exploitation in this area is extremely likely.

3.6. BIOCHEMICAL AND INDUSTRIAL APPLICATIONS

The chlorination of anisole as a guest in the α -cyclodextrin host cavity referred to in Section 3.3 not only gives products different from the corresponding reaction in the absence of α -cyclodextrin, but the reaction is also much faster [87] in the presence of α -cyclodextrin by a factor of 5.3. This thus introduces us to the expanding field of cyclodextrin inclusion compounds for biomimetic studies [124].

It is also likely that a major future use of cyclodextrins will be in the food and pharmaceutical industries, as the increased production of cyclodextrins leads to a decrease in price. It has already been shown that the use of cyclodextrin inclusion compounds has several advantages over the presently used technique of microencapsulation.

It has also been shown that cyclodextrin inclusion compounds can be used to mask or eliminate unpleasant odours, to increase the solubility of compounds, to provide protection against oxidation and photolysis, and to stabilize flavouring agents.

It is confidently expected that many, if not all, of the above uses will be used commercially in the near future. Full details of these uses can be found in Szejtli's recent book [15].

One interesting area where the principles of inclusion formation are being applied is in cancer chemotherapy where intercalation has been recognized as playing an important role [106]. Figure 33 illustrates the normal replication process in DNA where the double helix unwinds and the sequence of base pairs on the unwound strand ensures the exact replication of the original strand.

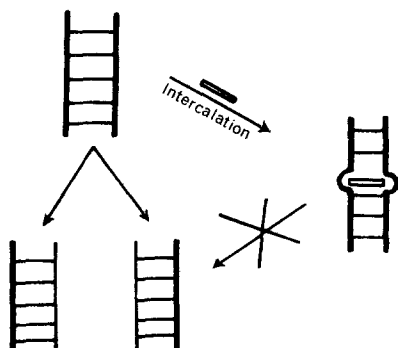


Fig. 33. The normal replication process in DNA, and its inhibition by an intercalated anti-cancer drug (*Nursing Mirror* 146 (12) 18 (1978)).

The mode of action of an anti-cancer drug is thought to be intercalation of the drug between the base pairs of the unwound double helix thus inhibiting the normal replication process. There is, not surprisingly, a steric requirement involved in this process, and it has been found that DNA shows a strong affinity for planar, aromatic, cationic heterocycles which can most easily fit between the base pair layers [107].

Size selectivity has long been recognized as the characteristic feature of most host lattices. This selectivity ranges from the selectivity between benzene and toluene shown by the Hofmann host lattice, the selectivity between methanol and ethanol shown by the β -quinol host lattice, the selectivity between linear and branched hydrocarbons shown by the urea host lattice, to the selectivity between *ortho*, *meta*, and *para* isomers shown by the $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$ and $\text{Ni}(\alpha\text{-arylalkylamine})_4(\text{SCN})_2$ host lattices.

Although these selectivities have been put to good use in small scale separations and in chromatographic applications, a disappointing aspect of industrial applications of inclusion compounds is the absence of any large scale commercial separation plants, apart from those utilizing zeolites.

A few pilot plants involving inclusion compounds have been described. Deutsche Erdol AG designed a plant to dewax oil using urea [108]; the Union Oil Company built a plant to separate *meta* and *para* xylene using the known selectivity of $\text{Ni}(4\text{-Mepy})_4(\text{SCN})_2$ for the *para* isomer, and Figure 34 illustrates the flow diagram for the Labofina process for separating *meta*

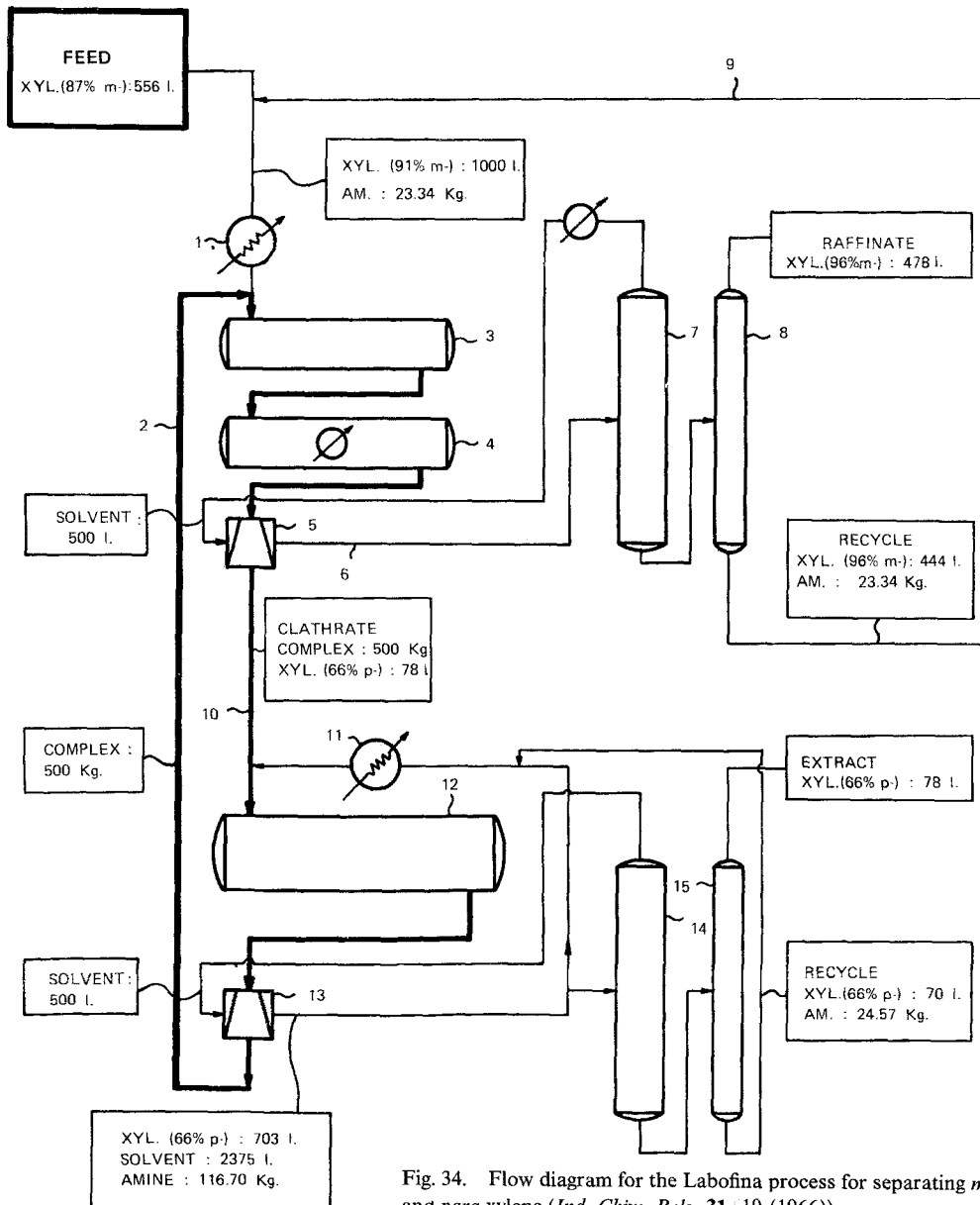


Fig. 34. Flow diagram for the Labofina process for separating *meta* and *para* xylene (*Ind. Chim. Belg.* 31, 19 (1966)).

and *para* xylene using the known selectivity of Ni(α -(*m*-chlorophenyl)ethylamine)₄(SCN)₂ for the *para* isomer [109].

The main problem in commercial scale separation plants would be the need to handle solids with the concomitant need for precipitation, filtration, and washing sequences which would require high cost filtration or centrifugation equipment and large volumes of washing liquid [110].

These difficulties can be overcome by the use of liquid inclusion complexes ('liquid clathrates'). These are formed between compounds of the general formula M[Al₂(CH₃)₆X] (M = alkali metal or tetraalkylammonium ion; X = N₃, SCN, SeCN, F, Cl, Br, I) and small aromatic molecules [111a].

Although the organometallic hosts do display selectivities, they are generally inferior to the selectivities shown by solid host lattices. They do however possess three major advantages over solid inclusion compounds as far as the operation of commercial separation plants are concerned:

- (a) the amount of guest loaded into the liquid clathrate is very high (60-90% by weight).
- (b) the guest may be recovered from the host efficiently by a small change in temperature.
- (c) since solid phases are not encountered, the separation follows the pattern of liquid-liquid extraction.

Although no commercial plants have been constructed as yet, the utility of liquid clathrates in separation processes is under study in several laboratories. Another interesting application of liquid clathrates is a low temperature coal liquefaction process [111b].

3.7. NEW PHYSICAL TECHNIQUES FOR STUDYING INCLUSION COMPOUNDS

Most of the structural information about inclusion compounds has been obtained using X-ray crystallography, but two recently-introduced techniques will in the future provide information complementary to that obtainable from X-ray crystallography.

3.7.1. Magic Angle Spinning NMR Spectroscopy

The magic angle spinning technique results in the dipolar interactions in a solid being cancelled out thus making possible the recording of high resolution spectra of solids. Since the technique does not require a single crystal, it can be used to provide structural information on samples which cannot be studied using X-ray or neutron crystallography.

The technique is only just beginning to be applied to inclusion compounds but it has already been shown to be a valuable structural technique since ¹³C NMR spectroscopy can distinguish between the different polymorphs of quinol [112]. It is also possible to observe the resonances of the guest molecule as illustrated in Figure 35 from the ¹³C NMR spectra of Dianin's compound and some of its clathrates [113].

¹³C NMR spectroscopy has also been used to characterize the carbonaceous residues arising from zeolite catalysed reactions [114]. Figure 36 illustrates the ¹³C spectrum of the residue obtained after the reaction of methanol over H-ZSM-5. The excellent quality of the spectrum allows the identification of alkane products [propane (16.8 ppm), *n*-butane (13.4 and 25.9 ppm), isobutane (10.9, 21.9, 29.9 and 32.2 ppm)], alkene products [propene (15.9 ppm), linear and branched olefins (~ 150 ppm)] and aromatic products [benzene, toluene, xylenes (129.2, 138.3 ppm)].

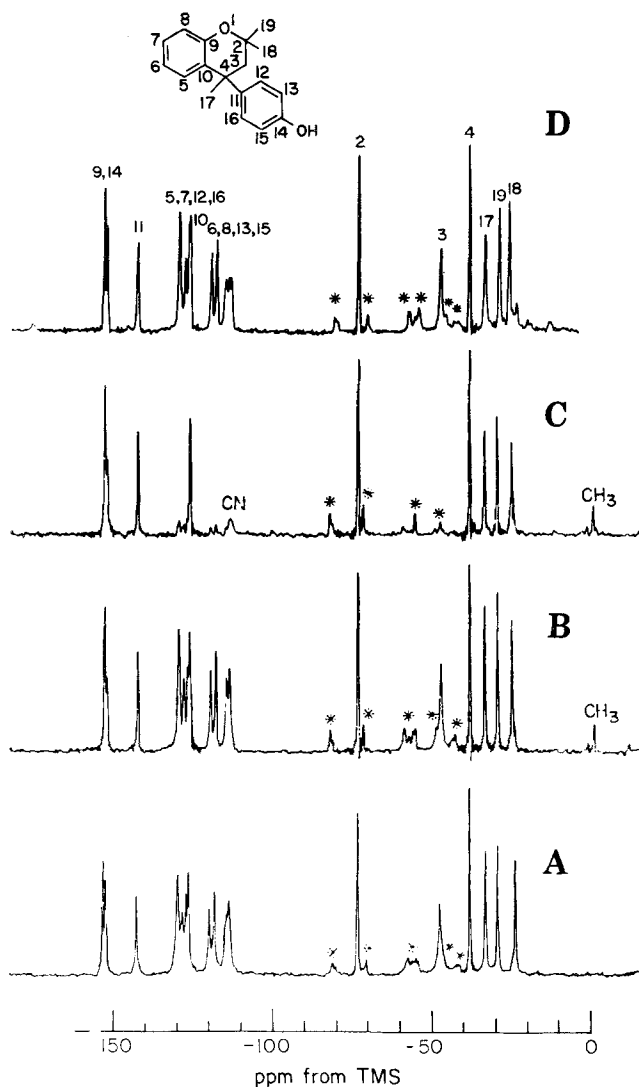


Fig. 35. ^{13}C NMR spectra of (A) Dianin's compound (B) the CH_3CN clathrate (C) the CH_3CN clathrate with suppression of the signals from carbon atoms strongly coupled to hydrogen (D) the octanoic acid clathrate. * Spinning side bands.

The ^{129}Xe chemical shift has been found to be very sensitive to the environment of the atom. The xenon β -phenol clathrate gives rise to three bands [115] (Figure 37) which can be assigned to the xenon atom in the small cavity; the two xenon atoms situated near the ends of the large cavity, and to the xenon atom in the middle of the large cavity.

Another technique which may become of greater importance in the future is the calculation of the potential energy of the inclusion compound. It has already been found that this method can be used to locate some guest molecules in deoxycholic acid inclusion compounds. This is another method which can be used when diffraction studies cannot be carried out [116].

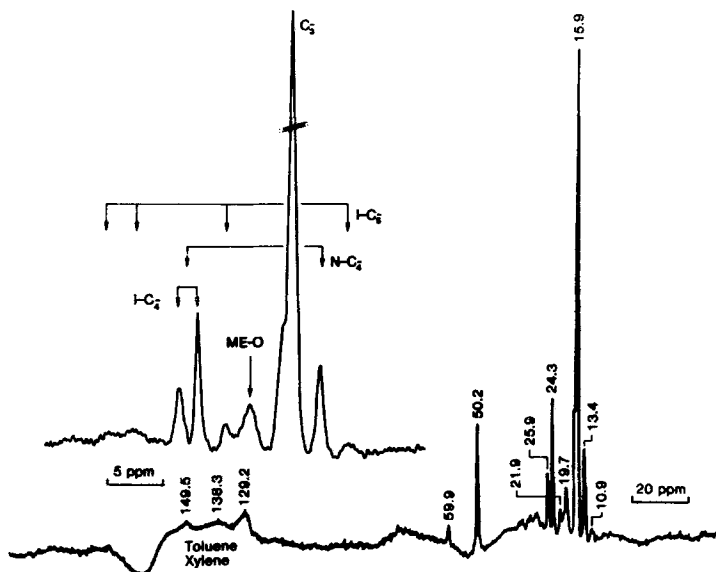


Fig. 36. The ^{13}C NMR spectrum of the carbonaceous residue after the reaction of methanol with the H-ZSM-5 zeolite (*Zeolites* **2**, 42 (1982)).

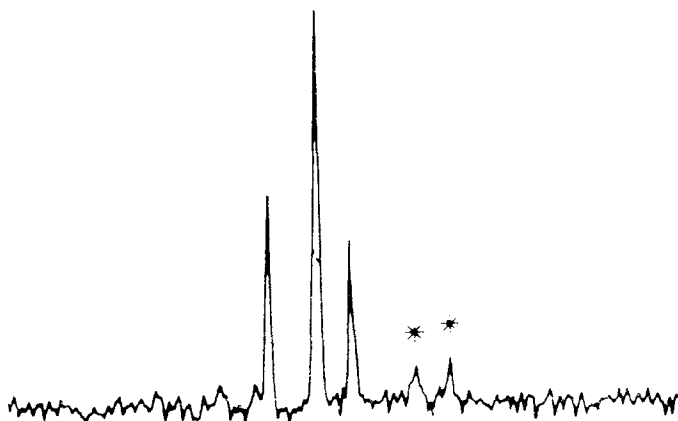


Fig. 37. The ^{129}Xe NMR spectrum of the xenon β -phenol clathrate.
* Spinning side bands (*J. Am. Chem. Soc.* **104**, 289 (1982)).

3.7.2. High Resolution Electron Microscopy

Resolution of the order of 3–5 Å can now be obtained with modern high resolution electron microscopes. A few inclusion compounds have been examined using this technique providing fascinating pictures of their structures.

Figure 38a illustrates the image obtained from a graphite FeCl_3 intercalate [117]. As the schematic drawing (Figure 38b) shows, the carbon layers and the intercalated FeCl_3 can be easily seen; the separation between adjacent carbon layers being about 3.4 Å, which increases to 9.2 Å in the presence of intercalated FeCl_3 . Figure 38 also illustrates the phenomenon of

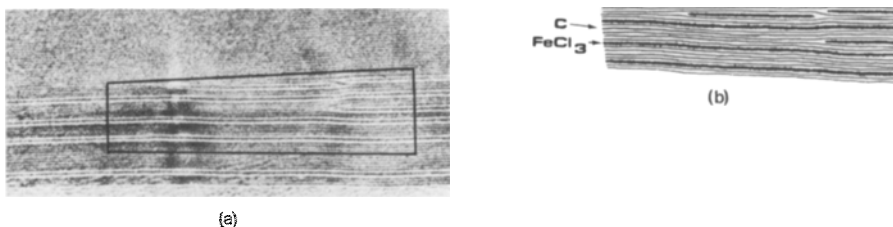


Fig. 38. The 2.9 Å resolution image of the FeCl₃ graphite intercalate (a) and the schematic drawing of the image (b) (*Mat. Res. Bull.* **15**, 671 (1980)).

the interpenetration of differently staged regions and points to the fact that the composition of a graphite intercalate is unlikely to be homogeneous.

Figure 39 illustrates the structural image of the ZSM-5 zeolite viewed along the *b* axis [118], where the array of channels running along the *b* axis can be clearly seen.

Although only a few inclusion compounds have been examined using high resolution electron microscopy, it is very clear that it is an extremely powerful structural technique. It should therefore be possible to examine samples which are difficult to examine using X-ray or neutron crystallography, but some of the limitations of the technique, such as the need for the evacuation of the sample, and the stability of the sample to electron bombardment, should be borne in mind [119].

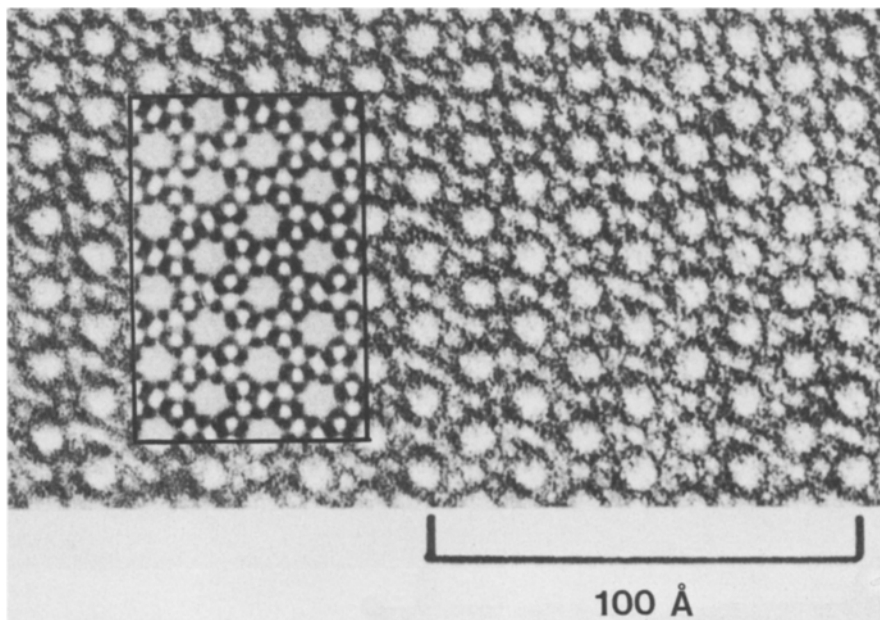


Fig. 39. The image of the ZSM-5 zeolite viewed along the *b* axis. The bright spots demarcate the channels illustrated in the idealized projection shown in the inset (J. M. Thomas and G. R. Millward, private communication).

3.7.3. Infrared and Raman Difference Spectroscopy

A study of the infrared and Raman spectra of inclusion compounds can provide useful information about aspects such as guest molecule motion and host lattice-guest molecule interactions [120]. One limitation is the masking of guest molecule bands by the generally more intense host lattice bands as illustrated in Figure 40. From Figure 40b it is possible to pick out the band at 3481 cm^{-1} arising from the $\nu(\text{O-H})$ vibration of the formic acid guest molecule, but the band arising from the $\nu(\text{C-H})$ vibration of the guest molecule is obscured by the broad, intense quinol band.

The difference spectrum [121] (Figure 40c) picks out a band at 2945 cm^{-1} , and comparison of the difference spectrum with the Raman spectrum (Figure 40d) of the clathrate confirms that this is the band arising from the guest molecule $\nu(\text{C-H})$ band.

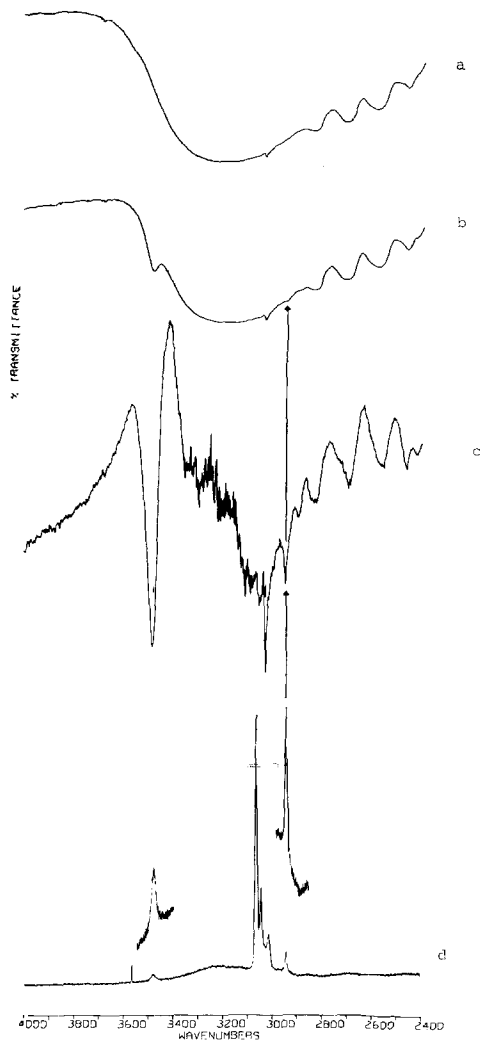


Fig. 40. The infrared spectra of (a) β -quinol (b) the β -quinol formic acid clathrate and (c) the difference spectrum compared with the Raman spectrum (d).

Application of this technique to both infrared and Raman spectra will increase substantially the amount of information obtainable from these two techniques.

3.8. APPLICATION OF HIGH ENERGY PARTICLE TECHNOLOGY

It has recently been reported that the irradiation of materials with energetic heavy ions can lead to the formation of extremely narrow diameter channels in the material [122]. Figure 41 illustrates the formation of channels of approximately $2\ \mu\text{m}$ diameter generated by the heavy ion irradiation of a mica single crystal and successive etching in hydrofluoric acid. An obvious application of these materials will be as molecular sieves.

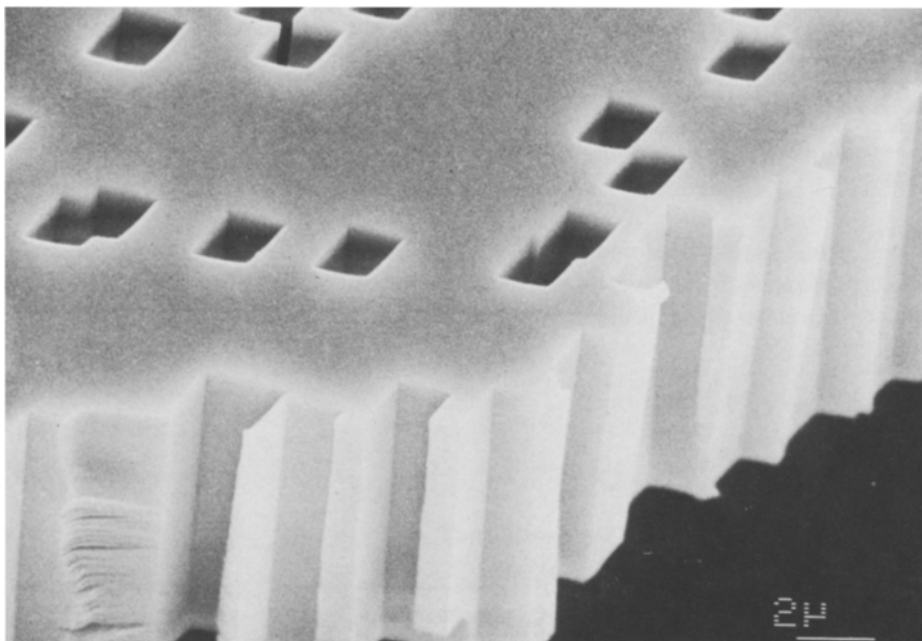


Fig. 41. The formation of $2\ \mu\text{m}$ diameter channels in a mica crystal after heavy ion irradiation (*Nature* **297**, 271 (1982)).

It is even possible to produce single hole membranes corresponding to the passage of one heavy ion through the material. Figure 42 illustrates a single hole of about $10\ \mu\text{m}$ diameter produced in a polycarbonate foil by the passage of a single ^{129}Xe ion. Single hole membranes of $6\ \mu\text{m}$ diameter are used as counting apertures for measuring the deformability of individual red blood cells [123].

One therefore looks forward with interest to future applications of these novel materials.

4. Conclusions

This article has attempted to give an oversight of the whole field of inclusion compounds covering the period from 1811 to 1982! Of particular interest is the question of how reliable will be the predictions made in the Future section. One unknown factor which cannot be

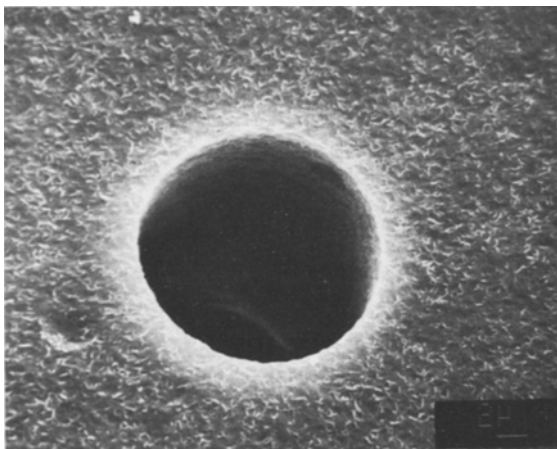


Fig. 42. The formation of a $10\mu\text{m}$ diameter hole in a polycarbonate film by the passage of a single ^{129}Xe ion (*Biomed. Techn.* **26**, 167 (1981)).

predicted is unexpected developments in synthesis or techniques. The authors obviously hope that their predictions will be reasonably accurate, but will, in fact, be delighted if future work turns out to bear no resemblance whatsoever to present foreseeable trends! It's all in your hands.

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