Tetra-porphyrin molecular tweezers: two binding sites linked via a polycyclic scaffold and rotating phenyl diimide core†

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The synthesis of a tetra-porphyrin molecular tweezer with two binding sites is described. The bis-porphyrin binding sites are aligned by a polycyclic scaffold and linked via a freely rotating phenyl diimide core. Synthesis was achieved using a divergent approach employing a novel coupling method for linking two polycyclic units to construct the core, with a copper(II)-mediated phenyl boronic acid coupling found to extend to our polycyclic imide derivative. We expect this chemistry to be a powerful tool in accessing functional polycyclic supramolecular architectures in applications where north/south reactivity and/or directional interactions between modules are important. Porphyrin receptor functionalisation was undertaken last, by a four-fold ACE coupling reaction on the tetra-epoxide derivative of the core.

Introduction

Molecular tweezers containing two ligand binding sites, where these are remote but interdependent, can benefit from cooperativity during complexation, to positively or negatively influence ligand binding. Several examples of cooperativity in molecular tweezers appear in the literature, from early architectures such as Rebek’s 2,2′-bipyridine/crown ether system,1–3 to more recent bis-porphyrin systems with either crown ether,4,5 pyridyl,6 or biindole7 effectors. Molecular-based stimuli can also be used to effect changes to guest binding in molecular tweezers. For example, a water-soluble polymer-tethered tweezer has shown progress towards the development of controlled drug release devices, using a proton-activated (pH) switching unit to change the conformation of bis-naphthalene receptors and release a substrate.8 Cooperativity has even been shown to arise from electronic rather than steric effects,9,10 by using the direction of charge transfer (CT) between a porphyrin host and an appropriate guest (CT donor or acceptor).

We have previously described the synthesis and binding characteristics of single binding site tweezer system 111 (Fig. 1), in which the bis-metalloporphyrin receptor offers strong intramolecular complexation with the diamino ligand 1,4-diazabicyclo[2.2.2]octane (DABCO).

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Polycyclic frameworks, based on norbornyl derivatives, provide several distinct advantages when incorporated into molecular tweezers; namely excellent control of the direction of both lateral and vertical extension and well defined positioning of pendant moieties. These structures are highly synthetically variable using chemistry developed extensively by the research groups of Warrener and Butler, Paddon-Row, and is very much modular, enabling the synthesis of supramolecular architectures with customisable dimensions. More recent examples include those by the groups of Johnston, Pfeffer, and Margetti. Molecular modelling by Warrener and Johnston, and experimental evidence by Margetti has shown that the inclusion of certain modules provides either linearity or curvature to the polycyclic scaffold. Importantly, a number of studies by several research groups has identified that polycyclic backbones are characterised by a higher degree of rigidity when only consisting of fused bridged polycyclic rings, with non-bridged cyclohexane(ene) rings and fused aromatic rings increasing flexibility. However, caution must be exercised, as small degrees of flexibility within rigid modular sections can be amplified across the complete scaffold.

Our original bis-porphyrin tweezer model architecture 1 has now been expanded to tetra-porphyrin system 2 with two homotropic binding sites (Fig. 1). We reasoned that with the inclusion of a largely rigid polycyclic backbone, the interporphyrin distance from the binding of one guest may be able to be transferred to a second remote site with interannular cooperativity. This type of cooperativity arises in systems when there is interplay between two or more intramolecular binding interactions. The two polycyclic backbones would be connected via a centrally located phenyl diimide structural unit, which would be fundamental in conferring the rotational degrees of freedom required by the host to facilitate interannular cooperativity between the two remote but interdependent binding sites. Furthermore, rotation about the porphyrin-polycyclic backbone bonds would allow for further cavity adjustment as required by different sized guests.

Results and discussion

Two overall approaches to synthesising 2 were considered; convergent and divergent (Fig. 2). The convergent approach, whereby p-phenylenediamine is used to link two bis-porphyrin alicyclic systems via their anhydride (Fig. 2a), is synthetically preferable as this route provides increased structural control; functionalisation of each half with porphyrin receptors involves two points of reactivity.

On the contrary, a divergent approach was envisaged in which two alicyclic systems were already linked to create a central core, to which porphyrin receptors could be subsequently attached (Fig. 2b). This avenue provides less structural control, as building out from the core would involve four simultaneous points of reactivity during receptor functionalisation.
HRMS (S5,† cale [M + 2H]2+ 1050.3421, found 1050.3432), as poor solubility, presumably due to aggregation, in many organic solvents prohibited characterisation by NMR.

As the bis-porphyrin anhydride 7 displayed poor solubility in common organic solvents, the Mitsudo anhydride 4 was employed as a soluble model compound in an attempt to ascertain whether the convergent synthesis could be completed as represented in Fig. 2a. 4 was frustratingly unable to be successfully reacted with aromatic amines under a variety of conditions. In summary, these problems stem from the exo-bis-oxa-polycyclic moiety, which unfortunately exhibits a combination of thermal instability prior to lateral functionalisation (retro-Diels–Alder),12,15,38,44,45 and poor anhydride reactivity via conventional condensation with aromatic amines,38,44 particularly following lateral functionalisation.45 It has been suggested by others that the anhydride is shielded by endo-hydrogen atoms at the ring junctions in laterally functionalised derivatives.45 Thus even if a highly soluble derivative of hydrogen atoms at the ring junctions in laterally functionalised (dotted line, Fig. 1) was undertaken and is shown in Fig. 4.

Divergent approach towards 2

The divergent approach comprised the synthesis of the phenyl diimide core and subsequent attachment of the porphyrin moieties. Retrosynthetic analysis of the phenyl diimide core and subsequent attachment of the porphyrin diimide core and subsequent attachment of the porphyrin (Fig. 4) was读者无法阅读中文,因此无法提供中文翻译。
identified in the literature that do not undergo the Mitsudo reaction,\textsuperscript{56} with no clear trends evident with our compounds, or similar compounds in the literature that allow this result to be rationalised. Further investigations are currently underway in our laboratory in an attempt to rationalise this lack of reactivity of this as well as several other substrates.

It became evident from both our own work and the work of others\textsuperscript{38,44,45} that the known syntheses currently employed for polycyclic substrates would be unsuitable to generate the tetra-functional core \textsuperscript{10} (Fig. 5) required for the tetra-porphyrin tweezer \textsuperscript{2}. Faced with the competing triad of thermal instability of \textsuperscript{3} and \textsuperscript{9}, poor anhydride reactivity of laterally functionalised \textsuperscript{4} with aromatic amines, and the inability of the core unit \textsuperscript{9} to undergo the Mitsudo reaction, we required a substrate to circumvent each of these complications. The imide \textsuperscript{13} (Fig. 7) alleviated all of these issues; (i) reactivity in the southern direction is moved from the carbonyl to the imide nitrogen avoiding the steric protecting effects of the adjacent endo-hydrogen atoms on anhydride reactivity, and (ii) pre-installed cyclobutene rings (Mitsudo reaction) both prevent thermal degradation and commence lateral functionalisation.

Fortunately, there was literature precedent for the non-Mitsudo imide \textsuperscript{12}\textsuperscript{18,50} in two steps from anhydride \textsuperscript{3}. This method uses \textit{p}-methoxybenzylamine (PMB) as a nitrogen source, with the intermediate PMB-protected derivative \textsuperscript{11} cleaved to yield the free imide \textsuperscript{12} (Fig. 7). We prepared \textsuperscript{12} using these literature methods and then applied Mitsudo conditions to afford the imide \textsuperscript{13}.

We were fortunate to obtain X-ray quality crystals for all three compounds in this synthetic series to confidently assign the structures of imides \textsuperscript{11}, \textsuperscript{12} and \textsuperscript{13} (Fig. 8). The structures of all three imide block derivatives contain two 7-oxabicycloheptane motifs with a 6-membered ring A and 5-membered ring B approximately perpendicular. The fusion of these rings adopt an envelope conformation in compounds \textsuperscript{11}–\textsuperscript{13} with an O atom as the flap. The skeletal framework of these molecules is a strained system (bridgehead O atom bond angles of 96–97° for \textsuperscript{11} and \textsuperscript{12}, and 98° for \textsuperscript{13}, refer to S15†).

![Fig. 7](image-url) (i) \textit{p}-methoxybenzylamine (2 eq.), deacidified CHCl\textsubscript{3}, 50 °C, N\textsubscript{2} atmosphere, overnight; (ii) NaOAc/\textsubscript{acetic}O, 50 °C, \textsubscript{N}2 atmosphere, over-night, 52%; (iii) 9 : 1 CH\textsubscript{3}CN/H\textsubscript{2}O, ammonium cerium(IV) nitrate (3.3 eq., 2 h; 2.3 eq, 90 min + 1 eq, 30 min), 40 °C, 73%; (iv) DMAD (4 eq.), 36 mol% [RuH\textsubscript{2}(CO)(PPh\textsubscript{3})\textsubscript{3}], dry DMF, 60 °C, \textsubscript{N}2 atmosphere, 24 h, 34%.

The non-Mitsudo imide \textsuperscript{12} is centrosymmetric and solved as the asymmetric unit with SHELX-97 in a monoclinic unit cell (space group \textit{P}21/c). In structure \textsuperscript{12}, the crystal packing features intermolecular N2–H2–O1 hydrogen bonding features (see S15†); whereas the PMB protected imide \textsuperscript{11} does not exhibit such interactions. Within the crystal lattice of the imide \textsuperscript{13} there exists hydrogen bonding contacts between the envelope flap oxygen atoms (O18/O5/O3 and O15/O2/O11) with a molecule of water (see S15†). The imide nitrogen atoms (N36, N48, N68) interact with the same water molecules, as do the C=O oxygen atoms from the methyl esters (O203, O87). This creates a pseudo coordination center about each H\textsubscript{2}O molecule. There are no interactions observed with the CH\textsubscript{3}CN molecules. Additional information on the crystal structures of compounds \textsuperscript{11}–\textsuperscript{13} can be found in the ESI (see S15†).

Furthermore, the X-ray crystal structures \textsuperscript{12} and \textsuperscript{13} reveal significant differences in the position of the hydrogen atoms at the ring junctions as the hybridisation of the carbon atom changes from sp\textsuperscript{2} to sp\textsuperscript{3} (marked with arrows in Fig. 8). This could support the notion previously reported by others that the anhydride is shielded\textsuperscript{55} in laterally functionalised derivatives.

The next step in the divergent approach towards \textsuperscript{2} was the coupling of two units of imide \textsuperscript{13} together through the imide nitrogen atom. On review of the literature, two candidates for coupling nitrogen-containing molecules with aryl species were identified, neither of which appeared to have been demonstrated on norbornyl imides to our knowledge.

**Imide-aryl halide Cu(0) coupling.** Initially, a microwave-assisted copper(0)-mediated aryl halide–imide coupling was explored, as reported for phthalimide with a mono-halo aryl species.\textsuperscript{57} We applied these reaction conditions to imide \textsuperscript{13}...
and model substrate iodobenzene (Fig. 9). This was found to successfully yield 14a by using excess iodobenzene (as the solvent) at 150 °C utilising several cycles through the microwave. These reaction conditions were then applied to the synthesis of diimide 10 using 1,4-diiodobenzene rather than iodobenzene. Unfortunately, the synthesis of the phenyl diimide 10 was more challenging and no appreciable amounts were detected in the reaction mixture. The solid nature of the 1,4-diiodobenzene required solvent for adequate mixing with 13, resulting in dilute reactant concentrations for stoichiometric quantities of aryl halide. This technique was further complicated by reaction vessels being prone to fracture from either spot heating of elemental copper by the microwave reactor, or from rapid temperature fluctuations and pressurisation in the case of a solventless melt.

A small quantity of the asymmetric phenyl 1-imide-4-iodo adduct 14b was generated by using excess 1,4-diiodobenzene in solvent and subjecting to microwave irradiation in several cycles over approximately 12 hours. However, the inefficiency associated with forming precursor 14b, along with the second coupling of 13 with 14b (not attempted) which would be required to generate diimide 10 led us to explore an alternative imide coupling procedure.

Imide–boronic acid Cu(ii) coupling. An alternative candidate involved the coupling of N-H with aryl boronic acids. This has been previously reported for aryl mono-boronic acid derivatives with nitrogen-containing compounds58,59 such as imidazoles, amines, amides, sulfonamides, and imides phthalimide and succinimide, under simple Cu(ii) salt catalysis. The reaction proceeds in protic solvent without additives such as bases or ligands.58,59 We found substitution of these nitrogen-containing compounds with our polycyclic imide 13, using phenyl boronic acid under the conditions described,58,59 gave 14a (based on 1H NMR spectra).

Given the success of this coupling reaction, we employed 1,4-phenyl diboronic acid and polycyclic imide 13, in a 1:2 stoichiometric quantity, to produce phenyl diimide 10 (Fig. 10). The identity of 10 was confirmed by HRMS (calcd [M + Na]+ 1127.2182, found 1127.2166), while the 1H and 13C NMR spectra (see S18 and S19†) both showed the expected number of resonances. A singlet in the 1H NMR at 7.38 ppm was assigned to the phenyl core and suggests that the rotation of both phenyl–imide bonds is rapid on the NMR timescale.

The optimum Cu(ii) catalyst loading was found to be less than 5%, at which the reaction yielded approximately equal quantities of unreacted starting material imide 13, desired product 10, but also an unexpected side product 15 (Fig. 10). This side product was identified as 15a or 15b depending on the solvent used for the reaction (see next paragraph). These products indicate a competitive reaction between boronic acid, imide, and solvent. At greater than 5% catalyst loadings, side product 15 became the major product. These side products were not reported in the original methods,58,59 which only use aryl mono-boronic acid derivatives, and this led us to briefly explore the effect of solvent on the coupling reaction.

As reported in the original methods, we also found that no coupling was obtained in aprotic solvents such as THF, but that successful coupling could be achieved protic solvents such as MeOH, or mixed aprotic/protic solvents such as THF/H2O.58,59 In our case, THF/H2O (9:1) yielded not only the phenyl diimide 10, but side product with hydroxy substitution 15b. When the solvent was MeOH, the side product was methoxy substituted 15a.

Even with this side reaction, a sufficient quantity of the tetra-functional phenyl diimide core 10 was obtained to allow further reactions to be carried out. Thus 10 was subsequently subjected to a four-fold nucleophilic epoxidation at the electron deficient alkene, which gave decent yields of tetra-epoxide 16 (Fig. 10). The identity of tetra-epoxide 16 was confirmed by using HRMS (calcd [M + Na]+ 1191.1978, found 1191.1984, 1191.2006). The successful incorporation of the epoxide
functionality set the stage for the ACE coupling to attach the porphyrin moieties.

Tetra-porphyrin tweezer

The tetra-epoxide core 16 was appended with exo-porphyrin receptors 6 via the alkene plus cyclobutane epoxide (ACE) reaction (Fig. 11), accelerated by the use of microwave irradiation. Although ACE chemistry has been well established for polycyclic scaffolds for some time, there appears to be no examples of tetra-functional substrates undergoing four simultaneous ACE reactions. The tetra-porphyrin tweezer 2 was found to be the major product of the reaction (by 1H NMR of the crude reaction mixture), however, the high degree of purity required for host-guest experiments resulted in significant loss of product from column chromatography and repeated recrystallisations to remove traces of the other porphyrin stoichiometries. The identity of the freebase tweezer 2 was confirmed by using HRMS [see S25† and S26†].

The 1H NMR spectra reflected the symmetry of the tetra-porphyrin tweezer 2, arising from free rotation about the phenyl diimide core and porphyrin receptors. Several features characteristic of ACE-coupled reaction products could be observed, including a small downfield shift for the methyl ester resonance, along with the disappearance of the norbornene proton resonance from the exo-receptor 6 at 6.45 ppm. The resonance at 90 ppm in the 13C NMR spectrum (not shown) is observed in similar polycyclic systems, and is assigned to the carbon bridgehead atoms in the newly formed oxanorbornane.

In the 1H NMR spectrum (see S24†), seven polycyclic resonances can be observed as expected (excluding the methyl ester); five singlets and two doublets. Of the five singlets, two arise from the central 7-oxanorbornane component, labelled 1–2, while the remaining three signals arise from the exo-component (labelled 3–5, Fig. 11). The doublets, which occur at chemical shifts of 1.27 and 2.62 ppm, correspond to the methylene bridge protons H4/H5 (Fig. 11), which appear at different chemical shifts due to the influence of the 7-oxanorbornane in these linear systems.25,26,30

There is some evidence of facial differentiation within the porphyrin macrocycles in the 1H NMR spectrum of the freebase tetra-porphyrin tweezer 2 (see S24†). While the β-pyrrole resonance appears as a singlet, there is slight splitting/desymmetrisation within some of the meso-phenyl resonances, and the linking meso-phenyl resonances are somewhat broad (see S24†). This facial differentiation indicates that there is some amount of either intramolecular interaction of opposing porphyrins or intermolecular aggregation at NMR concentrations (10−6–10−7 M).

The various porphyrin containing molecules were also examined using UV-Vis spectroscopy. Table 1 summarises the main spectral features of the freebase derivatives of the tetra-porphyrin tweezer 2 (see S26†), bis-porphyrin tweezer 1, and mono-porphyrin receptor 6. The Soret peak band width of 12.1 nm for tetra-porphyrin tweezer 2 is barely broadened compared to the value for mono-porphyrin receptor 6 (11.8 nm), indicating that exciton coupling interactions between the porphyrins in the tetra-porphyrin tweezer 2 are largely absent at UV-Vis concentrations (10−6–10−7 M). This suggests either the porphyrin units are able to undergo rotation either about the single bond between the imide and/or porphyrin moiety, and/or the two polycyclic arms can undergo rotation about the central phenyl diimide core.

**Molecular modelling**

It was envisaged that an unsubstituted central phenyl core would confer the rotational ability required by the polycyclic scaffold to facilitate interannular cooperativity between the two remote binding sites. A significant number of computational and experimental works exploring bond rotation in N-phenyl imide derivatives have been reported.60–76 In summary, the energy barrier to rotation increases as the size of the ortho-phenyl substituent increases due to steric repulsion between the substituent and the oxygen atom of the imide.60,64,65 Additionally, the angle between the aryl and imide rings increases towards perpendicular with increasing size of the ortho-substituent on the phenyl ring, to minimise steric repul-

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**Table 1 Summary of UV-Vis data in chloroform (10−6–10−7 M)**

<table>
<thead>
<tr>
<th>Species</th>
<th>Freebase mono-porphyrin receptor 6</th>
<th>Freebase bis-porphyrin tweezer 1</th>
<th>Freebase tetra-porphyrin tweezer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>λ&lt;sub&gt;max&lt;/sub&gt; (nm)</td>
<td>418.9</td>
<td>419.0</td>
<td>419.0</td>
</tr>
<tr>
<td>Width (nm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.8</td>
<td>12.5</td>
<td>12.1</td>
</tr>
</tbody>
</table>

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Fig. 11. (i) exo-Porphyrin receptor 6 (4 eq.), dry THF, microwave 80–220 W, 14–20 bar, 170 °C, 2 h, 16% after purification.
...eration between the substituent and the oxygen atom of the imide. This competes with the resonance delocalisation and conjugation favoured in the planar conformation. Free rotation is reported for unsubstituted N-phenyl imide derivatives, with rotation becoming restricted for ortho-substituents other than hydrogen. While meta- and para-phenyl substitution does not affect rotation in these systems.

To gain an increased understanding of the barrier to rotation about the imide–phenyl single bond at the core of tetraporphyrin tweezer 2, a rotational energy profile was calculated for a simplified model of the linker, compound 17. The relative energy difference between the global maximum and minimum is approximately 9 kJ mol$^{-1}$ (2.15 kcal mol$^{-1}$) and supports the notion of free rotation in this system at room temperature, from thermal energy available from the surroundings. Not surprisingly, the highest energy conformer occurs at a dihedral angle of 0°, when the phenyl ring proton atoms and imide carbonyl oxygen atoms are in the same plane and interacting sterically. The lowest energy conformation occurs at a dihedral angle of approximately 45°, while a local maximum occurs at approximately 90°.

Molecular modelling has been previously used to calculate the ground state optimised geometry in a polycyclic N-phenyl imide system. In this study, the global energy minimum corresponded to a phenyl–imide angle of 70–71° (RHF/3-21G, HF3-21G), and was 5.65 kJ (1.35 kcal) more stable than the case where the phenyl ring was constrained to the plane of the imide. While the phenyl-imide angle for the global energy minimum is different depending on the computational method employed (rotational energy profile in our work, and the ground state optimised geometry in the literature), both calculations confer that the highest energy state occurs when the phenyl ring is in the plane of the imide, where the hydrogen and oxygen atoms are sterically interacting.

In the absence of X-ray crystallographic data, molecular modelling was undertaken to provide information on the equilibrium geometry of the two binding site tweezer 2. Fig. 13 shows the equilibrium geometry (semi-empirical, AM1) of the zinc(II) metallated adduct of tetra-porphyrin tweezer 2 without guest, and indicates that the polycyclic scaffolds do not necessarily adopt a parallel alignment, as per the idealised structures shown in the reaction schemes, with the two polycyclic arms rotated with respect to each other around the central phenyl diimide group. The phenyl–imide angle from this model of 2 was calculated to be 43° or 21° (depending on whether measured from either the top or bottom half of the model), and is within the trough of the rotational energy profile shown earlier for compound 17 in Fig. 12.

In addition, the idealised parallel arrangement of the porphyrin units has been replaced by a skewed interporphyrin geometry as a result of rotation about the imide–phenylporphyrin bond. Rotation of porphyrins about unsubstituted meso-phenyl rings with respect to the porphyrin β-pyrrole region is well known. Thus the freely rotating porphyrin receptors provides the system with the ability to cofacially interact with...
align the bis-porphyrins after undergoing defined changes to interporphyrin distance upon guest binding as the polycyclic scaffold is rotated through the central core.

Another structural feature not accounted for by the reaction scheme structures is the high degree of curvature in polycyclic scaffolds with 7-oxanorbornane modules. This is clearly observable in the molecular models in Fig. 13, and is a crucial design feature in our tweezer which enables the bis-porphyrin binding sites to be coplanar in each half and cofacial between the two halves, if an idealised conformation is adopted in the presence of a guest.

Fig. 14 shows the equilibrium geometry of the zinc(n) metallated adduct of tetra-porphyrin tweezer 2 with diamino ligand; for (a) DABCO and (b) 4,4′-bipy. The system appears able to accommodate diamino ligands of different lengths (N–N distance for DABCO is 2.6 Å, 7.2 Å for 4,4′-bipy, semi-empirical AM1) as eluded to previously, by rotating both the rigid polycyclic arms (via the phenyl diimide core) and the porphyrin receptors, to adjust the interporphyrin distance as required. For example, the polycyclic arms are rotated further with respect to each other for bipy than for DABCO, due to the difference in ligand length. With respect to each guest, approximately equal interporphyrin distance was observed at both binding sites. Neither the DABCO nor bipy complexed structures appear to be significantly strained, and overlay of the polycyclic arms for molecular models with and without guest (not shown) revealed only minimal distortion, providing further evidence that the polycyclic arms are largely rigid. The experimental host–guest complexation of the zinc(n) metallated adduct of tetra-porphyrin tweezer 2 with diamino ligands, and analysis of interannular cooperativity will be described in a future publication.

Conclusions

Tetra-porphyrin tweezer 2 with two remote but interdependent binding sites was synthesised via a divergent approach from a tetra-functional phenyl diimide core. The key step in obtaining this target was the application of a copper(n)-mediated coupling of benzene-1,4-diboronic acid with a polycyclic imide, and represents a novel use of such coupling in polycyclic scaffolds.

We expect that the polycyclic imide coupling methodology presented in this paper, either via the phenyl boronic acid (superior for the synthesis of compound 10) and/or aryl halide route, is easily and widely applicable to other modular polycyclic systems. This will aid in the synthesis of functional supramolecular architectures where control of north/south reactivity or other directional interactions is required. Furthermore, the microwave-accelerated ACE reaction allowed simultaneous attachment of the four porphyrin moieties to afford the tetraporphyrin tweezer 2.

Molecular modelling of both the equilibrium geometry of tetra-porphyrin tweezer 2 and the rotational energy profile of a model of the phenyl–imide linker core suggests the architecture is well suited for the complexation of diamino ligands of varying lengths, such as DABCO and 4,4′-bipy. This appears to be facilitated by bond rotation about both the central phenyl diimide core and the porphyrin receptors.

The absence of reactivity at the anhydride of laterally functionalised systems such as compound 4 continues to complicate efforts towards the convergent synthesis of extended polycyclic architectures. Our laboratory is currently pursuing the imide analogue of bis-porphyrin anhydride 7, which is expected to be able to be coupled using the boronic acid method employed for the synthesis of compound 10. The establishment of a convergent strategy would enable architecture 2 to be expanded to include asymmetric molecular tweezers with two different receptor binding sites.

Experimental

Molecular modelling

Molecular modelling was undertaken using the Wavefunction Spartan ‘10 software package. Equilibrium geometry was calculated using a semi-empirical AM1 model. Rotational energy profiles were calculated using a Hartree–Fock 6-31G* model for each conformation about the bond specified by the dihedral angle constraint, with the energy of each conformation recalculated using a B3LYP/6-31G* Density Functional model to improve the fitting function.

Characterisation

Melting points were measured using a Barloworld Scientific SMP10 melting point apparatus.
NMR spectra were recorded on a Bruker UltraShield Avance III 400 MHz or 600 MHz NMR Spectrometer running the TopSpin software package at 299 K and 293 K respectively. Spectra were calibrated to the residual solvent signal. CDCl₃ was deaerated by passing through neutral activated alumina oxide (Scharlau, activity degree 1, 70–290 mesh, grain size 0.05–0.2 mm) and stored under a nitrogen atmosphere over silver foil/molecular sieves in a brown glass bottle.

Theoretical mass spectra were generated by using the mMass software package. Single crystals of compounds 11–13 suitable for X-ray diffraction experiments were covered in Paratone-N oil and mounted on a glass fibre. Data (2θmax 55°) were collected at 150 K using an Oxford Diffraction X-Calibur X-ray diffractometer and MoKα (0.7073 Å) radiation. After integration and scaling, the datasets were merged into N unique reflections (Rint). The structures were solved using conventional methods and refined by using full-matrix least-squares using the SHEXL-97 software in conjunction with the X-Seed interface. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were placed in calculated positions. Early refinement of compound 13 in an alternate monoclinic space group (P21/n) was attempted; however, structural solution in this space group failed. The structure was solved and refined in the more orthogonal space group P21/c. Structure solution and refinement succeeded with three crystallographically independent but structurally identical molecules in the asymmetric unit. Intensity data for compound 9 was collected with an Oxford Diffraction SuperNova CCD diffractometer using Cu-Kα radiation. The temperature during data collection was maintained at 100.0(1) using an Oxford Cryosystems cooling device. The structure was solved by direct methods and difference Fourier synthesis. Thermal ellipsoid plots were generated using the program ORTEP-3 integrated within the WINGX suite of programs. Additional information on the crystal structures of compounds 9 and 11–13 can be found in the ESI (see S8 and S15).

Where necessary, solvents and reagents for synthesis were purified according to the methods published. Dry THF was freshly distilled from sodium/benzophenone, dry CH₂Cl₂ freshly distilled from CaH₂, and dry DMF and DMSO were distilled under reduced pressure onto fresh molecular sieves after stirring on molecular sieves overnight. Potassium tert-butoxide was purified by sublimation under high vacuum at 0.17 mmHg at 160 °C, stored under a nitrogen atmosphere, and in a desiccator at room temperature.

Bis-epoxide anhydride 5. Mitsudo anhydride 4 (1.0 g, 1.94 mmol) was dissolved in dry CH₂Cl₂ (100 mL) under a nitrogen atmosphere and cooled to 0 °C. Anhydrous tert-butyl hydroperoxide in toluene (3.3 M, 1.47 mL, 4.85 mmol, 2.5 eq.) was added and stirred for a further 10 min at 0 °C, after which sublimed potassium tert-butoxide (0.21 g, 1.87 mmol, ~1 eq.) was added. The mixture was allowed to warm to room temperature over 30 minutes, during which a white precipitate formed. After stirring at room temperature for a further 3 hours, sodium sulfite (10% aqueous solution, 10 mL) was added with vigorous stirring for 15 minutes. The mixture was diluted with CHCl₃ (100 mL), washed with brine (200 mL), HCl (2 M, 100 mL), NaOH (2 M, 100 mL), H₂O (100 mL), dried with Na₂SO₄, filtered, and the solvent removed in vacuo to afford an off-white powder (0.52 g, 49%). The material was purified by passage through a plug (silica, CH₂Cl₂), followed by column chromatography (silica, CH₂Cl₂ to remove impurity, followed by elution of product with THF). This afforded white and pale yellow flakes used for subsequent reactions. A sample was recrystallised from CHCl₃/toluene (white powder precipitates during rotatory evaporation to reduce volume) for MS and melting point analysis. M.p. (solvent of crystallisation loss 180–185 °C, then partial
**An excess of warm DCC was added as a liquid.**

**PMB protected imide 11.** Using a modified procedure,\textsuperscript{18,50} anhydride 3\textsuperscript{99} (21 g, 0.090 mol) was dissolved in CHCl\textsubscript{3} (300 mL, deacidified by passing through neutral activated aluminium oxide) under a nitrogen atmosphere. 4-Methoxybenzylamine (2 eq., 25 g per 23.6 mL, 0.18 mol, Sigma-Aldrich) was added and the solution stirred at 50 °C overnight under a nitrogen atmosphere, during which a white precipitate formed. The mixture was cooled, filtered, and the precipitate washed with CHCl\textsubscript{3} (3 × 100 mL). The precipitate was dissolved in Ac\textsubscript{2}O (350 mL), NaOAc (2 eq., 24.6 g, 0.181 mol) added, and the mixture stirred overnight at 50 °C under a nitrogen atmosphere, after which the Ac\textsubscript{2}O was removed by distillation under reduced pressure at 50 °C. The solids were redissolved into CHCl\textsubscript{3} (300 mL), washed with H\textsubscript{2}O (2 × 200 mL), HCl (2 M, 200 mL), NaOH\textsuperscript{††} (2 M, 5 × 200 mL), H\textsubscript{2}O (200 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and the solvent removed in vacuo. The solid was washed with hexane (2 × 100 mL), Et\textsubscript{2}O (2 × 100 mL), and EtOH (5 × 100 mL, to remove significant brown byproduct) to afford a white powder (16.5 g, 52%). A sample was recrystallised from CHCl\textsubscript{3}/hexane for MS and melting point analysis. M. p. 231–233 °C. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, 20 °C): 7.15 (d, J = 8.8 Hz, 2H), 6.79 (d, 8.8 Hz, 2H), 6.37 (m, 4H), 5.20 (m, 4H), 4.28 (s, 2H), 3.77 (s, 3H). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): 173.86, 159.31, 138.90, 130.51, 127.28, 113.74, 81.39, 69.21, 55.30, 41.79. HRMS (ESI-TOF-MS) for C\textsubscript{130}H\textsubscript{96}N\textsubscript{10}O\textsubscript{19}Na\textsuperscript{+} [M + Na]\textsuperscript{†}: Calc.: 2707.7241. Found: 2707.7310.

**Imide 12.** Using a modified procedure,\textsuperscript{18,50–53} PMB protected imide 11 (16 g, 0.046 mol) was slowly dissolved in a mixture of 9:1 CH\textsubscript{3}CN/H\textsubscript{2}O (1 L) at 40 °C for 1 h. Ammonium cerium(IV) nitrate (82 g, 3.3 eq.) was added in two portions; 2.3 eq. for 90 min, followed by 1 eq. for a further 30 minutes; with reaction progress monitored by NMR. The volume of the solution was reduced by approximately two thirds in vacuo at 50 °C, or until a precipitate formed. The precipitate was filtered and put aside to later be combined with additional product. The filtrate volume was then further reduced in vacuo at 50 °C until only H\textsubscript{2}O remained. The mixture was diluted with further H\textsubscript{2}O, extracted with EtOAc (10 × 200 mL), and the EtOAc extracts combined. The volume of EtOAc was reduced in vacuo at 50 °C until a precipitate formed. The precipitate was filtered, and combined with the first crop of product. The filtrate volume was further reduced, and the precipitate collection cycle repeated until only an orange/brown oily sludge remained (p-anisaldehyde byproduct). The combined precipitate was washed with H\textsubscript{2}O (2 × 100 mL) and EtOH (10 × 100 mL) to afford a white powder (7.64 g, 73%). M. p. partial decomposition (darkens) >200 °C, violent decomposition (boiling) at 293–295 °C. Single crystals for X-ray analysis were grown from CH\textsubscript{3}CN/DMSO by slow evaporation. \textsuperscript{1}H NMR (600 MHz,
DMSO-d$_6$, 20 °C): 10.79 (s, 1H), 6.71 (s, 4H), 5.24 (s, 4H).

$^{13}$C NMR (150 MHz, DMSO-d$_6$): 175.34, 139.36, 80.39, 70.03.

HRMS (ESI-TOF-MS) for C$_{12}$H$_8$NO$_4$ [$M - H]^{-}$: Calc: 230.0453. Found: 230.0457. CCDC 1486428 contains the supplementary crystallographic data for this paper.

**Mitsudo imide 13.** A solution of imide 12 (5.0 g, 0.022 mol), DMAD$_{91,92}$ (12.3 g, 0.087 mol, 4 eq.), and [RuH$_2$(CO)(PPh$_3$)$_3$]$_{93}$ (7.2 g, 2.4 mmol, 36 mol%) in dry DMF (150 mL) was stirred at 60 °C under a nitrogen atmosphere for 1 day. The black solution was cooled, and the DMF removed by distillation under reduced pressure. The remaining sludge was purified by several rounds of column chromatography using different solvents to elute the product as follows: (1) (silica, plug, 20% THF/CHCl$_3$), collecting several large plug length fractions, recrystallised from EtOAc/hexane or CHCl$_3$/hexane to a crystallographic data for this paper.

**Mitsudo imide 14a.**

**Method A – microwave/aryl halide/Cu(0).** Using a modified procedure (N-aryl imides from succinimide/phthalimide and mono-halo aryl), Mitsudo imide 13 (100 mg, 0.19 mmol), activated elemental copper$_{59}$‡‡ (100 mg, 1.57 mmol), and 1,4-diiodobenzene (500 mg, 1.52 mmol, excess) were suspended in solvent (EtOAc, 1 mL) in a 10 mL microwave vessel. The microwave was operated in variable power (dynamic) mode with the following parameters: temperature 120–150 °C, power 300 W (automatically modulated around the set temperature), stirring high, compressed air cooling (PowerMAX) on. The mixture was microwaved at 120 °C for 1 h, further activated copper (100 mg, 1.57 mmol) added, and microwaved for an additional 1.5 h (total 2.5 h). The mixture was charged with toluene (1 mL), and microwaved at 150 °C for an additional 1 h (total 3.5 h), during which temperature and pressure stability seemed to be restored. NMR after 3.5 h total reaction time indicated just 30% conversion to the coupled adduct. The mixture was microwaved for a total of 12 h, after which NMR indicated approximately 66% conversion to the coupled adduct. The yellow/brown liquid was filtered, the solids washed with toluene (50 mL), EtOAc (50 mL), CHCl$_3$ (50 mL), the solvent removed in vacuo, and purified by column chromatography (silica, 20% EtOAc/CHCl$_3$) to afford a white powder.

**Mitsudo phenyl diimide 10.** Using a modified procedure developed for coupling nitrogen-containing compounds with aryl mono-boronic acid derivatives, Mitsudo imide 13 (380 mg, 0.74 mmol) was suspended in MeOH (25 mL), and compressed air bubbled through a large gauge needle into the reaction mixture at a flow rate of 3–4 bubbles per second. Benzene-1,4-diboronic acid (61 mg, 0.37 mmol, Sigma-Aldrich) was added, quickly followed by Cu(OAc)$_2$·H$_2$O (7.5 mg, 0.038 mmol, no more than 2.5–5 mol% per boronic acid). The mixture was refluxed for 12 hours during which a white precipitate formed. The volume of MeOH was monitored for evaporation and maintained. The air bubbler needle was changed every 1 hour to prevent clogging, while the air flow rate was varied as necessary to maintain the blue/green colour of the solution (greater air flow required if the solution was brown), yet without cooling the mixture and preventing reflux. The reaction produced two compounds, the Mitsudo phenyl diimide 10 (precipitate), and a solvent-dependent side product (filtrate). The side product in the filtrate (15a, 15b) was

†† Prior to precipitation of copper, the zinc dust was pre-treated with 2% hydrochloric acid to ensure it met the oxide-free requirement. Freshly precipitated elemental copper was dried in vacuo, and not at 100 °C. The elemental copper appeared as more of a brown powder (not metallic/lustrous in appearance).
characterised without further purification. The desired product (precipitate) was purified using the following method:

The mixture was cooled, the precipitate removed by filtration, and the solids washed with MeOH (100 mL). The solid was dissolved in CH2Cl2 (100 mL), washed with H2O (100 mL), dried with Na2SO4, the solvent removed in vacuo, and washed again with MeOH (100 mL) and hexane (100 mL) to afford a white powder (150 mg, 37%). This procedure was repeated several times on a similar scale to generate additional material. A sample was recrystallised from CHCl3/hexane for MS and melting point analysis. M.p. >300 °C (partial decomposition).

1H NMR (600 MHz, CDCl3, 20 °C): 7.38 (s, 4H), 4.87 (s, 8H), 3.80 (s, 24H), 3.23 (s, 8H). 13C NMR (150 MHz, CDCl3): 171.50, 160.17, 140.11, 131.21, 127.03, 77.61, 70.37, 52.49, 44.82. HRMS (ESI-TOF-MS) for C31H27NO13Na+ [M + Na]+: Calc: 644.1380. Found: 644.1362.

Side product with solvent MeOH, 15a. 1H NMR (600 MHz, CDCl3, 20 °C): 7.08 (d, 2H, J = 9.0 Hz), 6.99 (d, 2H, J = 9.0 Hz), 4.86 (s, 4H), 3.80 (s, 3H), 3.80 (s, 12H), 3.26 (s, 4H). HRMS (ESI-TOF-MS) for C266H194N2O36Na+ [M + Na]+: Calc: 1191.1984. Found: 1191.1975.

Tetra-epoxide phenyl diimide linker 16. Mitsudo phenyl diimide 10 (300 mg, 0.27 mmol) was dissolved in dry CH2Cl2 (100 mL) under a nitrogen atmosphere and cooled to 0 °C. Anhydrous tert-butyl hydroperoxide in toluene 94 (3.3 M, 0.55 mL, 1.82 mmol, at least 5 eq.) was added and stirred for a further 10 min at 0 °C, after which sublimed potassium tert-butoxide (70 mg, 0.62 mmol, approx. 2 eq.) was added. The mixture was allowed to warm to room temperature over 3 hours, the mixture was diluted with CH2Cl2 (50 mL) under a nitrogen atmosphere and cooled to 0 °C. Two equivalents of tert-butyl hydroperoxide were added with vigorous stirring for 15 minutes. The mixture was further diluted with CH2Cl2 (200 mL), washed with brine (200 mL), dried with Na2SO4, filtered, and the solvent removed in vacuo. This afforded a white powder (160 mg, 50%), used in subsequent reactions without further purification. A sample was recrystallised from CH2Cl2/hexane for MS and melting point analysis. M.p. >300 °C (partial decomposition).

1H NMR (600 MHz, CDCl3, 20 °C): 7.04 (d, 2H, J = 9.0 Hz), 6.99 (d, 2H, J = 9.0 Hz), 4.86 (s, 4H), 7.89 (d, 2H, J = 8.9 Hz), 5.31 (s, 1H), 4.86 (s, 4H), 3.80 (s, 12H), 3.25 (s, 4H). HRMS (ESI-TOF-MS) for C31H27NO13Na+ [M + Na]+: Calc: 644.1362. Found: 644.1360.

Free base tetra-porphyrin tweezer 2. A suspension of quadr-epoxide phenyl diimide linker 16 (55 mg, 0.047 mmol) and exo-imide porphyrin receptor 6 (180 mg, 0.23 mmol, 4.9 eq.) in dry THF (3 mL) was subjected to microwave irradiation using the conditions in the general procedure at the beginning of the experimental. This procedure was repeated several times on a similar scale until 150 mg (0.128 mmol) epoxide had been reacted. The material from each reaction was combined, the solvent removed in vacuo, and the material purified by column chromatography (silica, CHCl3) to recover unreacted exo-imide porphyrin receptor 6, after which the mobile phase was changed to 10% THF/CHCl3 and the strong porphyrin band collected. 1H NMR of this material suggested the band contained a majority of the desired tetra-porphyrin adduct with small amounts of other porphyrin stoichiometries. The material was recrystallised twice from CHCl3/MeOH to afford purple crystals of the pure tetra-porphyrin tweezer (88 mg, 16%). 1H NMR (600 MHz, CDCl3, 20 °C, approximately 0.8 mM): 8.83 (s, 32H), 8.30 (bs, 8H), 8.23–8.13 (m, 24H), 7.80 (s, 4H), 7.79–7.69 (m, 36H), 7.65 (bs, 8H), 4.94 (s, 8H), 4.02 (s, 24H), 2.96 (bs, 8H), 2.91 (s, 8H), 2.67 (s, 8H), 2.63 (d, 110.67 Hz, 4H), 2.36 (s, 8H), 1.28 (d, 11.67 Hz, 4H), -2.81 (s, 8H). HRMS (ESI-TOF-MS) for: C266H196N22O36Na+ [M + 4H]+: Calc: 1068.3540. Found 1068.3566. C266H196N22O36Na2+ [M + 3H]+: Calc: 1424.1363. Found 1424.1392. C266H194N22O36Na3+ [M + 2H]+: Calc: 2135.7022. Found 2135.7008. 2+ [M + H]+: Calc: 419.0 (shoulder around 400), 515.2, 550.8, 590.0, 644.6.

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Notes and references

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