Ladderane architecture: From molecular to supramolecular assemblies

GOVERDHAN MEHTA* AND R. UMA
*Molecular Design and Synthesis Laboratory, Jawaharlal Nehru Centre for Advanced Scientific Research, (JNCASR), Bangalore 560 064, and
School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

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 cycloaditions 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 equivalents of the molecular ladders in the solid state. In this context, trans-1, 2-diphenyl-1-cyclobutene-3, 4-diol diminate 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 cycloaditions, nano-architecture, supramolecular ladders

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 Stoddart1, Müller2, Mullen3, Schulte4, Alder5 and Cory6, among others, 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. Thus 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-
...R = TBOtMS, SiMe₂Bu

Additional connectivities and elaboration have generated molecular 'lines' (wires), e.g. 5 of nanometric dimension (5–10 nm).² Lehn et al.² 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 polycenes, which, besides predicting important properties associated with them, also pointed out the potential advantage of their cyclic variants.³ An example of such a maximally unsaturated entity is (9)-cyclacene 7 and quite interestingly this moiety has also been recognized⁴ as a key sub-structure in C₃₇-C₃₇ fullerene. However, no cyclic polycene of any size has been synthesized so far, although advanced precursors, e.g. 8, among others, of (8)-cyclene have been prepared.⁵
Coming to the next ring size, interest in the large arrays made up of fused five-membered rings (polycumulenes) began to receive particular attention in the 70s and 80s as dodecahedrane 9 \(^{10d}\) 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 polycumulenes like 10 \(^{12}\) and 11 \(^{13}\) in a relatively straightforward manner. Higher polycumulenes, 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.

In comparison to their six- and five-membered counterparts, polycarbocyclic frameworks composed exclusively of linearly fused four-membered rings (polyquadraneoids), e.g. 13 have received much less attention, although cubane (4-prene) 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.
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 polyquadranooids. 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 (polyquadranooids). Thus, bicyclo[2.2.0]hexane, tricyclo[4.2.0.0^2.6]octane and tetracyclo[6.2.0.2^1.0^4.6]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.

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^15 and their inaccessibility has precluded exploration of their rich chemistry. This has been primarily due to the relative dearth of methodologies for cyclobutanation 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 nanometric dimension (n > 8).
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. 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. 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.

![Diagram of cyclobutadiene structures](image)

**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). They were all subjected to delegation following standard protocols (ceric ammonium nitrate, CAN, in acetone or NMNO.
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). 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 inclusive 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 stereostructures 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 nanometric dimension. We are not aware of any carbo cyclic 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 rearrangements\textsuperscript{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 onto 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\textsubscript{60}-fullerene 34, among others, to furnish ladderane hybrids 35, 36 and 37, respectively (Scheme 4)\textsuperscript{18b,23,24}
Thus, it proved to be a relatively simple matter to install an object on one of the terminus 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 other end, by different molecular objects (Scheme 5). A distinguishing feature of the molecular assemblies 35, 36, 38 and 39 is that they are dipolar conformation 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 mutually 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.

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 cycloaddition 41 of diphenyl acetylene (tolan) and dichloroethylene 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. However, nitrate groups...
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.

\[ X = O, Cl, F \]

Scheme 6
The C$_2$-symmetric 40 crystallizes in centrosymmetric space group C$_2/c$ in a racemic form, with enanomers 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°, C2–H2 O3, d = 2.886 Å, $\theta =$ 107.19°, respectively, see, (1) 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°) [2], 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 complementarity, 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.
(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 the a axis (Fig 2). Thus, the tecton 40, with its C2-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 \( \pi-\pi \) stacking of the phenyl ring (distance 3.82 Å) along the a axis which is the shortest crystallographic axis (Fig 3). The C-H \( \cdot \) O hydrogen bonding in two adjacent \( ah \) 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 \( \cdot \) O and \( \pi-\pi \) 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
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 polycyclobutaneoid 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.

Acknowledgement

We thank the Indian National Science Academy and the Jawaharlal Nehru Centre for Advanced Scientific Research for supporting this research program. We had happy collaboration with Professor E D Jemmz and Drs A C Kunwar, K Ravikumar and Reddy Damavarapu during various stages of this work. RU thanks the Council of Scientific and Industrial Research (CSIR) for a research fellowship. The work on covalent ladderanes was initiated by Mr M B Vaisvanath and his contributions are duly acknowledged in references.

References

1a STOOGARD, J F
b KOHNKE, F H AND STOOGARD, J F
Chem Br, 1988, 1203

1b MATTHEWS, J P AND STOOGARD, J F
Pure Appl Chem, 1989, 61, 1581

2a TROUS, A D AND MILLER, L L

2b KENNY, P W AND MILLER, L L
J Org Chem, 1986, 51, 4160

3a SCHIFFER, U AND MULLER, K

3b POLLMANN, M AND MULLER, K
Synthesis, 1992, 25

b POOLE and MULLER, K

b ibid *idem*, 1993, 32, 123


Pray, G. I., Fuller, K. E., Gore, P. M., Hext, N. M., Perry, M. H., Thomas, A. R. and Turner, K. S.


11a Mehta, G. *J Sci Ind Res (India)*, 1978, 37, 256


e Mehta, G. and Srikeshana, A. *Chem Rev.*, 1997, 97, 571


16a Martin, H. D. and Heman, M. *Angew Chem Int Ed Engl.*, 1973, 12, 572


b Hup, F., Greiving, H., Jones, P. G. and Bubencichke, P. *Angew Chem Int Ed Engl.*, 1995, 34, 685

b Mehta, G., Viswanath, M. B. and Kunwar, A. C. 

19 Cristce, R. 

20 Mehta, G. and Usha, R. 

21a Bergens, G., Kaplan, F., Ridsman, R., Roberts, B. W. and Wissner, A. 

21b Adams, C. M., Schemenaur, J. E., Crawford, E. S. and Joslin, S. A. 


23a Mehta, G., Viswanath, M. B. and Kunwar, A. C. 

b Mehta, G., Viswanath, M. B., Neithal, M. and Venkatesan, K. 

24 Mehta, G. and Viswanath, M. B. 

25a Benedetti, E., Ceccolo, M. R., Declevecq, J. P. and Germain, G. 

25b Belleru, D., Mele, H. C. and Rhis, G. 

26a Mar, T. C. W. and Trotter, J. 

b Allin, H. and Trotter, J. 

27a Desraju, G. R. 

b Steiner, T. 

J Org Chem, 1994, 59, 6431 

Angew Chem Int Ed Engl, 1962, 1, 519 

Unpublished results 

J Am Chem Soc, 1975, 97, 7076 

Synth Commun, 1992, 22, 1385 


Synlett, 1995, 311 


Acta Crystallogr B, 1974, 30, 2873 

J Chem Soc, Perkin Trans 2, 1974, 884 

Acta Crystallogr., 1964, 17, 367 


Acc Chem Res, 1996, 29, 441 

Chem Commun, 1997, 727