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Diphenic Acid as a General Conformational Lock in the Design of Bihelical Structures

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Abstract: The bihelical (figure of "∞") topology was examined from vantages of design, crystal structures, chirality, circular dichroism (CD) studies and molecular-orbital calculations. The minimalistic design envisaged the sequential linking of cystine to the anchor diphenic acid, which proved to be a general conformational lock. The bihelical compound **4** was obtained in two steps from diphenic anhydride **1** and cystine di-OMe. The chirality of **4** arises largely from the L-cystine. The bihelical compound **5** obtained from D-cystine di-OMe was found, by X-ray crystallography, CD studies, and optical rotation, to be the perfect mirror image of **4** prepared from L-cystine. The crystal structure of prototype **8**, prepared by protocols used for **4** from the achiral cystine analogue cystamine, had a "U"-shaped conformation held together by intramolecular hydrogen bonds. Analysis of **4** and **5** show that the pairs of nine-membered β-turn-like constructs made compact through hydrogen bonding with DMSO hold the key for the bihelical conformation. Another factor is the need for the presence of a ligand at the Cα position. The absence of this, as in **8**, allows major flexibility in the torsional angles around this critical region, promoting flexible alternatives. The CD analysis of **4**, confirmed to be bihelical by X-ray crystallography, showed a typical negative band at about 210 Å attributed to the β-turn-like motif, and in the positive-band region a peak at about 227 Å, generally related to the twist of the biphenyl unit. The cystamine analogue **8**, which showed a "U"-type structure, presented a CD spectrum with no typical features. The total energy, derived from theoretical calculations by using the X-ray structure data, support the bihelical structure for **4** and a "U"-shaped one for **8**. The limited utility of such calculations was tested with composite **9**. Composite **9**, in which the anchor diphenic acid is linked to cystamine on the one hand and to cystine on the other, showed a CD spectrum similar to that of **4**, and this coupled with molecular-orbital calculations, using data from **4** and **8**, predict a bihelical structure for this compound.

Keywords: chirality · diphenic acid · helical structures · hydrogen bonds · topochemistry

Introduction

Closed bihelical modules (figures of "∞") have emerged as structural motifs across a variety of carbon substrates of natural and synthetic origin. Their uses include complexation, crafting therapeutic systems, molecular recognition, DNA mechanisms and ion sensors.

The present work should be viewed from a general context as it, inter alia, projects diphenic acid as a "conformational lock" for crafting a range of bihelical structures and

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elucidates analyses factors obtained from X-ray crystallography, circular dichroism and molecular-orbital calculations that govern the formation of these structures. Although a large number of bihelical systems have been reported, the basic elements related to the formation of such compounds over alternate conformations have been hardly explored. The principles that lead to the bihelical system reported here are general and hold promise of applications across chemical and biological domains.

The increasing role of bihelical structures is reflected in the following brief overview.

A number of bihelical systems have as their basis the formation of a closed system from an open one, which can be achieved only by severe folding. Such constraints have been imposed in several ways. Polyacetylenic systems built on a range of scaffolds have lead to a number of bihelical systems with potential for a variety of applications. For example, "bow-tie" shaped bihelical structures built on an acetylenic and 2,2′-bipyridyl scaffold have been used to detect several metal ions. The acetylene constructs have been replaced by several others to achieve bihelical systems on the same principle.[1] A variation is the open figure of "∞" structure; an elegant example of which is that created from chiral 1,1′-binapthalene units and phenanthroline whose cavity strongly binds metal ions.[2] An interesting strategy that leads to bihelical structures open at both ends takes advantage of strong ionic interactions.[3]

A noteworthy illustration of the generation of multitopological systems is the tethering of the circular frame of a rotaxane to the axle by a ligand pair.[4]

The recent synthesis of giant porphyrin systems has lead to the preparation of a variety of bihelical structures.[5] The mixing of porphyrin with other heterocycles has given rise to bihelical structures with specific metal-uptake properties. Results of NMR experiments have shown that the bihelical systems in these cases are dynamic and move in a " conveyer belt" fashion without undergoing racemization.[6] Figure of "∞" macropyrroles can be separated on a chiral column. The metal complexes resulting from the pure antipodes have potential as catalysts in asymmetric synthesis.[7] Interestingly, the large porphyrin Turcasarin forms crystals in both L and D configurations.[8] Metal complexes of oxidative degradation products of haem have been shown to have bihelical structures.[9]

Open compounds having proper substituents can be collapsed to bihelical structures by metal complexes.[10] An unusual process is the transformation of a figure of "∞" motif from palladium complexation to catenanes and other topological systems.[11] Palladium complexes of pyrroles flanked by oxazoles form bihelical structures in which one halogen is retained.[12]

Extended bihelical motifs mostly stabilized by hydrogen bonding have been either carefully crafted[13] or unexpectedly encountered, as in the case of fumaropumaric acid, a member of the rosin family that act as acceptors for a variety of small organic molecules.[14] In the extended helical domain, a recent interesting discovery is the formation of such species by metal-stabilized polyiodide. The metal support and that of the counter ion offer several possible variations in the construction of the species.[15]

Bihelical structures with extraordinary biological properties have been encountered in naturally occurring systems. An in-depth analysis of diverse topological forms present in proteins has been made.[16] In the domain of nucleic acids, bihelical motifs have been recognized for some time. Several have been associated with specific functions and some have been made synthetically. An interesting case is the bihelical sequence preceding the initiation system of transcription in *E. coli*.[17]

The highly cytotoxic cyclic hexapeptides from marine tunicates *Lissoclinum patella* are members of a closely related family harboring oxazoline and thiazole amino acids. Open structures are seen in symmetric and less-substituted members, whereas asymmetric-substituted members fold to bihelical forms. All members are biologically active. An examination of open and bihelical conformation of patellamides has shown that, topologically, an open frame folded by two β turns with compatible dihedral angles generates a bihelical structure. This is exemplified by patellamide D, which has a bihelical structure whose genesis is attributed to the pairs of β turns with isoleucine and cyclized threonine residues at the corners of the turns. On the other hand, lissoclinamide 7, which possess only a β turn and a β loop, is planar.[18] Didemnin, a highly active depsipeptide isolated from Caribbean tunicates, exhibits high activity against viruses and a range of cancers. The X-ray structure of didemnin shows a figure of "∞" topology.[19]

Regardless of their conformation, all of the members show activity. Ironically, ulithiacyclamide, which has a planar structure but possesses an unusual cystine band, is the most active in this category.

A unique example is the cyclic tryptophane-containing peptide arising from a rearrangement. This compound exhibits a bihelical structure both in solid and in solution. That an analogue that lacks the chiral group was found to have an open structure has implications regarding the choice between two conformers.[20]

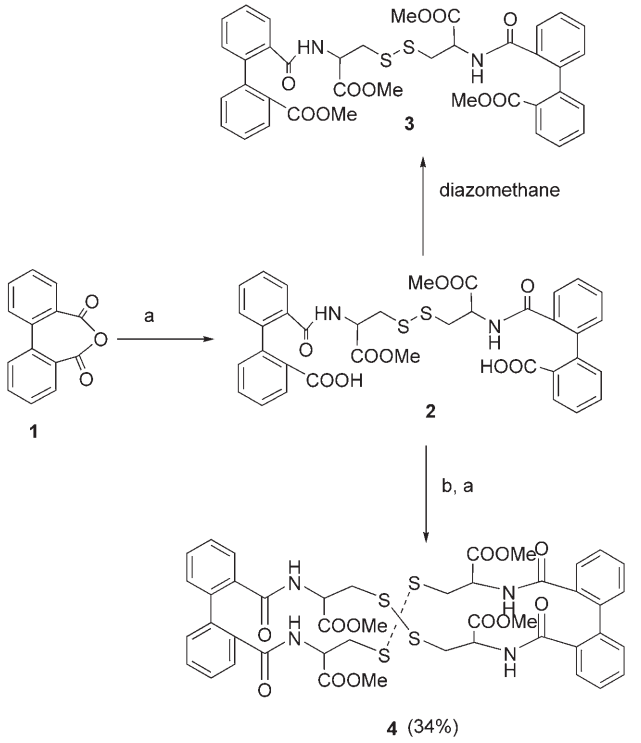
The relationship between bihelical topology and its biological activity requires an extensive study of a variety of analogues. The present work attempts to achieve this purpose.

Results and Discussion

Design of compounds: The increasing interest in the formation of bihelical structures made it attractive to design a minimalistic bihelical motif whose parameters can serve to discriminate other possible models obtained from theoretical predictions. The specific knowledge of parameters for one bihelical structure would narrow the choice among several possibilities. A general scaffold in the form of a "conformational lock" was identified in diphenic acid, as this molecule not only possesses the necessary functional groups, but also the nearly orthogonally aligned phenyl rings[21] that

were anticipated to generate the necessary β-turn-like element. Cystine was chosen as the key linker element because of its chiral nature and ability to take part in several topological forms.[22] The design envisaged the sequential linking of cystine to the anchor diphenic acid.

Synthesis and X-ray analysis: Diphenic anhydride **1** was considered a suitable substrate to join the initial linker to a second unit. The reaction of cystine di-OMe (freshly generated from hydrochloride with aqueous $NaHCO_3$) afforded the dicarboxylic acid **2**, which was characterized further as the methyl ester **3**. Reaction of **2** with another cystine di-OMe linker by using EDCI/HOBt (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide/1-hydroxy-1,2,3-benzotriazole) in CH_2Cl_2 afforded, as expected, **4** as the major compound (Scheme 1).[23,24]



Scheme 1. Preparation of compound **4**. a) cystine di-OMe; b) EDCI-HOBt.

The structural assignments for **2**, **3**, and **4** are fully supported by spectral and analytical data. Compound **4** deposited beautiful colorless rods from hot DMSO. An X-ray crystallographic analysis showed clearly its bihelical (figure of "∞") topology, edge-on and perpendicular views of which are presented in Figures 1 and 2, respectively.

A scrutiny of the X-ray structure of **4** (Figure 1) highlights the presence of two nine-membered β-turn-like features, made compact by the hydrogen bonding across the ring, and made possible by the twist of the biphenyl core. These observations are supported by circular dichroism (CD) spectra (see below).

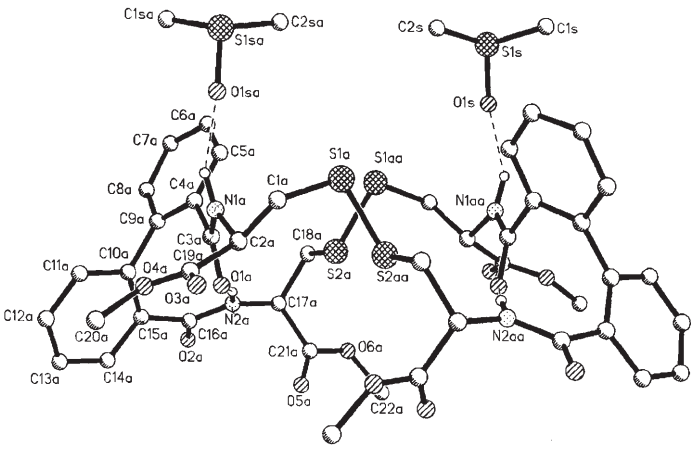


Figure 1. "Edge-on" crystallographic view of **4**. The molecule lies on a true crystallographic two-fold rotation axis. Hydrogen bonds are formed between DMSO molecules and N1a and N1aa, in which N1a···O1sa 2.82 Å and H···O1s 2.00 Å.

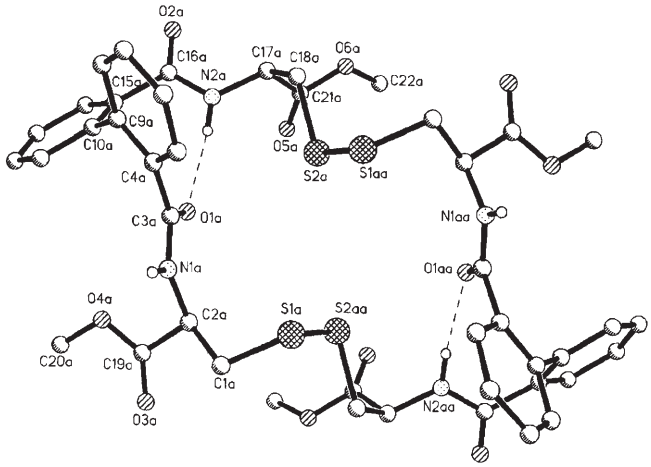


Figure 2. Perpendicular view of **4**. Nine-membered β turns are formed with N2a···O1a 2.86 Å and H···O1a 1.99 Å.

The core structure is further promoted by the hydrogen bonding of the remaining NH to DMSO. The importance of this hydrogen bonding was also revealed by molecular-orbital calculations.

In principle, the bihelical motif could have a left or right disposition of the intercrossing helices. The fact that only one arrangement of **4** (Scheme 1, Figures 1 and 2) with $[\alpha]_D^{31.6} = -36.0494$ ($c = 0.27$, $CHCl_3$) was obtained, suggests the existence of a control element. Analogous to the formation of right- or left-handed helices, which is controlled by the chirality of the amino acids involved, it is likely that the chirality observed in **4** (Scheme 1, Figures 1 and 2) arises from that of the L-cystine used in the construction of the bihelical motif **4**. This has been demonstrated experimentally by using D-cystine in place of the L-analogue. The reactions carried out as shown in Scheme 1 afforded compound **5** in 56% yield. This compound exhibited spectral data identical

to that of **4**, but precisely opposite rotation $[\alpha]_D^{31.6} = +38.00$ ($c = 0.275$, $CHCl_3$).

Crystallization of **5** from DMSO afforded beautiful colorless rods, whose structure was established by X-ray crystallography to be precisely the mirror image of **4**. A structural representation of **5** given in Figure 3 shows the mirror-image relationship between **4** and **5**.

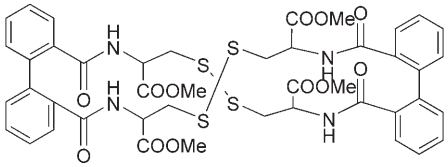


Figure 3. Structural representation of **5**.

Crystallographic edge-on and perpendicular views of **5** are presented in Figures 4 and 5. A comparison with Figures 1 and 2 clearly reveals the mirror-image relationship. The composite edge-on view of the antipodes presented in Figure 6 is striking.

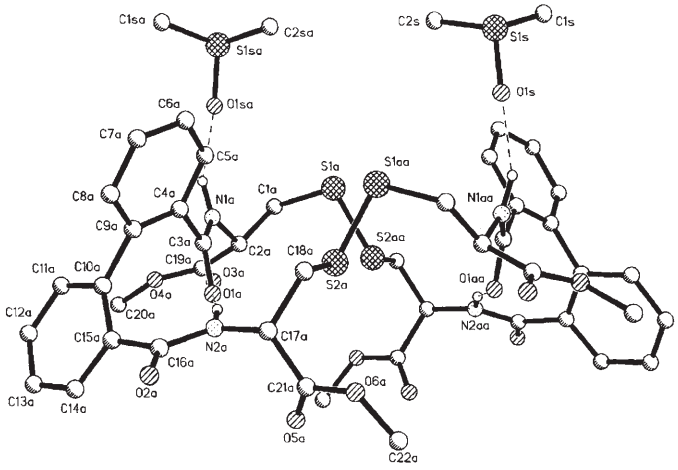


Figure 4. Crystallographic edge-on view of **5** (the mirror image of **4**).

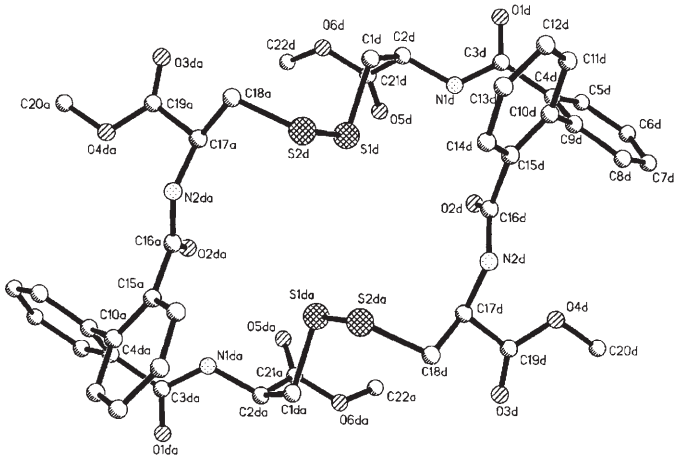


Figure 5. Perpendicular view of **5**.

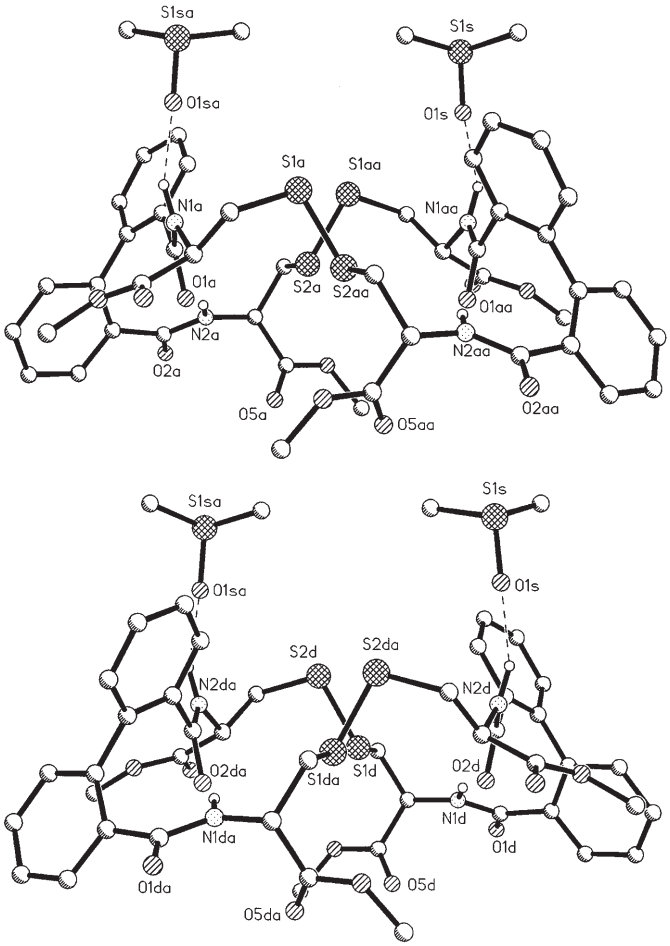
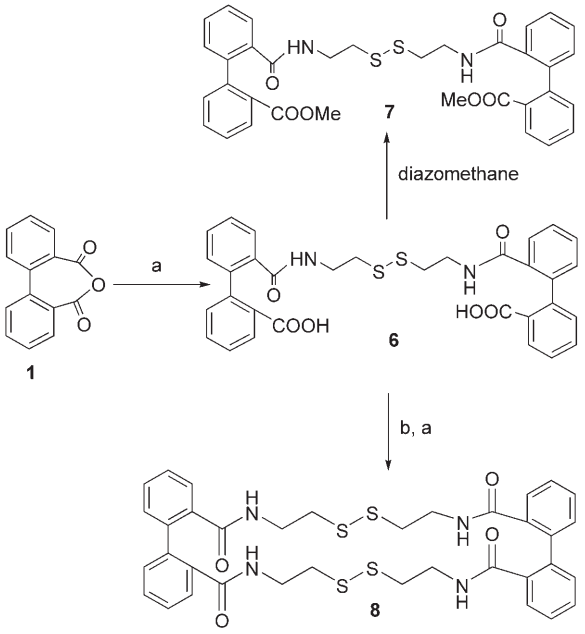


Figure 6. Composite picture of the mirror images of **4** and **5** obtained by X-ray crystallography (edge-on view).

The preparation and characterization of the bihelical structures **4** and **5** have shown that diphenic acid can be used as a general "conformational lock" for the possible synthesis of a variety of bihelical structures with the proper choice of linker element. The synthesis of a possible bihelical structure without a chiral centre seemed desirable, because in at least one case, a bihelical system having chiral centres was transformed to an open system in its absence.[20] The obvious option was the readily available cystamine; structurally similar to cystine, but without side groups and, therefore, without the chiral centre.

The reaction of diphenic anhydride with freshly prepared cystamine free base afforded dicarboxylic acid **6**, which was further characterized as the methyl ester **7**. The reaction of **6** with another unit of cystamine followed by chromatography afforded compound **8** (22%, m.p. 232–235°C; Scheme 2). Compound **8** formed colorless thick crystals from $CHCl_3$/MeOH 1:1. A crystallographic analysis showed that **8** had a rather "U"-shaped backbone structure, held together by three intramolecular hydrogen bonds.

The crystallographic representations of edge-on and perpendicular views of **8** are presented in Figures 7 and 8. Interestingly, the crystals of **8** obtained from MeOH and DMSO



Scheme 2. Preparation of compound **8**. a) cystamine; b) DCC-SuOH.

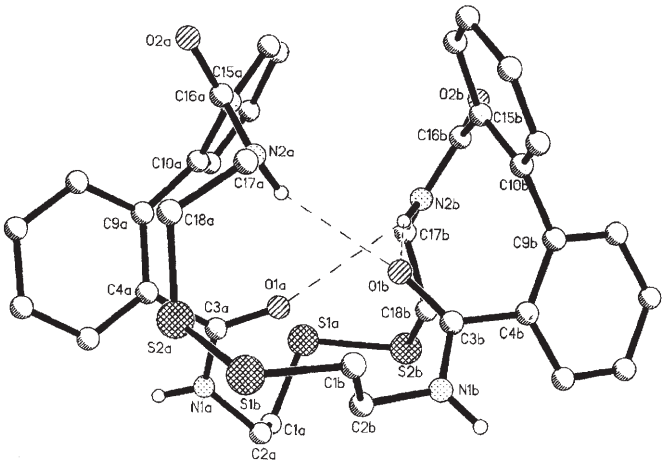


Figure 7. Crystallographic "edge-on" view of **8**. Intramolecular hydrogen bonds have the lengths: N2a···O1b 3.197, H···O1b 2.43, N2b···O1b 2.973, H···O1b 2.10; N2b···O1a 3.298, H···O1a 2.76 Å.

were identical.[25] No solvent was cocrystallized with **8**. A comparison of the torsional angles in **4** and **8** in Table 1 shows that the regions of the nine-membered β turns are quite similar, although the O1a···N2a distance has increased to 3.67 Å in **8**. Consequently, this is no longer considered as an NH···O=C hydrogen bond (Figure 7). However, large differences (greater than 100°) in torsional angles occur at or near C2a, C2b, C17a, and C17b, the atoms from which the side chains in **4** were removed. This accounts for the disparate shapes of the macromolecular rings in **4** and **8**.

Having shown that the absence of chiral groups in the linker favours a non-bihelical structure, it was logical to assess the preference with a single chiral linker. Such a system was prepared by linking the "conformational lock" with cystine on the one side and cystamine on the other.

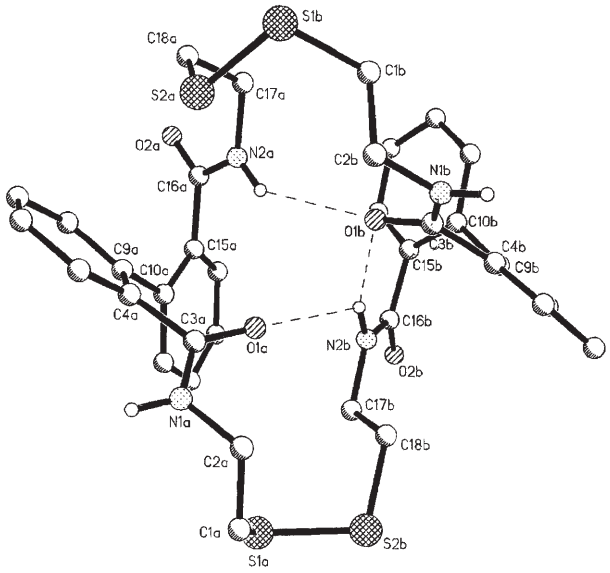


Figure 8. Perpendicular view of **8**.

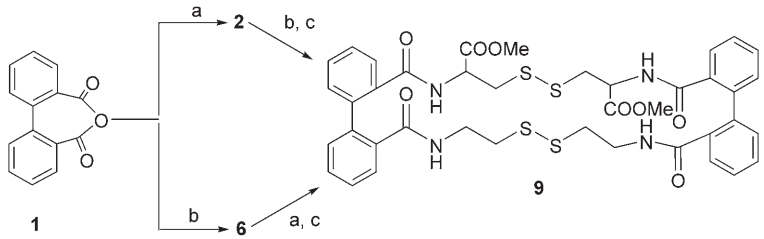
Table 1. Comparison of torsional angles [°] in macrocycles **4** and **8**.

Angle	**4**	**8**	lgΔ[a]
S2b-S1a-C1a-C2a	−68	+81	*
S1a-C1a-C2a-N1a	−66	+67	*
C1a-C2a-N1a-C3a	142	−113	*
C2a-N1a-C3a-C4a	−174	−171	
N1a-C3a-C4a-C9a	−137	−143	
C3a-C4a-C9a-C10a	6	12	
C4a-C9a-C10a-C15a	−103	−130	
C9a-C10a-C15a-C16a	10	11	
C10a-C15a-C16a-N2a	43	63	
C15a-C16a-N2a-C17a	−177	−175	
C16a-N2a-C17a-C18a	138	91	
N2a-C17a-C18a-S2a	70	67	
C17a-C18a-S2a-S1b	177	81	*
C18a-S2a-S1b-C1b	−77	−88	
S2a-S1b-C1b-C2b	−68	−58	
S1b-C1b-C2b-N1b	−66	175	*
C1b-C2b-N1b-C3b	142	−86	*
C2b-N1b-C3b-C4b	−174	−175	
N1b-C3b-C4b-C9b	−137	−153	
C3b-C4b-C9b-C10b	6	11	
C4b-C9b-C10b-C15b	−103	−111	
C9b-C10b-C15b-C16b	10	9	
C10b-C15b-C16b-N2b	43	55	
C15b-C16b-N2b-C17b	−177	−173	
C16b-N2b-C17b-C18b	138	128	
N2b-C17b-C18b-S2b	70	179	*
C17b-C18b-S2b-S1a	177	−60	*
C18b-S2b-S1a-C1a	−77	−94	

[a] Large differences (>100°) in values of torsional angles in the backbone.

The cystine–cystamine composite **9** was achieved by two complementary routes (Scheme 3).

Compound **9**, obtained by either of the two routes, exhibited identical ^{1}H NMR, MALDI-TOF MS, and CD features. Several attempts to secure crystals from **9** did not succeed. However, CD studies and molecular-orbital calculations support a bihelical profile for **9** (see below).



Scheme 3. Preparation of compound **9**. a) cystine di-OMe; b) cystamine; c) EDCl-HOBt.

Compounds **4**, **8**, and **9**, heavily endowed with amide and sulfur centres, are attractive for the formation of silver complexes.[26a] Such complexes have potential in ^{111}Ag-based radioimmuno therapy. Compounds **4**, **8**, and **9** readily formed 1:1 complexes with $AgBF_4$. Although crystals of these could not be secured, their structure is supported by results of ESI-MS analysis. Based on similar studies,[26b] a minimal tetrahedral coordination of the Ag^+ with the four sulfur atoms appears possible.

Circular dichroism studies: Results of CD studies in solution conducted in the present work not only corroborated the crystallographic findings, but also provided a mechanistic insight into possible conformational requirements for the formation of the bihelical topology.

The spectra of **4** in trifluoroethanol (TFE) (Figure 9), MeOH and CH_3CN were recorded. All of them showed a similar profile, characterized by a negative CD band at 211 nm (TFE), 214 nm (MeOH) and 214 nm (CH_3CN), and a positive CD band at aboout 230 nm. Although the negative CD band in TFE is reminiscent of a β-hairpin conformation,[27] the positions of negative CD bands in MeOH/CH_3CN are similar to spectra of a distorted β sheet.[28] A change in conformation from TFE to MeOH/CH_3CN is also reflected in the diminution of intensity of the positive band at 228–230 nm in these solvents. However, in all solvents, the molar-ellipticity values in the negative-band region remained unchanged. The band at ≈230 nm in the CD spectrum reflects the twist of the biphenyl core.[29]

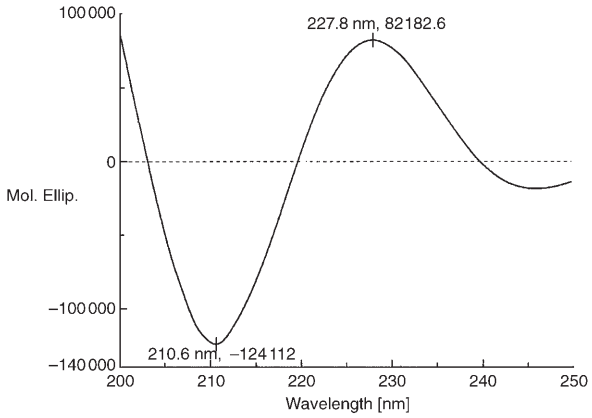


Figure 9. CD spectrum of **4** in TFE.

The CD spectrum of **5** (Figure 10) bears an almost exact mirror-image relationship to its antipode **4**, a fact that is illustrated effectively in the composite CD spectrum of **4** and **5** (Figure 11).

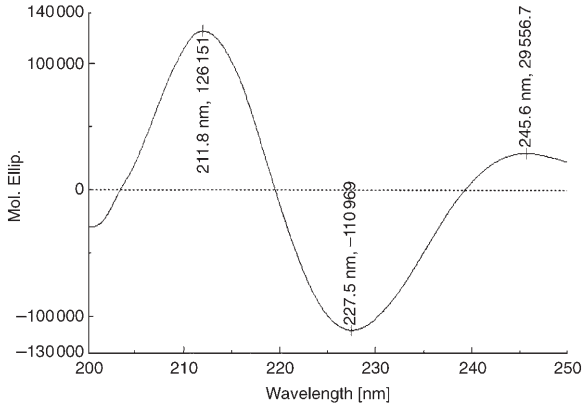


Figure 10. CD spectrum of **5** in TFE.

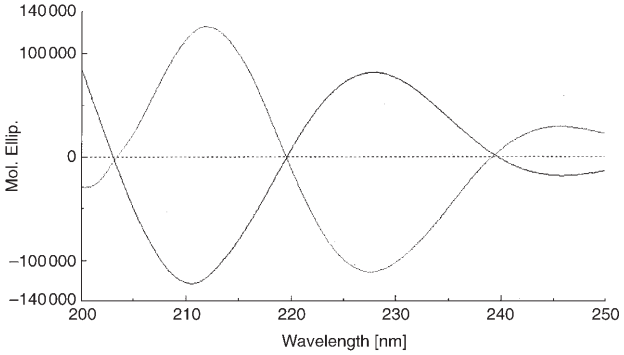


Figure 11. Composite picture of CD spectra of **4** and its mirror image **5** taken in TFE.

The suggested nine-membered β-turn motif finds support in the CD spectra of compound **3** in TFE (Figure 12), which shows a very similar profile to that of **4** with reduced molar ellipticity.

The crystal structure of **8**, which shows a "U"-type conformation (Figures 7 and 8), exhibited a random CD profile, similar to that of **7**.[30]

The stepwise synthesis of the macrocycles anchored on the motif of diphenic acid also enables the study of aspects related to the conformation of such compounds, as seen by CD analysis. It was stated above that the β-turn-like motifs present in **3** are responsible for the bihelical structure, which was absent in the achiral analogue **7**.

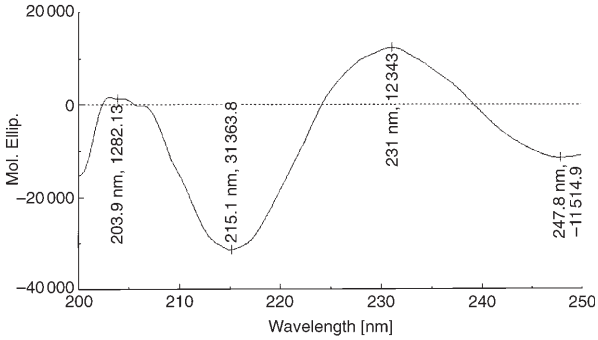


Figure 12. CD spectrum of **3** in TFE.

The CD spectrum of the composite **9** exhibited in TFE a negative band at 212 nm and a positive one at 228 nm (Figure 13) remarkably similar to that of **4**. The CD profile seen here predicts a bihelical conformation.

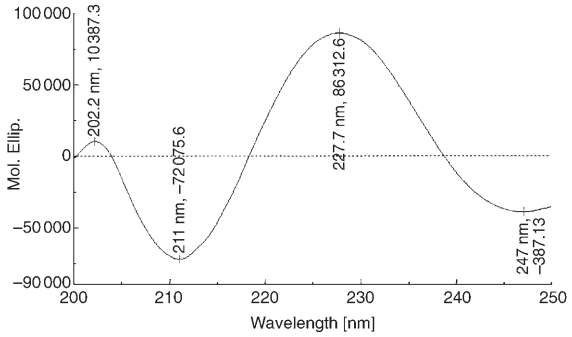


Figure 13. CD spectrum of **9** in TFE.

At this point, it would be interesting to compare the nature of the β-turn-like element possible in **3**, **4** and **9**. Compound **4**, which has two well-defined β turns, exhibits the invariance of the negative band, attributed to the β turn in different solvents, which perhaps arises from the inherent stabilization of the bonding by the chiral elements here. The open ester **3** with possible β-turn-like motifs, with increased torsional freedom, shows a considerably lower molar-ellipticity value. As this unit becomes part of **9**, the CD spectrum shows considerable enhancement of this value, possibly arising from placement in a restrained position.

Molecular-modelling studies: Quantum-mechanical calculations were carried out on **4**, **8**, and **9** in bihelical as well as in "U"-shaped conformations. The structures were modeled from the experimentally determined coordinates for **4** and **8**. The Gaussian 03 program package[31] was used. Quantum chemical calculations at the semiempirical AM1[32] level were carried out to evaluate the energies of the conformations. This was then followed by a single-point DFT calculation on AM1-optimized geometries. The results are summarized in Table 2. The total energies indicate preference for a bihelical conformation for **4** and "U"-shaped conformation for **8**. Similar calculations in which two molecules of DMSO are explicitly placed in orientation obtained from the experimental coordinates for **4** showed a preference for bihelical structures (Table 2) for **4** and **9**.

Table 2. Total energies [Hartrees] for the six conformations in vacuum and in DMSO at the AM1 level of theory.

Molecule	In vacuum (E)	With two molecules of DMSO[a] (E)
8 (U shaped)	−0.038521	−0.183388
8 (bihelical)	−0.031771	−0.177930
9 (U shaped)	−0.283986	−0.417100
9 (bihelical)	−0.289090	−0.431758
4 (U shaped)	−0.524169	−0.665396
4 (bihelical)	−0.539652	−0.684022

[a] Explicitly placed in the orientation obtained from the X-ray structure of **4**.

The data for **9** indicate a preference for a bihelical over a "U"-shaped conformation, particularly in the presence of DMSO. Work on the basic problems related to the topology of open cyclic systems is in progress.

Conclusion

We have shown that "diphenic acid" can be used as a "conformational lock" in a general strategy for the crafting of bihelical structures with appropriate linker elements. In a typical example, the linking of two diphenic acid anchors with cystine-diOMe generates a pair of compact nine-membered β-turn-like elements. It is suggested that any linker element that could satisfy this basic or equivalent criterion can lead to bihelical structures. In the present case the compact profile of the β-turn-like elements arises from hydrogen bonding of one of the NH bonds to the carbonyl oxygen across the ring, as seen in **4** (Figures 1 and 2). A second linker then completes the synthesis. In this strategy the basic criterion, namely the need for a pair of compact β-turn-like structures, seems to provide an explanation for open frames. The detailed analysis in the present work of the bihelical conformation secured by **4** and that of a "U"-shaped conformation with cystamine lacking the chiral groups is possibly related to this factor. X-ray crystallography results for **4** and **8** show a number of common features (Table 3). Besides, as could be seen, torsional angles that lead to the synthesis of these compounds (Table 1) are quite similar, except, notably, if the chiral ester is present. In the preference for bihelical structures, substituents at the Cα position appear to play a major role. The presence of such bulky substituents gives rigidity to the β turns involved and, in the case of **4**, leads to the bihelical structure. In the case of **8**, in which such substituents are absent, much more torsional freedom is available for the Cα atom, which now resembles that in glycine. This notion is supported by the fact that if a β turn nearly identical to **4** is inscribed in **8** (Figure 14, left), the rest of the molecule exhibits greater conformational flexibility, particularly around erstwhile ligand locations (COOMe), as seen by the wide divergence in dihedral angles.

Table 3. Crystal data and structure refinement.[35]

Compound	**4**	**8**
formula[a]	$C_{44}H_{44}N_4O_{12}S_4 \cdot 3\,C_2H_6OS$	$C_{36}H_{36}N_4O_4S_4$
M_r	1183.46	716.93
crystal size [mm^3]	$0.50\times0.25\times0.10$	$\approx0.30\times0.30\times0.30$
space group	$C2$	$P2_1/n$
a [Å]	21.803(9)	10.537(3)
b [Å]	9.046(4)	21.317(6)
c [Å]	15.571(7)	15.857(4)
α [°]	90.00	90.00
β [°]	114.948(6)	97.98(2)
γ [°]	90.00	90.00
T [°C]	203	293
λ [Å]	Mo, 0.71073	Cu, 1.54178
V [Å^3], Z	2784.6(20), 2	3527.3(17), 4
ρ_{calcd} [Mg m^{-3}]	1.411	1.350
μ [mm^{-1}]	0.352	
F(000)	1244	1504
limiting indices	$-28\le h\le28$	$-12\le h\le1$
	$-10\le k\le11$	$-25\le k\le1$
	$-20\le l\le20$	$-18\le l\le18$
reflns collected	13931	7829
independent reflns	5665	6186
data/restraints/parameters	4884/0/361	4214/0/434
goodness of fit on F^2	1.239	1.020
final R indices [$I>2\sigma(I)$]	0.0579, 0.1413	0.0657, 0.2002
R indices (all data)	0.0741, 0.1666	
extinction coeff.	–	0.00117
largest diff. peak/hole [e Å^{-3}]	1.25, −0.75	0.58, −0.45

[a] Formula given for asymmetric unit, except for **4** in which the asymmetric unit is doubled because the molecule lies on a crystallographic rotation axis.

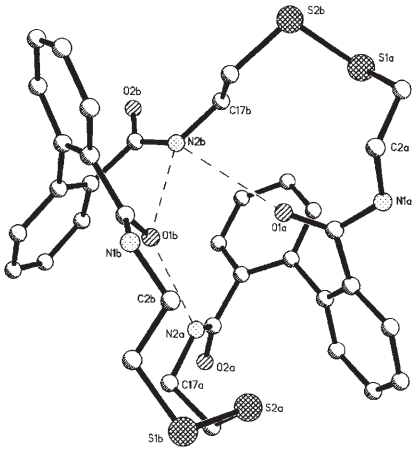


Figure 14. Illustration of the influence of the Cα ligand on torsional angles.

This also provides an explanation for a similar observation reported earlier.[33] This rationale finds particular support in the conformation of biologically active marine structures (see above), in which highly substituted members also invariably lead to bihelical structures.[18]

Here, we have attempted to link structural profiles obtained by X-ray crystallography and circular dichroism, and to use molecular-orbital data derived from X-ray structures to compute total energies in the presence of solvent molecules.

Our results suggest that, although the parent bihelical motif can be chiral, by far the major contribution to the chirality arises from the linker element, as clearly seen in the opposite optical rotations of **4** and its mirror image **5**. The presence of bihelical compounds generated from the use of diphenic acid as a "conformational lock" can be assessed by their CD profile, as in the case of **9**.

We have shown that cystine/cystamine is not only a linker element, but the presence of this unit can lead to complexes with silver and possibly other metal ions.

Experimental Section

General: Melting points were recorded by using Fisher–Johns apparatus and are uncorrected. Optical rotations were measured by using an automatic JASCO P-1020 polarimeter. Concentrations are given in g per 100 mL. Infrared spectra were recorded as KBr pellets by using a Thermo Nicolet Nexus 670 spectrometer and prominent peaks are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded by using Varian Gemini 200, Bruker Avance 300 and Inova 400 and 500 MHz spectrometers. The chemical shifts are expressed in ppm, with TMS at 0.0000 as internal reference. Fast atom bombardment mass spectrometry (FABMS) was performed by using a VG AUTOSPEC mass spectrometer, ESI-MS was conducted by using a micromass QUATTRO-LC instrument, MALDI-TOF spectra were recorded by using a KRATOS ANALYTICAL instrument and HRMS was obtained by using a QSTAR XL instrument. Elemental data were obtained by using automatic analysers. The CD spectra were recorded by using a JASCO J-810 spectrometer, mostly in TFE at a uniform concentration of 200 μmol L^{-1}. TLC was prepared on silica gel-coated plates made in the laboratory. ACD nomenclature for all compounds is listed.[34]

I. Reaction of diphenic anhydride with cystine di-OMe: preparation of 2: To an ice-cooled and well-stirred suspension of diphenic anhydride **1** (1.67 g, 7.46 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise cystine di-OMe free base in dry CH_2Cl_2 (50 mL) (freshly prepared from cystine di-OMe·2HCl (1.5 g; 4.4 mmol) and saturated $NaHCO_3$ (8 mL) under ice-cooling, extraction with CH_2Cl_2 (3×25 mL), drying (Na_2SO_4) and evaporation. The reaction yielded 1.0 g, 3.73 mmol). The reaction mixture was left to stir at room temperature for 12 h, filtered, the filtrate was washed sequentially with ice-cold 2N H_2SO_4 (2×5 mL), brine (10 mL), dried (Na_2SO_4) and evaporated to yield 2.18 g (82%) of crude **2** as a foamy solid that was triturated with saturated $NaHCO_3$ (25 mL), filtered, made acidic to pH≈4 with aqueous citric acid and filtered to give 1.5 g (56%) of **2**. M.p. 128–132°C; $[\alpha]_D^{31.6}=-86.50$ ($c=0.28$ in DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.62$ (m, 2H; $^\beta CH_2$), 3.02 (m, 2H; $^\beta CH_2$), 3.45, 3.58, 3.65 (s, s, s, 6H; COOMe), 4.75 (m, 2H; $^\alpha CH$), 6.25 (vbr, 2H; COOH), 7.37 (m, 16H; aromatic), 7.95 ppm (m, 2H; amide); IR (KBr): $\tilde{\nu}=3260$ (br), 3021 (br), 1727 (m), 1549 (m), 1244 cm^{-1} (m); MS (FAB): m/z (%): 739 (18) [M+Na$^+$]; HRMS calcd for $C_{36}H_{32}N_2O_{10}S_2$: 716.1576; found: 716.1588.

II. Reaction of 2 with diazomethane: preparation of diester 3: Ethereal diazomethane (≈0.113 g, 2.7 mmol, 11 mL), generated from *N*-methyl-*N*-nitroso-toluene-*p*-sulfonamide, was added to a solution of diacid **2** (0.650 g, 0.9 mmol) in methanol (5 mL). Evaporation of solvents afforded 0.680 g (≈100%) of the crude diester as a thick liquid. The crude product was subjected to chromatography on silica gel. Elution with $CHCl_3$/EtOAc (85:15) afforded 0.580 g (86%) of pure **3** as thick oil. $R_f=0.66$ ($CHCl_3$/EtOAc 6:4); $[\alpha]_D^{31.6}=+35.1698$ ($c=0.265$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.50$ (m, 2H; $^\beta CH_2$), 2.95 (m, 2H; $^\beta CH_2$), 3.64 (m, 12H; COOMe), 4.60 (br, 2H; $^\alpha CH$), 7.35 (m, 16H; Ar-H), 7.85 ppm (m, 2H; CONH); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta=40.14$, 51.54, 52.33, 127.62, 129.15, 129.68, 130.76, 131.52, 134.81, 139.36, 140.15, 168.60,

170.04, 170.40 ppm; IR (KBr): $\tilde{\nu}$ = 3418, 2922, 1720, 1662, 1516, 1288, 760 cm^{-1}; MS (FAB): *m/z* (%): 745 (18) [*M*+H^+], 767 (6) [*M*+Na^+]; HRMS calcd for $C_{38}H_{36}N_2O_{10}S_2$: 744.1889; found: 744.1872.

III. Reaction of 2 with cystine di-OMe: preparation of 4: HOBt (0.414 g, 3.07 mmol), EDCI (0.589 g, 3.07 mmol) and *N,N*-diisopropylethylamine (DIPEA) (0.534 mL, 3.07 mmol) were added sequentially to an ice-cooled and well-stirred suspension of **2** (1.0 g, 1.396 mmol) and cystine di-OMe dihydrochloride (0.523 g, 1.536 mmol) in dry CH_2Cl_2 (60 mL). The reaction mixture was left stirred overnight and under ice-cooling was quenched with saturated NH_4Cl (20 mL), admixed with additional CH_2Cl_2 (40 mL). The organic layer was washed with 1 N HCl (20 mL), water (20 mL), saturated $NaHCO_3$ (20 mL), water (20 mL), brine (2× 20 mL), dried (Na_2SO_4) and evaporated to give 1.355 g (≈100%) of solid; m.p. 134–136 °C. The crude product was subjected to chromatography on silica gel. Elution with benzene/EtOAc (1:1) afforded 0.450 g (34%) of pure **4**. R_f = 0.29 (PhH/EtOAc 1:1); m.p. 150–153 °C; $[\alpha]_D^{31.6}$ = −36.0494 (*c* = 0.27 in $CHCl_3$); ^{1}H NMR (400 MHz, [D]$_6$DMSO): δ = 2.70 (m, 8H; $^{\beta}CH_2$), 3.60 (s, 12H; COOMe), 4.50 (m, 4H; $^{\alpha}CH$), 7.00, 7.45 (m, m, 16H; Ar-H), 9.00 ppm (d, *J* = 8.0 Hz, 4H; CONH); ^{13}C NMR (100 MHz, [D]$_6$DMSO): δ = 37.13 (4×$^{\beta}CH_2$), 50.62 (4×$^{\alpha}CH$), 52.06 (4×OCH_3), 127.23, 127.64, 129.03, 129.44 (16×Ar-C), 135.04, 139.18 (8×Ar-quaternary carbons), 168.96 (*C*ONH), 170.36 ppm (*C*OOMe) (the ^{13}C-NMR peak assignments were confirmed by HSQC and HMBC); IR (KBr): $\tilde{\nu}$ = 3233, 3027, 2952, 1744, 1642, 1537, 1214 cm^{-1}; MS (MALDI-TOF): *m/z* (%): 949 (40) [*M*+H^+], 972 (100) [*M*+Na^+], 988 (42) [*M*+K^+]; HRMS calcd for $C_{44}H_{44}N_4O_{12}S_4$: 948.1916; found: 948.1968; elemental analysis calcd (%) for $C_{44}H_{44}N_4O_{12}S_4$ (948.1916): C 55.68, H 4.67, N 5.90, S 13.51; found: C 55.47, H 4.60, N 5.91, S 13.42. From a variable temperature study of **4** in the range of 20–70 °C in [D]$_6$DMSO, the dδ/dT value of the NH proton is < 4.0 ppb °C^{-1}, suggesting a significant population of intramolecular hydrogen-bonded structures in solution.

IV. Reaction of 4 with $AgBF_4$: preparation of a monosilver complex: A homogeneous solution of silver (I) tetrafluoro borate (8.4 mg, 0.043 mmol) and **4** (27 mg, 0.0286 mmol) in nitromethane/toluene (1.9 mL) was prepared. 0.63 mL of this solution was closed in a tube and kept in the dark for one week. The tube was opened, covered with perforated filter paper and solvents were allowed to evaporate in the dark. The residue was washed with chloroform to give a dark solid. M.p. 150–155 °C; MS (ESI): *m/z* (%): 1055, 1057 (25) [*M*+Ag^+], 949 (17) [*M*+H^+].

V. Preparation of 5, the mirror image of 4: Diphenic anhydride **1** (0.448 g, 2.0 mmol) was reacted with D-cystine di-OMe free base (0.268 g, 1.0 mmol), as described in procedure I, to afford 0.716 g of the crude dicarboxylic acid, which was used directly in the next experiment. HOBt (0.297 g, 2.2 mmol), EDCI (0.421 g, 2.2 mmol) and DIPEA (0.69 mL, 4.0 mmol) were added sequentially to an ice-cooled and well-stirred suspension of the dicarboxylic acid described above (0.716 g, 1.0 mmol) and D-cystine di-OMe dihydrochloride (0.341 g, 1.0 mmol) in dry CH_2Cl_2 (60 mL). The reaction mixture was worked up as described in procedure III to give 0.935 g (≈98%) of solid; m.p. 134–136 °C. The crude product was subjected to chromatography on silica gel. Elution with benzene/EtOAc (1:1) afforded 0.540 g (56%) of pure **5**. R_f = 0.29 (PhH/EtOAc 1:1); m.p. 148–150 °C; $[\alpha]_D^{31.6}$ = +38.00 (*c* = 0.275 in $CHCl_3$); ^{1}H NMR (400 MHz, [D]$_6$DMSO): δ = 2.70 (m, 8H; $^{\beta}CH_2$), 3.60 (s, 12H; COOMe), 4.50 (m, 4H; $^{\alpha}CH$), 7.00, 7.45 (m, m, 16H; Ar-H), 9.00 ppm (d, *J* = 8.0 Hz, 4H; CONH); ^{13}C NMR (100 MHz, [D]$_6$DMSO): δ = 37.12 (4×$^{\beta}CH_2$), 50.62 (4×$^{\alpha}CH$), 52.06 (4×OCH_3), 127.23, 127.64, 129.03, 129.44 (16×Ar-C), 135.04, 139.18 (8×Ar-quaternary carbons), 168.96 (*C*ONH), 170.36 ppm (*C*OOMe) (the ^{13}C-NMR peak assignments were confirmed by HSQC and HMBC); IR (KBr): $\tilde{\nu}$ = 3250, 3057, 2953, 1743, 1643, 1536, 1215 cm^{-1}; MS (MALDI-TOF): *m/z* (%): 949 (40) [*M*+H^+], 972 (100) [*M*+Na^+], 988 (42) [*M*+K^+]; HRMS calcd for $C_{44}H_{44}N_4O_{12}S_4$: 948.1916; found: 948.1937.

VI. Reaction of 1 with cystamine: preparation of 6: Compound **1** (0.558 g, 2.49 mmol) and cystamine·2HCl (0.304 g, 1.349 mmol), if processed as described in procedure I, gave 0.269 g (36%) of **6**. M.p. 130–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (m, 4H; S-CH_2), 3.43 (m, 4H; N-CH_2), 7.35 (m, 16H; aromatic), 7.90 ppm (d, *J* = 6.7 Hz, 2H; CONH); IR (KBr): $\tilde{\nu}$ = 3427, 1705, 1633, 1547, 1298 cm^{-1}; MS (FAB): *m/z* (%): 601 (6) [*M*+H^+], 623 (5) [*M*+Na^+]; HRMS calcd for $C_{32}H_{28}N_2O_6S_2$: 600.1467; found: 600.1486.

VII. Reaction of 6 with diazomethane: preparation of diester 7: Compound **6** (0.300 g, 0.5 mmol) was transformed to the dimethyl ester **7**, as described in procedure II, to afford 0.320 g (≈100%) of the crude diester as a thick liquid. Chromatography on silica gel and elution with $CHCl_3$/EtOAc (70:30) gave 0.270 g (85%) of pure **7** as a thick liquid. R_f = 0.66 ($CHCl_3$/EtOAc 6:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92, 2.32 (m, m, 4H; S-CH_2), 3.12, 3.44 (m, m, 4H; N-CH_2), 3.70 (m, 6H; COOMe), 7.15 (m, 16H; aromatic), 7.78 ppm (m, 2H; amide); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 37.32, 37.92, 52.36, 127.80, 128.96, 129.48, 130.47, 130.73, 131.49, 135.83, 138.85, 168.87, 169.22 ppm; IR (KBr): $\tilde{\nu}$ = 3325, 1717, 1650, 1524, 1294 cm^{-1}; MS (FAB): *m/z* (%): 629 (58) [*M*+H^+], 651 (12) [*M*+Na^+]; HRMS calcd for $C_{34}H_{32}N_2O_6S_2$: 628.1780; found: 628.1756.

VIII. Reaction of 6 with cystamine: preparation of 8: SuOH (0.287 g, 2.5 mmol) and *N,M′*-dicyclohexylcarbodiimide (DCC) (0.516 g, 2.5 mmol) were added sequentially to an ice-cooled and stirred solution of **6** (0.750 g, 1.25 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was admixed with a dry CH_2Cl_2 solution of cystamine free base (freshly prepared from cystamine 2HCl (0.42 g; 1.86 mmol) and saturated Na_2CO_3 (4 mL) under ice-cooling, extraction with CH_2Cl_2 (3×25 mL), drying ($MgSO_4$) and evaporation. The reaction yielded 0.228 g (80%) 1.5 mmol) and was left to stir at room temperature for two days. The precipitated dicyclohexylurea (DCU) was filtered, the residue was washed with CH_2Cl_2 (2×15 mL) and the combined filtrates were washed sequentially with ice-cooled 2 N H_2SO_4 (20 mL), water (15 mL), saturated $NaHCO_3$ (15 mL), dried (Na_2SO_4) and evaporated to yield 1.123 g (≈100%) of crude product; m.p. 215–225 °C, which was subjected to chromatography on silica gel. Elution with $CHCl_3$/EtOAc (60:40) afforded 0.200 g (22%) of **8**, a substantial portion of which was crystallized from $CHCl_3$/MeOH (1:1) to provide rectangular crystals; m.p. 251–254 °C. Most of the data were determined by using these crystals: R_f = 0.55 (EtOAc); ^{1}H NMR (400 MHz, [D]$_6$DMSO): δ = 2.15, 2.35, 2.55 (m, m, m, 8H; CH_2S), 3.00, 3.10, 3.40 (m, m, m, 8H; CH_2N), 7.00, 7.40, 7.50 (m, m, m, 16H; Ar-H), 8.65, 8.70 ppm (m, m, 4H; CONH); ^{13}C NMR (100 MHz, [D]$_6$DMSO): δ = 36.52, 36.86 (4×SCH_2), 37.69, 37.80 (4×NCH_2), 127.18, 127.30, 128.99, 129.14 (16×Ar-C), 135.95, 138.94 (8×quaternary Ar-C), 168.83 ppm (4×CONH) (the ^{13}C-NMR peak assignments were confirmed by HSQC and HMBC); IR (KBr): $\tilde{\nu}$ = 3266, 1642, 1532, 1299 cm^{-1}; MS (MALDI-TOF): *m/z* (%): 740 (100) [*M*+Na^+], 756 (32) [*M*+K^+]; HRMS calcd for $C_{36}H_{36}N_4O_4S_4$: 716.1697; found: 716.1676; elemental analysis calcd (%) for $C_{36}H_{36}N_4O_4S_4$ (716.1697): C 60.31, H 5.06, N 7.81, S 17.89; found: C 60.13, H 4.93, N 7.51, S 17.78.

IX. Reaction of 8 with $AgBF_4$: preparation of a monosilver complex: The reaction of silver (I) tetrafluoro borate (10.5 mg, 0.053 mmol) and **8** (25 mg, 0.035 mmol), as described in procedure IV, afforded the complex as a white powder. M.p. 145–150 °C; MS (FAB): *m/z* (%): 823, 825 (20) [*M*+Ag^+].

X(A). Reaction of 6 with cystine di-OMe: preparation of 9: The reaction of **6** (0.300 g, 0.5 mmol) and cystine di-OMe dihydrochloride (0.170 g, 0.5 mmol), as described in procedure III, gave 0.500 g (≈100%) of foamy solid. The crude product was subjected to chromatography on silica gel. Elution with benzene/ethyl acetate (1:1) afforded 0.176 g (42%) of **9**. R_f = 0.32 (PhH/EtOAc 1:1); m.p. 130–135 °C; $[\alpha]_D^{31.6}$ = −7.3580 (*c* = 0.27 in $CHCl_3$); ^{1}H NMR (200 MHz, [D]$_6$DMSO): δ = 2.49 (m, 12H; CH_2S (8H), CH_2N (4H)), 3.60 (s, 6H; COOMe), 4.6 (m, 2H; $^{\alpha}CH$), 7.26 (m, 16H; Ar-H), 8.62 (br, 2H; CONH), 9.22 ppm, (br d, 2H; CONH); ^{13}C NMR (75.47 MHz, [D]$_6$DMSO): δ = 35.42, 37.23, 50.30, 51.71, 126.89, 128.51, 134.66, 135.36, 138.64, 168.44, 169.51, 170.09 ppm; IR (KBr): $\tilde{\nu}$ = 3243, 1742, 1640, 1539 cm^{-1}; MS (MALDI-TOF): *m/z* (%): 840 (100) [*M*+Li^+]; HRMS calcd for $C_{40}H_{40}N_4O_8S_4$: 832.1807; found: 832.1812; elemental analysis calcd (%) for $C_{40}H_{40}N_4O_8S_4$ (832.1807): C 57.67, H 4.84, N 6.73, S 15.40; found: C 57.51, H 4.97, N 6.46, S 15.53.

X(B). Reaction of 2 with cystamine: preparation of 9: The reaction of **2** (0.400 g, 0.558 mmol) and cystamine dihydrochloride (0.138 g, 0.613 mmol), as described in procedure III, gave 0.500 g (≈100%) of foamy solid. The crude product was subjected to chromatography on

silica gel. Elution with benzene/ethyl acetate (1:1) afforded 0.090 g (19%) of **9**. $R_f = 0.32$ (PhH/EtOAc 1:1); m.p. 130–135 °C; $[\alpha]_D^{31.6} = -4.5000$ ($c = 0.28$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (m, 12H; CH_2S (8H), CH_2N (4H)), 3.68 (m, 6H; COOMe), 4.80 (m, 2H; $^{\alpha}$CH), 7.50 ppm (m, 20H; Ar-H+CONH); IR (KBr): $\tilde{\nu} = 3239$, 1744, 1639, 1538 cm^{-1}; MS (ESI): *m/z* (%): 833 (45) [*M*+H$^+$].

XI. Reaction of 9 with $AgBF_4$: preparation of a monosilver complex: The reaction of silver (I) tetrafluoro borate (15.3 mg, 0.0793 mmol) and **9** (22 mg, 0.0264 mmol), as described in procedure IV, afforded the complex. M.p. 150–155 °C; MS (ESI): *m/z* (%): 939, 941 (5) [*M*+Ag$^+$].

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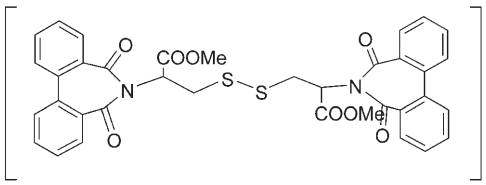
[22] Cystine, harboring generally an orthogonally disposed S–S bridge, plays a major role in the crafting of topological features in proteins. An attractive goal would be to design bihelical structures containing an S–S bridge in the hybrid peptide backbone that can assemble to nanotubes.

[23] The desired **4** has diphenic acid and cystine in the ratio of 2:2. Detailed chromatography of the reaction mixture afforded, in addition to **4** (34%), minor products, in which this ratio was 1:1 (**i**; 4.5%), 3:3 (**ii**; 3.5%) and 4:4 (**iii**; 2.3%). **i**: ($R_f = 0.38$ (PhH/EtOAc 8:2); m.p. 215–218° C; $[\alpha]_D^{27} = -266.688$ ($c = 0.16$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.00$ (m, 2H; $^{\beta}$CH$_2$), 3.45 (dd, $J = 13.3$, 3.1 Hz, 2H; $^{\beta}$CH$_2$), 3.80 (s, 6H; COOMe), 4.75 (m, 2H; $^{\alpha}$CH), 7.35 (m, 8H; Ar-H), 7.75 ppm (d, $J = 7.0$ Hz, 2H; CONH); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 41.25$, 52.45, 52.86, 126.67, 127.42, 130.59, 131.12, 132.66, 141.62, 168.15, 170.48 ppm; IR (KBr): $\tilde{\nu} = 3396$, 3341, 1744, 1733, 1666, 1644, 1523, 1219 cm^{-1}; MS (ESI): *m/z* (%): 475 (100) [*M*+H$^+$], 497 (60) [*M*+Na$^+$]; HRMS calcd for $C_{22}H_{22}N_2O_6S_2$: 474.543; found: 474.0921; elemental analysis calcd (%) for $C_{22}H_{22}N_2O_6S_2$ (474.543): C 55.68, H 4.67, N 5.90, S 13.51; found: C 55.58, H 4.94, N 5.71, S 13.15). Compound **i** afforded rigid crystals from methanol. Crystal structure was established by X-ray crystallography. In the absence of any usual interactions, the rigid structure is suggested to be maintained by weak attractive forces, disposed in all the three directions (I. L. Karle, P. Venkateshwarlu, S. Ranganathan, *Peptide Science* **2006**, *84*, 502–507). **ii**: ($R_f = 0.49$ (PhH/EtOAc 1:4); m.p. 115–118 °C; ^{1}H NMR (200 MHz, $CDCl_3$+[D]$_6$DMSO): $\delta = 2.75$ (m, 12H; $^{\beta}$CH$_2$), 3.59 (m, 18H; COOMe), 4.54 (m, 6H; $^{\alpha}$CH), 7.29 (m, 24H; Ar-H), 8.72 ppm (m, 6H; CONH); MS (MALDI-TOF): *m/z* (%): 1446 (100) [*M*+Na$^+$], 1462 (30) [*M*+K$^+$]). **iii**: ($R_f = 0.25$ (PhH/EtOAc 1:4); m.p. 115–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.93$ (br, 16H; $^{\beta}$CH$_2$), 3.69 (m, 24H; COOMe), 4.55 (br, 8H; $^{\alpha}$CH), 7.59 ppm (m, 40H; Ar-H+CONH); MS (MALDI-TOF): *m/z* (%): 1921 (17) [*M*+Na$^+$]). Efforts to secure crystals of **ii** and **iii** did not succeed.

[24] a) Initial efforts to incorporate the second cystine residue by the linking of **2** presented problems. DCC/SuOH afforded 32% of bisimide (**iv**). $R_f = 0.37$ (PhH/EtOAc 96:4); m.p. 120–125 °C; $[\alpha]_D^{31.6} = -353.630$ ($c = 0.135$ in DMSO); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 3.46 (dd, $J = 15.0$, 10.5 Hz, 2H; $^{\beta}$CH$_2$), 3.55 (dd, $J = 15.0$, 4.5 Hz, 2H; $^{\beta}$CH$_2$), 3.75 (s, 6H; COOMe), 5.82 (dd, $J = 10.5$, 4.5 Hz, 2H; $^{\alpha}$CH), 7.65 ppm (m, 16H; aromatic); ^{13}C NMR (75.47 MHz, [D]$_6$DMSO): $\delta = 38.05$, 52.42, 58.16, 128.78, 130.77, 132.71, 133.39, 133.88, 168.44, 170.25 ppm; IR (KBr): $\tilde{\nu} = 3054$, 2943, 2358, 1743, 1693, 1654, 1587, 1241 cm^{-1}; MS (FAB): *m/z* (%): 681 (32) [*M*+H$^+$], 340 (34) [(M/2)$^+$]; HRMS: calcd for $C_{36}H_{28}N_2O_8S_2$: 680.1365; found: 680.1380. Compound **iv** afforded colorless needles from chloroform/hexane. X-ray crystallography confirmed the structure assigned. The reaction afforded only 3.7% of **iv** . b) Activation of the acid with ethyl chloroformate followed by addition with cystine di-OMe gave a complex

mixture of products containing the bischloroformate ester and cystine di-OMe engaged in a single amide-bond formation. Various attempts to correct these to give desired cyclic products did not succeed.



iv

[25] Further chromatography of the reaction mixture afforded an isomeric compound (13%); R_f=0.33 ($CHCl_3$/MeOH 95:5); m.p. 135–137°C. In spite of the difference in the m.p., the ^{1}H-NMR data and mass spectrum clearly showed it was isomeric. ^{1}H NMR (200 MHz, $CDCl_3$+[D]$_6$DMSO): δ=2.30 (m, 8H; S-CH_2), 3.30 (m, 8H; N-CH_2), 7.20 (m, 16H; Ar-H), 8.57 ppm (brs, 4H; CONH); IR (KBr): $\tilde{\nu}$=3243, 2922, 1637, 1535, 1306 cm^{-1}; MS (ESI): *m*/*z* (%): 739 (100) [*M*+Na$^+$], 717 (20) [*M*+H$^+$]; HRMS: calcd for $C_{36}H_{36}N_4O_4S_4$: 716.1697; found: 716.1666. The CD spectrum showed a random profile.

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[30] Although induced chirality is possible in the crystal structure of **8**, it showed a random CD profile similar to its achiral precursor **7**.

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[33] These findings are in agreement with those reported, whereby the bihelical topology in a chiral compound becomes open if this ligand is absent (ref. [20a,b]).

[34] **2**: 2-[2-(2-2-[2-(2-carboxyphenyl)phenylcarboxamido]-2-methyloxycarbonylethyldisulfanyl-1-methyloxycarbonylethylcarbamoyl)phenyl]benzoic acid; **3**: methyl 2-[2-(1-methyloxycarbonyl-2-2-methyloxycarbonyl-2-[2-(2-methyloxycarbonylphenyl)phenylcarboxamido]-ethyldisulfanylethylcarbamoyl)phenyl] benzoate; **4**: tetramethyl 9,18,27,36-tetraoxo-9,10,11,12,15,16,17,18,27,28,29,30,33,34,35,36-hexadecahydrotetrabenzo[*g*,*i*,*u*,*w*][1,2,15,16,5,12,19,26]tetrathiatetraazacyclooctacosine-11,16,29,34-tetracarboxylate; **6**: 2-[2-(2-2-[2-(2-carboxyphenyl)phenylcarboxamido]ethyldisulfanylethylcarbamoyl)-phenyl]benzoic acid; **7**: methyl 2-[2-(2-2-[2-(2-methyloxycarbonylphenyl)phenylcarboxamido]ethyldisulfanylethylcarbamoyl)phenyl]-benzoate; **8**: 9,10,11,12,15,16,17,18,27,28,29,30,33,34,35,36-hexadecahydrotetrabenzo[*g*,*i*,*u*,*w*][1,2,15,16,5,12,19,26]tetrathiatetraazacyclooctacosine-9,18,27,36-tetraone; **9**: dimethyl 9,18,27,36-tetraoxo-9,10,11,12,15,16,17,18,27,28,29,30,33,34,35,36-hexadecahydrotetrabenzo[*g*,*i*,*u*,*w*][1,2,15,16,5,12,19,26]tetrathiatetraazacyclooctacosine-11,16-dicarboxylate.

[35] CCDC-609597 and CCDC-609598 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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