

The Sunday Gleaner

Omnibus Edition

Sunday 27 July 1986

4th Int. Symposium Inclusion Phenomena/3rd Int. Symposium Cyclodextrins
Lancaster 20-25 July 1986

"The experiment has been set up, the place is Lancaster and the theme is how one molecule recognises another...."

A collection of the reports which appeared in "The Daily Gleaner".

- No. 1 LEHN
- No. 2 SUTHERLAND/GOKEL/KOGA/NEWKOME
THOMAS/MAXWELL
- No. 3 BRESLOW/TABUSHI/NAGAI/UEKAMA/HARATA
STEZOWSKI/COLLET/WEBER/HART/SAENGER
- No. 4 DALE/HAMILTON/JURCZAK/RIPMEESTER
- No. 5 BELL/BUSCH/FENTON/REINHOUDT
WILLIAMS (DH)/WILLIAMS (DJ)/SAUNDERS/MURRAY-RUST
- No. 6 VÖGTLE
SHANZER/WHITLOCK/SAUVAGE

POSTERS

EVENING SESSIONS - SZEJTLI & WIFE

OVERVIEW - CRAMER & LANGLEY

Some Statistics

That was the week that was!

STOP PRESS : - LANCASTER 26 JULY
HOSTS RECOGNISE RECEPTIVE GUESTS : COMPLEX IDEAS WITH
EXCELLENT YIELDS.

The Daily Gleaner

No. 1

Monday 21 July 1986

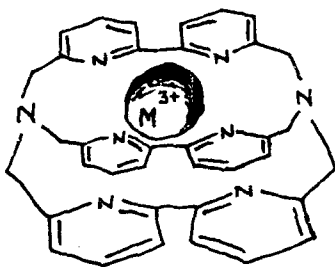
A report on yesterday's proceedings at the 4th Inclusion Phenomena/3rd Cyclodextrin Symposium.

In Today's Issue — **LEHN** : "It's the concepts that pull you"

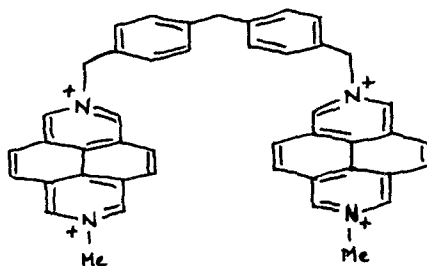
Following the opening of the Symposium and the welcome to the participants by the Vice-Chancellor of the University of Lancaster, the theme of the Meeting was set by **Fraser Stoddart** (Sheffield). In keeping with the previous Symposia, this Meeting will continue to be innovative and to promote discussion.

The opening Plenary Lecture by **Jean-Marie Lehn** (Strasbourg and Paris) illustrated how different molecular architectures can be conceived within a single philosophy.

The practical and effective synthesis of photoactive lanthanide cryptates (1), capable of effective light conversion, has found application in the design of novel fluorescent immunoassay systems. The macrobicyclic bipyridyl cryptands prevent the normal solvation quenching of these cations. Remarkably effective DNA cleavage was accomplished using intercalators (2) based on 2,7-diazapyrenium cations.

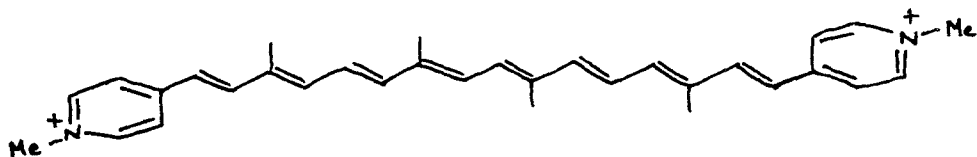


1 $M = \text{Eu, Tb}$



2

The pH-selective transport of K^+ and Ca^{2+} ions across a liquid membrane was achieved using bis-tartaro-18-crown-6 derivatives. The incorporation of caroviologens (3) into vesicle bilayer membranes promises to be a viable entry into molecular wires.



3

The discussion ranged from querying leaky vesicles to comparing the merits of inorganic and organic brains. It appears that what's between our ears is ahead.

The Daily Gleaner

No. 2

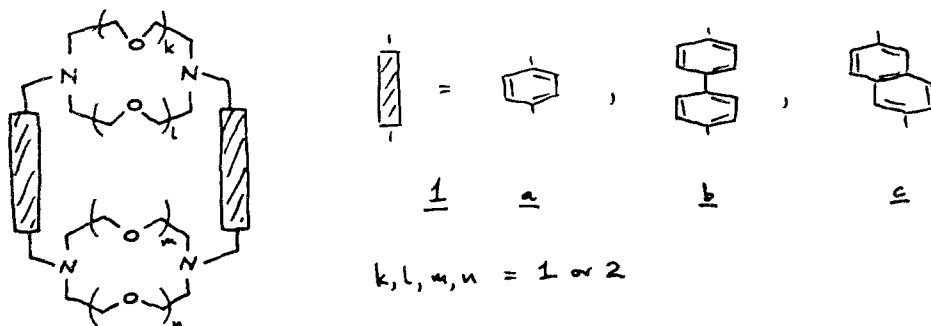
Tuesday 22 July 1986

A report on yesterday's proceedings at the 4th Inclusion Phenomena/3rd Cyclodextrin Symposium.

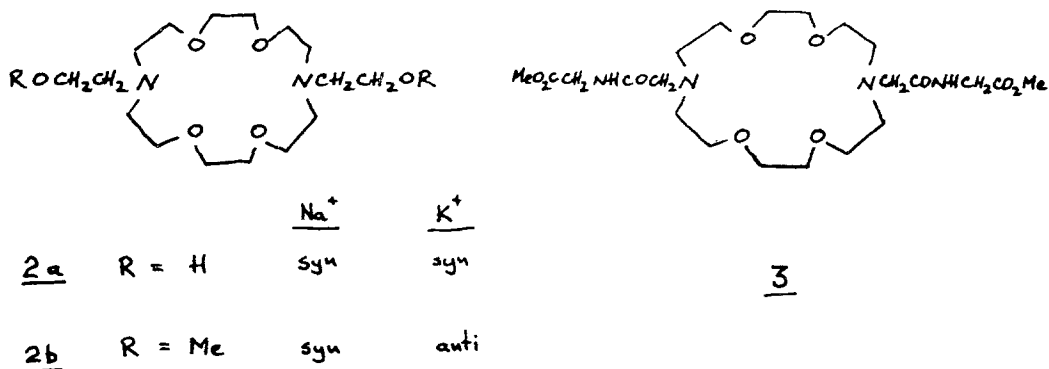
In Today's Issue —

SUTHERLAND	:	The hole lecture
GOKEL	:	More than "half a lecture"
KOGA	:	What amAZing hosts!
NEWKOME	:	Sensing the "two dollar bit"
THOMAS	:	Shapes of things to come
MAXWELL	:	Star-Wars catalysts

The development of selectivity in synthetic receptors was discussed by **Ian Sutherland** (Liverpool). The known affinity of crown ethers for alkylammonium ions was developed to produce recognition enhancement by use of tricyclic systems (1), incorporating two diaza crown ether rings bridged by aromatic sub-units. Complexation studies on alkyl- and dialkyl-ammonium ions employing NMR spectroscopy were described. As far as the stereochemistry of binding of organic cations is concerned, small (12- and 15-) rings were shown to be better than large (18-) ones. The use of rigid spacer groups (**a, b, c**) between the crown moieties maintained a well-defined cavity size producing substrate selectivity, which was described as "coarse tuning". Furthermore, changing the size of the diaza crown rings allowed "fine tuning" of this selectivity by controlling the penetration of the ammonium group into the ring. Replacement of one of the rigid aromatic bridges by a polyether chain produced an adjustable tricyclic system with somewhat broader substrate recognition.

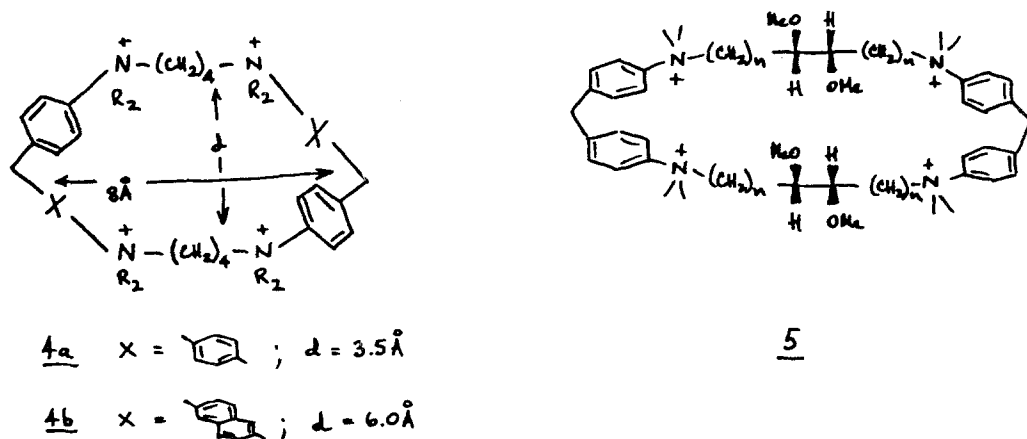


George Gokel (Miami) gave a vibrant presentation on the metal ion inclusion complexes of lariat ethers. These synthetic receptors are being designed to parallel the properties of natural hosts such as valinomycin. In addition, the investigation reveals the diverse potential of such systems. A brief resume of the properties of the simpler lariat ethers, copiously illustrated by X-ray crystal structures, preceded the development of new so-called brachial lariat ethers. The diaza macrocycles (**2a, 2b**) were demonstrated to have variable complexation geometries dependant on the metal cation and the group R. Potassium ion binding to the peptide lariats (**3**) utilises the amide carbonyl function on each side-chain. The analogy was drawn to the valinomycin binding.



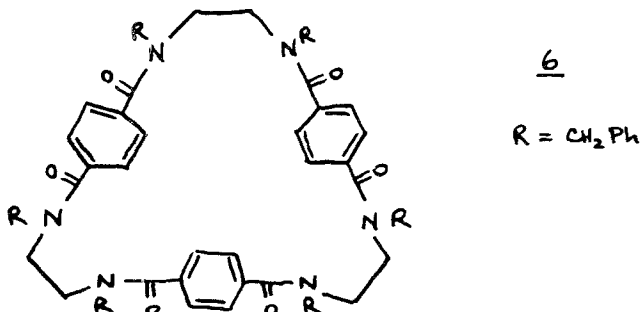
The subsequent debate entertained further applications and potential studies. Specifically, introduction of radical anions into the lariat could produce molecules suitable for electrochemical transport. An extension to the complexation of lanthanide ions echoed the concept alluded to by Jean-Marie Lehn the previous evening.

Cyclophanes incorporating the diphenylmethane skeleton (4a) with rigid hydrophobic cavities that complex aromatic guests such as durene and 2,7-dihydroxynaphthalene were described by Kenji Koga (Tokyo). By increasing the distance between the $(\text{CH}_2)_n$ spacers from 3.5 to 6.0 Å, the host (4b) can be rendered suitable for complexation with large aliphatic guests such as deoxycholate.



Also, the incorporation of chirality into cyclophanes afforded units (5) which have been used in the asymmetric reduction (NaBH_4) of 1-naphthylglyoxylic acid. Although the selectivity is rather low (10% ee), the potential of chiral cyclophanes in asymmetric synthesis is evident.

George Newkome (Miami) demonstrated the commercial application of inclusion complexes in electronic sensors. The macrocyclic hexalactam (**6**), which can complex chloroform, was coated on to the surface of a piezo-electric crystal. Complexation of chloroform produced changes in its vibration frequency with respect to a non-coated crystal, dependent upon the substrate concentration. Inexpensive devices (\$2) with sensitivities of parts per 10^{15} have been developed. They are being used in the detection of trace amounts of chloroform as an environmental pollutant.



John Thomas (Cambridge) opened his lecture by giving a brief introduction on the structure of zeolites. Examples of selective synthesis caused by Brönsted catalysis within the interlamellar space were given. The characteristics of ABC-6 type zeolites, composed of labelled 6- and 8-membered rings, were described and their structures were established by real space imaging and optical diffractometry resulting in a zeolite "signature". Structural studies of zeolites involved the use of spectroscopic techniques, including ESR, ^{13}C , ^{29}Si , ^1H and ^{27}Al NMR, together with neutron scattering and electron microscopy. Elegant use of computer graphics illustrated very clearly the position of the guests in the recently solved structures of pyridine and benzene in Zeolite L. Structures were suggested for some zeolites which have not as yet been proven to exist.

The day finished with a lecture by **Ian Maxwell** (Shell, Amsterdam) on the engineering of zeolites to produce highly selective catalysts. By reducing the Al content (acidity) in zeolites, the hydrocarbon cracking efficiency is decreased while the octane number of the products is increased, giving a commercially more valuable product. Zeolites can be used to select certain molecules based on their shapes because of their small pore size (5-7Å). para-Xylene can be produced from a mixture of ortho-, meta- and para-isomers in a 1:2:97 ratio using phosphorus-modified ZSM-5 Zeolite. Combining two or more zeolites in series leads to multifunctional catalysts. Two zeolites are used commercially to dewax gasoline; the first isomerises straight-chain hydrocarbons to the thermodynamic mixture of straight- and branched-isomers while the second is used for separation of the branched hydrocarbons. The straight-chain isomers are then recycled and re-isomerised. It appears now that zeolites can indeed be engineered to achieve selective catalysis on a large industrial scale.

The Daily Gleaner

No. 3

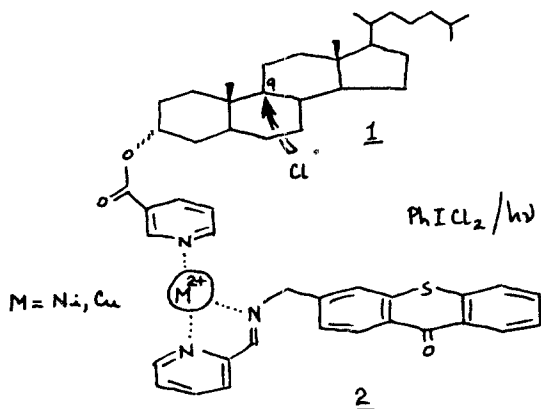
Wednesday 23 July 1986

A report on yesterday's proceedings at the 4th Inclusion Phenomena/
3rd Cyclodextrin Symposium.

In Today's Issue —

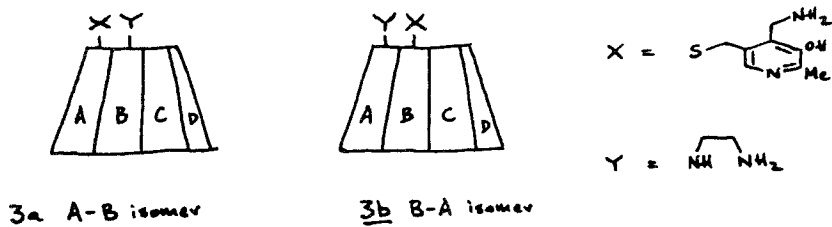
BRESLOW	:	That's the limit!
TABUSHI	:	AB BA CA DA BRA
NAGAI	:	Short stay guests
UEKAMA	:	Ins and outs...
HARATA	:	...ups and downs
STEZOWSKI	:	Models give ideas not answers
COLLET'	:	All that was vacant was the name
WEBER	:	Household Hosts
HART	:	Have wheels will travel
SAENGER	:	"It's neat chemistry, huh?"

"Somebody will have to check that I'm not making all this up" was one of **Ron Breslow's** (Columbia) comments during his high-speed presentation on a novel catalytic process he has developed. The remark was justified by his report of catalytic turnover numbers in the order of 10^{12} . Specific 9-chlorination of a steroid nicotinate ester (1) in >90% yield in 5 min. was achieved using metal/template systems like 2 to direct the reaction.

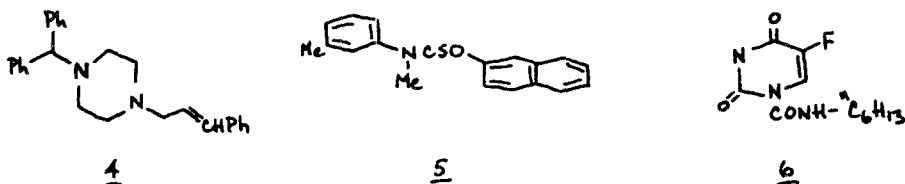


A mechanism which does not defy the diffusion limit was proposed and compared to "a double-barrelled shotgun where we reload both barrels at once". The astounding potential of this system was reinforced by his very latest results which reveal that he can now place an ester, thiocyanate and fluoride group with the same precision but as yet lower catalytic turnovers. Attempts to build some more complexity into the system are obviously under way since he mentioned that he is trying to incorporate a cyclodextrin. The reason behind this might be found in his closing comment- "I hesitate to call this an artificial enzyme because it's such a simple system".

The contribution from **Iwao Tabushi** (Kyoto) was based on his work with chemically-modified cyclodextrins as enzyme models. The asymmetrically bifunctionalised cyclodextrins (**3a, 3b**) were synthesised in order to mimic the aminotransferase activity of Vitamin B₆. The A-B regioisomer (**3a**) was used to effect the transformation of keto-acids into L-amino acids with 96% ee. The elegance of the system was demonstrated by the fact that the B-A regioisomer (**3b**) performs the same reaction on keto-acids to give the corresponding D-amino acids with identical enantiomeric excesses.



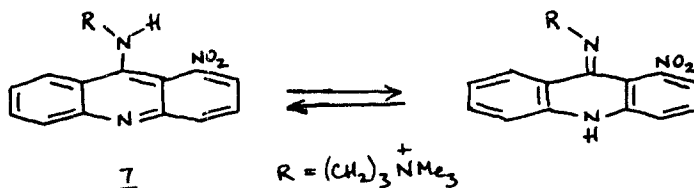
Tsuneji Nagai (Tokyo) reported some developments in the use of cyclodextrins (CDs) in drug formulation. The stability and dissolution rate of Cinnarizine (**4**) was greatly enhanced by adduct formation with β CD. However, the co-administration of a competing agent such as DL-phenylalanine was found to be necessary to enhance the bioavailability of the drug. The percutaneous penetration of the antifungal agent Tolnaftate (**5**) was increased by complexation with DM β CD.



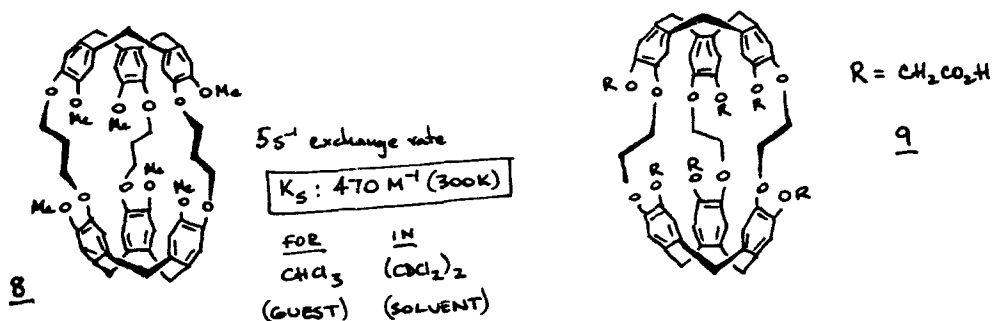
The pharmaceutical theme was maintained by **Kaneto Uekama** (Kumamoto) who concentrated on the use of chemically-modified cyclodextrins. He described how di- and trimethyl- α - and β -cyclodextrins could be used to improve the stability, solubility, dissolution rate and bioavailability of different drugs such as HCFU (**6**), Prednisolone and Vitamins K₁, K₂ and K₃. Looking to the future, the applications of hydroxypropylated, ethylated and maltosylated cyclodextrins were described.

Kazuaki Harata (Ibaraki) gave a well-illustrated lecture on host-guest interactions in cyclodextrins. His talk emphasised the indispensable role of X-ray single crystal structure determinations in the detailed study of the many varied host-guest interactions of these complexes. His many excellent slides clearly demonstrated how substitution at the hydroxy centres alter not only the size and shape of the free host cavity, but also changed the chiral recognition of the cyclodextrin. An interesting example of this was the take up in different fashions of D- and L-mandelic acid with TM β CD. Several carefully chosen examples of how the mode of complexation alters with substitution were given. For example, the mode of complexation of benzaldehyde in TM- α -CD was different compared to that found in native α -CD.

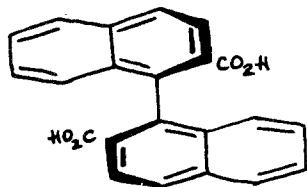
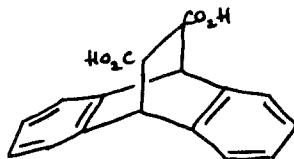
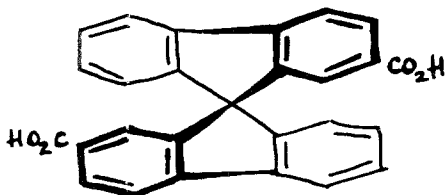
The post-prandial lecture was delivered by **John Stezowski** (Stuttgart) on the use of synthetic oligonucleotides as models for drug-DNA interactions. Studies on the interactions of anthracyclines with hepta- and octa-nucleotides gave similar results to those obtained with natural DNA, thus proving the usefulness of these as models. The nucleotides were then employed to study the behaviour of new alkyl-acridines as these drugs are known to intercalate with DNA. It was shown that, by alkylation of the amino nitrogen, the active form of the drug was now a tautomer of the free compound (7). This work should also allow the study of whether or not these drugs exert their toxic effects by cross-linking the DNA strands. Preliminary work showed that hepta- and octa-mers do not form double strands (i.e. stable duplexes), but that nona- and pentadeca-mers do. Duplexes of alkylated oligonucleotides were also synthesised in order to study the effect of reducing the number of hydrogen bonds between the two strands. Thus, these synthetic oligonucleotides offer viable and simple models to explore the effects of chemically-modifying the nucleic acid structure in DNA.



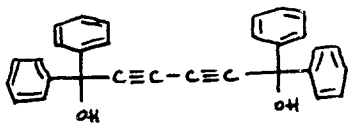
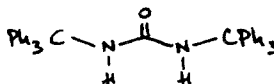
The cryptophanes, lucidly described by **André Collet** (Paris), are a family of rigid, lipophilic hosts which display elegant inclusion properties and tremendous aesthetic appeal. High selectivities and strengths were demonstrated for the complexation of the halomethanes within the context of unravelling the thermodynamics and kinetics of the inclusion process. In particular, cryptophane (8) exhibited high selectivity for chloroform over dichloromethane in $\text{CDCl}_2\text{CDCl}_2$. The conceptual extension to the water-soluble cryptophane (9), which scavenges trace amounts of the halomethanes from water, was equally successful regarding selectivity. Free energy measurements were cited to support the contention that the hydrophobic effect was greater for chloroform than for dichloromethane using (9) in D_2O . This calculation correlates with expectations based on the molecular volumes of the two guest species, a theme reiterated during the lecture. Enantiomeric differentiation is yet another elegant property displayed by these chiral systems. Furthermore, during the subsequent debate it was proposed that a kinetic resolution of racemic halomethanes could be effected using chiral cryptophanes with intrinsically slower exchange rates.



Edwin Weber (Bonn) introduced us to the term "coordinatoclathrate" which describes a species whose structure lies somewhere between a coordination complex and a true clathrate. 1,1'-Binaphthyl-2,2'-dicarboxylic acid (BNDA) (**10**) forms 1:1 and 1:2 crystalline inclusion compounds with more than 50 polar and apolar guests. The polarity of the guest determines the nature of the channels formed in the crystal. Of the two extremes (host-host hydrogen bonds or host-guest hydrogen bonds) the ring size of the resultant hydrogen bonded complex varies from the 7-membered dimer ring observed in the 1:2 complex of BNDA with DMF, to the 24-membered ring comprising an open channel structure as observed with ethylene glycol. The hydrocarbon scissor host with the functional groups removed, is capable of forming complexes with nonaliphatic hydrocarbons. Structural modifications include changes in the nature of the linkage, the functional groups and also in the basic structure of the molecule. Modification of the sensor group results in a change in the hydrogen bond functionality; in the methyl ester no inclusion behaviour is observed. The bridging linkage must be rigid and any change in position or length results in a loss of inclusion activity. Spiro-type hosts (**11**) were described, and also form 2:1 and 1:1 inclusion complexes with a large number of solvents. Roof-type hosts include FADA (**12**) and its maleic analogue MADA, which do not include the smaller alcohols but do include some larger molecules. A suggestion for future work involved the use of these hosts as active site models and an analogy was drawn between the BNDA complex with imidazole and water, and the protolytic enzyme *Streptomyces Griseus* Protease A.

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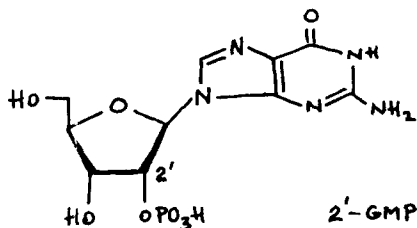
Harold Hart (Michigan) continued in the same vein as the previous speaker, but with more emphasis on the crystallographic aspects of the work. Compound (13) is a "wheels and axle" molecule, with the long molecular axis as the axle, and the sp^3 carbons at each end as the wheels. The host molecules line up forming channels with the bulky end groups acting as "spacers", preventing close packing of the hosts. These channels are continuous throughout the crystal, with various guest molecules therein included. Work was done on replacing the hydroxy groups by aryl substituents, and on varying the nature of the axle. Again, in many cases, a variety of inclusion compounds were formed.

13

DTU

The N,N' -ditritylurea (DTU) system possesses potential hydrogen bonding sites, as well as "spacers". Again many molecular complexes were formed, and the X -ray structures performed. Interesting is the strong correlation in crystallographic parameters; 6 out of the 10 complexes studied all had the same space group, which had, within narrow limits, similar cell parameters. However, despite this apparent similarity, the complexes exhibited completely different modes of complexation, although again the molecules had the long molecular axis lined up with the long crystallographic axis, with the guests running parallel. Further work was again carried out on variously substituted derivatives of DTU, including asymmetric compounds.

Wolfram Saenger (Berlin), with very little notice, gave a talk on the enzyme Ribonuclease T1 that is effectively both a catalyst and a host for guanosine-2'-phosphate (2'-GMP). A crystal structure determination clearly showed that the enzyme included the 2'-GMP. The negative charge was shown to be concentrated on the outside of the complex, with the positive charge in a band at the centre. The 2'-GMP was shown to be completely included, showing how one phosphate ester was in an exposed position from one face, enabling a facile removal.



2'-GMP

PRELOG TELEX

Professor V Prelog
Laboratorium für Organische Chemie
Eidgenössischen Technischen Hochschule
Zürich
Switzerland

WE WISH YOU A MOST HAPPY DAY. WE TOO ENJOY YOUR WORK AND THIS WEEK
WE SHALL CERTAINLY SLAUGHTER A PIG.

J Fraser Stoddart

On behalf of the Organising Committee and the Delegates from the
Fourth International Symposium on Inclusion Phenomena.

Jack Dunitz in this month's Chemistry in Britain (p606).....
On Prelog at 80:-

"If you want to be happy for an hour, buy a bottle of wine;
if you want to be happy for a week, slaughter a pig;
if you want to be happy for a year, get married;
if you want to be happy for your life, enjoy your work."

V Prelog

The Daily Gleaner

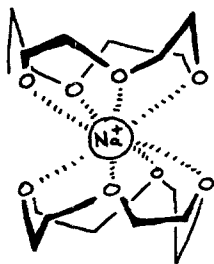
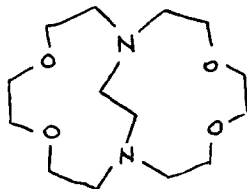
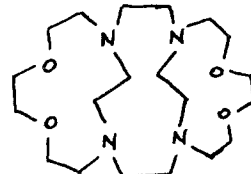
No. 4

Thursday 24 July 1986

A report on yesterday's proceedings at the 4th Inclusion Phenomena/3rd Cyclodextrin Symposium.

In Today's Issue - **DALE** : Got it all cornered
HAMILTON : Killer Pac-Man
JURCZAK : Success under great pressure!
RIPMEESTER : Listening to the guests

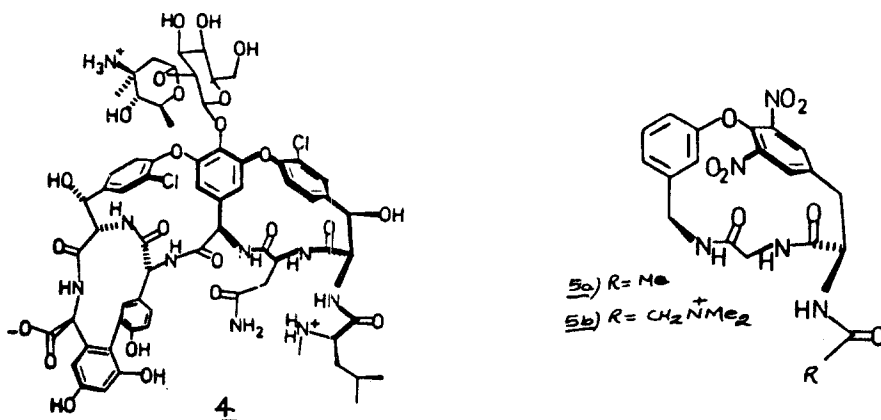
A comparison of conformations in various free and complexed crown ethers and aza-crowns using dynamic ^{13}C NMR spectroscopy was presented by **Johannes Dale** (Oslo). Crown ethers derived from the basic 12-crown-4 unit were examined since these exhibit the largest chemical shift changes when conformational changes occur on going from the free to complexed form. Simple complexes [e.g. (1)] of the ligands with alkali metals were examined in order to obtain information on the thermodynamics and kinetics of ligand exchange. These principles were then applied to more complex systems such as the bicyclic (2) and tricyclic (3) hosts. In all such systems, it was shown that conformational changes, such as those between so-called "corner-side" carbon and vicinal and geminal hydrogens involve a sequence of steps. For example, the process of geminal H-H exchange in derivatives of (2) involves both C-C rotation and nitrogen-inversion.

123

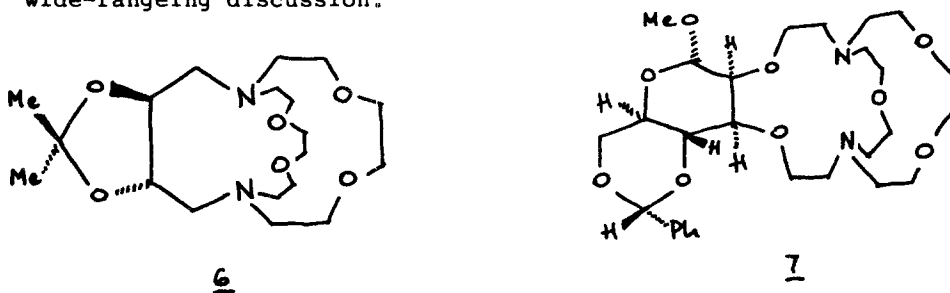
We were very fortunate that **Andrew Hamilton** (Princeton) agreed to present his lecture at extremely short notice.

Vancomycin (4), a natural heptapeptide antibiotic of intricate structure, was described by him as "almost a molecular Pac-Man". Vancomycin functions by highly selective binding of D-Ala-D-Ala residues, so interfering with the biosynthesis of bacterial cell walls. The strategy involves mimicking the biological construction of vancomycin in order to retain the antibiotic function as well as reducing the intrinsic toxicity. The binding site interaction involves six hydrogen bonds from the vancomycin to the D-Ala-D-Ala residues. The synthesis of analogues has been designed to incorporate the identified active groups without recourse to a total synthesis.

Preparations of analogous cyclic tripeptides (**5a,5b**) together with preliminary binding studies were reported. Tetramethylammonium acetate binds only weakly and this observation was ascribed to the lack of ammonium ion functionality which is present biologically. Studies using NMR spectroscopy (DMSO- d_6) suggest that acylated D-Ala-D-Ala binding is occurring: however, as yet, the evidence remains equivocal. Future studies will be concentrated upon the characterisation of the binding and in addition will involve synthesis of analogues more closely related to the natural systems.



An alternative approach to an old problem was demonstrated by **Janusz Jurczak** (Warsaw) in his use of high pressure rather than high dilution conditions to direct intramolecular reactions in the synthesis of diazamacrobicycles. Under reaction pressures of >5 kbar, the Menshutkin quaternisation was employed in the clean, high-yielding syntheses of chiral aza-crown ethers such as (**6**) and (**7**), the latter being produced in only one diastereoisomeric form. The novelty of the work described in the lecture provoked a lengthy and wide-ranging discussion.



John Ripmeester (Ottawa) has used CP/MAS ^{13}C NMR to study the orientation of the guests in the clathrates of Dianin's compound, β -quinol, α -cyclodextrin and urea. This gives useful information on the presence of different isomeric forms of the guest. Clathrate hydrates can also be characterised using an approach that utilises the NMR properties of heavier nuclei such as ^{129}Xe , where the spectrum depends both on cage shape as determined by the anisotropic shift and the cage size as determined by the chemical shift.

The Daily Gleaner

No. 5

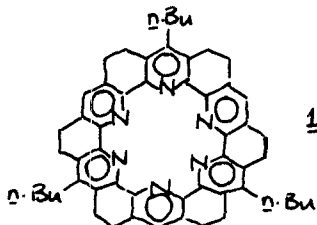
Friday 25 July 1986

A report on yesterday morning and afternoon's proceedings at the 4th Inclusion Phenomena/3rd Cyclodextrin Symposium.

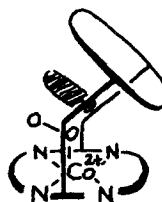
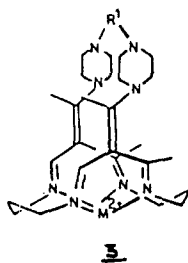
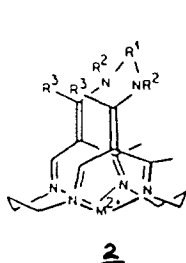
In Today's Issue -

BELL	:	The holy of holies
BUSCH	:	ContEMPLATING life
FENTON	:	Molecular heavy breathing
REINHOJDT	:	Chemistry beyond the catalogue
WILLIAMS (DH)	:	It's not so tough
WILLIAMS (DJ)	:	X-Rated picture show
SAUNDERS	:	Motion pictures
MURRAY-RUST	:	Cost-effective chemistry

Tom Bell (New York) presented a structured and lucid exposition on the design and synthesis of rigid, planar ionophores. The rigid/flexible dichotomy, the important contribution of dipoles in the cavity and problems of solubility were all taken into account in the design. The preparation of the hexaazacuculene derivative (1) was achieved via one of the proposed synthetic routes, although characterisation of the final product proved troublesome until it was realised that the compound was in fact the calcium adduct. The macrocycle's remarkable affinity for calcium ions was highlighted by the fact that all of the metal was sequestered from trace sources.

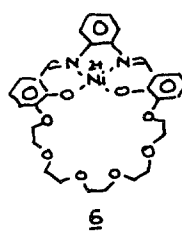
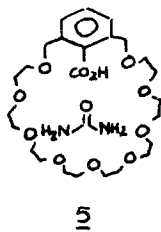
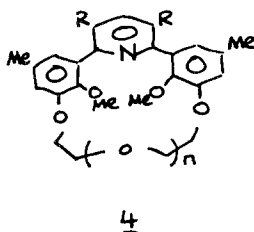


The fact that **Daryle Busch** (Ohio) "hadn't heard about a transition metal doing anything this week" must have prompted him to detail us with some of the systems he has developed as mimics for the cytochrome P-450 oxidation system. The cavity size of lacunar cyclidenes (2), controlled by varying the R groups, was shown to affect markedly some Fe oxidation reactions. The measurement of ^1H NMR relaxation times in the presence of bound paramagnetic Cu^{2+} very elegantly determined the position and orientation of guests such as $^n\text{BuOH}$ included in vaulted cyclidenes (3). Evidence for the simultaneous binding of alcohols and dioxygen in a Co^{2+} vaulted cyclidene to give a ternary complex was obtained in the same way, although the results elicited the remark- "If we were to believe these numbers... and I am not prepared to believe them!"



After quoting Lewis Carroll and telling us that "words mean what I want them to mean", **David Fenton** (Sheffield) discussed his studies of binucleating ligands. Simple synthetic routes, usually via a template method, provided both acyclic and cyclic Schiff bases. These molecules ligate two metal ions which are separated by a bridging donor species. X-Ray crystallography was the main tool of structural elucidation and provided some interesting and often slightly surprising results. The potential of these systems to complex anions was demonstrated by a crystallographic structure showing a perchlorate ion tetrahedrally surrounded by four bicopper macrocycles. This result asked a "chicken and egg" type question- did the perchlorate ion template the cavity or move into a cavity already created? Again the problem of rigidity versus flexibility in guest molecules was mentioned and these systems' flexibility was shown to be necessary for effective modelling of bimetallobiosites.

David Reinhoudt (Twente) gave a typically positive presentation on the complexation of neutral guests. The "Flexible Synthesis of Rigid Molecules" described his recent efforts on the design and synthesis of pyridohemispherands (**4**), including ^{13}C NMR T_1 measurements of their adducts with malononitrile. A study of the acidity of intra-annular functional groups enabled him to "have arrived at the ideal receptor molecule for urea", the carboxylic acid crown ether (**5**) which solubilises urea in CHCl_3 . The success of incorporating an electrophilic group into the molecule led him to the design and recently completed synthesis of the bireceptor (**6**) containing bound Ni^{2+} as the electrophilic centre. The obvious potential of this system and the elegant approach justify his final comment- "This is the future; and it is starting in our hands."



Dudley Williams (Cambridge) described his work in determining the active site of the vancomycin group of antibiotics in an easy and enjoyable way. These antibiotics prevent the cross-linking of the glycoprotein strands in the cell wall of Gram positive bacteria. This occurs by binding the D-Ala-D-Ala terminus of the protein. Acetyl-D-Ala-D-Ala was used as a model compound to study the binding of the protein to the antibiotic. Nuclear Overhauser effect NMR experiments carried out on this model with a number of these antibiotics (ristocetin and teicoplanin) allowed the characterisation of the binding site. This is basically a hydrophobic pocket into which the D-Ala-D-Ala residue fits and is held by hydrogen bonds between the carboxylate groups of the alanine residues and three amine groups of the amino acid backbone of the antibiotic. A number of modifications to the binding site allowed the determination of the of the other groups which form the hydrophobic pocket. Consideration was given as to how this antibiotic could be formed by modifications in the conformation of a linear heptapeptide. This lecture illustrated how important molecular recognition is in nature and how non-covalent forces can produce very selective complexes.

It was with great personal pleasure that many of our reporters listened to **David Williams** (London) discuss the role that X-ray crystallography does, and must, play in the design of receptor molecules. In a talk ranging from the second sphere coordination of transition metals to the encapsulation of the bipyridinium herbicides, David showed us how solid state crystal structures of inclusion complexes have been used to optimise the critical balance between H-bonding, charge transfer, and electrostatic interactions in molecular receptor design. Furthermore, comparisons of the X-ray structures of inclusion complexes with those of the free hosts has led to the design and synthesis of new receptor molecules requiring only the smallest possible conformational changes to accommodate specific guest species. And, as he promised not to mention the occasions when the crystals we supplied did not contain exactly what they should have, we in turn shall not mention that leaving crystals in their mother liquor on a radiator tends to diminish their solid state character!

A kaleidoscopic display of molecular graphics was given both by **Martin Saunders** (Smith, Kline and French) and by **Peter Murray-Rust** (Glaxo). Martin Saunders is clearly not of like mind with "people who think HCN is a large molecule". The lecture illustrated both the present uses and the future developments of simple and realistic electrostatic potential calculations to model molecular interactions. Applications include fascinating molecular-scale calculations of the dynamic trajectories of biologically-important molecules. Successful studies indicate the utility of electrostatic potentials in modelling interactions of a chiral hplc stationary phase with substrate molecules. In harmony with the previous lecture, the conformational changes during complexation of dibenzo-30-crown-10 with diquat was discussed. Calculations reinforce the solid state evidence that the total encapsulation of the diquat by the crown ether in a horse-shoe conformation is the most favourable conformation. However, the correlation of physical measurements with the empirical calculations should be treated with some caution according to Peter Murray-Rust. His lecture concentrated on the problems of molecular modelling and on methods of their refinement. Commonality in structure and functional group interactions between molecules are investigated using the Cambridge Crystallographic Data File. Qualitative predictions can thus be made if a sufficiently large sample size is taken. As examples, the directional H-bonding of alcohols to ketones, epoxides, and ethers were cited. In addition, the erudite conformational studies on the cyclic decapeptide Tyrocidine-A were also reported.

The Daily Gleaner

No. 6

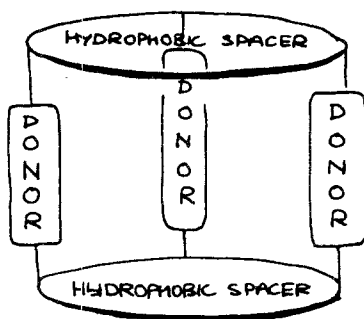
Friday 25 July 1986

A report on the proceedings not previously covered in other issues at the 4th Inclusion Phenomena/3rd Cyclodextrin Symposium.

In Today's Issue--

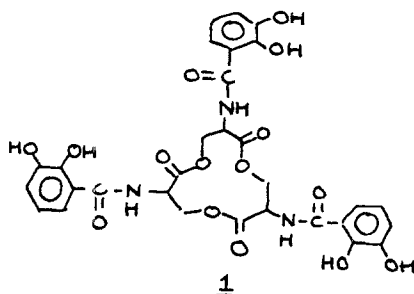
VÖGTLE	:	Gripping stuff
SHANZER	:	Let's twist again
WHITLOCK	:	The house that Howard built
SAUVAGE	:	A tricycle made for two

In a lecture of noteworthy clarity, **Fritz Vögtle** (Bonn) described his development of a series of novel synthetic receptors. Molecules were designed with large three dimensional cavities in which steric effects, hydrophobic binding, and more specific binding sites were all carefully considered. These concepts were condensed together in a family of receptor molecules containing donor groups held apart by hydrophobic spacer groups.

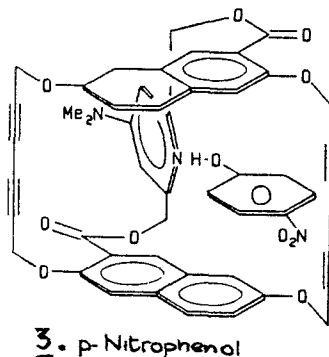
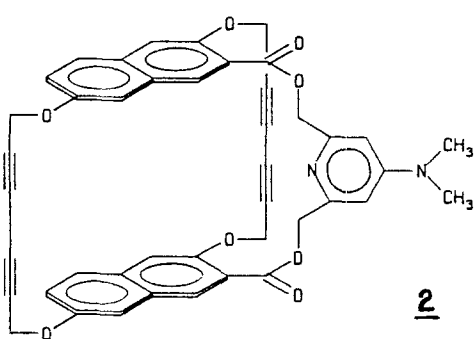


The first compound with three catechol residues and 1,3,5-substituted benzene rings as spacer groups demonstrated a remarkable affinity for Fe^{3+} , whilst a subsequent compound featuring bipyridyl donor groups showed an equally impressive ability to complex with Fe^{2+} . Another type of host featuring a 4,4',4''-triphenylmethyl group as a large spacer unit and carboxy-based groups as donors was described. These species were found to form complexes with simple aromatic guests. The synthesis of all of these polymacrocycles were effected elegantly and in yields not normally achieved with such complicated systems. He finished by touching on the wealth of potential chemistry promised by this series of compounds based on their novel selectivities and high complexing power. These included complexing anions and even ion pairs not to mention the possibility of carrying out and catalysing reactions in the cavity.

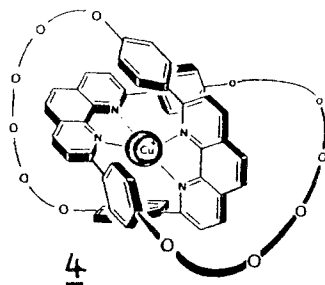
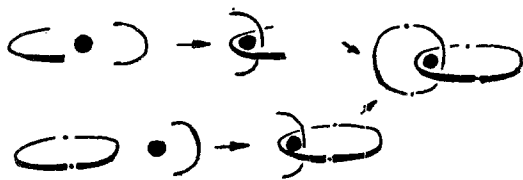
The opening lecture on the last day was given by **Abraham Shanzer** (Rehovot). Expanding upon a topic briefly mentioned the previous evening by Fritz Vogtle, he explained how his search for a flexible ionophore for Fe^{3+} transport led him to synthesise analogues of enterobactin (**1**). This exhibits an extremely high binding constant (10^{52} M^{-1}) for Fe^{3+} which cannot be explained by the coordination of the iron alone. There must also be some extra contribution and this is due to the formation of a helical arrangement by the three sidearms when coordinating the iron. He then outlined his efforts to reproduce this helical arrangement synthetically using acyclic polyamides.



"Substance is nothing, form is everything!" were the opening remarks of **Howard Whitlock** (Wisconsin) during his provocative discussion on the concept of molecular architecture - the use of molecular building blocks to make molecules for a specific purpose. He has designed a series of cyclophanes (e.g. **2** & **3**) incorporating naphthalene walls separated by spacer units and a rigidly held pyridinium group to provide a "stickiness" to the cavity. Already these new receptors have been shown to exhibit remarkable selectivity for the binding of phenols at the expense of everything else, including anilines and benzoic acids.



"As everyone knows, transition metals are magic" and **Jean-Pierre Sauvage** certainly used them as wands to weave together his threads. With Cu(I) as a template to hold them in the correct orientation, extended phenanthroline units were stitched together in high yields to give interlocking macrocycles named catenates (**4**). Demetallation with cyanide ion afforded the free catenand, which was shown to form a Ni(I) catenate, stabilising the Ni(I) towards oxidation with a topological factor of 10^5 relative to the $(dmp)_2Ni^+$ complex. The synthesis of [3]-catenands consisting of three interlocked macrocyclic rings was also described.



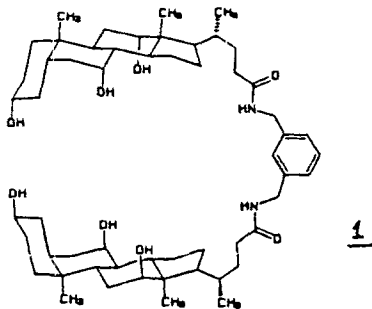
POSTERS

A review of some of the posters presented; poster numbers (as they appear in the abstracts) are included in brackets [].

The **POSTER OSCAR** (£150, donated by Royal Dutch Shell, Amsterdam) was won by **John Thomas'** group for their contribution [100] entitled - **The Inclusion of Benzene and Pyridine in the Tunnels of a Zeolite.** The runner's-up prize (£75, Royal Dutch Shell, Amsterdam) was won by **David Reinhoudt's** group for their poster [63] entitled - **The Use of Electrophiles in the Complexation of Urea by Macrocyclic Host Molecules.**

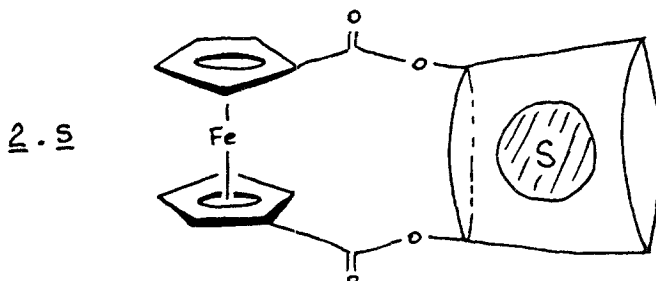
The posters on the topic of cyclodextrins were an interesting cross-section through the range of chemistry of these compounds. Most of the posters described work with natural cyclodextrins, but increasingly, attention is being focused on chemically-modified derivatives [24,108], especially the methylated cyclodextrins which show great promise in many applications. Several contributors studied cyclodextrin complexation at a fundamental level by many methods including solubility, filtration cell studies, thermal analysis, ^1H , ^2H , ^{13}C and ^{19}F NMR spectroscopy in solution and in the solid state, spectrophotometry, circular dichroism and X-ray crystallography [1,3,5,6,8,9,23,26,27]. The use of cyclodextrins to influence reactions selectively and/or catalytically was also described [2,11]. Reactions of cyclodextrin adducts in the solid state showed enhanced selectivities, and reactions in solution with possible industrial applications were described [12], as well as their uses in modelling biological reactions [21,22]. There was a lot of information on the potential pharmaceutical benefits of using cyclodextrins as drug-delivery systems [7,17,18], and in one case as a bile substitute to solubilise fat *in vivo* [13]. In an agrochemical application, cyclodextrins were found useful in plant protection because of their ability to complex non-ionic tenzides [19,20]. The increasing use of cyclodextrins to effect chromatographic separations also received deserving attention [14,15,16,109], and their potentially powerful applications as stationary phases are evident.

A study of open-chain and macrocyclic receptors based on bis-cholic acid in complexation with neutral polar guests was presented [36] in a clear and concise form by **Cynthia Burrows** (NY State). The open chain host (1) can exist in several conformations, of which the two extremes are the "open" and "closed" forms. Using ^1H NMR spectroscopy, it was shown that, in the latter case, the hydroxyl functions are directed towards a central cavity space and the conformation is stabilised by internal hydrogen bonding. When polar guests such as methanol are complexed by this host, a similar hydrogen bonding network between host and guest is observed.

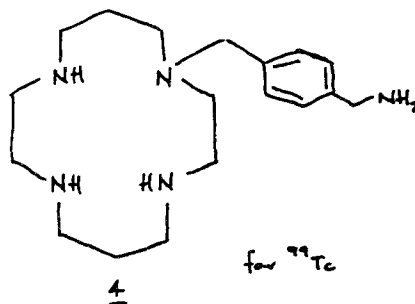
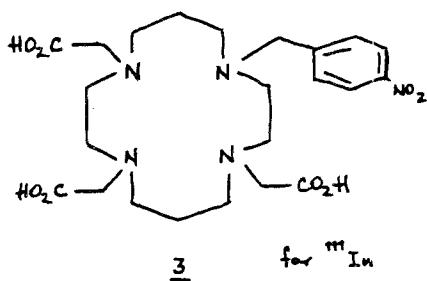


The challenge to complex uncharged lipophilic molecules was elegantly described [37] by **Israel Goldberg** (Tel Aviv). The requirement for well defined cavities of suitable properties for inclusion was emphasised. This work can be seen as part of a new trend to impart rigidity to well characterised (solution state) hosts normally associated with the solid state.

Among the redox active macropolycyclic molecules described [45] by **Paul Beer** (Birmingham), were the metallo-calix-[4]-arenes (2) which include neutral substrates. With ^tbutylamine as substrate (S) the oxidation potential of the iron atom in the ferrocene complex is increased, but unfortunately the process is irreversible.

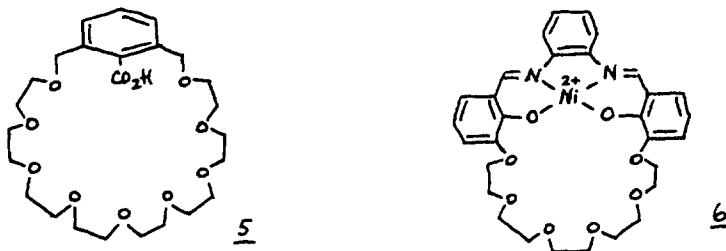


Potential developments in cancer therapy must include the utilisation of 'targetted macrocycles' for selective radionucleotide delivery. It is necessary to ensure rapid and complete radionucleotide complexation under physiological conditions to give a kinetically-stable complex. This goal has been achieved [49] using the water-soluble macrocycles (3) and (4). Targetting is achieved using monoclonal antibodies. While this ensures selectivity, it also requires specific monoclonal antibodies which do not cause radionucleotide accumulation in the biological system. The applicability is clearly reliant on the limitations of monoclonal antibody techniques.



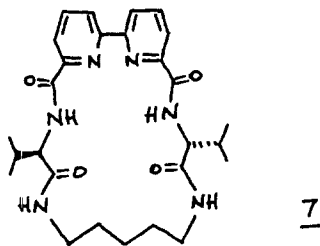
To many people the phrase "liquid clathrates" may appear at first to be a contradiction in terms, but **Jerry Atwood** (Alabama) has shown us [61] that the phrase can be used effectively to describe a new mesomorphic state, incorporating many of the features of solid state clathrates and also solution inclusion phenomena. The ability of these liquid clathrate phases to extract hydrocarbons from solutions in model studies represents an exciting advance in the possibility of producing cheap coal-derived petroleum.

In general, crown ethers do not form strong inclusion complexes with neutral molecules, thus much work on binding urea has instead focused on binding the more strongly held uronium cation. **David Reinhoudt** (Enschede) has solved many of the problems associated with this work [63] through the use of crown ethers possessing readily ionisable groups (5) and, more recently, biceptor molecules (6) capable of stabilising a urea complex through metal cation co-complexation.



With David's work in mind, it was therefore very interesting to see a poster [85] reporting crystal structures of stoichiometric 1:1 complexes of urea (NOT the uronium ion) with small crown ethers containing ionisable groups.

Andrew Hamilton (Princeton) reported [late submission] the recent synthesis and characterisation of a macrocycle (7), designed specifically to control the environment around a complexed metal in order to influence its catalytic properties. The macrocycle was synthesised from a bipyridyl unit and two valine residues. It was designed to provide (a) ligands capable of stabilising a range of metal oxidation states, (b) chiral groups which are close enough to influence the approach to the metal, (c) a cavity in order to effect substrate specificity and (d) sufficient stability to withstand oxidation. Complexation with a number of transition metals has been successful and preliminary studies on the Fe^{3+} complex show that in the presence of iodosylbenzene in acetonitrile, it will epoxidise cyclooctene in 55% yield.



Of the many other posters on the subjects of Macrocycles, Clathrates, Intercalates, Surface Absorption and Zeolites, many deserve mention but lack of space permits only the Oscar winner to be described. The contribution [100] of the group of **John Thomas** (Cambridge) showed how the positions of small organic molecules such as benzene and pyridine included within zeolites could be determined. The poster was particularly notable for its spectacular use of colour graphics special effects.

FOURTH INTERNATIONAL SYMPOSIUM INCLUSION PHENOMENA

THIRD INTERNATIONAL SYMPOSIUM CYCLODEXTRINS

Lancaster 20-25 July 1986

EVENING SESSIONS

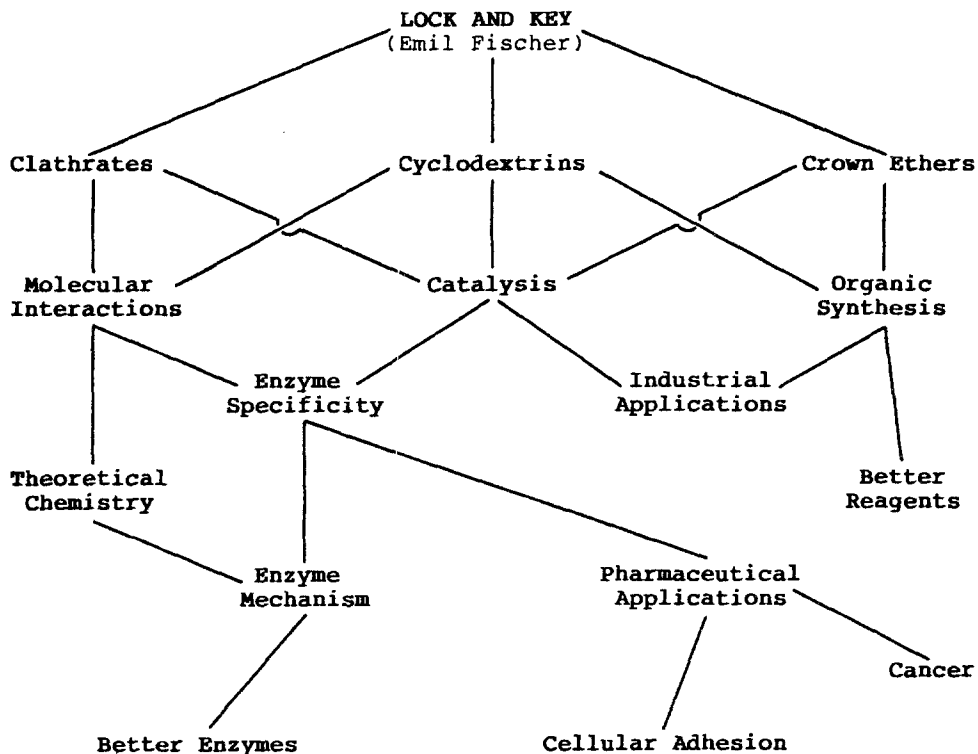
The **Evening Sessions** were an experiment. A unique mix of scientific debate and liquid refreshments were floated at a meeting for the first time to our knowledge. The idea was to promote informal discussion and argument, catalysed by short talks from some of the poster presenters. The activities were sustained and controlled by **Dick Wife** (Shell, Amsterdam) and **József Szejtli** (Chinoin, Budapest). The **First Evening Session**, nominally on solid state phenomena, was to some extent an acclimatisation. People were getting used to the idea and the format. **David Wernick** (Tel Aviv) discussed **Catalysis by Cyclodextrins in the Solid State**, **Roger Bishop** (New South Wales) talked at length on **Helical Tubuland Hosts** and **Ric Zarzycki** (Sheffield) spoke briefly on **Transition Metal Adducts with Cyclodextrins**. The response to the talks themselves was rather limited, but other topics surfaced in between the presentations and several impromptu discussions did ensue. By the end of the session, people were beginning to warm to the idea and this was one of the factors which led to the success of the **Second Evening Session**, nominally dealing with the solution state. The presentations were given by **Cynthia Burrows** (New York State) on **Chiral Hydrophobic Cavities from Cholic Acid**, **David Parker** (Durham) on **Macrocycles/Antibodies as Anti-Tumour Agents**, **John Toner** (Kodak, Rochester, USA) on **Specific Ionophores** and **Steve Lincoln** (Adelaide) on **Double Guests in Cyclodextrins**. There was a good deal of discussion and debate throughout the session, not only on the topics presented, but also on subjects introduced by speakers from the floor. Everyone present appeared to enjoy themselves and the general opinion voiced afterwards was that the experiment had been sufficient of a success to warrant repetition.



FOURTH INTERNATIONAL SYMPOSIUM INCLUSION PHENOMENA
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OVERVIEW

It was entirely appropriate that the fine statesman of science, **Friedrich Cramer** (Göttingen) had the last word today. In his own inimitable way he provided for us an overview of the whole area of molecular recognition illustrated simply by Emil Fischer's "Lock and Key" concept.



By leading us through the different processes which result in molecular recognition, he painted a picture of how important this whole area is in physical, chemical and biological sciences. Beginning with the simple example of pyrophosphate hydrolysis by cyclodextrins and building up to how cell walls in mammalian tissue recognise sugar residues, he succeeded in completing a picture to which many individual strokes had been added during the course of the week. One was left with the feeling of having been led through a park full of beautiful and exciting sights by a well-loved and knowledgeable teacher.

The Overview Session was chaired in an extremely lively manner by **Bernard Langley** (ICI, Academic Relations). The rapidity with which he spoke was matched only by the quickness of his wit and it was fitting that the meeting concluded on such a high note.

FOURTH INTERNATIONAL SYMPOSIUM INCLUSION PHENOMENA

THIRD INTERNATIONAL SYMPOSIUM CYCLODEXTRINS

Lancaster 20-25 July 1986

That was the week that was

The Lancaster meeting was a friendly meeting, a hard-working experiment. It was also a week filled with the many excellent presentations in lectures and posters, and discussions stretching into the early hours of the morning, some serious and some not so serious. We appreciate the effort and the energy of each delegate throughout this meeting. In the two years before the next meeting in Alabama, we wish you all success in your own experiments, and to seeing you as hosts or as guests.

SESSION CHAIRMEN

Fraser Stoddart (Sheffield), **Giovanni Andreotti** (Parma), **Wolfram Saenger** (Berlin), **David MacNicol** (Glasgow), **Eric Davies** (Lancaster), **Jerry Atwood** (Alabama), **Mary Truter** (London), **David Ollis** (Sheffield), **Bernard Langley** (ICI Academic Relations).

EVENING SESSION CHAIRMEN

Dick Wife (Shell, Amsterdam), **József Szejtli** (Chinoin, Budapest).

LOCAL ORGANISING COMMITTEE

Convener: **Eric Davies** (Lancaster) and **John Gibson** (Royal Society of Chemistry), **David MacNicol** (Glasgow), **Fraser Stoddart** (Sheffield), **Dick Wife** (Shell, Amsterdam), **David Williams** (London).

The REPORTERS and STEWARDS who toiled deep into the night to produce **The Daily Gleaner**.

Imperial College of Science and Technology
Alexandra Slawin

Lancaster University
Vivian Knott, Mark Houghton, Andrew Haise (Projectionist).

Sheffield University
David Berrisford, Paola Bonaccorsi, Surinder Chana, Lawrence Cullen, Mark Garner, Colin Gemmell, Franz Kohnke, David Leigh, John Mathias, David Mulligan, Mark Reddington, Neil Spencer, Michael Wali, Ric Zarzycki.