Cooperative AND receptor for ion-pairs

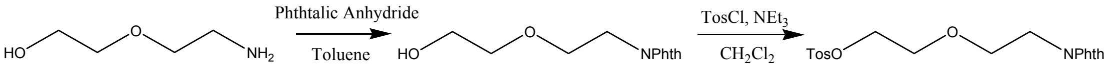
Michael D. Lankshear, Andrew R. Cowley and Paul D. Beer

Electronic Supplementary Information

1. Synthetic Procedures

All commercial grade reagents were used as supplied without any further purification. *p-tert*-butylcalix[4]arene was prepared by an adapted literature procedure[1]. Where solvents are referred to as dry, they were prepared via the following method[2, 3]: degassed by sparging with dinitrogen, dried by passing through a column of activated alumina using Grubbs apparatus and used immediately.

Compound ***2***[4]



2-(2-aminoethyl)-ethanol (10.5g, 0.1mol) and phthalic anhydride (14.8g, 0.1mol) were dissolved in toluene (450mL) and the resulting solution placed in a round bottomed flask fitted with a Dean-Stark apparatus. The solution was then heated under reflux for four hours, with the water evolved from reaction periodically removed from the system. The reaction mixture was allowed to cool, dried over $MgSO_4$, filtered, then the solvent removed *in vacuo* to give the pure, white phthalamide protected amine in quantitative yield. $\delta_H(CDCl_3$, 300MHz): 3.61 (2H, m, CH_2CH_2OH), 3.69 (2H, m, CH_2OH), 3.75 (2H, t, J = 5.3Hz, OCH_2CH_2N), 3.91 (2H, t, J = 5.3Hz, CH_2N), 7.73 (2H, m, Ar*H*), 7.85 (2H, m, Ar*H*); *m/z* (ES+) 236.0933 (M^+ - H. $C_{12}H_{14}NO_4$ requires 236.0923), 258.07 (M + Na^+), 493.16 (2M + Na^+).

This material (23.5g, 0.1mol) was then dissolved in dichloromethane (200mL), to which solution triethylamine (21mL, 0.15mol), tosyl chloride (19g, 0.1mol) and a catalytic quantity of DMAP were added. The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 16 hours, then H_2O (100mL) 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 H_2O (2 x 100mL), dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to give an off-white crude product. Overnight trituration under ether (100mL) gave pure white **2** (31.2g, 80%). $\delta_H(CDCl_3$, 300MHz) 2.47 (3H, s, CH_3), 3.70 (4H, m, CH_2OCH_2), 3.87 (2H, m, CH_2N), 4.14 (2H, m, CH_2OSO_2), 7.35 (2H, m, TosH), 7.77 (4H, m, Ar*H*), 7.88 (2H, m, PhthH); *m/z* (ES+) 380.0995 (M^+ - H. $C_{19}H_{20}NO_6S$ requires 390.1011), 412.08 (M + Na^+), 801.19 (2M + Na^+).

Compounds ***3*** *and* ***4***

p-Tert-butylcalix[4]arene (3.82g, 5.89mmol) and K_2CO_3 (1.63g, 12mmol) were suspended in dry CH_3CN (120mL). To this stirred suspension compound **2** (5.74g, 14.7mmol) 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 an solid mass which was triturated with 1M $HCl_{(aq)}$. The resulting suspension was extracted with CH_2Cl_2 (3 x 100mL), then the were extracts combined and washed with H_2O (2 x 100mL). 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 (75mL) to give the pure pale green product **3** (4.32g, 68%). δ_H($CDCl_3$, 300MHz): 1.03 (s, 18H, C(C*H*$_3$)$_3$), 1.25 (s, 18H, C(C*H*$_3$)$_3$), 3.07 (4H, d, J = 12.75 Hz, ArC*H*$_2$Ar (a)), 4.05 (m, 20H, 3 x OCH_2, NC*H*$_2$ & ArC*H*$_2$Ar (b)), 6.81 (4H, s, calixAr*H*), 6.84 (4H, s, calixAr*H*), 7.50 (4H, m, Phth*H*), 7.60 (4H, m, Phth*H*); δ_C($CDCl_3$, 75.47MHz): 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).

Compound **3** (1.13g, 1.04mmol) was suspended in ethanol (25mL), and hydrazine monohydrate (0.5mL, 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 (50mL) to give a milky white suspension which was extracted with CH_2Cl_2 (4 x 40mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to give the pure white diamine intermediate (0.86g, 100%). δ_H($CDCl_3$, 300MHz): 0.98 (s, 18H, C(C*H*$_3$)$_3$), 1.29 (s, 18H, C(C*H*$_3$)$_3$), 2.88 (4H, br, N*H*$_2$), 2.97 (4H, m, C*H*$_2$NH$_2$), 3.31 (4H, d, J = 13.05 Hz, ArC*H*$_2$Ar (a)), 3.71 (4H, M, OC*H*$_2$CH$_2$NH$_2$), 3.71 (4H, m, OCH$_2$C*H*$_2$O), 3.96 (4H, m, OCH$_2$C*H*$_2$O), 4.05 (d, 4H, ArC*H*$_2$Ar (b)), 6.82 (4H, s, Ar*H*), 7.06 (4H, s, Ar*H*); δ_C($CDCl_3$, 75.47MHz): 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).

Separate solutions of this amine intermediate (0.86g, 1.04mmol) in CH_2Cl_2 (100mL) and isophthaloyl chloride (0.21g, 1.04mmol) in CH_2Cl_2 (100mL) were added dropwise, simultaneously, to a stirred solution of triethylamine (0.56mL, 4mmol) in CH_2Cl_2 (250mL) over 2 hours, the whole system being kept under a nitrogen atmosphere. Once addition was complete, the reaction mixture was concentrated *in vacuo* to a volume of *ca* 100mL, then washed with 1M $HCl_{(aq)}$ (2 x 100mL), H_2O (100mL), 1M NaOH (100mL) and brine (100mL). The organic layer was dried over $MgSO_4$, filtered, then concentrated *in vacuo* to give a crude product which could be purified by silica gel chromatography (ethyl acetate/acetone 70:30) followed by trituration under hexane to give pure white compound **4** (0.52g, 52%. Found: C, 75.47; H, 7.91; N, 2.86. $C_{60}H_{76}N_2O_8$ requires C, 75.60; H, 8.04; N, 2.94%). δ_H($CDCl_3$, 300MHz): 0.84 (s, 18H, C(C*H*$_3$)$_3$), 1.28 (s, 18H, C(C*H*$_3$)$_3$), 3.21 (4H, d, J = 13.48 Hz, ArC*H*$_2$Ar (a)), 3.78 (12H, m, AlC*H*$_2$), 4.21 (8H, m, AlC*H*$_2$ & ArC*H*$_2$Ar (b)), 6.64 (4H, s, calixAr*H*), 6.79 (2H, s, O*H*), 6.94 (4H, s, calixAr*H*), 7.32 (1H, m, isophthalyl C*H*), 7.67 (2H, bm, N*H*), 7.91 (2H, m, isophthalyl C*H*), 8.18 (1H, m, isophthalyl C*H*); *m/z* (ES+) 975.52 (M + Na^+).

*Synthesis of Receptor **1**[5]*

Note that caution should be exercised when handling thallium derivatives due to their high toxicity. $Tl(O_2CF_3)_3$.TFA solution was prepared using a previously described method[6]; briefly, a suspension of Tl_2O_3 (5g) in TFA (25mL) was heated under reflux in the absence of light for 92 hours. The resulting solution was cooled, then filtered and stored in a light protected vessel until required.

Compound **4** (0.3g, 0.32mmol) was added to a portion of $Tl(O_2CF_3)_3$.TFA solution (4mL) and stirred at room temperature in the absence of light for 2 hours. The resulting orange solution was concentrated to approximately one third of its original volume, then added to ice-water (50mL). This orange suspension was extracted with $CHCl_3$ (3 x 50mL), then the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange solid. This was purified by recrystallisation from CH_2Cl_2/Et_2O to give the orange receptor **1** (116mg, 42%). δ_H(CD_3CN, 300MHz): 1.06 (s, 18H, C(C*H*$_3$)$_3$), 3.11 (4H, b, ArC*H*$_2$Qu (a)), 3.67 (12H, m, AlC*H*$_2$), 3.89 (8H, bm, AlC*H*$_2$ & ArC*H*$_2$Ar (b)), 6.62 (4H, bs, calixQu*H*), 6.81 (4H, s, calixAr*H*), 7.37 (1H, m, isophthalyl C*H*), 7.59 (2H, bm, N*H*), 7.96 (2H, m, isophthalyl C*H*), 8.25 (1H, m, isophthalyl C*H*); δ_C($CDCl_3$, 75.47MHz): 31.37, 32.43, 34.05, 41.05, 70.04, 71.14, 74.14, 124.06, 126.57, 129.01, 129.26, 131.96, 133.19, 133.85, 146.50, 147.35, 167.42, 185.48, 191.51; *m/z* (ES+) 891.3850 (M + Na^+. $C_{52}H_{56}N_2O_{10}Na$ requires 891.3833).

2. Titration Protocols

^{1}H NMR Titrations

All titrations were conducted on a Varian Unity Plus 500MHz spectrometer, at 298K in CD_3CN solution. Sample volumes used were 500μL, and all titrations were conducted at 1.5 x 10^{-3} moldm^{-3} concentrations (7.5 x 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, all metals as PF_6 salts except for Na and Li which were added as the ClO_4^- salts for solubility reasons. Aliquots of the anion solution (0.075 moldm^{-3}) were then added (10 x 2μL, 2 x 5μL, 2 x 10μL, 1 x 20μL & 1 x 30μL) so that ten equivalents of anion in total were used. Spectra were recorded after each addition, and the sample shaken thoroughly before measurement.

The resulting titration data were analysed by the WINEQNMR computer program[7] to attempt binding constant determination.

UV-visible Titrations

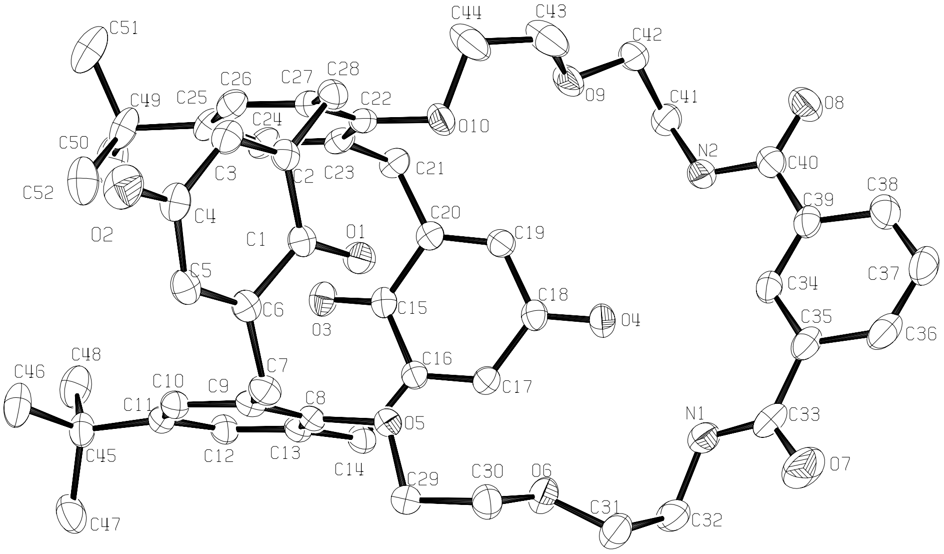
UV-visible experiments were conducted on a Perkin-Elmer Lamda 6 spectrophotometer, at 298K, in dry CH_3CN. The sample volume was 3mL, of 1 x 10^{-4} moldm^{-3} concentration. Where necessary, 1:1 mixtures of receptor and co-analyte were pre-prepared. All salts were thoroughly dried before use; all anions were added as TBA salts, all metals as PF_6 salts except for Li and Na which was added as the ClO_4^- salt for solubility reasons. Aliquots of the anion solution (0.03 moldm^{-3}) were then added (10 x 2μL, 2 x 5μL, 2 x 10μL, 1 x 20μL & 1 x 30μL) so that ten equivalents of analyte in total were used. Spectra were recorded after each addition, and the sample mixed thoroughly before each measurement.

The resulting titration data were analysed by the SPECFIT computer program[8] to attempt binding constant determination. Where only dilution effects were seen, it was inferred that the quinone units were not involved in cation binding.

3. Single X-Ray Crystal Data

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{52}H_{56}N_2O_{10}$·MeCN (ARC1262) (see attached .cif file).



Hydrogen atoms and solvent not shown

Crystals of **1** were grown by slow diffusion of diethyl ether into an acetonitrile solution of **1**. A single crystal having dimensions approximately 0.18 x 0.24 x 0.32 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Oxford Diffraction Gemini CCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the Crysalis software package[9].

The structure was solved in the space group $P\,\bar{1}$ using the direct-methods program SIR92[10], which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[11]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0447, wR = 0.0514.

Attached is a thermal ellipsoid plot (ORTEP-3[12]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comments:

The molecule does not adopt the typical conformation of a calixarene. The two *t*-butylphenyl rings are approximately parallel (the angle between the best planes of the C_6 rings is 1.0°). However, the two quinone rings are not parallel (interplanar angle 30.5°). The 'pendant ' polyether loop adopts an extended conformation such that the two amide NH groups can form relatively long intramolecular hydrogen bonds to one of the quinone O atoms (N(1)···O(4) 3.171(3), N(2)···O(4) 3.237(3) Å).

The molecule of solvent resides within a small pocket bounded by the polyether loop and hydrogen-bonded quinone. It does not participate in hydrogen bonding or any other apparent supramolecular interaction.

Acknowledgement

Oxford Diffraction Ltd are thanked for the loan of the Gemini diffractometer.

4. References

[1] C. D. Gutsche, M. Iqbal, and D. Stewart, *J. Org. Chem.*, 1986, **51**, 742.
[2] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
[3] P. J. Alaimo, D. W. Peters, J. Arnold, and R. G. Bergman, *J. Chem. Ed.*, 2001, **78**.
[4] J. W. Lown, R. R. Koganty, and A. V. Joshua, *J. Org. Chem.*, 1982, **47**, 2027.
[5] P. A. Reddy, R. P. Kashyap, W. H. Watson, and C. D. Gutsche, *Isr. J. Chem.*, 1992, **32**, 89.
[6] A. McKillop, J. S. Fowler, M. J. Zelsko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tet. Lett.*, 1969, **29**, 2423.
[7] M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, **2**, 311.
[8] SPECFIT, *v. 2.02, Spectrum Software Associates, Chapel Hill, NC.*
[9] Crysalis, Oxford Diffraction, 2005
[10] A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
[11] CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487
[12] ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.