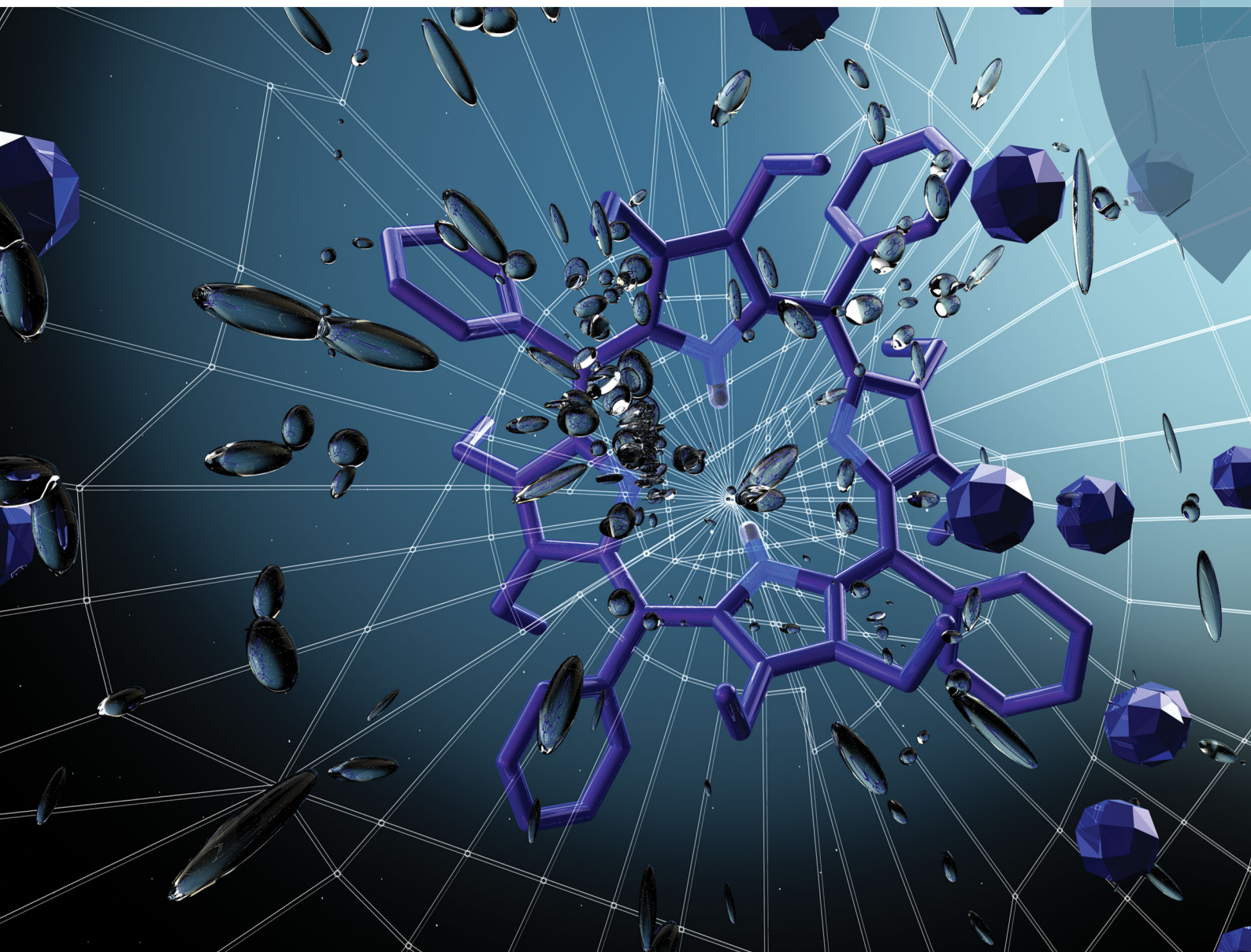


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ISSN 1359-7345



COMMUNICATION

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Cite this: *Chem. Commun.*, 2018, 54, 26

Received 19th October 2017,
Accepted 14th November 2017

DOI: 10.1039/c7cc08099a

rsc.li/chemcomm

Conformational control of nonplanar free base porphyrins: towards bifunctional catalysts of tunable basicity†

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For the first time, free base and *N*-methylated porphyrins have been utilized as bifunctional organocatalysts in Michael additions and it was found that distortion of the macrocycle is a vital prerequisite for their catalytic activity. Conformational design has been used to tailor the properties of nonplanar porphyrins with regards to availability of the N–H units for hydrogen bonding (distortion-dependent hydrogen bonding) and the basicity of the heterocyclic groups. NMR spectroscopic- and catalyst screening studies provided insight into the likely mode of catalyst action. This unprecedented use of free base and *N*-substituted porphyrins as organocatalysts opens a new functional role for porphyrins.

Do porphyrins always require a central metal to be catalytically active? The short answer is ‘No!’ and in the following we detail how conformational design can be used to entice free base porphyrins to act as organocatalysts, revealing a new mode of action for the ubiquitous ‘pigments of life’.¹

Porphyrins do not only give color to life but nature utilizes these tetrapyrroles as catalysts and cofactors par excellence for a plethora of essential reactions.² Some of the most fundamental biological processes involve metalloporphyrin cofactors, *e.g.*, hemes (Fe), (bacterio)chlorophylls (Mg), corphins (Ni) and corrins (Co).^{1–3} Synthetic porphyrin catalysts aim to reproduce many of these natural processes, notably oxidations, to facilitate synthetic reactions.⁴ A striking, common feature of all natural and synthetic catalytically active tetrapyrroles is the presence of a central metal ion, with the macrocyclic scaffold serving merely as a fine-tuning molecular frame. Accordingly, the catalytic activity of porphyrins almost exclusively arises from the central metal ion.

Rendering free base porphyrins catalytically active would require participation of the pyrrole N–H and N-lone pairs in chemical reactions and/or hydrogen bonding. In traditional porphyrins these moieties are buried in the macrocycle core and therefore are relatively inaccessible (*i.e.* 1, Fig. 1A). However, any macrocycle distortion resulting in an out-of-plane tilting of the pyrroles will alter this picture and render the core nitrogen atoms spatially accessible (Fig. 1B).⁵

Ring puckering can be achieved by steric strain from either core or peripheral substitution, as can be the case in highly substituted porphyrins for instance.⁶ Other classic examples are *N*-substituted porphyrins⁷ and (core) porphyrin (di)acids.^{8,9b} The core functionality of these nonplanar⁹ porphyrins can participate in hydrogen bonding, bind solvent molecules¹⁰ or anions,⁸ and be used as the functional unit of a chiral sensor.¹¹ Dodecasubstituted saddle-distorted porphyrins are metallated several orders of magnitude faster than planar porphyrins, and increased porphyrin distortion can lead to augmented thermodynamic basicity.¹² In addition, macrocycle nonplanarity plays a role in the biosynthesis of native porphyrins, where metal

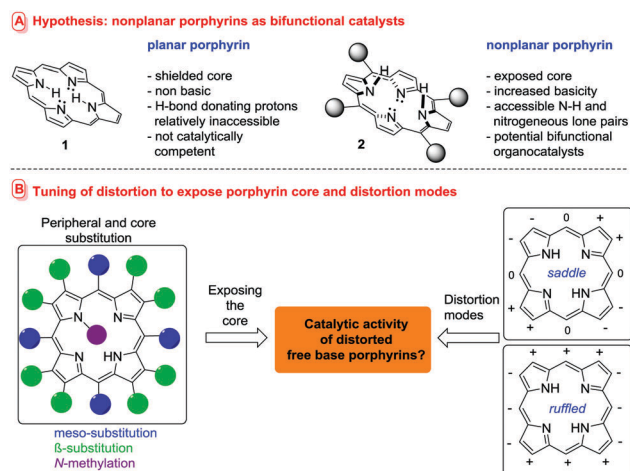


Fig. 1 Nonplanar porphyrins as bifunctional catalysts.

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† Electronic supplementary information (ESI) available: Catalytic tests, synthesis and characterization of compounds. See DOI: 10.1039/c7cc08099a



chelates rely on a distortion-mediated mechanism.¹³ Conformational control of the macrocycle is a key principle to fine-tune the different functional uses of metalloporphyrins in nature.²

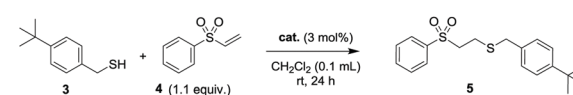
Thus, while the general effect of distortion on the availability of the porphyrin lone pairs has been known for decades, the phenomenon has been little studied and completely overlooked as a tool for exploitation in catalysis. We hypothesized that the use of a distortion mechanism⁵ to facilitate the participation of the metal-free porphyrin core in either hydrogen bonding or base catalysis (or both) could generate powerful and highly tunable organocatalysts (*i.e.* 2, Fig. 1A).

For example, (thio)ureas¹⁴ and squaramides¹⁵ incorporating basic functionalities have been shown to catalyze a host of reactions through the activation of both the nucleophilic and electrophilic reaction components. Such reactions can occur *via* either a general catalysis-like mechanism or a specific catalysis-like process (*vide infra* Fig. 2).^{16,17}

To test this hypothesis, we prepared and evaluated a suite of porphyrins, in which the degree of distortion from planarity, the electronic properties of the macrocycle, and the potential H-bond donating proclivities had been gradually varied as catalysts in the sulfa-Michael addition¹⁸ of *tert*-butyl benzylmercaptan (3) to phenyl vinyl sulfone (4) to afford adduct 5: a reaction likely to be susceptible to bifunctional catalysis. The results of these studies are outlined in Table 1.

In the absence of a catalyst, no background reaction was observed at ambient temperature (entry 1). The *de facto* planar 5,10,25,20-tetraphenyl- and 2,3,7,8,12,13,17,18-octaethylporphyrins (6 and 7, entries 2 and 3)¹⁹ possessed no catalytic activity under the conditions employed at 3 mol% loading. Gratifyingly, a chimera of both these materials – *i.e.* the highly distorted porphyrin 8²⁰ – promoted the reaction to full conversion (entry 4). Under diluted conditions ([cat] = 3.6×10^{-3} M) 80% conversion to 5 was possible. This catalyst system exhibited extraordinary sensitivity to variation of its electronic properties: the tetrakis(4-bromophenyl) analogue 9 was inactive (entry 5) while the tetrakis(4-tolyl) analogue 10 displayed a level of activity on a par with 8 itself (entry 6).²¹ While a *p*-bromo substituent is not regarded as a powerful electron withdrawing group ($\sigma_p = 0.26$), we posited that bringing four such substituents to bear on the

Table 1 Catalyst screening



Catalysts

Non-alkylated

6 R¹ = C₆H₅, R² = H
 7 R¹ = H, R² = Et
 8 R¹ = C₆H₅, R² = Et
 9 R¹ = 4-Br-C₆H₄, R² = Et
 10 R¹ = 4-Me-C₆H₄, R² = Et

Neutral alkylated

11 R¹ = NO₂, R² = Et
 12 R¹ = C₆H₅, R² = Br
 13 R¹ = C₆F₅, R² = Br
 14 R¹ = *i*Bu, R² = H
 15 R¹ = H, R² = Et
 16 R¹ = C₆H₅, R² = H
 17 R¹ = C₆H₅, R² = Et
 18 R¹ = 4-Cl-C₆H₄, R² = H
 19 R¹ = 4-MeO-C₆H₄, R² = H

Cationic alkylated

20
 21 R = 4-Cl-C₆H₄
 22
 23

| Entry | Catalyst | $\Delta 24^a$ [Å] | λ_{\max}^b [nm] | #NH | Yield ^c (%) |
|-------|--------------------|---------------------------|-------------------------|-----|--------------------------|
| 1 | — | n/a | n/a | n/a | 0 |
| 2 | 6 ^{19a} | 0.05, 0.19 ^{19a} | 417, 515 | 2 | 0 |
| 3 | 7 ^{19b} | 0.02 ^{19b} | 399, 498 | 2 | 0 |
| 4 | 8 ^{20a} | 0.54 ^{20b} | 456, 555 | 2 | > 98 (80 ^d) |
| 5 | 9 | — | 459, 515 | 2 | 0 |
| 6 | 10 ²¹ | — | 457, 710 | 2 | > 98 (75 ^d) |
| 7 | 11 ²² | 0.40 ^{22a} | 422, 663 | 2 | 0 |
| 8 | 12 ^{12c} | 0.62 ^{23b} | 468, 739 | 2 | 0 |
| 9 | 13 ^{23c} | — | 495, 711 | 2 | 0 |
| 10 | 14 ^{9a} | — | 446, 692 | 2 | 0 |
| 11 | 15 ^{26a} | — | 410, 642 | 1 | < 5 |
| 12 | 16 ^{26b} | 0.26–0.3 ^{26c,d} | 433, 677 | 1 | 50 |
| 13 | 17 ^{25b} | — | 477, 735 | 1 | > 98 (< 5 ^d) |
| 14 | 18 ^{t.w.} | — | 435, 678 | 1 | 3 |
| 15 | 19 ^{t.w.} | — | 437, 685 | 1 | 62 |
| 16 | 20 ^{27a} | — | 457, 630 | 0 | 5 |
| 17 | 21 ^{t.w.} | — | 461, 710 | 1 | > 98 (20 ^d) |
| 18 | 22 ^{27b} | 0.44 ^{27b} | 463, 715 | 0 | 0 |
| 19 | 23 ^{27c} | 0.61 ^{25b} | 506, 756 | 0 | 0 |

^a $\Delta 24$ = average deviation of the 24-macrocycle atoms from their least-squares plane as a measure of overall degree of nonplanarity in the solid state. ^b λ_{\max} = soret and long wavelength *Q* absorption bands in CH₂Cl₂ (+1% NEt₃) as a measure of macrocycle distortion in solution. ^c Determined by ¹H NMR spectroscopy using an internal standard, [cat] = 7.1×10^{-2} M. ^d Performed under dilute conditions: [cat] = 3.6×10^{-3} M.

Design- and mechanistic rationales

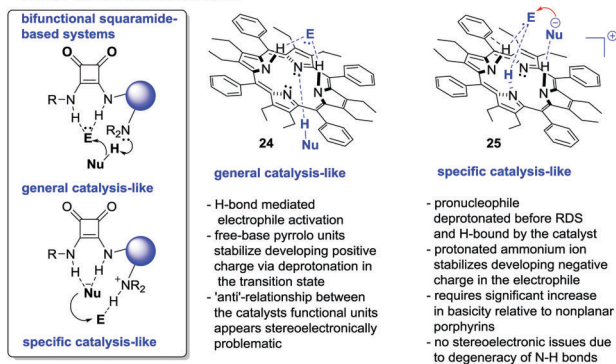


Fig. 2 Catalyst design rationale.

conjugated macrocycle core brings about the observed modulation of catalyst basicity, leading to inefficient deprotonation of the pronucleophilic substrate.

In line with these observations, the highly sad-distorted⁹ free base porphyrins 11,²² 12 and 13^{12c,23} equipped with multiple electron withdrawing substituents at the *meso*- and/or β -positions failed to accelerate the reaction (entries 7–9). Ensuing the investigation of sad-distorted porphyrins, an alternative distortion mode, the ruf-distorted 5,10,15,20-tetra(*tert*-butyl)porphyrin (14, entry 10), was explored. Though highly distorted, no promotion of the reaction was observed due to the N–H being concealed in the porphyrin plane.^{9a}

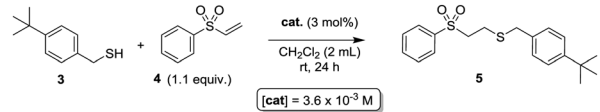
Next, we examined *N*-methyl-porphyrins⁷ as potential catalysts. They are classic inhibitors of ferrochelatase,^{7,24} where the

N-substitution and the consequential macrocycle distortion²⁵ is known to result in increased porphyrin basicity.^{12a} Thus, while these porphyrins contain one less H-bond donating pyrrole N–H unit than **6–14**, they should possess a more accessible and reactive functionality. While *N*-methylation of **7** (*i.e.* cat. **15**)^{26a} led to only a marginal increase in catalyst efficacy (entry 11), the *N*-methyl analogue of the similarly inactive catalyst **6** (*i.e.* **16**, entry 12)^{26b–d} resulted in a significant improvement to 50% conversion. Disappointingly, the alkylated variant of the efficient catalyst **8** (*i.e.* **17**, entry 13)^{25b} was able to catalyze the smooth, quantitative formation of **5** under standard conditions, but not when diluted. Catalysts **18** and **19**, which possess *N*-methyl and *meso*-aryl groups, but are devoid of octaethyl substitution (entries 14 and 15) did not serve as highly active promoters of the reaction, yet they did exhibit the electronic sensitivity observed in the archetypal free base systems. The *N,N'*-dimethyl porphyrin **20**^{27a} proved a poor catalyst, although it is noteworthy that it is more efficient than **6** (entries 2 and 16). Thus, it is clear that *meso*-aryl (electron donating) groups, octaethyl substitution, and *N*-alkylation can be used to improve distortion and catalytic activity. However, the effects of all three modifications together are not additive, and the former two are best utilized in concert from a catalyst design standpoint.

Finally, we were interested in the performance of cationic porphyrins. Compound **21** has a '*cis*'-21,22-dimethylation pattern with a higher degree of distortion than that of the '*trans*'-21,23-dimethylation mode. Despite the presence of the electron-withdrawing aromatic groups, the cationic **21** displayed promising activity under standard conditions, but was a poor promoter of the process under dilute conditions (entry 17). Interestingly, the analogue **22**, in which the remaining N–H unit was methylated^{27b} and the electronegative chlorine atom removed could not catalyze the addition (entry 18). A dicationic, permethylated version of the most efficacious catalyst **8** (*i.e.* **23**, entry 19)^{27c} was also inactive.

The situation involving cationic porphyrins seems complex. Methylation at both the N21 and N22 positions brings about high levels of distortion^{25b} (which we have shown to be beneficial to activity), however it also generates a positive charge, and we had previously shown (*vide supra*) that rendering the porphyrin less electron-rich leads to slower catalysis. It is conceivable that delocalization of the charge around the very large aromatic system lessens its impact. In addition, increasing the acidity of the lone pyrrole N–H unit may be relevant. In any case, since **21** is active, despite the presence of electron-withdrawing *meso*-substituents, it is clear that the contribution from distortion is dominant. Of considerable interest is the failure of **22** as a catalyst, which strongly supports the hypothesis that hydrogen bonding by two porphyrin N–H units – *i.e.* the original pyrrole N–H and an ammonium ion generated after protonation by the substrate (see 25, Fig. 2) – is also a key facet of catalysis (*i.e.* a bifunctional mode of operation) in these systems. This correlates well with the fact that **16** (possessing one pyrrole N–H unit) is a mediocre promoter while its analogue with none (*i.e.* **20**) is incapable of catalysis under these conditions.²⁹

Table 2 A comparison of the activity of **8** with amines under dilute conditions



| Entry | Catalyst | pK _{AH} ^a (H ₂ O, 25 °C) | Yield ^b (%) |
|----------------|------------------|---|------------------------|
| 1 | Aniline | 4.6 | 0 |
| 2 | Pyridine | 5.2 | 0 |
| 3 | DMAP | 9.7 | 43 |
| 4 | NEt ₃ | 10.9 | 76 |
| 5 ^c | 8 | n/d | 80 |
| 6 | DBU | ca. 13 | > 98 |

^a Refers to the conjugate acid of the base listed. ^b Determined by ¹H NMR spectroscopy using an internal standard. ^c Data from Table 1.

In order to provide some context regarding the catalytic activity of these distorted porphyrins, we compared the performance of the superior system identified here (**8**) with a range of amines of disparate basicity under diluted conditions (Table 2). The use of weak amine bases fails to lead to product formation (entries 1 and 2). DMAP promotes the reaction with moderate efficiency (entry 3) while both NEt₃ (which is an order of magnitude more basic than DMAP) and **8** can catalyze the reaction to ca. 80% conversion after 24 h (entries 4 and 5).

To confirm that the distorted porphyrins are capable of basicity exceeding some standard amines, we mixed a 1 : 1 ratio of **8** and DMAP·HCl in CDCl₃ (Fig. S2, ESI†). Rapid and quantitative deprotonation of the DMAP conjugate acid was observed using ¹H NMR spectroscopic methods, indicating a substantial difference in basicity between the two catalysts.

Given the formation of the bis-protonated analogue of **8** in the experiment outlined above, we investigated if it was possible to form such species under the reaction conditions. Accordingly, we added substrate thiol **3** to **8** and monitored the interaction using ¹H NMR spectroscopy (Fig. S9, ESI†). At equimolar levels only traces of porphyrin protonation were detected, however at 10 fold excess of **3** the starting material disappeared and N–H resonances tentatively assigned to both mono- and bis-protonated **8** were observed, with mono-protonation being dominant. Increasing the excess of thiol to those present at the outset of the catalytic process gave rise to significantly more bis-protonated material, which becomes the major product at a substrate : catalyst ratio of 100 : 1 and the sole discernible porphyrin species present at a ratio of 200 : 1.

This strongly supports a specific catalysis-like mechanism (see 25, Fig. 2), in which a porphyrin-thiolate ion-pair is catalytically relevant. Given that all porphyrin catalysts evaluated required at least one N–H unit in its free base form to be active, it also seems likely that activation by the electrophile H-bond donation *via* at least two N–H units (one formed *via* protonation of the porphyrin by substrate thiol **3**) is a feature of the catalysis, *i.e.* the system is bifunctional. It is unclear at this juncture whether the mono- or bis-protonated cationic porphyrin species (or both) are catalytically competent; however, based on NMR data (see ESI†), it appears likely that the mono-protonated



species is the dominant catalyst in solution at both low and high reaction concentration.

In conclusion, we showed that free base and *N*-substituted porphyrins display catalytic activity in sulfa-Michael reactions and suggest a bifunctional mechanism involving porphyrin amine and imine groups. Distortion and availability of pyrrolic protons appear to be crucial for the catalytic activity. We envisaged that while appropriately designed distorted porphyrins had potential to act *via* either pathway (*i.e.* **24** or **25**, Fig. 2), in view of the 'saddle' nature of distorted porphyrins and the experimental data, they appeared to be more amenable to act *via* the specific-catalysis-type mechanism **25**, in which porphyrin protonation allows the catalyst's nucleophile- and electrophile-activating units to reside on the same catalyst hemisphere in an orientation conducive to synergistic cooperation. Studies on the concept of activation, mechanism and structural correlations of an incremental increase of distortion are currently under way.

This work was supported by a grant from Science Foundation Ireland (SFI IvP 13/IA/1894) and the School of Chemistry, TCD.

Conflicts of interest

There are no conflicts to declare.

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- 28 Nonplanar, saddle-distorted porphyrins show a bathochromic shift of the absorption bands.^{2,6}
- 29 Conformational issues may also impact here, however, **20** is likely to be more distorted than **16**.

