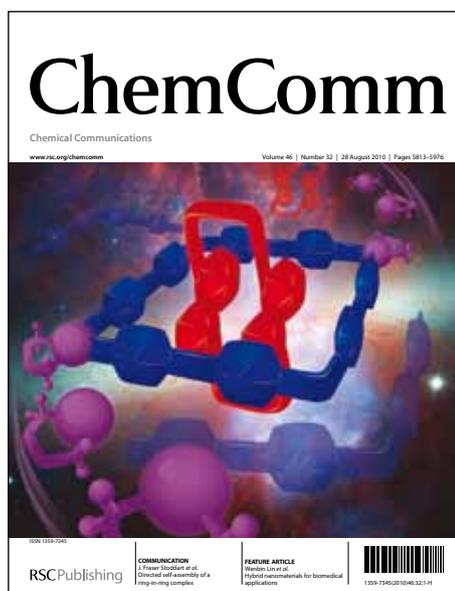


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COMMUNICATION

A low pH sensor from an esterified pillar[5]arene

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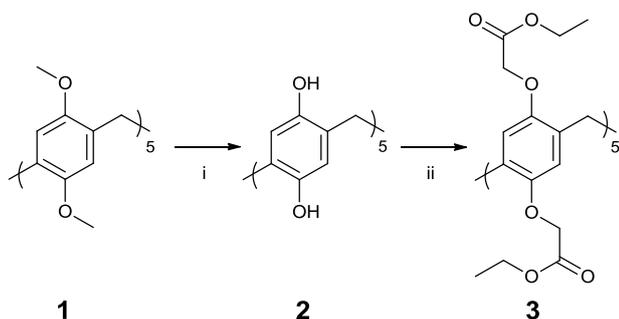
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An esterified pillar[5]arene has been incorporated into a PVC electrochemical membrane. The resulting pH-responsive sensor functions in the range of pH 1 to 4 in a non-linear manner.

Pillar[5]arenes, first reported in 2008¹, are macrocycles comprised of five 1,4-dialkoxybenzene moieties linked in the 2- and 5-positions by methylene groups. Since their discovery numerous derivatives have been prepared² and larger homologues reported.³ The pillar[5]arenes, in particular, possess valuable properties as host molecules for small linear species such as alkylamines.⁴ Extending pillar[5]arenes through cleavage of the methyl substituents from 1,4-dimethoxypillar[5]arene (**1**) to give pillar[5]arene (**2**) and subsequent *O*-alkylation facilitates the introduction of numerous functional groups designed to enhance guest recognition or to signal guest binding. Reaction of the cleaved pillar[5]arene with ethyl bromoacetate results in the expected ester (**3**)⁵ but the compound has unexpected properties. In the solid state the molecules align to form tubes which absorb guest water molecules.⁶ Treatment of water-containing crystals of **3** with D₂O led to H₂O/D₂O substitution.



Scheme 1 Synthesis of ester **3** from 1,4-dimethoxypillar[5]arene: i) BBr₃, CHCl₃ then H₂O (91%), ii) ethylbromoacetate, K₂CO₃/KI, CH₃CN (82%).

Related compounds have shown activity as transmembrane channels for water⁷ and amino acids⁸ raising the possibility that **3** could act as a proton channel. Other applications of **3**, and its corresponding acid, range from quantum dot functionalization⁹ and

gold nanoparticle synthesis¹⁰ to ¹²⁹Xe NMR-based biosensors¹¹ and amino acid detection.¹² It has been demonstrated that **1**, when incorporated within a graphite matrix, performs well as a Na⁺-selective modifier across the physiological concentration range.¹³ Consequently we wished to determine if, given its ability to form insulated 'water wires', the properties of **3** at the molecular level could be translated into a pH-sensitive device.

Esterified pillar[5]arene **3** was prepared from **1** by literature methods^{5,10,14†‡} and was investigated for its ability to facilitate the transport of protons using through an indicator agar gel matrix. Control gels were prepared by combining 1% agar and 1.25% phenolphthalein by weight in 0.1 M NaOH; modified membranes contained an additional 0.5% by weight of **3**.¹⁵ In a preliminary experiment 0.1 M HCl was added to the upper surface of gels formed within pipette tips. Figure 1 shows transport of protons in the gels is facilitated by **3** as the membrane changes from pink to clear at a greater rate following the addition of acid.

The overall population data from multiple trials gave the time taken for the indicator to completely turn clear in the absence of **3** as 413 ± 69 s (n=16) (see ESI, S10). Protonation of phenolphthalein was significantly faster when **3** was present (p<0.001, t-test) as the indicator turned clear in 289 ± 70 s (n=14). This indicated that **3** had the potential to facilitate the transport of protons when incorporated within an agar matrix. Investigations at 0.05 M and 0.01 M HCl, gave similar results in the presence of **3**.

To further understand the role of **3** in the transport of protons an ion-selective electrode (ISE) incorporating the pillar[5]arene derivative was fabricated, with a 0.1M KCl internal solution interface, in an analogous fashion to valinomycin-containing ISEs (see ESI, S11-12).¹⁶ Measurements were made in solutions ranging from pH 1 to 4. In Figure 2A an experimental trace is shown for an ISE which exhibits a decrease in the open-circuit potential with increasing pH. The electrode had minimal drift at each pH step, indicating good stability during measurements. Identical results were observed whether the pH was adjusted from 1 to 4 or vice versa. Surprisingly, the response time following each addition was the same regardless of pH whereas traditional ISEs have to reach

equilibrium. Data from five ISEs (Figure 2B) reveal a non-linear pH dependence whereas in commercial ISEs pH decreases with a linear -59 mV/pH unit Nernstian response.¹⁷ From these measurements it can be shown that the variance in the response is limited indicating good reproducibility of individual electrode behaviour.

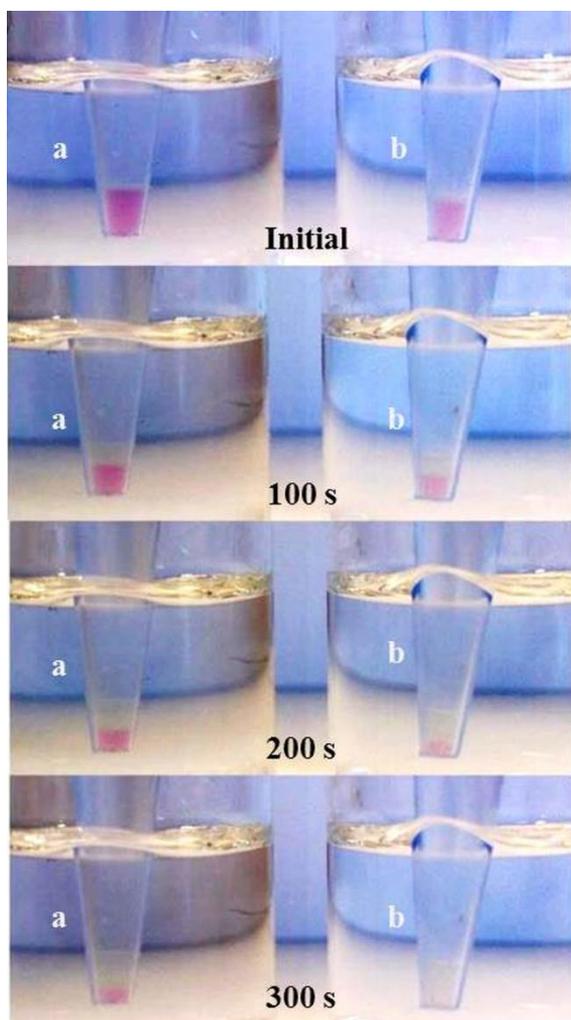


Figure 1. Response of the indicator gel to 0.1 M HCl over 300 s in the absence (a) and presence (b) of **3**.

Examples of macrocycles used as modifiers in pH-sensitive electrodes are rare but include a *p*-tert-butylcalix[4]arene-oxacrown-4 derivative¹⁸, *N,N'*-bis(ethoxycarbonyl)diaza-18-crown-6,¹⁹ and a *p*-tert-butylcalix[6]arene with two lower rim ethoxythiophosphoryl substituents.¹⁹ Unlike the pillar[5]arene example, these modifiers follow Nernstian behaviour with a linear response to pH.

The sub-Nernstian pH dependence of ISEs incorporating **3** may be due the background effect from K^+ becoming more dominant or a mechanism where the activity of H^+ does not correlate directly with its concentration. Alternatively, it may be indicative of a novel flux dependent catalytic process as similar behaviour is seen for catalytic metal-metal oxide electrodes exhibiting non-Nernstian responses.²⁰

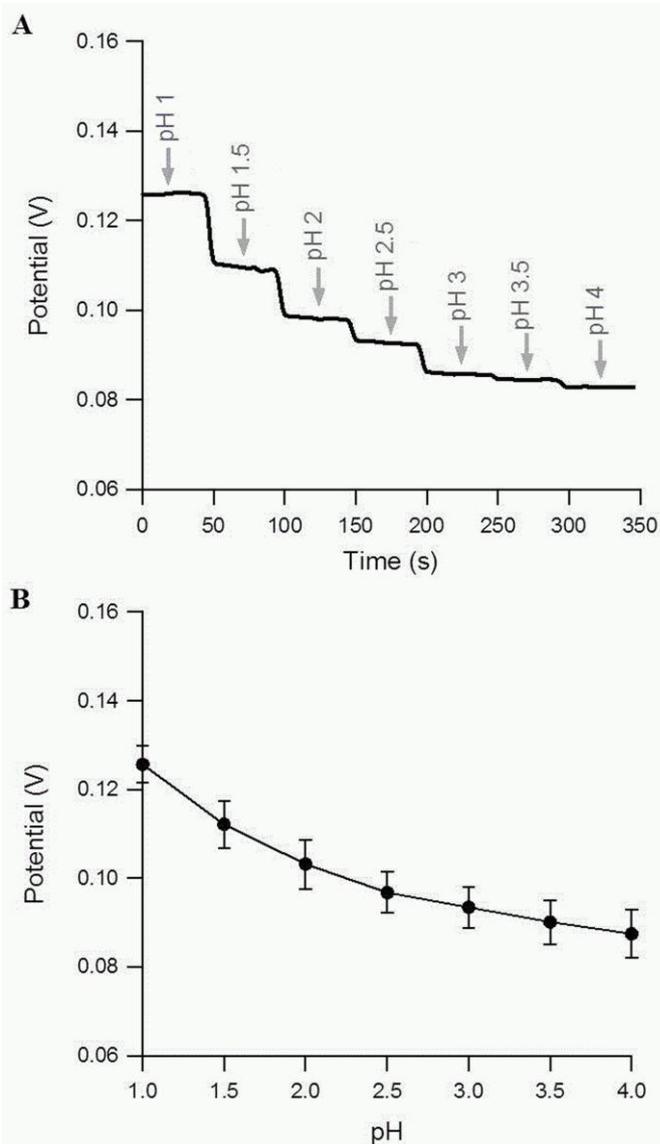


Figure 2. Non-linear response to pH observed for ISEs prepared with **3**: A) raw data and B) population data (mean \pm S.D, n = 5).

We have demonstrated that the molecular scale transport of protons by **3** persists into the macroscale even in the non-crystalline state. Incorporation of **3** into a PVC matrix results in the formation of a sensor that responds to protons with a non-linear dependence between pH 1 and 4.

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Notes and references

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† Electronic Supplementary Information (ESI) available: synthesis and spectra of compounds **1**, **2** and **3**; sensor fabrication methods; sensor data. See DOI: 10.1039/b000000x/

‡ In our hands, and despite good analytical data, **1** often appears to incorporate trace impurities which leach out over time; we have therefore developed a rigorous purification regime as described in the ESI.

- 1 T. Ogoshi, S. Kanai, S. Fujinami, T. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022
- 2 Reviews: P. J. Cragg and K. Sharma, *Chem. Soc. Rev.*, 2012, **41**, 597; T. Ogoshi, *J. Inclusion Phenom. Macrocyclic Chem.*, 2012, **72**, 247; M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294; T. Ogoshi and T. Yamagishi, *Bull. Chem. Soc. Jpn.*, 2013, **86**, 312; T. Ogoshi and T. Yamagishi, *Eur. J. Org. Chem.*, 2013, 2961
- 3 D. Cao, Y. Kou, J. Liang, Z. Chen, L. Wang and H. Meier, *Angew. Chem. Int. Ed.*, 2009, **48**, 9721; Y. Chen, H. Q. Tao, Y. H. Kou, H. Meier, J. L. Fu and D. R. Cao, *Chinese Chem. Lett.*, 2012, **23**, 509; X. B. Hu, Z. Chen, L. Chen, L. Zhang, J. L. Hou and Z. T. Li, *Chem. Commun.*, 2012, **48**, 10999
- 4 N. L. Strutt, R. S. Forgan, J. M. Spruell, Y. Y. Botros and J. F. Stoddart, *J. Am. Chem. Soc.*, 2011, **133**, 5668; H. Deng, X. Shu, X. Hu, J. Li, X. Jia and C. Li, *Tetrahedron Lett.*, 2012, **53**, 4609
- 5 T. Ogoshi, M. Hashizume, T. A. Yamagishi and Y. Nakamoto, *Chem. Commun.*, 2010, **46**, 3708
- 6 W. Si, L. Chen, X. B. Hu, G. F. Tang, Z. X. Chen, J. L. Hou and Z. T. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 12564; W. Si, X. B. Hu, X. H. Liu, R. H. Fan, Z. X. Chen, L. H. Weng and J. L. Hou, *Tetrahedron Lett.*, 2011, **52**, 2484; M. Barboiu, *Angew. Chem. Int. Ed.*, 2012, **51**, 11674
- 7 X. B. Hu, Z. Chen, G. Tang, J. L. Hou and Z. T. Li, *J. Am. Chem. Soc.*, 2012, **134**, 8384
- 8 L. Chen, W. Si, L. Zhang, G. F. Tang, Z. T. Li and J. L. Hou, *J. Am. Chem. Soc.*, 2013, **135**, 2152
- 9 D.-X. Chen, Y.-L. Sun, Y. Zhang, J.-Y. Cui, F.-Z. Shen and Y.-W. Yang, *RSC Adv.*, 2013, **3**, 5765
- 10 H. Li, D. X. Chen, Y. L. Sun, Y. B. Zheng, L. L. Tan, P. S. Weiss and Y. W. Yang, *J. Am. Chem. Soc.*, 2013, **135**, 1570
- 11 T. Adiri, D. Marciano and Y. Cohen, *Chem. Commun.*, 2013, **49**, 7082
- 12 C. Li, J. Ma, L. Zhao, Y. Zhang, Y. Yu, X. Shu, J. Li and X. Jia, *Chem. Commun.*, 2013, **49**, 1924
- 13 L. Dube, B. A. Patel, A. Fagan-Murphy, R. R. Kothur and P. J. Cragg, *Chem. Sensors*, 2013, **3**, 18
- 14 T. Boinski and A. Szumna, *Tetrahedron*, 2012, **68**, 9419
- 15 A. L. Odom and P. V. Kelly, *Sci. Educ.*, 2001, **85**, 615
- 16 M. Dror, E. A. Bergs and R. K. Rhodes, *Sensor. Actuat.*, 1987, **11**, 23
- 17 W. Nernst, *Z. Phys. Chem.*, 1889, **4**, 129
- 18 A. Demirel, A. Doğan, E. Canel, S. Memon, M. Yilmaz and E. Kiliç, *Talanta*, 2004, **62**, 123
- 19 M. M. Zareh, *Anal. Sci.*, 2009, **25**, 1131
- 20 E. Bitziou, D. O'Hare and B. A. Patel, *Anal. Chem.*, 2008, **80**, 8733