Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **7** (1989), 227–245.

The Making of Molecular Belts and Collars[1]

J. FRASER STODDART
Department of Chemistry, The University, Sheffield S3 7HF, Great Britain

(Received: 1 February 1988)

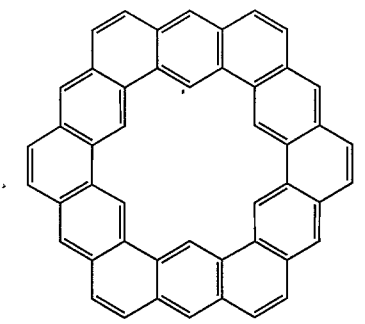
Abstract. This article relates the first encouraging steps towards the fulfilment of a long-standing research goal aimed at turning the chemistry of laterally-fused six-membered rings through 90° . . . or, more specifically, the making of (i) beltenes, in which 1,4-cyclohexadiene rings are linked in a polycyclic array by lateral fusion through their carbon–carbon double bonds, (ii) collarenes, in which alternating benzene and 1,4-cyclohexadiene rings are fused to form macropolycyclic hydrocarbons and (iii) cyclacenes, which may be considered as two annulenes joined to each other by carbon–carbon single bonds between every other atom around the annulene rings. The synthesis of the key macropolycyclic compound, which is a potential precursor of [12]beltene and [12]collarene, exploits the amazing stereoelectronic control that exists in the Diels–Alder reaction between a bisdiene and a bisdienophile with the appropriate structural features and reactivity characteristics.

Key words. Cavitands, Diels–Alder reactions, stereoelectronic control, kohnkene, clathrate formation, chemical sensor, [12]collarene, [12]beltene, [12]cyclacene, organic zeolites.

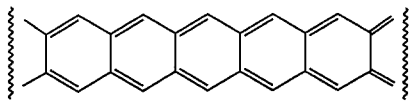
Over the years, the thrust of my research effort has been dictated largely by the challenge to design and synthesise molecular receptors to bind with a particular substrate or to promote a chosen reaction. However, we do try to invest a small amount of our time in chasing fantasies, rather than pursuing, what at least we think are realities. It is a flight of fancy that I am going to relate to you in this lecture. Just forget all about molecular recognition, as either a ground state or a transition state phenomenon, and let us take a trip into dreamland in search of new synthetic molecular materials and receptors that are rigid and have some of the topological features of belts and braces not to mention clips and collars.

Rigid molecules with belt- and collar-like structures, although relatively rare, are not exactly new: carbohydrates provide perhaps the best known examples in the shape of the cyclodextrins [1]: then chance has played its part in the spontaneous assembly of cucurbituril [2] from glyoxal, urea, and formaldehyde: and careful design and synthesis has led to the realisation of the so-called cavitands [3]. Although all three of these hosts have proved to be rich hunting grounds for both ground and transition state receptor chemistry, they have their limitations: cavitand manufacture often involves a lot of synthetic effort, cucurbituril is a one-off job, and cyclodextrins, despite yielding increasingly to reliable chemical modification [4], remain locked into something of a structural straight-jacket. Against this background, we have been seeking an approach to the design and synthesis of rigid doughnut-shaped molecules which would offer a lot of flexibility in terms of (i) structure, (ii) size, (iii) shape, (iv) electronic characteristics, (v) functionality, and (vi) properties. Topologically, the molecules I am going to describe in this lecture are similar to the cyclodextrins, cucurbituril, and the cavitands: structurally,

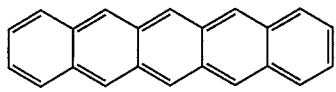
however, they constitute a completely new class of potential receptor molecule with, I suspect, their own unique physical and rich material properties.



Kekulene (1)



Polyacenes (2)



Pentacene (3)

Since Kekulé proposed [5] the first satisfactory structure for benzene in 1865 to the synthesis of kekulene (**1**), for example, in 1978 by Diederich and Stabb [6], the cyclic homologation of the benzenoid nucleus has proceeded in the planes of the benzene rings. To any benzene ring, one can envisage *ab*-, *ac*-, and *ad*-fusion of another benzene ring: kekulene (**1**) contains twelve benzene rings, six fused *ac* and six fused *ad*. Pure *ad*-fusion leads, of course, to the polyacenes (**2**): they have been isolated and characterised up to heptacene [7] and very recently a much improved synthesis of pentacene (**3**) has been reported [8]: they are linear molecular strips. Imagine, however, the bending of a polyacene containing a repeating unit of twelve benzene rings into a molecular belt in which the plane of the macropolycycle is orthogonal to the mean plane of the benzene rings now forced to adopt boat-like conformations: we have just constructed (Figure 1) [12]cyclacene (**4**). Bent benzene rings are not uncommon and exist, for example [9], in the [*n*]paracyclophane series of compounds where $8 \geqq n \geqq 4$. It will be useful during this lecture for me to project this 3-dimensional structure on to a 2-dimensional surface as shown in Figure 1. This constitutional formula suggests that [12]cyclacene (**4**) – a constitutional isomer of kekulene (**1**) – might best be thought of as two antiaromatic [24]annulenes linked by twelve carbon–carbon bonds. The polyacenes (**2**) and [*n*]cyclacenes could become very important organic compounds if the predictions [10] that their con- densed phases might possibly show high temperature ferromagnetism and warm superconductivity are realised. Whatever their electronic character, and always assuming they are stable enough to be isolated, what are we going to do with them chemically?

Scheme 1 outlines some of the directions that could be pursued starting from the [*n*]cyclacenes. We could attempt to (i) effect electrophilic-like substitutions upon the unsaturated rings, (ii) reduce the benzene-like rings to 1,4-cyclohexadiene rings and obtain the so-called [*n*]beltenes [11], which could, in turn, become substrates for (iii) allylic substitutions, (iv) cleavage of the carbon–carbon double bonds with ozone to give cyclic [*n*]ketones, and (v) epoxidation of the carbon–carbon double bonds to afford [*n*]epoxides. In principle, this addition could occur on either the inside or the

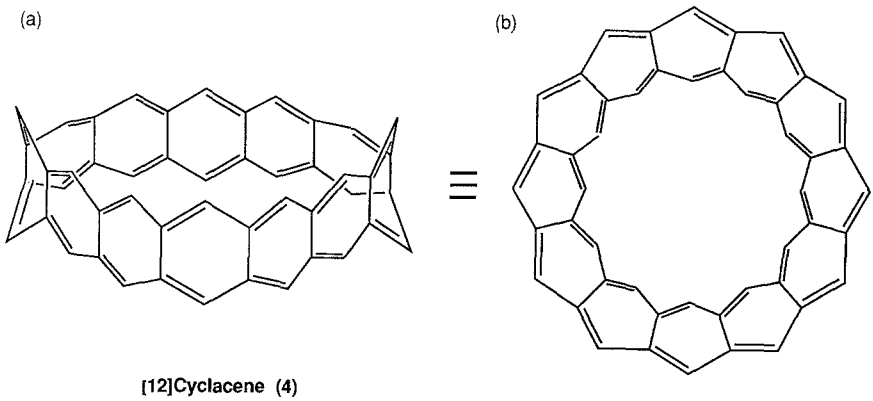
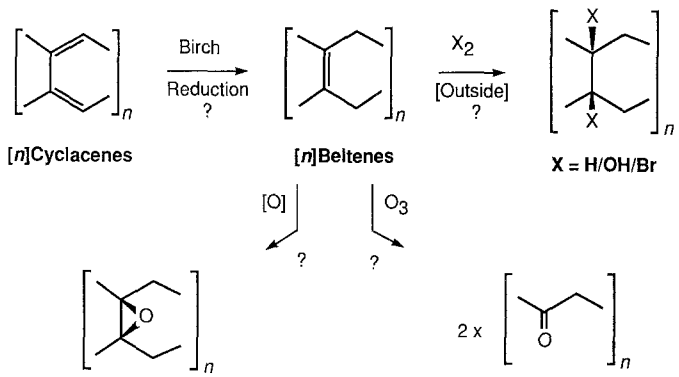


Fig. 1. (a) Conformational and (b) constitutional formulae for [12]cyclacene. They indicate how **4** can be considered to be composed of two [24]annulenes linked by twelve carbon–carbon bonds.

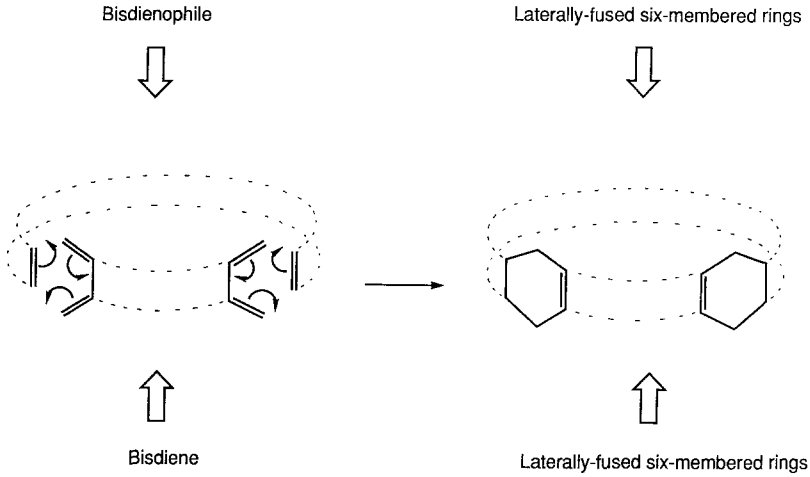
outside of the beltene – as could (vi) hydrogenation, (vii) hydroxylation, and (viii) halogenation, for example.



Scheme 1

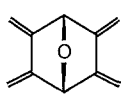
How are we going to make macropolycycles built up of laterally-fused six-membered rings? We recommend a synthetic approach that relies upon the Diels–Alder reaction. I find it quite remarkable that so far, to my knowledge, no one has used this well-known reaction, where not one but, two bonds are formed simultaneously between a diene and a dienophile, to make a molecular receptor. Just imagine incorporating the diene and the dienophile into the same molecule: then, an intramolecular Diels–Alder reaction, always assuming it is stereochemically feasible, will lead to intramolecular macropolycyclisation. Or more realistically, by employing a bisdiene and a bisdienophile, the Diels–Alder reaction could be used (Scheme 2) sequentially to build laterally-fused six-membered rings into a macropolycycle.

Why appeal to the Diels–Alder reaction? I suggest two reasons. Firstly, its practice extends over half a century [12]: the reaction (i) can involve cheap and readily-available starting materials, (ii) gives six-membered rings, (iii) goes in high

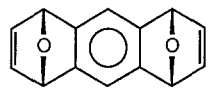


Scheme 2

yields very often, (iv) can be performed in a range of solvents including water [13], (v) can be carried out over a wide range of temperatures, (vi) can be promoted by very high pressures [14], and (vii) can be catalysed by Lewis acids [15]. Secondly, the reaction mechanism is well understood [16]: the Diels–Alder reaction exhibits (i) high regioselectivity, (ii) complete stereospecificity, i.e. *cis*-addition, and (iii) high stereoselectivity, *nota bene*, with respect to bicyclic systems, for 'close' stereochemistry, the descriptors *endo* and *exo* are usually used to define relative configurations, whereas for 'remote' stereochemistry, the terms *anti* and *syn* can be employed as relative configurational descriptors.



The bisdiene 5



The bisdienophile 6

With reference to Scheme 2, the main problem was identifying a bisdiene and a bisdienophile that worked: after 10 years of learning the hard way, we finally uncovered two building blocks that worked well [17, 18]: they are 2,3,5,6-tetramethylene-7-oxabicyclo[2.2.1]heptane (**5**), first described in the literature [19] by Professor Pierre Vogel from Lausanne in Switzerland in 1974 and the *syn*-isomer **6** of 1,4:5,8-diepoxy-1,4,5,8-tetrahydroanthracene, first isolated and characterised [20] by Professor Harold Hart at Michigan State University in 1983.

The choice of the bisdiene **5** as one of the starting materials was based on the following observations and features: (i) it can be prepared [21] in four steps from the maleic anhydride adduct of furan, 100 g of the latter yielding 10 g of the bisdiene **5**: (ii) it forms [19, 21–23] monoadducts *ca.* 100 times faster than bisadducts and so repetitive Diels–Alder reactions can be done in discrete steps by starting with mild conditions and making them progressively more forcing: (iii) in

its cycloadditions with bisdienophiles such as benzoquinone, *one* of two possible diastereoisomers predominates overwhelmingly (>95 : <5), indicating that high stereoselectivity is operating at the 'remote' stereochemical level. The choice of the bisdienophile **6** as the other starting material was based on the following observations and features: (i) it can be prepared [20] from 1,2,4,5-tetrabromobenzene and furan, 100 g of the latter yielding 10 g of the bisdienophile **6** after chromatography to remove any by-products and the *anti*-isomer of 1,4 : 5,8-diepoxy-1,4,5,8-tetrahydroanthracene (X-ray crystallography [24] established the relative configurations of both isomers beyond any doubt): (ii) when **6** is reacted with anthracene only *one* of the three possible diastereoisomeric bisadducts is formed [20], indicating that high stereoselectivity is also operating at the 'close' stereochemical level. Both the bisdiene **5** and the bisdienophile **6** share another two important characteristics: (i) they are rigid molecules with concave and convex surfaces (Figure 2); bring them together in the correct way and they should be able to close a molecular loop and make a molecular belt; (ii) it should be possible to remove the oxygen atoms somehow (e.g. deoxygenation or dehydration) at the end of the sequence of Diels–Alder reactions.

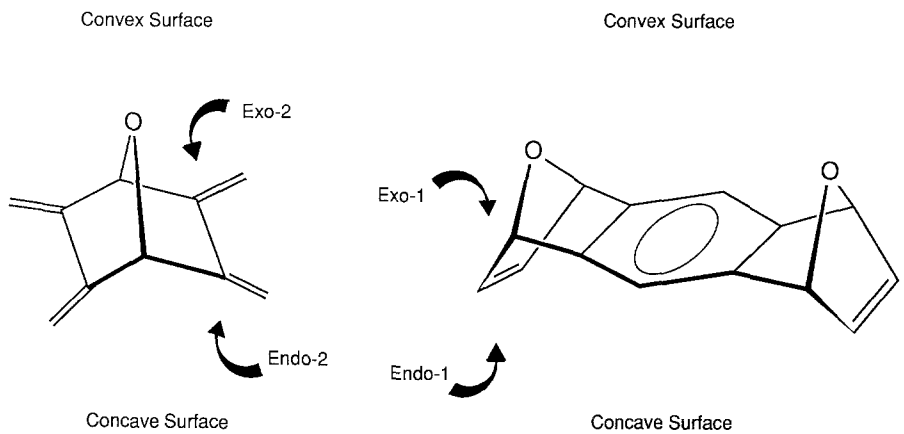
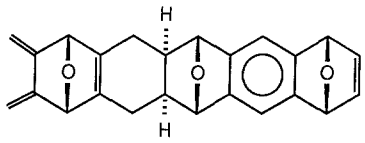


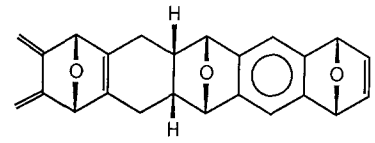
Fig. 2. The shapes of the bisdiene **5** and the bisdienophile **6**, showing their convex and concave surfaces as well as their *exo* and *endo* faces ('2' represents a diene unit whereas '1' represents a dienophilic unit).

Given the fact that both **5** and **6** have diene and dienophilic components respectively with *endo* and *exo* faces, there are *eight* different ways of bringing the two components together to give *four* diastereoisomeric 1 : 1 adducts, i.e. there is a two-fold degeneracy in the reaction pathways with respect to the reaction products. In practice, one of the two diastereoisomeric transition states can be discounted for steric reasons in each case in the formation of the *syn*/*endo*-H, *syn*/*exo*-H, *anti*/*endo*-H, and *anti*/*exo*-H isomers, **7**, **8**, **9**, and **10**, respectively.

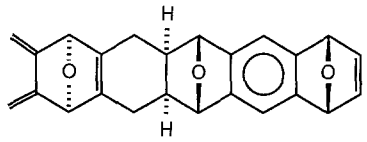
Examination of framework molecular models shows that, while the *anti* isomers **9** and **10** can only undergo polymerisation, the *syn* isomers **7** and **8** can, in principle at least, dimerise and cyclise: the *syn*/*exo*-H isomer **8** might conceivably be capable of cyclisation, i.e. it could undergo an intramolecular Diels–Alder reaction. At



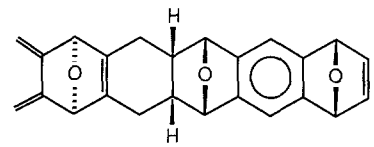
Syn/Endo-H Isomer 7



Syn/Exo-H Isomer 8



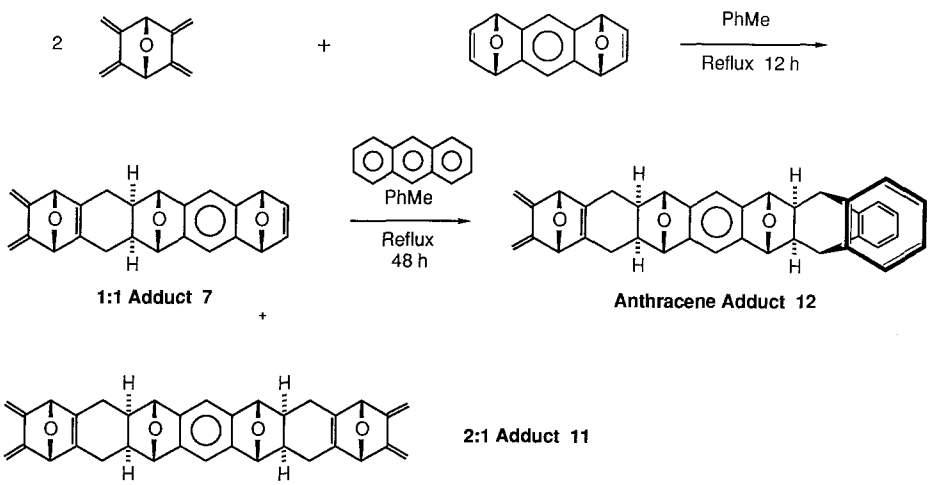
Anti/Endo-H Isomer 9



Anti/Exo-H Isomer 10

worst, only **9** and/or **10** with the *anti* configuration might be obtained: at best, we might get only **7** and/or **8** with the *syn* configuration: in truth, we were prepared to accept a mixture of all four isomers and face some demanding chromatography: in reality, we were only able to isolate (Scheme 3) and characterise **7**, the *syn/endo*-H isomer. When you reflect on the fact that the reaction has the option to go down eight different pathways, then the exclusive choice of *one* is all the more remarkable. I alluded earlier to the high stereoelectronic control of 'close' and 'remote' stereochemistries *separately*: now, we see that when these two stereochemistries exist *in tandem*, the stereoelectronic control is just as tight. This realisation opens up the exciting prospect of the existence[2] of a land of molecular 'lego'.

Reaction of the bisdiene **5** with the bisdienophile **6** afforded (Scheme 3) the 1 : 1 adduct **7** and the 2 : 1 adduct **11** in yields of 24 and 61% respectively after chromatography. The 'close' stereochemistry in both these adducts could be estab-



Scheme 3

lished easily by ^{1}H NMR spectroscopy: the sharp singlets observed in each case for the methine protons at the newly formed ring junctions indicate [19, 21–23] that these hydrogen atoms have the *endo* configuration. The 'remote' stereochemistry (*nota bene*, when the oxygen atoms in the bisdiene and bisdienophilic components of the adducts are on the same side, the relative configuration is defined *syn* and when they are on opposite sides it is defined *anti*) was quite another matter and it soon became clear that this configurational information could only be secured with certainty by appealing to X-ray crystallography. Neither adduct could be persuaded to yield good quality single crystals and so we had to go in search of a derivative of the 1 : 1 adduct **7**; eventually, after several months and numerous disappointments, the anthracene adduct **12** of **7** (see Scheme 3) afforded good single crystals

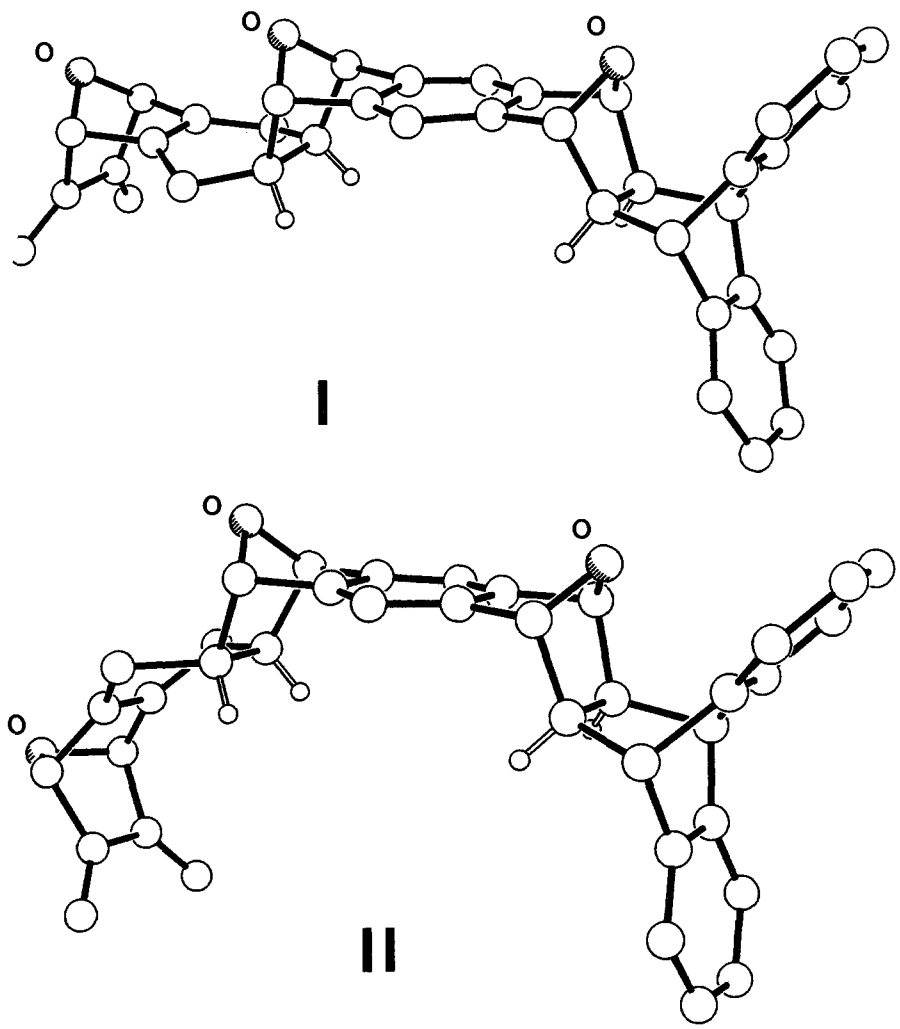
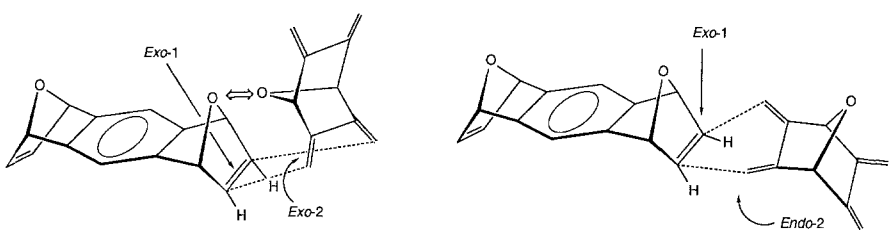


Fig. 3. Ball-and-stick representations of the solid state structures of the two crystallographically independent molecules (with the same configuration but differing in conformation) of the anthracene adduct **12**.

suitable for X-ray crystallography after employing chloroform-1,2-dichloroethane-light petroleum in a vapour diffusion method [25]. Although X-ray structural analysis revealed (Figure 3) the presence of two crystallographically-independent molecules, I and II, both have the same relative configuration consistent with the original 1 : 1 adduct having the *syn*/*endo*-H configuration **7**. Molecules I and II differ mainly in the conformations of their substituted cyclohexene rings: compounds of this type have pincer-like qualities to them such that, if they were adorned in the region of their claws with appropriate functional groups, then they could provide expandable and contractible molecular grooves and clefts, adaptable to a whole range of molecular recognition phenomena (cf. Ref. [26]). What happens stereochemically on 'the left of centre' during the formation of the 1 : 1 adduct **7** presumably also happens on 'the right of centre' during the formation of the 2 : 1 adduct **11**. This implies the production of a 2 : 1 adduct with a *syn*/*endo*-H//*syn*/*endo*-H configuration **11** having C_{2v} symmetry. This implication is supported strongly by the observation of (a) only *nine* signals in the ^{1}H-decoupled ^{13}C NMR spectrum for the *nine* heterotopic carbon atoms in **11**, and (b) only *eight* resonances in the ^{1}H NMR spectrum for the *eight* heterotopic hydrogen atoms in **11**. Also, the subsequent macropolycyclisation (*vide infra*) of **11** with **6** establishes the stereochemical assignment I have just made to **11** beyond question.

The amazing stereoselectivity which is exercised during the formation of the 1 : 1 adduct **7** – and indeed the 2 : 1 adduct **11** – is worthy of comment. The *syn*/*endo*-H stereochemistry of **7** could, in principle, ensue (Figure 4) from transition states exhibiting *syn*/*endo*-1/*exo*-2 or *syn*/*exo*-1/*endo*-2 geometries. The former can be ruled out on steric grounds: the latter is presumably favoured for stereoelectronic reasons. As far as the dienophilic component of **6** is concerned, there is evidence [23] of the pyramidalisation of the carbon–carbon double bond such that the electron density in the π-bonding orbital is much greater on the *exo*-1 face than on the *endo*-1 face: and so *exo*-1 attack is favoured. What controls the approach of the dienophilic component of **6** to the diene orbitals of **5**? We believe that stereoelectronic control could be dictated in this instance by secondary factors similar to those postulated by Paquette [27] to account for the favoured *endo*-2 attack of the 2,3-dimethylene-7-methanobicyclo[2.2.1]heptane constitution by dienophiles.

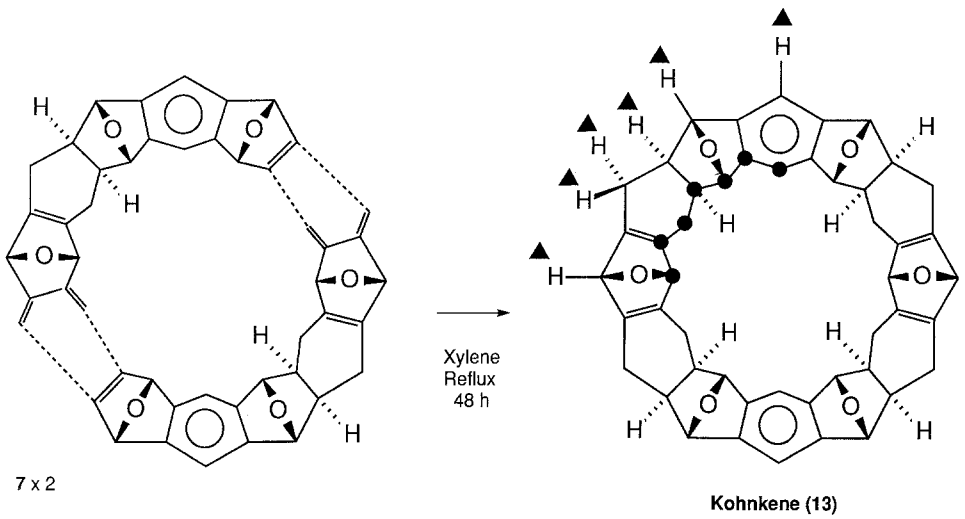
At last, we were in a position to attempt the cyclodimerisation (Scheme 4) of the 1 : 1 adduct **7**. After heating **7** under reflux at ca. 150°C in xylene for 2 days, we managed to isolate, in 3.5% yield, after painstaking chromatography, a compound



Syn/Exo-1/*Exo*-2 Transition State

Syn/Exo-1/*Endo*-2 Transition State

Fig. 4. The sterically disfavoured *syn*/*exo*-1/*exo*-2 and stereoelectronically favoured *syn*/*exo*-1/*endo*-2 transition states which afford a 1 : 1 adduct **7** with *syn*/*endo*-H stereochemistry.



Scheme 4

which got us really excited when we examined its spectroscopic properties: (a) positive ion FABMS gave a very intense peak at 713 for $[M+H]^+$, (b) the ^{1}H-decoupled ^{13}C NMR spectrum revealed *seven* signals, and (c) the ^{1}H NMR spectrum, *six* resonances. The macropolycycle **13** formulated in Scheme 4 has D_{2h} symmetry, consistent with the molecule having *seven* heterotopic carbon atoms and *six* heterotopic hydrogen atoms. Now, I am sure you will all agree that the real advances in synthetic chemistry occur at the laboratory bench and not on the office desk: in this instance, it was Franz Kohnke from the University of Messina who brought **13** into the world. I believe it is the professional duty of more senior scientists to recognise openly and encourage vigorously the remarkable achievements of their younger colleagues: in recognition of the outstanding talent and considerable tenacity shown by Dr Kohnke in synthesising **13**, I propose to call this compound – the first macropolycyclic one of its kind to be isolated and characterised – *kohnkene*[3]. It should be added that this proposal has been advanced after considering and rejecting many alternatives: it should also be emphasised that it was made in the face of considerable opposition from the maker of **13**.

Has anyone been trying to draw kohnkene (**13**)? Without a plan, it is not easy. Here are some tips. Refer to Figure 5. Draw (**A**) a clock-face. Sketch (**B**) a 12-pointed star. Add spokes of equal length to the star emanating out from the points and drawn (**C**) collinear with the centre. Construct (**D**) another larger 12-pointed star. Equipped with this basic saturated carbon skeleton, it is a trivial matter (**E**) to introduce the unsaturation and add the oxygen atoms whilst also denoting the stereochemistry. We find the clock numbering system illustrated in **E** on kohnkene (**13**) in Figure 5 particularly useful when discussing its physical properties and chemical reactivity. While rings can be identified as occurring on the hour at 1, 2, 3, . . . o'clock, the ring junctions correspond to half-past the hour and so can be identified as 1:30, 2:30, 3:30, . . . etc.

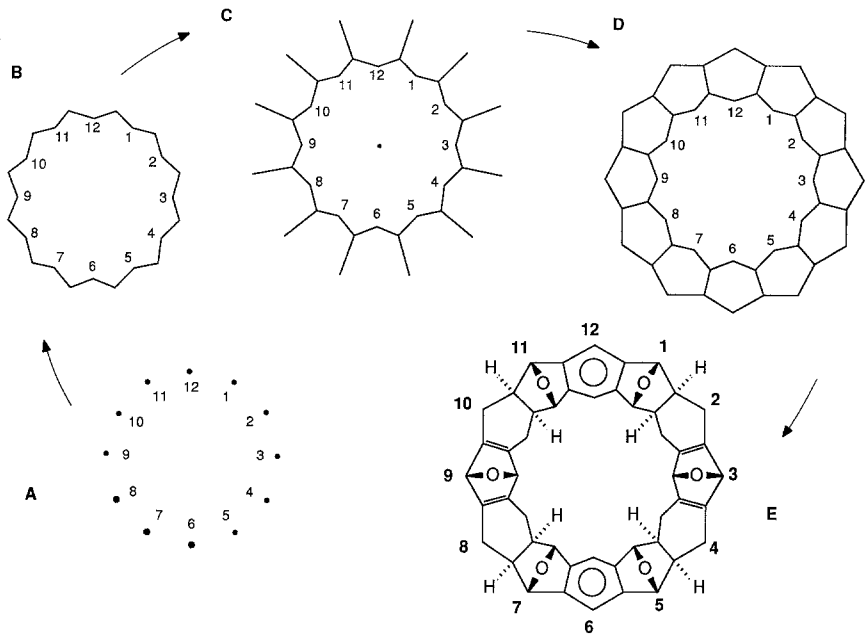
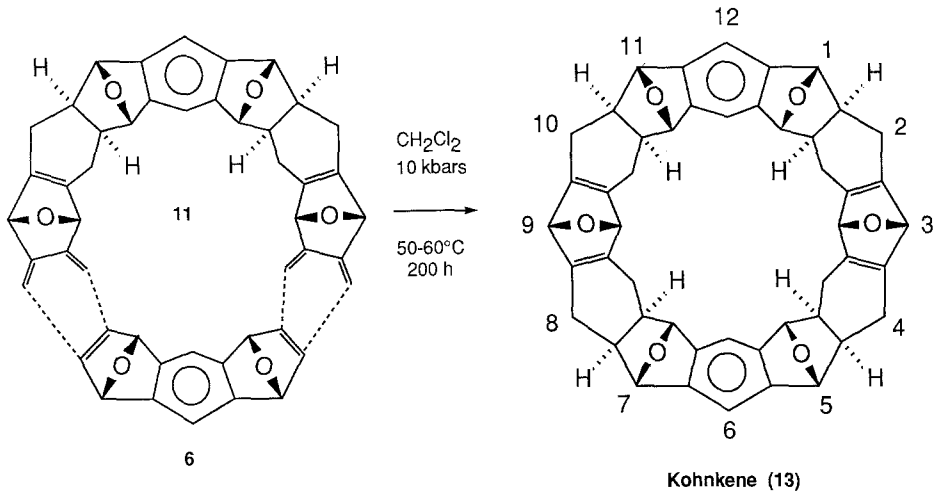


Fig. 5. The steps (**A–E**) in the recommended approach to drawing the configurational formula of kohnkene (**13**).

We have learnt to draw kohnkene (**13**) and to identify its parts but remember we have only obtained it in very low yield (3.5%) from the 1 : 1 adduct **7**. This is not very encouraging if kohnkene (**13**) is ever going to be any more than an academic curiosity. Now, it is well known that Diels–Alder reactions have *negative* volumes of activation [14], i.e. the coming together at the transition state of a diene and a dienophile is accompanied by a reduction in the molar volume of the reactants: thus, Diels–Alder reactions are accelerated by very high pressures. Previously, I recounted how we had first made (Scheme 4) kohnkene (**13**) from the 1 : 1 adduct **7** by inducing it to cyclodimerise thermally. The problem with **7** is that it is not all that stable: it is prone to polymerisation on standing. By contrast, the 2 : 1 adduct **11** can be stored for months on end without any sign of decomposition. And so we decided in the high pressure experiment, carried out at Reading University under the expert guidance of Dr Neil Isaacs, to react (Scheme 5) **11** with the bisdienophile **6** at 10 kbar in dichloromethane for 8 days at 60°C: we obtained a welcome increase in the yield of kohnkene (**13**) – to 20%. Armed with half-gram quantities of **13**, we could now do more chemistry on it. First of all, however, let me tell you about the difficult, but ultimately successful, solid state characterisation of kohnkene (**13**).

Good, single crystals of kohnkene (**13**) for X-ray crystallography were not at all easy to grow: finally, they emerged from slow evaporation of a chloroform solution of **13** during several weeks. They were not all that stable and Dr David Williams and Sandra Slawin at Imperial College London were only able to collect the required data by sealing the single crystal in a tube so that it was kept for the duration of the data collection in a vapour pressure of the solvent. Why are the



Scheme 5

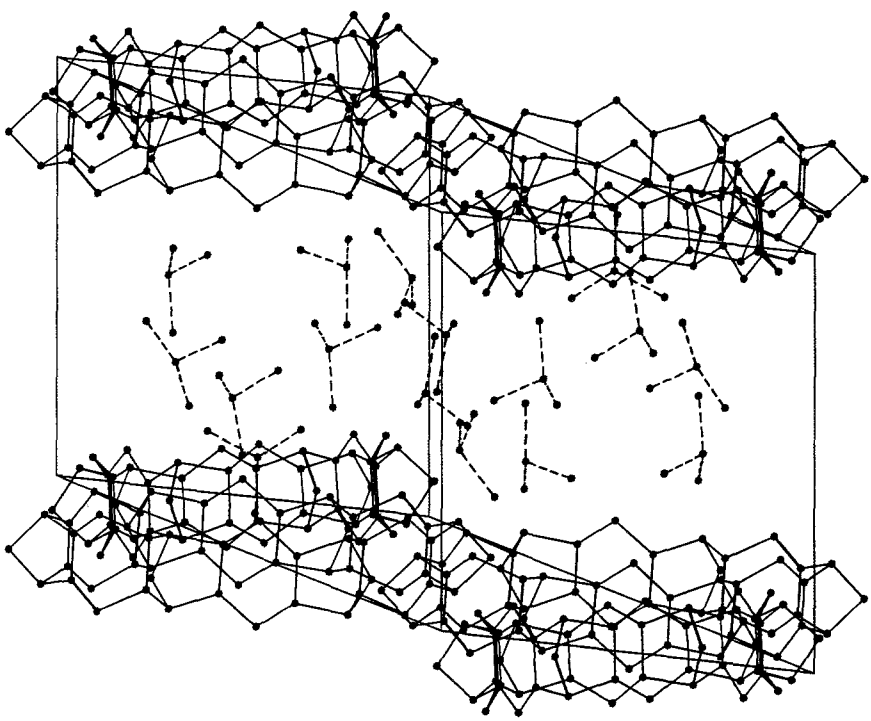


Fig. 6. The unit cell in the solid state structure of kohnkene (**13**). Note that there are 12 disordered chloroform molecules included in the unit cell in 16 different orientations.

crystals so unstable? The explanation follows from how the molecules choose to pack in the unit cell (Figure 6). This picture reveals that the molecules are arranged in parallel approximate fall-to-face layers with 12 disordered chloroform molecules sandwiched between them in the unit cell in 16 discrete orientations. This clathration phenomenon explains the instantaneous loss of chloroform with concomitant collapse of the crystals on removal from the mother liquor. The X-ray crystal structure (Figure 7) of **13** discloses the elegance of the molecular structure: six

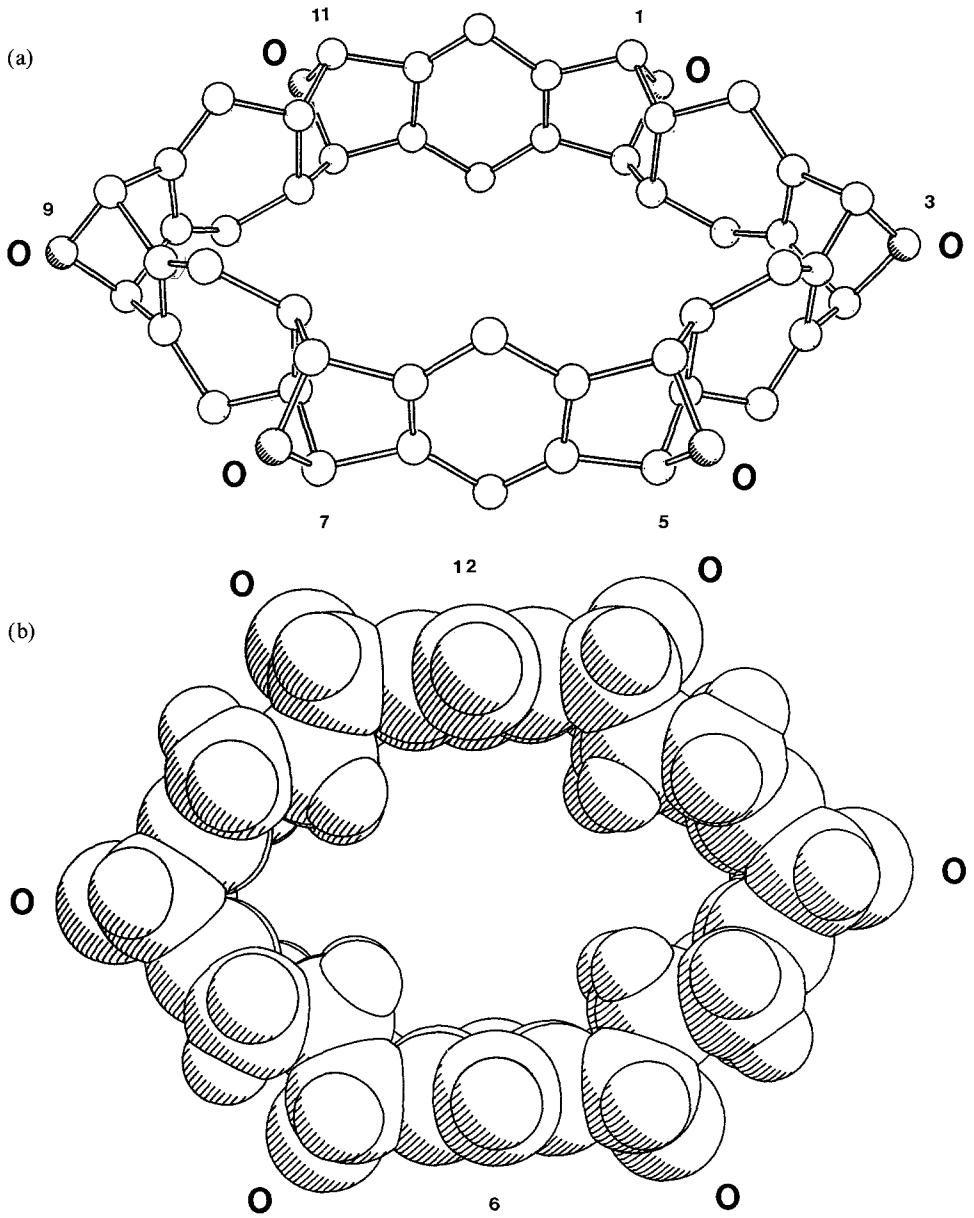
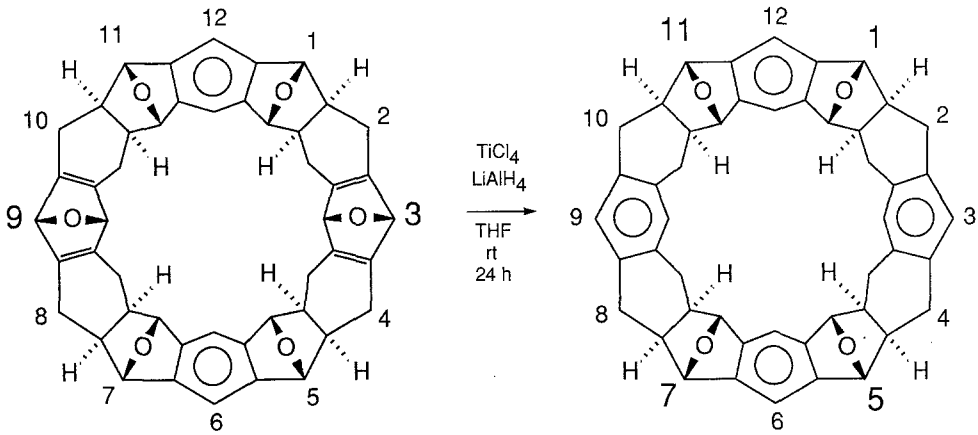


Fig. 7. (a) Ball-and-stick and (b) space-filling representations of the solid state structure of kohnkene (**13**).

oxygen atoms are almost evenly spaced around the outside of an elliptical molecular belt. The interplanar separation between the two benzene rings at 6 and 12 o'clock is 7.9 Å. This leaves enough room (ca. 5 Å between the van der Waals surfaces of the benzene rings) for a substituted benzene molecule to be accommodated orthogonally with respect to these two benzene rings. We argued that, particularly for a phenyl group (Ph) carrying an electron withdrawing substituent (X), the resulting edge-to-face interaction [28, 29] with **13** could be sufficiently stabilising electrostatically to allow PhX molecules to enter inside its rigid molecular cavity. Indeed, in collaboration with the UWIST Chemical Sensor Group, led by Dr Ron Thomas in Cardiff, we were able to demonstrate [30] the piezoelectric quartz crystal detection of nitrobenzene ($PhNO_2$) using kohnkene (**13**) as a detector coating.

Let us return to the synthetic trail with [12]cyclacene (**4**) firmly in our sights. Looking at kohnkene (**13**), one is reminded that there is more than one way to skin a rabbit. Why not try (a) deoxygenation at 3 and 9 o'clock, followed by (b) dehydration at 1, 5, 7, and 11 o'clock, and then finally, (c) dehydrogenation at 2, 4, 8, and 10 o'clock? Deoxygenation of **13** went [31] smoothly (Scheme 6) in 43%



Kohnkene (13) **Dideoxykohnkene (14)**

Scheme 6

yield to afford dideoxykohnkene (**14**). The positive ion FABMS had a peak of 690 for M^+ and NMR spectroscopic data were totally in agreement with the structural assignment given to **14**. The vapour diffusion method [25], using chloroform–methanol, produced single crystals suitable for X-ray cyrstallography, which revealed (Figure 8) that the rigid cavity now has an approximately square cross-section with distances between the mean planes of the parallel-disposed aromatic rings of 8.9 Å (3 to 9 o'clock) and 9.6 Å (6 to 12 o'clock). The most striking feature of the structure is the Celtic cross-like hydrophobic cavity within which a water molecule is trapped like a gem. Yet, the water molecule does not enter into any hydrogen bonding with **14**. The water oxygen atom is >3.5 Å removed from any of the four pairs of inward pointing methine hydrogen atoms in

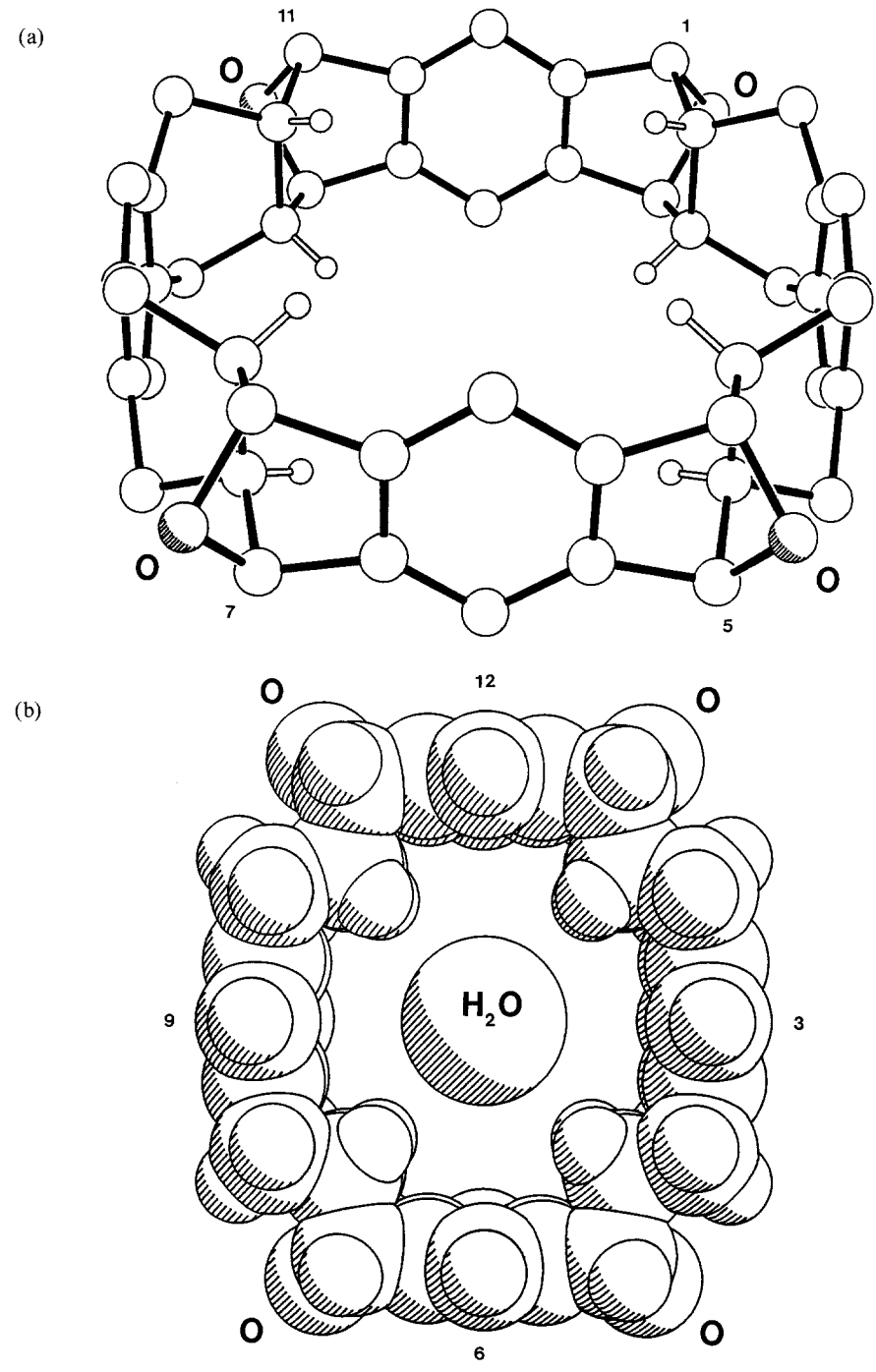


Fig. 8. (a) Ball-and-stick and (b) space-filling representations of the solid state structure of dideoxykohnkene (**14**). In view of the disorder in the positions of the hydrogen atoms, the included water molecule has been represented in (b) as a sphere with radius equivalent to the envelope of a water molecule.

14. The individual hydrogen atoms, which are >2.7 Å away from any potential interactive sites within the cavity, are directed principally towards the pairs of methine hydrogen atoms at 1:30 and 7:30.

Naïvely, we might have anticipated that dehydration (Figure 9) of dideoxykohnkene (**14**) would afford a hydrocarbon **15** containing two anthracene and two benzene units. However, in the knowledge [7, 8] that partially hydrogenated polyacenes reshuffle their aromatic rings to maximise their resonance

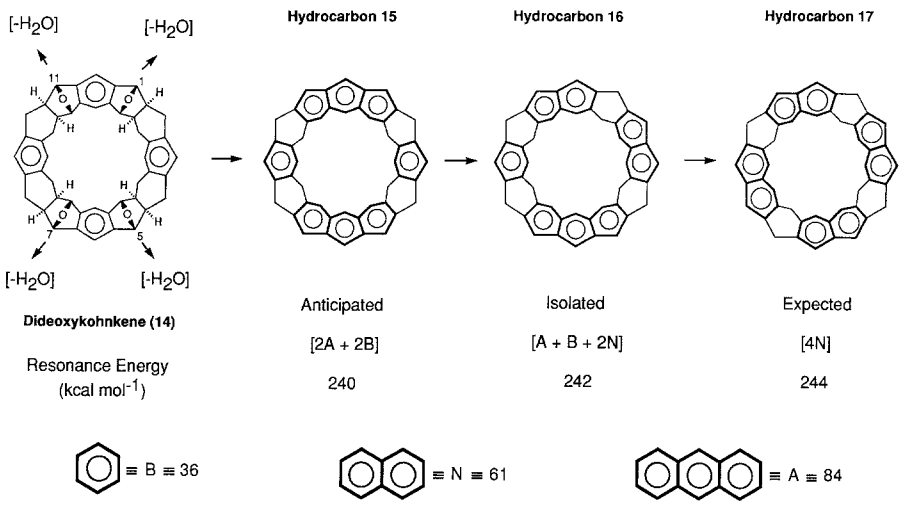
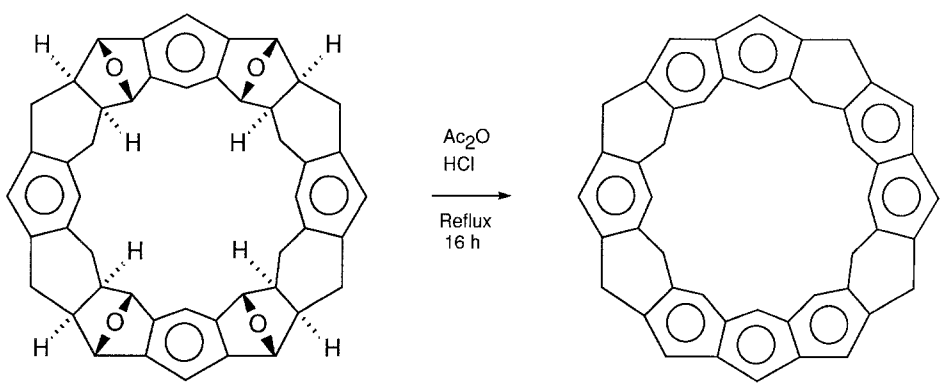


Fig. 9. The dehydration of dideoxykohnkene (**14**) showing three possible hydrocarbons, i.e., **15**–**17**, which could be formed. The resonance energies have been estimated, to a first approximation, on the basis of the literature values for benzene, naphthalene, and anthracene.

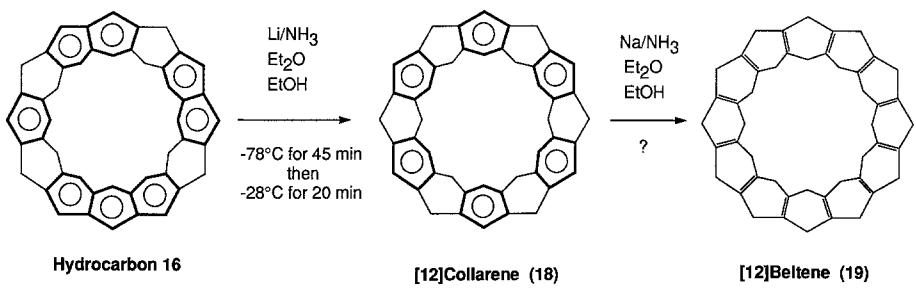
energies, we might have expected the hydrocarbons **17** with four naphthalene units to have emerged as the thermodynamically most stable product. In the event, dehydration gave (Scheme 7) a mixture of hydrocarbons, all displaying molecular



Scheme 7

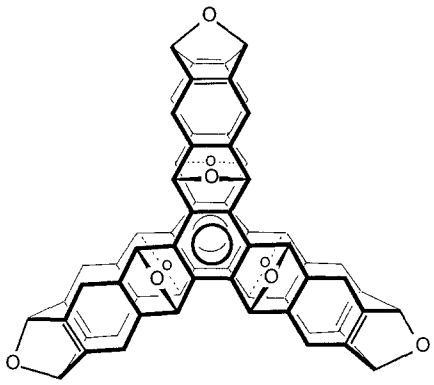
ions with m/z 608 in their EIMS. After chromatography on silica gel using a lot of hot benzene, the hydrocarbon **16** of low solubility and high thermal stability was isolated and characterised by high field ^{1}H NMR spectroscopy. The presence of *four* anisochronous AB systems, along with chemical shift evidence for a benzene and an anthracene unit, clinches the constitution of this hydrocarbon as being **16** with two naphthalene units in addition to the benzene and anthracene units. Of the three hydrocarbons (i.e. **15**, **16**, and **17**) in Figure 9, only **16** has four constitutionally heterotopic cyclohexadiene units which are essential to explain the ^{1}H NMR spectroscopic data. In addition to the peak at m/z 608, the EIMS of **16** shows an intense M^{2+} ion at m/z 304 as well as the characteristic patterns for loss of hydrogen observed in the EIMS of compounds such as 1,2-dihydronaphthalene and 9,10-dihydrophenanthrene. The behaviour of **16** in the mass spectrometer augurs well for the eventual synthesis of [12]cyclacene (**4**).

The hydrocarbon **16** is a common and immediate precursor of [12]collarene[4] (**18**) and [12]beltene (**19**) as well as [12]cyclacene (**4**). With [12]beltene (**19**) singled out as our next synthetic objective, Birch reduction of **16** has revealed (Scheme 8) the presence in the desorption electron impact mass spectrum of a dodecahydro[12]cyclacene derivative (with m/z 612), which is probably [12]collarene (**18**), the most stable isomer with six alternating benzene rings along the route to [12]beltene (**19**). Although the road to **19** is an uphill one in energy terms, we feel confident that this synthetic objective – seen [11] not so long ago as requiring 'a major synthetic effort' – can now be reached: the incentives to prepare [12]beltene (**19**) are numerous, not least of all because of its high symmetry and molecular appeal.



Scheme 8

And now, let us look into the future for a moment. What can one see amongst the galaxy of molecular stars? I suggest a veritable constellation of macropolycyclic compounds, given the supply of bisdienes and bisdienophiles that exists. And, not to be forgotten, some of the synthetic intermediates and by-products provide the additional opportunity to increase the availability of rod-like molecules containing linearly-annulated rings [32]. And then, what about the production of molecular columns and molecular nets, not to mention molecular barrels, such as the macrobipolycyclic compound **20**, that Dr Kohnke has designed and all but made. In the final analysis, organic zeolites could soon be within our grasp [33–35].



The macrobipolycyclic compound 20

As yet, we do not know much about the molecular recognition properties of this new family of compounds. But, there is no doubt that we have stumbled upon a simple way of creating new molecular materials that are rigid, ordered, and large. They can be assembled in a stepwise manner under a level of stereochemical control [36] that is quite breathtaking in its precision. The chemistry of laterally-fused six-membered rings has been turned through 90°. There is also a philosophical message to emerge from these experiences: it is a simple but a fundamental one – let us not try to plan everything in our research: let us leave something to chance: let us find time to dream a little and allow Nature to take over and unfold its wonders before us.

Acknowledgements

During the course of this lecture, I have given credit – where it was so handsomely earned – to the individuals involved directly in the making and in the assessment of these new molecular belts and collars. Behind the scenes, however, many other people have played crucial roles: they include Mr Peter Ashton (mass spectrometry) and Dr Catriona Spencer (NMR spectroscopy) who were always willing to respond to impossible requests without a moment's hesitation. Moral support, underlined by some financial backing, came freely from Prof. G. Stagno d'Alcontres (University of Messina) and Dr Bob Handscombe (Univeristy of Sheffield). Dr Peter Beadle, formerly of the BP Venture Research Unit, forced us to sharpen up our ideas and objectives during the writing of a research proposal which went through numerous drafts before being finally rejected. Now that the ideas have been shown to work, there is no shortage of generous financial sponsors, including the Science and Engineering Research Council in the United Kingdom.

Notes

[1]This article is dedicated to the memory of the late Professor Iwao Tabushi. The tale told here is based on a lecture delivered on 6 November 1987 at the US/Japan Joint Seminar on Molecular Recognition in Miami and is a highly personal account of the trapping at the end of a ten-year hunt for what became known as 'the crazy molecule' at Sheffield. The lecture was dedicated to the three pioneers of small molecule molecular recognition, the 1987 Nobel Laureates in Chemistry, Charles Pedersen, Jean-Marie Lehn, and Donald Cram – three men attracted as much by the art of chemistry as by its science.

[2]Reference was also made at the US/Japan Joint Seminar in Miami to the concept of molecular 'lego' by Professor Richard D. Gandour from Louisiana State Univeristy.

[3]With the help of Dr Alan McNaught at The Royal Society of Chemistry in London we have arrived at the following systematic name for kohnkene (**13**): rel(1*R*,4*S*,4a*S*,7a*R*,8*R*,10*S*,10a*S*,13a*R*,14*R*,17*S*,17a*S*, 20a*R*,21*R*,23*S*,23a*S*,26a*R*)1,4 : 6,25 : 8,23 : 10,21 : 12,19 : 14,17-hexaepoxy-1,4,4a,5,6,7,7a,8,10,10a,11,12, 13,13a,14,17,17a,18,19,20,20a,21,23,23a,24,25,26,26a-octacosahydro-2,16 : 3,15-dimethenoundecacene.

[4]We propose to refer to the macropolycyclic hydrocarbons which are comprised to alternating benzene and 1,4-cyclohexadiene rings as [*n*]collarenes.

References

1. M. L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer-Verlag, New York (1978); W. Saenger: *Angew. Chem. Int. Ed. Engl.* **19**, 344 (1980); J. Szejtli: *Cyclodextrins and their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982; R. Brewlow: *Chem. Brit.* **19**, 126 (1983); W. Saenger: *Inclusion Compounds* (Volume 3, Ed. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 231, Academic Press, London (1984); J. Szejtli: *Inclusion Compounds* (Volume 3, Ed. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 331, Academic Press, London (1984); R. J. Bergeron: *Inclusion Compounds* (Volume 3, Ed. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 391, Academic Press, London (1984); I. Tabushi: *Inclusion Compounds* (Volume 3, Ed. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 445, Academic Press, London (1984); R. Breslow: *Inclusion Compounds* (Volume 3, Ed. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 473, Academic Press, London (1984); M. Komiyama and M. L. Bender: *The Chemistry of Enzyme Action* (Ed. M. I. Page), pp. 505, Elsevier, Amsterdam (1984); M. L. Bender; *Enzyme Mechanisms* (Eds. M. I. Page and A. Williams), pp. 56, The Royal Society of Chemistry, London (1987).
2. W. A. Freeman, W. L. Mock, and N.-Y. Shih: *J. Am. Chem. Soc.* **103**, 7367 (1981); W. L. Mock and N.-Y. Shih: *J. Org. Chem.* **48**, 3618 (1983); **51**, 4440 (1986); W. L. Mock, T. A. Mirra, J. P. Wepsiec, and T. L. Manimaran: *J. Org. Chem.* **48**, 3619 (1983).
3. D. J. Cram: *Science* **219**, 1177 (1983); D. J. Cram, K. D. Stewart, I. Goldberg, and K. N. Trueblood: *J. Am. Chem. Soc.* **107**, 2574 (1985).
4. A. P. Croft and R. A. Bartsch: *Tetrahedron* **39**, 1417 (1983); C. M. Spencer, J. F. Stoddart, and R. Zarzycki: *J. Chem. Soc., Perkin Trans.* 2, 1323 (1987).
5. P. Garratt: *Endeavour* **11**, 36 (1987).
6. F. Diederich and H. A. Staab: *Angew. Chem. Int. Ed. Engl.* **17**, 372 (1978); H. A. Staab and F. Diederich: *Chem. Ber.* **116**, 3487 (1983); H. A. Staab, F. Diederich, C. Krieger, and D. Schweitzer: *Chem. Ber.* **116**, 3504 (1983).
7. E. Clar: *Polycyclic Hydrocarbons* (Volume 1), Academic Press, New York (1964); W. J. Bailey and C.-W. Liao: *J. Am. Chem. Soc.* **77**, 992 (1955).
8. J. Luo and H. Hart: *J. Org. Chem.* **52**, 4833 (1987).
9. J. E. Rice, T. J. Lee, R. B. Remington, W. D. Allen, D. A. Clabo, Jr., and H. F. Schaefer III: *J. Am. Chem. Soc.* **109**, 2902 (1987).
10. S. Kivelson and O. L. Chapman: *Phys. Rev.* **B28**, 7236 (1983).
11. R. W. Alder and R. B. Sessions: *J. Chem. Soc., Perkin Trans.* 2, 1849 (1985); A. Nickon and E. F. Silversmith: *Organic Chemistry: The Name Game*, pp. 110, Pergamon Press, New York (1987).
12. A. Wasserman: *Diels Alder Reactions: Organic Background and Photochemical Aspects*, Elsevier, Amsterdam (1965).
13. R. Breslow and U. Maitra: *Tetrahedron Lett.* **25**, 1239 (1984) and references therein.
14. N. S. Isaacs and A. V. George: *Chem. Brit.* **23**, 47 (1987) and references therein.
15. M. Bednarski and S. Danishefsky: *J. Am. Chem. Soc.* **105**, 3716, 6968 (1983) and references therein.
16. I. Fleming: *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester (1976).
17. F. H. Kohnke and J. F. Stoddart: *Abstracts of 194th ACS National Meeting*, New Orleans, 30 Aug–4 Sept 1987, CARB 32.
18. F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams: *Angew. Chem. Int. Ed. Engl.* **26**, 892 (1987).
19. P. Vogel and A. Florey: *Helv. Chim. Acta* **57**, 200 (1974).
20. H. Hart, N. Raja, M. A. Meador, and D. L. Ward: *J. Org. Chem.* **48**, 4357 (1983).

21. C. Mahaim, P.-A. Carrupt, J.-P. Hagenbuch, A. Florey, and P. Vogel: *Helv. Chim. Acta* **63**, 1149 (1980).
22. P. -A. Carrupt and P. Vogel: *Tetrahedron Lett.* 4537 (1979); Y. Bessiére and P. Vogel: *Helv. Chim. Acta* **63**, 232 (1980).
23. A. A. Pinkerton, D. Schwarzenbach, J. H. A. Stibbard, P.-A. Carrupt, and P. Vogel: *J. Am. Chem. Soc.* **103**, 2095 (1983); J.-M. Tornare, P. Vogel, A. A. Pinkerton, and D. Schwarzenbach: *Helv. Chim. Acta* **68**, 2195 (1985).
24. F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams: *Acta Cryst. C.* **44**, 736, 738, 740, 742 (1988).
25. P. G. Jones: *Chem. Brit.* **17**, 222 (1981).
26. J. Rebek, Jr., B. Askew, P. Ballester, C. Buhr, S. Jones, D. Nemeth, and K. Williams: *J. Am. Chem. Soc.* **109**, 5033 (1987); J. Rebek, Jr., K. Williams, K. Parris, P. Ballester, and K.-S. Jeong: *Angew. Chem. Int. Ed. Engl.* **26**, 1244 (1987).
27. L. A. Paquette: *Stereochemistry and Reactivity of Systems Containing π-Electrons* (Ed. W. H. Watson), pp. 41, Verlag Chemie International, Deerfield Beech, FL (USA) (1983).
28. R. O. Gould, A. M. Gray, P. Taylor, and M. D. Walkinshaw: *J. Am. Chem. Soc.* **107**, 5921 (1985); S. K. Burley and G. A. Petsko: *Science* **229**, 23 (1985); *J. Am. Chem. Soc.* **108**, 7995 (1986); *FEBS Lett.* **203**, 139 (1986).
29. A. M. Z. Slawin, N. Spencer, J. F. Stoddart, and D. J. Williams: *J. Chem. Soc., Chem. Commun.* 1070 (1987); D. R. Alston, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams, and R. Zarzycki, *Angew. Chem. Int. Ed. Engl.* **26**, 692 (1987); G. J. Moody, R. K. Owusu, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, J. D. R. Thomas, and D. J. Williams: *Angew. Chem. Int. Ed. Engl.* **26**, 890 (1987); P. R. Ashton, E. J. T. Chrystal, J. P. Mathias, K. P. Parry, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams: *Tetrahedron Lett.* **28**, 6367 (1987).
30. M. A. F. Elmosalmy, G. J. Moody, J. D. R. Thomas, F. H. Kohnke, and J. F. Stoddart: *Anal. Proc.* in press.
31. P. R. Ashton, N. S. Isaacs, F. H. Kohnke, A. M. Z. Slawin, C. M. Spencer, J. F. Stoddart, and D. J. Williams: *Angew. Chem. Int. Ed. Engl.* **27**, 966 (1988).
32. L. L. Miller, A. D. Thomas, C. L. Wilkins, and D. A. Weil: *J. Chem. Soc., Chem. Commun.* 661 (1986); A. D. Thomas and L. L. Miller: *J. Org. Chem.* **51**, 4160 (1986); W. C. Christopfel and L. L. Miller: *J. Org. Chem.* **51**, 4169 (1986); P. W. Kenny and L. L. Miller: *J. Chem. Soc., Chem. Commun.* 84 (1988).
33. J. F. Stoddart: *Nature* **334**, 10 (1988).
34. J. F. Stoddart: *Chem. Brit.* **24**, 1203 (1988).
35. L. Milgrom: *New Scientist* No. 1641, 3 December 1988, p. 61.
36. P. Ellwood, J. P. Mathias, J. F. Stoddart, and F. H. Kohnke, *Bull. Soc. Chem. Belg.* **97**, 669 (1988).