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Triply bridged (1,3,5) cyclophanes from cystine and lanthionine linkers—a comparison

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ABSTRACT

The condensation of benzene 1,3,5-tricarbonylchloride with cystine-di-Me [H_2N–CH(COOMe)–CH_2–S–S–CH_2–CH(COOMe)–NH_2] yielded triply bridged (1,3,5) cyclophane **1**, which was shown by detailed spectral studies and molecular orbital calculations to have a D_3 symmetry with conformationally identical linkers and a spherical topology. In sharp contrast, the (1,3,5) cyclophane **2** from the rarely studied lanthionine di-Me [H_2N–CH(COOMe)–CH_2–S–CH_2–CH(COOMe)–NH_2], showed only a equatorial twofold symmetry. This work highlights the special properties of the –S–S– bridge in cystine, which makes it an exceptional synthon in nature and organic synthesis.

1. Introduction

Amongst the cyclophanes, triply bridged (1,3,5) cyclophanes (2_3 cyclophanes) have attracted more attention, possibly because they represent optimum potential for further non-covalent assembly. A number of strategies are available for the synthesis of 2_3 cyclophanes.[1] In the present work, the synthesis has been achieved by linking of the core unit, benzene 1,3,5-tricarbonylchloride to either cystine or lanthionine. Amongst the strategies for 2_3 cyclophanes the linker method is sparingly used.[2–5]

For quite some time, our group has highlighted the versatility of the naturally occurring L-cystine, in the crafting of a variety of structures. Cystine endowed with H_2N–CH(COOH)– groups at the terminals and having a mid, nearly orthogonally disposed disulfide bridge, has proved itself an exceptionally versatile molecule in structural chemistry.[6]

Other citations include the use of cystine in studies related to protein de novo design,[7] in the synthesis of collagen triple helix models[8] and in the synthesis of peptide dendrimers.[9] Interestingly as a variant to the normal DNA synthesis the possibility for the formation of the disulfide end groups has been realised.[10]

The wealth of chemistry available relating to cystine—arising from genetically coded cysteine—in organic and biological domains, sharply contrasts to that of non-ribosomally synthesized lanthionine, originally isolated from wool,[11] where the –S–S– bridge in the former is replaced by a single '–S–'. Whilst the biochemistry of lanthionine is impressive, its organic chemistry is sparsely studied. Lanthionine figures prominently in 'lantibiotics' the most important being 'nisin', the universal food preservative. The chemistry and biochemistry of lanthionine have been recently reviewed.[12]

The rigid –CH_2–S–S–CH_2– module present in cystine plays an important role in maintaining the specific molecular conformations of proteins. The universal adaptability of cystine is likely to arise from this module having a dihedral angle close to 90°,[13] that imparts a screw sense making it chiral.[14] The unit is rigid because of considerable π-type interaction of the filled 3p-orbital of S with the lowest vacant σ* orbital of the neighboring S, which, in turn, makes the proximate methylenes more acidic. The unit is also part of chromophore involved in d–d transition.[14] None of these features are present in lanthionine, which can be considered having a thio ether profile that can be expected to show considerable flexibility. The genesis of the present work is to design an appropriate system that can explain in terms of variation of structural features arising from replacement of cystine with lanthionine within the same structural framework. To the best of our knowledge such a comparison has not been reported. Of various options, we selected the

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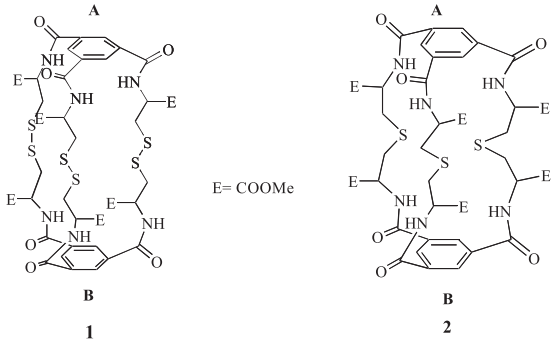
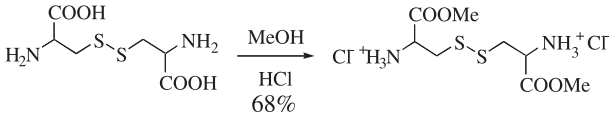
2_3 cyclophanes, **1** and **2** prepared from the linking of benzene 1,3,5-tricarbonylchloride with, respectively, cystine-dimethyl ester dihydrochloride (**3**) and lanthionine dimethyl ester dihydrochloride (**4**).



In principle, compounds **1** and **2** could exhibit a threefold symmetry, which in the case of **1** would have a spherical profile and harbor, in the equatorial plane, six sulfur centers.

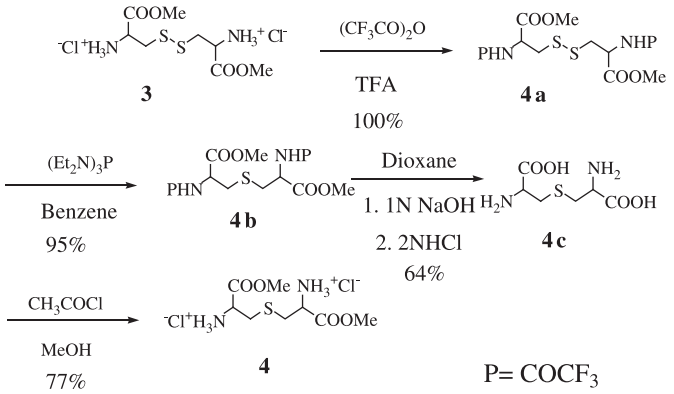
2. Results and discussion

Cystine-di-Me·2HCl (**3**) was prepared in 68% yields by the reaction of MeOH–HCl on L-cystine (Scheme 1).



Scheme 1.

The cystine linker **3** was transformed to the lanthionine linker [(lanthionine di-Me·2HCl), (**4**)], in an overall yield of ~50%, involving as the key step, the facile removal of a single sulfur as shown in Scheme 2.[15]



Scheme 2.

A ^{1}H NMR comparison of the linkers **3** and **4**, the latter lacking a single sulfur, shows that the β-methylene protons are up field shifted from 3.38 to 3.14 ppm. Similarly the $C^{\alpha}H$ protons are shifted from 4.60 to 4.38 ppm.

2.1. Triply bridged (1,3,5) cyclophane from cystine (1)

The reaction of the cystine linker **3** with benzene 1,3,5-tricarbonylchloride in presence of NEt_3 and excess methylene chloride led to the gradual precipitation of the desired **1**, in quantitative yields, as a white powder, mp 220–265 °C. Surprisingly, the compound was quite insoluble in most organic solvents except DMSO in which it exhibited limited solubility. After several efforts at purification of the crude product, Soxhlet extraction proved satisfactory. The crude product was charged on to a Soxhlet thimble and extracted with a range of organic solvents (CCl_4, $CHCl_3$, MeOH). This procedure enabled the removal of extraneous impurities to afford 87% of pure **1** as a white granular powder, mp 258–262 °C (dec). The compound gave acceptable elemental (C, H, N, S) analysis and spectra (IR, ^{1}H NMR, ^{13}C NMR, MALDI-TOF MS, and HRMS) in complete agreement with the assigned structure. Several attempts to secure crystals of the compound were not successful.

The 500 MHz ^{1}H NMR of **1** taken in DMSO-d_6 showed very clearly a threefold axial symmetry as well as a twofold equatorial symmetry. Thus, all the three linkers were spatially equivalent from vantage of NMR. The $C^{\beta}H_2$ protons appeared as two sets of doublet of doublets (dd), the ester as a single peak, the $C^{\alpha}H$ protons as a clean quartet, the aromatic protons as a sharp singlet, and the amide protons as a doublet. The TOCSY spectrum of **1** (Fig. 1) enabled the assignment of peak positions and coupling constants were obtained from ^{1}H NMR (Table 1).

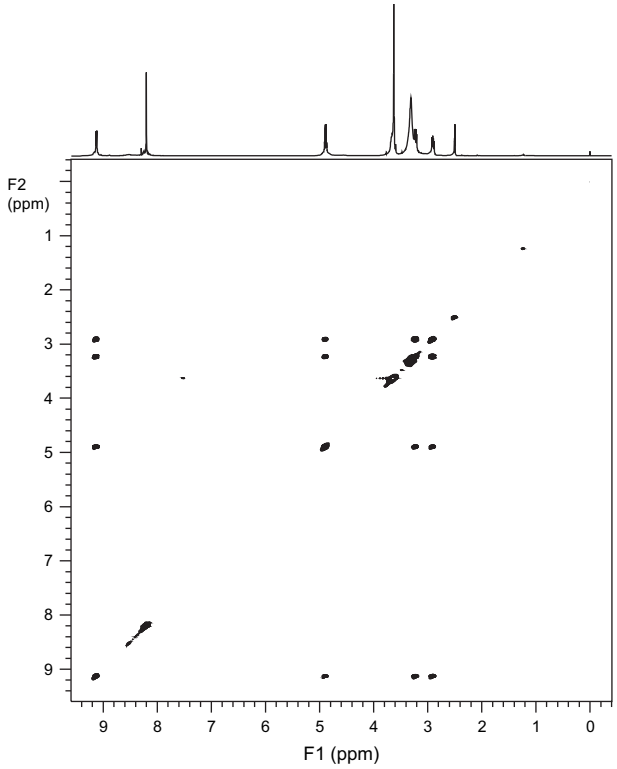


Figure 1. TOCSY spectrum of **1**.

Table 1
^{1}H NMR of **1** (500 MHz, DMSO-d_6): δ

$C^{\beta}H$, 2.89, dd, 6H, J=7.4, 13.6 Hz
$C^{\beta}H'$, 3.23, dd, 6H, J=7.4, 13.6 Hz
Ester, 3.62, s, 18H
$C^{\alpha}H$, 4.90, q, 6H, J=7.4 Hz
Ar–H, 8.21, s, 6H
NH, 9.16, d, 6H, J=7.4 Hz

The ROESY spectrum (Fig. 2) clearly brought out strong connectivity between aromatic protons and amide protons and a weaker one between the aromatic protons and the $C^{\alpha}H$ as well as $C^{\beta}H$.

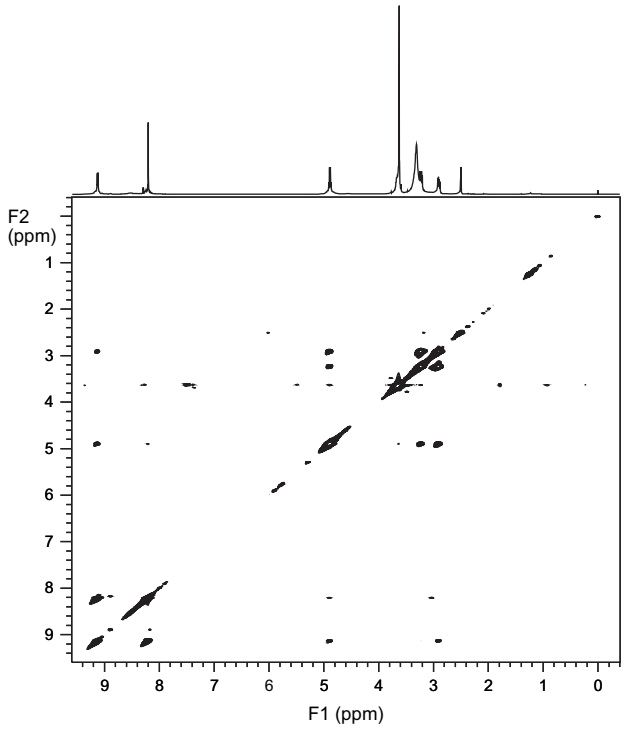


Figure 2. ROESY spectrum of **1**.

2.2. Triply bridged (1,3,5) cyclophane from lanthionine (2)

The reaction of 3 equiv of the linker **4** with 2 equiv of benzene 1,3,5-tricarbonylchloride and slight excess of NEt_3 in CH_2Cl_2 resulted in a clear solution in contrast to that with linker **3**. Work up followed by chromatography afforded 16% (TLC) of pure triply bridged (1,3,5) cyclophane **2**, mp 205–210 °C. The structural assignment for **2** is fully supported by ^1H and ^{13}C NMR and HRMS data. Two different batches of **2** have been prepared recently and they showed similar chromatographic behavior, TLC, and spectral profile. Thus compound **2**, like compound **1** is a single compound.

The TOCSY spectrum of **2** presented in Figure 3 exhibited normal through bond correlations, which enabled the assignment of peak positions and coupling constants. For many of the protons, these were obtained from resolution enhanced ^1H NMR spectrum (Table 2). The result of the ROESY spectrum, presented in Figure 4 afforded spatial connectivity that exists between several protons.

The strong NOE connectivities between amide protons and aromatic protons facilitated the identification of the three linkers. The NOE correlation between $C^{\alpha}H$ and aromatic protons further confirmed the above observation. Figure 5 illustrates the individual NMR assignment and spatial connectivity found in compound **2**, in which the aromatic protons labeled a, b, and c and the three chains are distinguished by labeling the amide protons as 1, 2, and 3. As Table 2 shows, the peak positions of NH in all the three chains are up field shifted compared to **1**. This may be because the amide protons are further shielded by the π-system as compared to **1**. For similar reason, the $C^{\alpha}H$ protons in the three chains of **2** appear within a small range are also up field shifted compared to **1**. Weak spatial interaction is also seen between $C^{\beta}H$ and amide protons of **2**.

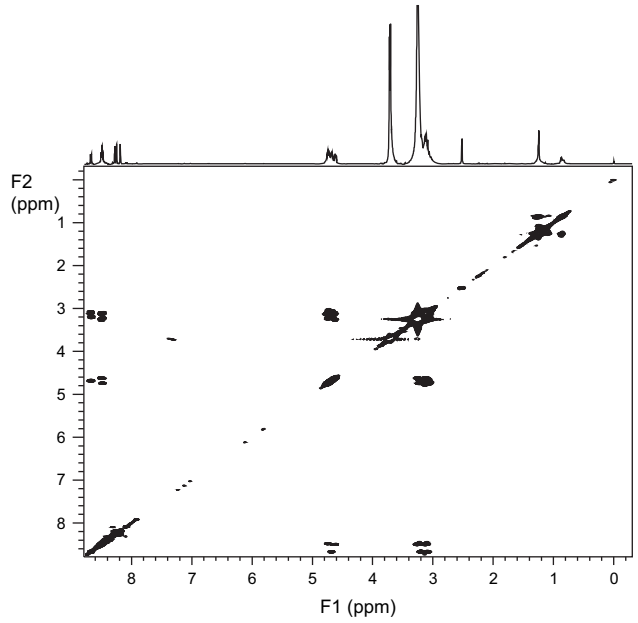


Figure 3. TOCSY spectrum of **2**.

Table 2
^1H NMR for **2** (500 MHz, DMSO-d_6): δ

Linker 1	Linker 2	Linker 3
$C^{\beta}H$, 3.09, dd, 2H, $J^{\alpha\beta}_{CH-CH}$=4.8 Hz[a]	$C^{\beta}H$, 3.12, dd, 2H, $J^{\alpha\beta}_{CH-CH}$=5.4 Hz[a]	$C^{\beta}H$, 3.12, dd, 2H, $J^{\alpha\beta}_{CH-CH}$=5.4 Hz[a]
$C^{\beta}H'$, 3.20, dd, 2H, $J^{\alpha\beta}_{CH-CH'}$=8.2 Hz[a]	$C^{\beta}H'$, 3.25, dd, 2H, $J^{\alpha\beta}_{CH-CH'}$=7.8 Hz[a]	$C^{\beta}H'$, 3.23, dd, 2H, $J^{\alpha\beta}_{CH-CH'}$=7.9 Hz[a]
Ester, 3.70, s, 2×3H	Ester, 3.72, s, 2×3H	Ester, 3.72, s, 2×3H
$C^{\alpha}H$, 4.68,dt, 2H, J=8.2, 4.8 Hz	$C^{\alpha}H$, 4.62, dt, 2H, J=7.8, 5.4 Hz	$C^{\alpha}H$, 4.74, dt, 2H, J=7.9, 5.4 Hz
Ar–H_a, 8.25, t, 2H, J=1.6 Hz	Ar–H_b, 8.19, t, 2H, J=1.6 Hz	Ar–H_c, 8.28, t, 2H, J=1.6 Hz
NH, 8.67, d, 2H, J=8.2 Hz	NH, 8.50, d, 2H, J=7.8 Hz	NH, 8.48, d, 2H, J=7.9 Hz

[a] Geminal coupling could not be measured due to the overlap with residual water (DMSO-d_6) and among themselves.

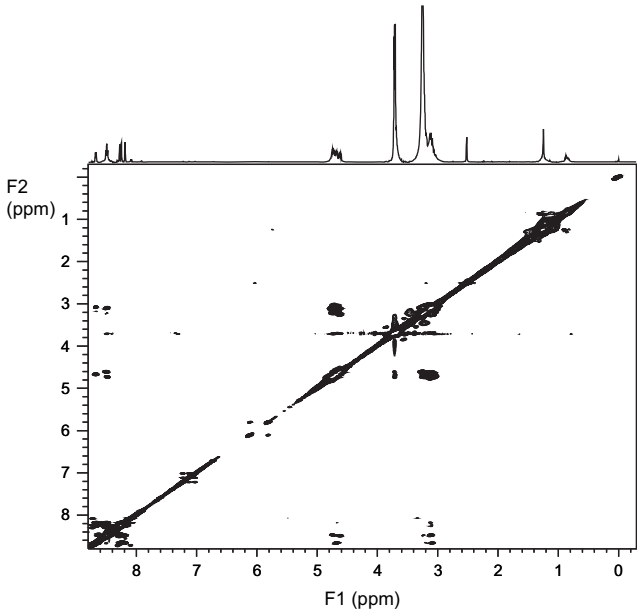


Figure 4. ROESY spectrum of **2**.

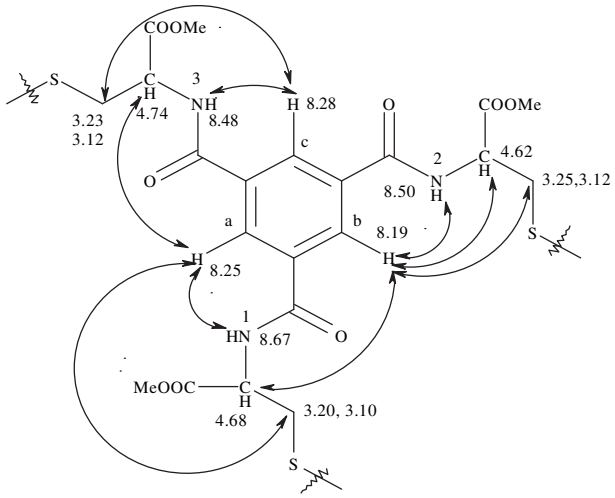


Figure 5. Individual NMR assignment and spatial connectivity in **2**(only one half of the symmetrical pair is shown).

The ^{1}H and ^{13}C NMR of **1** and **2** suggest an axial threefold symmetry and an equatorial twofold symmetry for **1**and a equatorial twofold symmetry for **2**. This is best exemplified by the ^{1}H NMR in DMSO-d_6, where, for **1** the amide protons appear as a single doublet and the aromatic protons as a sharp singlet and that for **2** the amide protons are seen as three clean doublets and the aromatic protons as three clean triplets with a meta coupling of 1.6 Hz. In the ^{13}C NMR in DMSO-d_6 the aromatic carbons of **1** appear as two clean peaks, and the multiple profile of **2** has been analyzed by HMBC and HSQC.

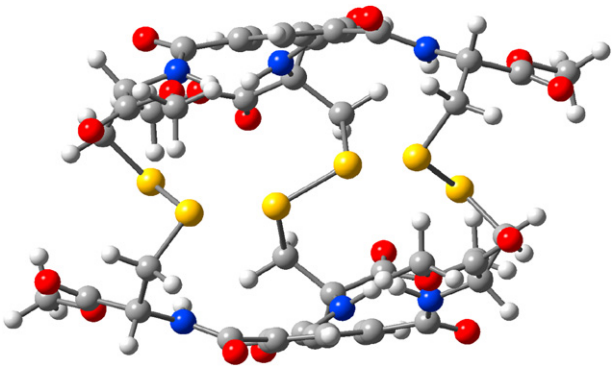
3. Dynamic ^{1}H NMR studies

A dynamic NMR experiment on **2**[16] has been carried out in DMSO-d_6. For clarity, the three clear amide proton signals were chosen for analysis. The outcome as shown below, clearly indicates a propensity for the merger of the amide protons with increasing temperature:

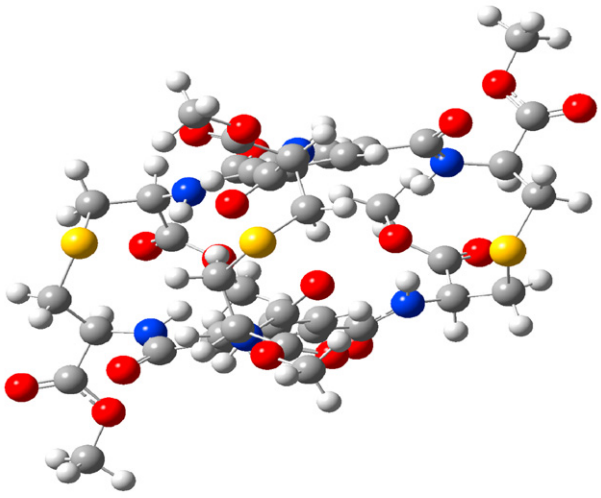
T °C	Δ(δ): **1**–**2**	Δ(δ): **2**–**3**
30	0.185	0.09
40	0.179	0.066
50	0.16	0.051
60	0.149	0.029
70	0.117	0.027

4. Molecular orbital calculations

The foregoing analysis of the NMR data clearly reveals that cystine derivative **1** possesses an axial threefold symmetry and an equatorial twofold symmetry. We have undertaken an exhaustive conformational search for the cystine derivative **1** at AM1 level. The presence of the amide groups in the molecule can lead to intramolecular hydrogen bonding. Keeping the symmetry constraints and the possibility of intramolecular hydrogen bonding in mind, eight conformations were generated with D_3 symmetry (wherein both equatorial and axial symmetry are present), C_3 symmetry (with only axial symmetry), and C_1 symmetry. The conformations were initially optimized at the AM1 level,[17] and as expected, the hydrogen bonded systems have shown marginally higher stability. However, as the NMR data indicate absence of any intramolecular hydrogen bonding, only the D_3 symmetric model was subjected to further optimization at B3LYP/6-31G* level (see Fig. 6). For lanthionine derivative **2** the initial conformational search was carried out at AM1 level and eight different conformations with C_3, C_2, and



2_3 cyclophane from cystine (1)



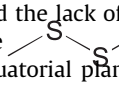
2_3 cyclophane from lanthionine (2)

Figure 6. Cystine and lanthionine derived **1** and **2** from B3LYP/6-31G* calculations.

C_1 symmetry were considered. As the NMR data for **2** indicates the presence of an equatorial twofold symmetry and lack of any intramolecular hydrogen bonding the only conformation that satisfies the NMR description was chosen and further optimized at B3LYP/6-31G* level leading to Figure 6, which exhibits a virtual equatorial twofold symmetry.

The space filling reorientations of **1** and **2** shown in Figure 7 clearly show the consequence of the replacement of the –S–S– in cystine (**1**) with –S– of lanthionine (**2**). All calculations have been carried out using Gaussian 03 program package.[18]

5. Conclusion

The perfect threefold symmetry seen in the cystine compound **1** and the lack of it in the lanthionine analog **2** possibly arises from the  (dihedral angle ~90°) segment present along the equatorial plane providing a spherical profile. In the lanthionine analog **2** this element  offers considerable flexibility. A profile of the linkers present in **1** and **2** is presented in Figure 8. It can be seen from Figure 8, that while the cystine linker consists of rigid modules that are stabilized in several ways excepting for the chiral centers, the lanthionine module is highly flexible and devoid of stabilizing factors with the exception of the terminal amide

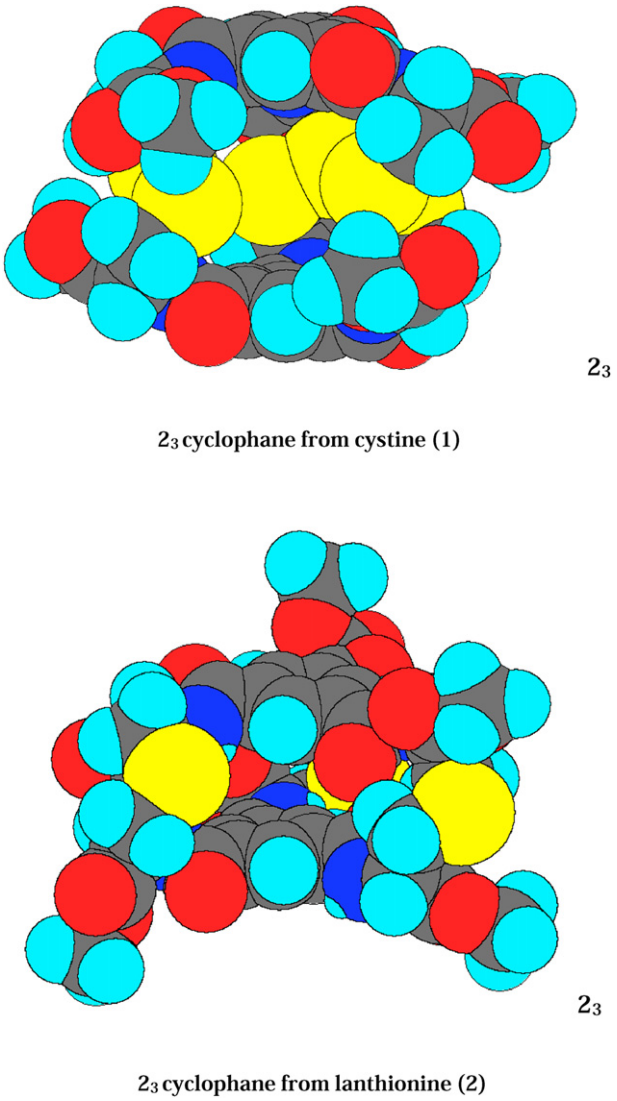


Figure 7. Space filling representations of cystine and lanthionine derived **1** and **2** from B3LYP/6-31G* calculations.

groupings. The significant presence of cystine in nature and synthesis, compared to lanthionine may arise from these factors.

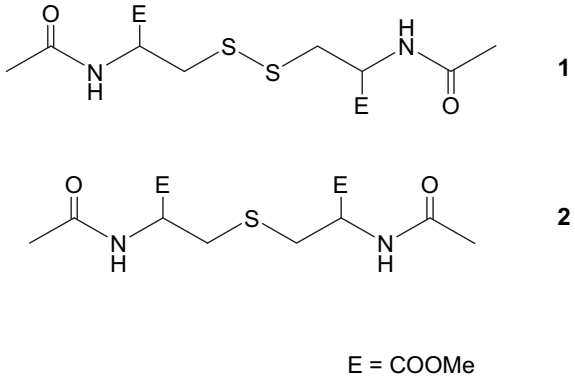


Figure 8. A profile of linkers.

In sum whilst incorporation of cystine could lead to rigid systems that, with lanthionine may result in flexible ones.

6. Experimental

6.1. General

Melting points were recorded on Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with an automatic JASCO P1020 polarimeter (concentrations were in g/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 ^{13}C NMR spectra were recorded on a Varian Gemini 200, Bruker Avance 300, Varion Inova 400, Inova 500, and Bruker Avance 600 NMR spectrometer. The chemical shifts are expressed in δ (parts per million) 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. Reactions were monitored, wherever possible by TLC. Silica gel G (Merck) was used for TLC and column chromatography was done on silica gel (100–200 mesh). Columns were generally made from slurry in chloroform and products were eluted with a mixture of chloroform–methanol.

6.2. Synthesis

*6.2.1. Cystine-di-Me dihydrochloride (**3**).* To a suspension of L-cystine (4.15 g, 17.30 mmol) in dry methanol (125 mL), a steady stream of dry HCl was passed for 5 h, concentrated to 30 mL, refrigerated overnight, filtered, and crystallized from methanol–ether to afford 4.00 g (68%) of **3** mp 165–171 °C.

^1H NMR (400 MHz, D_2O): δ 3.30–3.45 (m, 4H, Cyst $C^{\beta}H_2$s), 3.88 (s, 6H, COOMe), 4.60 (m, 2H, Cyst C^{α}Hs).

FABMS (m/z) (%): 269 $(M-HCl_2)^+$ (100).

*6.2.2. Preparation of L-(+)-lanthionine dimethyl ester dihydrochloride (**4**).*

*6.2.2.1. N,N′-Bis(trifluoroacetyl)-L-cystine-dimethyl ester (**4a**).* A stirred suspension of **3** (4.5 g, 13.2 mmol) in trifluoroacetic acid (15 mL) was cooled to −5 °C and admixed with, in drops, trifluoroacetic anhydride (10 mL). The resulting solution was stirred for 1 h at −5 °C and then 1 h at rt. The reaction mixture was poured over 200 mL of ice-H_2O, stirred for 10 min, filtered, the crystalline **4a** was washed with water (~50 mL), and dried in vacuo to yield 6.0 g (~100%) of **4a** as white crystals, mp 151–153 °C (lit.[15] 152–154 °C).

^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.98–3.30 (m, 4H, Cyst $C^{\beta}H_2$s), 3.77 (s, 6H, COOMe), 4.62–4.81 (m, 2H, Cyst C^{α}Hs), 9.60 (d, J=8.3 Hz, 2H, amide NHs).

*6.2.2.2. N,N′-Bis(trifluoroacetyl)-L-lanthionine dimethyl ester (**4b**).* Under dry nitrogen, to a stirred suspension of **4a** (8.0 g, 17.4 mmol) in dry benzene (87 mL) was added, in drops, neat tris(diethylamino)phosphine (4.869 g, 19.7 mmol). The resulting mixture was stirred under N_2 for 10 min. The suspension of **4a** slowly dissolved and precipitated as a gel. The reaction mixture was diluted with hexane (150 mL), the resulting suspension filtered, and the white crystals of **4b** were further washed well with hexane (50 mL) to yield 7.057 g (95%) of **4b**, mp 110–115 °C (lit.[15] 117–118 °C). $[\alpha]_D^{25}$ −32.66° (*c* 0.4 MeOH); (lit.[15] $[\alpha]_D^{25}$ −32.4° (*c* 0.4 MeOH)).

^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.92–3.30 (m, 4H, Lan $C^{\beta}H_2$s), 3.77 (s, 6H, COOMe), 4.54–4.80 (m, 2H, Lan C^{α}Hs), 9.23–9.45 (m, 2H, amide NHs).

*6.2.2.3. L-(+)-Lanthionine (**4c**).* A stirred solution of **4b** (2.78 g, 6.5 mmol) in dioxane (30 mL) was cooled to 0 °C and admixed with, in drops, 1 N NaOH (54 mL, 54 mmol). After 0.5 h at 5 °C, the

reaction mixture was acidified with 2 N HCl (24 mL, 48 mmol). After adjusting the pH to 6.0 (2 N HCl), the solvent was removed in vacuo. The residue was triturated with water (30 mL) and filtered to afford 0.870 g (64%) of **4c**, mp 280–285 °C, which was used as such in the following experiment.

*6.2.2.4. L-(+)-Lanthionine dimethyl ester dihydrochloride (**4**).* An ice-salt cooled and stirred suspension of **4c** (0.870 g, 4.183 mmol) in dry MeOH (20 mL) was admixed with acetyl chloride (1.313 g (1.19 mL), 16.732 mmol). The reaction mixture was allowed to attain rt, refluxed for 6 h, solvents evaporated in vacuo, and the residue crystallized from methanol–ether to afford, 1.0 g, 77% of **4** as a white powder, mp 155–157 °C.

^{1}H NMR (300 MHz, D_2O): δ 3.01–3.27 (m, 4H, Lan C$^\beta$H$_2$s), 3.80 (s, 6H, COOMe), 4.35–4.41 (m, 2H, Lan C$^\alpha$Hs).

*6.2.3. Reaction of benzene 1,3,5-tricarbonylchloride with **3**: synthesis of triply bridged (1,3,5) cyclophane: hexamethyl 4,13,19,28,31,40-hexaoxo-8,9,23,24,35,36-hexathia-5,12,20,27,32,39-hexaazatetracyclo[14.14.10.1^{3,29}.1^{14,18}]dotetraconta-1,3(41),14,16,18(42),29-hexaene-6,11,21,26,33,38-hexacarboxylate **1**.* To an ice-cooled and stirred solution of **3** (1.023 g, 3 mmol) in CH_2Cl_2 (35 mL), was added triethylamine (0.65 g (0.89 mL), 6.4 mmol) followed by, after 0.5 h, a further lot of triethylamine (1.33 g (1.83 mL), 13.18 mmol) and admixed with, in drops, a solution of benzene 1,3,5-tricarbonylchloride (0.53 g, 2 mmol) in CH_2Cl_2 (16 mL). The reaction mixture was left stirred at 0 °C for 3 h, left stirred at rt for 30 h, and the product filtered; yield 1.2 g (~100%), mp 220–265 °C (dec).

The above product was, in two batches, charged on to a Soxhlet thimble and each batch extracted with, CCl_4 (120 mL, 5 h), 2×$CHCl_3$ (120 mL, 5 h), EtOAc (150 mL, 6 h), $CHCl_3$–MeOH (1:1) (150 mL, 7 h) and finally with MeOH (150 mL, 7 h). The insoluble residues, collected from the thimbles were combined to afford 0.970 g (87%) of white granular powder, mp 258–262 °C (dec).

IR (KBr): 3384, 3221, 3059, 2951, 1743, 1637, 1541, 1436, 1405, 1339, 1212, 1103, 1015 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.89 (dd, J=7.4, 13.6 Hz, 6H, Cyst C$^\beta$Hs), 3.23 (dd, J=7.4, 13.6 Hz, 6H, Cyst C$^\beta$Hs), 3.62 (s, 18H, COOMe), 4.90 (dd, J=7.4 Hz, 6H, Cyst C$^\alpha$Hs), 8.21 (s, 6H, Ar Hs), 9.16 (d, J=7.4 Hz, 6H, amide NHs). ^{13}C NMR (100.579 MHz, DMSO-d_6): δ 38.05 (Cyst C$^\beta$), 51.36 (Cyst C$^\alpha$), 52.15 ($COOCH_3$), 129.26, 132.44 (Ar C), 164.69(CONH), 171.13 (COOMe).

ESI-MS (m/z) (%): 1117 (M+1) (45), 1139 (M+Na$^+$) (100). HRMS (ESI): m/z calcd for C_{42} H_{48} N_6 O_{18} S_6Na (M+Na$^+$) 1139.1247, found 1139.1268.

MALDI-TOF MS (m/z) (%): 1116 (M)$^+$ (100). Anal. Calcd for $C_{42}H_{48}N_6O_{18}S_6$: C, 45.15; H, 4.33; N, 7.52; S, 17.22. Found: C, 44.78; H, 4.47; N, 7.27; S, 17.26.

Temperature dependent NMR (500 MHz, DMSO-d_6) in the range of 30–70 °C afforded a dδ/dT value of 6.5 ppb/°C suggesting absence of intramolecular hydrogen bonding.

*6.2.4. The reaction of **1** with $AgBF_4$: preparation of mono silver complex (**1**·Ag).* Under total darkness, a suspension of **1** (0.015 g, 0.0134 mmol) in nitromethane (1.5 mL) was admixed with $AgBF_4$ (0.004 g, 0.02 mmol) in nitromethane (1 mL), the mixture warmed in a water bath (~50 °C), filtered and the filtrate allowed to evaporate to afford dark powder, mp 220–225 °C (dec), whose MS showed clear complexation **1**·Ag. The ^{1}H NMR (200 MHz, DMSO-d_6) was almost similar to the precursor **1**.

MALDI-TOF MS (m/z) (%): 1223, 1225 (M+Ag)$^+$ (**5**).

*6.2.5. Reaction of benzene 1,3,5-tricarbonylchloride with **4**: synthesis of triply bridged (1,3,5) cyclophane: hexamethyl 4,12,18,26,29,37-hexaoxo-8,22,33-trithia-5,11,19,25,30,36-hexaazatetracyclo[13.13.9.1^{3,27}.1^{13,17}]nonatriaconta-1,3(38),13,15,17(39),27-hexaene-6,10,20,24,31,35-hexacarboxylate **2**.* To an ice-cooled and stirred suspension of **4** (1.0 g, 3.24 mmol) in CH_2Cl_2 (100 mL) was added in drops, NEt_3 (1.36 g (1.88 mL), 13.57 mmol) followed by, after 0.5 h, in drops, over a period of 0.75 h, a solution of benzene 1,3,5-tricarbonylchloride (0.572 g, 2.157 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was left stirred at rt overnight, washed with 2 N H_2SO_4 (20 mL), water (20 mL), satd $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), and evaporated to yield 0.450 g (41%), mp ~225 °C, of the crude product **2**, which was chromatographed on silica gel. Elution with $CHCl_3$–MeOH, 95:5, gave 0.180 g (16%), mp 205–210 °C.

IR (KBr): 3390, 3066, 2954, 2925, 1741, 1671, 1529, 1437, 1348, 1219, 1103, 1019 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.09, 3.12, 3.12 (dd, dd, dd, J=4.8, 5.4, 5.4 Hz[†], 6H, Lan C$^\beta$H), 3.20, 3.25, 3.23 (dd, dd, dd, J=8.2, 7.8, 7.9 Hz,[†] 6H, Lan C$^\beta$H), 3.70, 3.72, 3.72 (s, s, s, 18H, COOMe), 4.68, 4.62, 4.74 (dt ,dt, dt, 6H, J=8.2, 4.8; 7.8, 5.4; 7.9, 5.4 Hz Lan C$^\alpha$Hs), 8.25, 8.19, 8.28 (t, t, t, J=1.6 Hz, 6H, Ar H), 8.67, 8.50, 8.48 (ddd, J=8.2, 7.8, 7.9 Hz, 6H, NH).

^{13}C NMR (150 MHz, DMSO-d_6): δ 32.97, 32.82, 32.82 (Lan C$^\beta$), 53.18, 52.93, 52.95 (Lan C$^\alpha$), 52.08, 52.13, 52.16 (OCH_3), 133.15, 132.33, 132.27, 130.21, 129.12, 127.15 (Ar C), 164.46, 164.18, 164.11 ($CONH_2$), 171.01, 170.93, 170.83 (COOMe).The assignments were made with the help of HMBC and HSQC experiments. ESI-MS (m/z) (%):1021(M+H)$^+$ (28), 1043 (M+Na)$^+$ (100). HRMS (ESI): m/z calcd for $C_{42}H_{48}N_6O_{18}NaS_3$ (M+Na)$^+$ 1043.2084, found 1043.2075.

Temperature dependent NMR (500 MHz, DMSO-d_6) in the range of 30–70 °C afforded for the three amide NHs dδ/dT values, respectively, 9.02, 7.6, 5.75 ppb/°C suggesting absence of intramolecular hydrogen bonding.

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