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Supramolecular Stacking in a High Z' Calix[8]arene – Porphyrin Assembly

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A co-crystal structure of sulfonato-calix[8]arene (sclx₈) and trimethylanilinium-porphyrin (tmap) at 1.0 Å resolution is reported. The oppositely charged macrocycles formed an alternating stacked assembly. Crystal packing was completed by peripheral porphyrins that interlinked neighbouring stacks. Numerous cavities, presented by the calixarenes, were occupied by 2-methyl-2,4-pentanediol (the precipitant) resulting in an unusually high Z'.

Calixarenes^{1,2} and porphyrins^{3,4} are versatile supramolecular building blocks with wide-ranging applications in sensing,² catalysis,^{5,6} and light harvesting.⁷⁻⁹ The upper and lower rims of calixarenes and the porphyrin ring periphery can be substituted with diverse groups to favour (bio)molecular recognition, and/or to facilitate self-assembly.^{3,4,10,11} Sheet¹² or layered¹³ calixarene assemblies and ring-¹⁴ and pillar-like¹⁵ structures of porphyrins have been achieved. Porphyrin – calixarene complexation has yielded hybrid assemblies including porous frameworks.¹⁶⁻²¹ In these cases, the calixarene appears to be a templating agent for porphyrin assembly. Co-crystallization of N-methyl-4-pyridyl-porphyrin with a calix[4]arene derivative resulted in complexes with varying calixarene:porphyrin ratios,^{16,17} that could be modulated either by pH or metal ions.¹⁹⁻²¹

Porphyrins and calixarenes are useful reagents for protein recognition and assembly.^{10,11,22-27} Recently, we have shown that the highly anionic sulfonato-calix[8]arene (**sclx₈**) forms relatively large interfaces (~550 Å) with cationic proteins.^{25,27} Highly porous crystalline frameworks have been obtained with cytochrome c (cytc) in which the calixarene plays pivotal roles.^{25,27} The present study began as an attempt to co-crystallize **sclx₈** with cytc and a porphyrin. The tetra(4-N,N,N-trimethylanilinium) porphyrin (**tmap**; Fig. 1) was selected considering the high affinity of calix[n]arenes for methylated amines.¹¹ Currently, there are at least ten X-ray structures of **sclx₈** with different guests.²⁸⁻³⁶ Only limited X-ray data, including a remarkable cubic cage, is available for tetra(4-aminophenyl)-porphyrin, the precursor to **tmap**.^{37,38} And although calix[4]arene-porphyrin complexes have been explored extensively,¹⁶⁻²¹ no data is available for calix[8]arene. Co-crystallization experiments yielded an interesting result that contained **sclx₈** and **tmap** but no protein. Here, we report a 1.0 Å resolution crystal structure of **sclx₈** – **tmap**. The porphyrin occurs in two distinct

conformations depending on its location within the assembly. The molecular recognition features that appear to stabilize the assembly are discussed.

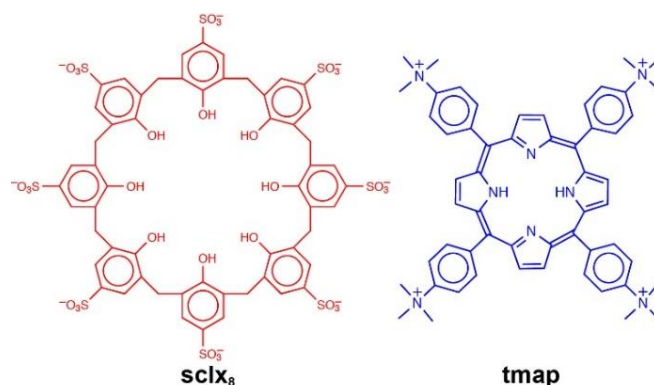


Fig. 1. Molecular ions used in this study. Note, at least two of the phenolic groups can be deprotonated.

A sparse matrix screen (JCSG++ Biosciences) and an Oryx8 Robot (Douglas Instrument) were used for co-crystallization trials. 1 mM cytc, 10 mM **sclx₈** and 6.5 mM **tmap** yielded a single crystal (Fig. S1) in condition A11 with 50 % 2-methyl-2,4-pentanediol (**mpd**), 0.1 M TRIS-HCl pH 8.5 and 0.2 M ammonium di-hydrogen phosphate (no crystals were obtained in the other 95 conditions). A dataset extending to 1.0 Å resolution was collected at SOLEIL synchrotron. The crystal belonged to the monoclinic space group $P2_1$ (Table S1) and the electron density map was generated *ab initio* in ACORN (CCP4 suite).³⁹ Unambiguous electron density was evident for the two macrocycles. Interestingly, the asymmetric unit comprised four **sclx₈**, six **tmap**, ten **mpd** and two glycerols, resulting in $Z' = 22$ (Fig. 2).^{40,41} The structure was refined using ShelXL⁴² (version 2018/3) with the crystal data listed in Table S1. The complex was highly solvated with 145 waters (deposited as CCDC 1956108). However, the R factor was greater than 20 % and there were large parameter shifts. Application of the Platon-Squeeze program⁴³ resulted in greatly reduced R factors and parameter shifts (deposited as CCDC 1956128).

Currently, about ten structures with $Z' > 16$ are available (<http://zprime.co.uk/>).^{40,41} There are 12 structures in the CCDC (Table S2) with more than 999 atoms, none of which are high Z' structures. The present structure (without Squeeze - non-H: 1005; H: 1639 and with Squeeze - non-H: 860; H: 1494) provides insight into the conditions / interactions that lead to high Z' . Four **tmap** alternated with four **sclx₈** in a stacked assembly (Fig. 2B). The remaining two porphyrins bound the stack peripherally. The stacked porphyrins were puckered⁴ while the peripheral porphyrins were planar (Fig. 2A and S2). Using least squares planes defined by the four pyrrole ring atoms plus the bridging carbons the maximum deviation in the puckered and peripheral porphyrins were 0.9 Å and 0.2 Å, respectively (ORTEX module in Oscale⁴⁴). **sclx₈** adopted a pleated conformation that consisted of 'calix[2]arene' and 'calix[3]arene'

cavities. These cavities hosted the trimethylanilinium group of the porphyrins, or a **mpd** or a pyrrole group of the peripheral porphyrin (Fig. 2B). **mpd** was the precipitant and the 10 **mpd** molecules in the asymmetric unit are mostly occupying cavities and appear to improve the packing.

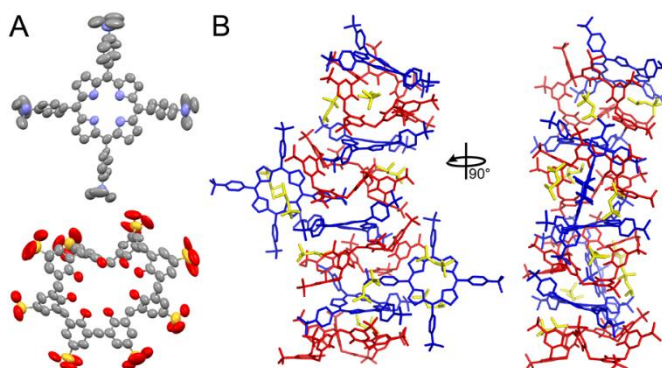


Fig. 2. (A) ORTEP diagrams of **tmap** and **sclx₈** with thermal ellipsoids drawn at 50 % probability level. **(B)** The asymmetric unit comprised four **sclx₈** (red), six **tmap** (blue), and ten **mpd** (yellow). Stacking porphyrins were puckered, while peripheral porphyrins were planar.

Porphyrin – calixarene co-crystals have been characterized previously.^{16,19-21} These structures comprised porphyrin stacks with peripherally-bound calixarenes. In contrast, in the **sclx₈ – tmap** complex both macrocycles participated in the stack and formed multiple noncovalent interactions (Fig. 2). This binding mode appears to have been favoured by the charge and shape complementarity of the trimethylanilinium with the **sclx₈** conformation. For example, in a **sclx₈ – tmap – sclx₈** sandwich the trimethylanilinium groups interacted with the flanking calixarene cavities *via* charge-charge interactions, cation- π bonds, CH- π and in some cases π - π interactions. Furthermore, the pyrrole rings of each stacking porphyrin formed CH- π bonds with the methylene groups of the flanking calixarenes.

The conformations adopted by the stacking macrocycles appear to have facilitated interactions with the peripheral **tmap**. A ‘calix[2]arene’ cavity of **sclx₈** accommodated the pyrrole ring of a peripheral **tmap**. Interestingly, the trimethylamine group of this porphyrin was inserted close to the (deprotonated) phenolic OH groups, consistent with charge-charge interactions. The peripheral **tmap** acted as “bridges” between the neighbouring stacks, facilitating crystal packing / assembly (Fig. 3).

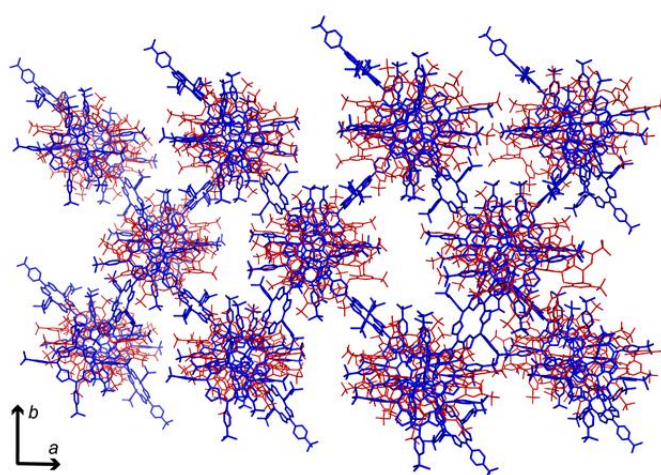


Fig. 3. Crystal packing involves **sclx₈** – **tmap** stacks (top-down view) interacting with each other *via* bridging peripheral porphyrins.

To determine how well the macrocycles were packed, the number of intermolecular van der Waals contacts were measured in ORTEX (Table 1).⁴⁴ In the stack, ~60 % of the **tmap** atoms were in contact with the flanking **sclx₈**. Only ~35 % of the peripheral **tmap** atoms contacted the calixarenes. Similar results were obtained by measuring the solvent accessible surface areas.⁴⁵ ~70 % of the surface of the stacking porphyrin was buried by the calixarenes, while 15 % of the peripheral porphyrin was buried. Protonation of the porphyrin core results in puckering.⁴ Apparently, the chemical environment afforded by the flanking **sclx₈** favoured protonation of the stacking porphyrins. In contrast, the more exposed peripheral porphyrins were planar.

Table 1. **tmap** – **sclx₈** contact surfaces.

	% van der Waal contacts			% buried surface		
	tmap^p	tmap^s	sclx₈	tmap^p	tmap^s	sclx₈
tmap^p	-	25	35	-	15	20
tmap^s	25	-	60	15	-	70
sclx₈	35	55	-	15	70	-

^pperipheral; ^sstacking

sclx₈–**tmap** interactions were investigated in solution by UV/vis spectroscopy (SI methods and Fig. S3). In the presence of increasing concentrations of **sclx₈**, the **tmap** Soret band exhibited a ~6 nm bathochromic shift (from 412 to 418 nm) as well as gradual hypochromicity followed by gradual

hyperchromicity. These spectral changes are consistent with complexation, and suggest the formation of complexes with varying stoichiometry.

In conclusion, we have described an alternating stacked assembly of **sclx₈** and **tm_{ap}** in the solid state, as well as complexation in solution. Numerous interactions, including charge-charge, CH- π and cation- π , appear to stabilize the complex. The numerous weak intermolecular contacts, the non-planar macrocycle conformations, and the inclusion of crystallization additives (**mpd**) all contributed to this high Z' assembly.^{40,41} The inherent "floppiness" of the calix[8]arene scaffold ensured a suitable conformation that complements the topology and charge of the partner porphyrin. Thus, compared to the rigid calix[4]arenes,^{11,16,19-21} the conformational flexibility offered by calix[8]arenes may be utilized to yield stacking hybrid architectures. Such complexes, containing porphyrins, may have applications in the development of sensors or light-harvesting systems.^{2,7-9}

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Conflicts of interest

There are no conflicts to declare.

References

- 1 D.-S. Guo and Y. Liu, *Acc. Chem. Res.*, 2014, **47**, 1925.
- 2 R. Kumar, A. Sharma, H. Singh, P. Suating, H. S. Kim, K. Sunwoo, I. Shim, B. C. Gibb, and J. S. Kim, *Chem. Rev.*, 2019, **119**, 9657.
- 3 W. Auwärter, D. Ćija, F. Klappenberger and J. V. Barth, *Nat. Chem.*, 2015, **7**, 105.
- 4 M. Kielmann and M. O. Senge, *Angew. Chem. Int. Ed.*, 2019, **58**, 418.
- 5 C. Schöttle, E. Guan, A. Okrut, N. A. Grosso-Giordano, A. Palermo, A. Solovyov, B. C. Gates and A. Katz, *J. Am. Chem. Soc.*, 2019, **141**, 4010.
- 6 P. T. Smith, B. P. Benke, Z. Cao, Y. Kim, E.M. Nichols, K. Kim and C. J. Chang, *Angew. Chem. Int. Ed. Engl.*, 2018, **57**, 9684.
- 7 P. Kubát, J. Šebera, S. Záliš, J. Langmaier, M. Fuciman, T. Polívka and K. Lang, *Phys. Chem. Chem. Phys.*, 2011, **13**, 6947.
- 8 J. Otsuki, *J. Mater. Chem. A*, 2018, **6**, 6710.
- 9 P. Pathak, W. Yao, K. D. Hook, R. Vik, F. R. Winnerdy, J. Q. Brown, B. C. Gibb, Z. F. Pursell, A. T. Phan, and J. Jayawickramarajah. *J. Am. Chem. Soc.*, 2019, **141**, 12582.

- 10 H. Zhou, L. Baldini, J. Hong, A. J. Wilson, A. D. Hamilton. *J. Am. Chem. Soc.* 2006, **128**, 2421.
- 11 (a) M. Giuliani, I. Morbioli, F. Sansone and A. Casnati, *Chem. Commun.*, 2015, **51**, 14140; (b) C. S. Beshara, C. E. Jones, K. D. Daze, B. J. Lilgert, F. Hof, *ChemBioChem*. 2010, **11**, 63.
- 12 D. Shetty, T. Skorjanc, J. Raya, S. K. Sharma, I. Jahovic, K. Polychronopoulou, Z. Asfari, D. S. Han, S. Dewage, J.-C. Olsen, R. Jagannathan, S. Kirmizialtin, and A. Trabolsi, *ACS Appl. Mater. Interfaces*, 2018, **23**, 17359.
- 13 M. Moradi, N. L. Opara, L. G. Tulli, C. Wäckerlin, S. J. Dalgarno, S. J. Teat, M. Baljovic, O. Popova, E. van Genderen, A. Kleibert, H. Stahlberg, J. P. Abrahams, C. Padeste, P. F.-X. Corvini, T. A. Jung, P. Shahgaldian, *Sci. Adv.*, 2019, **5**, e4489.
- 14 R. Haver, L. Tejerina, H.-W. Jiang, M. Rickhaus, M. Jirasek, I. Grübner, H. J. Eggimann, L. M. Herz, and H. L. Anderson, *J. Am. Chem. Soc.*, 2019, **141**, 7965.
- 15 P. Martinez-Bulit, C. A. O'Keefe, K. Zhu, R. W. Schurko and S. J. Loeb, *Cryst. Growth Des.*, 2019, **19**, 5679.
- 16 L. Di Costanzo, S. Geremia, L. Randaccio, R. Purrello, R. Lauceri, D. Sciotto, F. G. Gulino, and V. Pavone, *Angew. Chem. Int. Ed.*, 2001, **40**, 4245.
- 17 G. Moschetto, R. Lauceri, F. G. Gulino, D. Sciotto, and R. Purrello, *J. Am. Chem. Soc.*, 2002, **124**, 14536.
- 18 F. G. Gulino, R. Lauceri, L. Frish, T. Evan-Salem, Y. Cohen, R. De Zorzi, S. Geremia, L. Di Costanzo, L. Randaccio, D. Sciotto, R. Purrello, *Chem. Eur. J.*, 2006, **12**, 2722.
- 19 R. De Zorzi, N. Guidolin, L. Randaccio, R. Purrello, and S. Geremia, *J. Am. Chem. Soc.*, 2009, **131**, 2487.
- 20 R. De Zorzi, N. Guidolin, L. Randaccio and S. Geremia, *CrystEngComm*, 2010, **12**, 4056.
- 21 G. Brancatelli, R. De Zorzi, N. Hickey, P. Siega, G. Zingone, and S. Geremia, *Cryst. Growth Des.*, 2012, **12**, 5111.
- 22 M. Goel, R. S. Damai, D. K. Sethi, K. J. Kaur, B. G. Maiya, M. J. Swamy and D. M. Salunke, *Biochemistry*, 2005, **44**, 5588.
- 23 P. B. Crowley, P. Ganji, and H. Ibrahim, *ChemBioChem.*, 2008, **9**, 1029.
- 24 O. Kokhan, N. Ponomarenko, P. R. Pokkuluri, M. Schiffer and D. M. Tiede, *Biochemistry*, 2014, **53**, 5070.
- 25 M. L. Rennie, G. C. Fox, J. Pérez and P. B. Crowley, *Angew. Chem. Int. Ed.*, 2018, **57**, 13764.
- 26 J. M. Alex, M. L. Rennie, S. Engilberge, G. Lehoczki, H. Dorottyá, Á. Fizil, G. Batta and P. B. Crowley, *IUCrJ*, 2019, **6**, 238-247.
- 27 S. Engilberge, M. L. Rennie, E. Dumont, and P. B. Crowley, *ACS Nano*, 2019, **13**, 10343.

- 28 S. J. Dalgarno, M. J. Hardie, J. L. Atwood, J. E. Warren and C. L. Raston, *New J. Chem.*, 2005, **29**, 649.
- 29 F. Perret, V. Bonnard, O. Danylyuk, K. Suwinska, A. W. Coleman, *New J. Chem.*, 2006, **30**, 987.
- 30 C. B. Smith, L. J. Barbour, M. Makha, C.L. Raston, A. N. Sobolev, *New J. Chem.*, 2006, **30**, 991.
- 31 O. Danylyuk, F. Perret, A.W. Coleman, K. Suwinska, *The Open Crystallo. J.*, **2008**, **1**, 18.
- 32 W. He, Y. Bi, W. Liao, Deqian Li, *J. Mol. Struct.*, 2009, **937**, 95-99.
- 33 Y. Liu, W.Liao, Y. Bi, M. Wang, Z. Wu, X. Wang, Z. Sub, H. Zhang, *CrystEngComm*, 2009, **11**, 1803.
- 34 B. Leśniewska, F. Perret, K. Suwińska, A. W. Coleman, *CrystEngComm*, 2014, **16**, 4399.
- 35 B. Leśniewska, A. W. Coleman, Y. Tauran, F. Perret, K. Suwińska, *CrystEngComm*, 2016, **18**, 8858.
- 36 O. Danylyuka, H. Butkiewiczza, A. W. Coleman, K. Suwińska, *J. Mol. Struct.*, 2017, **1150**, 28.
- 37 W. Meng, B. Breiner, K. Rissanen, J. D. Thoburn, J. K. Clegg, J. R. Nitschke, *Angew. Chem. Int. Ed.*, 2011, **50**, 3479.
- 38 Y. Park, J. Y. Koo, H. C. Choi, *Cryst. Growth Des.*, 2018, **18**, 7239.
- 39 E. J. Dodson and M. M. Woolfson, *Acta Crystallogr D Biol Crystallogr.*, 2009, **D65**, 881.
- 40 K. M. Steed and J. W. Steed, *Chem. Rev.* 2015, **115**, 2895.
- 41 W. Clegg, *Acta Crystallogr C Struct. Chem.*, 2019, **C75**, 833.
- 42 G.M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **C71**, 13.
- 43 A. L. Spek, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2009, **D65**, 148.
- 44 P. McArdle, *J. Appl. Crystallgr.*, 2017, **50**, 320.
- 45 J. Ribeiro, C. Ríos-Vera, F. Melo and A. Schüller, *Bioinformatics*, 2019, **35**, 3499.