

Tuning the strength and selectivity of ion-pair recognition using heteroditopic calix[4]arene-based receptors

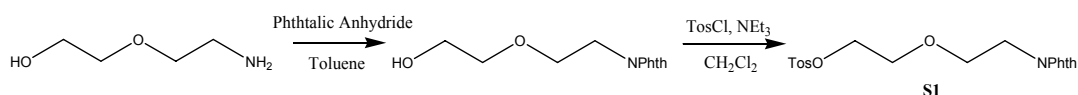
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Supplementary Information

1. Syntheses of Known Compounds

(i) Synthesis of compound 4¹

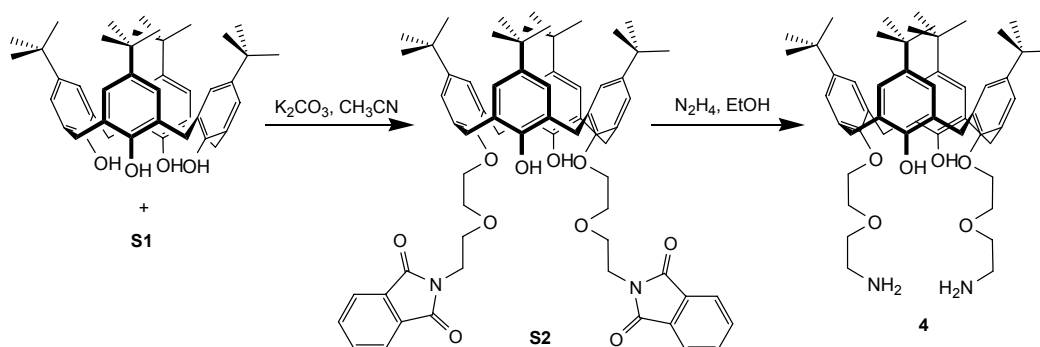
*Precursor Formation*²



2-(2-aminoethyl)-ethanol (10.5 g, 0.1 mol) and phthalic anhydride (14.8 g, 0.1 mol) were dissolved in toluene (450 mL) and the resulting solution placed in a round bottomed flask fitted with a Dean-Stark apparatus. The solution was then heated under reflux for 4 hours, with the water evolved from reaction periodically removed from the system. The reaction mixture was allowed to cool, dried over MgSO₄, filtered, then the solvent removed *in vacuo* from the filtrate to give the pure, white phthalimide protected amine in quantitative yield. δ_{H} (CDCl₃; 300 MHz) 3.61 (2H, m, CH₂CH₂OH), 3.69 (2H, m, CH₂OH), 3.75 (2H, t, ³J 5.3, OCH₂CH₂N), 3.91 (2H, t, ³J 5.3, CH₂N), 7.73 (2H, m, ArH), 7.85 (2H, m, ArH); *m/z* (ES⁺) 236.0933 (M⁺ - H. C₁₂H₁₄NO₄ requires 236.0923), 258.07 (M + Na⁺), 493.16 (2M + Na⁺).

This material (23.5 g, 0.1 mol) was then dissolved in dichloromethane (200 mL), to which solution triethylamine (21 mL, 0.15 mol), tosyl chloride (19 g, 0.1 mol) and a catalytic quantity of DMAP were added. The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 16 hours, then H₂O (100 mL) was added. The vigorously stirred biphasic mixture was neutralised by portionwise addition of a 10% aqueous citric acid solution, then separated. The organic phase was washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed *in vacuo* to give an off-white crude product. Overnight trituration under ether (100 mL) gave pure white S1 (31.2 g, 80%). δ_{H} (CDCl₃; 300 MHz) 2.47 (3H, s, CH₃), 3.70 (4H, m, CH₂OCH₂), 3.87 (2H, m, CH₂N), 4.14 (2H, m, CH₂OSO₂), 7.35 (2H, m, TosH), 7.77 (4H, m, ArH), 7.88 (2H, m, PhthH); *m/z* (ES⁺) 380.0995 (M⁺ - H. C₁₉H₂₀NO₆S requires 390.1011), 412.08 (M + Na⁺), 801.19 (2M + Na⁺).

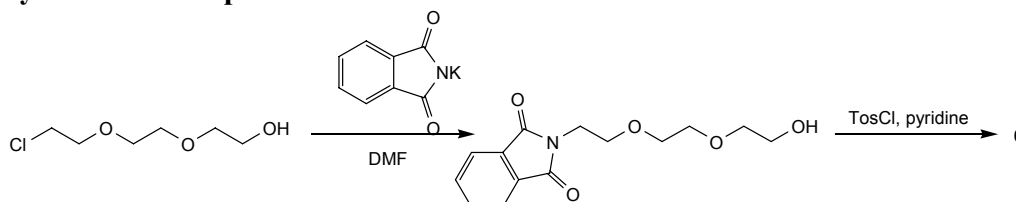
Bisamine Formation



p-Tert-butylcalix[4]arene (3.82 g, 5.89 mmol) and K_2CO_3 (1.63 g, 12 mmol) were suspended in dry CH_3CN (120 mL). To this stirred suspension the above precursor **S1** (5.74 g, 14.7 mmol) was added, and the resulting mixture was heated under reflux under a nitrogen atmosphere for 4 days. After this time, the suspension was allowed to cool, then the solvent carefully removed *in vacuo* to give a solid mass which was triturated with 1M $HCl_{(aq)}$. The resulting suspension was extracted with CH_2Cl_2 (3 x 100 mL), then the extracts were combined and washed with H_2O (2 x 100 mL). The solution was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to give a crude material which could be further purified by trituration under ethanol (75 mL) to give the pure pale green product **S2** (4.32 g, 68%). $\delta_H(CDCl_3; 300\text{ MHz})$ 1.03 (s, 18H, *t*-Bu), 1.25 (s, 18H, *t*-Bu), 3.07 (4H, d, 2J 12.75, $ArCH_{in}H_{out}Ar$), 4.05 (m, 20H, 3 x OCH_2 , NCH_2 & $ArCH_{in}H_{out}Ar$), 6.81 (4H, s, calixArH), 6.84 (4H, s, calixArH), 7.50 (4H, m, PhthH), 7.60 (4H, m, PhthH); $\delta_C(CDCl_3; 75.5\text{ MHz})$ 31.07, 31.49, 31.67, 33.70, 33.95, 38.09, 68.41, 69.96, 74.92, 122.67, 124.73, 125.38, 125.92, 127.80, 131.86, 133.35, 141.04, 146.90, 149.48, 149.87, 168.57; $m/z(ES^+)$: 1105.5552 ($M + Na^+$. $C_{68}H_{78}N_2O_{10}Na$ requires 1105.5554).

S2 (1.13 g, 1.04 mmol) was suspended in ethanol (25 mL), and hydrazine monohydrate (0.5 mL, excess) added carefully. This suspension was then heated under reflux for 15 hours, during which time the solid was seen to dissolve. The reaction mixture was allowed to cool, then poured into H_2O (50 mL) to give a milky white suspension which was extracted with CH_2Cl_2 (4 x 40 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to give the pure white diamine **4** (0.86 g, 100%). $\delta_H(CDCl_3; 300\text{ MHz})$: 0.98 (s, 18H, $C(CH_3)_3$), 1.29 (s, 18H, $C(CH_3)_3$), 2.88 (4H, br, NH_2), 2.97 (4H, m, CH_2NH_2), 3.31 (4H, d, 2J 13.05, $ArCH_{in}H_{out}Ar$), 3.71 (4H, m, $OCH_2CH_2NH_2$), 3.71 (4H, m, OCH_2CH_2O), 3.96 (4H, m, OCH_2CH_2O), 4.05 (4H, d, 2J 13.05, $ArCH_{in}H_{out}Ar$), 6.82 (4H, s, ArH), 7.06 (4H, s, ArH); $\delta_C(CDCl_3; 75.5\text{ MHz})$ 31.07, 31.59, 31.73, 33.85, 33.98, 42.09, 69.74, 73.43, 75.24, 125.11, 125.57, 127.80, 132.77, 141.45, 146.94, 149.78, 150.45; $m/z(ES^+)$: 412.28 ($M + 2H^+$), 432.79 ($M + 2Na^+$), 823.5590 ($M^+ - H$. $C_{52}H_{75}N_2O_6$ requires 823.5625).

(ii) Synthesis of compound 6³



2-(2-(2-chloroethoxy)ethoxy)-ethanol (9 g, 0.053 mol) and potassium phthalimide (9.82 g, 0.053 mol) were suspended in dry DMF (50 mL) and heated at 110°C for 18 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, filtered, and then concentrated *in vacuo*. The crude material was purified by silica gel chromatography (hexane/EtOAc/MeOH 7:7:1) to give the desired intermediate as a colourless oil (10.71 g, 72%); δ_{H} (300 MHz; CDCl_3) 3.52 (2H, t, ^3J 5.0, $\text{CH}_2\text{CH}_2\text{OH}$), 3.61 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 3.65 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.74 (2H, t, ^3J 5.6, $\text{NCH}_2\text{CH}_2\text{O}$), 3.90 (2H, t, ^3J 5.6, $\text{NCH}_2\text{CH}_2\text{O}$), 7.71 (2H, dd, ^3J 5.4, ^4J 3.1, ArH), 7.84 (2H, dd, ^3J 5.4, ^4J 3.1, ArH). $m/z(\text{ES}^+)$: 302.10 (M + Na^+).

The material prepared in the previous stage (10.71 g, 0.03825 mol) was dissolved in pyridine (50 mL) and cooled to 5°C. Tosyl chloride (14.58 g, 0.0765 mol) was added portionwise, maintaining the temperature at 5°C, and the resulting mixture was then stirred at room temperature, under a nitrogen atmosphere, for 18 hours, after which time the solution was poured over a mixture of 20% $\text{HCl}_{(\text{aq})}$ (25 mL) and ice (~25 g). This mixture was extracted with ethyl acetate (3 x 200 mL), with the organic extracts being combined and reduced *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc 3:2) gave the colourless oil 6 (10.64 g, 61%); δ_{H} (300MHz; CDCl_3) 2.41 (3H, s, CH_3), 3.51 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.58 (2H, t, ^3J 4.8, $\text{OCH}_2\text{CH}_2\text{N}$), 3.66 (2H, t, ^3J 5.8, $\text{CH}_2\text{CH}_2\text{OSO}_2$), 3.84 (2H, t, ^3J 4.8, CH_2N), 4.06 (2H, t, ^3J 5.8, CH_2OSO_2), 7.30 (2H, d, ^3J 8.3, TosH), 7.68 (2H, dd, ^3J 5.4, ^4J 3.0, PhthH), 7.74 (2H, d, ^3J 8.3, TosH), 7.80 (2H, dd, ^3J 5.4, ^4J 3.0, PhthH). $m/z(\text{ES}^+)$: 456.11 (M + Na^+).

2. Titration Protocols

All titrations were conducted on either an Oxford Instruments Venus 300 or Varian Unity Plus 500MHz spectrometer, at 298K. Sample volumes used were 500 μL . A typical concentration for the titrations was $1.5 \times 10^{-3} \text{ mol dm}^{-3}$ concentrations (7.5×10^{-7} moles/sample). Where necessary, 1:1 mixtures of metal salt and receptor were pre-prepared. All salts were thoroughly dried before use; all anions were added as TBA salts, Na and Li were added as the ClO_4^- salts, K and NH_4 as the PF_6^- salts, and Rb as the BPh_4^- salt, for solubility reasons. Aliquots of the anion solution were then added (10 x 2 μL , 2 x 5 μL , 2 x 10 μL , 1 x 20 μL & 1 x 30 μL) so that ten equivalents of anion in total were used (total volume added 100 μL). Spectra were recorded after each addition, and the sample shaken thoroughly before measurement.

The resulting titration data were analysed by the winEQNMR computer program⁴ to attempt binding constant determination.

3. References

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1. M. D. Lankshear, A. R. Cowley and P. D. Beer, *Chem. Commun.*, 2006, 612.
2. J. W. Lown, R. R. Koganty and A. V. Joshua, *J. Org. Chem.*, 1982, **47**, 2027.
3. S. Botros, A. W. Lipkowski, A. E. Takemori and P. S. Portoghese, *J. Med. Chem.*, 1986, **29**, 874.
4. M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.