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

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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 2008,¹ 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 (Scheme 1). 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.

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



 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme1} & \mbox{Synthesis of ester 3 from 1,4-dimethoxypillar[5]arene: (i) BBr_{3,} \\ \mbox{CHCl}_3 \mbox{ then } H_2O \ (91\%), \ (ii) \mbox{ etal} \mbox{Expression} \mbox{Scheme1} & \mbox{Scheme1} & \mbox{Scheme1} \\ \mbox{Scheme1} & \mbox{Scheme1} & \mbox{Scheme1} & \mbox{Scheme1} & \mbox{Scheme1} \\ \mbox{Scheme1} & \mbox{Schem$

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. Fig. 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 \pm 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 0.1 M KCl

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Fig. 1 Response of the indicator gel to 0.1 M HCl over 300 s in the absence (a) and presence (b) of ${\bf 3}$.

Fig. 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).

internal solution interface, in an analogous fashion to valinomicin-containing ISEs (see ESI,† S11 and S12).¹⁶ Measurements were made in solutions ranging from pH 1 to 4. In Fig. 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 (Fig. 2B) reveal a non-linear pH dependence whereas in commercial ISEs pH decreases with a linear -59 mV pH⁻¹ 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.

Examples of macrocycles used as modifiers in pH-sensitive electrodes are rare but include a *p-tert*-butylcalix[4]arene-oxacrown-4 derivative,¹⁸ 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

We have demonstrated that the molecular scale transport of protons by 3 persists into the macroscale even in the noncrystalline 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.

RRK thanks the University of Brighton for a University Studentship and JH thanks the Nuffield Foundation for funding a Nuffield Research Placement. [‡] 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.[†]

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