Engineering macrocyclic figure–eight motif

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Abstract.   The design and synthesis of figure–eight macrocycles are very scarce owing to the intricacies and lack of predictability from first principles. This review emphasizes on discrete macrocyclic systems both synthetic and natural with a defined figure eight knotted topology. In almost all the helical macrocycles, the helical arrangement is held by intramolecular hydrogen bonding or as a backbone requirement, but in all cases, a planar graph can be drawn and so these compounds are trivial from the topological stand point. Nature presents great deal of complexity in terms of structures in macromolecules like DNA and proteins and also displays intriguing topology in simple natural products. Patellamide, tawicyclamides, nosiheptide and thiostrepton are natural products with figure eight topology which shows interesting biological activity. Expanded porphyrins, Cu(II) complexes of thiomacrocycles, cyclic peptides and oligoesters are synthetic macrocycles showing intriguing topology. Analysis of structure and folding behaviour will enable chemists to design molecules with intriguing topology.

Keywords.   Macrocycles; helical structures; Knots, figure-eight; topology.

1. Introduction

The mathematical theory of knots was emerged from attempts to model atoms. Lord Kelvin suggested that different atoms were actually different knots tied in ether. Michelson and Morley did an experiment in 1887 to prove the absence of ether. Their results discredited the ether theories and ultimately led to the acceptance of Albert Einstein's 1905 proposal that the speed of light is a universal constant. This may probably have made Physicists and Chemists to loose interest in knots for some time, but mathematicians are intrigued by the beauty and mathematics of such structures. Recently, knotted molecular structures attracted chemist's attention not only due to its complex aesthetic architecture, but also due to its presence in biological macromolecules.[1] Explosive developments in the last fifty years in Organic chemistry and computer aided molecular design renewed chemist's interest in designing molecules of unusual architecture. Molecules which adopt intriguing topology and its functional properties are emerging areas of potential significance in chemical, biological and other areas in science.[2]

1.1 *Synthetic supramolecular double helices, catenanes and trefoil knots*

Helical structures have long attracted the curiosity and ingenuity of chemists, material scientists, artists and architects as well. The rational design and synthesis of novel knotted molecular structures is still in its infancy and continue to challenge the synthetic chemist's ability to engineer intricate systems.

The pioneering work of Cram, Pedersen and Lehn resulted in a better understanding for designing molecules for supramolecular chemistry. Lehn and coworkers reported many helical and double helical systems crafted from linear precursors based on metal assisted self-assembly (figure 1a).[3a] The molecular knots and topologically interesting structures were synthesized by the pioneering work of Sauvage, Dietrich–Buchecker and co-workers (figure 1b). In all these cases, the concept of templation by metal ions was exploited for making such knotted structures.[3b-c] Catenanes and rotaxanes like structures were studied by Stoddart and colleagues by exploiting $\pi-\pi$ and hydrogen bonding interactions (figure 1c).[4] In contrast to these methods; covalent bonds have been used less frequently in the synthesis of topologically intriguing structures.
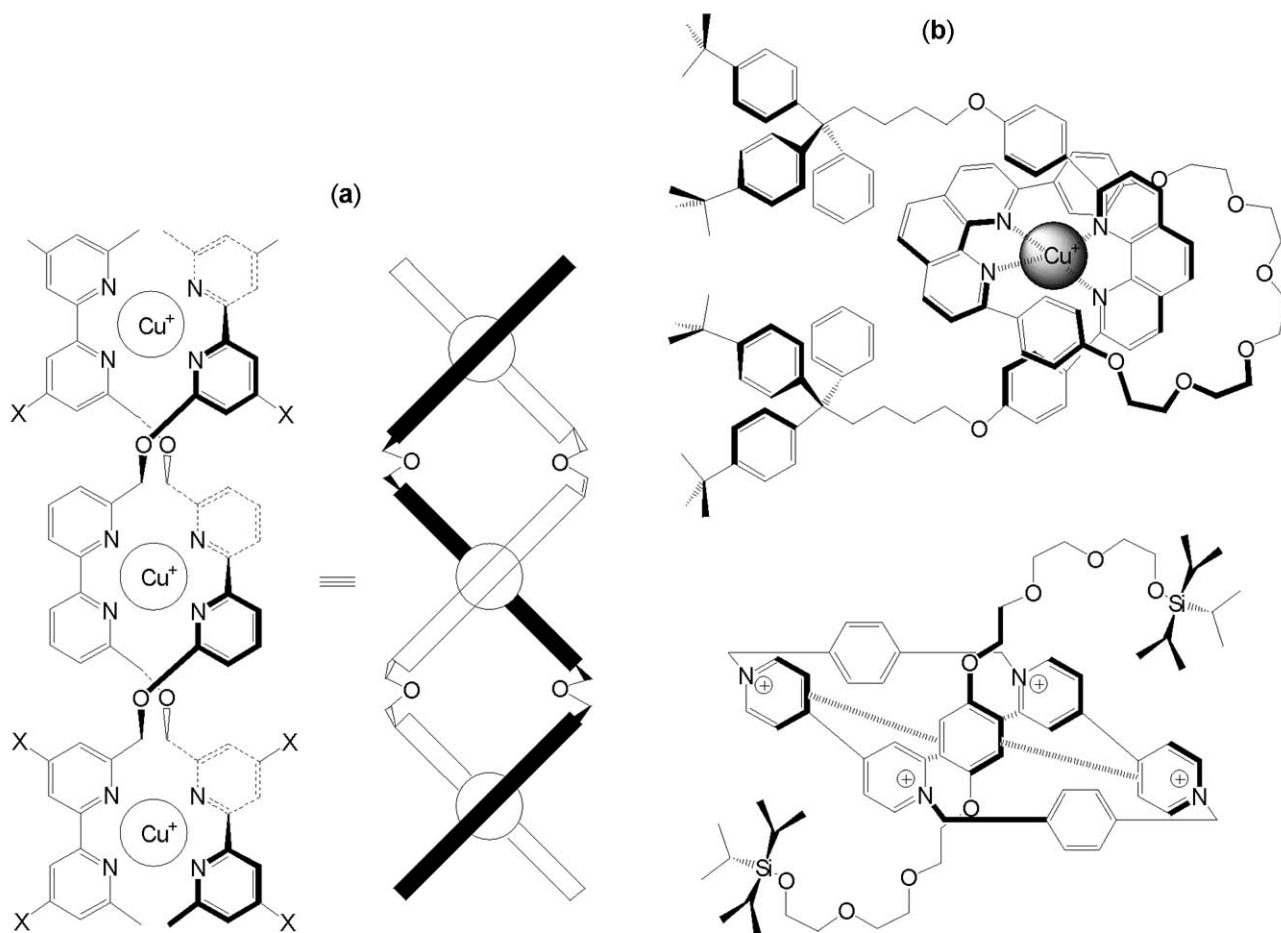
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Figure 1. (**a**) Metal coordinated double helical self-assembly (Lehn) (**b**) Rotaxane assembly by Cu(I) (Sauvage) (**c**) Rotaxane by π–π interaction (Stoddart).

2. Natural macromolecular systems

2.1 *DNA and proteins*

The central dogma in molecular biology is DNA $\rightarrow$ RNA $\rightarrow$ Protein and the important guiding principle in molecular biology is the structure-function relationship. Proteins and nucleic acids are known to adopt knotted topology. The physical, chemical and mathematical understanding of knots will not only unravel many uncharted frontiers but also unfold many of life's mysteries.[5]

The double helical structure of DNA discovered by Watson and Crick in 1953 still remains one of the greatest discoveries of our time.[6] DNA when expanded will have a yard's length, but is packaged in a way that minimizes the space so as to store in a cell of size smaller than the head of a pin. The packaged DNA contains many cross overs and knotted structures essential for dense packing in the cell. For transcription to happen; the entangled DNA has to be unknotted and these unknotting the knots are done by the enzyme topoisomerase (figure 2). The mathematics of knots and unknotting will give the inner working mathematics of enzymes in detail. The topological approach to enzymology is thus an interesting challenge for mathematicians.[7] The DNA, for example of bacteriophage has been studied and the packaging unravels the knotted topology nature uses.[8]

Proteins with its differently arranged amino acid sequences from the 20 amino acids pool creates overwhelmingly complex architectures, which are not yet fully understood. The secondary and tertiary structures of proteins play a wide variety of roles in controlling and orchestrating many biological roles. Normally, proteins possess a C and N-terminal ends and has a linear uncyclized structure. Proteins with

knotted topology through disulfide bonds are called knottins.[9] A knottin with cyclic structure is called a cyclotide, which exhibits interesting biological activity. Plant protein acetohydroxy acid isomeroreductase has a figure eight knotted structure, which was discovered from the protein structure database by using a knot detecting computer algorithm.[10] Interestingly, many knotted structure are not knots in the mathematical sense.

A typical figure eight motif is represented as in figure 3. The zero knots (a) and Figure eight knot (b) and trfoil knots are examples of very simple knots.

2.2 *Figure–eight macrocycles*

The design and synthesis of knotted molecular structures especially the figure-eight macrocycles are very scarce owing to the intricacies and lack of predictability from first principles. Interestingly, there is no report of rational design of figure-eight macrocycles, which emphasize the fact that how little we know about the overall topology of molecules and the intrinsic forces responsible for the folding behaviour.

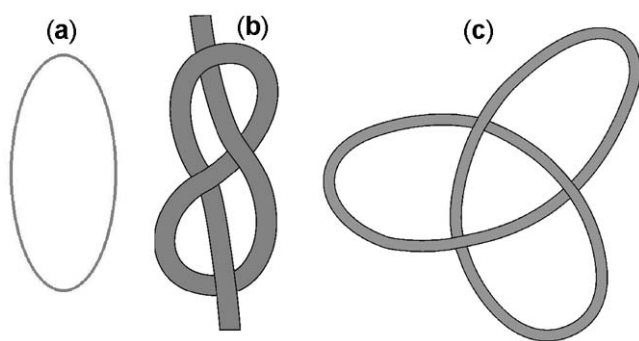This review emphasizes on discrete macrocyclic systems, either synthetic or natural, with a defined figure-eight knotted topology. In almost all the synthetic macrocycles, the helical arrangement is held by intramolecular hydrogen bonding or as a backbone requirement, but in all cases a planar graph can be drawn and so these compounds are trivial from the topological stand point. There are many reviews[11] devoted to the complex topological structures designed from self-assembly of linear molecules, but none about the macrocycles, that adopt interesting topological motifs.
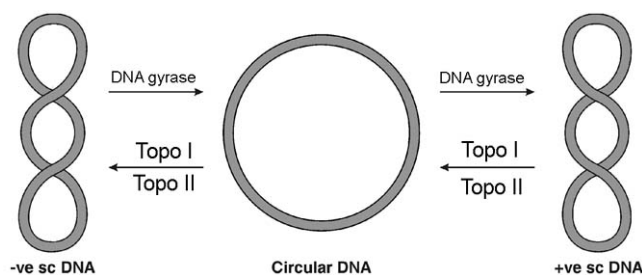
2.3 *Simple natural products with figure–eight topology*

Some natural products are characterized by an alternating sequence of 5-membered heterocyclic and hydrophobic amino acid residues and thereby constricting their conformation to triangle, square and figure-eight conformation in solution and in solid state (figure 4).[12] Natural products like patellamide, tawicyclamide, Nosiheptide, Thiostrepton etc. are simple organic molecules with figure-eight architecture on a simple molecular scale.

2.4 *Patellamides*

Marine invertebrates are well known for their production of bioactive natural products with interesting structural features. Patellamide A, B, C and D are cytotoxic cyclic hepta peptides from marine tunicates (Lissoclinum patella); unravel interesting molecular folding. Actually the bacterium Prochloron didemnii that live inside the sea squirt Lissoclinum Patella produces Patellamide. Now, the gene sequence responsible for this can be transplanted into *E. coli* and can effectively produce patellamide. Patellamides contain thiazole and oxazoline units in its frame work as part of the cyclic peptide backbone. These features are as a result of its nonribosomal peptide biosynthetic pathway. In solution, Patellamide takes a type IV conformation stabilized by four intramolecular hydrogen bonds (figure 4). The solution structure was studied by detailed NMR spectroscopy and solid state structure was determined by X-ray crystallographic analysis. It exist both in solution and solid state as a figure eight structure.[13]

Figure 2. Knotted topology in DNA.

Figure 3. Representation of zero knot (trivial knot), figure-eight knot and trefoil knot.

2.5 *Nosiheptide and thiostrepton*

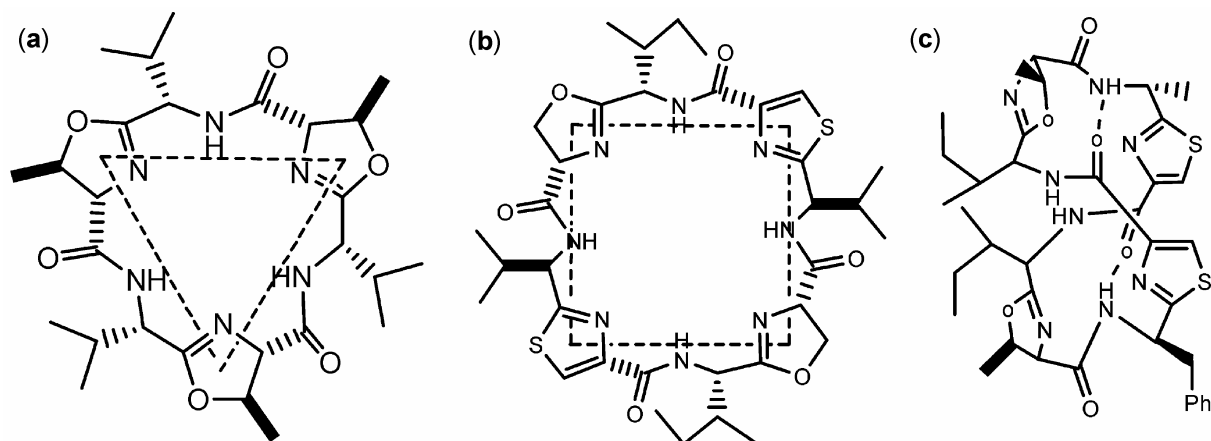Nosiheptide and thiostrepton, metabolites isolated from *S. actuosus*, with a strong *in vitro* activity has a

Figure 4. Molecular structure of natural product with varying topology; (**a**) Cycloxazoline (triangle), (**b**) ascidiacyclamide(square) and (**c**) Patellamide D (figure–eight).
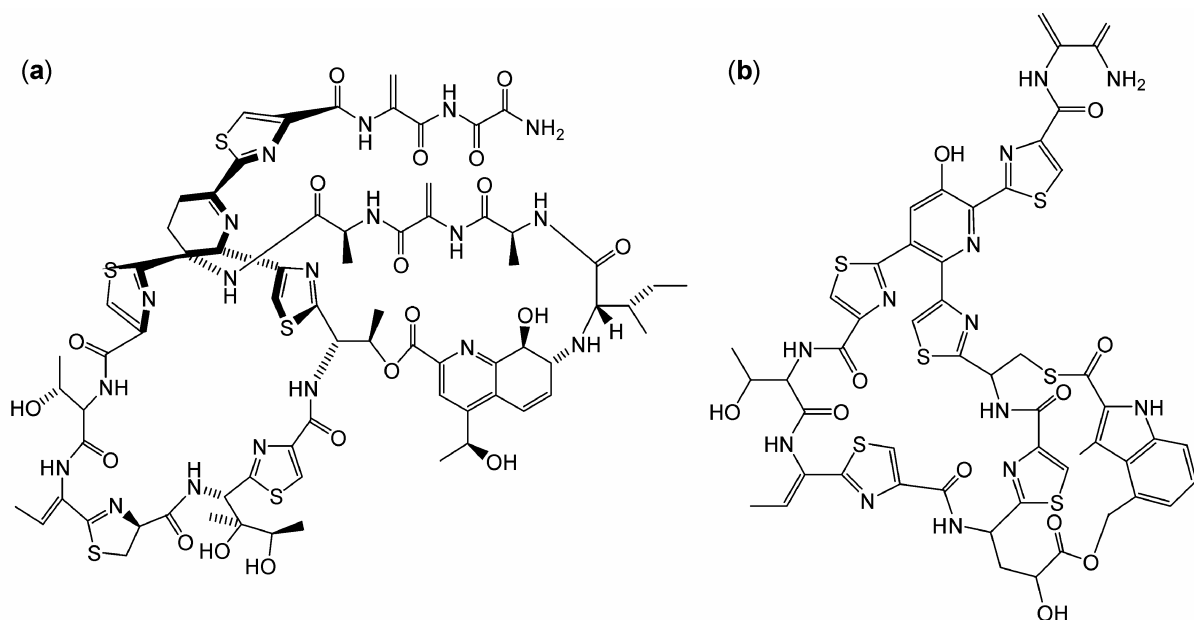

Figure 5. Structure of (**a**) Thiostrepton and (**b**) Nosiheptide.

figure-eight conformation.[14,15] The antibiotic nosi-heptide is a member of the thiopeptide antibiotics, was isolated in the early 1960s by French workers. It is also active against the malaria parasite, being powerful inhibitors of protein synthesis in the organism acting directly on the ribosome and inhibiting the action of GTP dependent elongation factors. Its structure was determined by chemical degradation and X-ray crystallography. Nosiheptide (figure 5) with a 26-membered macrocyclic ring can be described as the ring of four twisted planes in a helix arrangement around the central pyridine ring to form

the figure eight, stabilized by Van der Waals contact.

First isolated from bacteria in 1955, thiostrepton has an unusual antibiotic activity. It is the most complex member of a family of thiopeptide antibiotics and the structure was solved by Dorothy Hodgkin in 1970. It disables protein biosynthesis by binding to ribosomal RNA. Thiostrepton consists of eleven peptide bonds, extensive unsaturation, and seventeen stereogenic centers. Thiostrepton's structure (figure 5) contains two macrocycles-a 26-membered thiazoline-containing ring and a 27-

membered quinaldic acid system. The two rings are united at the dehydopiperidine moiety. A bisdehydroalanine tail also extends out from the dehydopiperidine.

2.6 *Tawicyclamides*

Tawicyclamides A and B were isolated from the ascidian Lissoclinum patella collected in the Philippine Islands and their structures were determined by NMR, chemical methods, mass spectrometry and X-ray crystallography. Tawicyclamides A and B are cyclooctapeptides possessing thiazole and thiazoline amino acids without oxazolidine rings which are characteristic of patellamides. It contains a cis-valine-proline amide bond that facilitates an unusual three-dimensional conformation. The X-ray crystal structure studies on tawicyclamide B shows a figure eight conformation (figure 6).[16] The thiazole rings are essentially parallel with an interplanar angle of 13° and with a distance of 3·7 Å ideal for aromatic stacking distance. The valyl and leucyl side chains point away from the cavity. The conformation is stabilized by an intramolecular hydrogen bond. Solution conformational analysis also supported the figure eight structure. Oxidation of thiazoline ring to thiazole ring (dehydrotawicyclamide) resulted in a change of conformation.

2.7 *Synthetic Systems with figure–eight topology*

Synthetic molecules constitute the other end of the spectrum, where molecules as simple as cyclo octene, heterocyclic macrocycles, porphyrins, cyclic peptides and other class of molecules exhibit defined figure eight knotted topology. The rational design and synthesis of discrete and pre-organized molecular systems with defined topology are of interest due to their ion binding properties, conformational control and allows us to explore uncharted frontiers in chemistry, biology and other related areas.
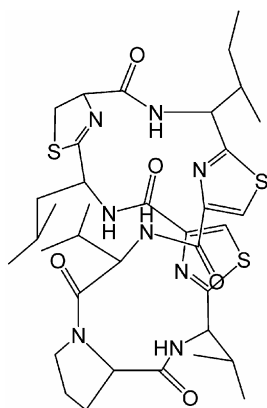
The examples illustrated below exemplify how the hydrogen bonding, co-ordinate bonds and constrained molecular structures fix figure eight knotted topology in synthetic molecules.

2.8 *Cycloalkene*

Trans cyclooctene is one of the earliest system with figure eight like topology in which the chirality arises from conformational restriction (figure 7). The hexamethylene, bridges around the double bond in the front or back. These stereo isomers have a mirror image relationship; each can be converted to the other by simple reorganization of the geometry without breaking any bonds.[17] Both isomers can be isolated and the optical rotation is opposite in sign and magnitude to the other isomer. These are basically conformational enantiomers.

2.9 *Peptide based systems*

Hydrogen bond as such is not exploited much for generating topologically intriguing molecules, the reason being lesser understanding and predictability of hydrogen bonding. The indole based Tryptophan-derived macrocycle synthesized by Mark Mascal is one of the first figure eight macrocycle (figure 8a).[18] The tryptophan-derived azamacrocycle (**3**) which through strong transannular hydrogen bonding interactions is tightly wound into a left-handed double helix. The helical macrocycle (**3**) was made from Dichloro-acetyl tryptophan methyl ester (**1**), which was cyclized with UV light and worked up in presence of NaN_3 to give 7-azidopyrrolobenzazonine
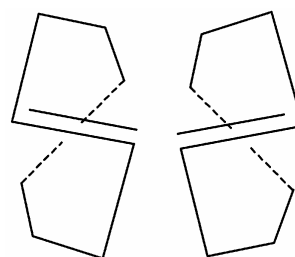

Figure 6. Figure-eight structure of tawicyclamide.

Figure 7. Trans-cyclooctene exists as a figure-eight structure.
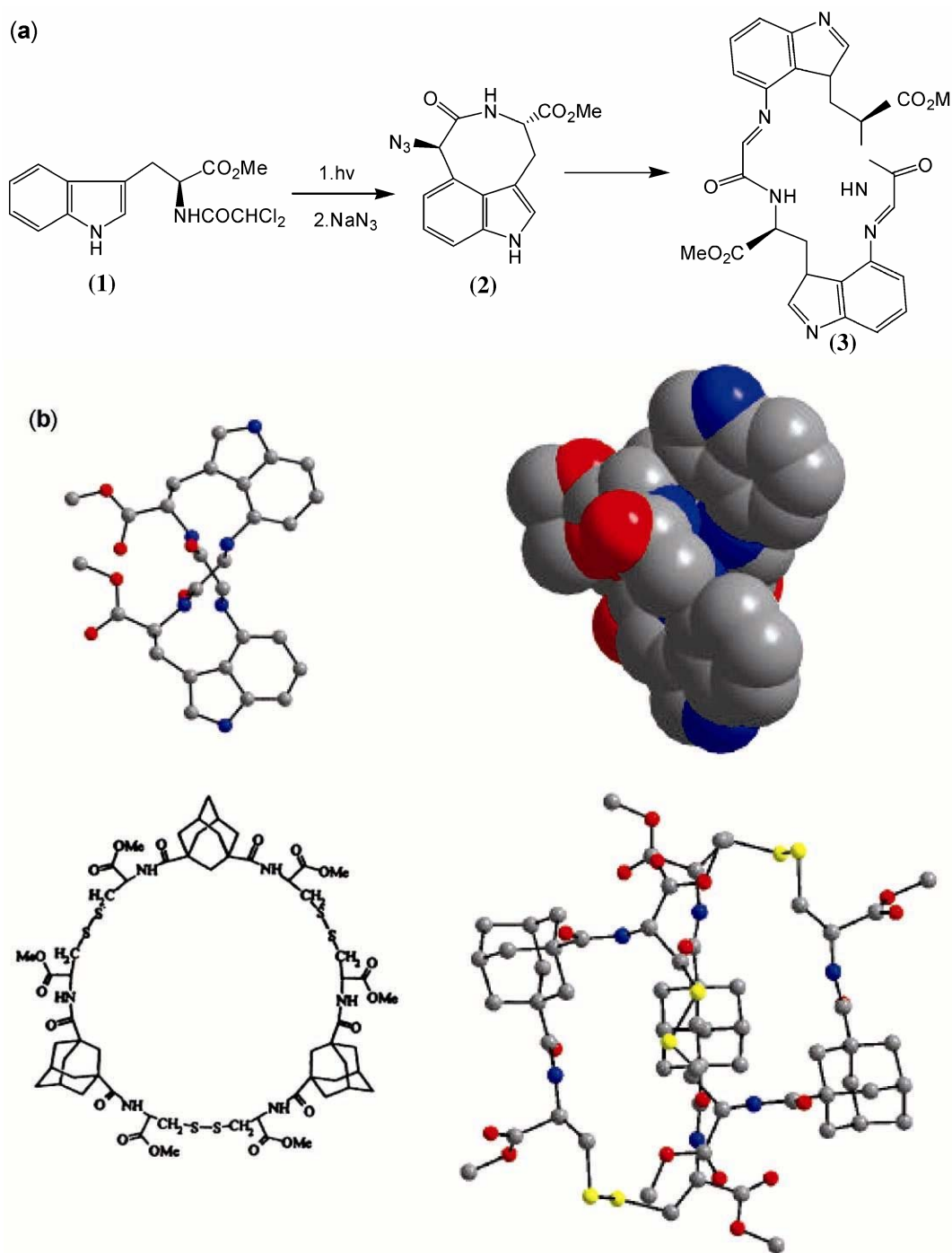
(a)

(b)

Figure 8. (**a**) Synthesis of Indole based macrocycle exhibiting figure-eight topology, The X-ray crystal structure and the CPK model, (**b**) Disulfide based figure-eight macrocycle.

(**2**). Decomposition of **2** either thermally or photochemically gave product **3** as a result of dimerization and metathesis of **2**. Macrocycle **3** is locked into a single helical conformation directed by the chirality of tryptophan. Reduction of imine double bond resulted in amine, which can no longer make trans annular hydrogen bond and thus does not exist in a helical conformation.

Cystine based macrocycle is also reported to adopts a figure–eight topology.[19] The molecule is isolated from a single step synthesis from 1,3-adamantane dicarbonyl chloride and Cystine methyl ester to give a series of macrocyclic structures. This disulfide macrocycle adopts a figure eight structure owing to the necessity to make the S–S dihedral angle 90° (figure 8b). The rigid scaffold and the L-chirality
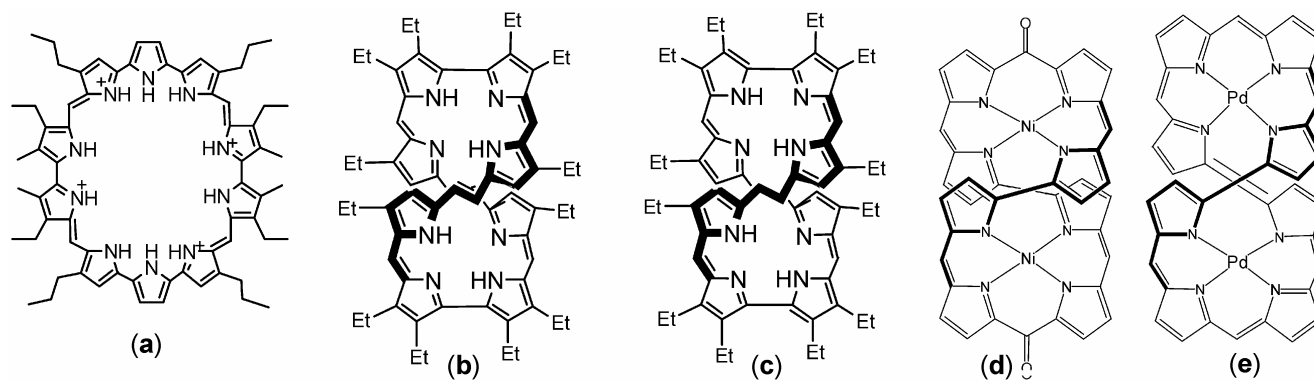
Figure 9. Figure–eight topology seen in porphyrins (**a**) Turcasarin an expanded porhyrin adopts a figure–eight structure (**b**) Vogel's expanded porphyrins.
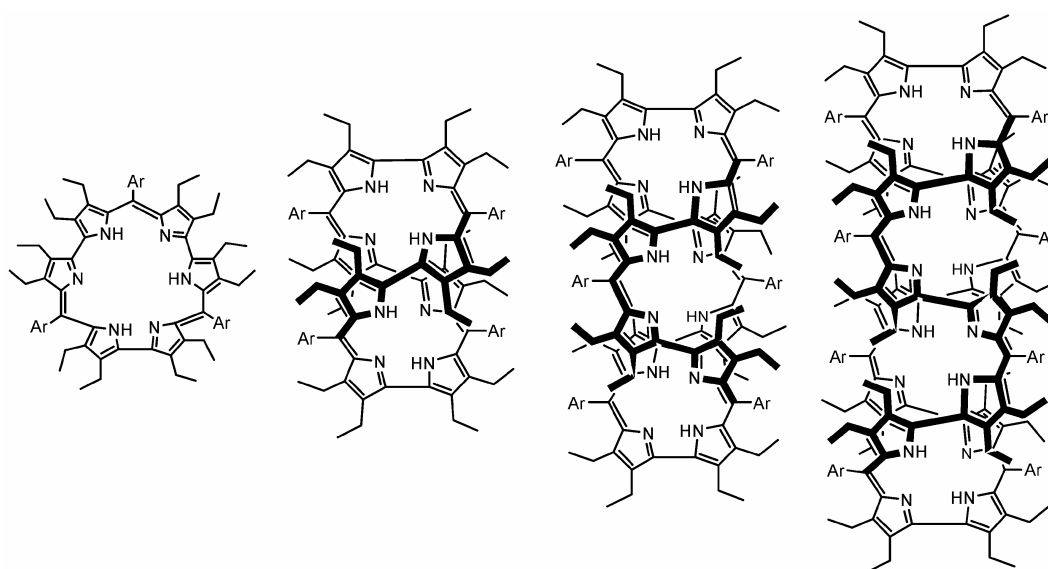
Figure 10. Setsune's figure–eight and expanded figure–eight porphyrin macrocycles.

of the amino acid dictates the handedness of the double helix.

2.10 *Porphyrin based systems*

Large pyrrole containing macrocycles are known generally as expanded porphyrins. They display chemical properties which have no parallel in the chemistry of porphyrins. These molecules display extended conjugated π-electrons and exist as double helical structures.

Jonathan Sessler's Turscasarin (figure 9), an expanded porphyrin constitutes the first example of this sort in porphyrins.[20] Turcasarin may be considered as a 40π electron annulene. Turcasarin will not obey Huckel's $(4n + 2)\pi$ rule. Thus it can be considered as non-aromatic compound with delocalized π-systems. X-ray crystal structure of the tetrahydro

chloride salt of Turcasarin was in accordance with NMR experiments. The tetraprotonated form of Turcasarin adopts a nearly C-2 symmetric figure–eight conformation in the solid state. Both the conformational enantiomers were seen in the X-ray structure. Turscasarin exist in solution as a mixture of two topoisomeric form (left-right and right-left) which is inter converted with an intermediacy of open ring form. The solution structure was probed by extensive NMR study. The complex splitting patterns in ^{1}H NMR spectrum suggested that the macrocycle may exist in two limiting conformations in solution. The NOESY spectrum showed significant exchange crosspeaks indicating that the two enantiomers can readily interconvert on the NMR time scale. This finding that the conjugated poly-pyrrolic macrocycles need not be flat, but can adopt chiral conformations generated much interest in expanded porphyrins.

Expanded octapyrroles are reported by Emanuel Vogel exhibit figure-eight topology (figure 9b–e).[21] The synthesis was based on acid catalyzed Mac-Donald type condensation of a bipyrrole derivative and a complementary unit. Vogel *et al* separated the enantiomers of expanded porphyrin on chiral HPLC column. Interestingly, these enantiomers were stable and showed mirror-image CD spectra. Heating a hexane solution of one enantiomer to 60°C showed no racemization. In a related work, the metal complexes Pd, Ni were made and separated into enantiomeric antipodes having figure-eight topology (figure 9d–e).[22]

Setsune *et al* synthesized a series of octa-, dodeca-, and hexadecacyclopyrroles exploiting Rothemund chemistry (figure 10).[23] A complex mixture was obtained when a reaction of an acid catalyzed condensation between tetraethylbipyrrole and 2,6-dichloro benzaldehyde in the presence of Zn^{+2} ions. Crystal structure analysis revealed the presence of a large cavity with a wall of zigzag-tracked π-conjugation and figure-eight topology.

Furuta and co-workers reported a variety of meso-aryl substituted octa and nona porphyrins based on Rothemund condensation of pyrrole and pentafluorobenzaldehyde.[24] They obtained porphyrins (~12%), N-fused pentaphyrin (~15%), hexaphyrin (~20%), heptaphyrin (~5%), octaphyrin (~6%), nonaphyrin (~3%), as well as several higher homologues in very low yield. These expanded fluorinated porphyrins exist in figure-eight and the expanded figure-eight topology.

Tetrathia octa porphyrins reported by Latos-Grazynski *et al* consist of a figure eight motif.[25] The condensation reaction of 2,5-*bis*(*p*-tolylhydroxy-methyl) thiophene and pyrrole under acid catalysis yielded A and B in 2% yield (figure 11). Exposure of A to NaBH$_4$ in THF transformed to B. B can in turn be converted to A by oxidation with *p*-chloranil or DDQ. These macrocycles adopt figure eight conformation in solution; in A, the thiophene rings occupy at the crossing part, while in B, two pyrrole rings occupy those position. The authors observed residual diatropic and paratropic ring current effects in the case of B (36π) and A (38π) electrons. These molecules are not yet crystallized to get the solid state structures.

Furan containing analogues of Turcasarin have been prepared by acid catalysed condensation of oxaterpyrrole with diformylbipyrrole. On the basis of NMR studies, it was assigned figure-eight structure in solution. Crystal structure analysis showed that it adopts figure eight geometry in the solid state.[26]

2.11 *Quinoxaline-bridged porphyrinoids*

Sessler, Furuta *et al* have reported a new type of expanded porphyrin consisting of an imine part and an anion sensing dipyrrolquinoxaline. Quinoxaline-bridged porphyrinoids were synthesized from acid-catalysed condensation of diformyl-substituted dipyrrolylquinoxaline derivatives and 1,8-diamino-anthracene. The structure was analysed by X-ray crystallography.[27] The two quinoxaline subunits point toward one another and appear to be π-stacked head-to-tail. The macrocycles are also found to bind with Fluoride ion by UV spectroscopy. The binding of fluoride to dipyrrolylquinoxaline(DPQ) triggers a change in colour that can be detected by the naked eye.
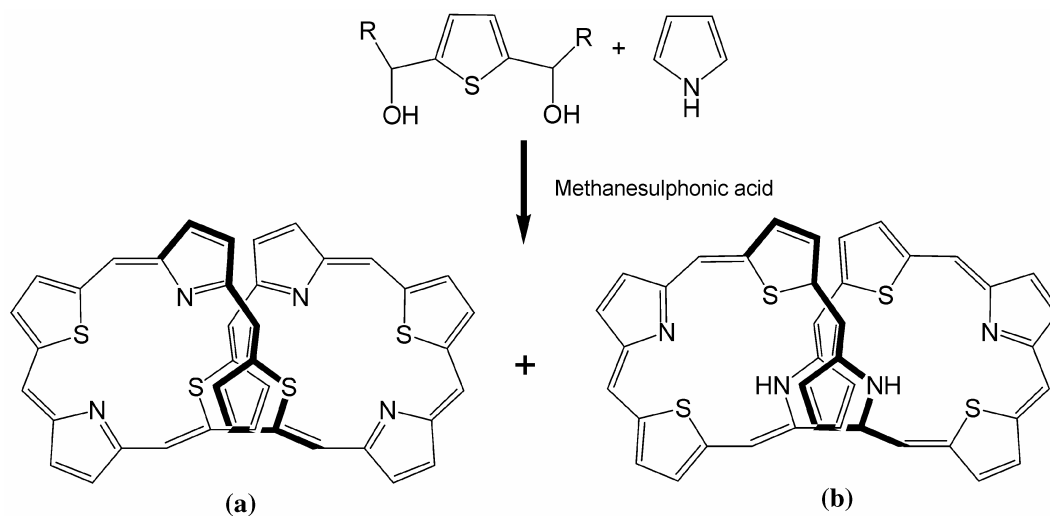

Figure 11. Tetrathia octaporphyrins with figure–eight structure.

Possible anion binding modes are shown in (figure 12), where in the F^- binds to the inside and outside the cavity, but the inner binding is energetically favourable.

2.12 *Copper complexes*

Helical transition metal compounds have attracted considerable attention due to their shape, intrinsic chirality, supramolecular properties and relevance to biology and material sciences.

Peter Comba's group synthesized sulphur based macrocyclic copper complexes constitute very fascinating class of figure eight macrocyclic compounds.[28] The Cu (I) complex of macrocyclic thio ethers was folded to figure eight or double helical topology with intramolecular forces responsible for it. The Cu (I) is in tetrahedral coordination geometry with co-ordinatively bonded to nitrogen and sulphur. The figure eight topology in these complexes is stabilized by the preference of Cu (I) for tetrahedral geometry and the π-stacking of the phenyl rings. These folded structures are preserved in the solution as well. However, in solvents like acetonitrile, the macrocyclic Cu (I) complex unfold the figure-eight structure by co-ordination of solvent molecules to the metal centre. The solvent dependant nature is very

interesting, since there is a reversal of chirality (figure 13).

Table 1 represents different ligands synthesized by Peter Comba's group. All the structures are similar, with Cu-S ($2 \cdot 39 \pm 0 \cdot 03$ Å) and Cu-N ($2 \cdot 00 \pm 0 \cdot 02$ Å), with Cu(I) in near tetrahedral geometry. The Cu–Cu distance is $7 \cdot 95 \pm 0 \cdot 18$ Å and π-stacked benzene rings at a distance around $3 \cdot 54$ Å. The bit angle S–Cu–S and S–Cu–N is around $90°$ and N–Cu–N angle is around $145°$. The folded nature of these compounds was confirmed by ^{1}H NMR in CD_3NO_2 and the analysis of coupling patterns of geminal protons of methylene groups.

2.13 *Benzenediimide based systems*

Schimizu *et al* reported bridged N,N-di(aryl)-1,2,4,5-benzenediimide, which has a figure eight conformation (figure 14).[29] The diimide acid can exist in two isomeric forms, one anti diacid and other syn diacid. Macrocycles with triethylene glycol linker with diimide acid chloride (syn or anti) gave the corresponding 28-membered macrocycle. The anti-2 macrocyclic polyether compound exhibited figure eight conformation. The anti (+) can convert to anti (–) by thermal isomerization. The mechanism

Figure 12. Quinoxaline based macrocyclic figure–eight.
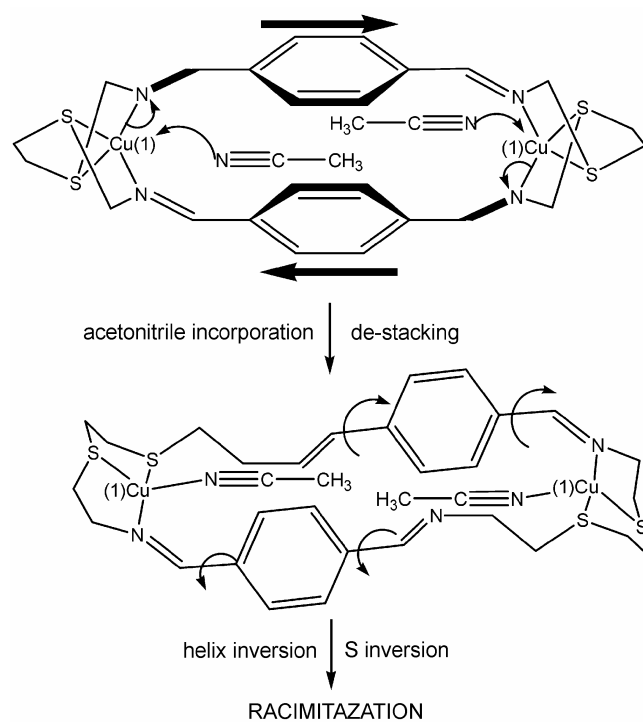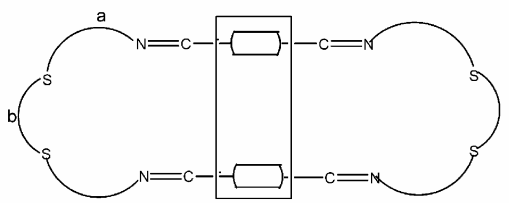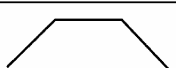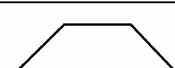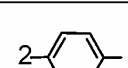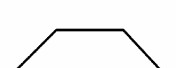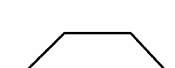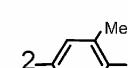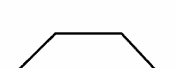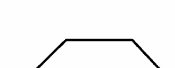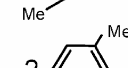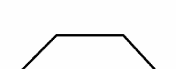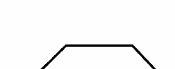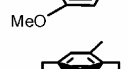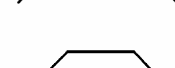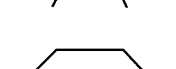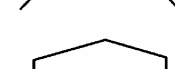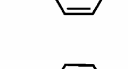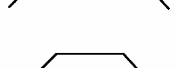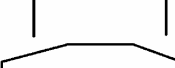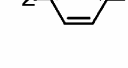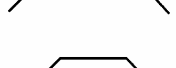
Figure 13. Mechanism of racemization of figure–eight Cu(I) complex.

of such isomerization could be a "jumping rope" mechanism or through the intermediacy of syn isomer. Thermal isomerization studies favour the second mechanism due to the fact that syn form accumulates in such thermal reaction. This is con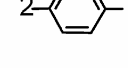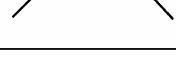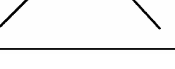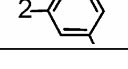trary to the cyclooctene interconversion, where two mechanisms are operative. The X-ray crystal structures of both syn and anti macrocycles were reported. More importantly, the authors could isolate three isomers by chiral HPLC column.

2.14 *Oligo esters*

Kyoko Nozaki et al reported double helical oligo esters (figure 15).[30] Unlike common macrocyclic compounds, the conformation of these cyclic oligo-

Table 1. Macrocyclic ligands synthesized by Peter Comba's group. Cu(I) complexes of these ligands exist in figure-eight topology.

esters is much more restricted because of binaphthyl groups. In these molecules, the biphenyl group is sandwiched between the two binaphthyl groups, thus giving a helical twist to the molecule. The biphenyl group in these cyclic esters takes the same configuration as the binaphthyl group. Because of the chiral twist, the molecule adopts figure eight geometry. The specific rotation of esters increases with increasing number of biphenyl groups in the molecule. This increase was attributed to double helical character. The results were supported by modelling studies and CD spectral studies. The increase of CD absorption with increasing biphenyl group supports the observed increasing helical character in solution.

2.15 *Fused figure–eight like structure*

Fujita and colleagues synthesized figure-eight shaped molecule with palladium at the node.[31] This was further self-assembled by catenation. Monomer (I) was formed spontaneously in DMSO from *bis*(4-pyridyl) ligand and Pd(NO$_3$)$_2$ at 60°C. The Pd(II) adopted a square planar geometry with four pyridyl groups. All the pyridyl groups are orthogonal and phenyl groups are in the plane. The figure-of-eight monomer was transformed into organic supra-
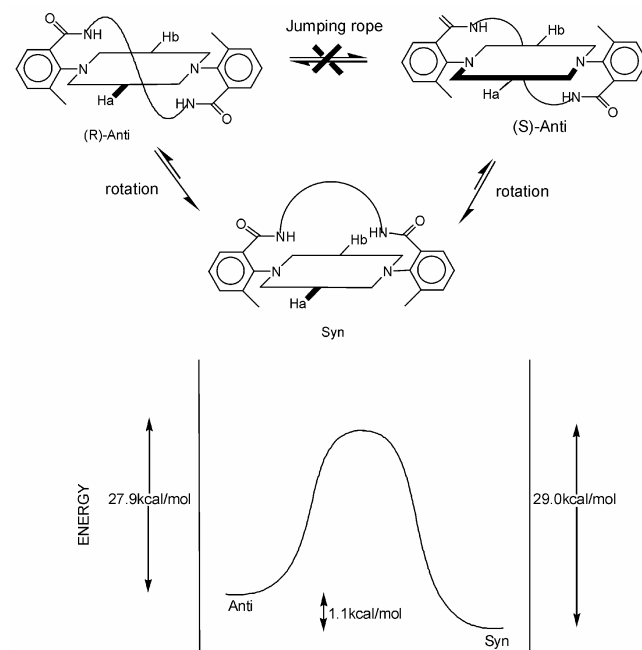

Figure 14. Mechanism of enantiomer interconversion of Schimizu's benzenediimides and the energy diagram of the interconversion of *syn* and *anti*.
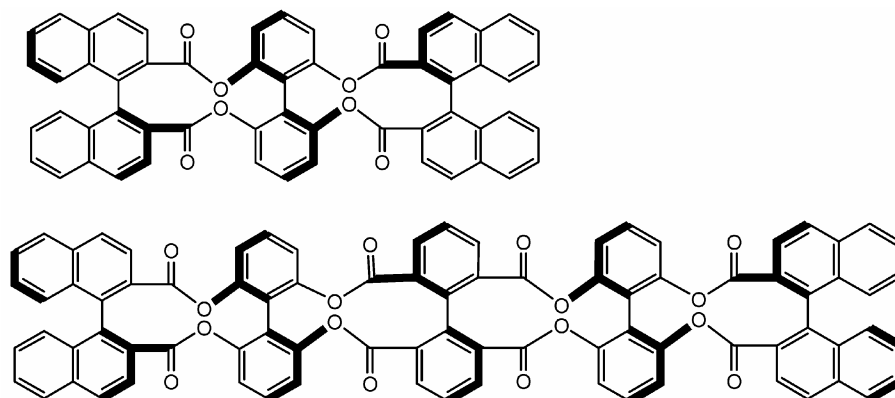
Figure 15. Nozaki's double helical oligo esters based on biphenyl and binaphthyl linkers.
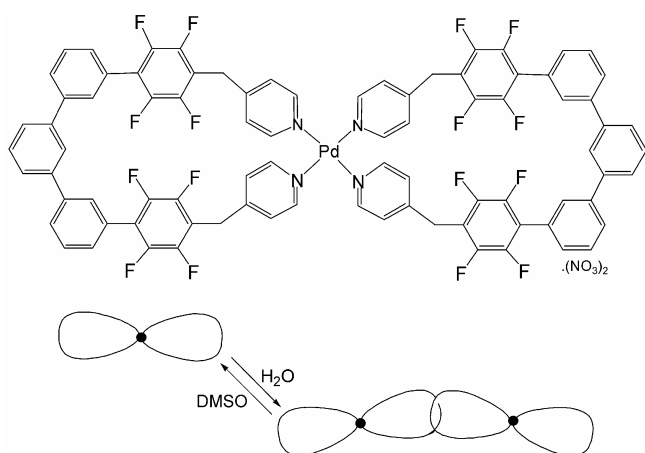

Figure 16. Fujita's Pd-based, fused figure-eight structure.

molecular structures by organic stack-driven catenation in D_2O-DMSO-d_6 to give a dimeric unit (figure 16). Under more aqueous condition, catenated trimer was formed in greater amount. The molecule was characterized by detailed ^1H NMR and cold spray ionisation mass spectrometry.

3. Conclusion

In conclusion, the design and synthesis of molecules with intriguing topology remains an elusive goal and will bridge chemistry, physics and mathematics. The above mentioned molecules range from naturally occurring molecules to a wide array of synthetic systems. The functional properties, dynamics, energetics and the folding behaviours are potential subjects of study in the future. This shows much more things to be explored which will be beneficial to our understanding of molecular origami.

References

1. Wasserman S A and Cozzarelli N R 1986 *Science* **232** 951
2. Mao C, Gate R J D and Seeman N C 1997 *Nature* (*London*) **386** 137; (b) Yan H, Zhang X, Shen Z and N C Seeman 2002 *Nature* (*London*) **415** 62
3. (a) Koert U, Harding M M and Lehn J M 1990 *Nature* (*London*) **346** 339; (b) Nierengarten J-F, Dietrich-Buchecker C O and Sauvage J-P 1994 *J. Am. Chem. Soc.* **116** 375; (c) Sauvage J-P 1990 *Acc. Chem. Res.* **23** 319
4. (a) Balzani V, Gomez-Lopez M and Stoddart J F 1998 *Acc. Chem. Res.* **31** 405 and references there in; (b) Bissell R A, Cordova E, Kaifer A E and Stoddart J F 1994 *Nature* (*London*) **369** 133
5. (a) Vinograd J, Lebowitz J, Radloff R, Watson R and Laipis P 1965 *Proc. Natl. Acad. Sci. USA* **53** 1104; (b) Wang J C 1971 *J. Mol. Biol.* **55** 523
6. Watson J D and Crick F H C 1953 *Nature* (*London*) **171** 737
7. Wasserman S A, Dungan J M and Cozzarelli N R 1985 *Science* **229** 171; (b) Wang J C 1982 *Sci. Am.* **247** 94
8. Arsuaga J, Vazquez M, McGuirk P, Trigueros S, Sumners, D W and Roc J 2005 *Proc. Natl. Acad. Sci. USA* **102** 9165
9. (a) *Chemical and Engineering News* 2004 **82** 40; (b) Craik D J, Daly N L, Bond T and Waine C 1999 *J. Mol. Biol.* **294** 1327
10. Taylor W R 2000 *Nature* (*London*) **406** 916

11. (a) Markus Albrecht 2001 *Chem. Rev.* **101** 3457; (b) Piguet C, Bernardinelli G and Hopfgartner G 1997 *Chem. Rev.* **97** 2005; (c) Shalley C A, Beizai K and Vogtle F 2001 *Acc. Chem. Res.* **34** 465

12. Wipf P and Fritch P C 1996 *J. Am. Chem. Soc.* **118** 12358; and references cited there in

13. Schmitz F J, Ksebati M B, Chang J S, Wang J L, Hossain M B and Helm D v d 1989 *J. Org. Chem.* **54** 3463; (b) Ishida T, In Y, Shinozaki F and Doi M 1995 *J. Org. Chem.* **60** 3944

14. Wipf P, Fritch P C, Geib S J and Sefler A M 1998 *J. Am. Chem. Soc.* **120** 4105

15. Pascard C, Ducruix A, Lunel J and Prange T 1977 *J. Am. Chem. Soc.* **99** 6418

16. McDonald L A, Foster M P, Philips D R and Ireland C M 1992 *J. Org. Chem.* **57** 4616

17. Cope A C, Ganellin C R, Johnson Jr. H W, Auken T V V and Winkler H J S 1963 *J. Am. Chem. Soc.* **85** 3276

18. Mascal M, Moody C J, Morrell A I, Slawin A M Z and Williams D J 1993 *J. Am. Chem. Soc.* **115** 813

19. Karle I L, Ranganathan D and Haridas V 1996 *J. Am. Chem. Soc.* **118** 10916

20. (a) Sessler J L, Weghorn S J, Lynch V and Johnson M R 1994 *Angew. Chem. Int. Ed.* **33** 1509; (b) Sessler J L and Seidel D 2003 *Angew. Chem. Int. Ed.* **42** 5134

21. (a) Werner A, Michels M, Zander L, Lex J and Vogel E 1999 *Angew. Chem. Int. Ed.* **38** 3650; (b) Vogel E, Broring M, Fink J, Rosen D, Schmickler H, Lex J, Chan K W K, Wu Y-D, Plattner D A, Nendel M and Houk K N 1995 *Angew. Chem. Int. Ed. Engl.* **34** 2511; (c) Broring M, Jendrny J, Zander L, Schmickler H, Lex J, Wu Y-D, Nendel M, Chen J, Plattner D A, Houk K N and Vogel E 1995 *Angew. Chem. Int. Ed. Engl.* **34** 2515

22. Vogel E, Michels M, Zander L, Lex J, Tuzun N S and Houk K N 2003 *Angew. Chem. Int. Ed.* **42** 2857

23. Setsune J-I, Katakami Y and Iizuna N 1999 *J. Am. Chem. Soc.* **121** 8957

24. (a) Shin J-Y, Furuta H, Yoza K, Igarashi S and Osuka A 2001 *J. Am. Chem. Soc.* **123** 7190; (b) Shimizu S, Shin J-Y, Furuta H, Ismael R and Osuka A 2003 *Angew. Chem. Int. Ed.* **42** 78

25. Sprutta N and Latos-Grazynski L 2001 *Chem. Eu. J.* **7** 5099

26. Sessler J L, Seidel D, Gebauer A, Lynch V and Abboud K A 2001 *J. Heterocycl. Chem.* **38** 1419

27. Sessler J L, Maeda H, Mizuno T, Lynch V M and Furuta H 2002 *J. Am. Chem. Soc.* **124** 13474

28. (a) Comba P, Fath A, Huttner G and Zsolnai L 1996 *Chem. Commun.* 1885–1886; (b) Comba P, Kuhner A and Peters A 1999 *J. Chem. Soc. Dalton. Trans.* 509; (c) Comba P, Fath A, Hambley T W and Richens D T 1995 *Angew. Chem. Int. Ed.* **34** 1883; (d) Comba P, Fath A, Hambley T W, Kuhner A, Richens D T and Vielfort A 1998 *Inorg. Chem.* **37** 4389

29. Degenhardt III C F, Smith M D and Shimizu K D 2002 *Org. Lett.* **4** 723

30. Nozaki K, Terakawa T, Takaya H and Hiyama T 1998 *Angew. Chem. Int. Ed.* **37** 131

31. Hori A, Yamashita K, Kusukawa T, Akasaka A, Biradha K and Fujita M 2004 *Chem. Commun.* 1798