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Bimolecular Catalysis and Turnover from a Macromolecular Host System

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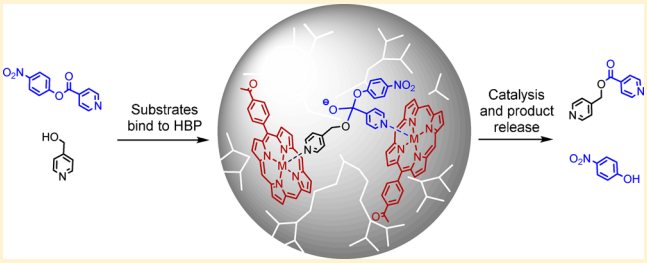
ABSTRACT: The synthesis of a globular macromolecule and its application as a bimolecular catalyst are reported. The macromolecular structure supports (at least) two zinc-metalated porphyrin units, each capable of binding a single reactant. The proximity of the two bound reactants results in an increased local concentration, leading to a maximum 300-fold increase in the reaction rate. In contrast to other synthetic catalysts, where bidentate products inhibit further reactions, this macromolecular system allows the product to be displaced by the reactants leading to turnover and catalysis. We believe that this is due to the dynamics of the macromolecular host system, which maintains enough flexibility to adopt a favorable/reactive geometry, which allows the reactants to get close and react while possessing sufficient rigidity/poor geometry to reduce and disrupt any cooperative/inhibitive bidentate binding.



INTRODUCTION

The ability to design and implement hosts capable of binding two substrates and catalyzing a bimolecular reaction represents a considerable challenge.[1] Although there have been a number of synthetic and biomimetic attempts over the years, they are far from perfect and demonstrate various problems limiting their use. For instance, antibody and ribosome approaches can exhibit poor catalytic activity and are generally expensive and time-consuming to produce.[2,3] In an attempt to overcome these problems, synthetic hosts have been developed, and these fall into two general areas. The first involves the use of cavities designed to encapsulate two reactive species, resulting in a faster reaction by virtue of an increase in local concentrations.[4−6] A second approach uses molecules that possess *specific binding sites* designed to bind both reactants in close proximity, again allowing them to react faster. Examples include the macrocyclic hosts designed by Sanders,[7] which could accelerate the reaction of two bound reagents to form a bidentate product. However, the binding and reactive processes are soon inhibited by the bidentate nature of the products, which bind much more strongly than either set of monodentate starting materials (when catalytic quantities of hosts were used). In principle, this problem could be overcome by using a smart host system capable of *reversibly* changing its structure and then displacing any bound dimeric product (i.e., when heated up or light is applied).[8] Unfortunately, even at relatively low product concentrations, the bidentate product would still bind to the host (and inhibit catalysis) when it returned to its *reactive* geometry.

To overcome this problem, we proposed the use of a polymer system whose structure retained a certain amount of strain and limited flexibility. An additional advantage in using macromolecules is that their globular structures can be tailored to mimic those of proteins and enzymes.[9] That is, the bulk structure of polymers can be tailored allowing control of the steric and electronic environment within their internal spaces and around any specific binding sites.[10,11] Initially, we considered using linear polymers, but this idea was quickly rejected. Although linear polymers possess the desired globular shape when in solution, their structures and conformations are dynamic. This results in the constant movement of any binding sites. Consequently, the relative positions of the binding sites would be impossible to control and the chance of any two being close enough to enable bound guests to react would be very low. In addition, it is unlikely that there would be enough "strain" in these systems to displace any bidentate product. Dendrimers[12] are structurally more rigid and have fixed globular shape (dependent on generation)[13] and are capable of being exploited in a number of interesting and exotic catalytic systems.[14] As such, it is theoretically possible to position and orient binding sites in a controlled manner. However, constructing such a molecule represents a considerable synthetic challenge, which does not represent an improvement over the cavity based systems described above. Therefore, we decided to use a polymer system whose structure was intermediate between the overly flexible linear polymers and the relatively rigid dendrimers. These polymers are known as hyperbranched polymers (HBPs).[15] Unlike dendrimers, HBPs can be synthesized in one step using a branching monomer. Due to the random nature of the polymerization, not every branching point is reacted and imperfections occur throughout the structure. These imperfections reduce the degree of branching,[16] which restricts internal packing. As a result the ensuing structures have a relatively fixed globular structure, but remain relatively open and flexible inside.

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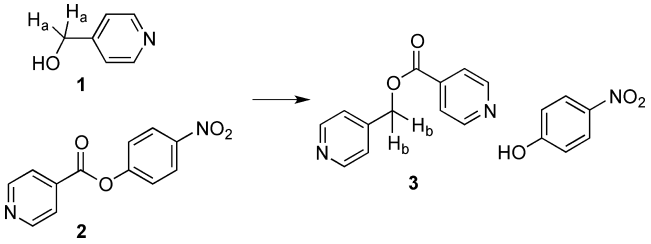
Therefore, even at relatively high molecular weights, it is less likely that any binding sites will become prohibitively hindered (compared to dendrimers). As such we decided to focus our attention on the use of functionalized hyperbranched polymers.

Our next decision regarded the choice of binding group/interaction. We have previously reported the facile synthesis of a porphyrin-cored hyperbranched polymer and its ability to catalyze a (monomeric) oxidation reaction.[17] In this case, the size of the polymer did not hinder or prevent substrates binding to the porphyrin. In fact, subsequent binding studies revealed that as the molecular weight of the HBP increased, then so did substrate binding affinity.[18] Encouraged by these results we decided to incorporate a number of zinc-metalated porphyrin binding sites within our HBP (at least two binding sites). These porphyrin units would then be able to bind reactive groups attached to pyridine ligands through Zn−N coordination.

RESULTS AND DISCUSSION

To test the (bimolecular) catalytic activity of the proposed HBPs, a relatively simple esterification was selected; specifically, the reaction between an alcohol and an activated ester. Esterifications proceed through a tetrahedral intermediate that possess a very different structure to the trigonal planar products. This change in geometry, coupled with some host flexibility, should encourage a situation that favors product release, turnover and catalysis. The particular reaction used in our study is shown in Scheme 1. Both reactants contain a pyridine, which is required for porphyrin binding. Substrate **1** is a simple alcohol, whereas substrate **2** is an activated ester of nicotinic acid. These react giving the bis-pyridine product **3** and 4-nitrophenol. Having chosen our model system and binding interaction, we focused our attention on the synthesis of the porphyrin functionalized HBP capable of coordinating the pyridine units of substrates **1** and **2**.

Scheme 1. Bimolecular Reaction Used To Test the Catalytic Host System. Reaction Followed by Monitoring the Relative Intensities of Resonance Signals for Protons H_a and H_b (^{1}H NMR)

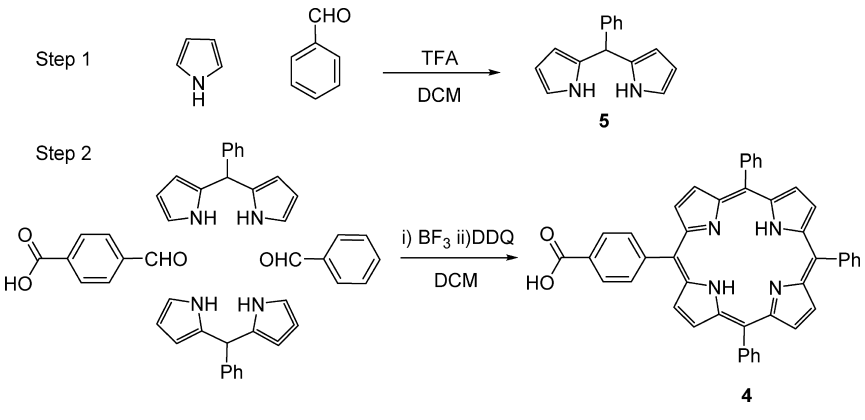


The exact polymer was a variant of a hyperbranched polyester based on the branching monomer, 3,5-diacetoxybenzoic acid.[19] We have previously used this method to construct a variety of functionalized HBPs, including a polymer with a porphyrin center[20] and another with an activated/reactive core group.[21] We have also shown that copolymers can be constructed if simple carboxylic acid containing comonomers are added.[22] This method allows a number of functionalized units to be incorporated throughout the structure of a HBP. Our target molecule can therefore be obtained if the branching monomer 3,5-diacetoxybenzoic acid is copolymerized with a monofunctionalized acid porphyrin.

The carboxylic acid porphyrin **4** was synthesized using a two step-procedure, Scheme 2. The first step involved the formation of a dipyrromethane **5** using standard conditions. This was then condensed under statistical conditions with 0.5 equiv each of benzaldeyde and 4-carboxybenzaldehyde. The monofunctionalized porphyrin **4** was obtained after purification by column chromatography. ^{1}H NMR confirmed the structure and monofuntionalized nature of the porphyrin. The doublets from the carboxylic acid containing aromatic resonated at 8.45 and 8.35 ppm, and the integration ratio confirmed that only one carboxylic acid was present. In addition, mass spectroscopy indicated a molecular ion at 659 Da (MH^+).

The synthetic procedure for the construction of the porphyrin containing HBP is shown in Scheme 3 and involved reacting the 3,5-diacetoxybenzoic acid and the porphyrin **4** in a 1:20 ratio. The polymer obtained after initial precipitation was purified by preparative size-exclusion chromatography (SEC) using a biobead column. ^{1}H NMR spectra of the purified polymer **6** indicated the presence of shielded protons around minus 2.00 ppm. This is a characteristic resonance for the NH protons at the center of an aromatic macrocycle, thus confirming the presence of the porphyrin units. Other peaks corresponding to the porphyrin's pyrrole group could also be seen at 8.91 ppm. Although the remaining aromatic peaks from the tetraphenyl units are hidden beneath the aromatic peaks of the polymer, integration of the aromatic region confirms that additional protons were present (when compared to the polymers acetate peak). The remainder of the spectrum was consistent with that obtained for similar HBPs based on the same monomer.[23] The dark brownish/red polymer **6** had a molecular weight of just over 6000 Da (Mn) as determined by

Scheme 2. Two-Step Procedure for the Synthesis of the Monoacid Porphyrin



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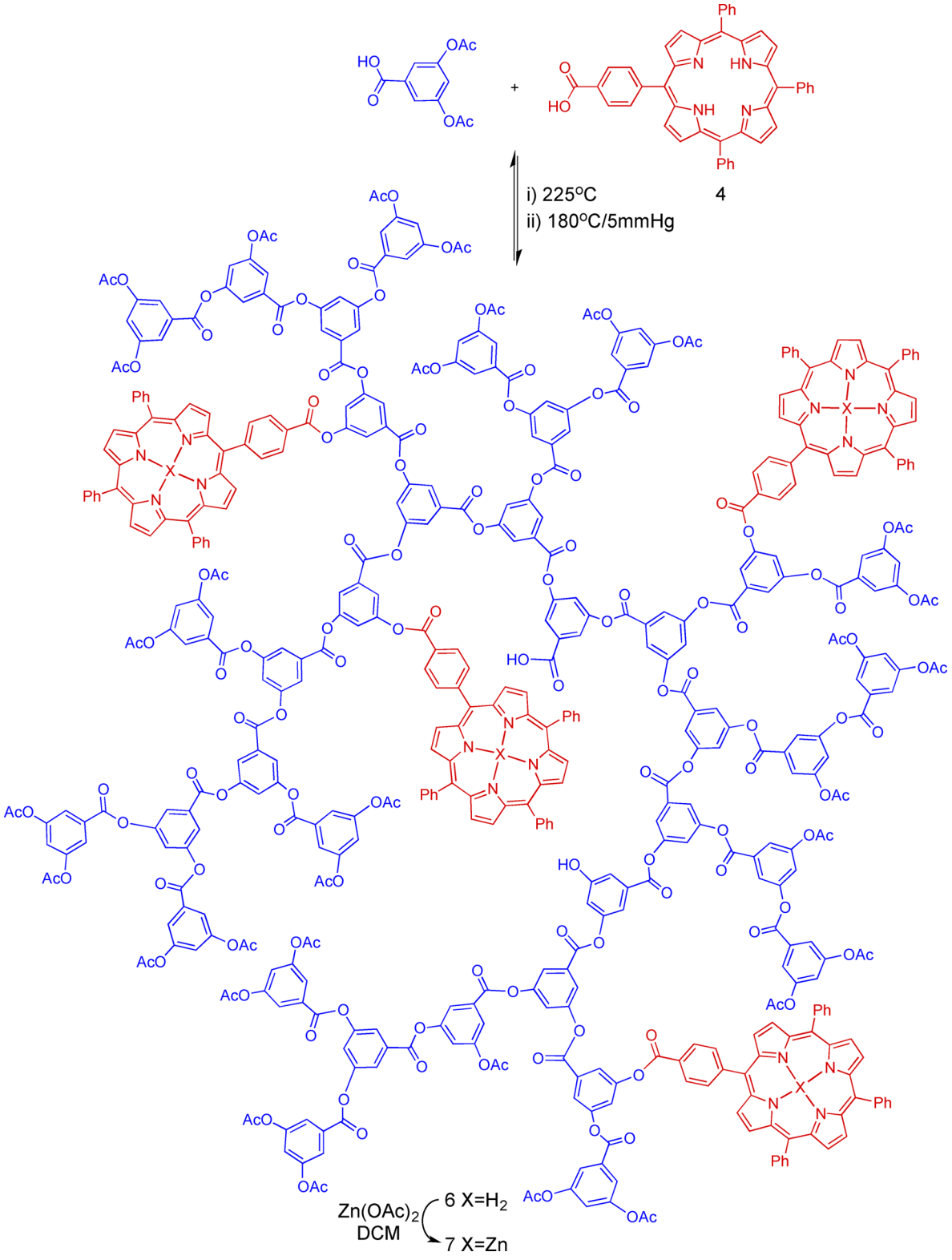
Scheme 3. Synthesis of Free Base Porphyrin Cored HBP 6 and Zinc Metalloporphyrin Cored HBP 7[a]



[a]The purpose of heating to 180 °C at 5 mmHg was to remove the acetic acid byproduct and drive the equilibrium toward product.

analytical SEC. Furthermore, SEC detection using RI and UV (set to the porphyrins λ_{max}) produced overlapping traces; confirming that the porphyrin was present across the polymers complete molecular weight range. Spectroscopic analysis determined that on average approximately two porphyrins were incorporated per polymer molecule (exact calculation indicated 2.4 porphyrins per polymer based on a molecular weight of 6000). This was calculated using known amounts of polymer **6** and comparing its porphyrin UV absorption to that obtained from a Beer–Lambert analysis of the simple

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porphyrin **4**. Although this technique assumes that all polymers in the poly disperse mix are the same, it does represent the *minimum* number of porphyrins present in the polymer. As such, any errors related to molecular weight are in our favor with respect to porphyrin incorporation. This is a direct consequence of the calibration characteristics of SEC, which are known to underestimate the M_n values for globular branched polymers.[24] As a result, any *porphyrin* calculation based on *polymer* molecular weight (and therefore concentration) will always underestimate the number of porphyrins per polymer. To help explain, let us consider an equal mass of two porphyrin polymers with differing M_n values, the first with an M_n of 1000 Da and a second of M_n 2000 Da. At any given porphyrin absorption (and therefore concentration) each of the two polymer solutions would have exactly the same number of porphyrins. However, as there are exactly half the numbers of polymer molecules in the larger polymer fraction (for a given mass), then the same number of porphyrins would be spread over fewer molecules. That is, the larger polymers possess more porphyrins. Therefore, if we acknowledge that molecular weight measurements are underestimated via SEC, then we can conclude that our polymers are larger than indicated via SEC and as a consequence, porphyrin loadings are higher than the two per polymer previously calculated.

The intended interaction between ligand and porphyrin involves a metal to pyridine coordination, which first requires insertion of a zinc atom to the porphyrin center. This was achieved by gently warming polymer **6** in a solution of excess zinc acetate in dichloromethane. After purification, metalated polymer **7** was isolated in quantitative yield. SEC and UV analysis confirmed that the metalation process had been successful and that the reaction conditions had not damaged or changed the polymeric structure. That is, the number of Q bands in the UV spectra had been reduced from four to two and the data obtained from SEC was unchanged after metalation. Having successfully synthesized a globular polymer possessing (at least) two internal porphyrin units we then set about ascertaining its binding affinity to reactants **1**, **2**, and product **3** (Table 1).[25] Specifically, we wanted to determine

Table 1. Binding Affinities for Substrates and Products to Zinc Metalloporphyrin Cored HBP 7

compd	binding affinity to **7** Ka/M^{-1}
substrate **1**	1.55×10^{-4}
substrate **2**	1.60×10^{-4}
product **3**	5.80×10^{-4}

whether or not the product would bind with sufficient cooperatively to inhibit the reaction. This would indicate whether or not our theory regarding polymer mobility and lack of product inhibition, was possible. Binding constants (K_a) were assessed by UV titration measurements, and changes in porphyrin λ_{max} absorption with respect to increased *pyridine* concentration were fitted to a 1:1 binding analysis. The measurements and analysis were repeated four times. The product **3** bound with a K_a of 5.80×10^4 M^{-1}, which is around 4 times higher than the starting materials, which possessed K_a values of 1.55×10^4 M^{-1} and 1.60×10^4 M^{-1} for **1** and **2**, respectively. Although the product bound more tightly than the reactants, it is clearly not binding with an efficient cooperative effect. Therefore, the binding data confirms that the product is not binding as an efficient bidentate ligand. Furthermore, as the association constants were the same order of magnitude, it was likely that the difference in binding would not be high enough to inhibit reasonable turnover. For comparison, in earlier work by Sanders the difference in reactant and product binding was 1000 fold.[6] In this case turnover was completely inhibited and stoichiometric quantities of host were required. Therefore, our binding analysis clearly demonstrate that our system is capable of binding either reactant well, but its conformation is not predisposed to recognize or bind (strongly) the product. As such there was a strong probability that a catalytic bimolecular reaction could take place.

The catalytic experiments were carried out with polymer **7** using an amount that corresponded to a porphyrin concentration of 5 mol % with respect to the reactants **1** and **2**. Specifically, reactions were carried out such that the final concentrations were 0.2 M in reactants **1** and **2** and 0.01 M in porphyrin. As UV analysis had already indicated that on average 2.4 porphyrins were present in each polymer, a polymer concentration of 0.042 M was used for the catalytic experiments (i.e., equivalent to a porphyrin concentration of 0.01 M or 5%).[26] The reaction was followed using ^{1}H NMR and monitoring the signals from the product's benzyl protons Hb, which resonate at 5.45 ppm (compared with 4.75 for Ha in the starting material), Scheme 1. The yield was calculated by comparing the ratio of these signal intensities with respect to initial concentration. The yield was then plotted against time and the graph obtained is shown in Figure 1. The *uncatalyzed*

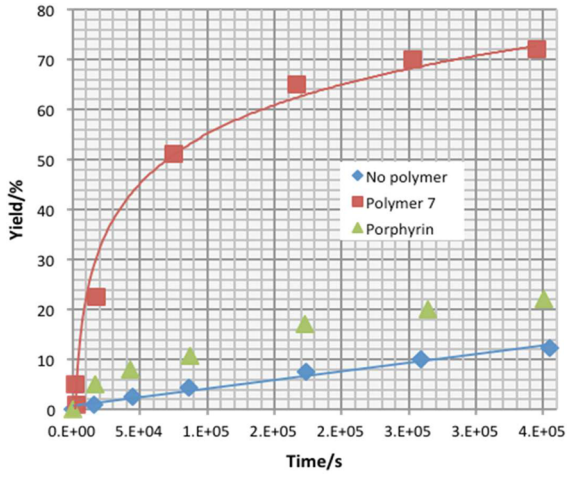

Figure 1. Plots showing yield of ester **3** over time in the absence of catalyst and in the presence of HBP **7**. A control reaction using Zn-tetraphenylporphyrin is also shown.

control reaction was carried out using just the reactants **1** and **2** and the same reaction conditions as described (i.e., without any porphyrin or polymeric catalyst).

The results show that the uncatalyzed reaction was very slow, with only 10% of product being detected after nearly 100 h. However, when the porphyrin-containing polymer was added the reaction proceeded to almost 80% after the same 100-h period (the concentration of porphyrin was identical in both cases).[26] The initial rates were 1.08×10^{-5} M^{-1} and 1.92×10^{-8} M^{-1} for the catalyzed and uncatalyzed reactions, respectively, which corresponds to around a 60-fold increase in rate. Therefore, the rate increase of the polymer-catalyzed reaction can be attributed directly to the polymer structure, which provides a framework capable of binding/supporting

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specific binding groups/ligands in close proximity (as shown schematically in Figure 2). Although relatively flexible, the

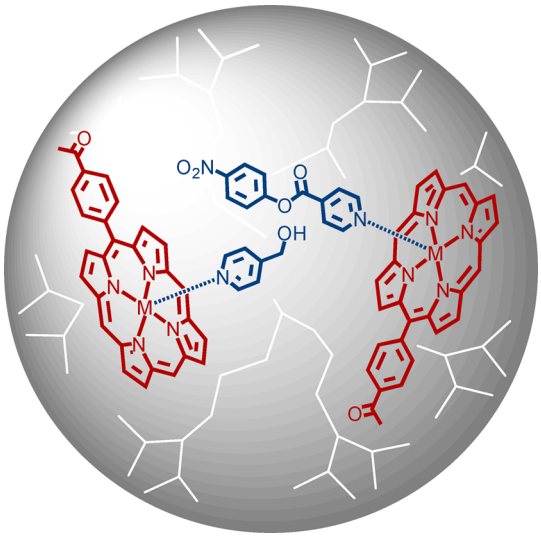

Figure 2. Schematic showing starting materials **1** and **2** bound productively within the macromolecular host **7**.

polymer remains rigid enough to maintain an average distance/geometry between the porphyrins, such that reactions can take place. After reaction, the porphyrin-containing polymer has enough free motion (strain) to break or prevent any strong chelate or bidentate interactions. Alternatively, it could be argued that the binding sites are not optimally arranged to bind the product. Thus, although the geometry does not prevent the starting materials **1** and **2** binding, the polymer is not able to bind product **3** with any efficiency, leading to weak or incomplete binding to one of the porphyrin binding sites. Either way, if bidentate binding is broken or prevented, product **3** is only bound through a single pyridine/porphyrin interaction. Therefore, any unbound reactants **1** or **2** can easily compete for binding and displace the product **3**. This effect is greatest at the start of the reaction, where the concentration of reactants is much higher than the product. However, as the reaction proceeds the concentration of product steadily increases. When the reaction has reached 50% we have an equimolar concentration of product **3** and reactants **1** and **2**. However, as this is a bimolecular reaction, the concentration of reactants will be twice that of the product and the catalytic host bound reactions can still proceed. It is only after the process has reached 66% that we have the same concentration of products and reactants (i.e., the concentration of **1** and **2** *combined* equals that of product **3**). At this stage it will become much harder for the reactants to compete with the product for binding. This effect is substantiated by the fact that the reaction does not go to completion, only reaching around 70% after 100 h. This confirms that the product is beginning to inhibit catalysis at this point (although only as a monodentate ligand).[28]

A number of control reactions were also carried out. The first involved the use of the nonmetalated porphyrin host. The reaction was repeated using the free base HBP **5**, in place of the catalytic HBP **6**. On this occasion no enhancement in rate was observed. A further control reaction using 5 mol % of the zinc-metalated tetraphenylporphyrin was also carried out to probe any effect of porphyrin on the yield and rate of reaction (i.e., no polymer backbone). Interestingly, this control reaction led to some rate enhancement. Specifically, when an equivalent amount of Zn−tetraphenylporphyrin was added to the reaction between **1** and **2**, an initial rate of 2.94×10^{-8} M^{-1} was observed. This corresponds to a 2-fold increase in rate when compared to the unanalyzed reaction. This small increase is likely due to a simple Lewis acid catalysis where coordination to the carbonyl can increase the reactivity of the carbonyl carbon on reactant **1**, and/or stabilize the charged tetrahedral intermediate (leading to a lower E_a and faster reaction).[27] Alternatively, coordination to the pyridine unit of **1** can enhance the electrophillicity of the carbonyl carbon (via delocalized electron withdrawal). Following on from this, another control experiment was carried out using similar substrates to **1** and **2**, but exchanging the pyridine moiety for benzene on one of the substrates. Removal of either pyridine caused a significant drop in the rate of the reaction, with both reactions only reaching 10−15% completion after 100 h (giving an initial rate between 1.00×10^{-8} M^{-1} and 1.50×10^{-8} M^{-1}, which corresponds to a less than 2-fold increase in rate). This is roughly the same as the uncatalyzed reaction and confirms that catalysis requires *both* ligands to bind to the host polymer **7**. A final control was performed using the catalytic host polymer **7**, the pyridine substrates (**1** and **2**) and an excess of pyridine. In this case the reaction was significantly less efficient, only reaching about 20% completion after 100 h. This reduction is due to the fact that the excess pyridine competes for the porphyrin binding sites and effectively inhibits substrate binding, which slows the reaction. The fact that the reaction reaches 20% is due to the basic nature of the pyridine, which can help deprotonate the tetrahedral intermediate, resulting in a slightly faster reaction.

■ CONCLUSIONS

The rate acceleration obtained using our hyperbranched polymer was not as high as those observed for rigid host systems, which are predisposed to bind intermediate transition states and products. Nevertheless, even though our polymeric host only displayed a modest rate enhancement, turnover was possible and the system was catalytic. The reaction yield plateaus around 70% after 100 h. At this point we have an eqimolar solution of reactants and products and the product can now compete with starting materials for the binding sites,[29] and catalysis slows down. In addition, as reactions can only take place when reactants **1** and **2** bind in a "productive" manner, some of the binding events are wasted (i.e., the host binding the same reactant twice or the reactant binding to the wrong face of the porhyrin). The productive binding required for a successful reaction cannot be controlled and is a statistical phenomenon. Therefore, the rate of reaction for reactants **1** and **2** bound in a productive way is much higher. If we use the porphyrin to polymer ratio that the data suggests and we apply the "productive-pair" argument put forward by Sanders,[6] then there are only a limited number of binding events that can lead to catalysis. That is, the catalytic reaction can only take place when reactants **1** and **2** are bound to the correct face on each of the two porphyrins. As such, statistical analysis indicates that productive binding can only take place 20% of the time. Therefore, the polymer-catalyzed reaction between **1** and **2** bound in a product manner, corresponds to a 300-fold increase in rate.

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EXPERIMENTAL SECTION

General Experimental Conditions and Equipment. ^{1}H and ^{13}C NMR spectra were acquired at 250 and 62.5 MHz, respectively, using a 5 mm CH probe. Chemical shifts are quoted in ppm relative to residual $CHCl_3$, and J values are quoted in Hz. UV/vis was performed in wavelength mode standardized using a user baseline configuration. Molar extension coefficients are given in M^2/mol. FT-IR transmissions maxima are given in cm^{-1}. Electrospray ionization mass spectrometry (ESI-MS) and matrix-assisted laser desorption (MALDI) mass spectrometry were carried out using a time-of-flight detector. Dithranol or dihydroxy benzoic acid were used as the matrices in the MALDI mass spectrometer. Analytical GPC samples were run at room temperature on either a low or high molecular weight column (calibrated with polystryrene samples with M_n values ranging from 500 to 100000 Da) and a 1 mL/min flow rate. All samples were run using GPC THF and samples were prepared in the same grade THF and spiked with toluene as a flow rate marker. Eluent product concentration was monitored by an refractive index detector or in conjunction with a UV/vis LC spectrophotometer. Melting points were recorded using open-ended capillary tubes. Flash chromatography was performed using flash silica (35−70 μm particles with 60 Å pore size) and eluted under an applied pressure supplied from a standard bellows system. Preparative GPC was carried out using Biobeads (available from Radleys) and eluted under gravity.[30]

Synthesis. *4-Nitrophenyl Isonicotinate* **2**.[31] Isonicotinoyl chloride (5.00 g, 36.00 mmol), 4-nitrophenol (5.00 g, 36.00 mmol), and THF (100 mL) were added to a round-bottom flask. The mixture was brought to reflux (65 °C), and once all the starting materials were completely dissolved triethylamine (3.60 g, 36.00 mmol) was added via syringe and the reaction was refluxed for 24 h. The THF was removed on the rotary evaporator and the crude mixture was dissolved in DCM (100 mL). The DCM layer was then washed with a saturated sodium hydrogen carbonate solution (3 × 300 mL). The DCM layer was collected and dried with magnesium sulfate before filtering and rotary evaporation, to reveal a very pale yellow solid: yield 7.30 g (80%); pale yellow solid; ^{1}H NMR ppm ($CDCl_3$) 8.95 (d, 2H, J = 6.0 Hz), 8.40(d, 2H, J = 9.0 Hz), 8.05(d, 2H, J = 6.0 Hz), 7.45(d, 2H, J = 9.0 Hz); ^{13}C NMR ppm ($CDCl_3$) 162.3, 155.0, 151.0, 146.4, 135.2, 125.4, 123.2, 122.5; FT-IR (ν/cm^{-1}) 3024, 1738, 1520, 1486; MS(EI) 245 Da/MH^+, ($C_{12}H_8N_2O_4$ = 244 Da); mp 136−137.5 °C (lit.[5] 137−138 °C). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.04; H, 3.21; N, 11.42.

(Pyridin-4-yl)methyl Isonicotinate **3**. 4-Nitrophenyl isonicotinate **2** (330 mg, 1.40 mmol), (pyridin-4-yl)methanol **1** (150 mg, 1.40 mmol), and chloroform (100 mL) were added to a round-bottom flask fitted with a condenser and heated to reflux (68 °C). Triethylamine (20 mL, excess) was the added via syringe. The reaction mixture was stirred for 10 days before being cooled to room temperature. The mixture was washed with saturated sodium hydrogen carbonate solution (5 × 300 mL). The DCM layer was collected and the solvent removed: yield 0.26 g (88%); white solid; ^{1}H NMR ppm ($CDCl_3$): 8.85(d, 2H, J = 6.0 Hz), 8.67(d, 2H, J = 6.0 Hz), 7.95(d, 2H, J = 6.0 Hz), 7.35(d, 2H, J = 6.0 Hz), 5.42(s, 2H); ^{13}C NMR ppm ($CDCl_3$):164.7, 150.8, 150.1, 144.3, 134.3, 122.9, 122.0, 65.4; MS(EI) 215 Da/MH^+, ($C_{12}H_{10}N_2O_2$ = 214 Da); FT-IR (ν/cm^{-1}) 1735, 1593, 1443; mp 92.5−93.5 °C. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.52; H, 4.81; N, 12.92.

5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **4**.[32] A two-step procedure was used to synthesis the required monofunctionalized porphyrin. The first step was the preparation of a dipyrromethane intermediate, 2-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole. The second step involved a mixed condensation of this dipyrromethane and two aldehydes.

Step 1: 2-(Phenyl(1H-pyrrol-2-yl)methyl)-1H-pyrrole **5**.[33] Benzaldehyde (5.00 g, 47.20 mmol), pyrrole (20 mL, 289 mmol), and DCM (500 mL) were added to a round-bottom flask which was protected from the light by aluminum foil. To the mixture was added trifluoroacetic acid (200 mg, 2.60 mmol). The reaction was stirred at room temperature for 30 min, during which time the reaction warmed up and turned pink before turning black. The solvent was concentrated on a rotary evaporator to leave around 100 mL of solvent, which was then washed with saturated sodium hydrogen carbonate solution (5 × 500 mL). The DCM and was then removed on the rotary evaporator. The resulting black solid was recrystallized from 1:1 water and methanol. The resulting pale yellow solid then collected by filtration and washed using a 1:1 cold solution of water and methanol: yield 3.41g, (33%); yellow solid; ^{1}H NMR ppm ($CDCl_3$) 7.91(b, s, 2H), 7.30(m, 5H), 6.70(s, 2H), 6.20(s, 2H), 5.95(s, 2H), 5.50(s, 1H); ^{13}C NMR ppm ($CDCl_3$) 143.4, 132.6, 128.7, 128.5, 127.0, 117.4, 108.4, 107.3, 44.0; MS(EI) 221 Da/MH^+, ($C_{15}H_{14}N_2$ = 222 Da); FT-IR (ν/cm^{-1}) 3338, 1737, 1553, 1454, 1366; mp 101−103 °C (lit.[4] mp 102.0−102.5 °C).

Step 2: 5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **4**.[32] 2-(Phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole **5** (1.50 g, 6.80 mmol), benzaldehyde (0.70 g, 6.70 mmol), 4-carboxybenzaldehyde (1.01g 6.70 mmol), and DCM (1500 mL) were added to a 2 L round-bottom flask. The round-bottom was put under a nitrogen atmosphere and protected from the light using aluminum foil. To the mixture borontrifluoride (200 uL, 3.20 mmol) was added. The reaction was stirred at room temperature for 1 h, during this time reaction turned pink. After 1 h, DDQ (5.00 g, 22.00 mmol) was added, and the reaction was stirred at room temperature for a further hour. To the mixture was added 15.00 g of silica and the solvent removed by rotary evaporator. The residue was dry loaded onto a 30 cm diameter silica column. The column was initially eluted with DCM, and a purple fraction was recovered and analyzed and found to be tetraphenylporphyrin. The column was then eluted with 2% methanol in DCM, and a purple fraction was collected. Analysis confirmed that it was 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin. On some occasions the product was not completely pure; when this occurred the chromatography was repeated until the sample was pure: yield 150 mg (3.0%); purple solid; ^{1}H NMR-ppm ($CDCl_3$): 8.95(s, 8H, 8.45(d, 2H, J = 7.0), 8.35(d, 2H, J = 7.0), 8.25(d, 6H, J = 6.5), 7.9(m, 9H); FT-IR (ν/cm^{-1}) 1687, 1605, 1557, 1471; UV/vis absorbance(CH_2Cl_2) λ_{max} 419 nm (ε 181100); MS(EI) 659 Da/MH^+, ($C_{45}H_{30}N_4O_2$ = 659 Da). Anal. Calcd for $C_{45}H_{30}N_4O_2$: C, 82.05; H, 4.59; N, 8.51. Found: C, 82.03; H, 4.25; N, 8.28.

3,5 Diacetoxybenzoic Acid.[34] 3,5-Dihydroxybenzoic acid (77.00 g, 0.50 mol) was added to excess acetic anhydride (250 mL, 2.65 mol), and the mixture was refluxed (150 °C) for 5 h. Over this time the mixture turned gradually yellow. After heating, the excess acetic anhydride and acetic acid byproducts were removed by vacuum distillation, being careful to keep the temperature below 100 °C (to prevent premature polymerization). After distillation, a white solid remained. The crude product was dissolved in hot chloroform 60 °C (200 mL) and then filtered. Petroleum ether 60−80 (70 mL) was then added causing a white solid to precipitate. The mixture was then left overnight to allow further precipitation. The white solid was collected by filtration and dried under vacuum: yield 74.3 g (62%); ^{1}H NMR ppm ($CDCl_3$) 7.75 (d, 2H, J = 2.0), 7.25 (t, 1H, J = 2.0), 2.30 (s, 6H); ^{13}C NMR ppm ($CDCl_3$): 170.3, 168.9, 151.0, 131.4, 121.1, 120.9, 20.0; FT-IR (ν/cm^{-1}) 2944, 1763, 1688, 1594; MS(EI) 239-MH^+ ($C_{11}H_{10}N_4O_6$ = 238 Da); mp 158−160 °C (lit.[1] mp 157−159 °C). Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.29; H, 4.19.

Multi Zn-Porphyrin Hyperbranched Polymer **7**. 5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **4** (200 mg, 0.30 mmol), 3,5 diacetoxybenzoic acid (1.00 g, 4.10 mmol), and diphenyl ether (5.00 g) were heated in a 50 mL round-bottom flask to 225 °C for 1 h. The temperature was then reduced to 180 °C, and the reaction was fitted with a one piece distillation kit and put under high vacuum for 2 h. During this time acetic acid could be seen to distill off from the reaction vessel. The reaction was then allowed to cool, but while still warm the crude mixture was dissolved in 20 mL of THF and then precipitated into 500 mL of ice-cold methanol. After filtering, a brown precipitate was collected and then washed with cold methanol. To remove unincorporated porphyrin the crude product were loaded to a 15 mm diameter biobead column (preparative SEC), which was eluted with DCM (to avoid overloading the column, the chromatography was run a number of times with a maximum loading of 200 mg crude

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product). The collected fractions of free base multiporphyrin polymer **6** were redisolved in DCM (25 mL) and an excess of zinc acetate added (1.00 g). The resulting solution was then gently warmed for 30 min before being filtered (to remove excess zinc acetate) and concentrated on a rotary evaporator. The red/brown solid was then dissolved in the minimum amount of THF and the final product obtained via trituation into methanol. The solid was collected and dried under vacuum. The crude product was then purified using preparative SEC/GPC: total yield, 1.02 g, red/brown solid; ^{1}H NMR ppm ($CDCl_3$) 8.90 (br, m, 8H), 8.60 (br, m, 4H, *CTPP**), 8.35 (br, m, 6H, *CTPP**), 8.25 (br, m, 9H, *CTPP**), 8.05−7.55 (br, m, 2H, *polymer**), 7.55−7.10 (br, m, 1H, *polymer**), 2.25(br, s, 3H, CH_3 *polymer**); UV/vis absorbance nm (CH_2Cl_2) λ_{max} 418; FT-IR (ν/cm^{-1}) 3019, 1746 (COOH), 1595, 1444; GPC M_n 6000, PD 2.36. *The exact ratio of porphyrin to repeat units is dependent on molecular weight. As a result, integration ratios are reported relative to either porphyrin or polymer.

Multi Zn−Porphyrin Hyperbranched Polymer Catalysis Procedure. 4-Nitrophenyl isonicotinate **2** (33.0 mg, 0.14 mmol), (pyridin-4-yl)methanol **1** (15 mg, 0.14 mmol), and multi Zn−porphyrin HBP **7** (18.5 mg, 5 mol % with respect to porphyrin) were dissolved in 0.7 mL of $CDCl_3$. The reaction was then monitored via ^{1}HNMR at various time intervals for a period of 100 h. The reaction was followed by monitoring the signal intensity of the product's emerging benzyl protons (5.45 ppm) and those of the starting material (4.75 ppm). The yield was calculated by comparing the ratio of these signal intensities with respect the substrates initial concentration.

General Procedure for UV Titrations. A stock solution of porphyrin containing material in DCM was prepared with a concentration of 1×10^{-6} M with respect to porphyrin. Pyridine solutions were made up to 1×10^{-2} M with respect to pyridine using the stock porphyrin solution described above (so as to maintain a constant porphyrin concentration). The porphyrin solution (1 mL) was measured into a quartz cuvette, and a UV/vis wavelength scan between 350 nm and 800 nm was performed. To the cuvette were added aliquots of ligand solution, between 10 and 20 μL, and the absorption of the Soret band at 430 nm (bound peak) was monitored by measuring the peak intensity. Absorptions were plotted against pyridine concentrations and binding constants calculated using fitting software (GraphPad). Titrations on each material were performed a minimum of four times to ensure consistent results.

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Notes

The authors declare no competing financial interest.

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