Isothiocyanato-calix[4]phyrin-(1,*1*,*1*,*1*): a useful intermediate for the synthesis of derivatised anion sensors

Sushil C. Jha, Mark Lorch, Robert A. Lewis, Stephen J. Archibald* and Ross W. Boyle*

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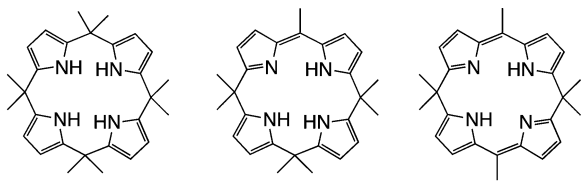
A calix[4]phyrin-(**1**,*1*,*1*,*1*) substituted with a 4-isothiocyanatophenyl group has been synthesised and used to attach the macrocycle to a solid support. The NCS group can also be used to further functionalise the calix[4]phyrin-(**1**,*1*,*1*,*1*) by reaction with amines and amino acids. Stability constants for anion binding by the calix[4]phyrin-(**1**,*1*,*1*,*1*) are reported and these show a clear ability to differentiate F^- and HSO_4^- from Cl^-, Br^-, I^- which can be detected by both NMR and UV–visible spectroscopy.

Introduction

The last decade has seen a growing interest in the chemistry of tetrapyrrolic macrocycles with mixtures of sp^2 and sp^3 carbon atoms bridging the four pyrroles. These molecules, which can be regarded as partially reduced porphyrins, have shown interesting properties as sensors for anions and neutral substrates.[1] The cation binding properties of these macrocycles have also been studied in detail.[2] This class of molecules as a whole is referred to as calixphyrins, with those containing four pyrrole rings being sub-classified as calix[4]phyrins[3] to differentiate them from the so-called "expanded" or hetero-calixphyrins, such as those introduced by Sessler *et al.*[4,5] Macrocycles in which four pyrroles are linked exclusively by sp^3 hybridised carbons are termed calixpyrroles.[6]



Calix[4]pyrrole Calix[4]phyrin(**1**,*1*,*1*,*1*) Calix[4]phyrin(**1**,*1*,**1**,*1*)

Perhaps the most studied property of these molecules has been their ability to bind anions, which can be exploited in sensing mode[7] or for purification/removal of anions from mixtures when bound to solid supports.[1] The majority of these studies have been performed on the calix[4]pyrroles, as these molecules present four hydrogens bound to pyrrolic nitrogens in a suitable orientation for interaction with the anionic species. Only one report, to our knowledge, has mentioned anion binding ability for the related calix[4]phyrin-(**1**,*1*,**1**,*1*)s, however this short communication[8] provided no stability constant data and reported qualitative changes in UV–visible spectra linked to mass spectral evidence for binding. In a further study, Sessler *at al.*[9] also attached calixpyrroles to silica gel by carbodiimide coupling and demonstrated their utility in HPLC separation of nucleotides, oligonucleotides, N-protected amino acids and perfluorinated biphenyls.

Few reports have appeared on calix[4]phyrin-(**1**,*1*,*1*,*1*),[3] and only recently have Kral *et al.*[10] published a rational synthesis of this class of calixphyrin bearing functional groups suitable for further modification. Here we present for the first time an efficient synthetic route to 4-isothiocyanatophenyl calix[4]phyrin-(**1**,*1*,*1*,*1*) and demonstrate how this molecule can be used as a common intermediate to generate a range of substituted derivatives. We also show that the isothiocyanato group allows facile attachment, without the requirement for carbodiimide activating groups, of the calix[4]phyrin-(**1**,*1*,*1*,*1*) to an amino substituted tentagel resin and demonstrate the ability of the resulting material to bind fluoride anions.

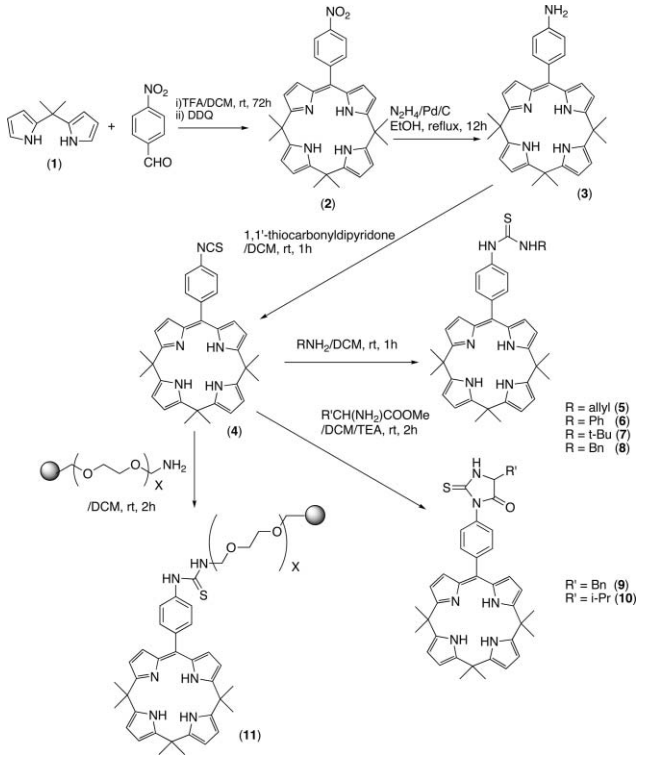
Results and discussion

In order to synthesise 4-isothiocyanatophenyl calix[4]phyrin-(**1**,*1*,*1*,*1*) (**4**), 5,5′-dimethyldipyrromethane (**1**)[11] was condensed with 4-nitrobenzaldehyde in the presence of trifluoroacetic acid to give 5-(4-nitrophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(**1**,*1*,*1*,*1*) (**2**) in 35% yield. The reaction mechanism involves partial "scrambling" of the dipyrromethane (**1**) as described by Kral *et al.*[10] Catalytic hydrogenation of **2** over palladium on charcoal gave 5-(4-aminophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(**1**,*1*,*1*,*1*) (**3**) in 90% yield. Finally, **3** was treated with 1,1′-thiocarbonyldi-2,2′-pyridone in dichloromethane to give 5-(4-isothiocyanatophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(**1**,*1*,*1*,*1*) (**4**) in 92% yield (Scheme 1).

In order to investigate the utility of **4** for generating a variety of functionalised calix[4]phyrin-(**1**,*1*,*1*,*1*)s, a small number of representative amines was selected and reacted by stirring in a 2 : 1 ratio with **4** at room temperature for 1 hour. All amines reacted as expected to give derivatives **5–8** (Scheme 1) in good to excellent yields (76–95%).

In addition to being an efficient group for reaction with amines to form covalent thiourea bonds under ambient conditions, isothiocyanates are also known to react with amino acids to give heterocyclic products. In order to investigate if this was a viable route to calix[4]phyrin-(**1**,*1*,*1*,*1*) heterocyclic conjugates, **4** was reacted with the methyl esters of phenylalanine and valine

Department of Chemistry, University of Hull, Kingston-upon-Hull, E. Yorks, UK HU6 7RX. E-mail: r.w.boyle@hull.ac.uk; Fax: +44 1482 466410; Tel: +44 1482 466353



Scheme 1 Synthesis and reactions of 5-(4-isothiocyanatophenyl)-10,15, 20-tris-(dimethyl)-calix[4]phyrin-(**1**,*1*,*1*,*1*).

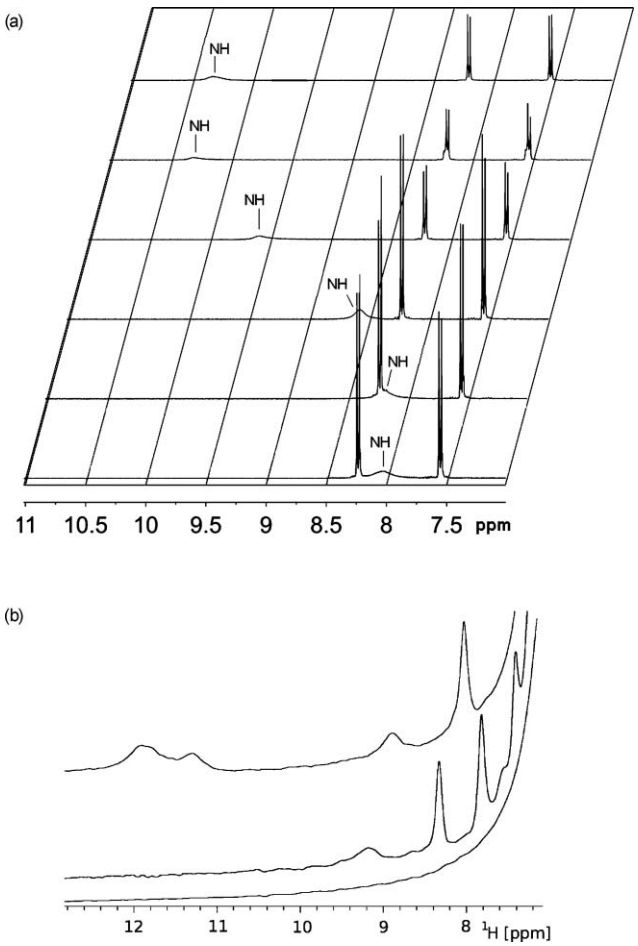


Fig. 1 (a) Partial ^{1}H NMR spectra for **2** showing effect of increasing concentrations of Bu_4NF (0, 0.25, 0.5, 1, 2, 4 equivalents from front to back); (b) ^{1}H magic angle spinning spectra of tentagel resin (lower), **11** (middle) and **11** in the presence of fluoride anions (upper). Upon addition of fluoride anions, peaks at 10.2 and 8.35 ppm are both shifted downfield by about 1.5 ppm. In an analogous situation to that seen in the liquid state spectra, peaks at 7.4 and 7.8 ppm are significantly broadened and shifted upfield by over 4 ppm. Spectra were collected at 500 MHz with 10 kHz sample spinning, at 293 K and externally referenced to TMS at 0 ppm. Spectra are the sum of 8 scans.

respectively. In both cases, efficient reaction occurred to give the corresponding thioxoimadazolidine derivatives **9**, **10** (Scheme 1) in 84 and 95% yields.

The chemistry of calix[4]pyrroles has been widely reported, along with their anion and neutral substrate binding properties; however, there are relatively few reports of the related calix[4]phyrin-(**1**,*1*,*1*,*1*) systems, probably due to the lack of efficient synthetic routes to this macrocycle. To our knowledge, there are no reports of anion binding by calix[4]phyrin-(**1**,*1*,*1*,*1*)s. We were therefore interested to determine if the calix[4]phyrin-(**1**,*1*,*1*,*1*) core, which is significantly structurally and electronically different from calix[4]pyrroles and calix[4]phyrin-(**1**,*1*,**1**,*1*), also possessed anion binding ability. A solution of the free base of **2** in CD_2Cl_2 was prepared and titrated with a solution of $Bu_4N^+F^-$ in CD_2Cl_2. Following the signal from the inner NH protons at 7.9 ppm as the number of equivalents of $Bu_4N^+F^-$ was increased showed a significant downfield shift, associated with formation of hydrogen bonding interactions between the anion and calix[4]phyrin-(**1**,*1*,*1*,*1*) core (Fig. 1a).

We have previously demonstrated that the isothiocyanato group can be used as an efficient conjugation "handle" for attaching porphyrins to solid supports.[12] It was therefore of interest to investigate if the structurally related 4-isothiocyanatophenyl calix[4]phyrin-(**1**,*1*,*1*,*1*) (**4**) could similarly be used to introduce anion binding ability to solid supports bearing amines. Tentagel S NH_2 was selected to investigate this potential application. **4** was stirred with the solid supported amine in dichloromethane for two hours at room temperature (Scheme 1). After filtration and washing of the resin, the conjugate (**11**) was investigated using diffuse reflectance UV–visible spectroscopy, which clearly showed the absorbance band at 470 nm associated with the chromophoric calix[4]phyrin(**1**,*1*,*1*,*1*) unit (Fig. 2).

Having successfully loaded **4** onto a solid support, it remained to investigate if the resin-bound **4** retained the ability to bind fluoride anions already demonstrated in solution. In order to ascertain this, a series of solid phase NMR experiments was performed with the conjugate (**11**) before and after addition of a soluble fluoride salt. Characteristic shifting in the peak at 7.8 ppm assigned to the inner NHs demonstrated the ability of **4** to bind fluoride anions after conjugation to a solid support (Fig. 1b).

In order to determine the relative binding properties of different anions to the calix[4]phyrin-(**1**,*1*,*1*,*1*), a CD_2Cl_2 solution of **2** was titrated with tetrabutylammonium fluoride, chloride, bromide and iodide, respectively, and chemical shift values were fitted using the WinEQNMR program.[13] Stability constants generated in this way clearly show that **2** binds fluoride, chloride and bromide, but not iodide; however, while minor differences in these values

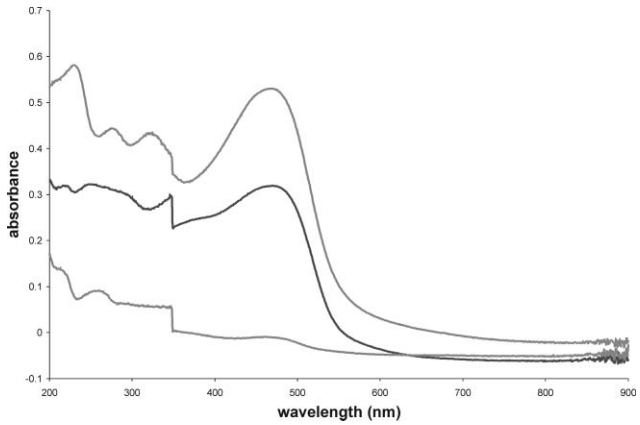


Fig. 2 Diffuse reflectance UV–vis. spectra of tentagel (lower), the isothiocyanate calixphyrin (upper) and the calixphyrin immobilized on tentagel (middle).

were seen for chloride and bromide, comparison with fluoride indicates binding for this anion that is approximately two orders of magnitude greater (Table 1). A non-halogen anion, hydrogen sulfate, was also investigated and this gave a stability constant of 0.689 M^{-1}.

Finally, it was of interest to determine whether the large difference in stability constants found for fluoride relative to the other halogens, combined with the optical properties of calix[4]phyrin-(**1**,*1*,*1*,*1*), could be used to discriminate between halogens using UV–visible spectroscopy. In order to investigate this, equimolar solutions of **2** were treated with excess tetrabutylammonium fluoride, chloride, bromide and iodide respectively. Molar absorptivities were then calculated at two wavelengths, 458 nm and 433 nm, corresponding to the λ_{max} for **2** before and after addition of fluoride (Fig. 3). Comparison of ε values at these two wavelengths, before and after addition of halogen anion to **2** (Table 1), indicates that fluoride undergoes a significantly larger decrease in this value (-3200 M^{-1} cm^{-1}) compared to chloride (-1000 M^{-1} cm^{-1}), bromide (-1100 M^{-1} cm^{-1}) and iodide (-900 M^{-1} cm^{-1}); this, combined with the 433 nm value, which for fluoride is virtually unchanged, suggests potential applications for calix[4]phyrins-(**1**,*1*,*1*,*1*) in ratiometric sensing of fluoride. Interestingly, treatment with tetrabutylammonium hydrogen sulfate resulted in a smaller, but significant, bathochromic shift (12 nm). The hypsochromic shift in absorption maxima, which only occurs for fluoride binding (25 nm) with calix[4]phyrin-(**1**,*1*,*1*,*1*) and bathochromic shift for hydrogen sulfate binding (12 nm) is in contrast to the behaviour for calix[4]phyrin-(**1**,*1*,**1**,*1*) as reported by Sessler *et al.*,[8] who observed no shift in λ_{max}, but rather a minor increase in absorption value for chloride and fluoride and no change for bromide; binding of iodide was not investigated.

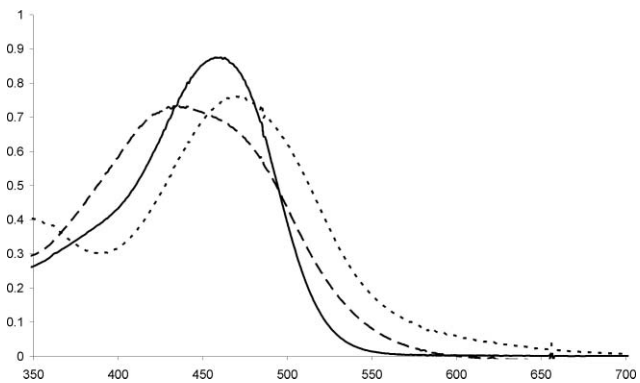


Fig. 3 UV–visible spectra of **2** before (solid) and after addition of tetrabutylammonium fluoride (dashed) and tetrabutylammonium hydrogen sulfate (dotted).

Table 1 Stability constants and UV–visible spectroscopic data for complexes of **2** with anions in CD_2Cl_2 at 293 °K

Anion	Stability constant/M^{-1}	$\Delta G°$/kJ mol^{-1}	ε (458 nm)	ε (433 nm)
None	—	—	14 400	11 700
F	63.9	−10.2	11 200	11 800
Cl	0.9	0.413	13 400	11 100
Br	0.4	2.41	13 300	10 900
I	0	0	13 500	11 500

Conclusions

In conclusion, we have demonstrated that the calix[4]phyrin-(**1**,*1*,*1*,*1*) core can be derivatised with an isothiocyanatophenyl substituent in excellent yield, and that this group is a versatile functional group, which can be used to attach a variety of amine bearing substituents, including amino presenting solid supports, and fabricate calix[4]phyrin-(**1**,*1*,*1*,*1*)s with attached heterocycles. We have also shown, for the first time, that the calix[4]phyrin-(**1**,*1*,*1*,*1*) macrocycle demonstrates significantly different stability constants for anion binding with fluoride compared to chloride, bromide and iodide and that this can be detected by both NMR and UV–visible spectrometry. Finally, the calix[4]phyrin-(**1**,*1*,*1*,*1*) core represents an interesting hydrid between calix[4]pyrrole, which binds anions but has no absorption in the visible spectrum, and calix[4]phyrin-(**1**,*1*,**1**,*1*), which absorbs light in the visible region, but shows no variation in wavelength of absorption on anion binding.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA-400 spectrometer and are referenced downfield to tetramethylsilane. Solid-state NMR measurements were performed on a Bruker Avance 500 at 500 MHz with 10 kHz sample spinning. UV–vis spectra were recorded on an Agilent 8453 UV–visible spectrophotometer. Accurate masses were obtained from the EPSRC Mass Spectrometry Service, Swansea, Wales. All commercial chemicals and solvents were of reagent grade or higher and were used as received, unless otherwise specified. All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a nitrogen atmosphere. TLC analyses were performed on Merck silica gel 60 plates (F_{254}, 0.2 mm thick). Flash column chromatography was performed with MP silica gel 60 (32–63) with all of the crude reaction mixtures being pre-adsorbed onto silica gel prior to separation, unless otherwise stated. All purified compounds were found to contain only one component by TLC analysis. Stability constants were determined by NMR using the WinEQNMR program.[13]

5-(4-Nitrophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (2). To a degassed solution of 5,5-dimethyldipyrromethane (2.65 g, 15 mmol) and *p*-nitrobenzaldehyde (1.13 g, 7.5 mmol) in CH_2Cl_2 (500 mL) under argon, was added TFA (0.11 mL, 1.5 mmol) and the mixture was stirred at RT for 72 h. DDQ (3.41 g, 15 mmol) was added, the reaction mixture stirred for 2 h and then filtered through a fritted funnel. The organic layer was washed with saturated aq. Na_2CO_3 solution (3 × 100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the crude residue was purified by silica gel column chromatography (hexane–EtOAc (5 : 1)) to give the product as a dark red solid (35%, 1.36 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 6.02 (t, 2H, J = 2.7 Hz, H_β), 6.08 (t, 2H, J = 2.7 Hz, H_β), 6.26 (d, 2H, J = 4.4 Hz, H_β), 6.35 (d, 2H, J = 4.4 Hz, H_β), 7.56 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.91 (br s, 3H, H_{NH}), 8.26 (d, 2H, J = 8.8 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.76, 28.94, 35.68, 37.08, 103.49, 104.35, 115.15, 122.71, 128.91, 131.51, 135.93, 136.14, 138.94, 139.16, 144.62, 165.98. HRMS(ESI): *calculated* 520.2707; *found* 520.2706.

5-(4-Aminophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (3). To a solution of **2** (0.26 g, 0.5 mmol) in ethanol (10 mL) were added hydrazine hydrate (1.5 eq.) and a catalytic amount of palladium on carbon. The reaction mixture was heated under reflux overnight, cooled and filtered through a pad of celite. The solvent was removed under vacuum and the residue purified by silica gel chromatography (CH_2Cl_2–EtOAc (9 : 1)) to give **3** as a red solid (90%, 0.22 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.64 (s, 6H, H_{Me}), 3.47 (br s, 2H, H_{NH2}), 5.99 (t, 2H, J = 5.9 Hz, H_β), 6.03 (t, 2H, J = 5.9 Hz, H_β), 6.34 (d, 2H, J = 4.2 Hz, H_β), 6.50 (d, 2H, J = 4.2 Hz, H_β), 6.63 (d, 2H, J = 8.4 Hz, H_{Ar}), 7.18 (d, 2H, J = 8.4 Hz, H_{Ar}), 11.58 (br s, 1H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.99, 29.09, 35.70, 37.08, 103.38, 104.10, 113.86, 114.04, 128.12, 129.58, 132.67, 138.94, 139.84, 147.12, 164.26. HRMS(ESI): *calculated* 490.2965; *found* 490.2959.

5-(4-Isothiocyanatophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (4). To a solution of **3** (0.24 g, 0.5 mmol) in CH_2Cl_2 (10 mL) was added 1,1′-thiocarbonyldi-2,2′-pyridone (TDP) (2 eq.) and the solution was stirred for 1 h. The solvent was removed under vacuum and the solid residue was purified by silica gel column chromatography (hexane–EtOAc (9 : 1)) to give **4** as a red solid (92%, 0.24 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 6.01 (t, 2H, J = 6.2 Hz, H_β), 6.06 (t, 2H, J = 6.2 Hz, H_β), 6.33 (d, 2H, J = 4.2 Hz, H_β), 6.35 (d, 2H, J = 4.2 Hz, H_β), 7.24–7.27 (m, 2H, H_{Ar}), 7.36–7.39 (m, 2H, H_{Ar}), 7.92 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.91, 29.01, 35.73, 37.13, 103.52, 104.31, 114.79, 124.84, 129.15, 131.59, 131.99, 136.14, 137.09, 137.64, 138.94, 139.64, 165.48. HRMS(ESI): *calculated* 532.2529; *found* 532.2525.

Reaction of 5-(4-isothiocyanatophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (4) with amines. To a solution of **4** (0.2 mmol) in CH_2Cl_2 (5 mL) was added amine (2 eq.) at RT with stirring. Progress of the reaction was monitored by TLC. Solvent was removed under vacuum and the crude solid purified by silica gel column chromatography to give the product in 76–95% yield.

Table 2

Entry	Substrate	*t*/h	Yield (%)
5	Allylamine	1	76
6	*t*-Butylamine	1	90
7	Benzylamine	1	95
8	Aniline	0.5	82

5. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 4.35 (t, 2H, J = 5.3 Hz, H_{CH2}), 5.21–5.26 (m, 2H, CH_2=), 5.91–5.96 (m, 1H, $H_{CH=}$), 6.01 (t, 2H, J = 3.1 Hz, H_β), 6.07 (t, 2H, J = 3.1 Hz, H_β), 6.22 (br s, 1H, H_{NH}), 6.35 (m, 4H, H_β), 7.25 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.45 (d, 2H, J = 8.1 Hz, H_β), 7.86 (br s, 1H, H_{NH}), 7.95 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.92, 29.01, 35.73, 37.13, 48.05, 103.51, 104.32, 114.76, 117.45, 123.54, 129.21, 132.68, 133.18, 136.15, 136.31, 137.74, 138.97, 139.68, 165.50, 180.76. HRMS(ESI): *calculated* 589.3108; *found* 589.3108.

6. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.65 (s, 6H, H_{Me}), 6.00 (t, 2H, J = 3.1 Hz, H_β), 6.05 (t, 2H, J = 3.1 Hz, H_β), 6.34 (d, 2H, J = 4.2 Hz, H_β), 6.39 (d, 2H, J = 4.2 Hz, H_β), 7.30–7.40 (m, 5H, H_{Ar}), 7.44–7.48 (m, 4H, H_{Ar}), 7.87 (br s, 1H, H_{NH}), 7.96 (br s, 1H, H_{NH}), 8.01 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.94, 28.99, 35.72, 37.11, 103.45, 104.27, 114.62, 115.15, 123.17, 125.42, 127.53, 129.45, 129.97, 131.87, 136.18, 136.71, 137.79, 138.31, 138.99, 139.67, 160.00, 179.63. HRMS(ESI): *calculated* 625.3108; *found* 625.3104.

7. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.56 (s, 9H, H_{Me}), 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 6.01 (t, 2H, J = 3.1 Hz, H_β), 6.06 (t, 2H, J = 3.1 Hz, H_β), 6.17 (br s, 1H, H_{NH}), 6.35 (m, 4H, H_β), 7.22 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.43 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.54 (br s, 1H, H_{NH}), 7.96 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.93, 28.98, 35.73, 37.13, 54.31, 103.51, 104.30, 114.72, 123.05, 129.20, 132.55, 136.16, 136.28, 137.11, 137.93, 138.97, 139.70, 165.43, 179.24. HRMS(ESI): *calculated* 605.3421; *found* 605.3422.

8. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.62 (s, 12H, H_{Me}), 1.65 (s, 6H, H_{Me}), 4.93 (d, 2H, J = 5.4 Hz, H_{CH2}), 6.00 (t, 2H, J = 3.1 Hz, H_β), 6.11 (t, 2H, J = 3.1 Hz, H_β), 6.32 (m, 4H, H_β), 6.44 (br s, 1H, H_{NH}), 7.22 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.30–7.36 (m, 5H, H_{Ar}), 7.41 (d, 2H, J = 8.2 Hz, H_{Ar}), 7.95 (br s, 3H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.91, 29.00, 35.73, 37.12, 103.50, 104.30, 114.73, 123.44, 127.69, 128.93, 129.24, 132.69, 136.14, 136.33, 137.15, 137.75, 138.97, 139.63, 165.46, 180.86. HRMS(ESI): *calculated* 639.3264; *found* 639.3259.

Reaction of 5-(4-isothiocyanatophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (4) with amino acids. To a solution of **4** (0.2 mmol) in CH_2Cl_2 (5 mL) was added amino acid–OMe–HCl (2 eq.) and NEt_3 (3 eq.) at RT with stirring. The progress of the reaction was monitored by TLC. A facile intramolecular cyclisation was observed *via* attack of amine nitrogen on the ester carbonyl to give a five membered thioxoimidazolidinone system. Solvent was removed under vacuum and the crude solid purified by silica gel column chromatography to give the product in 84–95% yield.

9. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 3.10 (dd, 1H, J = 14.0 Hz, 7.9 Hz, H_{CH2}), 3.37 (dd, 1H, J = 7.9, 3.9 Hz, H_{CH}), 3.73 (br, 2H, H_{NH}), 4.53 (dd, 1H,

$J = 7.9, 3.9$ Hz, H_{CH}), 6.01 (t, 2H, $J = 3.1$ Hz, H_{β}), 6.34 (d, 2H, $J =$ 4.2 Hz, H_{β}), 6.41 (d, 2H, $J = 4.2$ Hz, H_{β}), 7.12 (d, 2H, $J = 4.8$ Hz, H_{Ar}), 7.27–7.41 (m, 5H, H_{Ar}), 7.42–7.46 (m, 2H, H_{Ar}), 7.98 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.96, 29.03, 35.73, 37.13, 37.76, 60.87, 103.46, 104.27, 114.69, 127.17, 127.97, 129.16, 129.40, 129.68, 132.61, 134.20, 136.23, 138.06, 138.80, 138.97, 139.65, 165.39, 172.49, 183.42. HRMS(ESI): *calculated* 679.3214; *found* 679.3212.

10. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 (d, 3H, $J =$ 6.8 Hz, H_{Me}), 1.16 (d, 3H, $J = 6.8$ Hz, H_{Me}), 1.63 (s, 12H, H_{Me}), 1.66 (s, 6H, H_{Me}), 2.40 (m, 1H, H_{CH}), 4.04 (br, 2H, H_{NH}), 4.19 (d, 1H, $J = 3.9$ Hz, H_{CH}), 6.01 (t, 2H, $J = 3.1$ Hz, H_{β}), 6.06 (t, 2H, $J =$ 3.1 Hz, H_{β}), 6.34 (d, 2H, $J = 4.5$ Hz, H_{β}), 6.44 (d, 2H, $J = 4.5$ Hz, H_{β}), 7.32–7.35 (m, 2H, H_{Ar}), 7.48–7.52 (m, 2H, H_{Ar}), 7.98 (br s, 2H, H_{NH}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.31, 18.70, 28.95, 29.04, 31.28, 35.73, 37.13, 64.91, 103.46, 104.28, 114.70, 127.24, 129.68, 131.41, 132.73, 136.23, 138.06, 138.78, 138.97, 139.68, 165.39, 172.86, 184.02. HRMS(ESI): *calculated* 631.3214; *found* 631.3210.

Procedure for loading of 5-(4-isothiocyanatophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(1,*1*,*1*,*1*) (4) onto a solid support. To a suspension of tentagel S NH_2 resin (100 mg, 0.27 mM g^{-1}) in CH_2Cl_2 (5 ml) was added **4** (15 mg, 0.028 mmol) and the resulting suspension was stirred at room temperature for 12 hours. The reaction mixture was filtered and the resin washed with CH_2Cl_2 (5 ml), then dried under vacuum to give **11** as a dark red-orange solid (115 mg).

Solid state NMR

Magic angle spinning proton NMR spectra were collected on a 500 MHz, Avance 500 widebore instrument (Bruker biospin) with a MAS DVT 500 probe. Approximately 20 mg of sample were packed into a 4 mm CRAMPS rotor. The samples were spun at 10 kHz, the temperature outside the sample rotor was maintained at 293 K. Proton spectra were collected with a single $\pi/2$ pulse of 3 μs and an acquisition time of 200 ms. Each spectrum is the sum of 8 scans separated by a 4 second delay. Spectra were referenced to TMS at 0 ppm.

Reflectance UV–visible spectroscopy

Diffuse reflectance spectra were recorded on samples (1 mg) diluted in $BaSO_4$ (50 mg) using a Harrick praying mantis diffuse reflectance accessory mounted in a Varian Cary5E UV–Vis–NIR spectrophotometer. $BaSO_4$ was used as the reference material.

Determination of stability constants

^{1}H NMR spectra were recorded on a Jeol JNM-LA-400 in CD_2Cl_2 and referenced to tetramethylsilane (δ 0). Aliquots were added for each anion as their tetrabutylammonium salt in CD_2Cl_2 to a 0.4 M solution of 5-(4-nitrophenyl)-10,15,20-tris-(dimethyl)-calix[4]phyrin-(**1**,*1*,*1*,*1*) (**2**). The change in chemical shift of the three equivalent NH resonances (δ 7.91) was recorded. The total amount of each anion added was: fluoride (10 equivalents), chloride (18.2 equivalents), bromide (20 equivalents), iodide (20 equivalents) and hydrogensulfate (20 equivalents). The WinEQNMR[13] least squares fitting procedure was employed to obtain the stability constant for a 1 : 1 complex; errors were estimated to be less than 15%.

UV–visible binding studies

Spectra were recorded on an Agilent 8453E diode array UV–visible spectrophotometer. Aliquots (10 ml) of a solution of **2** in dichloromethane (70 μM) were titrated with a solution of tetrabutylammonium anion in dichloromethane (10 mM) until no further spectral change occurred.

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