Fluorescent switches with high selectivity towards sodium ions: correlation of ion-induced conformation switching with fluorescence function

A. Prasanna de Silva, H. Q. Nimal Gunaratne, Thorfinnur Gunnlaugsson and Mark Nieuwenhuizen

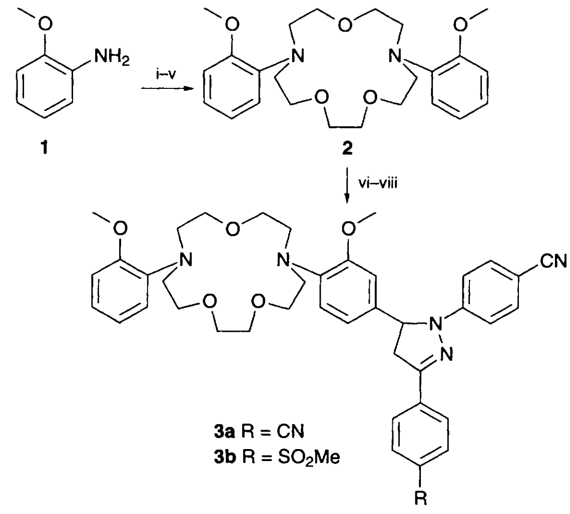
School of Chemistry, Queen's University, Belfast, UK BT9 5AG

Diazacoronand 2 undergoes drastic conformational switching upon binding sodium ions as demonstrated by solution- and solid-state studies, which permit the design of efficient fluorescent PET (photoinduced electron transfer) switches 3a,b.

Ionically controlled fluorescence is a particularly attractive approach to switchable molecular devices.[1] The growth of the field depends critically on the availability of highly selective receptors for the chosen ions. For instance, the development of molecular AND logic gates for information processing[2] required two intramolecular receptors each of which recognised its target ion essentially specifically. We are particularly interested in building a fluorescent switch which could be operated by Na^+ while discriminating against K^+, since these two ions are principal signal carriers during information processing within the nervous system. We now demonstrate that the fluorescence quantum yield of **3** can be selectively switched by an order of magnitude by Na^+ across a concentration range where K^+ is largely ineffective.

The fluorescence revival in **3** is particularly efficient due to a special conformational effect orchestrated by the guest cation. Therefore, the second theme of this paper is the direct correlation of fluorescence switching function with Na^+-induced conformation switching. Crystallographic structure–photoactivity relationships are rare.[3] To the best of our knowledge, no structural evidence is available for the function of any macrocyclic switch displaying simple 'off–on' fluorescent behaviour with s-block ions.

In some fine work, Minta and Tsien have produced a fluorescent sensor, with an inbuilt Na^+ receptor of high selectivity, which measures intracellular Na^+ *via* shifts in excitation spectra.[4] We have now synthesised the isolated receptor unit (which is unknown) and incorporated it into a 'fluorophore–spacer–receptor' system[1c] so that Na^+-induced fluorescence switching can be arranged by suppression of photoinduced electron transfer (PET).[1c,5] The synthesis of **3** is outlined in Scheme 1. Surprisingly, derivatisation of the parent receptor **2** proceeded only on one aniline moiety. Such monoderivatisation leads to lower molecular masses and more convenient solubility properties.



Scheme 1 *Reagents and conditions*: i, TosCl, py;[6] ii, K_2CO_3, NaI, $ClCH_2(CH_2OCH_2)_2CH_2Cl$;[7] iii, H_2CO_4, $MeCO_2H$;[8] iv, $ClCOCH_2OCH_2COCl$, py, C_6H_6;[9] v, B_2H_6;[9] vi, $POCl_3$, dmf;[10] vii, 4-R-C_6H_4COMe, piperidine;[11] viii, 4-$NCC_6H_4NHNH_2$, $MeCO_2H$[11]

The fluorescence emission spectrum of **3a** displays large Na^+-induced increases in intensity. The maximum enhancement of the fluorescence quantum yield is by a factor of 16.[12] This large fluorescence switch arises as follows: when free of ions, the bis(2′-anisyl) diaza 15-crown-5 unit can easily engage in photoinduced electron transfer to the excited pyrazoline fluorophore[13] resulting in very weak fluorescence of **3a** and **3b**. Upon Na^+ complexation, the receptor achieves a pseudocryptand conformation with axial methoxy caps which deconjugates the nitrogen electron pairs from the rest of the 2′-anisidine π-electron systems. This, along with the direct electrostatic effect of Na^+, causes a large increase in the ionisation potential of the receptor and the PET process becomes thermodynamically unfavourable. Fluorescence is therefore re-established as the dominant de-excitation route. The smaller Li^+ can also enter the pseudocryptand cavity and achieves good fluorescence switching, although the binding constant is smaller than that for Na^+. Solution-phase evidence for the Na^+-induced conformational change is available from the hypochromism seen in the UV spectrum of the parent receptor **2** upon addition of Na^+ which signals the deconjugation

Table 1 Ion-induced fluorescence and binding parameters of **3a** and **3b**[a]

	Cation							
Parameter	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	H^+
$\phi_{Fmax.}$ (**3a**)[b]	0.31	0.31	0.082	0.031	0.019	0.019	0.067	0.44
FE (**3a**)[c]	16.3	16.3	4.3	1.6	1.0	1.0	3.5	23
$\phi_{Fmax.}$ (**3b**)[b]	0.17	0.17	0.048	0.018	0.018	0.018	0.039	0.34
FE (**3b**)[c]	9	9	2.7	1.0	1.0	1.0	2.2	19
log β (**3a**)[d]	2.2	3.1	< 1.8	—[e]	—[e]	—[e]	1.2	4.2
log β (**3b**)[d]	2.1	2.8	< 2.0	—[e]	—[e]	—[e]	1.2	4.1

[a] 10^{-5} mol dm^{-3} **3a** or **3b** in MeOH–H_2O (1 : 1, *v*/*v*), pH 7.2 (morpholino propanesulfonate buffer), 10^{-2} mol dm^{-3} NMe_4Cl (for ionic strength control), with excitation at the wavelength of maximum absorption (λ_{abs}). λ_{abs} (**3a**) = 389 nm, log ε (**3a**) = 4.40, λ_{abs} (**3b**) = 385 nm, log ε (**3b**) = 4.34. $\Phi_{Fmin.}$ (**3a**) = 0.019, $\Phi_{Fmin.}$ (**3b**) = 0.018. $\lambda_{flu.}$ (**3a**) = 480 nm, $\lambda_{flu.}$ (**3b**) = 480 nm. [b] Quantum yields obtained by comparison with 9,10-diphenylanthracene.[14] [c] Ion-induced Fluorescence Enhancement factor = $\Phi_{Fmax.}/\Phi_{Fmin.}$ [d] Determined from fluorescence quantum yield (Φ_F)–pM profiles and the equations[1c] $\log[(\Phi_{Fmax.} - \Phi_F)/(\Phi_F - \Phi_{Fmin.})] = pM - \log\beta$. The log β values for **2** with various ions are: 2.5 (Li^+), 3.1 (Na^+), < 2.3 (K^+), < 1 (Ca^{2+}) and 4.7 (H^+) as determined by ion-dependent UV spectroscopy and the equation[15] $\log[(A_{max.} - A)/A - A_{min.})] = \log\beta - pM$, where *A* is the absorbance at a suitable wavelength. The λ_{abs} (log ε) values for **2** when ion-free are 253 nm (3.42) and 277 (sh) (1.79). These values are 260 (2.33) and 278 (sh) nm (1.58) when **2** is Na^+ bound. [e] Fluorescence changes are too small to allow determination of binding constants.

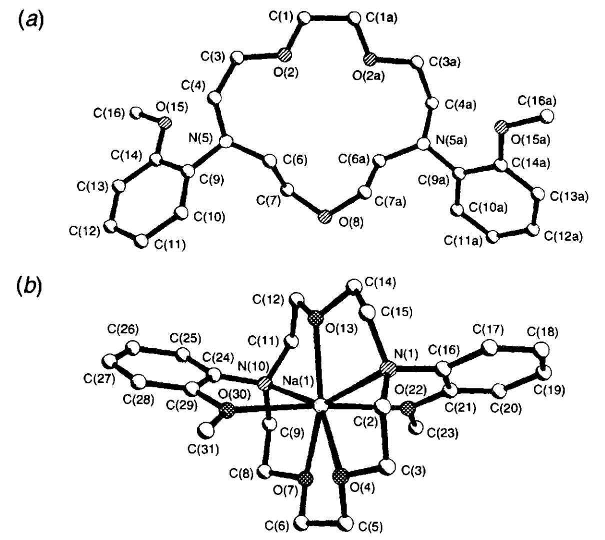


Fig. 1 Structures of (*a*) **2** and (*b*) **2**·$NaPF_6$. Selected dihedral angles for **2** (°); C(4)–N(5)–C(9)–C(14) 71.6, C(6)–N(5)–C(9)–C(10) 26.3; For **2**·$NaPF_6$; C(15)–N(1)–C(16)–C(17) 63.2, C(11)–N(10)–C(24)–C(25) 54.6, C(2)–N(1)–C(16)–C(21) 111.8, C(9)–N(10)–C(24)–C(29) 103.7, Na(1)–N(1)–C(16)–C(21) 2.2, Na(1)–N(10)–C(24)–C(29) 14.4; selected bond lengths for **2**·$NaPF_6$ (Å); Na(1)–N(1) 2.492, Na(1)–O(22) 2.446, Na(1)–N(10) 2.443, Na(1)–O(30) 2.441.

of the nitrogen electron pairs (Table 1, footnote *d*). More direct evidence can be obtained by examining the conformations of the parent receptor **2** with and without Na^+ complexation in the solid state by X-ray crystallography.† Suitable crystals of **2** and **2**·$NaPF_6$ were obtained by slow evaporation from CH_2Cl_2 and $CHCl_3$–MeOH solutions respectively. Fig. 1(*a*), (*b*) clearly show the drastic conformational changes[16] induced by Na^+ binding. The nitrogen electron pairs in **2** are prevented from achieving full conjugation with the anisidine π-electron systems due to the steric effect of the 2′-methoxy groups. Nevertheless, the degree of conjugation is reduced to nearly zero (2.2° in the better case) in **2**·$NaPF_6$, with a rotation of *ca.* 39° about the anisidine carbon–nitrogen bond with reference to **2**. The fluorescence band position and shape of **3a** remains essentially constant as does the UV–VIS absorption spectrum. Thus **3a** represents a fluorescence switch with uncomplicated characteristics. The cation selectivity pattern is seen clearly. The Na^+ response occurs over the range 10^{-4}–10^{-2} mol dm^{-3} whereas the Li^+ and K^+ response requires at least tenfold larger concentrations. It is particularly notable that the fluorescence enhancement factor for K^+ is smaller (4.3, 2.7 respectively for **3a, b**) presumably due to the inability of K^+ to nest within the pseudocryptand cavity. Several other ions cause almost no effect. Protons naturally give rise to large fluorescence enhancements[17] but the effects are negligible above pH 6.

We thank the EPSRC and Queen's University of Belfast for support.

Footnote

† *Crystal data* for $C_{24}H_{23}F_6N_2NaP$ (**2**·$NaPF_6$): M = 430.53, monoclinic, space group $P2_1/c$, a = 11.264(1), b = 16.135(2), c = 15.352(2) Å, β = 98.83(1)°, U = 2757.1(6) Å^3, Z = 4, D_c = 1.442 Mg m^{-3}, $F(000)$ = 1248, μ = 0.194 mm^{-1}, crystal dimensions = 0.71 × 0.31 × 0.24 mm. A total of 5118 reflections were measured for $4 < 2\theta < 50$ and 4856 unique reflections were used in the refinement. The final parameters were $wR2$ = 0.1777 and $R1$ = 0.0640 ($I > 2\sigma I$), S = 1.015, 354 parameters, weighting scheme g_1 = 0.069, g_2 = 1.76, $(\Delta/\sigma)_{max} < 0.001$, $(\Delta\rho)_{max,min.}$ = 0.413, −0.284 e Å^{-3}. An empirical absorption correction was applied using ψ scans, maximum and minimum transmission range 0.761, 0.743. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/161.

References

1 (*a*) V.Balzani and F. Scandola, *Supramolecular Photochemistry*, Ellis-Horwood, Chichester, 1991; (*b*) J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995; (*c*) R. A. Bissell, A. P. de Silva, H. Q. N. Gunaratne, P. L. M. Lynch, G. E. M. Maguire and K. R. A. S. Sandanayake, *Chem. Soc. Rev.*, 1992, **21**, 187; (*d*) *Fluorescent Chemosensors for Ion and Molecule Recognition*, ed. A. W. Czarnik, *ACS Symp. Ser.*, 1992, **538**; (*e*) A. P. de Silva and C. P. McCoy, *Chem. Ind.*, 1994, 992; (*f*) B. Valeur and E. Bardez, *Chem. Br.*, 1995, **31**, 216; (*g*) L. Fabrizzi and A.Poggi, *Chem. Soc. Rev.*, 1995, **24**, 197. Recent work: (*h*) T. D. James, P. Linnane and S. Shinkai, *Chem. Commun.*, 1996, 281; (*i*) D. Parker and J. A. G. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1305.

2 A. P. de Silva, H. Q. N. Gunaratne and C. P. McCoy, *Nature*, 1993, **364**, 42. For an interesting variation, see: S. Iwata and K. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1995, 1491.

3 Photophysics: the work of the Bordeaux group is summarised in J.-P. Desvergne, F. Fages,H. Bouas-Laurent and P. Marsau, *Pure Appl. Chem.*, 1992, **64**, 1231; J.-P. Desvergne, J. Lauret, H. Bouas-Laurent, P. Marsau, N. Lahrahar, H. Andrianatoandro and M. Cotrait, *Recl. Trav. Chim. Pays-Bas*, 1995, **114**, 504; related studies with Ag^+: S. A. Jonker, J. W. Verhoeven, C. A. Reiss, K. Goubitz and D. Heijdenrijk, *Recl. Trav. Chim. Pays-Bas*, 1990, **109**, 154; S. A. Jonker, S. I. Van Dijk, K. Goubitz, C. A. Reiss, W. Schuddeboom and J. W. Verhoeven, *Mol. Cryst. Liq. Cryst.*, 1990, **183**, 273; photochemistry: H. Greiving, H. Hopf, P. G. Jones, P. Bubenitschek, J.-P. Desvergne and H. Bouas-Laurent, *Liebigs Ann.*, 1995, 1949; see T. Y. Fu, J. R. Scheffer and J. Trotter, *Can. J. Chem.*, 1994, **72**, 1952 and earlier papers.

4 A. Minta and R. Y. Tsien, *J. Biol. Chem.*, 1989, **264**, 19449. Recent related work: R. Crossley, Z. Goolamali, J. J. Gosper and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 2*, 1994, 513; 1615; C. Blackburn, M. Bai, K. A. leCompte and M. E. Langmuir, *Tetrahedron Lett.*, 1994, **35**, 7915; M. T. Alonso, E. Brunet, C. Hernandez and J. C. Rodriguez-Ubis, *Tetrahedron Lett.*, 1993, **34**, 7465.

5 R. A. Bissell, A. P. de Silva, H. Q. N. Gunaratne, P. L. M. Lynch, G. E. M. Maguire, C. P. McCoy and K. R. A. S. Sandanayake, *Top. Curr. Chem.*, 1993, **168**, 223; A. W. Czarnik, *Acc. Chem. Res.*, 1994, **27**, 302.

6 B. R. Baker, D. V. Santi and H. S. Shapiro, *J. Pharm. Sci.*, 1962, 1317.

7 J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, *Aza Crown Macrocycles*, Wiley, New York, 1993.

8 F. Diederich, K. Dick and D. Gariebel, *Chem. Ber.*, 1985, **118**, 3588.

9 A. A. Formanovskii and A. S. Murakhovskauya, *Khim. Geterotsikl. Soedin.*, 1985, **2**, 267; *J. Heterocycl. Chem.*, 1985, 225.

10 R. Y. Tsien, *Biochemistry*, 1980, **19**, 2396.

11 D. E. Rivett, J. Rosevear and J. F. K. Wilshire, *Aust. J. Chem.*, 1979, **32**, 1601.

12 *Bioprobes*, 1993, **17**, 11 describes a system of undisclosed structure which gives a Na^+-induced fluorescence enhancement of 7.

13 A. P. de Silva and H. Q. N. Gunaratne, *J. Chem. Soc., Chem. Commun.*, 1990, 186.

14 A. Maciejewski and R. P. Steer, *J. Photochem.*, 1986, **35**, 59.

15 K. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, 1987.

16 See: P. D. Beer, Z. Chen, A. Grieve and J. Haggitt, *J. Chem. Soc., Chem. Commun.*, 1994, 2413 for an ion-induced conformational switch with electrochemical consequences.

17 A. P. de Silva and R. A. D. D. Rupasinghe, *J. Chem. Soc., Chem. Commun.*, 1985, 1669.

Received, 28th May 1996; Com. 6/03659G