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Synthesis of cyclic mono- and bis-disulfides and their selective conversion to mono- and bis-thiosulfinates

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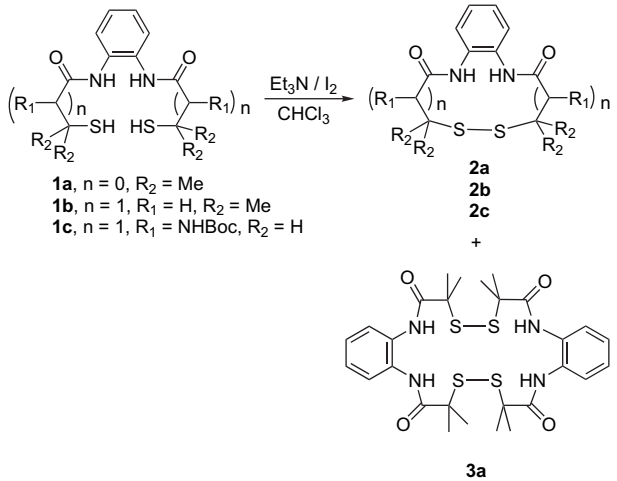
Abstract—Twelve-membered ring pseudopeptidic cyclic disulfides have been prepared by iodine oxidation of the parent dithiols. However, oxidation of *N*,*N*′-(1,2-phenylene)bis(2-mercapto-2-methylpropanamide) afforded a 25/75 mixture of cyclic mono- and bis-disulfides that were separated by selective precipitation in $CHCl_3$. The cyclic bis-disulfide was selectively prepared by iodine oxidation of the Ni complex of this dithiol and crystallized. Its crystal structure was solved by X-ray diffraction. All these cyclic mono- or bis-disulfides were selectively converted to cyclic mono- and bis-thiosulfinates upon stoichiometric oxidation with dimethyldioxirane at low temperature. ^{1}H NMR of the cyclic bis-thiosulfinate revealed the presence of four isomers, two couples of stereoisomers, as expected from the insertion of two oxygen atoms in this compound, one on each disulfide bond. The two couples of cis/trans isomers were separated by preparative TLC and identified after alkaline cleavage of the two S(O)–S bonds and metalation with Ni(II). As HO^- attack is selective for the sulfinyl sulfur, the nature of the Ni complexes obtained is a signature of each couple of stereoisomers.

1. Introduction

Recently glutathion has been reported to be converted to disulfide-*S*-oxides under oxidative stress conditions.[1] These reactive sulfur oxidized species can then react with nucleophiles in proteins such as free thiols[2] or zinc bound thiolates leading to glutathionylation of proteins or zinc metallothioneins.[3] This finding emphasizes that more generally disulfide-*S*-oxides might play an important role in biology. This requires developing the synthesis of new disulfide monooxides (thiosulfinates) or dioxides (thiosulfonates). Herein we report the synthesis of cyclic mono- and bis-disulfides from the parent dithiols and their further oxidation into cyclic disulfide-*S*-oxide and cyclic bis(disulfide-*S*-oxides) (bis(thiosulfinates)).

2. Results and discussion

The linear dithiols $N_2S_2H_4$, **1a**, **1b**, and **1c**, shown in Scheme 1, are the precursors of 10- or 12-membered ring disulfides **2a**, **2b**, and **2c**, respectively. While the synthesis of **1b** has been previously described,[4] the synthetic route for the dipeptide **1c** is outlined in Scheme 2. Acylation of *o*-phenylenediamine with 2 equiv of *S*-benzyl-protected *N*-Boc-cysteine afforded the S-protected dithiol, which was further debenzylated with Na in liquid NH_3. Compound **1a** was prepared



Scheme 1. Synthesis of disulfides.

Keywords: Cyclic disulfide; Disulfide-*S*-oxide; Thiosulfinate; Bis(disulfide-*S*-oxides); Bis-thiosulfinates.
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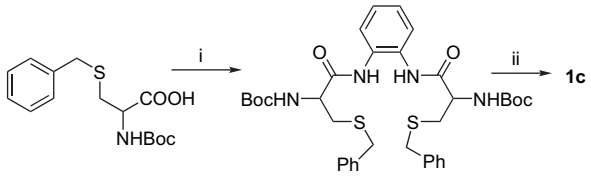


Scheme 2. Synthesis of dithiol **2c**: (i) *i*-BuOCOCl/*o*-phenylenediamine/NMP; (ii) Na/NH_3.

in situ from the bis(*S*-acetylated) form of **1a**[5] after deprotection with K_2CO_3 in MeOH.

Oxidative cyclization of the dithiols **1** with iodine in $CHCl_3$ in the presence of triethylamine[6] affords cyclic mono-disulfides **2** and bis-disulfide **3a** (Scheme 1) depending on the size of the $N_2S_2H_4$ chelate, while oxidation of **1b** and **1c** provides **2b** and **2c** as the only products identified by ^1H NMR. At this stage, we tried to remove the Boc protection of **2c** by an acidic treatment, but this results in a poorly soluble species that was difficult to characterize further. Oxidation of **1a** leads to a mixture of the cyclic mono- and bis-disulfides **2a** and **3a**, in a 25/75 ratio.

Fortunately, **2a** and **3a** could be easily separated by repeated crystallizations from $CHCl_3$, **2a** being only sparingly soluble in this solvent. The 10-atom chelate **1a** does not favor the ring closure into **2a** whose structure appears to be rigid and twisted in solution as shown by the lack of any symmetry revealed by ^1H NMR analysis. The methyl protons are split into two groups (6H each) appearing at two different chemical shifts. In contrast, the methyl protons of the bis(disulfide) **3a** are equivalent and appear as a single resonance, showing the larger flexibility of the dimer in solution.

Oxidation of dithiols usually provides mixtures of cyclic disulfides containing one or more disulfide bridges depending on the reaction conditions. Thus, oxidation with iodine under high-dilution conditions[7] or using thiol-disulfide interchange reactions[8] are reported to provide monomeric disulfides and higher disulfide-containing species, respectively, but these reactions are either not very selective, or afford by-products. Interestingly, selective synthesis of bis(disulfide)-tetramine macrocycles from the parent dithiol/diamine precursor has been described either when using vanadyl species as oxidizing agent[9] or by oxidative coupling of Ni(II) or Cu(II) complexes of the linear tetradentate N_2S_2 ligand.[10,11] In this latter case, the cleanest synthesis was described by Fox et al.[11] Iodine oxidation of the diamine/dithiolate nickel(II) or copper(II) complexes followed by removal of the metal led to the unique and selective formation of the bis(disulfide) in high yield.[11] To get a larger amount of **3a**, this method was applied to the oxidation of the diamidato dithiolato nickel(II) complex of **1a**, prepared as previously described by Krüger and Hanss.[12] Compound **3a** was isolated in almost quantitative yield and subjected to crystallization by slow evaporation of a CH_2Cl_2 solution.

A view of its X-ray crystal structure is shown in Figure 1. As other cyclic bis(disulfides),[7] **3a** adopts a cage conformation with a center of symmetry. The metric parameters of the disulfides (S1–$S2^i$, S1–C1, and S2–C10 distances

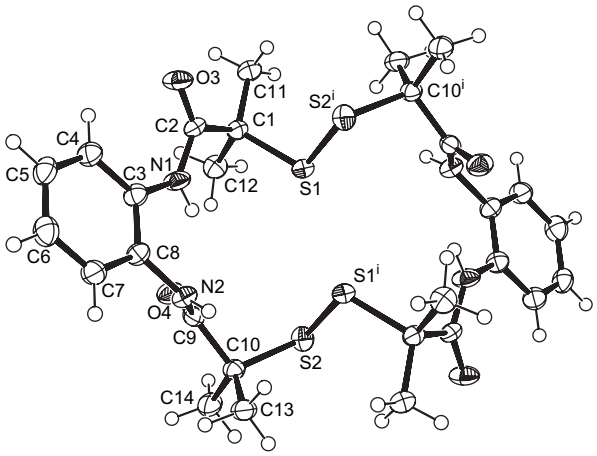


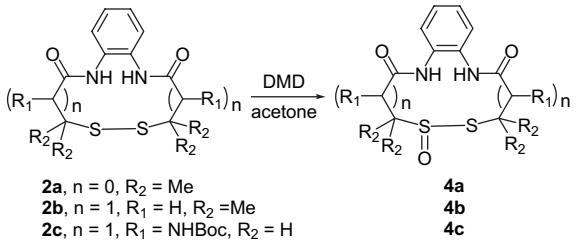
Figure 1. ORTEP view of the cyclic bis(disulfide) **3a** showing 50% probability displacement ellipsoids. Selected bond distances (Å): S1–C1: 1.856(2), S2–C10: 1.864(3); selected bond angles (°): C1–S1–$S2^i$: 106.31(8), C10–S2–$S1^i$: 105.65(8); [i: $1-x$, $1-y$, $1-z$].

of 2.0294(9), 1.856(2), and 1.864(3) Å, respectively; C1–S1–$S2^i$ and C10–S2–$S1^i$ bond angles of 106.31(8)° and 105.65(8)°, respectively) compare well with those of structurally related 20-membered ring disulfides such as a tetrabenzo-tetrathia-tetraazacycloeicosane[13] or an octamethyl-diperhydrobenzo-tetrathia-tetraazacycloeicosane.[11] Two features characterize the structure of **3a**, namely, (i) a very short cross cage distance S1–$S1^i$ of 3.393(1) Å, which puts the two sulfur atoms within van der Waals contact and (ii) a quite large value of the C1–S1–$S2^i$–$C10^i$ torsion angle (111.9(1)°). This value, which has been established to be 80–85° in strain-free disulfides,[14] is indicative of the stability of the disulfides. Torsion angles can be compared within cyclic disulfides of the same size. In that regard, the value determined in **3a** is slightly larger than that found in the structure described by Fox et al. (110.1(2)°).[11] Replacement of the two 1,2-diamino-cyclohexyl groups in this structure by two phthalamide groups in **3a** is likely to account for the increase of the torsion as well as for the short cross cage distance revealed in **3a**.

The second part of this work deals with the oxidation of disulfides **2** and bis(disulfide) **3a** into cyclic mono- and bis-thiosulfinates. While oxidation of linear disulfides is well documented, only a few papers describe the oxidation of cyclic disulfides into cyclic thiosulfinates[15] and to the best of our knowledge, there is no report on the oxidation of cyclic bis(disulfides).

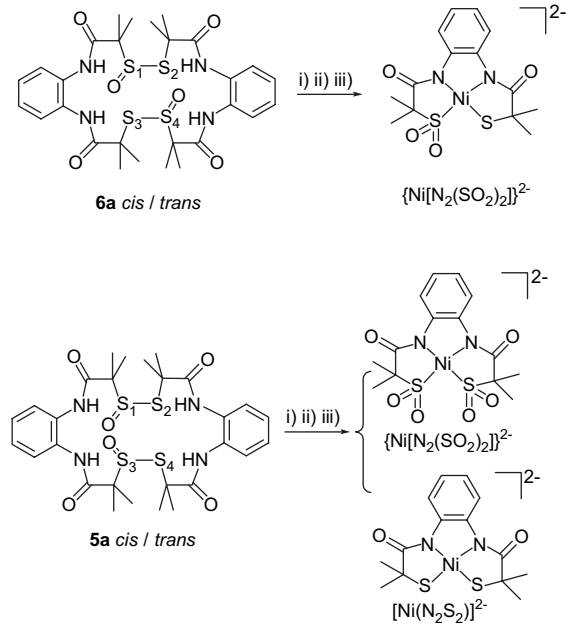
Dimethyldioxirane (DMD) was chosen as a clean oxidant since acetone was the only by-product after oxygen transfer. The solvent used was either acetone or a mixture of CH_2Cl_2/acetone, when the starting product was only sparingly soluble in acetone at the low temperature required for the reaction. In these conditions, the cyclic disulfides **2** were completely and selectively converted with 1 equiv of DMD to the monothiosulfinate **4** (Scheme 3).

Oxidation of the bis(disulfide) **3a** was performed in a CH_2Cl_2/acetone mixture at −50 °C with 2 equiv of DMD (Scheme 4). ^1H NMR analysis of the raw material isolated



Scheme 3. Synthesis of mono-thiosulfinates.

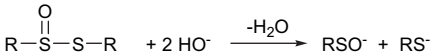
after oxidation of **3a** shows the existence of four different products in the same amount. ESI$^+$ MS analysis of this mixture shows only two peaks at *m/z* 653 and 675, corresponding to the incorporation of two oxygen atoms in the four products (653, $[M+H]^+$; 675 $[M+Na]^+$). The IR spectrum does not show strong bands in the range 1100–1300 cm^{-1} as expected for thiosulfonates $RS(O_2)$–SR, but exhibits only one strong stretching frequency at 1082 cm^{-1} supporting the formation of thiosulfinates. The two oxygens can be incorporated either on both sulfur atoms of the same disulfide bond, or on one sulfur atom of each disulfide bond leading, respectively, to *vic*-disulfoxides or bis(thiosulfinates). Only two stereoisomers are expected in the case of *vic*-disulfoxides and four isomers, as observed by ^{1}H NMR, in the case of thiosulfinates. These four isomers correspond to two couples of cis/trans stereoisomers, resulting from the incorporation of one oxygen atom at S_1 and S_3, or S_1 and S_4, leading to **5a** (cis/trans) and **6a** (cis/trans), respectively. Moreover our compounds being stable at rt, we can rule out definitively the possible involvement of *vic*-disulfoxides, whose S–S bond is relatively weak, and which are only stable at low temperature.[16a] Such compounds have been isolated in unusual structures such as bridged bicyclic α-disulfoxides[16b] and more recently as tetrathiolane-2,3-dioxides.[15c,d]



Scheme 4. Cyclic bis(thiosulfinates) and their conversion to Ni complexes: (i) 4 equiv Et_4NOH, DMF, −40 °C; (ii) 2 equiv $NiCl_2$; (iii) 4 equiv Et_4NOH.

Despite several attempts, we did not succeed in separating the four isomers but two clean fractions were isolated after separation over preparative TLC (SiO_2, RP-18). The upper fraction contained two stereoisomers in a 1/1 ratio while the lower fraction contained the other two stereoisomers in a 35/65 ratio. The different ratio in both couples of stereoisomers after separation arises from the slight difference in migration of the two slow-migrating isomers and by the quite arbitrary cut-off, the in-between fraction being a mixture of the four isomers.

A definitive assignment of the ^{1}H NMR spectrum of each fraction to cis/trans **5a** or cis/trans **6a** being difficult, we used an indirect evidence to do this attribution. In a recent paper,[17] we have shown that alkaline cleavage of the S(O)–S bond in **4b** selectively takes place at the sulfinyl sulfur as previously described for related compounds (Eq. 1),[18] leading after insertion of Co(III) to the corresponding mixed thiolate/sulfinate complex.[17]



(1)

This reaction was then applied to the metalation of **4a** and **4b** with Ni(II) with the same selectivity toward mixed thiolate/sulfinate derivatives (paper in preparation). To characterize and attribute the regioisomers to each fraction, the two collected fractions were subjected to alkaline cleavage of both S(O)–S bonds followed by Ni(II) insertion in the opened structures. By comparison with an authentic sample prepared from **4a**, a unique square planar complex with a mixed thiolate/sulfinate environment, $\{Ni[N_2S(SO_2)]\}^{2-}$, was obtained from the lower fraction, indicating clearly that it corresponds to the mixture of stereoisomers **6a** cis and trans. Treatment of the upper fraction leads to a 1/1 mixture of bis(thiolate) and bis(sulfinate) nickel complexes consistent with the mixture of stereoisomers **5a** cis and trans. The IR spectra of $\{Ni[N_2S(SO_2)]\}^{2-}$ and $\{Ni[N_2S(SO_2)]\}^{2-}$ display two bands between 1000 and 1200 cm^{-1}, assigned to $\nu(SO)_{asym}$ and $\nu(SO)_{sym}$ stretching typically observed in S-bonded metal sulfinate complexes. For an O-bonded sulfinate, only one strong vibration around 1000 cm^{-1} is expected. Because the yields of pure isomers **5a** and **6a** were very low, this has hampered the attempts to get crystal structures of the resulting Ni complexes. Finally, an assignment of the ^{1}H NMR signals to **6a1** and **6a2** (cis or trans isomer) was possible on the basis of their relative intensities since these two compounds are in 35/65 ratio. However, **5a1** and **5a2** being in a 1/1 ratio, a complete attribution of the signals to **5a1** and **5a2** was not possible.

3. Conclusion

In conclusion, we have described efficient syntheses of cyclic mono- and bis-disulfides and their selective conversions to thiosulfinates and bis-thiosulfinates with dimethyldioxirane as oxidant. In addition, we propose a simple method to identify the two regioisomers derived from the 20-membered ring cyclic bis(thiosulfinates), which can be applied to other cyclic pseudopeptidic bis(thiosulfinates).

4. Experimental

4.1. Dithiol 1c

To a THF solution (20 mL) of *S*-benzyl-*N*-Boc-L-cysteine (1.1 g, 3.53 mmol) and *N*-methylmorpholine (442 μL, 4 mmol), isobutyl chloroformate (521 μL, 4 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h. *o*-Phenylenediamine (173 mg, 1.6 mmol) in THF (25 mL) was slowly added at rt. After stirring overnight, the solution was filtered and the solvent evaporated to dryness. Ethyl acetate was then added and the solution was washed with water, saturated aq NaCl, water, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography over silica gel (CH_2Cl_2/AcOEt 95/5) gave the *S*-benzyl intermediate. Yield: 72% (800 mg). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.46 (s, 18H), 2.9 (m, 4H), 3.74 (m, 4H), 4.39 (m, 2H), 5.39 (m, 2H), 7.17–7.46 (m, 16H), 8.46 (s, 2H). Mass (CI$^+$, NH_3) *m*/*z* 695 [M+1]$^+$; 712 [M+NH_4^+]. Anal. Calcd for $C_{36}H_{48}N_4O_6S_2$: C, 62.22; H, 6.67; N, 8.06. Found: C, 62.09; H, 6.82; N, 8.17. The *S*-benzyl derivative (800 mg, 1.15 mmol) dissolved in THF (3 mL) was stirred with anhydrous ammonia (50 mL). An excess of sodium (4–10 equiv) was then added until persistence of a blue color for 1 h. After addition of NH_4Cl, and removal of NH_3 and THF, aq HCl (0.1 M) was added and the acidic solution was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Yield: 86% (510 mg). Compound **1c**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 18H), 1.65 (m, 2H), 2.83–3.17 (m, 4H), 4.5 (m, 2H), 5.59 (m, 2H), 7.2 (m, 2H), 7.13–7.46 (m, 2H), 8.63 (s, 2H). Mass (CI$^+$, NH_3) *m*/*z* 515 [M+1]$^+$; 532 [M+NH_4^+]. Anal. Calcd for $C_{22}H_{34}N_4O_6S_2$: C, 51.34; H, 6.66; N, 10.89. Found: C, 51.14; H, 6.86; N, 10.77.

4.2. 2-Mercapto-*N*-[2-(2-mercapto-2-methyl-propionylamino)-phenyl]-2-methyl-propionamide 1a

A 0.07 M methanol solution of thioacetic acid *S*-{1-[2-(2-acetylsulfanyl-2-methyl-propionylamino)-phenyl-carbamoyl]-1-methyl-ethyl} ester[5] was deprotected in methanol with K_2CO_3 (2.2 equiv). After stirring overnight under argon, the solution was acidified with an ethereal solution of HCl(g) (2 equiv). After removal of the solvents and dissolution of the solid in a large volume of EtOAc, the solution was washed with water and dried over $MgSO_4$. Evaporating the solvent in vacuo afforded **1a** in quantitative yield. ^{1}H NMR (250 MHz, CD_2Cl_2) δ 1.31 (s, 3H), 1.60 (s, 6H), 1.71 (s, 6H), 7.28 (m, 2H), 7.42 (m, 2H). Yield from 443 mg of the thioacetic derivative, 95% (324 mg).

4.3. Typical procedure for synthesis of disulfides

0.13 M solutions of dithiol **1** and I_2 (1 equiv relative to **1**) in $CHCl_3$ were added dropwise and simultaneously, under argon, into a 0.26 M solution of triethylamine (2 equiv relative to **1**) in $CHCl_3$. Then the solution was washed with saturated aq $Na_2S_2O_3$, aq HCl (0.1 N), and water and the solvent was removed. In the case of **1a**, **2a** and **3a** were isolated by selective precipitation of **2a** in $CHCl_3$ leading to a 25/75 ratio of **2a**/**3a**. Compounds **2b** and **2c** were purified by column chromatography over silica gel using dichloromethane/ethyl acetate mixtures as eluants (7/3 for **2b** and 8/2 for **2c**).

4.3.1. 7,7,10,10-Tetramethyl-5,12-dihydro-8,9-dithia-5,12-diaza-benzocyclodecene-6,11-dione 2a. IR (ATR): 3300 (NH), 1653 (amide), 1503, 1441, 747. ^{1}H NMR (250 MHz; DMSO-d_6) δ 1.56 (s, 6H), 1.59 (s, 6H), 7.2 (m, 2H), 7.35 (m, 2H), 9.13 (s, 2H_{NH}). Mass (ESI$^+$) *m*/*z* 333 [M+Na]$^+$. Anal. Calcd for $C_{14}H_{18}N_2O_2S_2\cdot 0.5H_2O$: C, 52.64; H, 6.00; N, 8.77. Found: C, 52.44; H, 5.56; N, 8.8. Yield from 240 mg of **1a**, 24% (58 mg).

4.3.2. 8,8,11,11-Tetramethyl-5,7,8,11,12,14-hexahydro-9,10-dithia-5,14-diaza-benzocyclododecene-6,13-dione 2b. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 12H), 2.64 (s, 4H), 7.18 (m, 2H), 7.41 (m, 2H), 8.24 (s, 2H_{NH}). Anal. Calcd for $C_{16}H_{22}N_2O_2S_2$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.76; H, 6.48; N, 8.09. Yield starting from 4.47 g of **1b**: 61% (2.71 g).

4.3.3. (12-*tert*-Butoxycarbonylamino-6,13-dioxo-5,6,7,8,11,12,13,14-octahydro-9,10-dithia-5,14-diaza-benzocyclododecen-7-yl)-carbamic acid *tert*-butyl ester 2c. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47 (s, 18H), 3.22–3.38 (m, 4H), 4.57 (m, 2H), 5.52 (s, 2H_{NH}), 7.22–7.36 (m, 4H), 8.34 (s, 2H). Anal. Calcd for $C_{22}H_{32}N_4O_6S_2\cdot AcOEt\cdot H_2O$: C, 50.47; H, 6.84; N, 9.05. Found: C, 50.71; H, 7.05; N, 8.86. Yield starting from 400 mg of **1c**: 58% (231 mg).

4.3.4. 7,7,10,10,19,19,22,22-Octamethyl-5,12,17,24-tetrahydro-8,9,20,21-tetrathia-5,12,17,24-tetraaza-dibenzo-[*a*,*k*]cycloeicosene-6,11,18,23-tetraone 3a. IR (ATR, cm^{-1}): 3306 (NH), 1670 (amide), 1527, 1472, 747. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.66 (s, 24H), 7.0 (m, 4H), 7.26 (m, 4H), 8.73 (s, 4H_{NH}). Anal. Calcd for $C_{28}H_{36}N_4O_4S_4\cdot H_2O$: C, 52.64; H, 6.00; N, 8.77. Found: C, 53.36; H, 6.00; N, 8.77. Mass (FAB$^+$) *m*/*z* 621 [M+1]$^+$. Yield from 240 mg of **1a**, 75% (180 mg).

4.4. Typical procedure for synthesis of thiosulfinates 4

Disulfide **2** was dissolved in acetone (0.02 M for **2b**) or in a 60/40 v/v mixture of CH_2Cl_2/acetone (3 mM for **2a**) and DMD (0.08 M in acetone, 1 equiv) was added dropwise at −40 °C under argon. Removal of the solvents afforded the thiosulfinates **4** in almost quantitative yields.

4.4.1. 7,7,10,10-Tetramethyl-8-oxo-5,7,8,12-tetrahydro-8λ^4,9-dithia-5,12-diaza-benzocyclodecene-6,11-dione 4a. IR (ATR, cm^{-1}): 1662, 1506, 1089 (S=O), 749. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.71 (s, 3H), 1.75 (s, 3H), 1.96 (s, 3H), 7.19 (m, 2H), 7.37 (m, 2H). Mass (FAB$^+$) *m*/*z* 327.2 [M+1]$^+$. ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.53 (s, 3H), 1.76 (s, 6H), 7.18 (m, 2H), 7.37 (m, 2H), 9.18 (s, 1H_{NH}), 9.76 (s, 1H_{NH}). ^{13}C NMR (500 MHz, DMSO-d_6) δ 16.32, 22.15, 25.57, 28.17, 54.78, 70.24, 128.27, 128.53, 129.23, 135.55, 167.63, 172.64. Mass (FAB$^+$) *m*/*z* 327 [M+1]$^+$. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2\cdot 1/6CH_2Cl_2$: C, 49.66; H, 5.40; N, 8.16. Found: C, 49.57; H, 5.24; N, 8.56. Yield from 200 mg of **2a**, 97% (217 mg).

4.4.2. 8,8,11,11-Tetramethyl-9-oxo-5,8,9,11,12,14-hexahydro-7*H*-9λ^4,10-dithia-5,14-diaza-benzocyclododecene-6,13-dione 4b. IR (ATR, cm^{-1}): 1665, 1527, 1070 (S=O), 733. ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.45 (s, 3H), 1.61 (s, 3H), 1.65 (s, 6H), 2.78–2.9 (m, 2H), 3.1–3.2 (m, 2H), 7.17 (m, 2H), 7.3 (m, 2H), 8.95 (s, 1H_{NH}), 9.67 (s, 1H_{NH}).

^{13}C NMR (500 MHz, $CDCl_3$) δ 24.04, 24.84, 30.70, 31.80, 45.66, 49.54, 52.36, 63.10, 126.46, 127.00, 130.96, 131.70, 167.30, 168.76. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2\cdot 0.5H_2O$: C, 53.31; H, 6.34; N, 7.77. Found: C, 53.33; H, 6.16; N, 7.56. Yield from 500 mg of **2b**, 94% (508 mg).

4.4.3. (12-*tert*-Butoxycarbonylamino-6,10,13-trioxo-5,7,8,10,11,12,13,14-octahydro-6*H*-9,10λ^4-dithia-5,14-diaza-benzocyclododecen-7-yl)-carbamic acid *tert*-butyl ester 4c. The product was purified by flash chromatography (SiO_2, CH_2Cl_2/AcOEt 60/40). IR (ATR, cm^{-1}): 1692, 1660, 1076 (S=O), 756. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47 (s, 18H), 3.52–3.83 (m, 4H), 4.53–4.59 (m, 1H), 4.87 (s, 1H), 5.69–5.77 (m, 2H$_{NH}$), 7.13–7.65 (m, 4H$_{Ar}$), 8.58 (s, 1H$_{NH}$), 8.64 (s, 1H$_{NH}$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 28.32, 37.36, 51.62, 53.70, 57.99, 80.81, 124.00, 125.39, 126.40, 127.00, 127.59, 128.31, 128.97, 130.74, 154.97, 167.00, 168.24. Anal. Calcd for $C_{22}H_{32}N_4O_7S_2\cdot 0.5$AcOEt: C, 50.33; H, 6.34; N, 9.78. Found: C, 50.62; H, 6.42; N, 9.45. Yield from 50 mg of **2c**, 63% (35 mg).

4.5. Bis-thiosulfinates 5a and 6a

To a CH_2Cl_2/acetone (30/70 v/v mixture) solution of **3a**, cold DMD in acetone (2 equiv) was added dropwise at −50 °C. ^{1}H NMR analysis of the mixture isolated after removal of the solvents revealed the unique presence of **5a** and **6a** in a 1/1 ratio. Mass (ESI$^+$) *m*/*z* 653 [M+H]$^+$; 675 [M+Na]$^+$. Anal. Calcd for $C_{28}H_{36}N_4O_6S_4\cdot 0.5H_2O$: C, 50.81; H, 5.63; N, 8.46. Found: C, 50.79; H, 5.88; N, 8.29. Yield from 205 mg of **3a**, 96% (260 mg of **5a** and **6a**). Compounds **5a** and **6a** were separated by three successive migrations on preparative TLC silica gel 60 F_{254} (1 mm) eluted with hexane/AcOEt (4/6 v/v mixture).

4.5.1. 7,7,10,10,19,19,22,22-Octamethyl-8,21-dioxo-5,7,8,12,17,21,22,24-octahydro-8λ^4,9,20,21λ^4-tetrathia-5,12,17,24-tetraaza-dibenzo[*a*,*k*]cycloeicosene-6,11,18,23-tetraone 5a. Two isomers **5a1** and **5a2** unrespectively cis and trans in a 1/1 ratio. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.93, 1.89, 1.87, 1.85, 1.76, 1.60 (s, 6×3H), 1.76 (s, 6H), 6.88, 6.95, 7.16, 7.61 (m, 8H$_{Ar}$ **5a1**), 6.86, 6.94, 7.65, 7.2 (m, 8H$_{Ar}$ **5a2**), 7.08 (m) not attributed, 8.40, 8.85 (s, 2×2H$_{NH}$ **5a1**), 8.37, 8.90 (s, 2×2H$_{NH}$ **5a2**). IR (ATR, cm^{-1}): 3272, 1650 (amide), 1513, 1082 (S=O), 747. Yield from 42 mg of the mixture **5a/6a**, 14% (6 mg).

4.5.2. 7,7,10,10,19,19,22,22-Octamethyl-8,20-dioxo-5,7,8,12,17,19,20,24-octahydro-8λ^4,9,20λ^4,21-tetrathia-5,12,17,24-tetraaza-dibenzo[*a*,*k*]cycloeicosene-6,11,18,23-tetraone 6a. Two isomers **6a1** and **6a2** unrespectively cis and trans in a 7/3 ratio. ^{1}H NMR (250 MHz, $CDCl_3$) δ **6a1**: 1.95, 1.78, 1.74, 1.72 (s, 4×3H), 7.14, 7.66 (m, 2×4H), 8.60 (m, 4H); δ **6a2**: 1.98, 1.84, 1.77, 1.66 (s, 4×3H), 7.66, 7.14 (m, 2×4H), 8.54 (s, 4H). Yield from 42 mg of the mixture **5a/6a**, 47% (20 mg).

4.6. Typical procedure for characterization of the stereoisomers 5a and 6a

To a DMF solution of **5**a or **6a** at −40 °C was first added, under a stream of argon and stirring, Et_4NOH (1 M in MeOH, 4 equiv) to cleave the S(O)–S bonds and to produce the sulfinates and the thiolates. A concentrated DMF solution of $NiCl_2$ (2 equiv) was then added and immediately 4 equiv of Et_4NOH to deprotonate the amides. The solution was then allowed to warm to rt. After removal of the solvents in vacuo, the complexes were isolated upon precipitation at 0 °C from CH_3CN into diethylether and characterized by ^{1}H NMR. Synthesis and spectroscopic characterizations of $[Ni(N_2S_2)](Et_4N)_2$ are described in Ref. 12.

{Ni[N$_2$S(SO$_2$)]}(Et$_4$N)$_2$: IR (ATR, cm^{-1}): 1588 (C=O), 1154 and 1034 (SO_2), 1173, 1001 (Et_4N). ^{1}H NMR (250 MHz, CD_3CN) δ 1.18 (m, 24H), 1.27 (s, 6H), 1.45 (s, 6H), 3.24 (q, *J*=7.3 Hz, 16H), 6.62 (m, 2H), 8.58 (m, 2H). Anal. Calcd for $C_{60}H_{56}N_4NiO_4S_2\cdot 1.5H_2O$: C, 52.48; H, 8.66; N, 8.16. Found C, 52.57; H, 8.65; N, 8.37.

{Ni[N$_2$(SO$_2$)$_2$]}(Et$_4$N)$_2$: IR (ATR, cm^{-1}): 1599, 1562, 1180, 1170, 1057, 1031. ^{1}H NMR (250 MHz, CD_3OD) δ 1.26 (t, *J*=7.3 Hz, 24H), 1.45 (s, 12H), 3.26 (q, *J*=7.3 Hz, 16H), 6.75 (m, 2H), 8.47 (m, 2H). Mass (ESI$^-$) *m*/*z* 560 (50%) [{Ni[N$_2$(SO$_2$)$_2$]}(Et$_4$N)]$^-$. Anal. Calcd for $C_{60}H_{56}N_4NiO_6S_2\cdot H_2O\cdot 0.5CH_3CN$: C, 50.99; H, 8.21; N, 8.63. Found: C, 50.82; H, 8.09; N, 8.60.

4.7. X-ray crystallography for 3a

Formula $C_{28}H_{36}N_4O_4S_4$; monoclinic, space group $P2_1/a$; a=11.958(2), b=10.662(2), c=13.373(2) Å, β=116.15(1)°, V=1530.4(4) Å^3, Z=2. The structure was solved by SHELXS 97[19] and refined using SHELXL 97.[20] The hydrogen atoms were positioned geometrically and refined riding on their carrier atom with isotropic thermal displacement parameters fixed at 1.2 times those of their parent atoms. Convergence was reached at $R1$=0.0636 for 2733 reflections ($I>2\,\sigma(I)$), $wR2$=0.186 for all data and S=0.934 for 185 parameters. The residual electron density in the final difference Fourier does not show any feature above 0.698 eÅ^{-3} and below −0.571 eÅ^{-3}. An ORTEP[21] view is given in Figure 1.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 249662. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]

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