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FULL PAPER

Molecular Engineering of β-Substituted Oxoporphyrinogens for Hydrogen-Bond Donor Catalysis

Mandeep K. Chahal, [a]† Daniel T. Payne,*[a]† Yoshitaka Matsushita,[b] Jan Labuta,[a] Katsuhiko Ariga[a,c] and Jonathan P. Hill*[a]

Abstract: A new class of bifunctional hydrogen-bond donor organocatalyst using oxoporphyrinogens having increased intramolecular hydrogen-bond donor distances is reported. Oxoporphyrinogens are highly non-planar rigid macrocycles containing a multiple hydrogen bond forming binding site. In this work we describe the first example of non-planar OxPs as hydrogen-bond donor catalysts prepared using a molecular engineering approach of the binding site for dual activation of substrates. The introduction of β-substituents is key to the catalytic activity and the catalysts are able to catalyze 1,4-conjugate additions and sulfa-Michael additions, as well as, Henry and aza-Henry reactions at low catalyst loadings (≤ 1 mol%) under mild conditions. Preliminary mechanistic studies have been carried out and a possible reaction mechanism has been proposed based on the bifunctional activation of both substrates through hydrogen-bonding interactions.

Introduction

Organocatalysis[1] has been widely studied over the past two decades, demonstrating synthetic utility in a wide range of transformations involving various methods for substrate activation. Hydrogen-bonding promoted catalysis[2] has become commonplace as a mode of activation in organocatalytic processes with different structural motifs reported as being useful including ureas, thioureas, and squaramides.[3] The incorporation of additional basic moieties adjacent to the H-bond donor site gives a new bifunctional catalyst capable of the simultaneous activation of multiple substrates.[4] However, organocatalysts can suffer from poor efficiencies leading to high catalyst loadings, and their activities can be limited to particular reactions leading to reaction-specific catalysts.[1f]

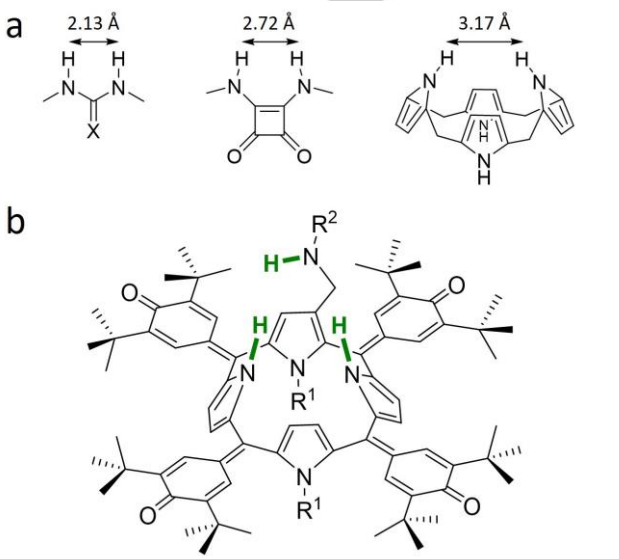

Figure 1. **a.** NH-NH distances for thioureas,[3d] squaramides,[3d] and non-planar porphyrinoids, structures have been truncated for clarity. **b.** The proposed (this work) augmentation of OxP by β-substitution to investigate its potential organocatalytic properties. For R groups see Figure 2. Bonds capable of forming H-bond interactions are highlighted in green.

The overall catalyst structural motif, including the inter-hydrogen-bond donor distance and the requirement for additional proximal functionality in these systems, suggested to us that non-planar porphyrinoids (Figure 1) might be of interest for catalytic applications. In this case, non-planarity is based on large dihedral angles between planes of pyrrole groups and the mean macrocyclic plane of the tetrapyrrole. Also, a comparison of reported intramolecular NH-NH hydrogen-bond donor distances for thioureas, squaramides and non-planar porphyrinoids, such as oxoporphyrinogens (OxPs), suggested that an increase in the distance between the donors might be achieved by using a porphyrinoid based H-bonding motif rather than a thiourea or squaramide.[3] This is of interest for applications involving a synthetic mimic of oxyanion holes, which are active sites in enzymes capable of stabilizing negatively charged oxoanions through H-bonding interactions.[5] Many studies have been carried out on synthetic mimics for this purpose including several common H-bond catalyst motifs such as thioureas.[6] Studies have shown that the hydrogen bond donor intramolecular orientations and distances have a significant effect on catalytic activity, suggesting that new motifs with tunable properties and increased H-bond donor distances might be of interest.[7]

Metallated porphyrins[8] and porphyrinoids,[9] including naturally occurring metalloporphyrins such as hemes,[10] are highly effective catalysts. However, the use of porphyrinoids as organocatalysts has been largely neglected because the H-

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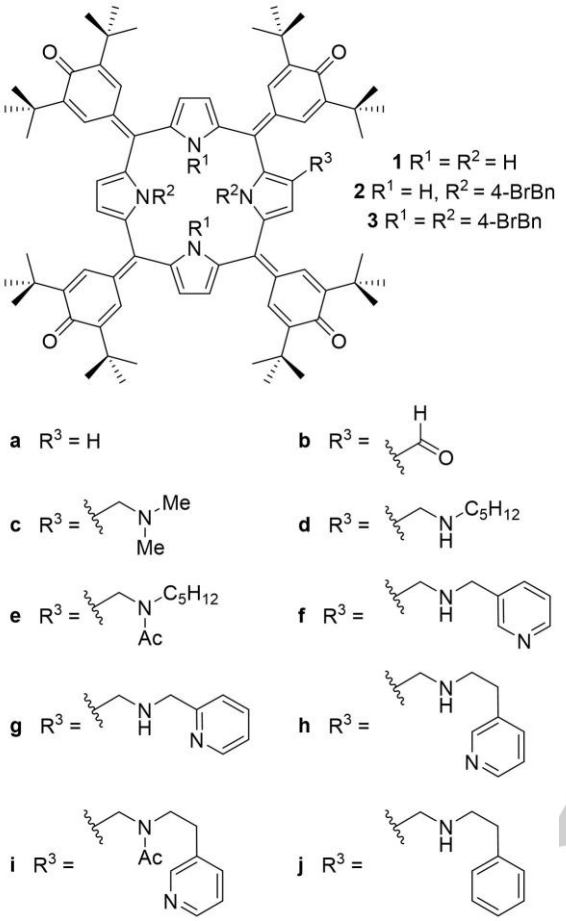


Figure 2. Chemical structures of the oxoporphyrinogen compounds used in this work. For purposes of catalysis screening, all compounds **2a-j** were prepared. Control compounds non-N-alkylated **1a, 1b** and **1h** and tetra-N-alkylated **3a, 3d** and **3h** were prepared to confirm that catalytic activity requires pyrrolic NH groups.

bonding sites are inaccessible being situated within the plane of the porphyrin macrocycle[11] so that observation of any organocatalytic activity requires interruption of macrocycle planarity, which is typically achieved by β-substitution,[12] protonation[13] or N-alkylation.[14] Senge and co-workers have demonstrated that some non-planar porphyrins catalyze a sulfa-Michael reaction.[15] Calix[4]pyrroles (non-conjugated porphyrinoids) have also been used as organocatalysts despite their conformational flexibility, which leads to less well-defined binding sites. At its extreme, the flexibility of calix[4]pyrroles allows pyrrole inversion through the plane of the macrocycle so that the NH-NH H-bond donor distance at the binding site is not fixed.[16] These limited examples indicate that porphyrins and porphyrinoids are a promising class of compounds for organocatalysis.

The required characteristics of non-planarity, H-bonding site availability and synthetic flexibility are also fulfilled by OxPs derived from the oxidation of meso-tetrakis(3,5-di-t-butyl-4-hydroxyphenyl)porphyrin.[17] OxPs are essentially calix[4]pyrrole macrocycles with rigidifying conjugated substituents at their meso positions with the additional attractive feature that they can be selectively N-alkylated,[18] for instance at N^{21} and N^{23}, leading to formation of a highly non-planar rigid macrocycle with a stable conformation containing a multiple hydrogen bond forming reaction site. Although the degree of non-planarity of the macrocycle is similar to that of calix[4]pyrroles the main advantage of OxPs is that the pyrroles are relatively inflexible (i.e., cannot invert through the plane of the macrocycle), leading to a stable macrocycle form. The intramolecular NH-NH donor distance is typically 3.17 Å for a di-N^{21},N^{23}-benzyl-OxP derivative lacking β-substituents (Figure 1a), although this distance can be varied somewhat according to the N-alkylating group. Non-planar OxPs may be β-substituent free or contain different multiplicities of β-substituents, and are not charged.[19] These features have allowed their study for different applications including enantiomeric excess estimation,[20] water sensing[21] and alcohol differentiation.[22] In this case, their propensity to bind analytes, including anions[23] or solvents,[24] through hydrogen bonding interactions, along with their high degree of non-planarity and ease of synthetic modification, suggested that they might be suitable materials for organocatalytic transformations.

Herein, we describe the development of a new class of bifunctional H-bond organocatalysts based on β-substituted OxPs and demonstrate their utility in several transformations. The OxPs prepared are active at low catalysts loadings under mild conditions, can be used in several different reactions, and are easily recovered following reaction completion.

Results and Discussion

Catalyst design, synthesis and structure. Non-planar OxP **1a**[17] and di-alkylated **2a**, which renders only one face of the macrocycle accessible to interactions, have been reported.[25] However, contrary to previously reported non-planar porphyrinoids,[15,16] compounds **1a** and **2a** were not catalytically active for the addition of 2,4-pentanedione to β-nitrostyrene (Table 1) despite the intramolecular H-bond donor distance for di-alkylated OxP, which is typically 3.17 Å,[18,23,25,26] being similar to squaramide catalysts (Figure 1).[3d] In order to induce catalytic

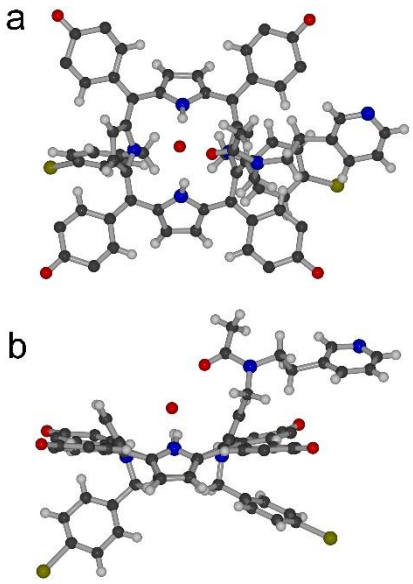


Figure 3. X-Ray crystal structure of compound **2i**. (a) Top view of the calix[4]pyrrole macrocycle with a molecule of water hydrogen bonded at pyrrolic NH groups. (b) Side view of the molecule reveals the disposition of the β-substituent sidechain. The t-butyl groups have been removed for clarity.

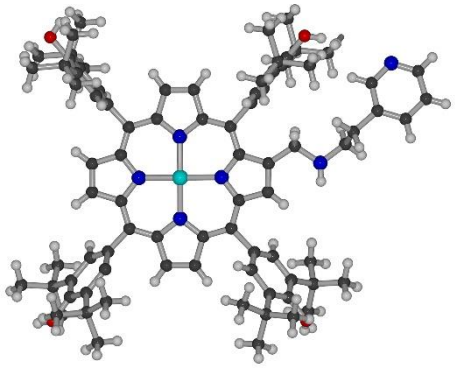


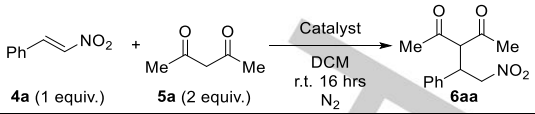
Figure 4. X-Ray crystal structure of Ni-**1*h**: the nickel(II) porphyrin analogue of **1h** prepared to investigate the behaviour of the β-substituent. 3-Pyridyl group does not interact with the metalloporphyrin but forms chains through mutual hydrogen bonding with a phenol group in an adjacent molecule (see also Figures S19,S20)

activity further functionality analogous to that observed in squaramides was required,[4] such as basic functionality in proximity to the proposed catalytically active site of **2a**. In order to achieve this β-substitution on the same face as the H-bond donors is required, giving the general structure shown in Figure 1b.

The β-substitution of OxP was achieved by treatment of the Ni(II) or Cu(II) complexes of meso-tetrakis(3,5-di-t-butyl-4-hydroxyphenyl)porphyrin[27] (Ni/Cu-**1*a**, * denotes the non-oxidised porphyrin) with Vilsmeier reagent[28] with an appropriate work-up leading to Vilsmeier adduct hydrolysis and acid induced demetallation, followed by treatment of the crude material with hydroxide to induce oxidation under aerobic conditions to give OxP-β-CHO (**1b**). Selective N-alkylation of **1b**, here with 4-bromobenzyl bromide to increase solubility and reduce compound polarity to facilitate purification, can be accomplished[29] ending with pyrrolic NH and the formyl group on the same face of the molecule (**2b**). Regiochemistry was confirmed by 2D NMR spectroscopy (see Figures S1-7) of **2b** which supports the X-ray crystallography of its derivative **2i** (Figure 3) with further confirmation of substituent identity found in the X-ray crystal structure of a nickel complex of a precursor (Figure 4). Tetra-alkylated **3b** was synthesized as a negative control to confirm catalytic activity of the pyrrole units. Reductive aminations with a structurally diverse range of amines were carried out with Ni-**1*b**, **2b**, and **3b** to synthesize a library of catalysts containing various amino functionalities at the β-position of OxP proximal to the H-bonding site (Figure 2) allowing for preliminary structure-catalytic activity relationships of the amino β-substituent to be probed.

An interesting property of these compounds is that due to the removal of symmetry from the porphyrin macrocycle caused by the β-substitution, compound **2b** and those derived from it are chiral. Also, the OxP macrocycle, which is chiral itself under certain conditions and has been demonstrated to interconvert between its enantiomeric forms by pyrrole group inversion,[20c] has a fixed conformation due to the presence of N-4-bromobenzyl alkylating groups, allowing the formation of a stable, but racemic, enantiomer pair based only on the presence of the β-substituent. Regardless of the chiral properties of OxP derivatives, the purpose of this work has been to determine how to introduce catalytic activity to the OxP macrocycle core (since **1a**, **2a** and **3a** are not organocatalytically active). Catalytic properties of asymmetric OxP derivatives will be discussed elsewhere.

Table 1. Optimization of catalyst for addition of 2,4-pentanedione to β-nitrostyrene.[a]

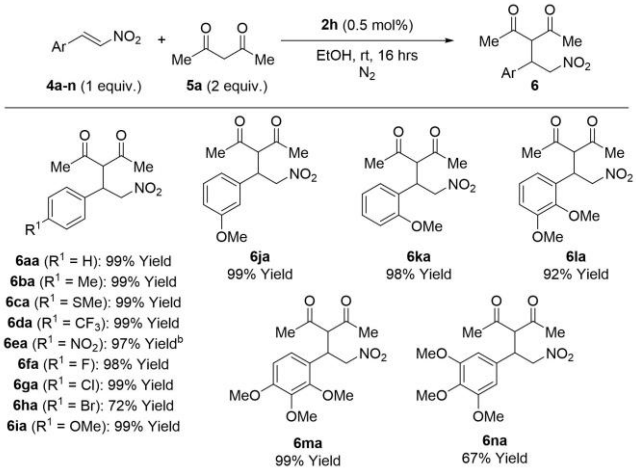


4a (1 equiv.) **5a** (2 equiv.) **6aa**

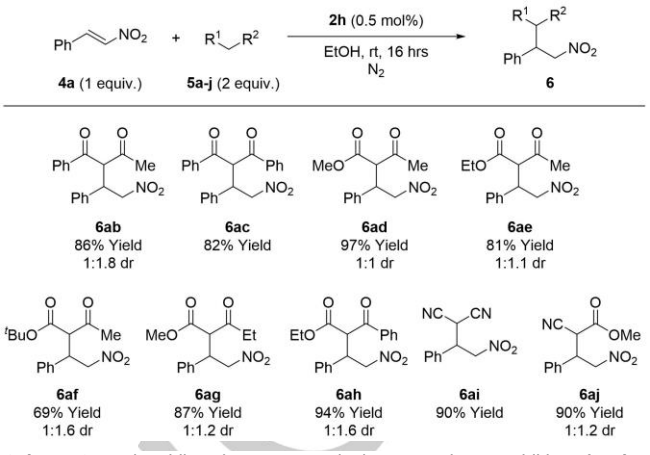
Entry	Catalyst	Catalyst loading (mol%)	Conversion (%)[b]
1	-	-	0
2	C_5H_5N	1.0	0
3	**1a**	1.0	0
4	**2a**	1.0	0
5	**3a**	1.0	0
6	**2c**	1.0	10
7	**2d**	1.0	100
8	**2d**	0.5	60
9	**3d**	0.5	0
10	**2e**	0.5	0
11	**2f**	0.5	9
12	**2g**	0.5	<5
13	**2h**	0.5	71
14	**1h**	0.5	60
15	**3h**	0.5	0
16	**2i**	0.5	0
17	**2j**	0.5	63

[a] Reaction conditions: **5a** (140 µL, 1.36 mmol, 2 equiv.) was added to **4a** (102 mg, 0.68 mmol, 1 equiv.) and catalyst (3.42 µmol, 0.5 mol% or 6.84 µmol, 1.0 mol%) in DCM (2 mL) and stirred under N_2 for 16 hours. [b] Conversion was determined by ^{1}H NMR of the reaction mixture.

Catalysis results and substrate scope. Catalysts were screened for activity in the 1,4-conjugate addition of 2,4-pentanedione (**5a**) to β-nitrostyrene (**4a**) as this has been used as a benchmark reaction for a number of hydrogen-bond donor catalysts.[2-4] No conversion was observed for compounds lacking β-substituents (**1a**, **2a**, **3a**, Table 1, Entries 3-5) while the introduction of a dimethylamino group (**2c**, Table 1, Entry 6) lead to 10% conversion to the expected product **6aa**. The use of a secondary amine pentylamino group (**2d**, Table 1, Entry 7-8) in place of the tertiary amine group resulted in a dramatic increase in reactivity with complete conversion observed to **6aa** at 1 mol% catalyst loading. This suggests that, in addition to the basicity of the β-substituent, a hydrogen-bond donor moiety is required for catalytic activity. Catalyst loading was subsequently decreased to 0.5 mol% in order to more accurately compare the activity with other derivatives. Reactions with a decreased loading of **2d** (to 0.5 mol%) gave a reduced conversion of 60%. The tetra-N-alkylated derivative **3d** and the acetylated form **2e** exhibited no catalytic activities (Table 1, Entries 9-10), indicating that both pyrrolic and β-substituent amine functionality is required. Exchange of the pentylamino of **2d** for 3-picolyl (**2f**) and 2-picolyl (**2g**), both lead to a decrease in catalytic activity to less than 10% conversion (Table 1, Entries 11-12). However, increasing the linker length between the amino group and the pyridyl substituent by a single carbon (**2h**, Table 1, entry 13) restored activity to levels above those previously obtained for **2d**. The reasons for this increased activity are unclear although X-ray crystallographic structures of the precursor shown in Figure 4 and derivative **2i** (Figure 3) indicate that the pyridyl group in **2h** may be positioned remote from the catalytic site, further suggesting that in **2f** and **2g** the pyridyl groups interfere with the catalysis reaction. To confirm catalytic activity, OxP compounds lacking pyrrole N-alkyl groups (**1h**), tetra-N-alkylated (**3h**) and β-position aminoacylated (**2i**) were studied with all exhibiting lower or no catalytic activity relative to **2h** (Table 1, Entries 14-16). The lower conversion obtained with catalyst **1h** compared to **2h** (Table 1, entries 13 *vs*. 14) could be due to the increased rigidity of **2h** because of the



Scheme 1. Nitrostyrene substrate scope in the 1,4-conjugate addition of **5a** to **4a-n** catalysed by **2h**. Reaction conditions: **5a** (140 µL, 1.36 mmol, 2 equiv.) was added to **4** (0.68 mmol, 1 equiv.) and **2h** (5.46 mg, 3.42 µmol, 0.5 mol%) in EtOH (2 mL) and stirred under N_2 for 16 hours. Isolated yields after purification by column chromatography are reported.



Scheme 2. Nucleophile substrate scope in the 1,4-conjugate addition of **5a-j** to **4a** catalysed by **2h**. Reaction conditions: **5** (1.36 mmol, 2 equiv.) was added to **4a** (102 mg, 0.68 mmol, 1 equiv.) and **2h** (5.46 mg, 3.42 µmol, 0.5 mol%) in EtOH (2 mL) and stirred under N_2 for 16 hours. Isolated yields after purification by column chromatography are reported.

presence of the alkylated pyrrolic nitrogens, which prevent inversion through the plane of the macrocycle. Also, pyridine (Table 1, Entry 2) did not catalyze the reaction and the phenyl analogue **2j** gave a similar conversion (Table 1, Entry 17) indicating that pyridyl groups introduced to the β-substituent do not participate in the catalytic process and are furthermore not responsible for product formation. The bifunctional requirement of the catalyst was demonstrated by control compounds **1a** and **2a**, which lack a β-substituent, with the addition of an external base. This demonstrates the synergistic effect of a covalently bound basic moiety in the β-position *versus* an externally added base, as the OxP actually retards the catalytic activity of an external base such as triethylamine (Table S1).

After having successfully used derivatives of **2** to catalyze the Michael addition of 2,4-pentanedione (**5a**) to β-nitrostyrene (**4a**) an optimization of reaction conditions was performed (see Table S2). At 0.5 mol% loading of **2h**, solvents containing carbonyl-type oxygen atoms capable of competitively hydrogen-bonding to the active site of oxoporphyrinogens (e.g. acetone, ethyl acetate) hinder the reaction and significantly lower conversions were obtained. Surprisingly, solvents with alcohol moieties, which typically also bind to OxPs, gave large improvements in conversion with ethanol giving quantitative conversion to **6aa** at 0.5 mol% catalyst loading whilst the background rate in the absence of catalyst was shown to remain negligible. It is important to note the significance of the use of a solvent such as ethanol in successful catalytic reactions. First, it is a relatively environmentally friendly solvent compared to more typical solvents employed for these reactions, such as dichloromethane or toluene.[2-4,30] Second, protic solvents are capable of competitively forming H-bonds and therefore can interrupt interactions required for the successful outcome of H-bond catalysts although, interestingly, this does not appear to effect the activity of catalysts such as **2h**.

The substrate scope of the reaction with optimized conditions was examined based on variation of aryl-substituted nitrostyrenes using **5a** as the nucleophile for the Michael addition (Scheme 1). The variation of substrate aryl substituent was tolerated with greater than 90% yields maintained regardless of the electron-donating (**6ba**, **6ca**, **6ia**) or electron-withdrawing (**6da**, **6fa**, **6ga**) properties and substituent position (**6ja**, **6ka**, **6la**, **6ma**). Compound **6na** was obtained in a lower isolated yield despite appearing to have occurred quantitatively according to thin layer chromatography analysis of the reaction mixture due to losses incurred during chromatographic purification. Substrate **4e** is poorly soluble in the reaction solvent but increasing the catalyst loading to 2 mol% led to an improved yield of **6ea** of 97%. Nitroolefin **4h** gave an acceptable yield of 72% for the formation of **6ha**. Interestingly, the products (**6**) are insoluble in the reaction media and precipitate from the reaction mixture facilitating their isolation by filtration albeit in slightly lower yield than obtained using purification by column chromatography. The catalysts can also be recovered by using this method because of their intense color and high polarity relative to the product. In this study, catalyst **2h** was recovered and combined from multiple reactions

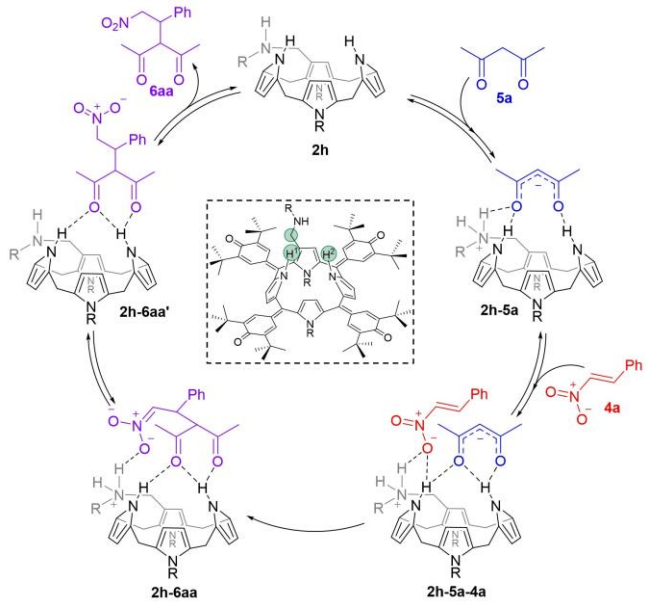


Figure 5. Plausible reaction mechanism for the addition of **5a** to **4a** catalysed by **2h**. Structure of **2h** has been truncated for clarity, for full structure see Figure 2. Centre - Structure of catalyst **2h** with protons of interest for ^{1}H NMR binding studies highlighted in green.

then purified as a single batch using the chromatographic conditions as outlined for its synthesis.

Variation of the nucleophile used led to greater variation in the yields of the Michael addition products (Scheme 2). The substitution of the terminal methyl groups of 2,4-pentanedione with simple phenyl groups (**6ab**, **6ac**) resulted in only a small reduction in reactivity while the substitution of one ketone of the 1,3-dione with an ester (**6ad**, **6ae**, **6af**) lead to decreases in yield depending on the bulk of the ester. The steric and electronic properties of the remaining ketone could be modified (**6ag**, **6ah**) without considerable loss in product yield in both examples. The reaction conditions also allowed for the use of nitriles, with both malononitrile (**6ai**) and cyanoacetate (**6aj**) adducts successfully synthesized in high yields. Low diastereoselectivity (dr) was observed for the unsymmetrical substrates studied here with the majority isolated as essentially 1:1 mixtures of diastereoisomers with the highest dr observed for **6ab** at 1:1.8. Variation of nucleophile **4** had a greater effect on the yields of the Michael addition products (Scheme 2), which is consistent with the mechanism proposed in Figure 3 as it is the substrate being activated by the catalyst.

Mechanistic Studies. A plausible mechanism is shown in Figure 5 based on that reported by Soós and co-workers.[31c] ^{1}H NMR binding and kinetic studies were carried out in order to support the proposed mechanism. However, it is important to note that this mechanism has been proposed by comparison to mechanistic and computational studies for a number of literature reported catalysts.[31]

Analyses of substrate-catalyst NMR titration spectral data are known to give information regarding the active site and binding modes of H-bond catalysts.[31a] Therefore, we undertook ^{1}H NMR spectroscopic titrations (see Figures S8-S10) of either **4a**, **5a** or **6aa** with catalyst **2h** to determine binding constants[32] and the locations of interaction by monitoring the protons highlighted in green in Figure 5 (centre). Binding constants were determined using the two exchangeable pyrrolic NH and the benzylic type protons at the β-position (shown in Figure 5), these were used due to the large variation in chemical shift of these resonance and there being no interfering proton resonances during the course of the titration. The NH proton of the β-substiuent of **2h** is not visible in its ^{1}H NMR spectrum and therefore could not be used for the mechanistic studies. To ensure that competing analytes, such as residual acid from the photo-degradation of chlorinated solvents, were not present during titration, all NMR solvents were neutralized (by standing over solid K_2CO_3) prior to use and the measurement temperature was kept constant to avoid shifts in exchangeable protons. The highest binding constant of 0.43 ± 0.05 M^{-1} was observed with **5a**, whereas both **4a** and **6aa** showed lower binding constants of 0.27 ± 0.03 M^{-1} and 0.026 ± 0.01 M^{-1}, respectively. It should be noted here that the saturation point of **6aa** was reached at 212 equivalents, which could lead to binding constant inaccuracy. Based on the magnitude of changes in the ^{1}H NMR shifts, and by comparison with reported mechanisms,[31] dicarbonyl **5a** interacts with all three NH functionalities (**2h**-**5a**) through two H-bonds to the pyrrolic NH and by deprotonation of substrate **5a** by the amino functionality in the β-substituent of **2h**. Indeed, this deprotonation step appears to be the key role of the β-substituent and, although non-β-substituted OxPs have previously been shown to undergo H-bond interactions,[20-24] those compounds (such as **2a**) are not catalytically active in the above studied reactions. This demonstrates the importance of the β-substituent for catalytic activity. Nitrostyrene **4a** interacts with a single pyrrolic NH and the β-substituent suggesting the formation of a complex such as **2h**-**5a**-**4a** with introduction of the H-bonding interaction with the β-substiuent further demonstrating its importance for the induction of catalytic activity. The pre-organisation of the substrates, as well as the substrate activation due to H-bond interaction, facilitates and promotes bond

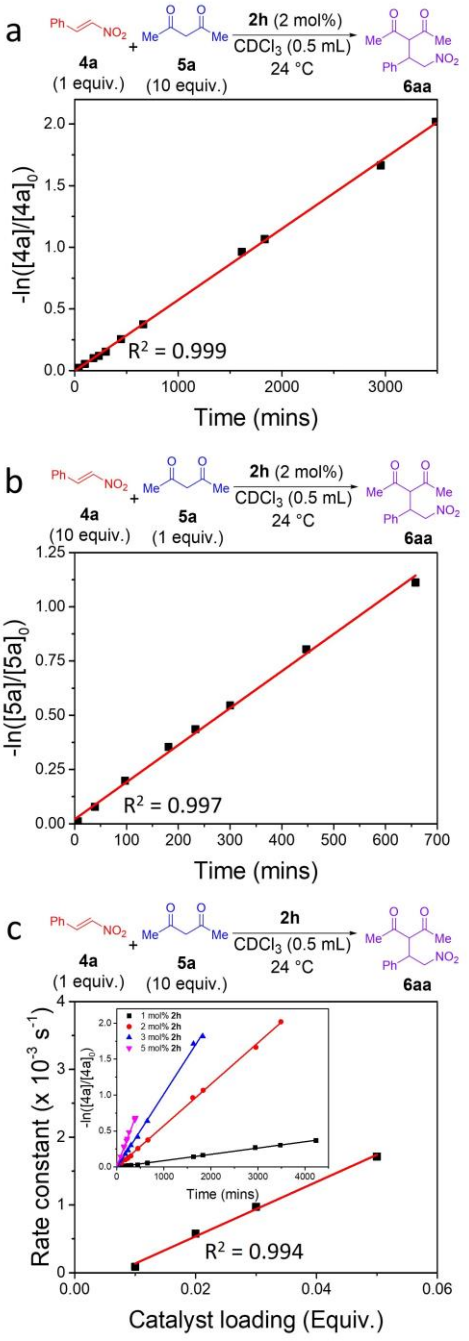
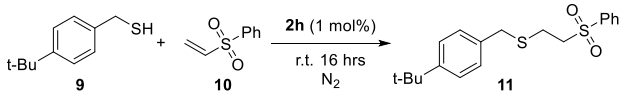


Figure 6. Kinetics measurements for the addition of **5a** to **4a** catalysed by **2h**. **a.** Pseudo first-order kinetics measurement for **4a** with **5a** in excess (10 equiv.) in $CDCl_3$ (0.5mL) at 24 ± 2 °C. [**2h**] = 3.2 x 10^{-3} M. **b.** Pseudo first-order kinetics measurement for **5a** with **4a** in excess (10 equiv.) in $CDCl_3$ (0.5mL) at 24 ± 2 °C. [**2h**] = 3.2 x 10^{-3} M. **c.** Pseudo first-order kinetics measurement for catalyst **2h** at 1,2,3 and 5 mol% catalyst loading with **5a** in excess (10 equiv.) in $CDCl_3$ (0.5mL) at 24 ± 2 °C. [**4a**] = 0.16 M. Inset shows the data used to determine the rate constants.

Table 2. Catalyst and condition screening for sulfa-Michael reaction.[a]



Entry	Catalyst	Cat. Loading (mol%)	Solvent	Conversion[b] (%)
1[c]	**2h**	3.0	DCM	>99
2	-	-	DCM	0
3	**2a**	1.0	DCM	0
4	**3a**	1.0	DCM	0
5	**2c**	1.0	DCM	3
6	**2h**	1.0	DCM	44
7	**2h**	1.0	EtOH	>99
8	**-**	-	EtOH	72

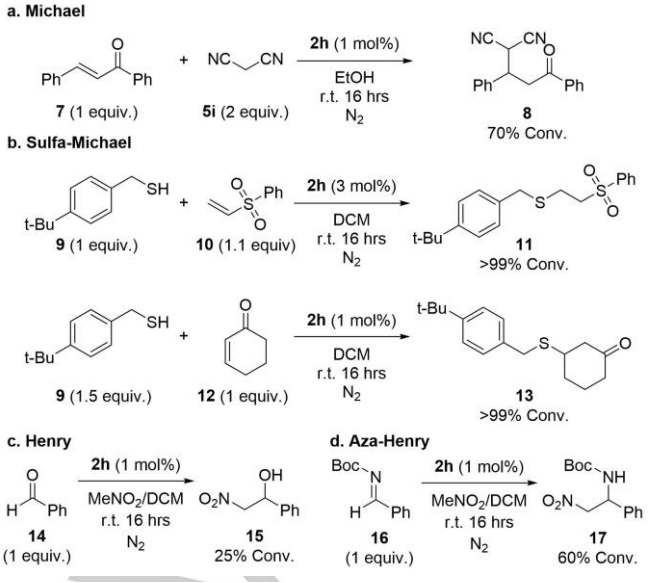
[a] Reaction conditions: Thiol **9** (43.8 µL, 0.0705 mmol, 1 equiv.) was added to alkene **10** (43.5 mg, 0.0776 mmol, 1.1 equiv) and catalyst (1.0 – 3.0 mol%) in solvent (2 mL) and stirred under N_2 for 16 hours. [b] Conversion was determined by ^{1}H NMR spectroscopy in $CDCl_3$ with CH_2Br_2 as internal standard (1mL, 19.2 mM). [c] Literature reported reaction conditions were used.[15]

formation leading to **2h**-**6aa**. No variation in the chemical shifts of benzylic protons was observed in titrations of product **6aa** with **2h**, indicating that following product formation H-bond interaction with the β-substituent is substantially attenuated to give **2h**-**6aa'**. Weak binding of **6aa** allows catalysis to proceed since it is released (or displaced by fresh substrate through competitive binding) regenerating **2h**, which can re-enter the catalytic cycle.

Competitive binding studies were also performed by monitoring the effect of the addition of **5a** to a preformed complex of **2h**-**4a** and *vice versa* (see Figures S11,S12). Addition of 100 equivalents of **4a** to the catalyst causes a shift in the NMR signals of <0.1 ppm. However, upon addition of 100 equivalents of **5a** to the **2h**-**4a** complex a large shift of 0.6 ppm for pyrrolic NH is observed.

In the opposite case, the formation of the **2h**-**5a** complex causes a large shift in the ^{1}H NMR signals which is followed by only minor changes upon addition of nitrostyrene **4a**. This result supports the hypothesis that the catalyst forms a stronger interaction with the nucleophile (**5a**) than electrophile (**4a**) and demonstrates that **5a** exhibits a strong binding interaction even in the presence of **4a** supporting the proposed mechanism in this report, more specifically the initial formation of **2h**-**5a**. The mechanism proposed by Takemoto and co-workers[4] was believed to involve activation of the electrophile through H-bonding interactions whereas later studies, including mechanistic studies by Soós and co-workers[31c] amongst others,[31] demonstrated nucleophile activation, which is more in-line with results obtained using **2h**.

In order to further support the proposed mechanism, kinetic parameters were determined by carrying out the reaction in $CDCl_3$ at 23.5 °C utilizing the pseudo-first-order kinetics method (Figure 6 and Figures S13-S18).[31a] By using separate ^{1}H NMR studies with variations in the reagent equivalents and catalyst loading the reaction was shown to be pseudo first order for **4a**, **5a** and **2h**, indicating that the rate equation for this reaction is: rate = k[**2h**][**4a**][**5a**]. As only reaction events that occur at or prior to the rate-determining step (RDS) are included in the rate equation, and can be studied in these kinetics experiments, the formation of **2h**-**5a** adduct and related catalyst protonation cannot be the RDS due to the presence of **4a** in the rate equation. Due to first order kinetics observed for **4a**, the RDS is most likely the tertiary complex formation (**2h**-**5a**-**4a**) or the subsequent C-C bond formation. Weak binding of **6aa** by the catalyst, as determined by ^{1}H NMR titrations, suggest that the release of the product from the catalyst is a facile process, excluding this as the RDS.



Scheme 3. Screening of reaction scope for catalyst **2h**. Conversion was determined by ^{1}H NMR spectroscopy in $CDCl_3$ with 1,3,5-trimethoxybenzene (1 mL, 5.95 mM) or CH_2Br_2 (1mL, 19.2 mM for **11**) as internal standard.

Unfortunately, mechanistic studies could not be performed in methanol or ethanol due to deuterium-hydrogen exchange rendering the protons of interest unobservable in the ^{1}H NMR spectra and due to the poor solubility of the catalyst in these solvents causing signal broadening. However, upon repetition of the control reactions with **3h** and **2i** in ethanol, no conversion to **6aa** was observed suggesting that **2h** continues to act by the same mechanism despite the use of a polar protic solvent capable of competing with H-bonding interactions.

Reaction Scope. Preliminary investigations into the synthetic utility of catalyst **2h** for a range of other transformations (Scheme 3) typically catalyzed by H-bond donor catalysts were performed.[2-4,15] It was found that **2h** is catalytically active in Michael addition reactions with other substrates, such as the addition of malononitrile (**5i**) to chalcone (**7**) for which there was no conversion obtained in the absence of a catalyst in ethanol. Additionally, **2h** is highly effective for the activation of sulfa-Michael reactions leading to products **11** and **13** in quantitative conversions, again no conversion was obtained in the absence of a catalyst in dichloromethane. The Henry and aza-Henry reactions were also successfully catalyzed by **2h** in moderate conversions furnishing products **15** and **17** under standard conditions.[33]

Further studies were carried out for the sulfa-Michael reaction (Table 2), in order to gain a direct comparison with previously reported porphyrinoid catalysts for this transformation. First, when compared to the pioneering work in the field reported by Senge and co-workers, where 80% conversion was obtained for the formation of **11**,[15] catalyst **2h** gave quantitative conversion to **11** under the same conditions (Table 2, Entry 1). Second, it was found that for non-β-substituted (**2a**, **3a**) and tertiary amine (**2c**) catalysts, analogous results were obtained as to those for the addition of acetylacetone to nitrostyrenes outlined above, further demonstrating the importance of the β-substituent. The modified conditions used earlier in this study, with catalyst loading reduced by 2/3 and the reaction solvent as ethanol, gave quantitative conversion (Table 2, Entry 7), however the background reaction

in the absence of a catalyst was shown to be significant when ethanol was employed as a reaction solvent (Table 2, entry 8).

Conclusions

In conclusion, a novel class of OxPs has been synthesized and their application as bifunctional H-bond donor catalysts has been investigated. The catalysts possess multi-reaction activity with wide substrate scope and operate at low catalysts loadings (≤ 1 mol%). We have demonstrated that β-substitution is essential to establish catalytic activity, and preliminary mechanistic studies indicate that they interact with substrates in a similar fashion to already reported catalysts. The catalysts exhibit activity in the Michael addition reactions and preliminary results reveal the catalyst's excellent activity for sulfa-Michael additions compared to literature reported porphyrinoids, as well as moderate activity for Henry and aza-Henry reactions. We believe that these OxP systems offer an extremely adaptable scaffold for the development of H-bond catalysts due to a concave 3-dimensional structure at their binding sites, which can be modified to affect and optimize any catalytic processes occurring there. These OxP systems possess excellent potential for the design of supramolecular catalysts beyond what is currently possible. We are currently continuing to investigate their applications as organocatalysts.

Supporting Information

The Supporting Information contains experimental procedures, characterization data, X-ray crystal structure in the form of Cifs for compounds Ni-**1*h** and **2i**, and copies of ^{1}H and ^{13}C NMR spectra and mass spectra. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre with CCDC reference numbers 1915045 (Ni-**1*h**) 1915046 (**2i**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK http://www.ccdc.cam.ac.uk/perl/catreq/catreq.cgi, e-mail: data_request@ccdc.cam.ac.uk, or fax: +44 1223 336033.

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Author Contribution

M.K.C carried out the synthesis of catalysts and D.T.P and M.K.C. performed catalysis reactions and mechanistic studies. M.K.C, D.T.P. and J.P.H designed the experiments, analyzed spectroscopic data and directed the research. Y.M. performed X-ray crystallography. J.L. undertook spectroscopic measurements and aided with binding constant measurements. All authors contributed to discussions throughout the project and the manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Keywords: Organocatalysis • Porphyrinoids • Oxoporphyrinogens • Conjugate Addition • Catalysis

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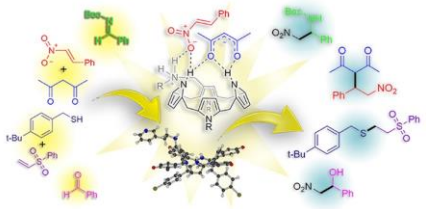
Entry for the Table of Contents

Key Topic: Porphyrinoid Organocatalysis

FULL PAPER

Beta functionalization of oxoporphyrinogens as H-bond donor catalysts with binding site designed for dual activation of substrates is reported. Introduction of β-substituents enables catalysis of 1,4-conjugate additions, sulfa-Michael additions and Henry/aza-Henry reactions at low catalyst loadings (≤ 1 mol%) under mild conditions.



Mandeep K. Chahal, Daniel T. Payne, Yoshitaka Matsushita, Jan Labuta, Katsuhiko Ariga and Jonathan P. Hill**

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Molecular Engineering of β-Substituted Oxoporphyrinogens for Hydrogen-Bond Donor Catalysis