DOI: 10.1002/ejoc.200500681

Synthesis of Some New Substituted Photochromic *N*,*N*′-Bis(spiro[1-benzopyran-2,2′-indolyl])diazacrown Systems with Substituent Control over Ion Chelation

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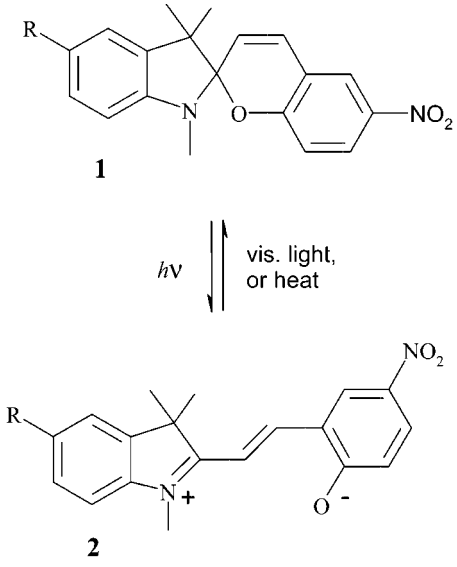
Keywords: Photochromism / Ion chelation / Diazacrown systems / UV/Vis spectroscopy / Spiro compounds

The reversible photochemical ion chelation of the newly synthesised substituted *N*,*N*′-bis(spiro[1-benzopyran-2,2′-indolyl])diazacrown systems **15a–c** and the subsequent molecular electronic control of this process using appropriately placed substituent groups on the spiro-benzopyran skeleton is reported. The principle of molecular electronic control of ion chelation is demonstrated by comparing the behaviour of the newly synthesised nitro-substituted and pyrido-annulated spiro-benzopyran system **9b** with that of the unsubstituted compound **9a**. Electronic substituent control over ion chelation is then exemplified for the new *N*,*N*′-bis(5′-nitrospiro[1-benzopyran-2,2′-indolyl])diazacrown system **15c** and further exemplified for the corresponding 5′-trifluoromethyl derivative **15b**, which contains the photochemically more robust trifluoromethyl group. The crown system **15a**, unsubstituted in the spiro-indole moiety, is also reported.

Introduction

There is ongoing interest in the development of reversible metal-chelating agents in which chelation can be switched on and off by exposure to light of different wavelengths.[1] Several groups have made contributions to this area.[2] A popular substrate for such studies is the 6-nitrospiro[1-benzopyran-2,2′-indole] system **1** and its analogues since these have well-documented photochemical properties.[3] Photoirradiation with UV light at 380 nm leads to the ring-opened zwitterionic (merocyanine) form **2**, which can be converted back to the ring-closed form either by photoirradiation with visible light or thermally. This process may be repeated many times and has formed the basis of light-induced ionic switches. The reversible chelation of specific metal ions has been reported in other systems.[4–7]



Results and Discussion

In order to test our hypothesis that the specific placement of substituents on the spiro-benzopyran moiety could be used to indirectly exert control over metal-ion chelation we firstly synthesised the unsubstituted, pyrido-annulated spiro-benzopyran system[8] **9a** and subsequently the new 5′-nitro-substituted system **9b** in order to undertake comparative studies (see Scheme 1).

In a solution containing metal ions such as cupric, ferric and also Li^+ and Zn^{2+}, **9a** was found to convert rapidly and totally to the chelated open merocyanine form **9c** at room temperature. When metal ions were not present, **9a**/**9c** existed in an equilibrium state of both the open and closed forms. We thus believe the presence of metal ions results in the chelation of the open form, driving the equilibrium towards the right, **9c**. However, when the temperature was reduced to –78 °C no coloration was noted for several minutes, indicating that energetically the ring-opening reaction was not so strong as to preclude possible thermodynamic influence/control by selective substituent placement. In the

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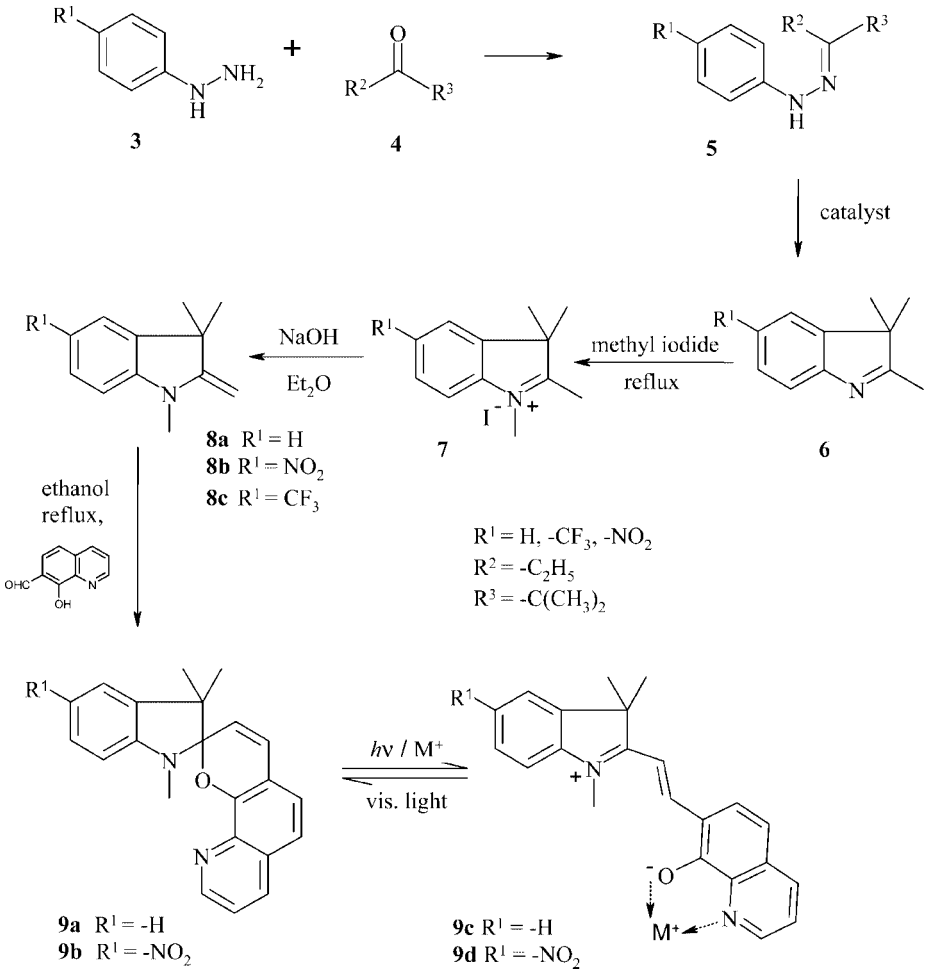


Scheme 1. Synthesis of 5-substituted indolenines.

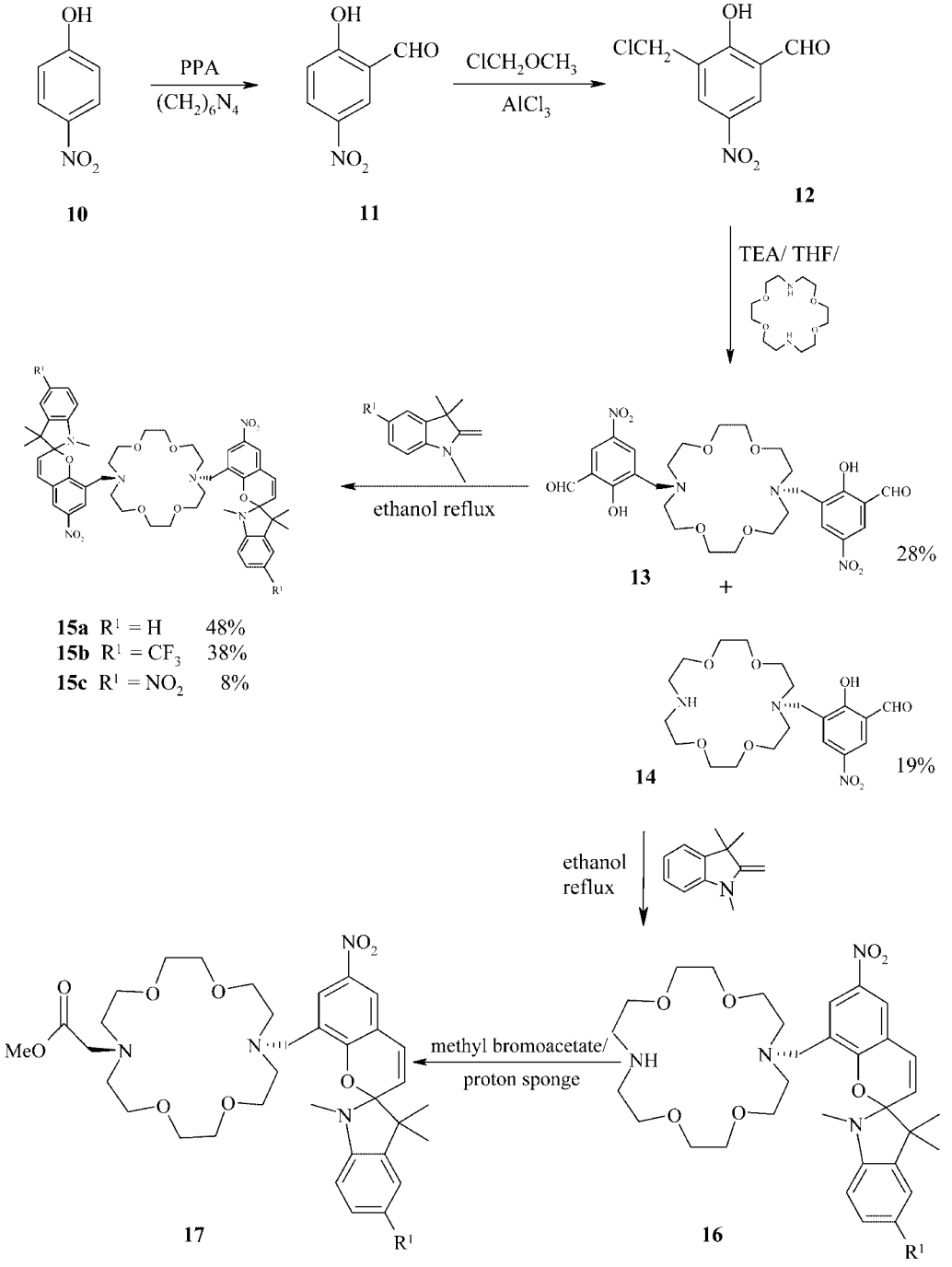
former case the thermodynamics of the chelation to metal ions far outweighed the energies available from visible light, required to photochemically convert this system back to the closed form, as it was not possible to bias this equilibrium by photoirradiation. We hypothesised that we could promote destabilisation of the iminium ion in **9d**, and hence the open zwitterionic form, by the introduction of a 5′-*para*-substituted electron-withdrawing substituent (R^1) in the spiro-benzopyran skeleton, which would further encourage/promote ring-closure to the spirocyclic structure **9b**. This would thus lead to some control over the thermodynamics of the system, thus allowing a degree of electronic/photochemical control over metal-ion chelation. Substituent effects in the quinoline portion of quinoline-spiro-pyranindolines have been reported.[9] Ultimately, we could make further use of this control when trying to influence photoreversibly induced metal-ion chelation.

Synthesis of the pyrido-annulated 5′-nitrospiro[1-benzopyran-2,2′-indole] system **9b** was achieved by refluxing 1,3,3-trimethyl-2-methylene-5-nitroindolenine (**8b**) and 8-hydroxyquinoline-7-carbaldehyde in ethanol. The electron-withdrawing nature of the *para*-substituted 5-nitro group was clearly demonstrated by the poor reactivity of the ene-amine group, which resulted in a mediocre yield (22%) and relatively long reflux times (24 h). Treatment of the 5-nitro system **9b** with Li^+ (perchlorate) at room temperature caused a high degree of ring-opening to the merocyanine form **9d** with only a small portion of the spiro system **9b** remaining, as evidenced by UV spectroscopy. Irradiation of the mixture with visible light caused an observable increase in the concentration of the closed form **9b**, and conversely photoirradiation with UV light promoted an increase in the concentration of the open form. These effects demonstrate the principle that thermodynamic control can be exerted over the photoreversible chelation of metal ions by suitably placed substituents on the spiro-benzopyran skeleton, and in particular, at room temperature.

We subsequently turned our attention to the synthesis of the bis(spiro-benzopyran) diazacrown systems **15a**–**c** (Scheme 2; R^1 = H, CF_3, NO_2). The synthesis of 1,3,3-trimethyl-2-methylene-5-(trifluoromethyl)indolenine (**8c**) was achieved through $BF_3{\cdot}OEt_2$-catalysed Fischer indole synthesis and subsequent steps,[10–12] as shown in Scheme 1. Attempts to prepare the 5-nitro-substituted indolenine **6** by direct nitration[13] of commercially available 2,3,3-trimethylindolenine resulted in a 1:1 mixture of the 5- and 6-nitrated indolenines (total yield 81%), which were almost inseparable by flash chromatography. The two isomers ran, by

TLC, as a figure-of-eight, however, by taking the leading and trailing fractions it was possible to obtain small, but pure fractions of both isomers. This is contrary to reports of the reaction yielding solely 5-nitroindolenine in 88% yield.[13] Since it was envisaged that a relatively large quantity of the 5-nitrated indolenine would be required to complete the synthesis of **15c** an alternative method was employed. We therefore prepared the 5-nitro-substituted indolenine[14–16] **6** ($R^1 = NO_2$) in good overall yield by the unambiguous but slightly longer Fisher indole synthesis, as shown in Scheme 1 (see Expt. Sect.).

We initially tried to synthesise the mono-*N*-substituted crown system **14** by the reaction of one equivalent of 3-(chloromethyl)-2-hydroxy-5-nitrobenzaldehyde[17] (**12**) with one equivalent of the diazacrown in dry THF. The reaction yielded a complex mixture from which the di-*N*-substituted derivative **13** was obtained as a crystalline solid (28% yield) together with a considerable amount of oil, chromatography of which gave the mono-*N*-substituted-azacrown system **14** in 19% yield. Synthesis of the *N*,*N*′-bis(spiro-benzopyran)-substituted crowns **15a**–**c** was achieved by treatment of the di-*N*-substituted crown **13** with the appropriate 5-



Scheme 2. Synthesis of the compounds **15a**–**c** and **17**.

substituted indolenines **8a**–**c** (R^1 = H, CF_3, NO_2) in boiling ethanol. For **15a** the reaction went to completion within eight hours, giving the required product in a reasonable 48% yield. However, when the 5-*para*-trifluoromethyl substituent was introduced into the indolenine structure significant deactivation of the tertiary-eneamine was noted, necessitating reaction times of 72 h for the reaction to go to completion, and resulted in a lower yield of 38%. Further, introduction of the strongly deactivating 5-nitro group into the indolenine resulted in a further decrease in reactivity of the tertiary eneamine, with reaction times of 96 h required to drive the reaction to completion. Consequently the yield for this reaction was only 8% and a considerable amount of polymeric material was also produced.

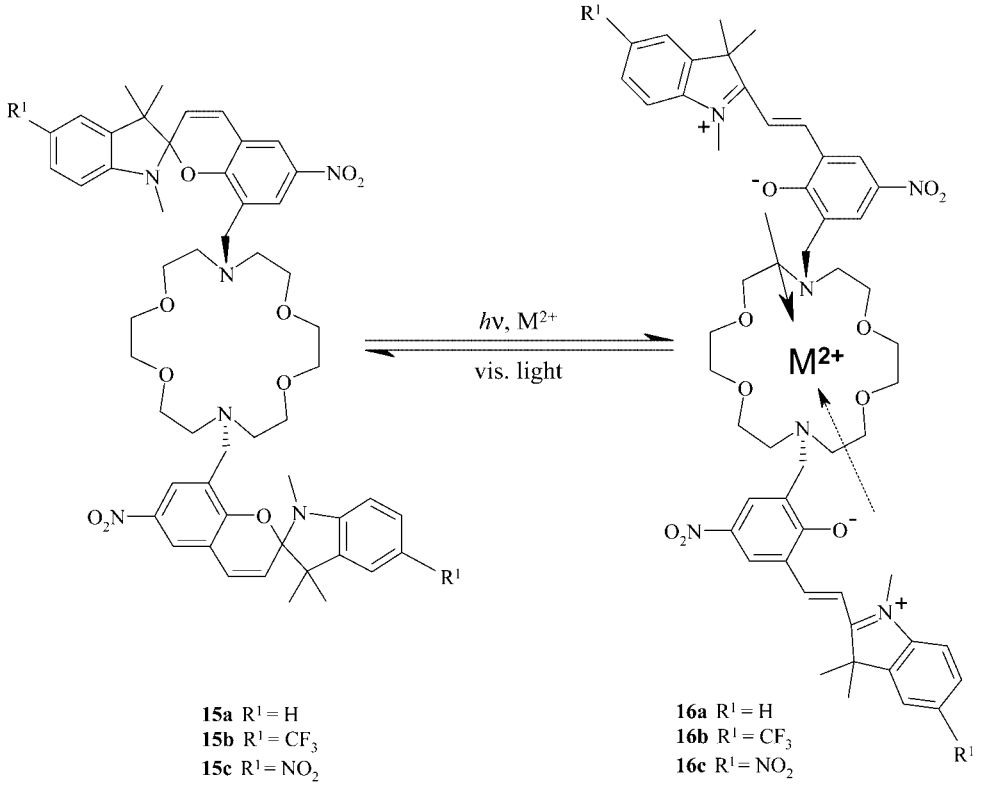
The mono-substituted crown system **16** was similarly synthesised, as shown in Scheme 2, by refluxing **14** with the unsubstituted indolenine in ethanol for 6 h. *N*-Methyl acetylation of the crown system **16** was achieved by treatment with methyl bromoacetate in the presence of a proton sponge to yield **17**.

All the bis-crowned spiro-benzopyrans **15a**–**c** (R^1 = H, CF_3, NO_2) are photochromic, as evidenced by UV spectroscopy, photoirradiation with UV light (see Expt. Sect.) generating the open zwitterionic forms **16a**–**c**, irradiation with visible light causing ring-closure to the starting spirocyclic structures.

The reactions of **15a**–**c** in the presence of selected group I and II metal ions were studied. When equilibrated in a "dark" solution of dried acetonitrile, no further increase in the amount of the open form of the above systems was observed in the presence of lithium or other group I metals, as evidenced by UV spectroscopy. This is perhaps not unexpected since 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane is known to exhibit selectivity for the larger group II metal ions. However, significant effects were noted in the presence of the larger group II metal ions Ba^{2+}, Mg^{2+} and Ca^{2+}.

The unsubstituted spiro-benzopyran system **15a** (R^1 = H) showed a strong affinity for Ca^{2+}, as has previously been found.[18] Additionally, we found that **15a** has a particularly strong affinity for Ba^{2+}, and in its presence converted entirely to its open zwitterionic form. It was not possible to bias this equilibrium with visible light indicating strong thermodynamic chelation. However, when the same system was investigated in the presence of Mg^{2+}, photoreversibility was noted. Photoirradiation with UV light in the presence of Mg^{2+} (2000-fold molar excess) resulted in large increases in the amount of the open form. This effect was reversible, photoirradiation with visible light causing ring-closure to a degree of approximately 14% below that of the dark equilibrium position.

The 5′-trifluoromethyl-substituted system **15b** proved to be largely photoreversible in the presence of Ba^{2+}, however, only small degrees of photoreversibility, as evidenced by UV spectroscopy, were noted with Mg^{2+} and Ca^{2+}, these ions causing almost complete isomerisation to the open zwitterionic form, it not being possible to bias this equilibrium using either UV or visible light. [The transformation of this system, in the presence of Mg^{2+}, to the open merocy-



15a R^1 = H
15b R^1 = CF_3
15c R^1 = NO_2

16a R^1 = H
16b R^1 = CF_3
16c R^1 = NO_2

anine form was followed and confirmed by ^{1}H NMR spectroscopy. Compound **15b** was dissolved in deuterioacetonitrile in an NMR tube and $Mg(ClO_4)_2$ was added (2000-fold molar excess). The ^{1}H NMR spectrum showed the complete disappearance of the *cis*-vicinal protons associated with the closed spirocyclic structure and the appearance of the *trans*-vicinal protons associated with the open merocyanine form **16b**.] In the case of Ba^{2+} this effect supports our hypothesis that the electron-withdrawing group of **16b** destabilises and disfavours the open zwitterionic form compared with the unsubstituted **16a** since far less of the merocyanine form is formed. However, our theory is not supported in the case of **16b** in the presence of Mg^{2+} since, similarly, far less of the merocyanine would be expected compared with the unsubstituted **16a**. We postulate (see below) that this is the result of a complex interplay of interactions involving not only the electron-withdrawing effects of the CF_3 group, but also the size, charge density and overall "fit" of the metal ions into the zwitterionic metal-ion chelated complex of **16b**. Thus, in this particular case, these other factors, in part, negate the electron-withdrawing effect of the CF_3 group, dominating the overall effect. A clearer trend is noted for the very powerfully electron-withdrawing 5-nitro-substituted compound **15c/16c** (see below).

The 5-nitro-substituted system **15c**, when subjected to the same molar excess of Ba^{2+} as the unsubstituted system **15a**, yielded some of the open zwitterionic structure, but considerably less than the unsubstituted system, and less than the CF_3-substituted system **15b**, confirming our hypothesis of the additional thermodynamic destabilisation conferred on the open zwitterionic structure by the 5-nitro group. It was possible to bias the position of this equilibrium by photoirradiation with either UV or visible light. Similarly, when comparing this system with that of the 5-trifluoromethyl system **15b**, both Ca^{2+} and Mg^{2+} ions caused a partial conversion to the open merocyanine form, however, to a smaller degree (note, this was slightly less for Ca^{2+}). It was possible to bias the resulting equilibrium by photoirradiation with either visible or ultraviolet light.

Finally, we attempted to assess the photochromic behaviour of the crowned spiro-benzopyran system **15c** in an aqueous-based medium for the reasons given below. Perhaps not surprisingly the systems were not entirely water soluble, however, they were solublised in 50% aqueous acetonitrile. The structure **15c** exhibited photoreversible behaviour in a solution containing either Ca^{2+} or Mg^{2+} ions, however, it was not possible to shift the equilibrium between the closed spirocyclic and open merocyanine forms to the same extent as that in the equivalent anhydrous system (it is felt that competing hydration of the metal ions, and probably the open merocyanine form, together with significant quenching, are the most likely reasons for the greatly reduced ability to bias the equilibrium position of this system).

In summary we believe the results described above are mostly, but not entirely, simple to qualify and quantify. The biasing of the equilibrium in these systems probably involves a complex set of interactions that are influenced by the following: 1) the type and nature of the substituent at the 5-position, 2) the crown, 3) the size of the metal ion, 4) the charge density of the metal ion, 5) the distribution of charge throughout the zwitterionic structure (in particular that on the phenoxide ion), 6) solvent interactions and 7) the conformation of the overall system in solution. However, despite the complexity of these systems some conclusions and trends can be ascertained. It is clear that the 5-nitro substituent of **9b** does energetically disfavour the open form **9d**, as described earlier. This system, therefore, has a clear advantage over the unsubstituted **9a** when considering their potential use as a possible photoactivated ion-chelation system since the unsubstituted system irreversibly converts to the open form **9c** under identical external physical conditions.

The dinitro crown system **15c** similarly allowed photoactivated control over ring-opening to the merocyanine **16c**, and thus switchable ion chelation, with Ba^{2+}, Ca^{2+} and Mg^{2+} ions. Incorporation of a 5-CF_3 group into the system **16b** does exert an influence over the open/closed equilibrium position, however, the results are far less pronounced than those of the 5-nitro-containing compound. The 5-CF_3 group exerts its effects purely through an inductive electron-withdrawing effect, as opposed to the 5-NO_2 group, which is powerfully electron-withdrawing as a result of both inductive and resonance effects. As such the 5-CF_3 group is not as effective as a 5-NO_2 group in exerting control over the equilibrium position, allowing the other factors, mentioned above, to dominate.

Finally, it is often necessary to determine intracellular Ca^{2+} levels when considering certain diseases as ionic calcium plays a role in mediating the actions of many biological structures such as proteins, catecholamines and hormones, which are responsible for the functioning of normal physiological process. Thus, these systems may ultimately be of potential use as intracellular pharmacological probes, in particular for Ca^{2+}. Further, these systems may have some use in measuring the potency of potential new drug structures that derive their activity from the moderation and hence transportation of ions through cellular ion channels.

Experimental Section

General: 1,3,3-Trimethyl-2-methyleneindoline was purchased from Aldrich. 3-Chloromethyl-2-hydroxy-5-nitrobenzaldehyde (**12**) was prepared from 5-nitrosalicylaldehyde and chloromethyl methyl ether in 71% yield. 8-Hydroxyquinoline-7-carbaldehyde was prepared in 39% yield using the method of Fiedler.[19]

Photoirradiation Studies: The photochromic properties of these compounds were explored by making-up solutions (2×10^{-5} mol dm^{-3} unless otherwise stated), in the dark, in freshly dried and redistilled solvents (generally tetrahydrofuran and acetonitrile). Perchlorate salts were dried with P_2O_5 for several days before use. Solutions were placed in a stoppered 1-cm cuvette at room temperature (20–25 °C) and allowed to equilibrate for 1 h before measurement of their UV/Vis absorption curves (dark curves). The solutions were then irradiated for 1 min with UV light of λ =

365 nm generated from a steady power source. The UV light source was a 200-W mercury/xenon lamp, focussed in a LOT-Oriel air-cooled lamp housing, with solution filters to eliminate light of <320 nm and >400 nm (this allows photoirradiation with a λ_{max} of around 380 nm, the absorption wavelength of the spiro-benzopyrans, and additionally avoids photoirradiation of the formed merocyanine, which has a λ_{max} of around 550 nm). The UV absorption spectra were measured (UV curve) and then the cuvette was exposed to a visible light source for 3 min using a 100-W tungsten spotlight, and the UV absorption spectrum remeasured. The solutions were used a second time to ensure reproducible results were obtained.

^{1}H NMR studies were carried out with a JEOL FX200 spectrometer using deuteriochloroform or [D_6]dimethyl sulfoxide as the solvent with tetramethylsilane as the internal reference. Elemental analyses were carried out in house by Medac. The mass spectrometry service at Swansea University recorded the FAB mass spectra of all the diazacrown systems **15a**–**c**.

UV spectroscopy was carried out using Perkin–Elmer Lambda 5 and Lambda 9 spectrophotometers; both instruments are double-beamed with thermostatically controlled cell blocks. The Lambda 9 is also fitted with an RS 232 port, which allows remote control by PC. All UV measurements were taken at 25 °C using 3-cm^3 quartz cells with a 1-cm path length and are referenced against air.

Compound 9a: 1,3,3-Trimethyl-2-methyleneindoline (**8a**) (0.2 g, 0.867 mmol) and 8-hydroxyquinoline-7-carbaldehyde (0.15 g, 0.867 mmol) were added to ethanol (20 mL) and the resulting mixture was refluxed for 16 h. After this period the solution was reduced in volume to approximately one half and allowed to stand whereupon a purple-coloured solid was formed. Recrystallisation from ethanol yielded **9a** as a slightly purple-coloured solid (0.22 g, 58%), m.p. 188–189 °C.[7]

Compound 9b: 1,3,3-Trimethyl-2-methylene-5-nitroindoline (**8b**) (0.2 g, 0.917 mmol) and 8-hydroxyquinoline-7-carbaldehyde (0.16 g, 0.917 mmol) were added to ethanol (10 mL) and the resulting mixture was refluxed for 24 h. After this period the solution was cooled to room temperature to yield a dark crystalline solid. The solid was removed and recrystallised from ethanol to give **9b** as a greenish solid (72 mg, 22%), m.p. 230–231 °C. IR ($CDCl_3$, film): $\tilde{\nu}_{(max)}$ = 2980, 1655, 1620, 1510, 1325 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.4–8.8 (m, 8 H, ArH), 6.95 (d, J_{vic} = 10.1 Hz, 1 H, C*H*=CH), 5.7 (d, J_{vic} = 10.1 Hz, 1 H, CH=C*H*), 2.9 (s, 3 H, NCH_3), 1.3 (s, 3 H, $ArCCH_3$), 1.2 (s, 3 H, $ArCCH_3'$) ppm; *m*/*z* (%) = 373 (26) [M]$^+$, 358 (100). $C_{22}H_{19}N_3O_3$ (373.41): calcd. C 70.8, H 5.1, N 11.3; found C 70.5, H 5.2, N 11.1.

Compounds 13 and 14: 3-Chloromethyl-2-hydroxy-5-nitrobenzaldehyde (**12**)[17] (1 g, 4.64 mmol) was added portionwise with stirring to 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (1.2 g, 4.64 mmol) in dried THF, containing a trace of TEA, over 20 min at ice temperature. After 5 h at ice temperature the mixture was allowed to warm to room temperature and stirring was continued for a further 16 h during which time a yellow solid was precipitated. The resulting mixture was then refluxed for 5 h before being cooled and concentrated to dryness. Methanol was added and the yellow solid that formed was filtered off to give compound **13** as a yellow crystalline solid (0.8 g, 28%), m.p. 183–185 °C. IR (KBr): $\tilde{\nu}_{(max)}$ = 3500, 2900, 1670, 1610, 1580 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$]: δ = 9.8 (s, 1 H, CHO), 8.1–8.4 (m, 2 H, ArH), 8.1 (s, 1 H, OH), 4.5 (s, 2 H, NCH_2Ar), 3.65–4.0 (m, 16 H, OCH_2), 3.3 (m, 8 H, NCH_2) ppm. $C_{28}H_{36}N_4O_{12}\cdot 2H_2O$ (640.64): calcd. C 51.2, H 6.1, N 8.5; found C 50.7, H 5.9, N 8.4.

The remaining filtrate was concentrated in volume and purified by chromatography over silica gel using methanol as eluent to give **14** as a yellow oil which solidified on standing (0.39 g, 19%), m.p. 165.5–166.5 °C. IR (KBr): $\tilde{\nu}_{(max)}$ = 3500, 3350, 1690, 1600, 1560, 1510, 1320 cm^{-1}; ^{1}H NMR [$(CDCl_3)$/$(CD_3)_2SO$]: δ = 9.8 (s, 1 H, CHO), 8.1–8.4 (m, 2 H, ArH), 8.1 (s, 1 H, OH), 4.5 (s, 2 H, NCH_2Ar), 3.65–4.0 (m, 16 H, OCH_2), 3.3 (m, 8 H, NCH_2) ppm; *m*/*z* = 442 [MH]$^+$, 464 [MNa]$^+$. $C_{20}H_{31}N_3O_8\cdot 2.5H_2O$ (486.52): calcd. C 49.4, H 7.4, N 8.6; found C 49.1, H 6.9, N 8.5.

Compound 15a: 1,3,3-Trimethyl-2-methyleneindoline (0.116 g, 0.644 mmol) and the diazadisalicylaldehyde **13** (0.2 g, 0.322 mmol) were added to ethanol (20 mL) and the resulting mixture was refluxed for 8 h. After this period the ethanol was removed under reduced pressure to yield a red oil which was purified by chromatography over silica gel using methanol as eluent to give **15a** as an off-white powder (143 mg, 48%), m. p. 142–3 °C. IR (KBr): $\tilde{\nu}_{(max)}$ = 2800–3000, 1650, 1610, 1590, 1520, 1490, 1450, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.4–8.2 (m, 12 H, ArH), 6.8 (d, J_{vic} = 10.2 Hz, 2 H, C*H*=CH), 5.8 (d, J_{vic} = 10.2 Hz, 2 H, CH=C*H*), 3.4 (m, 16 H, OCH_2), 3.45 (s, 4 H, $ArCH_2N$), 2.5 (s, 6 H, NCH_3), 2.4 (br. t, 8 H, NCH_2), 3.4 (s, 6 H, $ArCCH_3$), 1.2 (s, 6 H, $ArCCH_3'$) ppm; *m*/*z* = 931 [MH]$^+$, 953 [MNa]$^+$. $C_{52}H_{62}N_6O_{10}\cdot 2H_2O$ (967.13): calcd. C 64.6, H 6.8, N 8.7; found C 64.2, H 6.5, N 8.65.

Compound 15b: 1,3,3-Trimethyl-5-trifluoromethyl-2-methyleneindoline (0.15 g, 0.622 mmol) and the diazadisalicylaldehyde **13** (0.19 g, 0.31 mmol) were added to ethanol (9 mL) containing DMF (1 mL) and the resulting mixture was refluxed for 72 h until the disappearance, by TLC, of the starting materials. The hot solution was filtered and left for 24 h at room temperature where upon a light-tan-coloured powder was formed. This was filtered off and washed with ethanol to yield **15b** as a light-sand-coloured solid (0.13 g, 38%), m.p. 199–200 °C. IR ($CDCl_3$, film): $\tilde{\nu}_{(max)}$ = 2750–2900, 1640, 1610, 1580, 1510, 1310 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.5–8.2 (m, 10 H, ArH), 6.9 (d, J_{vic} = 10.2 Hz, 2 H, C*H*=CH), 5.7 (d, J_{vic} = 10.2 Hz, 2 H, CH=C*H*), 3.4 (m, 16 H, OCH_2), 3.2 (s, 4 H, $ArCH_2N$), 2.7 (s, 6 H, NCH_3), 2.6 (br. t, 8 H, NCH_2), 1.3 (s, 6 H, $ArCCH_3$), 1.2 (s, 6 H, $ArCCH_3'$) ppm; *m*/*z* = 1067 [MH]$^+$ (FAB MH$^+$: calcd. 1067.432263; found 1067.435337), 1089 [Mna]$^+$. $C_{54}H_{60}F_6N_6O_{10}\cdot 2H_2O$ (1103.12): calcd. C 58.8, H 5.8, N 7.5; found C 58.3, H 5.5, N 7.4.

Compound 15c: 1,3,3-Trimethyl-5-nitro-2-methyleneindoline (0.1 g, 0.46 mmol) and the diazadisalicylaldehyde **13** (0.142 g, 0.229 mmol) were added to ethanol (8 mL) containing DMF (1 mL) and the resulting mixture was refluxed for 96 h until the disappearance, by TLC, of the starting materials. After this period all the solvents were removed under high vacuum to give an oil which was triturated with ethyl acetate. The resulting solid was recrystallized from ethanol to yield compound (**15c**) as a light-tan-coloured powder (38 mg, 8%), m.p. 230–231 °C. IR (KBr): $\tilde{\nu}_{(max)}$ = 2800–3000, 1655, 1610, 1515, 1320 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.2–7.95 (m, 10 H, ArH), 6.6 (d, J_{vic} = 10.6 Hz, 2 H, C*H*=CH), 5.5 (d, J_{vic} = 10.6 Hz, 2 H, CH=C*H*), 3.15 (m, 16 H, OCH_2), 3.1 (s, 4 H, $ArCH_2N$), 2.5 (s, 6 H, NCH_3), 2.4 (br. t, 8 H, NCH_2), 1.05 (s, 6 H, $ArCCH_3$), 0.9 (s, 6 H, $ArCCH_3'$) ppm; *m*/*z* = 1021 [MH]$^+$, 1043 [MNa]$^+$. $C_{52}H_{60}N_8O_{14}\cdot 2H_2O$ (1057.12): calcd. C 59.1, H 5.7, N 10.6; found C 58.7, H 5.6, N 10.5.

Compound 16: 1,3,3-Trimethyl-2-methyleneindoline (40 mg, 0.226 mmol) was added to the monocrowned salicylaldehyde **14** (0.1 g, 0.226 mmol) in ethanol (10 mL) and the resulting mixture was refluxed until the disappearance, by TLC, of the starting materials (6 h). After this period the ethanol was reduced in volume to

one third and the mixture left to stand to give compound (**16**) as a golden-coloured crystalline solid (120 mg, 61%), m.p. 105–106 °C. IR ($CDCl_3$, film): $\tilde{\nu}_{(max)}$ = 3300, 2900, 1640, 1600, 1550, 1510, 1330 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.3–8.2 (m, 6 H, ArH), 6.3–7.1 (d, J = 10.2 Hz, 1 H, C*H*=CH), 6.3–7.1 (d, J = 10.2 Hz, 1 H, CH=C*H*), 4.1 (s, 2 H, $ArCH_2N$), 2.6–3.0 (m, 16 H, OCH_2), 2.6–3.0 (m, 8 H, NCH_2), 2.8 (s, 3 H, NCH_3), 1.6 (s, 3 H, $ArCCH_3$), 1.3 (s, 3 H, $ArCCH_{3'}$) ppm; m/z = 597 $[MH]^+$, 619 $[MNa]^+$. $C_{32}H_{44}N_4O_7{\cdot}2H_2O$ (632.75): calcd. C 60.75, H 7.6, N 8.9.; found C 60.3, H 7.3, N 8.6.

Compound 17: Compound **16** (0.1 g, 0.226 mmol) was dissolved in acetonitrile (5 mL) and cooled to ice temperature. After 15 min a proton sponge (0.0534 g, 0.24 mmol) was added and after a further 5 min methyl bromoacetate (42 mg, 0.272 mmol) was also added. The mixture was stirred at ice temperature for 1 h and then slowly allowed to warm to room temperature. Stirring was continued for a further 20 h at room temperature and then the mixture was refluxed for 2 h. After this period the solvent was removed under reduced pressure to give an oil. This oil was triturated with diethyl ether, which resulted in the precipitation of a solid. The solid (protonated proton sponge) was filtered off and discarded. The residue was reduced in volume and purified by chromatography over silica gel using methanol as eluent. The product, compound (**17**), was collected as a red semi-solid (80 mg, 29%). IR ($CDCl_3$, film): $\tilde{\nu}_{(max)}$ = 2800–3000, 1735, 1650, 1610, 1580, 1520, 1340 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.4–8.1 (m, 6 H, ArH), 6.7 (d, J_{vic} = 10.5 Hz, 1 H, C*H*=CH), 5.7 (d, J_{vic} = 10.5 Hz, 1 H, CH=C*H*), 3.6 (s, 2 H, $ArCH_2N$), 3.5 (s, 2 H, NCH_2CO_2Me), 3.4 (s, 3 H, OCH_3), 3.35 (m, 8 H, NCH_2CH_2O), 2.85 (m, 8 H, NCH_2), 2.7 (s, 8 H, OCH_2CH_2), 2.6 (s, 3 H, NCH_3), 1.2 (s, 3 H, $ArCCH_3$), 1.1 (s, 3 H, $ArCCH_{3'}$); m/z = 669 $[MH]^+$, 691 $[MNa]^+$. $C_{35}H_{48}N_4O_9{\cdot}2H_2O$ (704.82): calcd. C 59.65, H 7.4, N 7.95; found C 59.2, H 7.1, N 7.8.

Acknowledgments

C. J. R. thanks the S.E.R.C. for a postdoctoral fellowship.

[1] a) I. Willner, B. Wilner, "Chemistry of Photobiological Switches", in *Biological Applications of Photochemical Switches* (Ed.: H. Morrison), John Wiley & Sons, New York, **1993**, pp. 1–110; b) J. D. Winkler, K. Deshayes, B Shao, "Photochemical Binding, Release and Transport of Metal Ions", in *Biological Applications of Photochemical Switches* (Ed.: H. Morrison), John Wiley & Sons, New York, **1993**, pp. 171–196.

[2] a) M. Inouye, *Coord. Chem. Rev.* **1996**, 30; M. Inouye, K. Akanatsu, H. Nakazumi, *J. Am. Chem. Soc.* **1997**, *119*, 9160; b) J. Zhou, F. Zhao, Y. Li, F. Zha, X. Song, *J. Photochem. Photobiol. A: Chem.* **1995**, *92*, 193; c) M. V. Alfimov, Y. V. Fedorov, O. A. Federova, S. S. Gromov, R. E. Hester, I. K. Lednev, J. N. Moore, V. P. Oleshko, A. I. Vedernikov, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1441; d) M. V. Alfimov, A. V. Churakov, Y. V. Fedorova, S. P. Gromov, R. E. Hester, A. K. Howard, L. G. Kuzimina, I. K. Lednev, J. N. Moore, *J. Chem. Soc., Perkin Trans. 2* **1997**, 2249; e) O. A. Federova, Y. P. Strokach, S. P. Gromov, A. V. Koshkin, T. M. Valova, M. V. Alfimov, A. V. Feonfanov, I. S. Alaverdian, V. A. Lokshin, A. Samat, R. Guglielmetti, R. B. Girling, J. N. Moore, R. E. Hester, *New J. Chem.* **2002**, *26*, 1137.

[3] a) R. C. Bertleson, "Photochromism", in *Techniques of Organic Chemistry* (Ed.: G. H. Brown), Wiley Interscience, New York, **1971**, chapter 3, pp. 45–294; b) R. Guglielonetti in *Photochromism Molecules and Systems* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **1990**, chapter 8, pp. 314–466.

[4] a) K. Kimura, T. Yamashita, M. Yokoyama, *J. Chem. Soc., Chem. Commun.* **1991**, 147; b) K. Kimura, T. Yamashita, M. Yokoyama, *J. Chem. Soc., Perkin. Trans. 2* **1992**, 613.

[5] K. Kimura, *Coord. Chem. Rev.* **1996**, *148*, 41.

[6] K. Kimura, M. Kaneshiga, T. Yamashita, M. Yokoyama, *J. Org. Chem.* **1994**, *59*, 1251.

[7] M. Tanaka, K. Kamada, H. Ando, T. Kitagako, Y. Shibutani, S. Yajima, H. Sakamoto, K. Kimura, *Chem. Commun.* **1999**, 1453.

[8] J. P. Phillips, A. Mueller, F. Przystal, *J. Am. Chem. Soc.* **1965**, *87*, 4020.

[9] G. E. Collins, L. S. Choi, K. J. Ewing, V. Michelet, C. M. Brown, J. P. Winkler, *Chem. Commun.* **1999**, 321.

[10] E. J. Forbes, M. Stacey, J. C. Tatlow, R. T. Wragg, *Tetrahedron* **1960**, *8*, 67.

[11] V. I. Troitskaya, I. G. Oksengendler, *Khim. Geterotsiki. Soedin.* **1982**, *1*, 39 [*Chem Abstr.* **1982**, *97*, 57109Z].

[12] L. M. Yagupolskii, S. V. Pasenok, M. A. Gal'bershtam, G. K. Bobyleva, V. I. Popov, N. V. Kondratenko, *Dyes Pigm.* **1981**, *2*, 205.

[13] K. Brown, A. R. Katritzky, *Tetrahedron Lett.* **1964**, *14*, 803.

[14] D. S. Deorha, S. S. Joshi, *J. Org. Chem.* **1961**, *26*, 3527.

[15] V. I. Troitskaya, I. G. Oksengendler, S. V. Pazenok, M. S. Lyubich, S. M. Larina, L. M. Yagulpol'skii, *Khim. Geterotsiki. Soedin.* **1982**, *1*, 39.

[16] N. P. Samoilova, M. A. Gal'bershtam, *Khim. Geterotsiki. Soedin.* **1977**, *8*, 855.

[17] L. D. Taylor, R. B. Davis, *J. Org. Chem.* **1963**, *28*, 1713.

[18] a) K. Kimura, T. Teranishi, M. Yokoyama, S. Yajima, S. Miyake, H. Sakamoto, M. Tanaka, *J. Chem. Soc., Perkin Trans. 2* **1999**, 199; b) K. Kimura, T. Utsumi, T. Teranishi, M. Yokoama, H. Sakamoto, M. Okamoto, R. Arakawa, H. Moriguchi, Y. Miyaji, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2453; c) M. Nakamura, H. Sakamoto, T. Fujioka, K. Kimura, *New J. Chem.* **2002**, *26*, 554; d) K. Kimura, T. Teranishi, M. Yokoyama, *Supramol. Chem.* **1996**, *7*, 11.

[19] H. Fiedler, *Arch. Pharm. (Weinheim, Ger.)* **1964**, 108.

Received: September 7, 2005
Published Online: December 5, 2005

