Abstract

Molecular tweezers show significant promise for a variety of applications, from new agents for targeted drug delivery and controlled release, as enzyme mimics, and as components in molecular machines to perform specific functions at the nanoscale. For molecular tweezers with two ligand binding sites, where these are remote but interdependent, the system can benefit from cooperativity during complexation, to positively or negatively influence ligand binding. Recently, cooperativity in supramolecular systems been categorised into several different types depending on the modes of interaction between the architecture and ligands. These include allosteric, chelate, and interannular cooperativity. As such, assessing and quantifying cooperativity between remote ligand binding sites is more complex than previously envisaged. This work investigated cooperativity within tweezer **4**, which has two homotropic ligand binding sites.

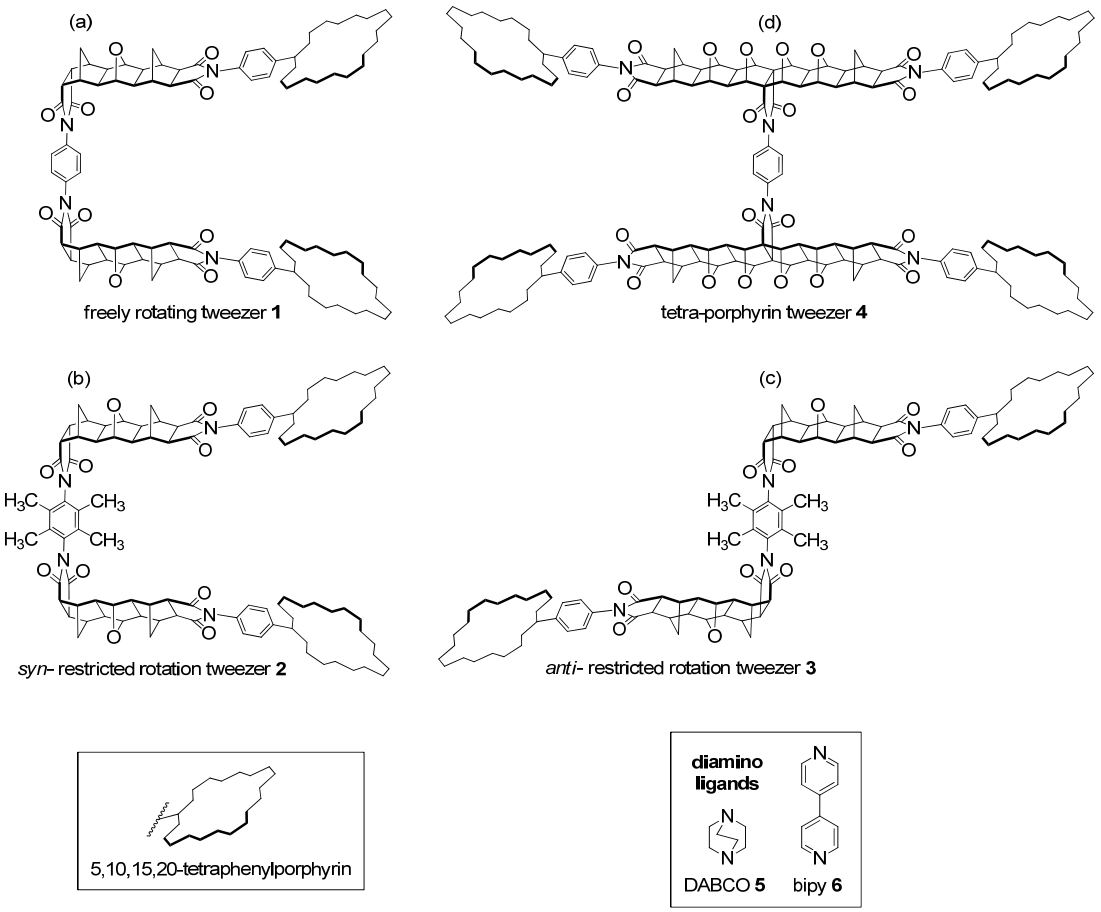

Figure i - Schematic representation of the four molecular tweezers synthesised in this work (a) freely rotating **1**, (b) *syn*- restricted rotation **2**, (c) *anti*- restricted rotation **3**, (d) tetra-porphyrin freely rotating **4**, each studied for complexation with diamino ligands DABCO **5** and bipy **6**.

Using molecular modelling as a guide, a tweezer architecture was designed to complex diamino substrates such as 1,4-diaza[2.2.2]bicyclooctane **5** (DABCO) and 4,4'-bipyridyl **6** (bipy). The modular tweezer design allowed for maximum synthetic variability and resulted in synthesis of three generations of the tweezer (Figure i), each containing rotating bis-porphyrin receptors, linked via a bridged polycyclic backbone, with a central phenyl diimide core of varying rotational freedom. Structural analogues included a freely rotating tweezer **1** with one binding site [1] (a), a rotationally restricted tweezer with non-interconvertible *syn*- **2** and *anti*- **3** conformations (b) and (c), and a freely rotating tetra-porphyrin tweezer **4** with two binding sites (d) [2]. With the exception of the *anti*- restricted system (c), each tweezer formed strong intramolecular sandwich complexes in chloroform with the target diamino substrates, as characterised by UV-Vis and NMR spectroscopy, with the binding model and association constants determined by multivariate global spectral analysis.

The first generation freely rotating single binding site tweezer **1** [1] (Figure i (a)) served as a good model to determine the feasibility of applying the bridged polycyclic scaffold to the tetra-porphyrin system **4**. This probed both the ability of the tweezer to form strong intramolecular sandwich complexes with diamino ligands, as well as the rigidity of the bridged polycyclic scaffold, including free rotation about single bonds at the central phenyl diimide core and porphyrin receptors.

The second generation tweezer (Figure i (b), (c)) was analogous to the first except for the subtle inclusion of sterically bulky methyl substituents about the central phenyl diimide core. In this case, non-interconvertible *syn*- **2** and *anti*- **3** conformations could be physically separated and studied independently of each other. For the *syn*- conformation, this removed the undesired *anti*- conformation only capable of intermolecular complexation with ligands.

After gaining an understanding about the behaviour of the model single binding site systems regarding both substrate complexation and core rotation, the third generation freely rotating tetra-porphyrin tweezer **4** (Figure i (d)) was synthesised [2]. The two bis-porphyrin binding sites are intrinsically linked via the freely rotating phenyl diimide core, which acts as a pivot through which equal and opposite rotation of a largely rigid polycyclic backbone can occur. Statistical evaluation of the interannular cooperativity factor, γ, was undertaken using a method reported in the literature, and

revealed the intramolecular sandwich complex with two molecules of DABCO, tetra-porphyrin:$(DABCO)_2$ was negatively cooperative ($\gamma = 2.41 \times 10^{-3}$), while that with bipy, tetra-porphyrin:$(bipy)_2$, was modestly positively cooperative ($\gamma = 4.65\text{-}5.24$). The negative cooperativity determined for DABCO was unexpected, given the large intramolecular association constants of the model tweezers, and suggests that DABCO could be too small to be bound optimally at both binding sites. The positive cooperativity observed for bipy could be explained by increased optimisation of the interporphyrin distance at the second binding site brought about by binding at the first binding site.