Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2159–2162
Tetrahedron Letters

Macrocyclic sulfamides: synthesis, hybridization, and metal binding properties

Patrick D. Bailey *, Anuparma Sethi, Robin G. Pritchard

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom

Received 30 December 2007; accepted 18 January 2008
Available online 30 January 2008

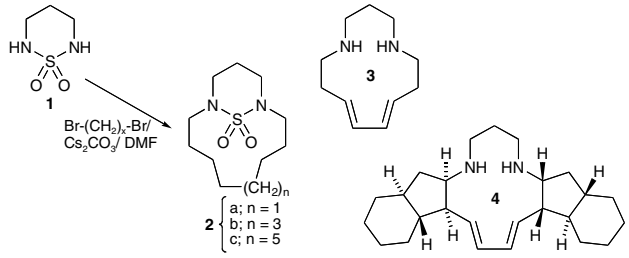
Abstract

Four cyclophanes incorporating the cyclosulfamide sub-unit have been synthesised in high yield. The X-ray crystal structures of three of them, and of cyclosulfamide itself, provide useful insight into the hybridisation of such compounds. The ionophoric properties of the macrocycles are also reported, with the sulfamides showing unusual selectivity for rubidium (benzyl trimer), barium (pyridyl dimer) and silver (pyridyl dimer and trimer).

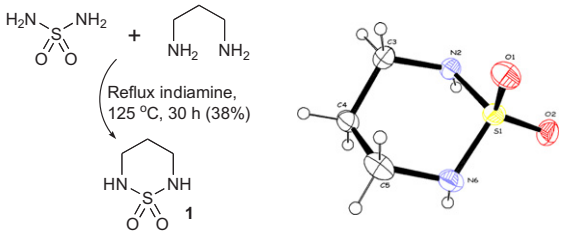
This Letter describes the synthesis of C_8–C_{12} cyclophanes and polydentate macrocycles that incorporate the sulfamide sub-unit, and that display interesting ion-binding properties. Our initial interest in the sulfamide heterocycle **1** was as a masked/activated diamine precursor of medium-sized cyclophanes **2a–c** (Scheme 1), as models for a new route to the heterocyclic core **3** of brevianamide **4**[1] and the related compounds.

Contrary to our expectations, the 6-membered sulfamide **1** could not be prepared in high yield using literature procedures,[2] and a modification of Ahn's method[2a] was eventually developed that gave **1** in 38% yield, and allowed large quantities to be prepared easily and cheaply.[3] The X-ray crystal structure of **1** is of interest concerning the geometry and hybridisation of the nitrogens, which both display sp^3 character, with heterocycle **1** adopting a 'cyclohexane' chair-like conformation[4a] (see Scheme 2).

The cyclisations in Scheme 1 provided cyclophanes **2**, but with large amounts of cyclic polymers (mainly di- and trimers) when $n < 5$. It occurred to us that the chemistry might be extended to provide access to a new series of macrocycles with interesting ionophoric potential.[5] We therefore reacted **1** with 1,3-di(bromomethyl)benzene,



Scheme 1. Macrocyclic targets from sulfamide **1**.

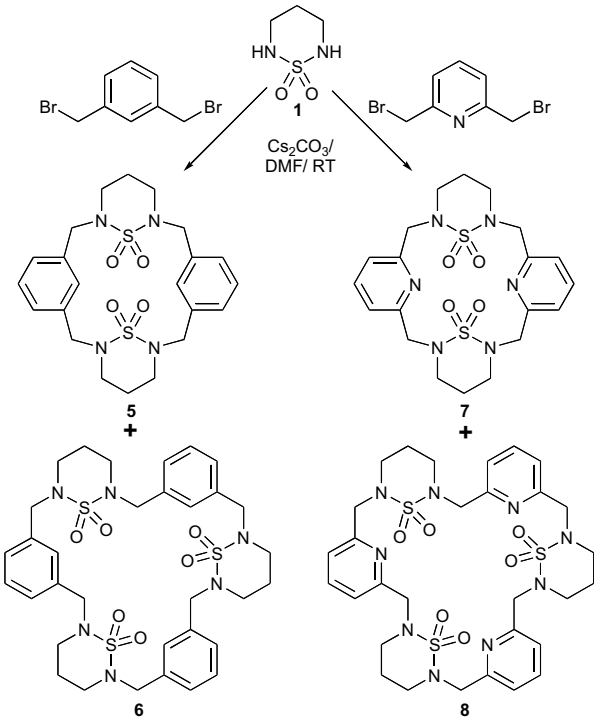


Scheme 2. Synthesis of sulfamide **1**, and its X-ray crystal structure.

which led to the highly efficient formation of the dimeric and trimeric macrocycles **5** and **6**, which were readily separated by flash chromatography in 52% and 31% isolated yields, respectively. With the principle established,

* Corresponding author. Tel.: +44 (0) 1782 584 583.
E-mail address: p.bailey@natsci.keele.ac.uk (P. D. Bailey).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.087



Scheme 3. Synthesis of benzyl macrocycles **5** and **6**, and pyridyl macrocycles **7** and **8**.

we extended the methodology to the pyridyl analogues **7** and **8**, which were isolated in 48% and 33% yields, respectively. The synthesis of both benzyl and pyridyl analogues is depicted in Scheme 3.

The structures of the benzyl trimer **6** and both pyridyl dimer **7** and pyridyl trimer **8** were confirmed by single crystal X-ray diffraction[4b–d] as shown in Figures 1–3, respectively. The most obvious attribute noted, with respect to the benzyl macrocycle **6**, was the approximately twofold symmetry, and the twist-chair conformation of the sulfamide heterocyclic units.

The X-ray structures of the pyridyl macrocycles demonstrate three particularly notable features. Firstly, whilst dimer **7** displays twofold symmetry, trimer **8** shows roughly

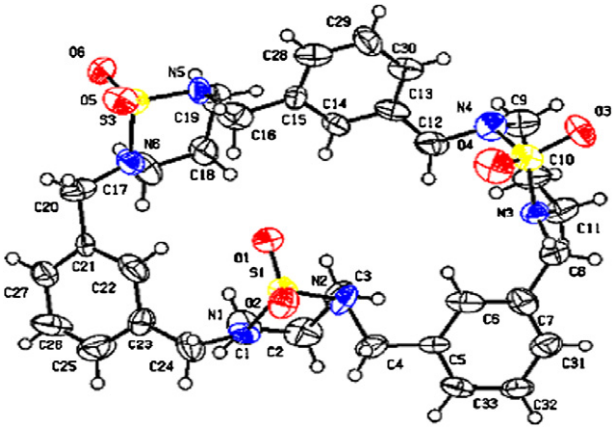


Fig. 1. X-ray crystal structure of benzyl trimer **6**.

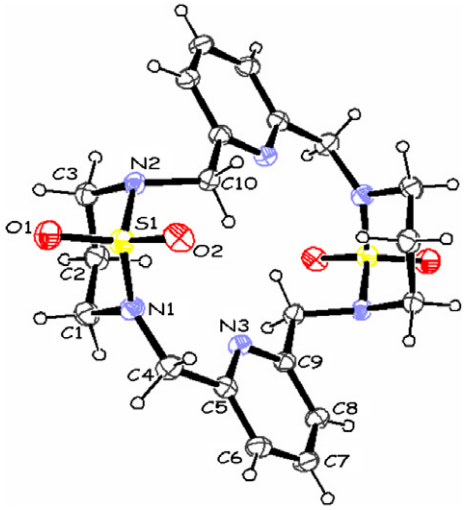


Fig. 2. X-ray crystal structure of the pyridyl dimer **7**.

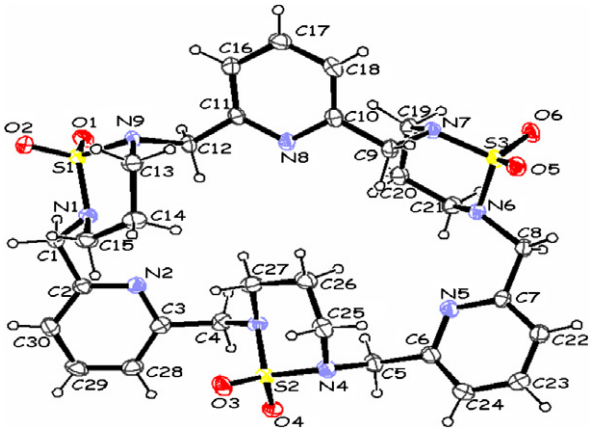


Fig. 3. X-ray crystal structure of pyridyl trimer **8**.

threefold symmetry (cf. **6**). Secondly, the sulfamide substituents alternate between axial and trigonal in the dimer, but alternate between axial and equatorial in the trimer, indicating that the hybridisation of sulfamides is finely balanced. Thirdly, and most strikingly, the sulfamide oxygens are directed into the centre of the macrocycle in the dimer, but point outwards to the external environment in the trimer.

The possibility that intriguing metal chelation properties might be more pronounced in the pyridyl analogues than in the benzyl analogues prompted us to investigate the cation-binding properties of macrocycles **5**–**8**. The pyridyl analogues **7** and **8** had more atoms with donor pairs of electrons available. In addition, the pyridyl molecules did not have any hydrogens pointing into the cavity, unlike the benzylic analogues, hence the repulsion between the donor ligand and the cation might also be reduced.

The cation-binding studies of the four macrocycles **5**, **6**, **7** and **8** were performed with various metal cation picrates (alkali, alkaline earth, transition and post-transition metals), using UV spectrophotometry at 375 nm at room

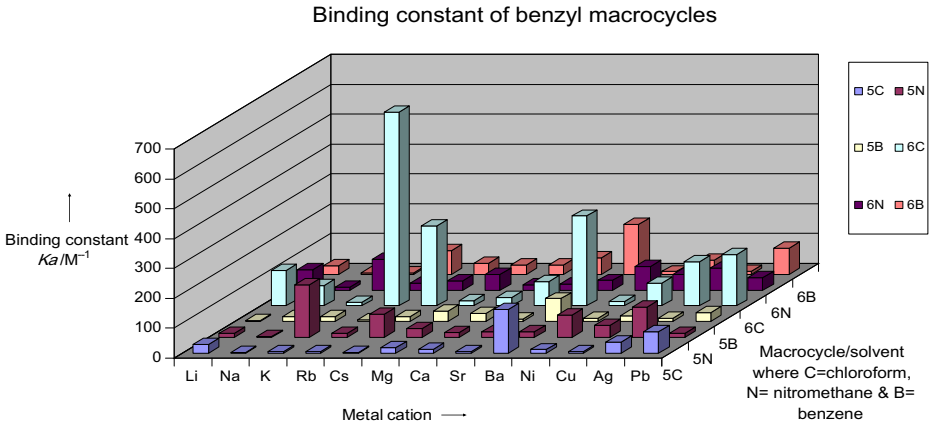


Fig. 4. Binding constants (M^{-1}) of the benzyl macrocycles (dimer **5** and trimer **6**).

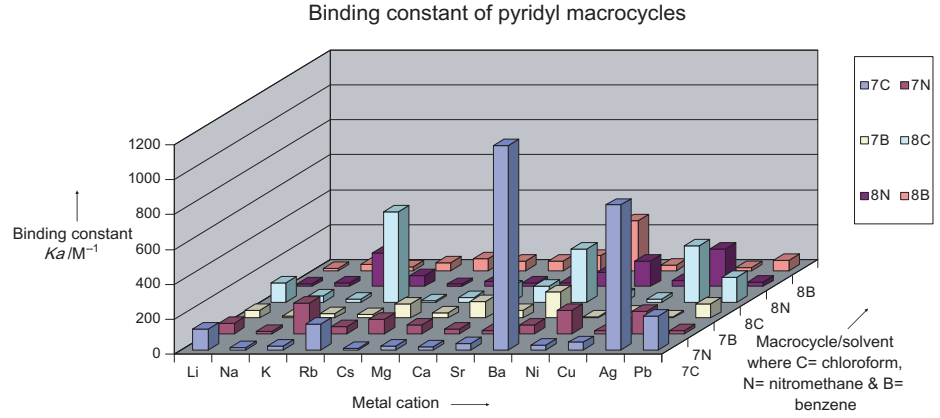


Fig. 5. Binding constants (M^{-1}) of the pyridyl macrocycles (dimer **7** and trimer **8**).

temperature. The binding constants at the equilibrium of the complexation were calculated using the solvent extraction technique developed by Cram and co-workers,[6,7] and this method is still widely used in picrate extractions.[8]

There were several particularly striking observations from the binding results displayed in Figures 4 and 5:

(a) The benzyl dimer **5** showed roughly 12:1 selectivity for K_K/K_{Na} in nitromethane (cf. 18-C-6 shows 50:1 selectivity[9] for K_K/K_{Na} in methanol). Much more striking, however, was the solvent dependence of the benzyl trimer **6** with sodium and potassium; K_K/K_{Na} was about 1:6 in chloroform, 12:1 in nitromethane, and 1:1 in benzene (Fig. 4).

(b) Both of the trimers (**6** and **8**) showed high selectivity for rubidium over other alkali metals in chloroform, with the rubidium–**6** complex in chloroform having the highest association constant from all the combinations of metals with benzyl dimers or trimers tested in any solvent (Fig. 5).

(c) In contrast, the pyridyl dimer **7** showed the highest affinity for barium in chloroform, with high selectivity over other alkali earth metals. Although barium is known to bind better than most metals to pyridyl macrocycles,[10] this level of selectivity is unusual. The only other ion to show relatively high binding to dimer **7** was Ag^+, presumably due to the pyridyl lone pair chelating effectively with the 'soft' silver.

(d) The pyridyl trimer **8** also showed quite high selectivity for barium and silver, again implicating the pyridyl lone pair as the primary coordinating ligand.

In conclusion, we have found that the sulfamide-based macrocycles **5**–**8** are extremely easy to prepare in high yield. Although the binding constants of these macrocycles for metal cations are modest, the selectivity of sulfamide-based macrocycles towards certain cations such as potassium, rubidium, barium and silver over other cations provide valuable insights into their unusual ionophoric properties. The simple synthetic procedure to obtain the dimeric and trimeric structures, and their ease of their purification, make these novel sulfamide-based macrocycles attractive for further study and elaboration.

Acknowledgement

We thank EPSRC for support for Anupama Sethi.

References and notes

1. Isolation: (a) Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 965; Structure: (b) Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W.; Faulkner, D. J.; Parkanyi, L.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 3427; Synthesis of (+)-papuamine via Stille coupling: (c) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881.
2. (a) Ahn, K. H.; Yoo, D. H.; Kim, J. S. *Tetrahedron Lett.* **1992**, *33*, 6661; (b) Berredjem, M.; Djebbar, H.; Regainia, Z.; Aouf, N.-E.; Dewynter, G.; Winum, J.-Y.; Montero, J.-L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 693; (c) Aouf, N.; Dewynter, G.; Montero, J.-L. *Tetrahedron Lett.* **1991**, *32*, 6545; (d) Gazieva, A.; Kravchenko, A. N.; Lebedev, O. V. *Russ. Chem. Rev.* **2000**, *69*, 221.
3. Synthesis of **1**. Sulfamide (1.82 g, 18.93 mmol) and 1,3-diaminopropane (4 g, $d = 0.888$, vol = 4.74 mL; 56.79 mmol) were added together in a round-bottomed flask. The white reaction mixture was refluxed at 130 °C for 72 h. The resulting pale yellow solution was left to cool at room temperature for 3 h. 4 M HCl (18 mL) was added to neutralize the reaction mixture. Once the fumes subsided, the solution was extracted using ethyl acetate (8 × 15 mL). The organic layers were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo to give [1,2,6]thiadiazinane-1,1-dioxide **1** (0.99 g, 38%) as white crystals; mp 115.1–115.9 °C δ_H (DMSO, 300 MHz) 1.5 (2H, m, CH_2-bridge), 3.25 (4H, s, 2 × CH_2–N); δ_C (DMSO, 75 MHz) 28.56 (*C*H_2-bridge), 45.10 (2 × *C*H_2–N). Found: C, 26.5; H, 5.9; N, 20.4; $C_3H_8N_2O_2S$ requires: C, 26.44; H, 5.93; N, 20.5.
4. All the X-ray crystal structures used molybdenum radiation, $\lambda = 0.71073$ Å, κ CCD φ and ω scans to full Ewald sphere; Lorentz and polarisation corrections were performed; absorption correction was semi-empirical from equivalents. H atoms were subjected to isotopic refinement and the final residuals were refined against |F2|. The structures were solved by direct methods using SHELXS-97 (Sheldrick, G. M. SHELXS-97. Program for crystal structure solution, 1997, University of Göttingen, Germany), and refinement method full matrix least squares on F_2 using SHELXL-97 (Sheldrick, G. M., SHELXL97. Program for crystal structure refinement, 1997, University of Göttingen, Germany). (a) Compound **1**: 0.30 × 0.05 × 0.03 mm^3, orthorhombic, space group $P212121$, $a = 5.2473(2)$ Å, $b = 9.4263(5)$ Å, $c = 12.0550(8)$ Å, $V = 596.27(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.517$ Mg/m^3, $2\theta_{max} = 52.50°$. Number of independent reflections included in the refinement 1142 (829 $I > 2\sigma(I)$), $wR^2 = 0.1571$ (all data), $R_1 = 0.0602$ ($I > 2\sigma(I)$), max and min residual electron density 0.600 and −0.611 e Å^{-3}. (b) Compound **6**: 0.15 × 0.10 × 0.05 mm^3, monoclinic, space group $P2_1$, $a = 10.8603(12)$ Å, $\alpha = 90°$, $b = 10.5103(15)$ Å, $\beta = 104.742(4)°$, $c = 15.445(2)$ Å, $\gamma = 90°$, $V = 1704.9(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.393$ Mg/m^3, $2\theta_{max} = 50.00°$. Number of independent reflections included in the refinement 3106 (2350 $I > 2\sigma(I)$), $wR^2 = 0.2676$ (all data), $R_1 = 0.0944$ ($I > 2\sigma(I)$), max. and min. residual electron density 0.425 and −0.373 e Å^{-3}. (c) Compound **7**: 0.25 × 0.07 × 0.07 mm^3, monoclinic, space group $P2_1/n$, $a = 6.3638(3)$ Å, $\alpha = 90°$, $b = 16.4846(8)$ Å, $\beta = 95.943(2)°$, $c = 10.0893(6)$ Å, $\gamma = 90°$, $V = 1052.73(9)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.510$ Mg/m^3, $2\theta_{max} = 52.74°$. Number of reflections included in the refinement 2141 (1520 $I > 2\sigma(I)$), $wR^2 = 0.1260$ (all data), $R_1 = 0.0478$ ($I > 2\sigma(I)$), max. and min. residual electron density 0.254 and −0.394 e Å^{-3}. (d) Compound **8**: 0.25 × 0.15 × 0.10 mm^3, monoclinic, space group $P2_1/n$, $a = 13.7789(3)$ Å, $\alpha = 90°$, $b = 14.7397(4)$ Å, $\beta = 90.474(2)°$, $c = 16.1933(4)$ Å, $\gamma = 90°$, $V = 3288.70(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.449$ Mg/m^3, $2\theta_{max} = 51.66°$. Number of measured/independent reflections 47882/6228 [R (int) = 0.0771], number of reflections included in the refinement 6228 (4709 $I > 2\sigma(I)$), $wR^2 = 0.1446$ (all data), $R_1 = 0.0563$ ($I > 2\sigma(I)$), max. and min. residual electron density 1.083 and −0.396 e Å^{-3}. CCDC 604775, CCDC 677356, CCDC 604773 and CCDC 604774 contain the supplementary crystallographic data for this Letter (compounds 1, 6, 7 and 8 respectively). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
5. For leading papers on macrocyclic ionophores, see: (a) Pederson, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021; (b) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89; (c) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009; (d) Vögtle, F.; Löhr, H.-G.; Franke, J.; Worsch, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 727; (e) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245; (f) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.
6. Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.
7. The metal picrate extraction experiments for each macrocyclic host **5**, **6**, **7** and **8** were run in nitromethane, chloroform and benzene. An aliquot of 0.5 mL of a metal picrate solution was measured using a micro syringe and transferred into a centrifuge tube. To each centrifuge tube an aliquot of 0.5 mL of the host, one from each solvent system, was added to the centrifuge tube. To one set of centrifuge tubes 0.5 mL of picrate solution was added along with 0.5 mL of the solvent system excluding the host. These were used to determine the distribution constant K_d. The contents of each tube were mixed vigorously using a vortex mixer, and then spun by centrifuge for 10 min at 12,500 rpm. The samples were left to equilibrate for 24 h. A 0.5 mL aliquot of the organic layer was measured into a 5 mL volumetric flask and diluted to the mark with acetonitrile, concentrations ranging from 10^{-4} to 10^{-6} M. For each sample, a blank extraction experiment was also carried out on the corresponding organic layers with water, excluding the picrate salt. The UV absorption of each solution was measured against the corresponding blank solution at 375 nm. The absorbance values were measured with the Cary 400 Series UV–vis Spectrophotometer at 25 °C. The cation concentration in the organic layer was calculated using the Beer–Lambert law, $A = \varepsilon cl$, where A = absorbance measured, ε = extinction coefficient, c = concentration of sample, l = the path length of the cell (1 cm). The values of the binding constant K_a were calculated according to Ref. 6.
8. (a) Marchand, A. P.; Hazelwood, A.; Huang, Z.; Vodlankonda, S. K.; Rocha, J.-D. R.; Power, T. D.; Mlinaric-Majerski, K.; Klaic, L.; Kragol, G.; Bryan, J. C. *Struct. Chem.* **2003**, *14*, 279; (b) Huber, V. J.; Ivy, S. N.; Lu, J.; Bartsch, R. A. *Chem. Commun.* **1997**, 1499; (c) Li, G.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 3804.
9. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
10. Gokel, G. W.; Goli, D. M.; Minganti, C.; Echegoyen, L. *J. Am. Chem. Soc.* **1983**, *105*, 6786.