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Ladderane architecture: From molecular to supramolecular assemblies

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Abstract

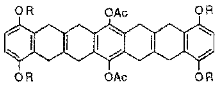
Construction of covalently bonded molecular arrays, composed of linearly fused cyclic rings of varying shape and size and of nanometric length continues to attract synthetic chemists around the world More recently, 'supramolecular' equivalents of such molecular arrays have also drawn attention We have devised a one-step approach to [*n*]-ladderanes, linearly fused assembly of cyclobutane rings, through cascade cycloadditions in an appropriately substituted cyclobutadiene synthon Following this strategy, it has been possible to access [*n*]-ladderanes of record length ($n = 13$) and of nanometric dimension in a regio- and stereoselective manner Reactions of our cyclobutadiene synthon with several interesting olefins have been studied to generate systems in which electron and energy transfer can occur with facility We have also sought and successfully designed supramolecular equivalent of the molecular ladders in the solid state In this context, *trans*-1, 2-diphenyl-1-cyclobutene-3, 4-diol dinitrate has been found to be a promising tecton which readily self-assembles in the solid state in an infinite ladderane motif as revealed by X-ray crystallography

Keywords· [*n*]-ladderanes, 1,2-dicarbomethoxy-cyclobutadiene, cascade cycloadditions, nano-architecture, supramolecular ladderanes

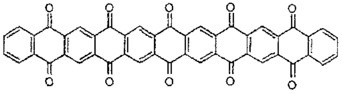
1. Introduction

One of the enduring interests and curiosities in organic synthesis is the design and construction of new molecular arrays that are architecturally novel, aesthetically pleasing and endowed with some useful functional attributes In this context, construction of covalently fused multicyclic rings of different shape, size and numbers has been receiving considerable attention from synthetic chemists as the resulting molecular entities are not only expected to display unusual physico-chemical characteristics but with tactical functionalization and modifications can also function as molecular hosts, 'smart' materials and devices for futuristic applications More recently, supramolecular equivalents of the fused ring arrays too have aroused interest

Early efforts towards the construction of linearly fused cyclic ring systems, quite understandably, focused on the assembly of six-membered rings as they could be readily accessed through the imaginative deployment of the well-established Diels–Alder reaction in a repetitive fashion, both in inter- and intramolecular modes In recent years, research groups led by Stoddart[1], Miller[2], Mullen[3], Schulter[4], Alder[5] and Cory[6], among others[7], have reported the syntheses of a range of linear arrays of fused six-membered rings, e g **1-4**, with variations in the number of rings, degrees of unsaturation, levels of functionalization and the presence of additional bridges, rings, etc This is just a window-selection from a number of such systems that have surfaced in the literature in recent years Some of these systems have been regarded as promis-



1 R = TBDMS, $SiMe_2tBu$



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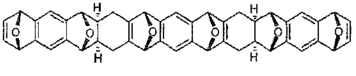

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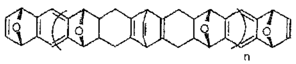
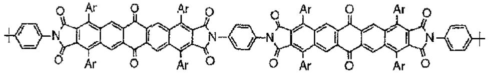


4 n = 1, 3, 5



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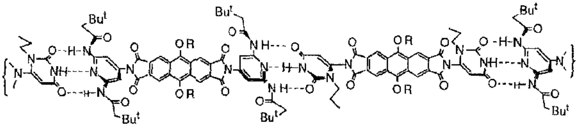

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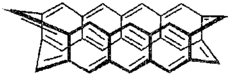
ing lead compounds towards developing molecular connectors ('rods') and 'spacers' for molecular electronics.[1-7]

Additional connectivities and elaboration have generated molecular 'lines' (wires), e.g. **5** of nanometric dimension (5–10 nm).[2] Lehn *et al.*[8] have recently described a supramolecular variant **6**, related to **5**, through a self-assembling process wherein a network of complementary hydrogen bonds plays a pivotal role in sustaining a rigid rod-like motif. Further fillip to endeavors towards the design of fused six-membered systems has been provided by theoretical studies on infinite linear polyacenes, which, besides predicting important properties associated with them, also pointed out the potential advantage of their cyclic variants.[9] An example of such a maximally unsaturated entity is (9)-cyclacene **7** and quite interestingly this moiety has also been recognized[10] as a key sub-structure in C_3-C_{78}-fullerene. However, no cyclic polyacene of any size has been synthesized so far, although advanced precursors, e.g. **8**, among others, of (8)-cyclene have been prepared.[6]



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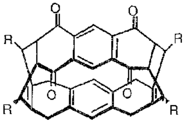

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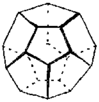
Coming to the next ring size, interest in the large arrays made up of fused five-membered rings (polyquinanes) began to receive particular attention in the 70s and 80s as dodecahedrane **9**,[10c,d] the 'supercyclopentanoid' with 12 five-membered rings, emerging as a challenging synthetic objective along with myriad natural products bearing polycyclopentanoid framework.[11] Many new cyclopentannulation methodologies, including those involving multiple and cascade cyclizations, have been developed during the past two decades and it is now possible to access polyquinanes like **10**[12] and **11**[13] in a relatively straightforward manner. Higher polyquinanes, e.g. **12**, may adopt helical or loop-like shape and are worthwhile objectives as they could exhibit some unusual characteristics. However, efforts in that direction are still awaited.



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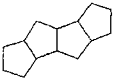

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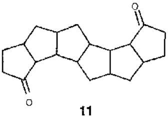

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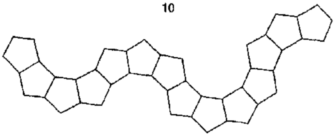

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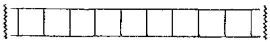
In comparison to their six- and five-membered counterparts, polycarbocyclic frameworks composed exclusively of linearly fused four-membered rings (polyquadranoids), e.g. **13** have received much less attention, although cubane (4-prismane) was synthesized[14] in the early 60s and its higher homologues continue to engage attention.[15] Lastly, while multiple ring systems made up exclusively of three-membered rings are conceivable, e.g. **14**, the prohibitive angle strain that is likely to build-up puts them beyond the realm of realization for the present.



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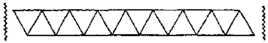

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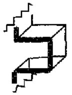
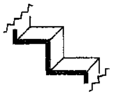
We were attracted by the prospect of creating a framework like **13**, through a general, flexible and modular approach as very little was known about these systems in literature. Herein, we describe our successful efforts towards rapid and efficient generation of a range of linearly fused and covalently bonded polyquadranoids. Attempts towards the creation of their supramolecular equivalents are also detailed.

2. Results and discussion

[*n*]-Ladderanes is a name given to molecular arrays composed entirely of linearly fused cyclobutane rings (polyquadranoids). Thus, bicyclo[2.2.0]hexane, tricyclo[4.2.0.$0^{2,5}$]octane and tetracyclo[6.2.0.$0^{2,7}$.$0^{3,6}$]decane are [2]-, [3]- and [4]-ladderane, respectively. Ladderanes can have either a *cis, syn, cis*-**15** or *cis, anti, cis*-**16** ring fusion. In addition, ladderane architecture can also be generated at supramolecular level through weak, non-covalent interactions, e.g. **17**.



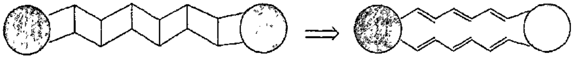
15 *cis-syn-cis*



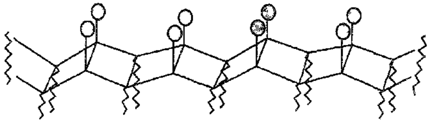
16 *cis-anti-cis*

17

Since [*n*]-ladderanes are considerably strained, rigid, and amenable to modular design, they have the potential to serve as excellent spacers for energy and electron transfer between two objects, see **18**. Furthermore, as cyclobutanes are known to undergo metathetic ring opening, induction of a 'cascade' cycloreversion process, driven by strain mitigation, could lead to the 'wiring' of the two objects as shown (**18–19**). [*n*]-Ladderanes fused in *cis, anti, cis* manner are uniquely constructed such that substituents on alternate carbons of the linear assembly project along the two opposite faces of the molecule. Thus, it is possible to induce facial amphiphilicity in the ensemble, with clearly defined polar and non-polar domains as in **20**, through judicious selection of substituents. It is also reasonable to expect that a linear assembly of cyclobutane rings like **13** will unfold a variety of deep-seated and interesting rearrangements on exposure to heat, light or protic acids. Despite such tempting possibilities, higher [*n*]-ladderanes ($n > 4$) have remained elusive[16,17] and their inaccessibility has precluded exploitation of their rich chemistry. This has been primarily due to the relative dearth of methodologies for cyclobutannulation and the susceptibility of the developing polycyclobutanoid framework to disintegrate during various reaction regimes. Prior to our efforts[18] in the area, it had not been possible to assemble a linear array of more than four cyclobutane rings and only a handful of [4]-ladderanes were known. Therefore, our first concern was to devise a simple, workable, strategy to rapidly access a range of higher [*n*]-ladderanes, preferably of nanometeric dimension ($n > 8$).

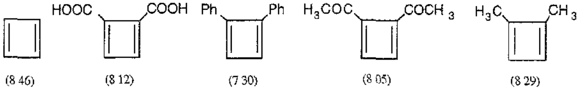


18 19



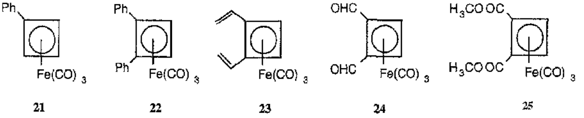
20 polar group
hydrophobic chain

While considering various strategies for the construction of array **13**, we recognized that just as squares serve as versatile building blocks for shapes in art and architecture, an appropriately substituted cyclobutadiene could be an effective molecular module for the rapid assembly of [*n*]-ladderanes Thus, controlled cycloaddition cascade from a suitably functionalized cyclobutadiene should constitute a short, modular route to diverse ladderanes However, a literature search revealed that parent cyclobutadiene and some of its derivatives only dimerize in the absence of a trapping agent and show little inclination towards unfolding a cycloaddition cascade leading to higher ladderanes [19] In order to overcome this reluctance of cyclobutadiene towards cascade cycloadditions, we decided to evaluate the frontier orbitals involved in this process Consequently, HOMO–LUMO energy gaps for the 4+2-cycloaddition, leading to dimerization and formation of [3]-ladderanes, in several substituted cyclobutadienes were calculated at AM1 level and are displayed in Scheme 1 [20] The HOMO–LUMO energy gaps for the dimerization in all these cases are in the normal range of FMO controlled 4+2-cycloadditions To test this prediction, we prepared the corresponding cyclobutadiene precursors



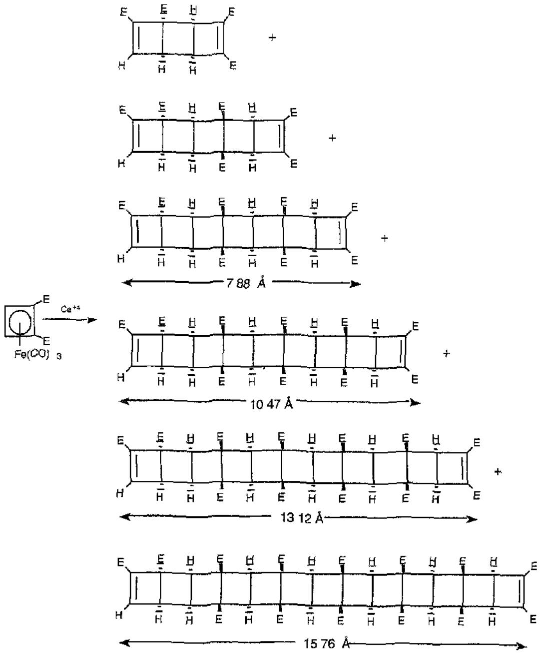
SCHEME 1 HOMO–LUMO energy gaps (eV)

Five cyclobutadiene irontricarbonyl complexes **21–25** were synthesized either through new routes or by the modification of existing procedures (Scheme 2)[21] They were all subjected to delegation following standard protocols (ceric ammonium nitrate, CAN, in acetone or NMMO



21 **22** **23** **24** **25**

SCHEME 2

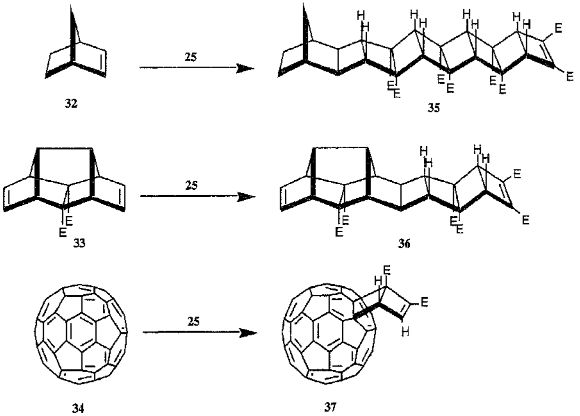


SCHEME 3

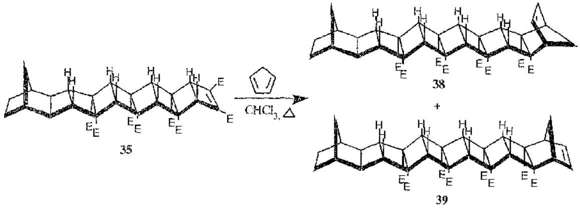
in DCM.) However, only in the case of **25**, it was possible to isolate a series of characterizable products. To our delight, we observed that in the case of cyclobutadiene diester liberated from **25**, the desired cycloaddition cascade had fully unfolded to furnish as many as six odd-numbered ladderanes ***26–31*** in about 60% yield (Scheme 3)[18]. All the ladderanes **26–31** were sharp-melting solids and amenable to ready chromatographic separation. They were fully characterized on the basis of extensive and incisive analyses of the spectral data. In particular, FAB-MS and high-field ^1H NMR (NOESY and n.O.e.) and ^{13}C NMR data were decisive in elucidating the complete stereostrutures of **26–31**.

Several features associated with the ready acquisition of ladderanes **26–31** from **25** deserve special mention Firstly, as many as 13 cyclobutane rings are acquired in a single pot reaction and the ensemble created is of record length and nanometeric dimension We are not aware of any carbocyclic system having as many as 13 fused rings Secondly, the cycloaddition cascade proceeds in a completely regio- and stereoselective manner While the selectivities in the first cycloaddition between the two cyclobutadiene moieties are controlled mainly through secondary orbital interactions to generate a *cis, syn, cis* pattern, stereoselectivities in the subsequent cycloaddition are under steric control to furnish the *cis, anti, cis* stereochemistry It is interesting to note that the ladder grows through regio-controlled cycloadditions on the more(tetra)-substituted cyclobutene double bond Lastly, we consider the efficiency of the process to be quite satisfactory, thus making it amenable to scaling-up We have also carried out 'end-correction' maneuvers on **28–31** and studied their deep-seated thermal reorganizations[18b,22] We do not fully understand the dramatic success with **25** while encountering failures with **21–24** This aspect has been briefly addressed to in our earlier paper

Having developed an efficient and straightforward entry into [*n*]-ladderanes from a simple and readily available precursor, our next concern was to explore the possibility of grafting the ladderane moiety on to other frameworks as depicted in **18** This could be accomplished by delegating **25** in the presence of several diverse olefins like norbornene **32**, Hedaya–Paquette ester **33** and C_{60}-fullerene **34**, among others, to furnish ladderane hybrids **35**, **36** and **37**, respectively (Scheme 4)[18b,23,24]



SCHEME 4



SCHEME 5

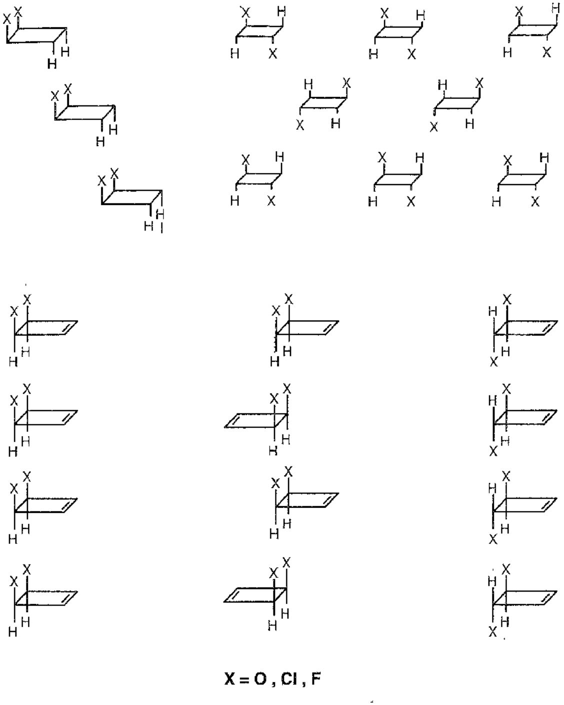
Thus, it proved to be a relatively simple matter to install an object on one of the termini of the ladder For further evolution to **18**, we sought to exploit the dienophilic character residing at the other end of the ladder Indeed, reaction between **35** and a cyclic diene like cyclopentadiene proceeded with great facility to furnish **38** and **39** in which the ladderane moiety is 'capped', at the either end, by different molecular objects (Scheme 5). A distinguishing feature of the molecular assemblies **35**, **36**, **38** and **39** is that they are dipolarofacial with amphiphilicity arising out of hydrogen atoms located on the top-face and the polar ester groups projecting on the bottom-face This aspect of the ladderane architecture has been alluded to the above

The successful design and construction of molecular (or covalent) ladders gave us the impetus to seek their supramolecular variants Supramolecular ladderanes can be visualized as an ensemble, wherein the four-membered building blocks are held by weak C–H O and/or π–π interactions in infinite ladder-like patterns (Scheme 6)

While such an architecture can be visualized both in solution as well as in solid state, we initially sought to look for ladder-like arrangement in the solid state It occurred to us that a cyclobutane ring, preferably a planar cyclobutene ring, which is appropriately embellished with donor and acceptor groups at two or all the four corners and having positional and stereochemical complementarity should be a good supramolecular tecton to self-assemble in the solid state to generate a ladderane motif (Scheme 7) Several functionalities that may promote C–H O and/or π–π interactions are also indicated in this scheme A CSD search indicated that crystal structure of a cyclobutene derivative bearing the functionalization pattern indicated in Scheme 7 has not been determined previously[25]

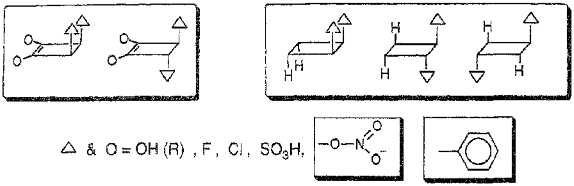
Our search for a suitable tecton to self-assemble a supramolecular ladder motif converged on the highly crystalline C_2-symmetric tetrasubstituted cyclobutene derivative **40**, readily available from the cycloaddend **41** of diphenyl acetylene (tolan) and dichloroketene as shown in Scheme 8

The phenyl groups in **40** are expected to function both as donor groups in C–H O type interactions and also promote self-assembly through π–π stacking The choice of the nitrate groups was somewhat of a gamble as little was known about their ability to sustain supramolecular interactions Indeed, a CSD search revealed that very few crystal structures with covalently bonded nitrate groups are known in literature[26] However, nitrate groups

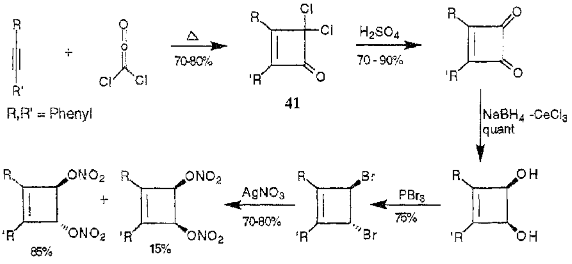


SCHEME 6

with their three oxygen atoms suitably disposed can act as a tridentate acceptor and thus provide considerable latitude in terms of the interactions it can generate Thus, **40** appeared to possess adequate functional attributes to sustain supramolecular ladderane architecture in the solid state



SCHEME 7



SCHEME 8

The C_2-symmetric **40** crystallizes in centrosymmetric space group C_2/c in a racemic form, with enantiomers forming a centrosymmetric pair. A single-crystal X-ray structure analysis (Fig. 1a) revealed that each monomeric unit is involved in four intramolecular short contacts, through the O2 and O3 of the nitrate with H8 cycloalkyl and H2 aryl protons, C8–H8 O2, $d = 2.367$ Å, $\theta = 90.88°$, C2–H2 O3, d = 2.886 Å, θ = 107.19°, respectively, see, (i) and (ii) in Fig. 1b. The packing pattern in the *ab* plane reveals that the tecton **40** is involved in four intermolecular C–H O hydrogen bonds (C6-H6 O1, $d = 2.716$Å, $\theta = 140.54°$)[27], with O1 of the *trans*-disposed nitrate groups as the two accepting sites and the H6 protons of the phenyl rings as the two donating sites. It may be noted that the interactions involving the H6 aryl protons (disposed in opposite directions) are facilitated by the twist of −7.1° present in the *cis*-stilbene moiety, as shown in Fig. 1b. As an outcome of donor–acceptor complimentarity, the molecules of **40**, consisting exclusively of a single enantiomer in the ab plane, are aligned as shown in Fig. 2 and are involved in four key C–H O interactions as indicated below.

(a) The O1 projecting downwards with the H6 proton on the phenyl ring of the nearest neighbor below it, see (iii) in Fig. 1b.

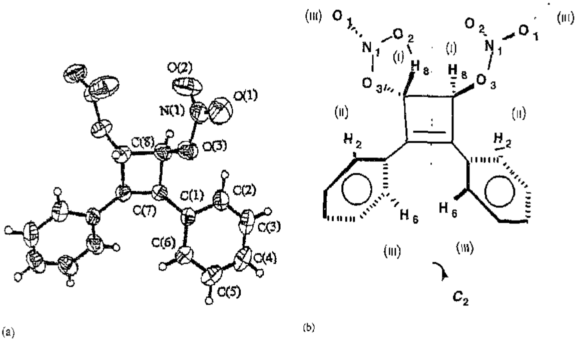


Fig 1 (a) ORTEP diagram of **40**, (b) Short contacts in C_2-symmetric **40**. (i) C8-H8 O2 $d = 2\ 367$Å, $\theta = 90\ 88°$ (Intra), (ii) C2-H2 O3 $d = 2\ 886$Å, $\theta = 107\ 19°$ (Intra), (iii) C6-H6 O1 $d = 2\ 716$Å, $\theta = 140\ 54°$ (Inter)

(b) The O1 projecting upwards with the H6 proton on the phenyl ring of the nearest neighbor above it, see (iii) in Fig 1b

(c) The H6 aryl proton disposed downwards with the O1 on the nitrate of the nearest neighbor below it, see (iii) in Fig 1b

(d) The H6 aryl proton disposed upwards with the O1 on the nitrate of the nearest neighbor above it, see (iii) in Fig 1b

As a result of these extensive interactions, each monomeric unit of **40**, disposed as shown in Fig 2, acts as a scaffold and positions the neighboring units so as to enable the growth of cyclobutene columns along *a* axis (Fig 2) Thus, the tecton **40**, with its C_2-symmetrically disposed complementary accepting and donating sites generates several interesting 'ribbon-like' hydrogen bonding patterns (Fig 2)

When viewed along the *C* axis, the adjacent planes having enantiomeric relationship are held by π–π stacking of the phenyl ring (distance 3 82 Å) along the a axis which is the shortest crystallographic axis (Fig 3) The C–H O hydrogen bonding in two adjacent *ab* planes has opposite directionality which is a direct consequence of their being constituted of enantiomers or inversion-related molecules. Thus, it is the combination of C–H O and π–π stacking which is mainly responsible for the self-assembly in **40** to generate infinite supramolecular ladderanes (Fig 2)

Another interesting aspect of the crystal packing in **40** is that all the hydrophilic nitrate groups are aligned and so are the hydrophobic phenyl rings which alternate with respect to each

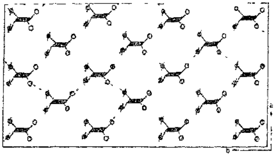


FIG 2 Schematic representation of infinite supramolecular ladderanes —C–H…O hydrogen bonds generating ribbon-like patterns [illegible]

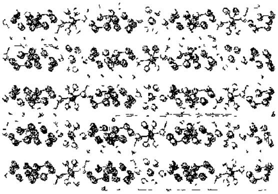


FIG 3 Crystal packing of 40 viewed along the crystallographic C axis [illegible] cavities and [illegible] ○Oxygen, ●Phenyl

other giving rise to alternate hydrophilic and hydrophobic columns, when viewed down the *C* axis This arrangement also leads to supramolecular host cavities, with aromatic walls and nitrate group occupying the periphery of the cavity to form infinite channels (Fig 3) The success with tecton **40** in generating the supramolecular ladderane architecture forebodes well for the application of crystal engineering tools for the creation of new polycyclobutanoid assemblies

3. Conclusion

In short, we have shown that by employing carefully crafted building blocks, it is possible to generate covalent arrays of linearly fused cyclobutane rings (*n*-ladderanes) of record length as well as infinite network of 'supramolecular ladderanes' in the solid state

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