

Intra- versus Inter-molecular Azine Formation in Thiocrown Ether Chemistry

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Azines are prepared from keto-functionalized thiocrown ethers; a diketo example reacts intramolecularly.

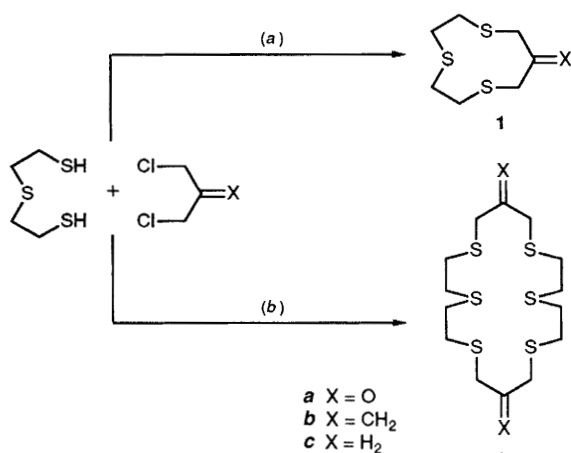
Macrocyclic thioether ligands have, in principle, the potential to work as extraction agents for soft, heavy-metal ions. Silver, copper, cadmium and mercury display especially strong affinities with the proximate sulfur ligating sites of thiocrown ethers.¹⁻⁶ The possibility of using these ligands as sequestering^{7,8} agents in, for example, treatment of heavy-metal poisoning, prompted us to study the functionalization of the molecular periphery of the crown ether system.^{9,10} The syntheses of **1** and **2** depicted in Scheme 1 illustrate routes developed to simple mono- and di-functionalized thiocrown ethers.^{10,11} Further functionalization should be possible *via* the methylene and keto groups. We describe here a specific type of functionalization of the keto-substituted macrocycles **1a** and **2a** as well as **3** and **4** prepared following route (a) given in Scheme 1.

Preliminary experiments with **3** and **4** in which additions to the carbonyl group were attempted (Wittig, Grignard reagents) were disappointing owing to the high tendency towards enolization. On the other hand, condensation of **1a**, **3** and **4** with hydrazine proceeded smoothly in 38 to 57% yields

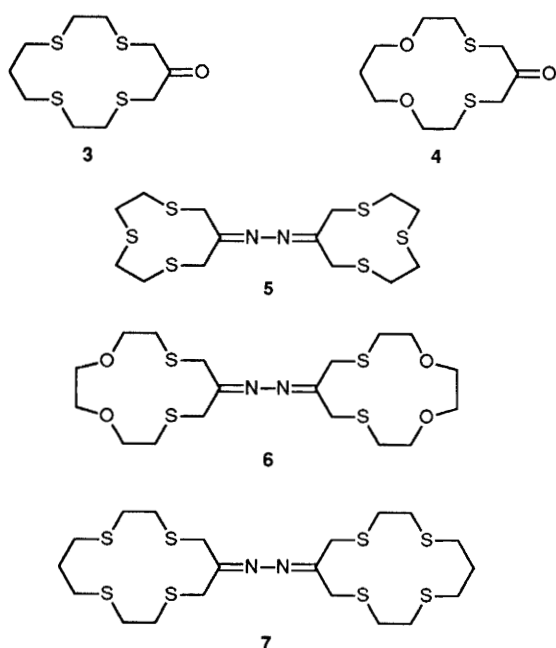
to provide the symmetrical azines **5-7**.[†] The hydrazides were not characterized but are doubtless intermediates. No evidence for tautomerization of the imine functionalities was found. Analytical and spectral data are in accordance with the suggested structures.

Although these azines are crystalline, the hair-like crystal shape hampered efforts to determine the molecular structure

[†] The macrocyclic ketones **1a**, **3** and **4** (1 mmol) were dissolved in toluene. Hydrazine hydrate (0.55 mmol) and a catalytic amount of *p*-TosOH was added and the resulting mixture was refluxed for 16 h in a Dean-Stark apparatus. Work-up, followed by recrystallization from CH₂Cl₂-cyclohexane gave the corresponding azines; **5**: yield 57%; ¹H NMR (CDCl₃) δ 2.00 (br s, 16H), 3.75 (s, 8H); IR (KBr, ν/cm⁻¹) 2950, 1650, 1425, 1280, 1220, 920, 740; mass M⁺ = 412 (calcd. for C₁₄H₂₄N₂S₆ 412) **7**: yield 38%, ¹H NMR (CDCl₃) δ 1.90 (m, 4H), 2.60 (t, 6H) 2.75 (s, 16H) 3.65 (s, 8H); IR (KBr, ν/cm⁻¹) 2950, 1660, 1430, 1280, 1220, 920, 760; mass M⁺ = 560 (calcd. for C₂₀H₃₆N₂S₈ 560) **6**: yield 64% ¹H NMR (CDCl₃) δ 2.70 (m, 8H), 3.60 (s, 8H), 3.81 (t + s, 16H); IR (KBr, ν/cm⁻¹) 2950, 1660, 1430, 1280, 1220, 920, 760; mass M⁺ = 468 (calcd. for C₁₈H₃₂N₂O₄S₄ 468).



Scheme 1 Reagents: (a) Cs₂CO₃, DMF; (b) B(OPrⁱ)₃, Al(OPrⁱ)₃



by X-ray diffraction methods. The mixed oxygen–sulfur crown azine **6** eventually provided suitable crystals.‡ The molecular structure of **6** is illustrated in Fig. 1.

The molecule is built up of two macrocyclic ring fragments interconnected as expected by the azine bridge. It possesses a twofold symmetry axis in the middle of the N–N bond vector. The bis-imine unit is bent from a coplanar *anti* arrangement as is indicated by the C(3')–N(14)–N(14') torsion angle of 139.88°. This nonplanar arrangement is also found in aromatic (ket)azines like those of benzaldehyde and *p*-salicylaldehyde and in the azine of butane-2,3-dione.^{12–15}

The N–N bond distance [1.406(3) Å] is fairly normal and compares well with those found for the azines of benzaldehyde [1.38(1) Å]¹⁵ and *p*-salicylaldehyde [1.417(7) Å].¹⁴

The macrocyclic ring is twisted with respect to this plane [S(1)–C(2)–C(3)–N(14) = –80.5(3), S(5)–C(4)–C(3)–N(14) = 96.0(3)°]. As a result of this rather open arrangement of

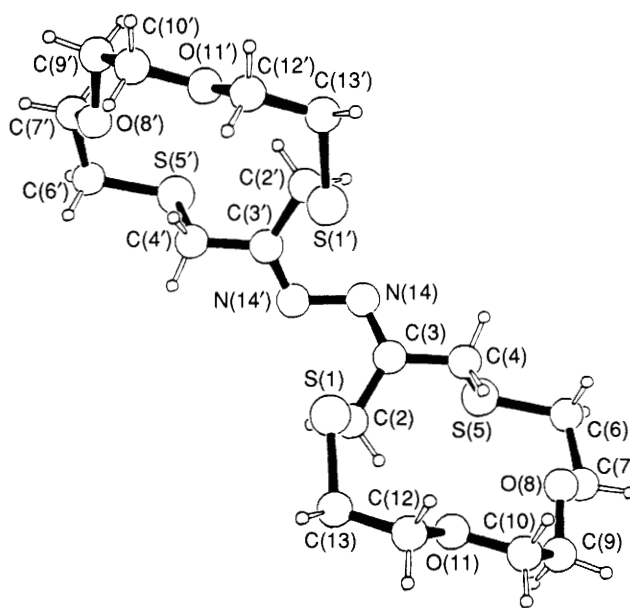
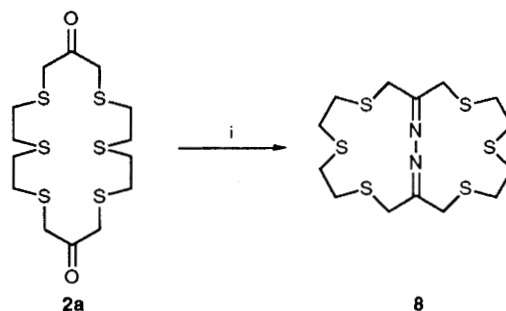


Fig. 1 Perspective plot of **6**. Selected bond distances (Å) and (torsion) angles (°): N(14)–N(14a) 1.4055(3), S(1)–C(2) 1.829(3), N(14)–C(3)–C(2) 125.6(2), S(5)–C(6)–C(7)–O(8) 64.1(3), N(14)–C(3)–C(4) 117.0(3), S(1)–C(2)–C(3)–N(14) 80.5(3), O(8)–C(9)–C(10)–O(11) 65.0(3), C(3)–N(14)–N(14a) 113.9(3), C(4)–S(5)–C(6) 100.6(1).



Scheme 2 Reagents: i, NH₂NH₂; *p*-TosOH

both macrocyclic units, the ligand will probably display two independent coordination sites.

The pronounced tendency of thiocrown ethers possessing ethylenic, propylenic, and propane bridges to place all the sulfur atoms *anti* is revealed here also.¹ The rigid three carbon bridge C(2)–C(3)–C(4) (constituting part of the bis-imine unit) separates the two sulfur atoms S(1) and S(5) in an *anti* arrangement as is best reflected by the distances of S(1) and S(5) from the plane defined by C(2)–C(3)–C(4)–N(14) [distance plane CCCN–S(1) = 1.712 Å and CCCN–S(5) = 1.728 Å]. The oxygen atoms O(8) and O(11) deviate somewhat from the pure *gauche* conformation about the dimethylene bridge C(9)–C(10) [O(8)–C(9)–C(10)–O(11) = 65.0° (3)].

With **2a**, an intramolecular, transannular condensation takes place with hydrazine hydrate. The reaction, as depicted in Scheme 2, proceeds smoothly in toluene with a catalytic quantity of toluene-*p*-sulfonic acid. The overall yield of the reaction to provide the unusual molecule **8** is approximately 15%, suggesting that oligo- and poly-meric azines are formed competitively.§ However, the experimental conditions for the synthesis of **8** have not been fully optimized.

‡ Crystal data for **6**: C₁₈H₃₂N₂O₄S₄; M_r = 468.72, block-shaped light-yellow crystal (0.2 × 0.25 × 0.20 mm), monoclinic, space group C₂/c with a = 11.578(1), b = 12.931(2), c = 16.454(1) Å, β = 106.71°, V = 2359.4(4) Å³, Z = 4, D_c = 1.319 g cm⁻³, Mo-Kα radiation (λ = 0.71073 Å), 3421 reflections (1° < θ < 30°) were measured on an Enraf-Nonius CAD 4 diffractometer (T 290 K); 2410 [I > 3σ(I)] reflections were used in the refinements. Scaling factors, Lorentz and polarization corrections were applied to the data. The structure was solved by direct methods H-atoms were located from succeeding Fourier syntheses. Final residuals were R = 0.032 and R_w = 0.046.

§ A solution of **2a** in toluene was allowed to react with an equimolar amount of NH₂–NH₂·H₂O and a catalytic amount of *p*-TosOH in toluene. This was refluxed with a Dean-Stark trap for 24 h. The mixture turned slowly reddish. After cooling, the solvent was removed *in vacuo* and the residual solid was chromatographed over silica gel using methylene chloride as eluent. The organic layer was evaporated leaving a tarry orange-red solid, which was difficult to purify; yield 15% based on diketone **2a**. Exact mass m/z = 412.742 (theor. 412.743 for C₁₄H₂₄S₆N₂).

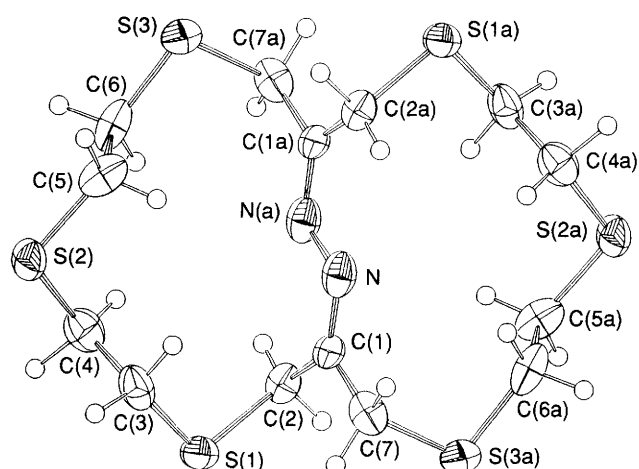


Fig. 2 Thermal motion ellipsoid (50% probability level) plot of **8**. Selected bond distances (Å) and angles (°): N(a)–N 1.356(10), N–C(1)–C(2)–S(1) –121.3(8), S(1)–C(3)–C(4)–S(2) –175.2(4), S(2)–C(5)–C(6)–S(3) 175.7(4), S(3a)–C(7)–C(1)–N –105.9(8), C(1a)–N(a)–N–C(1) 180.0, N(a)–N–C(1) 111.8(7), C(7)–C(1)–N 113.9(9).

The molecular structure of **8** was determined by X-ray diffraction methods[¶] and is shown in Fig. 2.

The molecule possesses a centre of symmetry and is slightly twisted [N–C(1)–C(2)–S(1) = –121.3 (8)°, S(3a)–C(7)–C(1)–N = –105.9(8)°]. It shows the same essential features as observed for the bis(keto) derivative **2a**¹¹ and other large ring systems. The sulfur atoms are arranged in an *anti* fashion as is evident from the S–C–C–S torsion angles S(1)–C(3)–C(4)–S(2) = –175.2 (4)°, S(2)–C(5)–C(6)–S(3) = 175.7(4)°.

[¶] Crystal data for **8**: C₁₄H₂₄N₂S₆; M_r = 412.75, block-shaped yellowish crystal (0.12 × 0.25 × 0.25 mm) orthorhombic, space group *Pbca* with *a* = 12.030(2), *b* = 9.270(1), *c* = 16.856(5) Å, *V* = 1879.7(7) Å³, *Z* = 4, *D_c* = 1.458 g cm⁻³; 7629 reflections (θ < 26°, ω/2θ scan, *T* 150 K) were measured on a CAD 4T/ rotating anode diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were corrected for Lp, a small linear decay of 7% and absorption (DIFABS). The structure was solved by direct methods (SHELXS-86) and refined by full-matrix least-squares (SHELXS-76) to *R* = 0.078 (*R_w* = 0.064) w⁻¹ = σ²(*F*) + 0.000084*F*², 1038 reflections with *I* > 3σ(*I*); 125 parameters. H-atoms were located from a difference Fourier map and their positions refined. For **6** and **8**, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

As a result of the internal N–N bond [N(a)–N = 1.356(10) Å], the molecule is more or less folded. This closely resembles the arrangement of **2a**¹¹ in which the two carbonyl moieties point inward into the molecular cavity¹¹ of the macrocycle.

We envisage the possibility to prepare new classes of cryptand-like systems by condensation reactions with primary α,ω-diamines. The intermolecular reactions with two separate macrocycles provide an entry into ditopic receptors. Further work is in progress and will be presented in forthcoming papers.

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