New Entry to Tetranuclear Clusters with Tetrathiol Ligands Anchored to Hydrophobic Macrocycles in Iron–Sulphur Protein Analogues; $Fe_4S_4\{cyclo\text{-}(XN[CH_2]_8)_4\}^{2-}$ and $Fe_4S_4\{cyclo\text{-}(XN[CH_2]_8NX\text{-}p\text{-}C_6H_4\text{-}p\text{-}CH_2C_6H_4)_2\}^{2-}$ (X = p-SC_6H_4CO)

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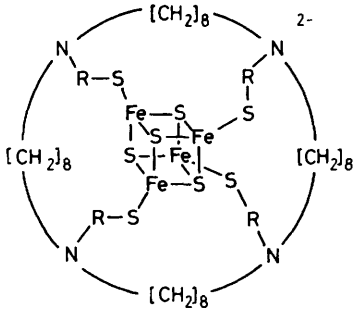
Efficient synthetic routes to novel tetrathiol compounds attached to a 36- or a 38-membered ring consisting of a methylene backbone or a cyclophane type macrocycle have been developed which involve a double condensation as the key reaction; a new class of synthetic 4Fe–4S analogues of iron–sulphur proteins could be introduced using these hydrophobic SH ligands.

There have been many important studies on active site analogues of biologically important iron–sulphur proteins.[1—4] While a series of related complexes with relatively small alkyl and aryl thiol ligands[1,5,6] have been synthesized and fully characterized, characterisation of environmental effects on the Fe–S core remains indefinite. We now report efficient synthetic routes to tetrathiol ligands attached to hydrophobic macrocycles such as (**9**) and (**11**), and preparation of new types of Fe_4S_4 clusters buried in a hydrocarbon environment [*e.g.*, (**1**) and (**2**)].

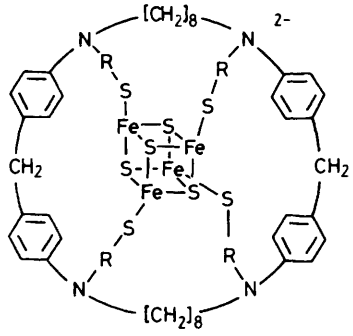
The 36-membered cyclic tetra-amine (**8**) was a key intermediate and was synthesized as follows: *N*,*N*′-ditosyloctane-1,8-diamine (**3**) was treated with the monobromo-octanol derivative (**4**) (2 mol. equiv.) in the presence of NaH for 1 day at room temperature in dimethylformamide (DMF), and compound (**5**) was obtained as a colourless oil (67% yield; 96% conversion yield).† After removal of the tetrahydropyran-2-yl (THP) groups from (**5**) [TsOH–MeOH, room temp., 30 min., 92%, m.p. 57—58.5 °C (CH_2Cl_2–ether)] and subsequent tosylation [TsCl–2-dimethylaminopyridine (DMAP)–CH_2Cl_2, room temp., 30 min, 91%, colourless oil], the dibromide (**6**) was obtained as colourless needles [85%, m.p. 36.5—37.5 °C (ether–light petroleum)], by treatment with LiBr in acetone.

The double condensation reaction[7] between (**6**) and (**3**) worked nicely even with a 10 mM concentration to afford

† All organic intermediates have been fully characterized and give satisfactory elemental analyses, but conditions have not been optimised. Details will be given in a full paper.



(1)



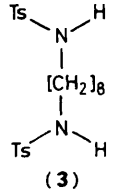
(2)

R = $-C(:O)C_6H_4-p-$

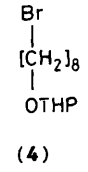
colourless leaflets of the 36-membered tetratosyl-amide (**7**) [Cs_2CO_3–DMF, 120 °C, 1.5 h, 57%, m.p. 104.5—142 °C ($CHCl_3$–hexane)]. This tosylate was then converted into the free amine (**8**) by treatment with HBr–phenol[8] [85%, colourless solid, m.p. 63—65 °C (MeOH), *m/z* 508.5415; calc. 508.5428].

The cyclophane tetra-amine (**10**) was also synthesized similarly, employing *N,N'*-ditosyl-*p,p'*-methylenedianiline instead of (**3**) [m.p. 147—149 °C ($CHCl_3$–EtOH)].

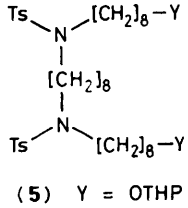
The tetrathiol ligand derivatives (**9**) and (**11**) were then prepared without difficulty by acylation of the macrocycles (**8**) and (**10**) with *p*-mercaptobenzoyl chloride. Interestingly, the 36-membered ring compound (**9**) was obtained as an oil, whereas the more rigid and hydrophobic cyclophane [*e.g.*, (**11**)] easily crystallized. Determination of the number of SH groups by colorimetry using DTNB [5,5'-dithiobis(2-nitrobenzoic acid)][9] showed close agreements: 3.98 and 4.02, respectively, for (**9**) and (**11**). This was confirmed by n.m.r. spectroscopy in $CDCl_3$, *i.e.*, singlet signals due to SH were observed at δ 3.54 (**9**) and 3.42 (**11**)‡ with the appropriate integration.



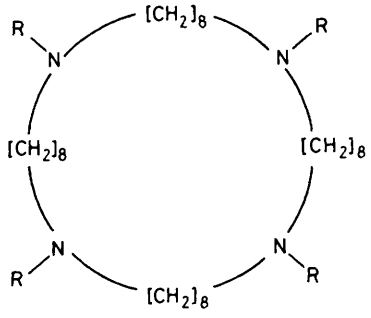
(3)



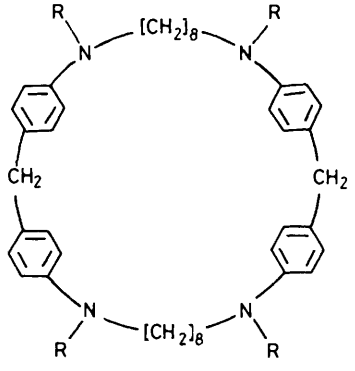
(4)



(5) Y = OTHP
(6) Y = Br



(7) R = Ts
(8) R = H
(9) R = $-C(:O)C_6H_4SH-p$



(10) R = H
(11) R = $-C(:O)C_6H_4SH-p$

Ts = p-$MeC_6H_4SO_2$; THP = tetrahydropyran-2-yl

The new types of 4Fe–4S active site analogues (**1**) and (**2**) were then prepared for the first time by ligand substitution reactions using the macrocycles and $Fe_4S_4(SBu^t)_4^{2-}$.[10] The products (**1**) and (**2**) were purified by reprecipitation from DMF–THF, and obtained as black powders with m.p.s >300 °C. The existence of the 4Fe–4S core in (**1**) and (**2**) was confirmed by the core extrusion method.§ Visible spectra in DMF showed a considerable blue shift of the maximum for (**1**) [$\lambda_{max.}$ (ε) 442 (14 300) and 365 nm (sh, 21 000)], but essentially no shift for (**2**) [$\lambda_{max.}$ 456 (16 800) and 380 (sh, 22 600); *cf.*

‡ N.m.r. data (270 MHz) for (**9**) are as follows: δ ($CDCl_3$), 1.14—1.4 (m, 32H, CH_2), 1.4—1.65 (m, 16H, N_β-CH_2), 3.18 (br., 8H, N_α-CH_2), 3.43 (br., 8H, N_α-CH_2), 3.54 (s, 4H, SH), and 7.20—7.29 (m, 16H, ArH); owing to hindered rotation, the N_α protons were resolved; at 80 °C in $(CD_3)_2SO$ a broad single peak was observed at δ 3.3; i.r. (Nujol), 2500 (SH) and 1630 cm^{-1} (N–CO). N.m.r. data (270 MHz) for (**11**): are δ ($CDCl_3$), 1.15—1.3 (m, 16H, CH_2), 1.47—1.6 (m, 8H, N_β-CH_2), 3.42 (s, 4H, SH), 3.78—3.84 (m, 8H, N_α-CH_2), 3.83 (s, 4H, Ar-CH_2-Ar), 6.89 (d, *J* 8.4 Hz, 8H, ArH), 6.97 (d, *J* 8.4 Hz, 8H, ArH), 7.01 (d, *J* 8.4 Hz, 8H, ArH), and 7.12 (d, *J* 8.4 Hz, 8H, ArH); i.r. (Nujol), 2500 (SH) and 1630 cm^{-1} (N–CO).

§ A series of spectral changes were observed from the initial spectrum of the Bu^t complex ($\lambda_{max.}$ 417 nm) indicating the final formation of the known phenyl derivative (~95% from the ε value) on addition of excess of PhSH to a solution of (**1**) or (**2**): *cf.* ref. 11.

uncomplexed tetrathiol [$\lambda_{max.}$ 457 (17 700)].[12] The aromatic protons in (**9**) showed sharp resonances at δ ~7, and the protons *ortho* and *meta* to the SH group in (**1**) were assumed to give the broad resonances at δ ~5.8 and ~8, respectively,[13] indicating the formation of the monomer complex. Similar behaviour was observed for (**2**) [δ ~5.3 (*o*-H) and ~8 (*m*-H)] but no shift of the aromatic protons of the cyclophane was evident.

Microanalysis (C,H,N,S) strongly supported the structures (**1**) and (**2**). Furthermore, their electrochemical behaviour and n.m.r. spectra exhibited clear and simple redox cycles [*e.g.* $E_{\frac{1}{2}}$ for (**1**) −0.36, −0.85, and −1.64 V *vs.* standard calomel electrode (s.c.e.) in DMF, respectively, for 1−/2−, 2−/3−, and 3−/4−] and reasonable n.m.r. signals,¶ supporting formation of homogeneous products, very likely the monomeric (**1**) and (**2**). Examinations of Corey–Pauling–Koltun (C.P.K.) models showed a snug fit of the Fe–S core in these. Attempts to obtain crystals of these complexes suitable for an *X*-ray structural study have so far been unsuccessful.

These hydrophobic cyclic amines are widely applicable to the formation of derivatives with various kinds of thiols, and we have in fact prepared a series of the related complexes with phenylmethanethiol and 2,2-dimethylbutanethiol derivatives attached to these macrocycles; these will be reported elsewhere.

¶ N.m.r. signals of (**1**) (Et_4N^+ salt) other than given in the text are at δ (CD_3SOCD_3) 1.07—1.49 (br., 24H + 48H, cation Me + skeleton CH_2), 3.16—3.37 (br., 16H, skeleton N_α-CH_2), and 3.18—3.20 (br., 16H, cation N_α-CH_2).

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References

1 J. M. Berg and R. H. Holm, in 'Iron-Sulfur Proteins,' ed. T. G. Spiro, Interscience, New York, 1982, Vol. 4, Ch. 1.
2 T. Herskovitz, B. A. Averill, R. H. Holm, J. A. Ibers, W. D. Phillips, and J. F. Weiher, *Proc. Natl. Acad. Sci. USA*, 1972, **69**, 2437.
3 R. H. Holm, *Acc. Chem. Res.*, 1977, **10**, 427.
4 J. A. Ibers and R. H. Holm, *Science*, 1980, **209**, 223.
5 T. O'Sullivan and M. M. Millar, *J. Am. Chem. Soc.*, 1985, **107**, 4096.
6 M. Ueyama, T. Sugawara, M. Fuji, A. Nakamura, and N. Yasuoka, *Chem. Lett.*, 1985, 175.
7 *Cf.* Y. Okuno, K. Horita, O. Yonemitsu, K. Shibata, T. Amemiya, and R. H. Holm, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1115.
8 *Cf.* H. Stetler and E. E. Ross, *Chem. Ber.*, 1955, **88**, 1390.
9 G. L. Ellman, *Arch. Biochem. Biophys.*, 1959, **82**, 70.
10 L. Que, Jr., M. A. Bobrik, J. A. Ibers, and R. H. Holm, *J. Am. Chem. Soc.*, 1974, **96**, 4169.
11 W. O. Gillum, L. E. Mortenson, J.-S. Chen and R. H. Holm, *J. Am. Chem. Soc.*, 1977, **99**, 584.
12 B. V. DePamphilis, B. A. Averill, T. Herskovitz, L. Que, Jr., and R. H. Holm, *J. Am. Chem. Soc.*, 1974, **96**, 4159.
13 R. H. Holm, W. D. Phillips, B. A. Averill, J. J. Meyerle, and T. Herskovitz, *J. Am. Chem. Soc.*, 1974, **96**, 2109.