exo-Selective Acceleration of an Intermolecular Diels–Alder Reaction by a Trimeric Porphyrin Host

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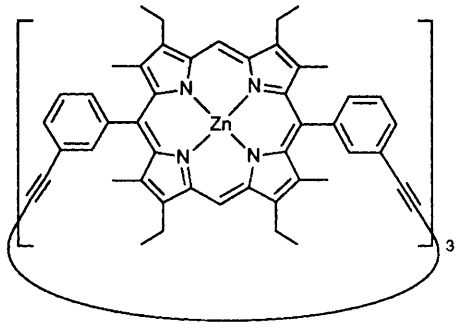
A bimolecular Diels–Alder reaction is accelerated substantially and stereoselectively by binding diene and dienophile within the cavity of a cyclic metalloporphyrin trimer.

One of the key goals of supramolecular chemistry[1] is to mimic the ability of enzymes to bind two substrate molecules and catalyse stereospecifically a reaction between them. There are many known examples of 'synthetic enzymes' which operate on a single bound substrate,[2] but relatively few which involve two substrates.[3,4] We now report the use of porphyrin trimer **1**[5] in stoichiometric amounts as a reagent to accelerate an intermolecular Diels–Alder reaction with complete *exo*-selectivity.†

When two or three pyridine ligands are bound within the cavity of **1**, their effective concentration is dramatically increased while at the same time their range of relative orientations is limited by the geometry of Zn–N coordination.[5] The trimer should, therefore, act as an 'entropic trap' and accelerate any reaction whose transition-state geometry matches the relative orientation of bound ligands. The Diels–Alder reaction is an attractive subject for such an approach because of its highly ordered transition state and interesting stereochemistry.

The substrates chosen for initial study were the furan-based diene **2** and the maleimide-based dienophile **3**.‡ Space-filling models indicate that binding to the inside of the host holds the reactive ends of the two substrates in close proximity, while



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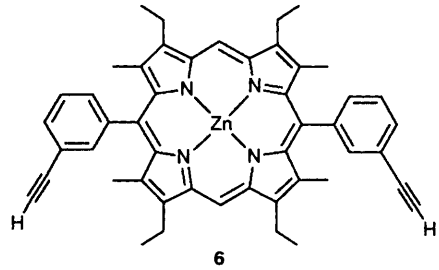

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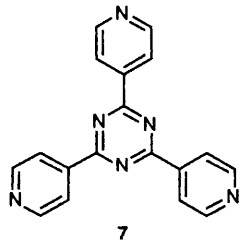

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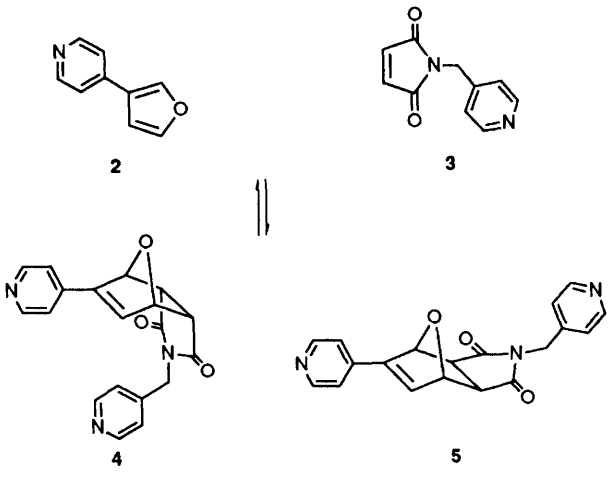
† Pericyclic reactions catalysed by antibodies also provide a close analogy to our fully synthetic system.[6]

‡ The maleimide dienophile **3** was prepared by condensing 4-(aminomethyl)pyridine with the maleic anhydride–furan Diels–Alder adduct, followed by sublimation to remove the furan protecting group. Furan **2** was prepared by modification of a published procedure.[7] All new compounds gave satisfactory spectroscopic and analytical results.



Scheme 1

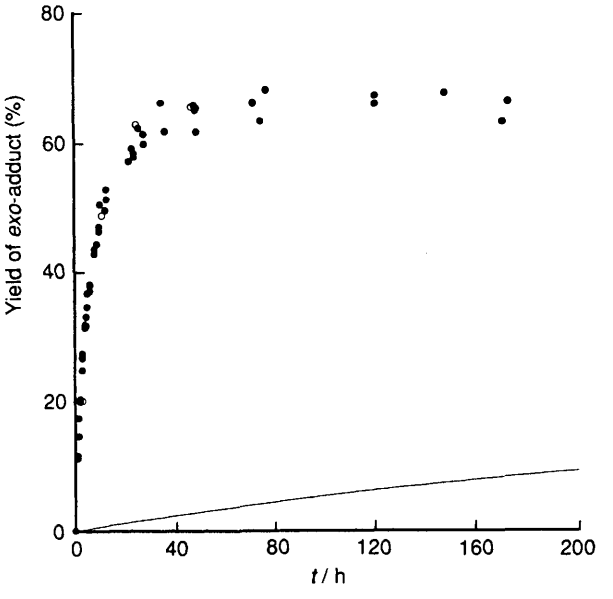


Fig. 1 Formation of *exo*-adduct **5** from **2** and **3** in the presence of equimolar trimer **1**. Reactions (60 °C, 0.9 mmol dm^{-3} reactants in $C_2H_2Cl_4$ solution) were monitored by NMR (○) or FTIR (●) spectroscopy. Calculated progress curve for the uncatalysed reaction (——).

the rigidity of the substrates ensures that the high effective concentration produced by their binding is transferred to the reactive site at the heart of the cavity. Furthermore, the Diels–Alder reaction between **2** and **3** is reversible,[8] offering the future opportunity of approaching the transition state from both directions.

Scheme 1 shows that, in the absence of any catalyst, the reaction between **2** and **3** yields two products, the kinetically favoured *endo*-adduct, **4**, which is seen only in the early stages of the reaction, and the thermodynamically favoured *exo*-adduct, **5**, which predominates and is the sole product at equilibrium. This is a rapid, synthetically useful reaction at preparative concentrations; at 60 °C with 9 mmol dm^{-3} substrates the measured bimolecular rate constant is 2×10^{-4} dm^3 mol^{-1} s^{-1}. With 0.9 mmol dm^{-3} reactants (a convenient test concentration for **1**), the reaction is much slower, and the equilibrium position lies on the side of the starting materials. The calculated progress curve under these more dilute conditions is shown as a solid line on Fig. 1.

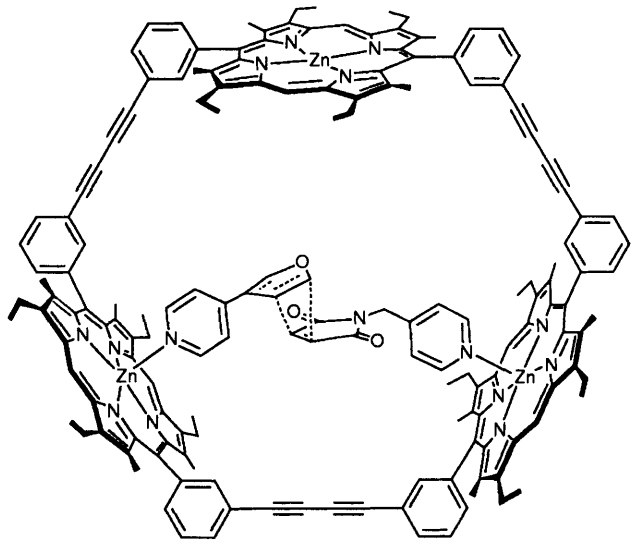


Fig. 2 Proposed transition-state geometry for the Diels–Alder reaction between **2** and **3** in the cavity of trimer **1**

The presence of one equivalent of trimer **1** enhances the initial forward rate 200-fold and the reaction reaches an equilibrium position of around 65% completion in under 50 h (Fig. 1).§ *exo*-Adduct **5** is the only product detected at any stage during this trimer-accelerated reaction, *endo*-adduct being completely suppressed. The shift in the equilibrium position in the presence of **1** corresponds to an increase in the effective bimolecular equilibrium constant for the reaction between **2** and **3** from ~300 dm^3 mol^{-1} for the uncatalysed reaction to ~6000 dm^3 mol^{-1}. The measured macroscopic binding constants reflect these results: under the reaction conditions at 60 °C the reactants **2** and **3** each have binding constants to **1** of ~400 dm^3 mol^{-1} while **5** binds at $\sim 4 \times 10^5$ dm^3 mol^{-1}.

The simplest interpretation of these results is that diene and dienophile can bind within a single cavity in a favourable relative orientation as shown in Fig. 2. At the beginning of the reaction only around 25% of the host trimers are bound to two or more substrate molecules. No more than one sixth of those are bound productively (*i.e.* diene and dienophile bound within a single cavity) so the initial rate of reaction for a diene–dienophile pair bound inside **1** as shown is around 6000-fold faster than the equivalent pair in free solution. More detailed studies of the rather complex kinetics are underway.

Control experiments support the idea of reactive pairwise binding within the cavity: no acceleration is observed in the presence of monomer **6**[9] and, most persuasively, the acceleration is completely abolished by tripyridyltriazine, **7**. This ligand binds extremely strongly within the cavity of **1**,[5] and so acts like a classical competitive enzyme inhibitor.

It is clear that trimer **1** is acting as a very effective linear template[10] both kinetically, to accelerate the reaction, and thermodynamically, to stabilise the product, proving that design on a microscopic level can lead to substantial and intended macroscopic effects. It should now be possible to design host–substrate systems that encourage the formation of conventionally unfavourable stereo- or regio-chemistries. Efficient catalytic turnover can, no doubt, be designed in using the same strategies as have been employed for catalytic antibodies.[6] As a first step, the present system, although far from optimized, yields encouraging results.

§ The reaction was followed by NMR spectroscopy of quenched reaction mixtures or by FTIR difference spectroscopy, monitoring the 5 cm^{-1} difference between the carbonyl absorptions of **3** and **5**.

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