Dynamic combinatorial libraries of metalloporphyrins: templated amplification of disulfide-linked oligomers

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Disulfide-linked cyclic porphyrin oligomers from dimer to tetramer can be selected and amplified virtually quantitatively from a dynamic combinatorial library using bis-thiol substituted zinc(II) porphyrin units with appropriate amine donor templates.

Dynamic combinatorial chemistry (DCC) provides access to new host–guest systems with the potential for catalysis and drug discovery that may be difficult to synthesise using traditional design approaches.[1] The salient feature of DCC is the dynamic combinatorial library (DCL) in which each library member is assembled from building blocks which are connected through reversible bonds. As a result of this reversibility, all library members are interconverting to give a distribution that is under thermodynamic control. Thus addition of a guest molecule that can selectively bind to one receptor in the library will serve to increase the concentration of that host at the expense of others in the DCL.

We, and others, have been developing thiol–disulfide exchange chemistry for use in DCLs.[2] Thiols can be readily oxidised to disulfides in the presence of air. Exchange between disulfides can be easily initiated and is rapid in the presence of a catalytic amount of thiol under neutral or mildly basic conditions. Disulfides are also stable towards many other functional groups. We have recently reported the first example of a catalyst obtained from a DCL using a Transition State Analogue as a template.[3]

Previously, we have described the use of template-directed synthesis to create porphyrin oligomers ranging in size from cyclic dimer to linear octamer.[4] The butadiyne-linked species were synthesised by the removal of trimethylsilyl protecting groups from alkynyl substituents on the *meso*-diarylporphyrins, followed by zinc metallation and irreversible Glaser coupling. Coupling in the presence of amines such as bipyridine was found to significantly alter the final product distribution obtained by kinetic templating.[5] Here we present the initial results from the unification of these two approaches.

Bis-benzylthiol substituted porphyrin **Zn-2** was obtained by the hydrazine mediated deprotection of bis-thioacetate appended porphyrin **Zn-1** (Fig. 1), which was synthesized by standard routes in good yield.[6] When a 5 mM CHCl$_3$ solution of **Zn-2** was treated with DBU in the presence of air, oxidative cyclisation of the monomer occurred, as illustrated schematically in Fig. 2. At thermodynamic equilibrium, achieved after 3 to 4 days, MALDI TOF mass spectrometry of fractions isolated from analytical runs of HPLC‡ showed that the major constituent of the library was porphyrin dimer (87%), with small amounts of cyclic trimer (11%) and higher oligomers (2%) present (Fig. 3).§
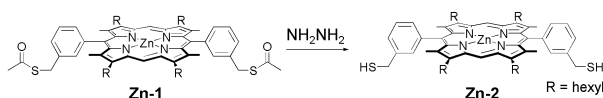

Fig. 1 Deprotection of thioacetate protected monomer **Zn-1**.

Previous work has shown the efficacy of templating the formation of a butadiyne-linked porphyrin dimer with 4,4′-bipyridine (Bipy; Scheme 1), in up to 70% yield.[5] Initiation of exchange in the dithiol porphyrin system in the presence of Bipy, however, resulted in a dramatically different equilibrium library composition, with a significant reduction in the amount of cyclic dimer present; so that the final mixture consisted mainly of trimer (50%) and higher oligomers (20%) at equilibrium. In fact, species up to cyclic decamer were detected by LC MS.

When cyclisation occurred in the presence of 0.5 equiv. 1,4-diazabicyclo(2.2.2)octane (DABCO) per porphyrin, there was a shift in the equilibrium composition of the library. An enhancement of the amount of dimer present, up to 99%, with a concomitant reduction in the amount of higher oligomers present, was seen. This contrasts with the Glaser coupling results, and is indicative of the geometric requirements of the hosts. The bis-disulfide dimer has a much smaller cavity than the butadiyne-linked dimer, and hence Bipy is too large to be encapsulated. When the linear intermediate binds to Bipy, it cannot achieve the optimum geometry for cyclisation and so the reactive thiols are held apart. By contrast, upon binding to DABCO, the smaller ligand, there is an excellent geometrical fit, leading to the exclusive formation of dimer (see X-ray crystal structure below).

Cyclisation in the presence of a saturated solution of 4-*s*-tripyridyltriazine (TPyT) promotes the formation of porphyrin
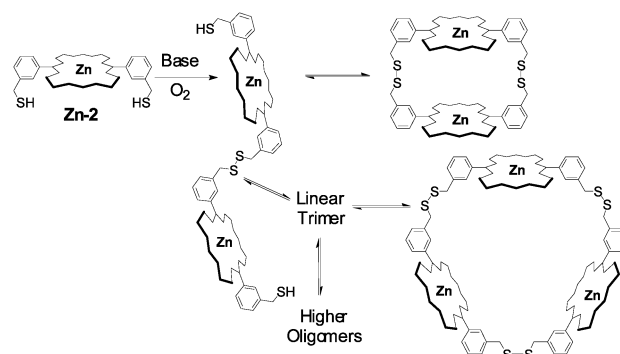

Fig. 2 Oxidation and cyclisation of dithiol monomer **Zn-2**.
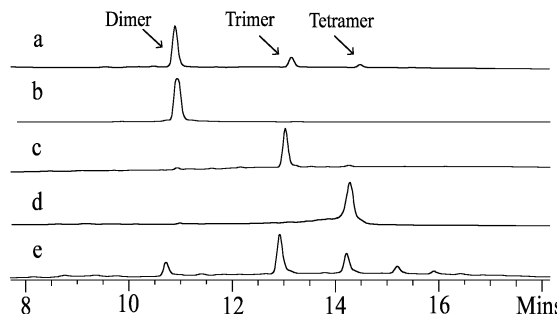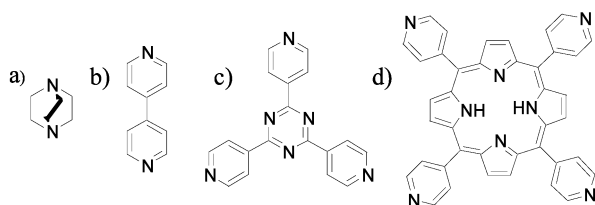

Fig. 3 HPLC traces of the porphyrin DCL in the a) absence of a template, b) presence of DABCO, c) presence of TPyT, d) presence of TPyP, and e) presence of Bipy.

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Scheme 1 Templates used in the disulfide porphyrin library: (a) 1,4-diazabi-cyclo(2.2.2)octane (DABCO), (b) 4,4′-bipyridine (Bipy), (c) 4-s-tripyridyl triazine (TPyT), (d) tetrapyridylporphyrin (TPyP).

tris-disulfide trimer to near quantitative yield, with again less than 1% of the equilibrium mixture consisting of other molecules. The same result was obtained when an isolated sample of dimer was re-equilibrated in the presence of TPyT. Initiation of exchange in this instance required the addition of dithiothreitol to reduce a proportion of the disulfide bonds to thiols. This experiment neatly demonstrated that the library is indeed under thermodynamic control, and hence the ability of the system to proof-read.

Use of tetrapyridylporphyrin (TPyP) as template in the disulfide library results in the formation of tetramer, which contrasts with earlier work. The direct synthesis of cyclic tetramer from monomer using TPyP was also attempted using Glaser coupling but proved unsuccessful.[5] Although some cyclic tetramer did form in the Glaser conditions, its separation from cyclic pentamer and cyclic trimer was very difficult, and so none was isolated in this way. Under the reversible conditions employed a tetrameric disulfide oligomer was formed in essentially quantitative conversion from monomer in the presence of up to 1 equiv. of TPyP, as judged by HPLC analysis.

The thermodynamically-controlled cyclisation of the bis-thiol porphyrin monomer was also carried out on the preparative scale in the presence of the DABCO template. After an HPLC check of the reaction, removal of solvent and purification by a flash alumina column, the bis-disulfide dimer **Zn-3** was obtained. The dimer was isolated with DABCO encapsulated within its cavity as indicated by the presence of a single DABCO CH$_2$ resonance at −5.1 ppm in the ^{1}H NMR spectrum. This represents an upfield shift of almost 8 ppm relative to unbound DABCO, which resonates at 2.8 ppm, and is due to the double ring current effect of the two co-facially arranged porphyrins. Furthermore, the relative simplicity of the NMR spectrum is suggestive of a highly symmetrical structure for the dimer. The ligand is in slow exchange with the host on the NMR timescale and just one equivalent remains fully bound within the cavity even in the presence of a 500-fold excess of free DABCO, indicative of the complementarity of the host cavity to the guest.

At the porphyrin concentration used for UV/vis titrations (10^{-7} M), binding of DABCO to monomer **Zn-1** results in a shift of the Soret band from 412 nm to 426 nm, typical of a 1 : 1 porphyrin–DABCO complex.[7] By contrast, **Zn-3**–DABCO complex has a Soret maximum at 418 nm. This blue shift, of 8 nm, is characteristic of a 2 : 1 porphyrin–DABCO complex, and is due to exciton coupling between the co-facial porphyrin units.[8]

Crystals suitable for structure determination were obtained by layering a CHCl$_3$ solution of dimer with MeOH. The highly symmetrical structure determined is in agreement with the proposed solution state structure.[¶] **Zn-3** crystallises with the DABCO ligand complexed in the cavity, between the two porphyrins (see Fig. 4), sited across a crystallographic centre of symmetry. The DABCO moiety is disordered about the Zn–N···N–Zn axis, suggesting that it is able to rotate within the cavity without decomplexation occurring. The Zn atoms are displaced towards the N atoms of DABCO by *ca*. 0.29 Å from the least-squares planes through the four N atoms of the porphyrins, and the Zn–N DABCO bond distance of 2.227(5) Å is typical of that in similar structures. The cross-cavity Zn···Zn
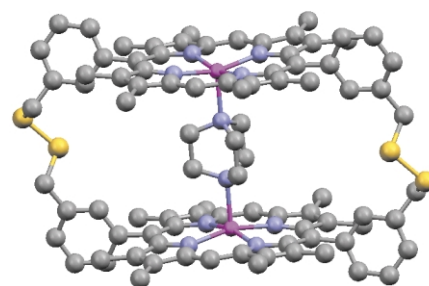
Fig. 4 Ball and stick representation of the crystal structure of DABCO encapsulated bis-disulfide dimer **Zn-3**·2CHCl$_3$ with hexyl side chains replaced by methyls, hydrogen atoms and solvent molecules omitted for clarity. (Zn atoms pink, N atoms blue, S atoms yellow.)

distance of 7.053(1) Å confirms that Bipy is geometrically precluded from the dimer cavity.[9]

In conclusion, we have extended the use of disulfide DCLs to non-polar solvents and demonstrated proof-reading in a library of disulfide porphyrin oligomers to selectively form a cyclic dimer. Current work is being undertaken to isolate larger porphyrin macrocycles.

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