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Spontaneous macrocyclization of L-cysteine with malononitrile

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Abstract—Condensation of L-cysteine with malononitrile in water solution followed by esterification gave the 22-membered C_2-symmetric macrocycle **1** as the major product (62% yield). The reactivity of **1** towards platinum(II) and palladium(II) species was studied, allowing us to isolate and characterize $[Pt_4(\mathbf{1})Cl_8]$ **5a**, $[Pd_4(\mathbf{1})Cl_8]\cdot 4H_2O$ **5b** and $[Pd_4(\mathbf{1}\text{-H})(AcO)_4]$ **6** in which the ligand behaves as a *N*,*S*-donor.

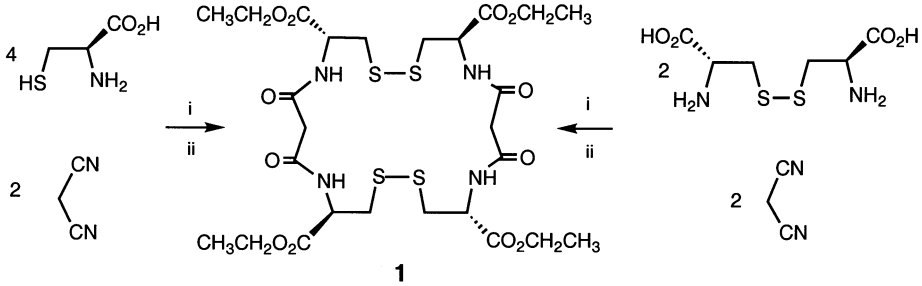
1. Introduction

Macrocyclic compounds have very important applications in a wide range of areas within chemical, biochemical and new materials research.[1] Macrocyclic ligand complexes are involved in a number of fundamental biological systems and in particular, macrocyclic polypeptides are examples of natural antibiotics.[2] The preparation of macrocycles from linear open chain compounds has many limitations and the procedures in which the cyclization proceeds in good yields usually rely on a high dilution technique or a template effect.[3]

Although the disulfide bond between two or more L-cysteine residues within the amino acid framework plays a very important role in defining many peptide and protein structures,[4] little is known about low molecular weight macrocyclic peptides including this key structural feature.[5] Some sulfur-containing macrocyclic diamides that show highly selective recognition of divalent palladium and platinum ions have been reported.[6] Furthermore, macrocyclic amides and polyamides are interesting ligands in the formation of complexes with anions[7] through hydrogen bond interactions, although few attempts have been made to rationally design macrocyclic hosts in which α-amino acids are exploited.[8]

We report herein the synthesis of the 22-membered macrocycle **1** with four L-cysteine residues bound together in a straightforward manner by two malonodiamide bridges (Scheme 1).

The synthesis of macrocycle **1** (methyl ester derivative) in *organic* solvents has been recently described using a two-step protocol.[9] Initial condensation of malonic acid dichloride with L-cysteine methyl ester hydrochloride in dichloromethane in the presence of thiethylamine under a nitrogen atmosphere gave an isolable dithiol, which, upon oxidation at room temperature, (O_2/Et_3N/DMSO) yielded the macrocycle **1** in good yield (69%). Prompted by this report[9] we wish to communicate our own findings on the preparation of **1** (ethyl ester derivative) using a different approach. Treatment of L-cysteine with malononitrile in *water* in the presence of ammonium chloride gave the macrocycle **1** (free acid) in one step, which was later esterified. In this sense it should be noted that there is great current interest in the use of environmentally benign solvents such as water.



Scheme 1. (i) H_2O, 85°C, 24 h; (ii) PCl_5, CH_3CH_2OH.

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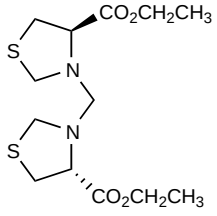
2. Results and discussion

2.1. Ligand design

We have recently reported the conversion of L-cysteine ethyl ester to the corresponding methylenebisthiazolidine **2** using excess paraformaldehyde and trifluoroacetic acid as reaction solvent in just one step.[10] As part of a programme aimed at the synthesis of novel C_2-symmetric ligands derived from L-cysteine as potential ligands in asymmetric catalysis,[11] we chose system **3** which has close structural features related with **2**. The new ligand includes two thiazoline rings instead of the thiazolidine bound together by a methylene bridge.



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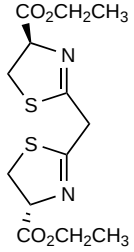

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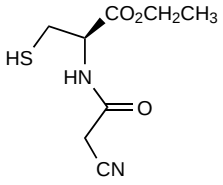

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The reaction between cysteamine and malononitrile was reported to give the parent unsubstituted methylenebisthiazoline in 84% yield.[12] We initially chose the condensation between L-cysteine ethyl ester hydrochloride and malononitrile as we considered it to be a reasonable model system. Under what we believed were optimised reaction conditions (EtOH, reflux 2 h in the presence or absence of triethylamine) no methylenebisthiazoline diethyl ester **3** was formed. On the other hand, if the reaction was carried out under aqueous conditions (room temperature or 85°C, 24 h), amide **4** was the only isolable product, formed in 46% yield as a white crystalline solid. The NMR spectra of **4** are in full agreement with the proposed structure. The ^{13}C-DEPT NMR indicated the presence of one methyl, three methylene groups, one methyne group and three quaternary carbons, the ester at δ 169.5 ppm and amide at δ 162.4 ppm, including a nitrile at δ 115.9 ppm. The mass spectrum exhibited an $(M+1)^+$ ion peak at m/e 217. This result is in agreement with a literature report on the condensation of L-cysteine derivatives with aliphatic nitriles to give the corresponding amides instead of the expected thiazolines, which could only be obtained with aromatic nitriles.[13]

We then turned our attention to the condensation of L-cysteine and malononitrile under the same experimental conditions (H_2O, 85°C, 24 h), the solvent was evaporated to dryness and the crude acid was converted to the ethyl ester with PCl_5 and ethanol. The product was purified by washing with acetone to give unexpectedly the 22-membered macrocycle **1** as the major product (33% yield after esterification). The ^{13}C-DEPT NMR spectrum indicated the presence of one methyl group, three methylenes, one methyne and two quaternary carbons, the ester at δ 170.0 ppm and amide at δ 166.7 ppm. Further evidence for the structure of **1** comes from its MALDI-TOF-MS, which exhibits an $(M+Na)^+$ ion peak at m/e 751.9 and correct elemental analysis. The one-step macrocyclization reaction involves an unusually high yield molecular assembly with six components (four L-cysteine and two malononitrile units).

For comparison a macrocyclization reaction study of L-cysteine was undertaken (Scheme 1). After condensation of L-cysteine and malononitrile under the same experimental conditions (H_2O, 85°C, 24 h), the crude product was evaporated to dryness and the product was esterified (PCl_5, ethanol). However, attempts to synthesize **1** by this route gave extremely low yields (3%). These results indicate that the formation of two disulfide bridges is the driving force for the macrocyclization of L-cysteine with malononitrile.

However, the yield from the condensation of L-cysteine and malononitrile to give the macrocyclic amide **1** ranged from 10 to 33% depending upon small changes in the experimental reaction conditions. In order to avoid the formation of by-products, the reaction was investigated in some detail and some facts deserve further comments. Firstly, we observed that the amount of the desired macrocycle increases when the aqueous solution was allowed to dry unaided in an open flask (about 3 weeks) before the esterification is performed. Secondly, the yield of **1** dropped dramatically when, directly after the initial condensation, water was rapidly evaporated from the reaction mixture under reduced pressure in less than 30 min. The process must involve the formation of an 11-membered open chain diamide with two free thiol groups in the condensation of two molecules of L-cysteine and one of malononitrile followed by a spontaneous slow double disulfide bond closure to give the 22-membered macrocyclic ring. Thirdly, in order to ascertain whether a template effect[14] was operating, when the initial condensation of L-cysteine and malononitrile was carried out in the presence of ammonium chloride the yield of **1** rose to 62%. Remarkably, it was found that neither cysteamine, D-penicillamine nor L-cysteine ethyl ester could be converted to the corresponding macrocycles using the same experimental procedure. This suggests that the carboxylic acid function of L-cysteine might play a role through hydrogen bond interactions that favors the macrocyclization process.

2.2. Characterization of platinum(II) and palladium(II) complexes of 1

Palladium complexes are involved in many carbon–carbon bond forming reactions such as Suzuki cross-coupling, Grignard-based couplings and Heck reactions. In many examples the palladium requires stabilization by phosphine ligands and one of the main

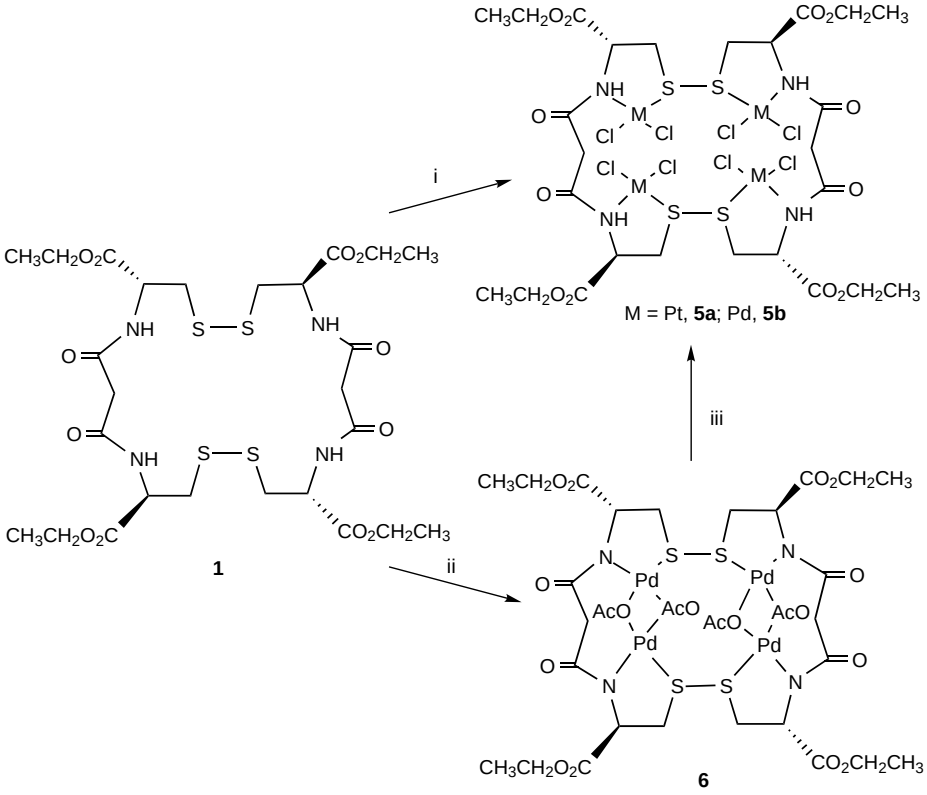
problems on preparative scale is the recovery of these catalysts. Therefore, the use of these synthetic methods is not usually so straightforward and the development of phosphine-free catalysts is a topic that has been addressed recently.[15] Curiously enough, very few palladium–sulfur complexes have found extensive use as catalysts until the recent description of $PdCl_2(SEt_2)_2$.[16] For these reasons, we undertook an investigation of the complexation of macrocycle **1** with palladium and platinum.

When macrocycle **1** was treated with the corresponding tetrachlorometallate(II) salt $K_2[PtCl_4]$ or $Na_2[PdCl_4]$ in an acetonitrile:water mixture (4:1) under reflux for 2 h, dissolution of the ligand took place leading to a bright yellow solution (for M = Pt) or an orange solution (for M = Pd). Slow evaporation of the solvent at room temperature (ca. 20°C) produced a yellow or an orange solid (for M = Pt **5a**, or Pd **5b**, respectively) (Scheme 2).

When this reaction was carried out using anhydrous acetonitrile (HPLC grade) as solvent, only the starting materials were recovered from the reaction medium, even after heating the mixture under reflux for 24 h. This finding suggests that water plays an important role in these reactions. Since the formation of compounds **5a** and **5b** requires the presence of water, we postulate that the binding of the Pt(II) and Pd(II) ions to the heteroatoms of the ligand may require the partial hydration of the initial $[MCl_4]^{2-}$ species.[17]

Compounds **5a** and **5b** are stable solids at room temperature, **5a** is slightly soluble in dimethylsulfoxide but exhibits higher solubility in acetonitrile and **5b** is only partially soluble in DMSO-d_6. Additionally, both compounds are practically insoluble in most common solvents. These complexes were characterized by elemental analyses, infrared and ^{1}H NMR spectroscopy. In both cases the IR spectrum showed the typical band due to the -NH stretching of the amide group, thus indicating that deprotonation of the ligand did not occur during the course of the reaction.

When the ^{1}H NMR spectra were recorded in DMSO-d_6, the resonances appeared as low intensity and poorly resolved signals due to the low solubility in this solvent. In addition, some of the resonances due to the protons that belong to the -S-C**H$_2$**- and to the -C**H$_2$**-CH$_3$ moieties were total or partially masked by the typical signal of the solvent or of the water present in commercial DMSO-d_6. Despite this, ^{1}H NMR spectroscopy has been a useful tool to elucidate the neutral or anionic nature of the ligand as well as the mode of binding of the macrocycle to palladium(II) or platinum(II) in compounds **5**. In particular, the most relevant feature observed in the ^{1}H NMR spectra of **5** in DMSO-d_6 is the presence of a broad signal in the region 8.10–8.8 ppm, which is assigned to the amide -NH proton. When the spectrum of **5a** was registered in acetonitrile-d_3 this signal appeared as a doublet at d = 7.7 ppm.



Scheme 2. (i) $K_2[PtCl_4]$ in CH_3CN/H_2O (4:1), 2 h at reflux for **5a**; and $K_2[PdCl_4]$ for **5b**; (ii) $Pd(CH_3COO)_2$ in CH_3CN, 1 h at room temp.; (iii) HCl in CH_3CN, 1 h at room temp. (M = Pd).

These findings confirm the results obtained from IR spectroscopy, which suggested that deprotonation of the macrocycle did not occur during complexation. Furthermore, the upfield shift of the resonances due to the protons of the -S-C**H**$_2$- and >C**H**- moieties in the spectra of **5a** and **5b** suggested the coordination of the sulfur to the M(II) ions.[11]

When macrocycle **1** was treated with palladium acetate in a 1/4 molar ratio in acetonitrile at room temperature for 1 h, an orange precipitate of **6** formed and was isolated in high yield (Scheme 2). This solid is practically insoluble in all common solvents and for this reason could only be characterized by elemental analysis and infrared spectroscopy. The IR spectrum indicated that in this case deprotonation of the ligand occurred during the course of the reaction since the band due to the -NH stretching of the amide group had disappeared. In addition this spectrum showed that the bands corresponding to $\nu_{asym.}$ and $\nu_{sym.}$ of the acetato ligand were separated by 149 cm^{-1} (1561 and 1412 cm^{-1}), which is consistent with the results reported for complexes having *O*,*O*′-bidentate bridging acetato ligands.[18] These data and the fact that the IR spectrum showed the presence of non-deprotonated macrocycle **1** when the amount of palladium acetate used in this reaction is less than that corresponding to a molar ratio of 1/4, allow us to propose tentatively the tetranuclear structure for compound **6** depicted in Scheme 2, but it should be noted that a polynuclear structure for this solid cannot be ruled out at this time as the insolubility of **6** makes its characterization difficult (good analytical results were not obtained for this solid) and we do not have conclusive evidence for our proposal.

The fact that the acetate anion is a stronger base than chloride could explain the finding that palladium acetate easily deprotonates the macrocycle **1** to afford **6**, in contrast, coordination compounds **5**, in which the N–H bonds are not deprotonated, can be obtained by reaction of **1** with tetrachlorometallate(II) salts.

To confirm this hypothesis and to elucidate whether the interconversion between **5b** and **6** could be achieved by means of an acid-base process, two independent experiments were performed. Treatment of **5b** with a stoichiometric amount of anhydrous sodium acetate in refluxing acetonitrile using reaction periods varying from 1 to 24 h. In this case, no evidence of deprotonation of the -NH units was detected by IR spectroscopy. This finding suggests that for the formation of **6**, deprotonation of the N–H bonds of the macrocycle occurs prior to coordination with palladium(II). In contrast, reaction of **6** with HCl in acetonitrile affords the coordination complex **5b** in quantitative yield and takes place under very mild conditions.

3. Conclusions

In summary, we have developed an efficient synthetic route to the 22-membered macrocycle **1**, one member of a new class of macrocyclic compounds.[5] The synthesis of higher members from higher homologue dinitriles is currently under investigation.

We have shown that macrocycle **1** is a versatile ligand for the complexation of transition metal ions such as palladium(II) and platinum(II), which could find use as catalysts in organic synthesis. Moreover, some examples of anti-tumor drugs based on mononuclear complexes containing a '$M(N,S$-donor$)Cl_2$' (M = Pd or Pt) core have been described in the literature[19] and, since each molecule of **5a** or **5b** contains four '$M(N,S$-donor$)Cl_2$' fragments, these complexes appear to be excellent candidates for further studies focused on examining their potential therapeutic properties.

4. Experimental

4.1. General comments

All chemicals were of commercial grade and used as received and $Na_2[PdCl_4]$ was prepared as described previously.[20] Elemental analyses (C, H, and N) were carried out at the Institut de Química Bio-Orgànica (C.S.I.C., Barcelona). Infrared spectra were recorded with a Nicolet-Impact-400 instrument using KBr pellets. ^{1}H NMR spectra were run using a Varian Gemini 200 or 300, Varian VXR-500 or a Bruker Avance 500 DMX instrument. The solvents used are specified in the characterization section of each compound.

4.2. Preparation of 1

To a solution of L-cysteine (2.7 g, 0.022 mol) in water (100 mL), malononitrile (0.74 g, 0.011 mol) and ammonium chloride (2.4 g, 0.044 mol) were added under an inert atmosphere (argon). The solution was stirred at 85°C for 24 h, cooled, allowed to dry unaided in an open flask (about 3 weeks) and the residue was kept in a dessicator over P_2O_5 for 24 h. The crude was suspended in dichloromethane (100 mL) and treated with PCl_5 (10.4 g, 0.05 mol) in three portions under stirring. After 24 h the reaction was quenched by the addition of absolute ethanol (100 mL) and the mixture was allowed to cool to room temperature overnight. The solvent was evaporated under reduced pressure, diluted with water (150 mL), neutralized with $NaHCO_3$ and the product was extracted with ethyl acetate. The crude was washed with acetone (2×50 mL) to give **1** (2.5 g, 62%). Mp = 224–25°C; $[\alpha]_D^{20} = -88$ ($c = 0.1$, DMSO); anal. calcd for: $C_{26}H_{40}N_4O_{12}S_4$ (728.9); found: C, 42.84 (42.56); H, 5.53 (5.50); N, 7.68 (7.61)%. IR (KBr): $\nu = 3442$, 3301, 1749, 1667, 1651, 1541, 1214, 1168, 1019 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.60 (d, 4H, $J = 7.8$ Hz), 4.61 (m, 4H), 3.18 (s, 4H), 3.06 (dd, 4H, $J = 13.8$ Hz, 5.1 Hz), 2.87 (dd, 4H, $J = 13.8$ Hz, 8.7 Hz), 1.17 (t, 12H, $J = 6.91$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 170.0 (C=O), 166.7 (C=O), 61.1 (CH_2), 51.1 (CH), 42.3 (CH_2), 38.3 (CH_2), 14.1 (CH_3). MALDI-TOF MS calculated for $C_{26}H_{40}N_4O_{12}S_4Na$: 751.9 $(M+Na)^+$; found: 751.9.

4.3. Preparation of $[Pt_4(1)Cl_8]$, 5a

$K_2[PtCl_4]$ (227 mg, 5.5×10^{-4} mol) was added to a suspension of **1** (100 mg, 1.37×10^{-4} mol) and acetonitrile (20 mL). Water (5 mL) was added and the reaction mixture was heated under reflux for 2 h. During this period the macrocycle dissolved gradually and the solution became bright yellow. The undissolved materials were removed by filtration and discarded and the filtrate was allowed to evaporate at room temperature. The bright yellow solid formed was collected by filtration, air-dried and then dried in vacuum for 2 days to afford **5a** (120 mg, 49%). Anal. calcd for: $C_{26}H_{40}N_4O_{12}Pt_4S_4Cl_8$; found: C, 17.42 (17.70); H, 2.25 (2.46); N, 3.13 (3.30)%. IR (KBr): ν(N–H) = 3295, ν(COO) = 1734, 1653 and 1520 cm^{-1}. ^1H NMR (DMSO-d_6): 8.61 (br., 4H, NH); 4.60 (m, 4H, >CH-), 2.66 and 2.81 (dd, 8H, J = 14 Hz, 8 Hz, -S-CH_2-), 4.16 (q, 8H, J = 6.3 Hz, -CH_2-), and 1.17 (t, 12H, J = 6.3 Hz, -CH_3 of the ethyl group). ^1H NMR (acetonitrile-d_3): 7.70 (d, 4H, J = 10 Hz, NH); 4.82 (m, 4H, >CH-), 2.02 (d, 4H, -S-CH_2-),[21] 4.22 (q, 8H, J = 6.8 Hz, -CH_2-), and 1.27 (t, 12H, J = 6.8 Hz, -CH_3 of the ethyl group).

4.4. Preparation of $[Pd_4(1)Cl_8]\cdot4H_2O$, 5b

This complex was prepared as described for **2**, but using ligand **1** (50 mg, 6.7×10^{-5} mol) and a stoichiometric amount of $Na_2[PdCl_4]$ (81 mg, 2.7×10^{-4} mol) as starting materials to afford **5b** (54 mg, 52%). Anal. calcd for: $C_{26}H_{40}N_4O_{12}Pd_4S_4Cl_8\cdot4H_2O$; found: C, 20.68 (20.26); H, 3.20 (3.10); N, 3.70 (3.70)%. IR (KBr): ν(N–H) = 3295, ν(COO) = 1734, 1653 and 1520 cm^{-1}. ^1H NMR (DMSO-d_6): 8.18 (br., 4H, NH); 4.40 (m, 4H, >CH-), 2.80 (d, 4H, -S-CH_2-),[21] 4.15 (q, 8H, J = 6 Hz,-CH_2-), and 1.19 (t, 12H, J = 6 Hz, -CH_3 of the ethyl group).

4.5. Preparation of $[Pd_4(1\text{-}H)(AcO)_4]$, 6

Palladium acetate (185 mg, 8.4×10^{-4} mol) was added to a suspension formed by mixing **1** (150 mg, 2.1×10^{-4} mol) and acetonitrile (20 mL) and the reaction mixture was stirred for 1 h at room temperature. The orange solid formed was collected by filtration, air-dried and then dried under vacuum. (Yield: 230 mg, 80%). Anal. calcd for: $C_{34}H_{48}N_4O_{20}Pd_4S_4$; found: C, 29.45 (26.7); H, 3.49 (3.1); N, 4.04 (4.5)%. IR (KBr): ν(COOEt) = 1727, ν(MeCOO) = 1561 and 1412 cm^{-1}.

Acknowledgements

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