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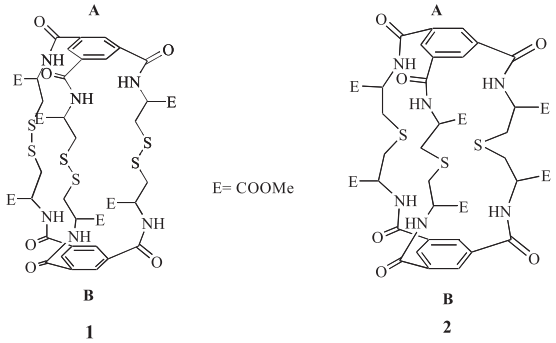
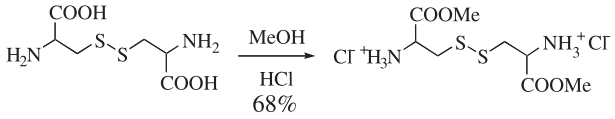
2_3 cyclophanes, **1** and **2** prepared from the linking of benzene 1,3,5-tricarbonylchloride with, respectively, cystine-dimethyl ester dihydrochloride (**3**) and lanthionine dimethyl ester dihydrochloride (**4**).



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.

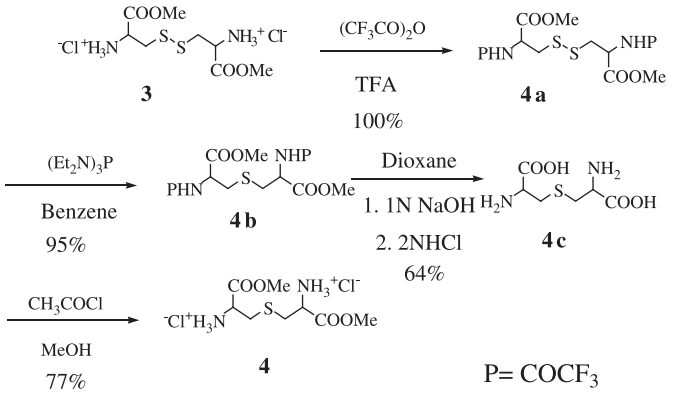
2. Results and discussion

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).

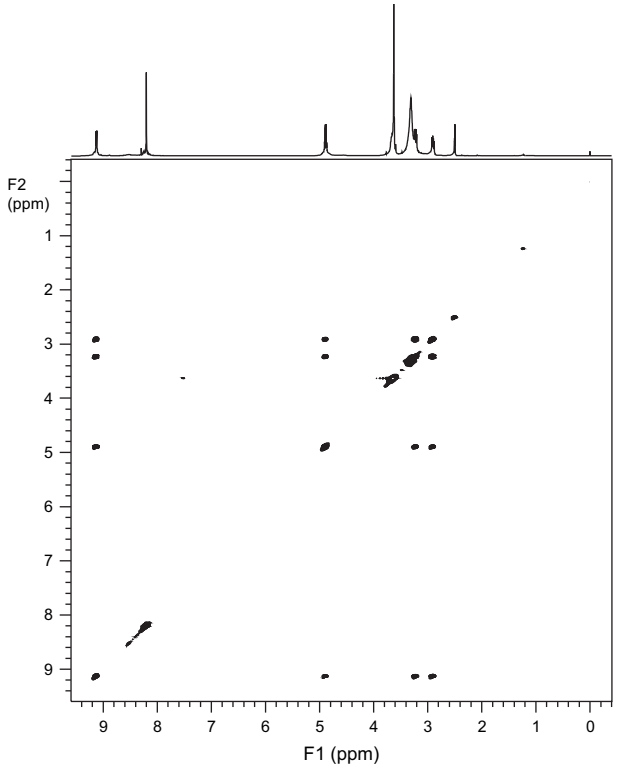


Figure 1. TOCSY spectrum of **1**.

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