

Tris(thioacetals) from benzene hexathiol: towards covalent self-assembly

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Mixtures of isomers are available from the reaction of benzene hexathiol with three equivalents of *p*-tolualdehyde and kinetic traps avoided under the reported catalytic conditions, establishing tris(thioacetals) as potential building blocks for covalently self-assembled complex structures.

Thermodynamic self-assembly is an attractive method for creating complex ångstrom- and nanoscale objects by the interaction of molecular recognition sites with particular topological preferences inherent in simpler precursor molecules.¹ Typically, both natural and artificial self-assembly involve non-covalent interaction, since the lability normally associated with such bonds allows the exploration of all possible permutations open to a particular system and the selection of the most thermodynamically stable assembly. However, non-covalent assemblies are not always the optimum solution to a given problem. In studies of encapsulation, for example, it is not always desirable that a guest be allowed freedom to leave its host, as is often the case for labile, non-covalent assemblies.²

Assemblies constructed by covalent bonding therefore have potential as complex architectures that retain their structural integrity at all times. The main challenge is squaring the circle of making kinetically stable covalent bonds capable of exploring structural permutations on a reasonable timescale.³ One very successful building block is the imine bond, as used in Robson's metal-templated macrocyclisations⁴ and in some of Cram *et al.*'s carcerand work,⁵ which is labile in acidic conditions but not at neutral or high pH.

We chose to investigate the thioacetal system, which can be made reversible under certain catalytic conditions but is otherwise quite stable.⁶ We hoped to benefit from the rigidity of thioacetals by restricting the configurations available to the system, enhancing the entropic advantage of macrocyclisation *vs.* polymerisation and promoting template-free self-assembly.^{1c} We designed an adamantoid capsule for C₆₀ based on the assembly of four benzene hexathiol units (**1**) and six terephthalaldehyde molecules. Such targets are expected to display interesting redox properties.⁷ We report here studies on model reactions of **1** with *p*-tolualdehyde (**2**) to give isomeric tris(thioacetals) **3** ($\alpha\alpha\alpha$) and **4** ($\alpha\alpha\beta$) and the X-ray crystal structure of **3**.

Compound **1** was synthesised by literature methods,⁸ making the hexa(benzylsulfide) from hexachlorobenzene and sodium benzylthiolate in DMF, followed by dealkylation with sodium in liquid ammonia.[†]

In order to determine a suitable catalytic regime for the smooth reaction of **1** to give tris(thioacetals) (Scheme 1, pathway A) we explored a number of permutations of catalyst and solvent. During our initial studies with Brønsted acids in ethanol, tetrahydrofuran or toluene, FAB-MS analysis of the reaction mixtures revealed the presence of a peak at $m/z = 473$ consistent with the bis(thioacetal)-dithiol as well as a product peak at $m/z = 576$, suggesting either incomplete reaction or trapping in the form of the 1,4-dithiol due to lack of reversibility in this non-productive equilibrium. Persistence of the peak at 473 upon extended reaction and upon addition of excess **2** supports the latter explanation (Scheme 1, pathway B).

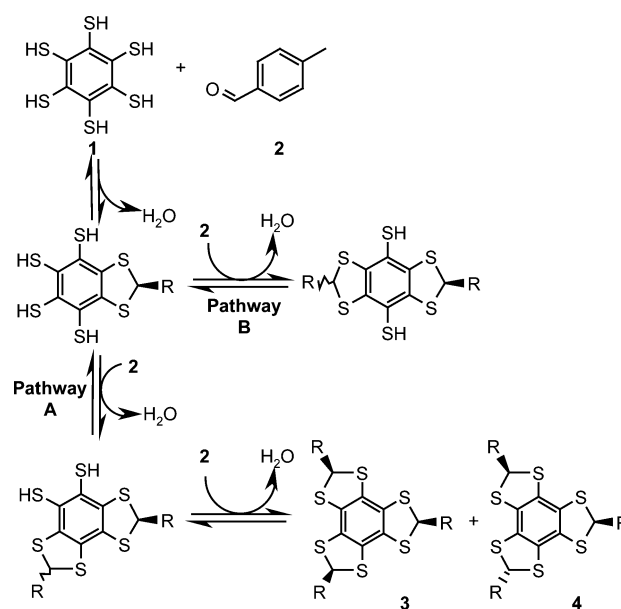
We therefore clarified the position that protic acids, whilst being useful in protection of carbonyls with dithiols in organic synthesis, do not promote the reversibility of thioacetal formation required for

thermodynamic control of reactivity. Hg(II) is often used to deprotect carbonyls, since the soft metal...S interaction is favourable, promotes C—S breaking and allows the sequestering of dithiol as a precipitate.⁶ This is too far for us; we required a compromise between the Lewis acidity of the catalyst to promote C—S cleavage and continued availability of dissolved dithiol for subsequent reaction.

Extended literature investigations revealed that Lewis acids such as BF₃·Me₂S, SnCl₂ and Zn(OTf)₂ may present such a compromise, the most promising being zinc trifluoromethanesulfonate based on its use by Corey and Shimoji⁹ as a soluble catalyst unlikely to hinder subsequent reaction due to the lability of Zn...S interactions.

Neither BF₃ nor SnCl₂ gave detectable quantities of **3** or **4** but reaction catalysed by Zn(OTf)₂ in a variety of solvents gave the appropriate peak in FAB-MS after around 1 h at elevated temperature. TLC analysis (alumina, hexane/toluene) was used to follow the reactions to completion in 24–72 h. No dithiol was observed by FAB-MS after this time. Work-up procedures involved partitioning the reaction mixture and recrystallising the organic-soluble product from methanol. This gives a high purity mixture of **3** and **4** in reasonable yields, up to 60% from the reaction with 10 mol% Zn(OTf)₂ in refluxing CHCl₃. The very similar, low polarities of **3** and **4** make them difficult to separate: decomposition occurred on silica gel whilst reverse-phase TLC was ineffective. Preparative TLC on neutral alumina with 4 : 1 v/v hexane/toluene was more effective, as was elution from alumina with successive hexane/toluene aliquots of increasing toluene content, the $\alpha\beta$ isomer **4** being eluted before $\alpha\alpha\alpha$ **3**.

This enabled the NMR characterisation of the compounds obtained. The spectra shown in Fig. 1 confirm that **3** and **4** are produced in a 1 : 3 ratio, consistent with random orientation of the



Scheme 1 Tris(thioacetal) formation from **1**. R = *p*-tolyl.

third thioacetal on insertion into either $\alpha\alpha$ or $\alpha\beta$ bis(thioacetal) dithiol.

Furthermore, crystals of **3** suitable for X-ray structure determination were grown by recrystallisation from methanol.[‡] The crystal structure (Fig. 2) confirms the isomerism of **3**, with the three thioacetal C—H bonds all on the same face of the central aryl ring. Bond lengths and angles are normal.

The quite large, isolated cavities between tolyl groups allowed by the molecular packing arrangement are filled by (H₂O)₁₂ clusters (Fig. 3).¹⁰ The origin of this water is probably wet recrystallisation solvent.

To conclude, we have demonstrated that benzene hexathiol can be used to produce mixtures of tris(thioacetal) products by its Zn(OTf)₂-catalysed condensation with *p*-tolualdehyde, the catalyst

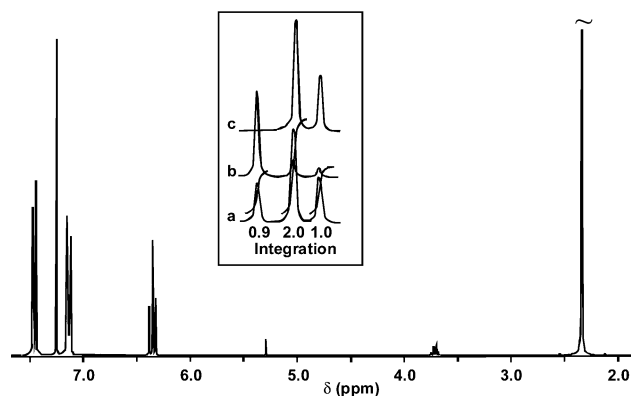


Fig. 1 ¹H NMR spectrum of the as-synthesised **3/4** mixture. Inset: thioacetal signals from the mixture (a) and purified **3** and **4** (b, c): δ = 6.39 (**3**); 6.35 (α , **4**); 6.32 ppm (β , **4**).

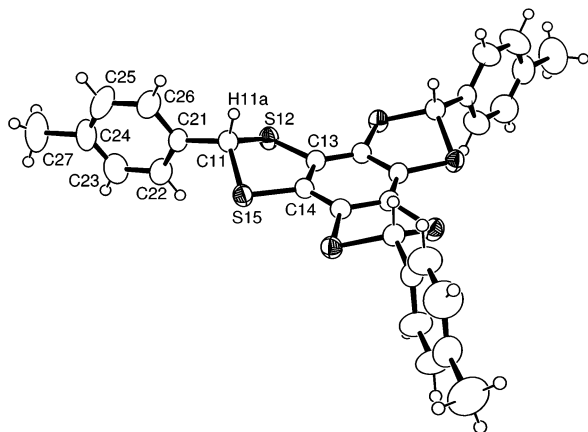


Fig. 2 X-ray crystal structure of **3**. Thermal ellipsoids shown at 50% probability. Solvate water omitted for clarity. Selected bond lengths: C11—S12 1.829(4), S12—C13 1.759(3), C13—C14 1.413(5) Å.

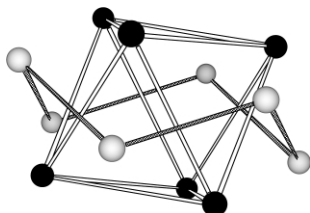


Fig. 3 (H₂O)₁₂ clusters in the X-ray crystal structure of **3**: H₂O molecules (grey O atoms) cap six faces of an (H₂O)₆ octahedron (black).

inducing reversibility in reaction pathway B (Scheme 1). The NMR spectra of **3** and **4**, the ability to separate them by chromatography and the X-ray crystal structure of **3** confirm the inertness of the compounds in the absence of catalyst. **3** templates an unusual water cluster in its crystal.

However, a number of drawbacks detract from the prospects of basing more elaborate structures on **1** using this chemistry. Although pathway B is reversible, the reactions described are still quite slow, taking up to 3 days to complete as assessed by TLC. As the number of permutations of possible configurations increases, so the required time increases geometrically.¹ Secondly, initial studies in exchanging the tolualdehyde bound in **3** and **4** with terephthalaldehyde using CHCl₃, Zn(OTf)₂ and a small quantity of added H₂O to generate more complex structures have produced no reaction. These factors suggest that the third thioacetalisation is *not* reversible under current conditions, possibly due to steric hindrance. Resolution of these difficulties is the target of future work, exploring alternative catalysts, larger substrates and the more labile, protic acid-catalysed acetal system using O-containing analogues.

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Notes and references

† **Caution:** benzyl mercaptan stinks. Best results were obtained with freshly prepared **1** under N₂; reactions with stored **1** often yielded a FAB-MS peak at *m/z* = 471, consistent with the bis(thioacetal) disulfide.

‡ Crystal data for **3**: C₃₀H₂₄S₆·6H₂O, *M* = 684.95, *Z* = 6, rhombohedral, space group *R*-3, *a* = *b* = 15.7694(5), *c* = 25.0354(6) Å, α = β = 90, γ = 120°, *U* = 5391.6(3) Å³, *T* = 173(2) K, μ (Mo—K α) = 0.418 mm⁻¹. Data were collected on a Nonius KappaCCD area detector. Of 13583 reflections measured, 2378 were independent (*R*_{eq} = 0.0578). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on *F*² (SHELXL-97). Final *R*₁ = 0.0677 (1975 reflections with *I* > 2 σ (*I*)) and *wR*₂ (*F*²) = 0.1874 (all data). CCDC 229167. See <http://www.rsc.org/suppdata/cc/b4/b401021c/> for crystallographic data in .cif or other electronic format.

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