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Diphenic acid as a general conformation lock in the design of bihelical structures

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Abstract

The bihelical (figure of “∞”) topology has been examined from vantages of design, crystal structures, chirality, 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 conformation lock.

The bihelical compound **4** was obtained in two steps from diphenic anhydride **1** and cystine di-OMe. The chirality of **4** largely arises from the L-cystine. The bihelical compound **5** from D-cystine di-OMe was found to be, by X-ray crystallography, CD studies, and optical rotation 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 analog, cystamine had a “U” shaped conformation held by intramolecular hydrogen bonds.

Analyses of **4** and **5** show that the pairs of nine-membered β -turn like constructs made compact with hydrogen bonding with DMSO holds the key for the bihelical conformation. Another factor is the need for the presence of a ligand at the C α position. The absence of this as in **8** allows major flexibility in the torsional angles around this critical region, promoting flexible alternatives.

The CD of **4**, confirmed bihelical by X-ray, showed a typical negative band at ~ 210 Å attributed to the β -turn like motif and in the positive band region a peak ~ 227 Å, generally related to the twist of the biphenyl unit. The cystamine analog **8**, which showed a “U” type structure, presented a CD with no typical features.

The total energy, derived from theoretical calculations 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 has been tested with composite **9**.

Composite **9** where the anchor diphenic acid is linked to cystamine on the one hand and cystine on the other showed a CD 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

figure of “8” motifs; diphenic acid as a “conformation lock” linked by cystines; chirality; helical structures; topochemistry

Introduction

Closed bihelical modules (figure of “ ∞ ”) have emerged as a structural motif across a variety of carbon substrates of natural and synthetic origin and their uses range from complexation, crafting therapeutic systems, molecular recognition, DNA mechanisms and ion sensors. The present work should also be viewed from a general context since, it, *inter alia*, projects diphenic acid as a “conformation lock” for crafting a range of bihelical structures and analyses factors that govern their formation using X-ray crystallography, circular dichroism and molecular orbital calculations. Although a large number of bihelical systems have been reported, the basic elements related to the formation of such compounds over alternate conformations hardly have been explored. The principles that lead to the bihelical system reported here, are general and hold promise of application 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 led to a number of bihelical systems, having potential for a variety of applications. For example “bow-tie” shaped bihelical structures built on an acetylenic and 2,2'-bipyridyl scaffold has 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 “open figure of “ ∞ ” structures; an elegant example is that created from chiral 1,1'-binaphthalene units and phenanthroline whose cavity strongly binds metal ions.^[2] An interesting strategy that leads to bihelical structures, open at both ends take the advantage of strong ionic interactions.^[3]

A noteworthy illustration of generation of multi topological 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 having specific metal up-take properties. NMR experiments have shown that the bihelical systems in these cases are dynamic and move in a “conveyor belt” fashion without undergoing racemisation.^[6] Figure “ ∞ ” 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 Turcasarin a large porphyrin forms crystals in L and D configuration.^[8] Metal complexes of oxidative degradation products of heme 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 where 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 fumaropimaric 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 variations possible 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 have been made.^[16] In the domain of nucleic acids bihelical motifs have been recognized early. Several have been associated with specific functions and some has been made synthetically. An interesting case is the bihelical sequence preceding the initiation system of transcription in E.Coli.^[17]

Members of the highly cytotoxic cyclic hexapeptides from marine tunicates *Lissoclinum patella* are 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 have shown that, topologically an open frame if folded by two β -turns with compatible dihedral angle generate a bihelical structure. This is exemplified with patellamide D, which has a bihelical structure whose genesis is attributed to the pairs of β -turns with isoleucine and cyclised threonine residues at the corner of the turns. On the other hand lissoclinamide 7, which possess only a β -turn and a β -loop is planar.^[18] Didemnins 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 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. The fact that an analog that lacks the chiral group was found to have an open structure has implication with reference to the choice between two conformers.^[20]

The relationship between bihelical topology and its biological activity would need an extensive study of a variety of analogs. The present work is very much suited for 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 “conformation lock” was identified in diphenic acid, since the molecule not only possesses the necessary functional groups but also the nearly orthogonally aligned phenyl rings,^[21] that were anticipated to generate the needed 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 as suitable substrate to place the initial linker to a second unit. The reaction of cystine di-OMe (freshly generated from hydrochloride with aq.

NaHCO₃) 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 in CH₂Cl₂ afforded expected **4** as the major compound. (Scheme 1).^{[23], [24]}

The structural assignment 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 (Figure 1, Figure 2).

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, observations supported by CD spectra (*vide infra*).

The core structure is further promoted by the hydrogen bonding of the remaining NH to DMSO. The importance of this has been also brought out 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 **4** [(Scheme 1) figure 1, figure 2] with $[\alpha]_D^{31.6} = -36.0494$ ($c = 0.27$, CHCl₃) was obtained, suggested the existence of a control element. From analogy in the formation of right or left handed helices where the control is that of the chirality of the amino acids involved, it is likely that the chirality observed in **4** (Scheme 1) (Figure 1 Figure 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-analog. The reactions carried out precisely as shown in Scheme 1, afforded in 56% yield, compound **5** which exhibited spectral data identical to that of **4** but precisely opposite rotation $[\alpha]_D^{31.6} = +38.00$ ($c = 0.275$, CHCl₃).

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 below show the mirror image relationship between **4** and **5**.

A crystallographic, edge-on and perpendicular view of **5** is presented in Figure 3 and Figure 4. A comparison of this with that of Figure 1 and Figure 2 clearly brings out the mirror image relationship. The composite edge on view of the antipodes presented in Figure 5 is striking.

The preparation and characterization of the bihelical structures **4** and **5** has shown that diphenic acid can be used as a general “conformation 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 since at least in one case, a bihelical system having chiral centres was transformed to an open one 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 CHCl₃: MeOH:: 1:1. A crystallographic analysis showed that **8** had a rather “U” shaped backbone structure, held by three intramolecular hydrogen bonds.

The crystallographic representation of edge on and perpendicular views of **8** are presented in Figure 6 and Figure 7. Interestingly crystals of **8** obtained from MeOH as well as DMSO were all identical.^[25] There was no solvent cocrystallized with **8**. A comparison of the torsional angles in **4** and **8** in Table 1 shows that the regions of the 9-membered β -turns are quite similar, although the O1a...N2a distance has increased to 3.67 Å in **8**, consequently, no longer considered as an NH...O=C hydrogen bond (Figure 6). However, large differences in torsional angles, greater than 100°, occur at or near C2a, C2b, C17a and C17b, the atoms from which the side-chains in **4** were removed, which accounts for the disparate shapes of the macromolecular rings in **4** and **8**.

Having shown that the absence of chiral groups in the linker favour a non-bihelical structure, it was logical to assess the preference with a single chiral linker. Such a system was prepared by linking the “conformation lock” with cystine on the one hand and cystamine on the other. The cystine-cystamine composite **9** was reached by two complementary routes (Scheme 3).

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

Compounds **4**, **8** and **9** heavily endowed with amide and sulfur centers are attractive for the formation of silver complexes.^[26a] Such complexes have potential in ¹¹¹Ag based radioimmuno therapy. Compounds **4**, **8** and **9** readily formed 1:1 complexes with AgBF₄. Although crystals of these could not be secured their structure is supported by ESI-MS. Based on similar studies^[26b] a minimal tetrahedral co-ordination of the Ag⁺ with the four sulfur atoms appears possible.

Circular dichroism studies

CD studies in solution carried out 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 TFE (Figure 9), MeOH and CH₃CN 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 (CH₃CN) and a positive CD band ~230 nm. While the negative CD band in TFE is reminiscent of a β -hairpin conformation,^[27] the positions of negative CD bands in MeOH/CH₃CN are similar to spectra of distorted β -sheet.^[28] A change in conformation from TFE to MeOH/CH₃CN 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 ~ 230nm in the CD reflects the twist of the biphenyl core.^[29]

The CD of **5** (Figure 10) bears a nearly precise mirror image relationship to its antipode **4**, a fact that has been effectively illustrated in the composite CD of **4** and **5** (Figure 11).

The suggested 9-membered β -turn motif finds support in the CD 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 of conformation (Figure 6, Figure 7) exhibited a random CD profile, precisely similar to that of **7**.^[30]

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

The CD 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.

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. When this unit becomes part of **9**, the CD shows considerable enhancement of this value possibly arising from placement in a restrained position.

Molecular modeling studies

Quantum mechanical calculations have been 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 semi-empirical 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 where 2 molecules of DMSO are explicitly placed in orientation obtained from the experimental co-ordinates for **4** showed a preference for bihelical structures (Table 2) for **4** and **9**.

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

Conclusion

The present work has shown, that “diphenic acid” can be used as a “conformation 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** (Figure 1 and Figure 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. A detailed analysis in the present work of the bihelical conformation secured by **4** and that of

a “U” shaped one with cystamine lacking the chiral groups is possibly related to this factor. The X-ray crystallography of **4** and **8** shows a number of common features. Besides, as could be seen, torsional angles that lead to the synthesis of these (Table 1), are quite similar excepting, notably, where the chiral ester is present. In the preference for bihelical structures, substituents at the C α -position appear to play a major role. The presence of such bulky substituents give rigidity to the β -turns involved and in the case of **4** leads to the bihelical structure. In the case of **8**, where such substituents are absent, much more torsional freedom is available for the C α atom, which now resembles that in glycine. This notion is supported by the fact that when a β -turn nearly identical to **4** is inscribed in **8** (Figure 8, left), the rest of the molecule exhibits greater conformational flexibility, particularly around erstwhile ligand locations (-COOMe) as seen by wide divergence in the dihedral 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 (*vide supra*), where highly substituted members also invariably lead to bihelical structures.^[18]

The present work has made a novel effort to link structural profiles arrived at by X-ray crystallography and circular dichroism and use molecular orbital data derived from X-ray structures to compute total energies and in presence of solvent molecules.

A fallout from the present work is 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 “conformation lock” can be assessed by their CD profile as in the case of **9**.

The present work has brought out cystine/cystamine not only as a linker element but also shown that the presence of this unit can lead to complexes with silver and possibly other metal ions.

Experimental Section

General

Melting points were recorded on Fisher-Johns apparatus and are uncorrected. Optical rotations were measured with an automatic JASCO P-1020 polarimeter. Concentrations are given in grams/100 mL. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer as KBr pellets and prominent peaks are expressed in cm⁻¹. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini 200, Bruker Avance 300, Inova 400 and 500 MHz spectrometers. The chemical shifts are expressed in δ (ppm) with TMS at 0.0000 as internal reference. FABMS was measured using VG AUTOSPEC mass spectrometer, ESI-MS was obtained on a micromass QUATTRO-LC instrument, MALDI-TOF spectra on KRATOS ANALYTICAL instrument and HRMS obtained on a QSTAR XL instrument. Elemental data were obtained using automatic analyzers. The CD spectra were recorded on JASCO J-810 spectrometer, mostly in TFE at a uniform concentration of 200 μ mol/Litre. TLCs were prepared on silicagel coated plates made in the laboratory. ACD nomenclature for all compounds is listed.^[34]

I. The 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 CH₂Cl₂ (20 mL) was added in drops cystine di-OMe free base in dry CH₂Cl₂ (50 mL) [freshly prepared from cystine di-OMe.2HCl (1.5 g; 4.4 mmol) and sat. NaHCO₃ (8 mL) under ice-cooling, extraction with CH₂Cl₂ (3 $\times$ 25 mL), drying (Na₂SO₄) and evaporation. The reaction yielded 1.0 g, 3.73 mmol]. The reaction mixture was left stirred at rt 12h, filtered, the filtrate washed sequentially with ice-cold 2N H₂SO₄ (2 $\times$ 5 mL), brine (10 mL), dried (Na₂SO₄) and evaporated to yield 2.18 g (82 %) of crude **2** as a foamy solid which was triturated with satd. NaHCO₃ (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); $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta=2.62$ (m, 2H, βCH_2), 3.02 (m, 2H, βCH_2), 3.45, 3.58, 3.65 (s, s, s, 6H, COOMe), 4.75 (m, 2H, αCH), 6.25 (v.br, 2H, COOH), 7.37 (m, 16H, aromatic), 7.95 (m, 2H, amide); IR (KBr): $\nu=3260$ (br), 3021 (br), 1727 (m), 1549 (m), 1244 (m) cm^{-1} ; MS (FAB): m/z (%): 739 (18) $[M + \text{Na}^+]$; HRMS calcd for: $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_{10}\text{S}_2$: 716.1576; found: 716.1588.

II. The reaction of **2** with diazomethane: preparation of diester **3**

To a solution of di acid **2** (0.650 g, 0.9 mmol) in methanol (5mL) was added ethereal diazomethane (~0.113 g, 2.7 mmol, 11 mL), generated from N-methyl-N-nitroso toluene p-sulphonamide. Evaporation of solvents afforded 0.680 g (~100 %) of the crude diester as a thick liquid; The crude product was chromatographed on silica gel. Elution with CHCl_3 : EtOAc (85: 15) afforded 0.580 g (86%) of pure **3** as thick oil. $R_f=0.66$ ($\text{CHCl}_3/\text{EtOAc}$ 6:4); $[\alpha]_D^{31.6} = +35.1698$ ($c=0.265$ in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta=2.50$ (m, 2H, βCH_2), 2.95 (m, 2H, βCH_2), 3.64 (m, 12H, COOMe), 4.60 (br, 2H, αCH), 7.35 (m, 16H, Ar-H), 7.85 (m, 2H, CONH); $^{13}\text{C NMR}$ (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; IR (KBr): $\nu=3418$, 2922, 1720, 1662, 1516, 1288, 760 cm^{-1} ; MS (FAB): m/z (%): 745 (18) $[M + \text{H}^+]$, 767 (6) $[M + \text{Na}^+]$; HRMS calcd for: $\text{C}_{38}\text{H}_{36}\text{N}_2\text{O}_{10}\text{S}_2$: 744.1889; found: 744.1872.

III. The reaction of **3** with cystine di-OMe: preparation of **4**

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) was added sequentially, HOBT (0.414 g, 3.07 mmol), EDCI (0.589 g, 3.07 mmol) and DIPEA (0.534 mL, 3.07 mmol). The reaction mixture was left stirred overnight and under ice cooling quenched with satd. NH_4Cl (20 mL), admixed with additional CH_2Cl_2 (40 mL). The organic layer washed with 1N 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 chromatographed 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); $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$): $\delta=2.70$ (m, 8H, βCH_2), 3.60 (s, 12H, COOMe), 4.50 (m, 4H, αCH), 7.00, 7.45 (m, m, 16H, Ar-H), 9.00 (d, $J=8.0$ Hz, 4H, CONH); $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO}-d_6$): $\delta=37.13$ (4 x βCH_2), 50.62 (4 x αCH), 52.06 (4 x OCH_3), 127.23, 127.64, 129.03, 129.44 (16 x Ar-C), 135.04, 139.18 (8 x Ar-quaternary carbons), 168.96 (CONH), 170.36 (COOMe); The $^{13}\text{C NMR}$ peak assignments have been confirmed by HSQC and HMBC; IR (KBr): $\nu=3233$, 3027, 2952, 1744, 1642, 1537, 1214 cm^{-1} ; MS (MALDI-TOF): m/z (%): 949 (40) $[M + \text{H}^+]$, 972 (100) $[M + \text{Na}^+]$, 988 (42) $[M + \text{K}^+]$; HRMS calcd for: $\text{C}_{44}\text{H}_{44}\text{N}_4\text{O}_{12}\text{S}_4$: 948.1916; found: 948.1968; elemental analysis calcd (%) for: $\text{C}_{44}\text{H}_{44}\text{N}_4\text{O}_{12}\text{S}_4$ (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 variable temperature study of **4** in the range of 20–70 °C in $\text{DMSO}-d_6$, the $d\delta/dT$ value of NH proton is < 4.0 ppb/°C, suggesting significant population of intramolecular hydrogen bonded structures in solution.

IV. The reaction of **4** with AgBF_4 : preparation of mono silver complex

In a tube 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: 0.63 mL was closed and kept in the dark for 1 week. The tube was opened, covered with perforated filter paper and solvents allowed to evaporate in the dark, washed with chloroform to give dark solid; m.p. 150–155 °C; MS (ESI): m/z (%): 1055, 1057 (25) $[M + \text{Ag}^+]$, 949 (17) $[M + \text{H}^+]$.

V. The 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) precisely as described in expt. I to afford 0.716 g of the crude dicarboxylic acid, which was used directly in the next experiment. 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) was added sequentially, HOBT (0.297 g, 2.2 mmol), EDCI (0.421 g, 2.2 mmol) and DIPEA (0.69 mL, 4.0 mmol). The reaction mixture was worked up precisely as described in expt. III, gave 0.935 g (~98 %) of solid; m.p. 134–136 °C; The crude product was chromatographed 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); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta=2.70$ (m, 8H, βCH_2), 3.60 (s, 12H, COOMe), 4.50 (m, 4H, ^aCH), 7.00, 7.45 (m, m, 16H, Ar-H), 9.00 (d, $J=8.0$ Hz, 4H, CONH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta=37.12$ (4 x βCH_2), 50.62 (4 x ^aCH), 52.06 (4 x OCH_3), 127.23, 127.64, 129.03, 129.44 (16 x Ar-C), 135.04, 139.18 (8 x Ar-quaternary carbons), 168.96 (CONH), 170.36 (COOMe); The ^{13}C NMR peak assignments have been confirmed by HSQC and HMBC; IR (KBr): $\nu=3250, 3057, 2953, 1743, 1643, 1536, 1215\text{ cm}^{-1}$; MS (MALDI-TOF): m/z (%): 949 (40) [$M + \text{H}^+$], 972 (100) [$M + \text{Na}^+$], 988 (42) [$M + \text{K}^+$]; HRMS calcd for: $\text{C}_{44}\text{H}_{44}\text{N}_4\text{O}_{12}\text{S}_4$: 948.1916; found: 948.1937.

VI. The 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) when processed precisely as described in expt. I, gave 0.269 g (36%) of **6**; m.p. 130–135 °C; ^1H NMR (300 MHz, CDCl_3): $\delta=2.38$ (m, 4H, S- CH_2), 3.43 (m, 4H, N- CH_2), 7.35 (m, 16H, aromatic), 7.90 (d, $J=6.7$ Hz, 2H, CONH); IR (KBr): $\nu=3427, 1705, 1633, 1547, 1298\text{ cm}^{-1}$; MS (FAB): m/z (%): 601 (6) [$M + \text{H}^+$], 623 (5) [$M + \text{Na}^+$]; HRMS calcd for: $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_6\text{S}_2$: 600.1467; found: 600.1486.

VII. The reaction of 6 with diazomethane: preparation of diester 7

Compound **6** (0.300 g, 0.5 mmol) was transformed to the dimethyl ester **7**, precisely as described in expt. 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; $R_f=0.66$ ($\text{CHCl}_3/\text{EtOAc}$ 6:4); ^1H NMR (300 MHz, CDCl_3): $\delta=1.92, 2.32$ (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 (m, 2H, amide); ^{13}C NMR (75.47 MHz, CDCl_3): $\delta=37.32, 37.92, 52.36, 127.80, 128.96, 129.48, 130.47, 130.73, 131.49, 135.83, 138.85, 168.87, 169.22$; IR (KBr): $\nu=3325, 1717, 1650, 1524, 1294\text{ cm}^{-1}$; MS (FAB): m/z (%): 629 (58) [$M + \text{H}^+$], 651 (12) [$M + \text{Na}^+$]; HRMS calcd for: $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_6\text{S}_2$: 628.1780; found: 628.1756.

VIII. The reaction of 6 with cystamine: preparation of 8

To an ice-cooled and stirred solution of **6** (0.750 g, 1.25 mmol) in dry CH_2Cl_2 (30 mL), was added sequentially SuOH (0.287 g, 2.5 mmol) and DCC (0.516 g, 2.5 mmol) and the reaction mixture admixed with a dry CH_2Cl_2 solution of cystamine free base [freshly prepared from cystamine 2HCl (0.42 g; 1.86 mmol) and satd. Na_2CO_3 (4 mL) under ice cooling, extraction with CH_2Cl_2 (3 x 25 mL), drying (MgSO_4) and evaporation. The reaction yielded 0.228 g (80%) 1.5 mmol] and left stirred at rt for 2d. The precipitated DCU was filtered, the residue washed with CH_2Cl_2 (2 x 15 mL) and the combined filtrates washed sequentially with ice-cooled 2N H_2SO_4 (20 mL), water (15 mL), sat. NaHCO_3 (15 mL), dried (Na_2SO_4) and evaporated to yield 1.123 g (~100 %); m.p. 215–225 °C of crude product, which was chromatographed 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 with these crystals:

$R_f=0.55$ (EtOAc); ^1H NMR (400 MHz, DMSO- d_6): $\delta=2.15, 2.35, 2.55$ (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 (m, m, 4H, CONH); ^{13}C NMR (100 MHz, DMSO- d_6): $\delta=36.52, 36.86$ (4 x SCH_2), 37.69, 37.80 (4 x NCH_2), 127.18, 127.30, 128.99, 129.14 (16 x Ar-C), 135.95, 138.94 (8 x quaternary Ar-C), 168.83 (4 x CONH); IR (KBr): $\nu=3266, 1642, 1532, 1299\text{ cm}^{-1}$; MS (MALDI-TOF): m/z (%): 740 (100) [$M + \text{Na}^+$], 756 (32) [$M + \text{K}^+$]; HRMS calcd for: $\text{C}_{36}\text{H}_{36}\text{N}_4\text{O}_4\text{S}_4$: 716.1697; found: 716.1676; elemental analysis calcd (%) for: $\text{C}_{36}\text{H}_{36}\text{N}_4\text{O}_4\text{S}_4$ (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. The reaction of 8 with AgBF_4 : preparation of mono silver complex

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

X

A. The reaction of 6 with cystine di-OMe: preparation of 9—The reaction of **6** (0.300 g, 0.5 mmol) and cystine di-OMe di hydrochloride (0.170 g, 0.5 mmol) precisely as described in expt. III, gave 0.500 g (~ 100 %) of foamy solid. The crude product was chromatographed 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); ^1H NMR (200 MHz, DMSO- d_6): $\delta=2.49$ (m, 12H, CH_2S (8H), CH_2N (4H)), 3.60 (s, 6H, COOMe), 4.6 (m, 2H, ^aCH), 7.26 (m, 16H, Ar-H), 8.62 (br, 2H, CONH), 9.22 (bd, 2H, CONH); ^{13}C NMR (75.47 MHz, DMSO- d_6): $\delta=35.42, 37.23, 50.30, 51.71, 126.89, 128.51, 134.66, 135.36, 138.64, 168.44, 169.51, 170.09$; IR (KBr): $\nu=3243, 1742, 1640, 1539\text{ cm}^{-1}$; MS (MALDI-TOF): m/z (%): 840 (100) [$M+\text{Li}^+$]; HRMS calcd for: $\text{C}_{40}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_4$: 832.1807; found: 832.1812; elemental analysis calcd (%) for: $\text{C}_{40}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_4$ (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.

B. The 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) precisely as described in expt. III, gave 0.500 g (~ 100 %) of foamy solid. The crude product was chromatographed 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); ^1H 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, ^aCH), 7.50 (m, 20H, Ar-H+ CONH); IR (KBr): $\nu=3239, 1744, 1639, 1538\text{ cm}^{-1}$; MS (ESI): m/z (%): 833 (45) [$M + \text{H}^+$].

XI. The reaction of 9 with AgBF_4 : preparation of mono silver complex

The reaction of silver (I) tetrafluoro borate (15.3 mg, 0.0793 mmol) and **9** (22 mg, 0.0264 mmol) precisely as described in expt. IV, afforded the complex; m.p. 150–155 °C; MS (ESI): m/z (%): 939, 941 (5) [$M + \text{Ag}^+$].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 nano tubes.
23. The desired **4** has the diphenic acid and cystine in the ratio of 2:2. Detailed chromatography of the reaction mixture afforded in addition to **4** (34%), as minor products, where 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); $^1\text{H NMR}$ (200 MHz, CDCl_3): $\delta = 3.00$ (m, 2H, $^{\beta}\text{CH}_2$), 3.45 (dd, $J = 13.3$, 3.1 Hz, 2H, $^{\beta}\text{CH}_2$), 3.80 (s, 6H, COOMe), 4.75 (m, 2H, $^{\alpha}\text{CH}$), 7.35 (m, 8H, Ar-H), 7.75 (d, $J = 7.0$ Hz, 2H, CONH); $^{13}\text{C NMR}$ (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; IR (KBr): ν^- = 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 whose 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, *Biopolymers(Peptide Science)* **2006**, 84, 502).**ii**. [R_f = 0.49 (PhH/EtOAc 1:4); m.p. 115–118 °C; 1H NMR (200 MHz, $CDCl_3$ + DMSO- d_6): δ = 2.75 (m, 12H, βCH_2), 3.59 (m, 18H, COOMe), 4.54 (m, 6H, αCH), 7.29 (m, 24H, Ar-H), 8.72 (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; 1H NMR (300 MHz, $CDCl_3$): δ = 2.93 (br, 16H, βCH_2), 3.69 (m, 24H, COOMe), 4.55 (br, 8H, αCH), 7.59 (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 bis imide (**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); 1H NMR (300 MHz, $CDCl_3$): δ = 3.46 (dd, J = 15.0, 10.5 Hz, 2H, βCH_2), 3.55 (dd, J = 15.0, 4.5 Hz, 2H, βCH_2), 3.75 (s, 6H, COOMe), 5.82 (dd, J = 10.5, 4.5 Hz, 2H, αCH), 7.65 (m, 16H, aromatic); ^{13}C NMR (75.47 MHz, DMSO- d_6): δ = 38.05, 52.42, 58.16, 128.78, 130.77, 132.71, 133.39, 133.88, 168.44, 170.25; IR (KBr): ν^- = 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 **4.b**) Activation of the acid with ethyl chloroformate followed by addition with cystine di-OMe gave a complex mixture of products containing the bis chloroformate ester and cystine di-OMe engaged in a single amide bond formation. Various attempts to correct these to give desired cyclic product did not succeed.

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 1H -nmr data and mass spectrum clearly showed it was isomeric. 1H NMR (200 MHz, $CDCl_3$ + DMSO- d_6): δ = 2.30 (m, 8H, S- CH_2), 3.30 (m, 8H, N- CH_2), 7.20 (m, 16H, Ar-H), 8.57 (br s, 4H, CONH); IR (KBr): ν^- = 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 showed a random profile.

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34. **2**: 2-[2-(2-[2-(2-carboxyphenyl)phenylcarboxamido]-2-methyloxycarbonyl)ethyl disulfanyl-1-methyloxycarbonyl)ethylcarbamoyl]phenyl]benzoic acid; **3**: methyl 2-[2-(1-methyloxycarbonyl-2-2-methyloxycarbonyl-2-[2-(2-methoxy carbonyl)phenyl]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-carboxyphenyl)phenylcarboxamido]ethyldisulfanylethylcarbamoyl) phenyl]benzoic acid; **7**: methyl 2-[2-(2-[2-(2-methyloxycarbonyl)phenyl] 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.

An "edge on" crystallographic view of **4**. The molecule lies on a true crystallographic 2-fold rotation axis. Hydrogen bonds are formed between, DMSO molecules and N1a and N1aa, where N1a...O1s = 2.82 Å and H...O1s = 2.00 Å.

Figure 2.

A perpendicular view of **4**. Nine-membered β -turns are formed with $N2a \cdots O1a = 2.86 \text{ \AA}$ and $H \cdots O1a = 1.99 \text{ \AA}$.

Figure 3.
A crystallographic edge on view of **5** (the mirror image of **4**).

Figure 4.
A perpendicular view of 5.

Figure 5.

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

Figure 6. A crystallographic “edge on” view of **8**. Intramolecular hydrogen bonds have the values: N2a...O1b = 3.197 Å, H...O1b = 2.43 Å, N2b...O1b = 2.973 Å, H...O1b = 2.10 Å; N2b...O1a = 3.298 Å, H...O1a = 2.76 Å.

Figure 7.
A perpendicular view of **8**.

Figure 8.
Illustration of the influence of the C α -ligand on torsional angles.

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

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

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

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

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

Scheme 1.

Scheme 2.

Scheme 3.

Table 1Comparison of Torsional Angles in Macrocycles **4** and **8** (deg.)

Angle	4	8	lg $\Delta^{[a]}$
S2bS1aC1aC2a	-68	+81	*
S1aC1aC2aN1a	-66	+67	*
C1aC2aN1aC3a	142	-113	*
C2aN1aC3aC4a	-174	-171	
N1aC3aC4aC9a	-137	-143	
C3aC4aC9aC10a	6	12	
C4aC9aC10aC15a	-103	-130	
C9aC10aC15aC16a	10	11	
C10aC15aC16aN2a	43	63	
C15aC16aN2aC17a	-177	-175	
C16aN2aC17aC18a	138	91	
N2aC17aC18aS2a	70	67	
C17aC18aS2aS1b	177	81	*
C18aS2aS1bC1b	-77	-88	
S2aS1bC1bC2B	-68	-58	
S1bC1bC2bN1b	-66	175	*
C1bC2bN1bC3b	142	-86	*
C2bN1bC3bC4b	-174	-175	
N1bC3bC4bC9b	-137	-153	
C3bC4bC9bC10b	6	11	
C4bC9bC10bC15b	-103	-111	
C9bC10bC15bC16b	10	9	
C10bC15bC16bN2b	43	55	
C15bC16bN2bC17b	-177	-173	
C16bN2bC17bC18b	138	128	
N2bC17bC18bS2b	70	179	*
C17bC18bS2bS1a	177	-60	*
C18bS2bS1aC1a	-77	-94	

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

Table 2

The total energies (in Hartrees) for the six conformations in vacuum and DMSO at the AM1 level of theory

Molecule	In vacuum	With 2 molecules of DMSO ^[a]
	E	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 from the X-ray structure of **4**

Table 3

Crystal Data and Structure Refinement

Compound	4	8
Identification CCDC	609597	609598
Empirical formula ^[a]	C ₄₄ H ₄₄ N ₄ O ₁₂ S ₄ ·3C ₂ H ₆ OS	C ₃₆ H ₃₆ N ₄ O ₄ S ₄
Formula weight	1183.46	716.93
Temperature, °C	203	293
Wavelength, Å	Mo, 0.71073	Cu, 1.54178
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
Volume, Å ³ , Z	2784.6(20), 2	3527.3(17), 4
Density (calc.) Mg/m ³	1.411	1.350
Absorption coeff., mm ⁻¹	0.352	
F(000)	1244	1504
Crystal size	0.50 × 0.25 × 0.10	~0.30 × 0.30 × 0.30
Limiting indices	-28 ≤ h ≤ 28 -10 ≤ k ≤ 11 -20 ≤ l ≤ 20	-12 ≤ h ≤ 1 -25 ≤ k ≤ 1 -18 ≤ l ≤ 18
Reflections collected	13931	7829
Independent refls.	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 > σ(I)]	0.0579, 0.1413	0.0657, 0.2002
R indices (all data)	0.0741, 0.1666	
Extinction coeff.	none	0.00117
Large diff. pk. & hole, e/Å ³	1.25, -0.75	0.58, -0.45

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