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FULL PAPER

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*p*H-Switchable Aqueous Organocatalysis with Amphiphilic Secondary Amine–Porphyrin Hybrids

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We dedicate this paper to the memory of Kilian Muñiz

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Abstract: A series of amphiphilic 5-(cyclic-secondary-amine)-10,15,20-tris(4-sulfonatophenyl)porphyrins, designed with the aim of using the amphiphilic porphyrin moiety for the modulation of the aggregation state of the compound by the pH of the medium, have been synthesised, and the relationship between their supramolecular behaviour in acidic aqueous media and their organocatalytic activity in Michael and aldol reactions has been investigated. In particular, we have found that the catalytic activity of the pyrrolidine moiety in an amphiphilic isoindoline–porphyrin hybrid for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde can be selectively and reversibly switched on and off by adjusting the homogeneity of its solutions through pH variations. The catalysis of the aldol reaction by the secondary amine moiety would otherwise take place regardless of the pH of the medium. We have demonstrated that the aggregation behaviour of these amine–porphyrin hybrids can be also used for the recovery and reutilization of the catalysts.

Introduction

Catalysis is a key concept in contemporary chemistry, with far-reaching implications in several fields ranging from molecular biology to the sustainable large-scale synthesis of drugs, agrochemicals or functional materials. While in the past four decades impressive advances with regard to catalytic efficiency and enantioselectivity have been achieved, we are still far from the exquisite degree of activity modulation by external stimuli exhibited by enzymatic catalytic systems. It is therefore not surprising that the emerging field of artificial switchable catalysis has recently become the object of much attention.[1,2]

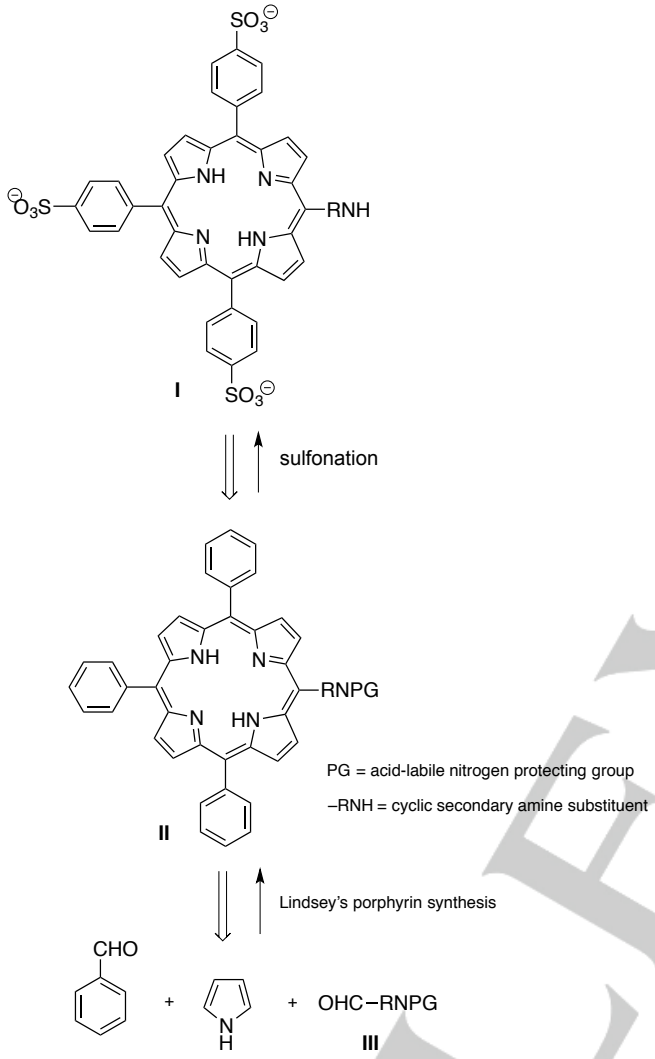
Intertwined chemical reaction networks may lead to the emergence of complex behaviour and new unprecedented properties in dissipative systems which can be kept out of chemical equilibrium.[3] These chemical systems can be amenable to external control if some of their component parts can be reversibly switched on and off by means of an external stimulus. Amphiphilic *meso*-(4-sulfonatophenyl)porphyrins constitute one of the simplest systems exhibiting this type of behaviour. In aqueous solutions at acidic pH, typically at values below 4.8, the protonation of the central pyrroleninic nitrogen atoms triggers the formation of the so-called J-aggregates[4] by the switching on of ion-pair contacts between the cationic porphyrin centres and the anionic sulfonate groups of the periphery. We have recently found that the J-aggregates derived from amphiphilic porphyrins behave as anionic heterogeneous co-catalysts in aqueous reactions mediated by cyclic secondary amines and taking place *via* an iminium activation pathway.[5] We envisaged next that by covalently binding a cyclic secondary amine with a 4-sulfonatophenylporphyrin moiety we could modulate the organocatalytic properties of the resulting hybrid structure in aqueous aminocatalytic reactions that are usually assumed to take place through enamine intermediates.[6] In particular, we reasoned that the catalytic activity of the cyclic secondary amine moiety might be indirectly regulated by varying the pH value of the medium, resulting in the aggregation/deaggregation state of the hybrid and allowing in this way the switching off of its catalytic activity at a pH value in which the cyclic amine unit would otherwise be catalytically active. It is worth noting here that although the modulation of catalytic activity or selectivity by the formation of self-assembled supramolecular systems has been the object of much attention in the past years,[7] the use of aggregation/dissociation properties to the reversible switching of the activity of synthetic catalysts still remains relatively scarce.[8]

Results and Discussion

Synthesis of amphiphilic porphyrin-piperidine and porphyrin-pyrrolidine hybrids.

We envisaged that a general route for the target amine-porphyrin hybrids **I** would be provided by the following retrosynthetic analysis (Scheme 1). In the synthetic way, the proposed route involves in the first step a mixed-porphyrin synthesis directly from pyrrole, benzaldehyde and a suitable protected amino aldehyde **III** (in a 4:3:1 molar ratio that, considering similar reactivities for both aldehydes, should maximize the statistical yield of the desired mono-functionalized porphyrin **II**) by the well-known Lindsey method,[9] leading to a mixture of *meso*-

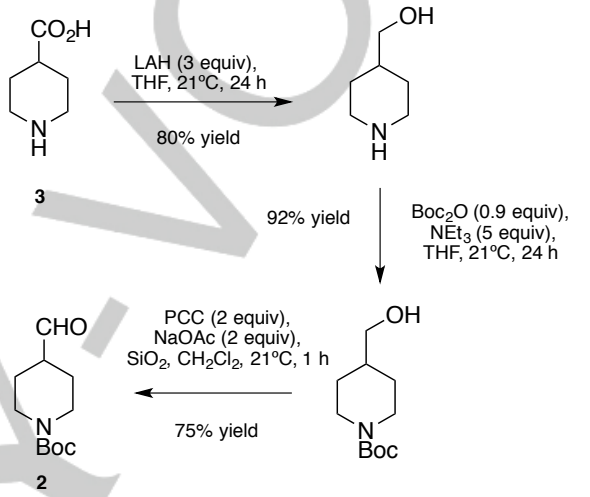
tetrasubstituted porphyrins from which **II** could be obtained after chromatographic purification. Sulfonation of this compound in the conditions used for the preparation of $TPPS_4$ (5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin)[10] would lead to the amphiphilic porphyrin **I** upon concomitant cleavage of the amine protecting group.



Scheme 1. General synthetic route to the amphiphilic porphyrin-secondary amine hybrids **I**

We first tried to implement this procedure in the synthesis of 5-(4-piperidyl)-10,15,20-tris(4-sulfonatophenyl)porphyrin (**1**). In this case, the known starting aldehyde **2**, in which the amine group is protected as a *t*-butylcarbamate, was readily prepared from commercial isonipecotic acid **3** by the modification of a previously described procedure,[11] in which the final oxidation step was performed by pyridinium chlorochromate (Scheme 2).

The mixed condensation of **2** (1 molar equivalent) with benzaldehyde (3 molar equivalents) and pyrrole (4.3 molar equivalents) in dichloromethane solution, in the presence of a catalytic amount of boron trifluoride etherate, followed by the *in situ* oxidation of the porphyrinogen ring by *p*-chloranil, led to the formation of the corresponding mixture of porphyrins, from which the desired 5-(*N*-Boc-4-piperidyl)-10,15,20-triphenylporphyrin **4** could be isolated in 6% yield (14% of the 42% theoretical statistical yield for the product with the A_3B substitution pattern; see Supporting Information), after two consecutive chromatographic purifications (silica gel). Small amounts of the two possible regioisomeric piperidyl-disubstituted porphyrins (5,10 and 5,15) were also isolated after further chromatographic purification. It is worth noting that the use of acetamide as the nitrogen protecting group of piperidin-4-methanol resulted in the complete failure of the mixed condensation reaction, probably due to the relatively higher basicity of the acetamide oxygen, that did not allow the activation of the formyl group by boron trifluoride.

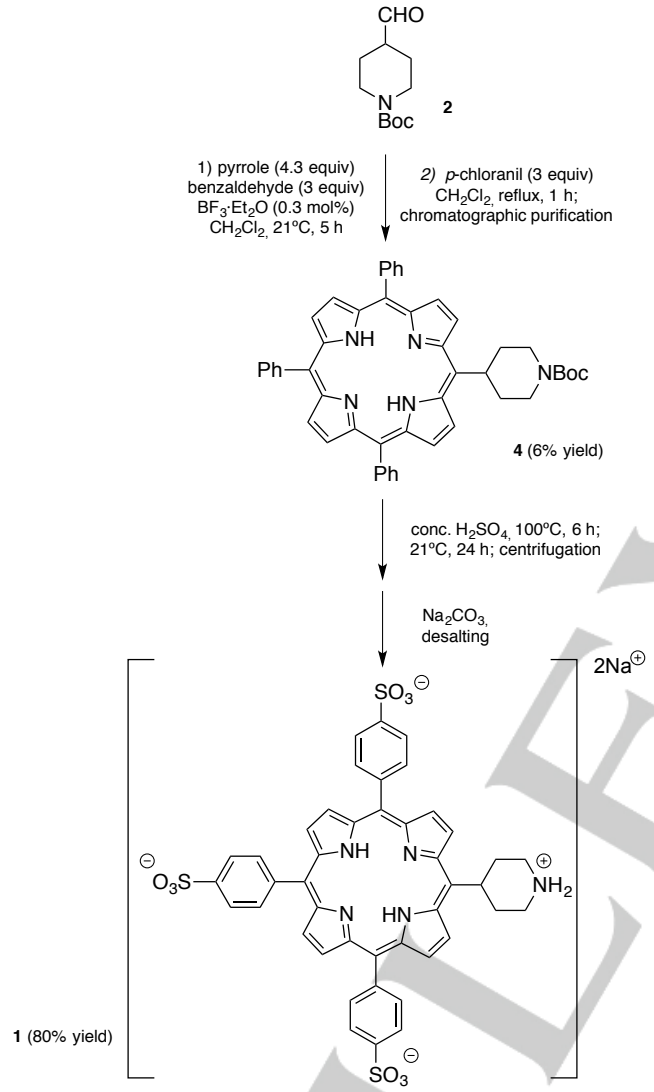


Scheme 2. Preparation of *N*-Boc-4-formylpiperidine **2**.

The sulfonation of **4** (concentrated H_2SO_4, 100ºC, 6 h; 21ºC, 24 h) took place as expected together with the cleavage of the *t*-butyl carbamate moiety. Isolation of the product was facilitated by the insolubility of the porphyrin aggregate in acidic medium; after centrifugation, neutralization of the wet precipitate with sodium carbonate and desalting by reverse-phase chromatography with a polyaromatic adsorbent resin (eluting with water/methanol mixtures), the disodium salt of the sulfonated porphyrin **1** was obtained in 80% yield after evaporation of methanol, concentration and lyophilization (Scheme 3). Note that although after basification with sodium carbonate the trisodium salt of **1** is the predominant species in solution, the purification by medium pressure reverse phase column chromatography should afford the dianionic form of **1**, in which the secondary amine nitrogen is protonated. Support for this hypothesis was provided by the observation that the purified compound did not show basic hydrolysis (a pH of 6.7 was measured for a 0.01M aqueous solution of **1**). On the other hand, HPLC analysis of this compound revealed that *meta*-sulfonated products were formed in very minor amounts (see Supporting Information).

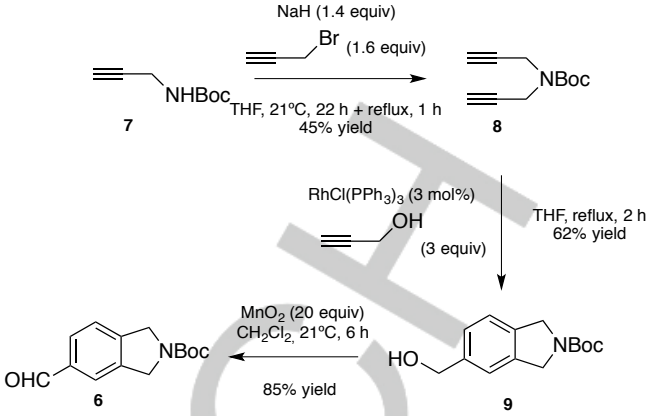
Taking into account the superior catalytic performance (with respect to that of piperidine derivatives) exhibited by the five-membered pyrrolidine ring,[12] we attempted next the synthesis of the (5-isoindolyl)-substituted amphiphilic porphyrin **5**. The required *N*-Boc-5-formylisoindoline **6** was prepared according to literature precedent (Scheme 4).[13]

Treatment of *N*-Boc propargylamine **7** (obtained in quantitative yield by reaction of propargyl amine with di-*t*-butyldicarbonate) with NaH and propargyl bromide gave the *N*-Boc-4-aza-1,6-heptadiyne **8** in 45% yield, after chromatographic purification. Rhodium(I)-catalysed cycloaddition with propargyl alcohol afforded the *N*-Boc-5-hydroxymethylisoindoline **9** in 62% yield, that upon oxidation with manganese dioxide was cleanly converted (85% yield) into the isoindoline-derived aldehyde **6**.

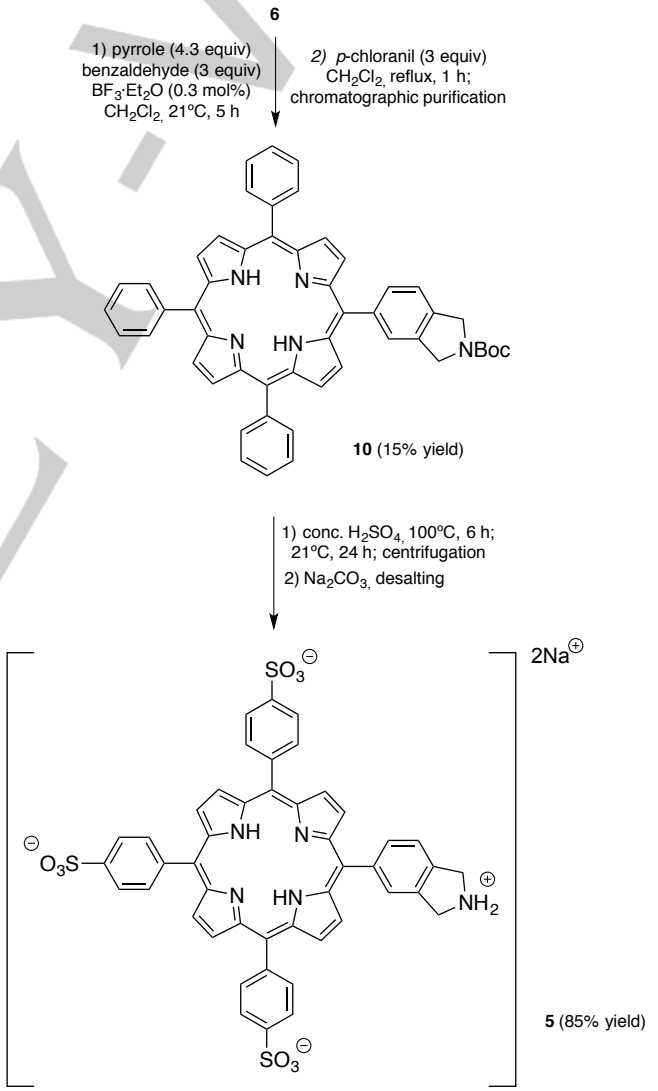


Scheme 3. Preparation of 5-(piperidin-1-ium-4-yl)-10,15,20-tris(4-sulfonatophenyl)porphyrin disodium salt **1**.

Aldehyde **6** was submitted to the mixed porphyrin synthesis protocol in the same conditions that those described above for **4** (see Scheme 3), affording 5-(*N*-Boc-5-isoindolyl)-10,15,20-triphenylporphyrin **10** in a remarkable 15% yield (36% of the 42% theoretical statistical yield); the subsequent sulfonation/deprotection/neutralization/desalting sequence took place uneventfully, providing the isoindoline-amphiphilic porphyrin hybrid **5** (as the disodium salt) in 85% yield (Scheme 5).



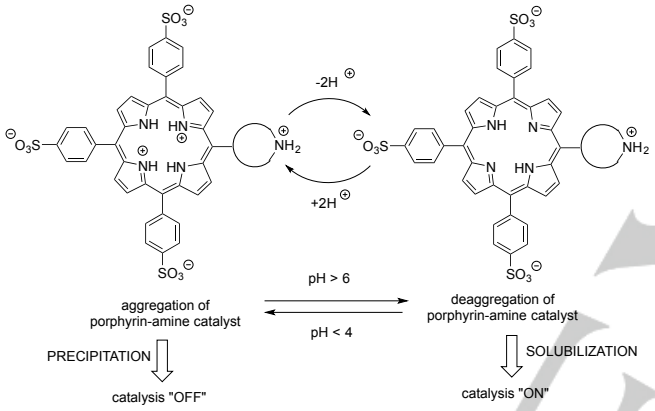
Scheme 4. Preparation of *N*-Boc-5-formylisoindoline **6**.



Scheme 5. Preparation of 5-(isoindolin-2-ium-5-yl)-10,15,20-tris(4-sulfonatophenyl)porphyrin disodium salt **5**.

Aggregation behaviour of the amphiphilic piperidine and porphyrin-isoindoline hybrids 1 and 5.

It is currently well established that *meso*-disubstituted porphyrins with 4-sulfonatophenyl groups at opposite methine bridges, in acidic aqueous media form supramolecular H- and J-aggregates stabilized by hydrophobic effects between the π-systems of the aromatic part of the macrocycle, together with electrostatic and hydrogen bond interactions.[4,14] In this regard, both porphyrins **1** and **5** have the correct substitution pattern that should enable a network of strongly stabilizing interactions between the negatively charged peripheral sulfonate groups (pK_a<0) and the protonated pyrroleninic protons of the porphyrin inner core. On the other hand, the free-base form of the porphyrin is unable to aggregate and it should thus remain in solution even at the high concentrations of the hybrids required for catalysis (Scheme 6). Therefore, we planned to take advantage of this pH-dependent solubility of the porphyrin hybrids **1** and **5** as a tentative way to regulate their catalytic activity through the homogeneity of their solutions.



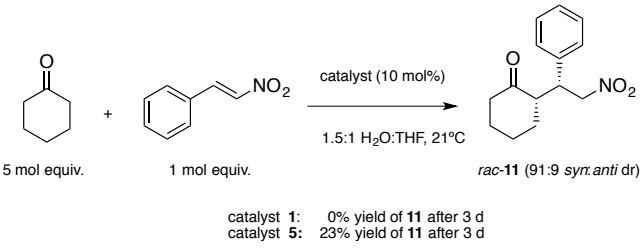
Scheme 6. pH-switchable catalysts based on *in situ* aggregation/dissociation.

Since the porphyrin aggregation necessarily takes place when the inner core of the porphyrin is fully protonated, as a first step we set out to determine the pK_a values of hybrids **1** and **5** by the standard spectrophotometric procedure.[15] Owing to the fact that the first protonation of the porphyrin inner core often facilitates the entrance of a second proton, the basicity of both pyrroleninic nitrogen atoms may be quite similar and, hence, the porphyrin (pK_{a1} + pK_{a2})/2 mean value was experimentally measured. We found a very small difference of pK_a values between porphyrins **1** and **5**, 4.56 and 4.51 ± 0,02 respectively (see Supporting Information, Figures ESI-3,4). This small difference was experimentally reproducible when the titrations were repeated several times, preparing in each case fresh solutions of all reagents. It is worth to note that the pK_a values of the hybrids do not differ substantially from that of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin, which has a pK_a of 4.85.[16] The slightly lower pK_a value for compounds **1** and **5** compared to their *meso*-tetrasulfonatophenyl counterpart can be attributed to a small destabilizing electrostatic effect of their acidic forms as a consequence of the additional positive charge due to protonation of peripheral amino group of the catalytically-active substituents. Once established that the acidity of the hybrids was suitable for our purposes, we then studied their aggregation behaviour. In order to quantitatively compare the homoassociation tendency of hybrids **1** and **5** we registered their UV-Vis spectra in solutions of increasing concentration under comparable conditions of aqueous HCl 0.1M (see Supporting Information). The presence of aggregation can be conveniently monitored through the appearance of a red-shifted J-aggregate band, compared to that of the free-base monomer (see Supporting Information, Figures ESI-5,6).[17] It turned out that both hybrids **1** and **5** form self-assembled structures at critical concentrations of the order of 10^{-7} M, being **5** slightly less prone to aggregation than **1**. These low critical concentration values, at least two order of magnitude smaller than that of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin ($TPPS_4$),[18] along with the higher tendency of the hybrids to flocculate, can be explained by their zwitterionic nature in acidic media. In effect, each porphyrin moiety in either **1** or **5** has three peripheral negatively charged sulfonate groups plus two positive charges at the centre of the ring, in addition to the protonated cyclic amine moiety, and in their zwitterionic form the monomers are electrically neutral (while the zwitterionic $TPPS_4$ monomer has a global negative charge of two units, so that two countercations per unit are required to stabilize the J-aggregate structure). Summing up, total flocculation of hybrids **1** and **5** in water can be conveniently fostered with variations of the pH values in a range which may be of significance for catalytic studies: i.e. at pH values ranging from 3.5 to 7.00 and at the high concentrations of the porphyrin needed for catalytic studies, the homogeneity of the system can be reversibly switched by varying the pH value of the medium. Altogether, the above results point to the fact that hybrids **1** and **5**, can indeed be, in principle, good candidates for our objective.

Aqueous organocatalysis with the amphiphilic porphyrin-piperidine and porphyrin-pyrrolidine hybrids 1 and 5.

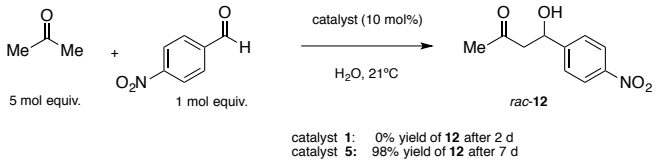
The enamine-mediated Michael addition of cyclohexanone to 2-nitrostyrene is an organocatalytic reaction that has been the object of several studies in aqueous media, although up to now only amphiphilic or heterogeneous catalysts have been used.[19,20] We began our study by evaluating the catalytic efficiency of the water-soluble amphiphilic porphyrin hybrids **1** and **5** in this process.

On the first place, we observed that addition of THF to the aqueous solution in order to increase the solubility of 2-nitrostyrene in the reaction medium was necessary for the reaction to proceed at an appreciable rate. Under these conditions, only the isoindoline-derived porphyrin **5** showed some catalytic activity, affording a mere 23% yield of the Michael adduct **11** (in a 91:9 *syn*:*anti* diastereomeric ratio) after three days at 21ºC (Scheme 7).



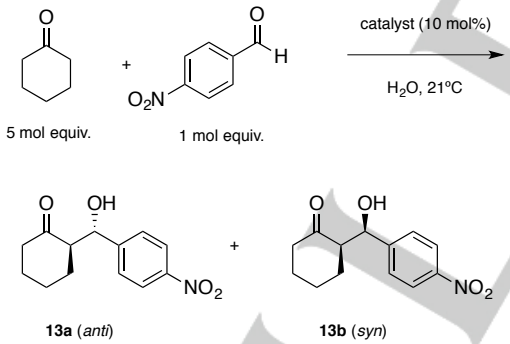
Scheme 7. Catalysis of the aqueous Michael addition of cyclohexanone to 2-nitrostyrene by the amine-porphyrin hybrids **1** and **5**.

We examined next the behaviour of these two organocatalytic porphyrins in the aqueous aldol addition of acetone to 4-nitrobenzaldehyde.[21] While both aqueous piperidine and isoindoline were able to catalyse this reaction in the presence of *p*-toluenesulfonic acid, the piperidine-porphyrin hybrid **1** again did not show any catalytic activity, in neutral conditions (pH 6.7); on the other hand, the use of the isoindoline-derived porphyrin **5** allowed the reaction to proceed in excellent yield, although 7 days were needed to achieve complete conversion (Scheme 8).



Scheme 8. Catalysis of the aqueous aldol reaction between acetone and 4-nitrobenzaldehyde by the amine-porphyrin hybrids **1** and **5**.

Finally, we were pleased to find that the well-known aldol addition of cyclohexanone to 4-nitrobenzaldehyde[22] could be efficiently catalysed (at neutral pH) by both amine-porphyrin hybrids and was therefore suitable for a more in-depth investigation of the aqueous organocatalytic behaviour of the amphiphilic amine-porphyrin hybrids. We studied first the catalytic ability both of piperidine and of the amphiphilic hybrid porphyrin **1** in aqueous solution, at different pH values (Scheme 9 and Table 1). The reactions were performed in the conditions previously described by Jiang *et al*. for aqueous tryptophan catalysis (1 mL of water, 0.5 mmol of cyclohexanone, 1 mmol of aldehyde, 0.01 mmol of catalyst, 21ºC).[23]



Scheme 9. Aqueous aldol reaction of cyclohexanone with 4-nitrobenzaldehyde.

Piperidine did not show any catalytic activity in aqueous acidic media (entries 1 and 2 in Table 1), but when the reaction was performed in neutral conditions (pH 6.7, entry 3) a *ca*. 70:30 *anti*:*syn* mixture of the aldols **13a**,**b** was obtained in essentially quantitative yield after 5 h. A similar reactivity profile with regard to pH was obtained with the amphiphilic piperidine-porphyrin hybrid **1**: the heterogeneous J-aggregate suspension obtained at pH values below 4.5 (entries 4 and 5 in Table 1) did not exhibit any catalytic activity, even after extended reaction times (5-7 days at 21ºC), but under neutral pH the aldol reaction was essentially complete after 8 h at 21 ºC, with an *anti*:*syn* ratio very similar to that obtained for piperidine alone (entry 6 in Table 1).

Table 1. Catalysis of the aqueous aldol reaction of cyclohexanone with 4-nitrobenzaldehyde by piperidine and by the amphiphilic porphyrin **1.**

Entry	Catalyst[a]	pH[b]	Time[c]	% Yield[d]	**13a**:**13b**[e]
1	piperidine	3.6	5 d[f]	0	–
2	piperidine	4.0	5 d[f]	0	–
3	piperidine	6.7	5 h	100	68:32
4[g]	**1**	3.6	7 d[f]	0	–
5	**1**	4.0	5 d[f]	0	–
6[h]	**1**	6.7[i]	8 h	100	66:34

[a] 10 mol% of the catalyst (relative to 4-nitrobenzaldehyde) was used in all instances. [b] Measured for 0.1 M AcOH/NaOAc buffer solutions. [c] Time necessary for total conversion of the aldehyde (entries 3 and 6), monitored by TLC. [d] Isolated yield of racemic aldol (**13a**+**13b**) after chromatographic purification. [e] Determined by ^{1}H NMR (400 MHz) of the reaction crude before chromatographic purification. [f] No reaction was observed after 5 days (entries 1, 2, 5) or after 7 days (entry 4). [g] The same results (no reaction after 7 d at 21ºC) were obtained when the reaction was performed in the presence of THF (10% v/v) or of surfactant (SDS). [h] Both the yield and the dr of the product remained unchanged after 6 d of reaction. [i] A pH of 6.7 was measured for an aqueous 0.01 M solution of **1**.

We turned then our attention to the amphiphilic isoindoline-porphyrin hybrid **5**, hoping that the higher catalytic efficiency of the pyrrolidine moiety would finally allow for a differentiated pH-dependent behaviour between the amine and the corresponding porphyrin hybrid (Table 2). As it can be seen in the first two entries of the Table 2, isoindoline is able to catalyse the aqueous aldol addition both at acidic (entry 1) and at neutral (entry 2) pH, but the corresponding amphiphilic porphyrin hybrid **5** is only active in neutral conditions (entry 4), due to the very low solubility of the aggregate at pH 3.6 (entry 3 in Table 2).

Table 2. Catalysis of the aqueous aldol reaction of cyclohexanone with 4-nitrobenzaldehyde by isoindoline and by the amphiphilic porphyrin **5.**

Entry	Catalyst[a]	pH[b]	Time[c]	% Yield[d]	**13a**:**13b**[e]
1	isoindoline	3.6	1 d	97	84:16
2	isoindoline	6.7	4 h	98	94:6
3	**5**	3.6	8 d[f]	0	–
4	**5**	6.7[g]	6 h	99	93:7

[a] 10 mol% of the catalyst (relative to 4-nitrobenzaldehyde) was used in all instances. [b] Measured for 0.1 M AcOH/NaOAc buffer solutions. [c] Time necessary for total conversion of the aldehyde, monitored by TLC. [d] Isolated yield of racemic aldol (**13a**+**13b**) after chromatographic purification. [e] Determined by ^{1}H NMR (400 MHz) of the reaction crude before chromatographic purification. [f] No reaction was observed after 8 days at 21ºC. [g] A pH of 6.7 was measured for an aqueous 0.01 M solution of **5**.

Thus, the results in Table 2 demonstrate that the catalytic activity of the pyrrolidine moiety in the amphiphilic isoindoline-porphyrin hybrid **5** can be selectively turned on and off at will by adjusting the homogeneity of its solutions through pH variations under bespoke conditions of reactivity and aggregation in which catalysis would otherwise take place, regardless of the pH of the reaction media.

Reuse and recovery of the catalysts.
Taking into account the very high solubility of the trisodium salts of the amphiphilic porphyrin hybrids **1** and **5** in neutral water, we investigated the possibility of their direct reutilization in aqueous solution. To that end, we performed the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in neutral water in the presence of **5** (10 mol%), and after 6 h the aldol adducts mixture and the excess of cyclohexanone were extracted by washing thrice with dichloromethane, and the resulting aqueous phase containing the catalyst was charged again with the reagents. This process was performed iteratively 5 times, but we observed a substantial decrease of the catalytic activity of the solution already in the third cycle (from 99% yield in the first cycle to only 6% yield in the third one). We were pleased to find, however, that after extraction of the organic products, acidification of the aqueous phase with sulfuric acid followed by centrifugation of the highly insoluble porphyrin aggregate, the disodium salt of **5** was recovered in *ca.* 80% yield (following removal of the excess acid by treatment with sodium carbonate/sodium hydrogen carbonate, desalting and lyophilization). The resulting purple solid was indefinitely stable at ambient temperature and in open air, retaining its full catalytic activity. Similar results were obtained for the piperidine-derived hybrid **1**.

Conclusion

The results reported in this work using several different amphiphilic secondary amine-porphyrin hybrids demonstrate how, by taking advantage of the supramolecular behaviour of their 4-sulfonatophenyl-substituted porphyrinic component part, it is possible to selectively turn on and off their organocatalytic activity of in response to pH variations of the media: In neutral aqueous solutions the free-base form of the hybrids is highly soluble allowing organocatalysis to take place whereas in acidic conditions the porphyrinic protonated core of the hybrid leads to the formation of self-assembled structures through a well-studied supramolecular motif and, as a consequence, the hybrids flocculate and their catalytic activity is fully supressed. It is noteworthy that the pH-triggered deactivation of the catalyst is not related to the pH dependency of the catalysed reaction under study but rather to the homoassociation properties of the catalyst. A specific example that illustrates the sought effect has been presented: the catalytic activity of the pyrrolidine moiety in an amphiphilic isoindoline–porphyrin hybrid for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde can be selectively and reversibly switched on and off by adjusting the homogeneity of its solutions through pH variations. To the best of our knowledge these results constitute the first example in organocatalysis in which the activity of a catalyst can be conveniently regulated in a reversible way by modulating its aggregation state as a response to pH variations of the media. From a practical point of view, it is also worth noting that the catalyst aggregates can be easily separated from the reaction products by centrifugation, and that after neutralization and desalting, the free-base forms of the sulfonated amine-porphyrin hybrids, retaining their full catalytic activity, can be recovered in high yield.

Experimental Section

Materials and methods

Commercially available reagents, catalysts, and solvents were used as received. Dichloromethane for porphyrin synthesis was distilled from CaH_2 prior to use, and THF was dried by distillation from $LiAlH_4$. Water of Millipore Q quality (18.2 MW.cm, obtained from Milli-Q1 Ultrapure Water Purification Systems, Millipore, Billerica, MA) was used.

^{1}H (400 MHz) NMR spectra were recorded with a Varian Mercury 400 spectrometer. Chemical shifts (δ) are given in ppm relative to the peak of tetramethylsilane (δ = 0.00 ppm); coupling constants (*J*) are given in Hz. The spectra were recorded at room temperature. TMS served as an internal standard. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. IR spectra were obtained in a Nicolet 6700 FTIR instrument, using ATR techniques. UV-vis spectra were recorded on a double-beam Cary 500-scan spectrophotometer (Varian); cuvettes (quartz QS Suprasil, Hellma) cm were used for measuring the absorption spectra. The porphyrin solutions in water were carefully degassed by gentle bubbling a nitrogen gas stream prior to the spectrophotometric measurement. pH measurements were performed on a CRISON Micro pH 2000 pH-meter (Crison 52-04 glass electrode) at room temperature. The pH-meter was calibrated prior to each measurement with buffers at pH=7.00 and 4.00 (Metrohm). Thin-layer chromatography was carried out on silica gel plates Merck 60 F_{254}, and compounds were visualized by irradiation with UV light. Flash column chromatography was performed using silica gel Merck 60 (particle size: 0.040 – 0.063 mm).

The HPLC analyses of the sulfonated porphyrins were performed on a Shimadzu high-performance liquid chromatograph equipped with two LC-10AS pumps, a Shimadzu CBM controller, an analytical precolumn Resolve C18 (Waters), and a Nucleosil 120-5C18 analytical column, using an elution gradient consisting of a mixture of methanol and tetrabutylammonium phosphate buffer (3 mmol·L^{-1}; pH=7.0) (1:1 v:v) to pure methanol over a period of 30 minutes at a flow rate of 0.6 mL min^{-1} (~2700 - 1050 psi). The elution profile was monitored at λ = 414 nm (UV-Vis detector SPD-6AV). Chiral HPLC analyses of aldol and Michael reaction products were performed on a Shimadzu instrument containing a LC-20-AD solvent delivery unit, a DGU-20AS degasser unit, and a SPD-M20A UV/VIS Photodiode Array detector, with chiral stationary phases (Daicel Chiralpak® IC and Phenomenex® i-cellulose-5 columns). All solvents were of HPLC grade and were carefully degassed prior to use. At time 0 the sample was injected.

N-Boc-protected aminoaldehydes **2**[11] and **6**[13] were obtained according to literature procedures (see Supporting Information for details).

Spectrophotometric titrations of the porphyrins. The (pK_{a1} + pK_{a2})/2 values of the diprotonated porphyrins were determined at 21ºC with an error of ±0.02 units of pK_a by monitoring the absorbance changes at a fixed wavelength (typically at an absorption maximum of one of the two species involved in the acid-base equilibrium) of micromolar solutions of the substance of identical concentration of the porphyrin at different pH values, which were prepared by the addition of small volumes (~0.2 mL) of a concentrated mother solution of the free-base porphyrin in water over solutions of acetic acid - sodium acetate buffers (10mL) of total

concentration 0.1 M. All titrations were experimentally reproducible when repeated several times, preparing in each case new fresh solutions of all the reagents. The porphyrin solutions in water were carefully degassed by gentle bubbling a nitrogen gas stream prior to the spectrophotometric titrations. The apparent pK_a values were then obtained from the Henderson-Hasselbach equation by graphic interpolation using the following expression: $(pKa_1 + pKa_2)/2 = pH + \log([diacid]/[base])$ where the ratio of acid to base in each solution was calculated, at a given wavelength, as: $[diacid]/[base] = (Abs_{base} - Abs)/(Abs - Abs_{diacid})$. All spectra used in the pK_a determinations showed accurate enough isosbestic points. The experimental numerical values and the regression plots for each porphyrin are presented in the Supporting Information.

Synthetic procedures and product characterization

General procedure for the mixed porphyrin synthesis.[9] Dry dichloromethane (380 mL/mmol *N*-Boc amino aldehyde) was introduced in a round-bottomed reaction flask equipped with magnetic stirring and a reflux condenser and purged for 15 min with nitrogen. The reaction flask was charged successively with the *N*-Boc amino aldehyde (1.0 equiv.), freshly distilled benzaldehyde (3.0 equiv.) and with freshly distilled pyrrole (4.0 equiv.). The resulting solution was stirred for 5 min at 21ºC and boron trifluoride etherate (0.40 equiv.) was added in one portion. Stirring was maintained for 3 h under nitrogen, after protecting the reaction flask from direct contact with light. At that point, *p*-chloranil (3.0 equiv.) was added, and the reaction mixture was heated to reflux for 1 h in open air. After cooling to 21ºC, most of the solvent was removed by rotary evaporation, taking care that the final volume is *ca*. 10 mL/mmol *N*-Boc protected amino aldehyde. This residue was submitted to chromatographic purification on silica gel, eluting with dichloromethane. A fraction containing 5,10,15,20-tetraphenylporphyrin (TPP) eluted first, followed by a more polar fraction containing a mixture of the amino-substituted porphyrins. This fraction was submitted to a second chromatographic purification on silica gel, eluting with dichloromethane/methanol mixtures of increasing polarity. In this way the target monosubstituted porphyrin was separated from the more functionalized porphyrins. Further purification can be achieved upon recrystallization from dichloromethane/hexane.

5-(*N*-Boc-4-piperidinyl)-10,15,20-triphenylporphyrin (4). Obtained in 6% yield (0.18 g, 0.25 mmol) from *N*-Boc-4-formylpiperidine **2** (0.88 g, 4.15 mmol) as a purple-coloured solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.59 (d, *J* = 4.9 Hz, 2H, C<u>H</u> pyrrole), 8.88 (d, *J* = 4.9 Hz, 2H, C<u>H</u> pyrrole), 8.78 (dd, *J* = 12.5 Hz, *J'* = 4.8 Hz, 4H, C<u>H</u> pyrrole), 8.21-8.16 (m, 6H, C<u>H</u> *o*-Ph), 7.82-7.70 (m, 9H, C<u>H</u> *m,p*-Ph), 5.45-5.32 (m, 1H, C<u>H</u>), 4.79-4.60 (m, 2H, C<u>H</u>$_2$-N), 3.43-3.27 (m, 4H, C<u>H</u>$_2$-N + C<u>H</u>$_2$), 2.74-2.63 (m, 2H, C<u>H</u>$_2$), 1.65 (s, 9H, C(C<u>H</u>$_3$)$_3$), -2.66 (br, 2H, pyrrole N<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 168.07, 142.53, 141.65, 139.10, 137.67, 134.54, 134.42, 131.60-130.91 (br, 4C), 128.86, 127.71, 127.66, 126.77, 126.56, 122.60, 119.70, 116.43, 114.61, 57.40, 53.40, 50.41, 45.08, 37.48, 30.91, 29.68, 28.63. **FTIR (ATR)**: ν = 3376, 1681, 1409, 1176, 1125, 882, 701 cm^{-1}. **UV-vis** [CH_2Cl_2, λ_{max} nm (ε, L·mol^{-1}·cm^{-1}), 3.75 x 10^{-5} M]: 418 (425000), 515 (16900), 550 (7200), 592 (4900), 648 (3900). **HRMS (ESI+):** *m/z* calcd. for $[M+H]^+$ $[C_{48}H_{44}N_5O_2]$ = 722.3495, found 722.3486.

5-(*N*-Boc-5-isoindolyl)-10,15,20-triphenylporphyrin (10). Obtained in 15% yield (0.21 g, 0.28 mmol) from *N*-Boc-4-formylisoindoline **6** (0.46 g, 1.90 mmol) as a purple-coloured solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.90-8.80 (m, 8H, C<u>H</u> pyrrole), 8.25-8.20 (m, 6H, C<u>H</u> *o*-Ph), 8.16-8.04 (m, 2H, C<u>H</u> Ar), 7.83-7.72 (m, 9H, C<u>H</u> *m,p*-Ph), 7.67-7.57 (m, 1H, C<u>H</u> Ar), 5.08-4.94 (m, 4H, C<u>H</u>$_2$-N), 1.61 (s, 9H, C(C<u>H</u>$_3$)$_3$), -2.77 (br, 2H, pyrrole N<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 154.75, 143.14, 142.13, 141.52, 141.47, 136.96, 136.61, 136.04, 135.70, 134.56, 133.82, 131.64-130.72 (br, 4C), 129.56, 128.82, 128.62, 127.74, 126.70, 120.96, 120.70, 120.27, 120.22, 119.56, 118.84, 52.53, 52.23, 29.71, 28.67, 28.64. **FTIR (ATR)**: ν = 3390, 1698, 1402, 1198, 1103, 883, 712 cm^{-1}. **UV-vis** [CH_2Cl_2, λ_{max} nm (ε, L·mol^{-1}·cm^{-1}), 3.90 x 10^{-5} M]: 418 (446000), 514 (18000), 550 (7600), 591 (5200), 645 (4000). **HRMS (ESI+):** *m/z* calcd. for $[M+H]^+$ $[C_{51}H_{42}N_5O_2]$ = 756.3260, found 756.3334.

General procedure for the sulfonation/deprotection of the mixed porphyrins.[10] In a round-bottomed flask, equipped with magnetic stirrer and a Dimroth reflux condenser capped with a calcium chloride tube, a stirred solution of the mixed porphyrin (1.0 mol equiv.) in concentrated (96% w/w) H_2SO_4 (20 mL/mmol porphyrin) was heated to 100ºC for 6 h. After stirring for 18 h at rt, water (2 mL/mL H_2SO_4) was carefully added dropwise and the resulting dark green suspension was centrifuged at 6000 rpm during 30 min. The supernatant was decanted, and the remaining sulfuric acid was neutralized with solid Na_2CO_3 to afford a purple-coloured solution. Inorganic salts were removed by medium pressure reverse phase column chromatography using MCI GEL CHP20P 75-150 μm (Diaion®, Supelco/Sigma-Aldrich, Billerica, MA, USA), in which the porphyrin is slightly retained thus allowing the elimination of inorganic salts using water as the eluent; increasing gradients of methanol (from 0% to 50%) conveniently eluted the porphyrin. Concentration of the sample by evaporation of the solvents under reduced pressure followed by lyophilization afforded the sodium salt of the sulfonated porphyrin as a purple-coloured solid.

5-(Piperidin-1-ium-4-yl)-10,15,20-tris(4-sulfonatophenyl)porphyrin disodium salt 1. Obtained in 80% yield (0.17 g, 0.20 mmol) from 5-(*N*-Boc-4-piperidinyl)-10,15,20-triphenylporphyrin **4** (0.18 g, 0.25 mmol) as a purple-coloured solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.05 (d, *J* = 5.0 Hz, 2H, C<u>H</u> pyrrole), 8.89 (d, *J* = 4.9 Hz, 2H, C<u>H</u> pyrrole), 8.83-8.73 (m, 4H, C<u>H</u> pyrrole), 8.18-8.13 (m, 6H, C<u>H</u> *o*-Ph), 8.08-8.02 (m, 6H, C<u>H</u> *m*-Ph), 5.75-5.64 (m, 1H, C<u>H</u>), 3.76-3.58 (m, 4H, C<u>H</u>$_2$-N), 3.56-3.46 (m, 2H, C<u>H</u>$_2$), 3.36 (br s, 1H, piperidine N<u>H</u>), 2.76-2.68 (m, 2H, C<u>H</u>$_2$), -2.87 (br, 2H, pyrrole N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) = 148.20, 148.14 142.24, 141.29, 134.18, 134.02, 132.70-131.82 (br, 4C), 124.77, 124.53, 123.25, 119.69, 119.55, 45.92, 41.58, 34.46. **FTIR (ATR)**: ν = 3437, 1624, 1177,1121, 1010, 736 cm^{-1}. **UV-vis** [H_2O, λ_{max} nm (ε, L·mol^{-1}·cm^{-1}), 3.62 x 10^{-5} M]: 413 (410000), 522 (14500), 560 (8700), 589 (5900), 647 (4100). **HRMS (ESI-):** *m/z* calcd. for $[M+2H]^{-}$ $[C_{43}H_{34}N_5O_9S_3]$ = 860.1519, found 860.1534. Calcd. for $[M+H]^{2-}$ $[C_{43}H_{33}N_5O_9S_3]$ = 429.5720 (*z* = 2), found 429.5739. Calcd. for M^{3-} $[C_{43}H_{32}N_5O_9S_3]$ = 286.0454 (*z* = 3), found 286.0477.

5-(Isoindolin-2-ium-5-yl)-10,15,20-tris(4-sulfonatophenyl)porphyrin disodium salt 5. Obtained in 85% yield (0.38 g, 0.40 mmol) from 5-(*N*-Boc-5-isoindolyl)-10,15,20-triphenylporphyrin **10** (0.35 g, 0.47 mmol) as a purple-coloured solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.92-9.76 (m, 2H, C<u>H</u> pyrrole), 8.89-8.84 (m, 4H, C<u>H</u> pyrrole), 8.82- 8.76 (m, 2H, C<u>H</u> pyrrole), 8.31-8.21 (m, 2H, C<u>H</u> Ar), 8.21-8.13 (m, 6H, C<u>H</u> *o*-Ph), 8.10-8.00 (m, 7H, 1C<u>H</u> + ArC<u>H</u> *m*-Ph), 7.86 (d, *J* = 7.9 Hz, 1H, C<u>H</u>-Ar), 4.92-4.80 (m, 4H, C<u>H</u>$_2$-N), 3.36 (br s, 2H, N<u>H</u> isoindoline), -2.92 (br, 2H, pyrrole N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) = 147.73, 144.08, 141.30, 135.17, 134.27, 133.74, 133.70, 132.04-130.82 br, 4C), 128.59, 124.24, 121.52, 120.74, 119.83, 119.76, 119.25, 50.33, 50.30. **FTIR (ATR)**: ν = 3403, 1618, 1178,1123, 1036, 736 cm^{-1}. **UV-vis** [H_2O, λ_{max} nm (ε, L·mol^{-1}·cm^{-1}), 3.37 x 10^{-5} M]: 413 (453000), 519 (15100), 557 (9200), 582 (6400), 642 (3700). **HRMS (ESI-):** *m/z* calcd. for $[M+2H]^{-}$ $[C_{46}H_{32}N_5O_9S_3]$ = 894.1362, found 894.1368. Calcd. for $[M+H]^{2-}$ $[C_{46}H_{31}N_5O_9S_3]$ = 446.5642 (*z* = 2), found 446.5647. Calcd. for M^{3-} $[C_{46}H_{30}N_5O_9S_3]$ = 297.3735 (*z* = 3), found 297.3741.

General procedure for the aqueous organocatalysis of the Michael addition of cyclohexanone to 2-nitrostyrene with the amphiphilic porphyrin-piperidine and porphyrin-pyrrolidine hybrids. A solution of the sulfonated amine-porphyrin hybrid (0.01 mmol) in a 1.5:1 water/THF mixture (0.20 mL) in a 10 mL round-bottomed flask was stirred at rt for 2 min; subsequently, cyclohexanone (49 mg, 0.50 mmol) and 2-nitrostyrene (15 mg, 0.10 mmol) were added sequentially, and the resulting suspension was stirred (open air conditions) at rt until complete consumption of the 2-nitrostyrene (TLC monitoring). After addition of more water (7 mL) the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and after filtration the organic solvent was eliminated *in vacuo*. Finally, the residue was purified by column chromatography in silica gel, eluting with 6:1 hexane/ethyl acetate.

(1'*R,2*S**)-2-(2-Nitro-1-phenylethyl)cyclohexan-1-one 11** (*syn*)**.**[19e] Yellow-coloured oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ (ppm) = 7.36-7.23 (m, 3H, C<u>H</u> Ph), 7.19-7.13 (m, 2H, C<u>H</u> Ph), 4.94 (dd, *J* = 12.5 Hz, *J'* = 4.5 Hz, 1H, C<u>H</u>H-NO_2), 4.64 (dd, *J* = 12.5 Hz, *J'* = 9.9 Hz, 1H, CH<u>H</u>-NO_2), 3.76 (td, *J* = 9.9 Hz, *J'* = 4.5 Hz, $1H_{syn}$, C<u>H</u>-Ph)*, 2.74-2.64 (m, 1H, C<u>H</u>-CO), 2.52-2.33 (m, 2H, C<u>H_2</u>-CO), 2.13-2.03 (m, 1H, C<u>H</u>H), 1.83-1.57 (m, 4H, (C<u>H_2</u>)$_2$), 1.30-1.18 (m, 1H, CH<u>H</u>).
*The minor *anti* isomer could be separated by chromatography and identified by the characteristic signal at 4.04-3.97 (m, $1H_{anti}$).

General procedure for the aqueous organocatalysis of aldol reactions with the amphiphilic porphyrin-piperidine and porphyrin-pyrrolidine hybrids.[22] An aqueous solution of the sulfonated amine-porphyrin hybrid (0.01 mmol) (Milli-Q water, 1 mL) in a 10 mL round-bottomed flask was stirred at rt for 2 min; subsequently, the donor ketone (0.50 mmol) and 4-nitrobenzaldehyde (0.10 mmol) were added sequentially, and the resulting suspension was stirred (open air conditions) at 21ºC until complete consumption of the aldehyde (TLC monitoring). After addition of water (10 mL) the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and after filtration the organic solvent was eliminated *in vacuo*. Finally, the residue was purified by column chromatography in silica gel, eluting with 1:1 hexane/ethyl acetate.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one 12.[23a] Yellow-coloured solid.

^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ (ppm) = 8.22 (d, *J* = 8.8 Hz, 2H, C<u>H</u> *o*-Ph), 7.54 (d, *J* = 8.7 Hz, 2H, C<u>H</u> *m*-Ph), 5.27 (dd, *J* = 8.1Hz, *J'* = 4.1 Hz, 1H, C<u>H</u>-OH), 3.55 (br s, 1H, O<u>H</u>), 2.87-2.83 (m, 2H, C<u>H_2</u>-CO), 2.22 (s, 3H, C<u>H_3</u>-CO).

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (13a, ***anti*** **+ 13b**, *syn***).**[24] Yellow-coloured solid.

^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ (ppm) = 8.25-8.18 (m, $2H_{anti}$, $2H_{syn}$, C<u>H</u> *o*-Ph), 7.54-7.47(m, $2H_{anti}$, $2H_{syn}$, C<u>H</u> *m*-Ph), 5.49 (t, *J* = 2.6 Hz, $1H_{syn}$, C<u>H</u>-OH), 4.90 (dd, *J* = 8.3 Hz, *J'* = 2.6 Hz, $1H_{anti}$, C<u>H</u>-OH), 4.06 (d, *J* = 3.0 Hz, $1H_{anti}$, O<u>H</u>), 3.15 (d, *J* = 3.0 Hz, $1H_{syn}$, O<u>H</u>), 2.67- 2.31 (m, $2H_{anti}$, $2H_{syn}$, 2C<u>H</u>-CO), 2.16-2.07 (m, $1H_{anti}$, $1H_{syn}$, C<u>H</u>-CO), 1.90-1.32 (m, $6H_{anti}$, $6H_{syn}$, (C<u>H_2</u>)$_3$).

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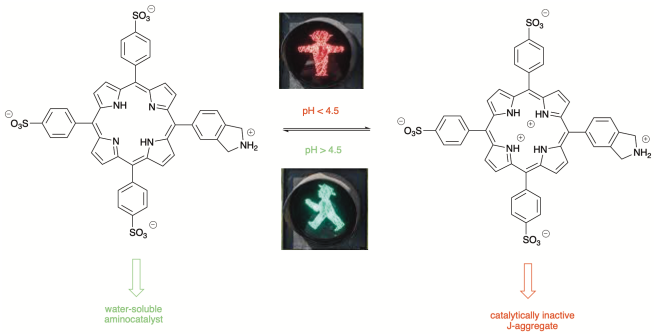
Entry for the Table of Contents

Key Topic: Switchable organocatalysis



A pH-sensitive, porphyrin-based "Ampelmännchen": The catalytic activity of an amphiphilic isoindoline–porphyrin hybrid for the aqueous aldol reaction can be selectively and reversibly switched *on* and *off* by modulating its aggregation state in water through the pH of the medium. In neutral solutions the anionic form of the hybrid is highly soluble, allowing aminocatalysis to take place, whereas in acidic conditions the protonated porphyrin core of the hybrid affords a highly insoluble, catalytically inactive J-aggregate.