Acceleration of a hetero-Diels–Alder reaction by cyclic metalloporphyrin trimers

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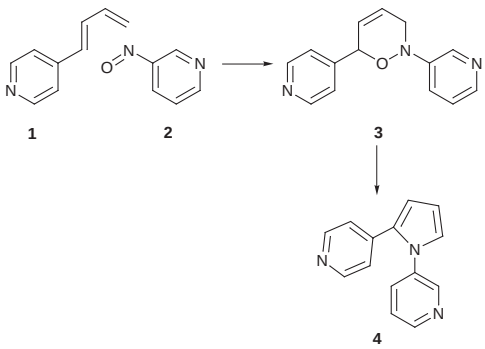
The hetero-Diels–Alder reaction between a pyridylbutadiene and 3-nitrosopyridine is accelerated by a variety of metalloporphyrin trimers; there is a weak correlation between rate acceleration and product binding strength.

The acceleration of Diels–Alder reactions by artificial receptor molecules is well documented,[1] but there are few systematic studies of how the rate of an intra-cavity reaction can be influenced by fine-tuning the size and flexibility of the host.[2] The examples described so far are special cases of Diels–Alder reactions that have been carefully chosen to match the available hosts, in part because of the synthetic difficulties associated with producing a range of hosts. We now show that the regiospecific hetero-Diels–Alder reaction[3,4] of pyridyl diene **1** with 3-nitrosopyridine **2** to give oxazine **3** (Scheme 1) is a second pericyclic reaction that can be influenced by porphyrin trimer systems such as **5–8**. This cycloaddition is more readily monitored kinetically than our original Diels–Alder reaction as the process is essentially irreversible‡ and forms only a single, fairly robust product. The product has been rearranged to the 1,2-disubstituted pyrrole **4**;[5] if this rearrangement could be induced to occur under conditions compatible with the porphyrin trimers then the possibility of catalytic turnover arises.§

Trimers **5**[6]¶ and **6**[7] each contain three conventional porphyrins while the new[8] heterotrimers **7** and **8** contain one or two dioxoporphyrins respectively. The control (host-free) Diels–Alder reaction between diene **1** and dienophile **2** was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ and in [$^2H_8$]toluene, and showed clean transformation of the starting substrates to the oxazine without significant formation of side products. However, HPLC was the preferred analytical technique for host-accelerated kinetic investigations. In a typical reaction, diene **1**, dienophile **2** and host were mixed in equimolar amounts, each at a concentration of 0.333 mM. The reaction was carried out at 25 °C in CH_2Cl_2 (and also in toluene for trimer **5**) and monitored by HPLC.‖ It proved to be first order with respect to both the diene and dienophile with a rate constant of 3.9×10^{-3} M^{-1}s^{-1} (Table 1). The host-induced rate accelerations (calculated relative to the host-free reaction) for the different hosts are summarised in Table 1.



Scheme 1

In order to gauge the affinity of the substrates and product to the various hosts, a series of UV–visible titrations were performed using the established procedure;[9] results for the oxazine product **3** are also summarised in Table 1, together with the effective molarity for binding **3** relative to the two substrates.** For trimer **6**, the values represent an average of all the possible binding interactions to that host (inside/outside for the monodentate substrates, or across acetylene/butadiyne for the bidentate oxazine). Complications arise for the mixed dioxo hosts because pyridine-binding gives no noticeable shift in the Soret band:[8] monitoring the shift of the porphyrin Soret band in these species can thus only yield information about binding interactions at the porphyrin sites and not at the dioxo sites.

In CH_2Cl_2 an acceleration of 1030-fold (relative to the control reaction) was observed for the unsymmetrical host **6**. This is coupled with a particularly high binding affinity of oxazine **3** to **6**, suggesting that the 'product-like' transition state

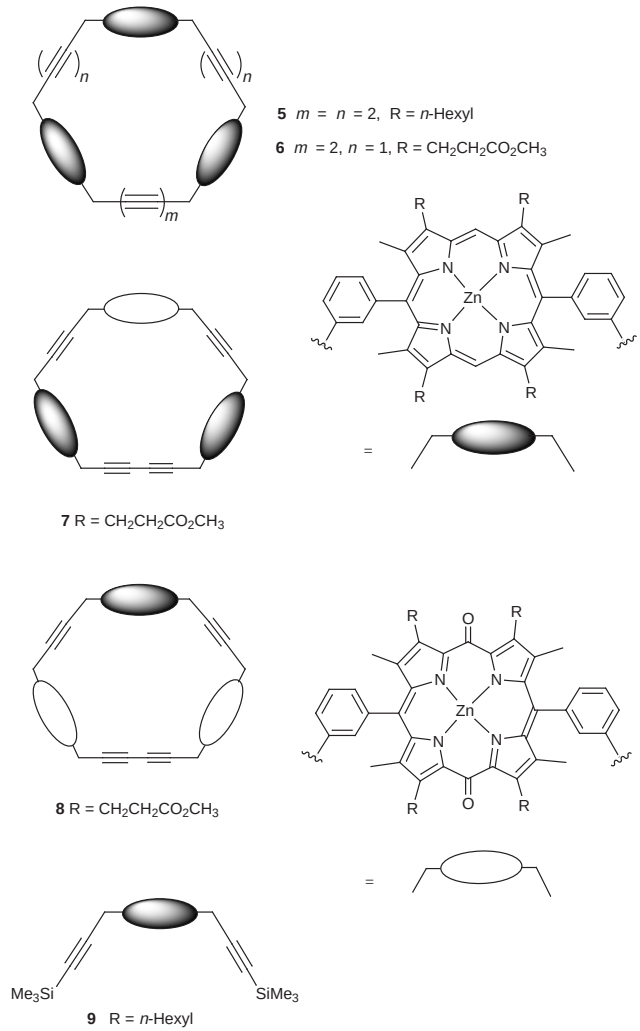


Table 1 Kinetic and equilibrium constant data for formation and binding of **3** with various hosts

Host	Solvent	k/M^{-1} s^{-1}	Rate acceleration (approx.)	Binding constant/M^{-1}	E.M.[a]
Control	CH_2Cl_2	0.0039	—		
Control	PhMe	0.0023	—		
9	CH_2Cl_2	0.0064	2	6.9×10^3	0.0035
9	PhMe	0.0025	1	8.2×10^3	0.0012
5	CH_2Cl_2	1.1	280	7.3×10^6	3
5	PhMe	1.9	830	5.6×10^7	3
6	CH_2Cl_2	4.0	1030	2.3×10^8	13
7	CH_2Cl_2	3.2	820	2.4×10^8	23
8	CH_2Cl_2	2.2	560	1.2×10^8	2

[a] See note **.

for the reaction prefers to bridge the shorter acetylene linker present in this host, rather than the butadiyne link in **5**. Further evidence to support this is obtained from molecular modelling of the oxazine using CERIUS[2] which confirms that the geometry is more complementary to the smaller porphyrin–porphyrin distance. A similar rate acceleration (820-fold) was observed for the mono-dioxo host **7**.

As the magnitude of binding constants and reaction rate constants are likely to display solvent dependence, and as this may subsequently lead to a different rate acceleration, the control reaction and the **5**-host accelerated reaction were also studied in toluene: the 830-fold rate acceleration is significantly higher in toluene than the 280-fold in CH_2Cl_2 (Table 1). The control reaction is 1.7 times faster in CH_2Cl_2 than in toluene, while the host-accelerated reaction is 1.7 times faster in toluene than in CH_2Cl_2 (Table 1). It is possible that in the control reaction the solvent stabilises the Diels–Alder transition state better than the reactants, and that this stabilisation is more significant in CH_2Cl_2 than in toluene, leading to a higher reaction rate in CH_2Cl_2. This is consistent with the observed binding constants being larger in toluene than in CH_2Cl_2.** This stronger binding in toluene will also lead to an increased concentration of the host–substrate reactive complex and to a larger rate enhancement. In addition, it is also possible that the reactants and transition state are not well solvated inside the trimer cavity. In this case, therefore, solvent stabilisation is not as significant as in the control reaction, where the reactive species are not shielded by the host and are easily solvated.

In order to prove that the cycloaddition reaction occurs inside the cavity of the trimeric porphyrin hosts, an inhibition experiment was carried out in which 1 equiv. of oxazine **3** was added to the reaction mixture in the presence of **5**. The resulting rate acceleration is reduced by roughly 20-fold in CH_2Cl_2 and 270-fold in toluene, giving a reaction rate similar to that observed in the presence of porphyrin monomer. Pyrrole **4** is a less effective inhibitor when added to the CH_2Cl_2 or toluene reaction mixture in the presence of **5**: although the initial reaction rate drops to one third of that observed for the **5**-accelerated reaction, complete inhibition does not occur and catalytic turnover is still feasible. The observed decrease is readily explained: if the pyrrole occupies one site inside the cavity, this leaves only two sites to bind the diene and dienophile, decreasing the number of constructive binding possibilities from six to two.

Preliminary results indicate that the hetero-Diels–Alder reaction described is well suited for intra-cavity kinetic studies. Future investigations will focus on initiating the pyrrole formation under conditions compatible with the Diels–Alder cycloaddition, exploring solvent effects, and exploring the influence of changes to the host geometry.

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Notes and References

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‡ If the reverse hetero-Diels–Alder reaction were to proceed at a significant rate, a solution of the oxazine would always contain some dienophile **2** which could be trapped by the use of a scavenger. In a control experiment, 10 equiv. of cyclopentadiene were added to a solution of the oxazine in CH_2Cl_2 at 25 °C; after 48 h, ^{1}H NMR analysis showed no evidence for a new adduct.

§ Model building suggests that the intracavity cycloaddition and rearrangement would be even more favourable for 4-nitrosopyridine, but this potential substrate proved too unstable to isolate.

¶ Porphyrins with solubilising *n*-hexyl side chains in place of esters are prepared by the procedure published previously (ref. 6) using the appropriate hexyl-substituted dipyrrole.

‖ Accelerated reactions were initiated by addition of the host and reaction progress was monitored by HPLC (normal phase 8 × 225 mm Spheris S5W column on a HP Series 1050 instrument) or GC (5% dimethyldiphenyl siloxane 25 m × 0.32 mm × 0.25 μm column on a HP GC 5890 Series II instrument). For all the reactions the decrease in concentration of diene and dienophile was monitored. After completion of the host-accelerated reactions a few drops of TFA were added to the reaction mixture to demetallate the porphyrin hosts. The oxazine product is thus released from the cavity and may then be detected by HPLC, confirming that the disappearance of the starting substrates correlates directly with oxazine formation.

** Thermodynamic effective molarity (E.M.) for binding = K(**3**)/[K(**1**)K(**2**)]. In CH_2Cl_2 K(**1**) and K(**2**) are generally *ca* 5×10^3 and 1×10^3 M^{-1} respectively, while in toluene they are around 2–3 times larger.

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