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Stabilisation of a heptamethine cyanine dye by rotaxane encapsulation†

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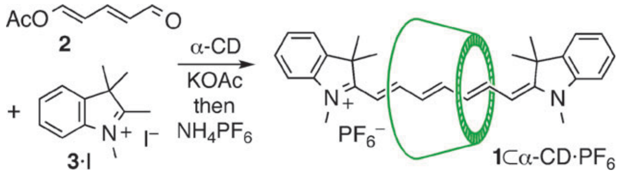
The crystal structure of a cyanine dye rotaxane shows that the cyclodextrin is tightly threaded round the polymethine bridge of the dye; encapsulation dramatically increases the kinetic chemical stability of the radicals formed on oxidation and reduction of the dye, making it possible to observe the rotaxane radical dication by ESR and UV-vis-NIR spectroscopy.

Cyanine dyes are an important class of chromophores because of their strong absorption and fluorescence at visible and near-IR wavelengths, although poor chemical and photochemical stability often limit the applications of the longer cyanines.[1] Rotaxane formation[2] is emerging as a useful strategy for the encapsulation and stabilisation of reactive chromophores.[3–5] Previously we have shown that unsymmetrical donor–acceptor cyanine-type dyes can be stabilised with respect to photobleaching by threading them through α-cyclodextrin to form rotaxanes.[5] However, it was only possible to synthesise these rotaxanes in small quantities using an unusual julolidine–pyridinium cyanine core. Here we present the synthesis and crystal structure of an extremely simple cyanine dye rotaxane, $\mathbf{1}^+ \subset$α-CD, consisting of the widely studied symmetrical heptamethine chromophore, 1,1′,3,3,3′,3′-hexamethylindotricarbocyanine, threaded through α-cyclodextrin. The trimethyl indole terminal groups of the standard dye are sufficiently bulky to lock the cyclodextrin permanently over the centre of the chromophore, without the need for any additional bulky stopper groups. This simple rotaxane can easily be synthesised on a gram scale in one step from readily available starting materials. Encapsulation of the chromophore increases its stability towards photobleaching, and increases the kinetic chemical stability of the radicals formed by oxidation and reduction, enabling us to record the ESR and absorption spectrum of the persistent dication-radical $\mathbf{1}^{2+} \subset$α-CD.

After screening a wide range of reaction conditions, we found that rotaxane $\mathbf{1} \subset$α-CD·PF_6 can be prepared in 13% yield (1.7 g) by reacting glutaconaldehyde acetate **2**[6] with a tetramethyl indolium salt **3**·I in the presence of α-cyclodextrin in aqueous potassium acetate, as shown in Scheme 1 (see Supporting Information†). $\mathbf{1} \subset$α-CD·PF_6 is a kinetically robust rotaxane; no unthreading was observed by ^1H NMR when a solution of $\mathbf{1} \subset$α-CD·PF_6 in d_6-DMSO was heated to 100 °C for 72 h. The rotaxane was authenticated by NMR, ESMS, elemental analysis and X-ray crystallography. The 2D NOESY spectrum reveals contacts between H3, H5 and H6 of the cyclodextrin and protons on the polymethine bridge of the cyanine dye. The asymmetry of the cyclodextrin also results in a splitting of all the proton resonances of the threaded dye: the ends of the dye become nonequivalent, and the geminal dimethyl groups become diastereotopic due to the chiral environment.

Single crystals of $\mathbf{1} \subset$α-CD·PF_6 were grown from aqueous solution by slow cooling. Several X-ray diffraction data sets were acquired for these crystals, and for crystals of the same rotaxane with other counter anions, using both laboratory and synchrotron X-ray sources. The structure proved extremely difficult to solve because of the large size of the unit cell (a = 24.8 Å, b = 20.5 Å, c = 30.8 Å; volume = 15 609 Å^3), the weak scattering of the atoms and extensive disorder of occluded water molecules, but we eventually obtained a solution using synchrotron data.‡ There are four molecules of the rotaxane in the asymmetric unit, but each rotaxane has essentially the same molecular structure; two orthogonal views of one rotaxane unit are shown Fig. 1. The cyclodextrin clasps the centre of the dye, but its asymmetric environment does not significantly distort the geometry of the chromophore. Within the resolution of this structure (standard deviation in bond lengths: 0.016 Å), there is no bond length alternation in the polymethine. There is only a slight helical twist between the mean-planes of the indole end groups (angle between mean planes: +14.1°, +18.1°, +4.0° and −5.6° for the four



Scheme 1 Synthesis of the cyanine dye rotaxane.

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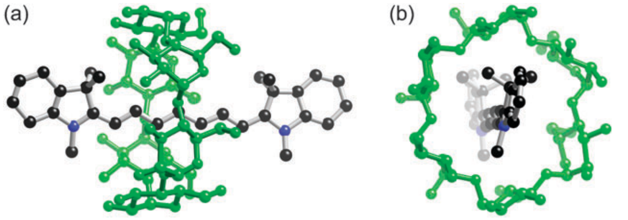

Fig. 1 Two orthogonal views of the structure of rotaxane **1**⊂α-CD·PF$_6$ in the crystal (one of the four molecules in the asymmetric unit; hydrogen atoms omitted for clarity; α-CD shown in green).

rotaxane molecules). The rotaxanes are packed so that every indole terminus makes an off-set face-to-face π-stacking interaction with an indole of another rotaxane unit to form infinite linear strands of chromophores (Fig. 2). Similar π-stacked strands have been observed in the crystal structures of other cyclodextrin rotaxanes, and are interesting because they suggest a mechanism for charge-transport in insulated molecular wires of this type.[4,7,8]

The solution-phase absorption and fluorescence spectra of rotaxane **1**$^+$⊂α-CD are similar to those of the free dye, **1**$^+$, although the spectra of the rotaxane are sharper and red-shifted. For example in methanol, the hexafluorophosphate salt of the rotaxane absorbs with $\lambda_{\max}$ 770 nm (ε = 2.8 × 10^5 M^{-1} cm^{-1}) and emits with $\lambda_{\max}$ 796 nm (ϕ_F = 0.23) whereas the free dye absorbs with $\lambda_{\max}$ 741 nm (ε = 2.3 × 10^5 M^{-1} cm^{-1}) and emits with $\lambda_{\max}$ 778 nm (ϕ_F = 0.37).[9] The presence of the threaded cyclodextrin reduces the fluorescence quantum yield,§ but increases the photostability of the dye. The relative photostabilities of **1**$^+$⊂α-CD and **1**$^+$ were compared by irradiating air-saturated aqueous solutions of the two compounds, at the same concentration, using a laser to excite both samples at the wavelength (752 nm) where they have the same extinction coefficient (Fig. 3); under these conditions the free dye is bleached 3.9 times faster than the rotaxane. An even more dramatic stabilisation effect is seen in the electrochemistry of **1**$^+$⊂α-CD. The cyclic voltammetry of the rotaxane is

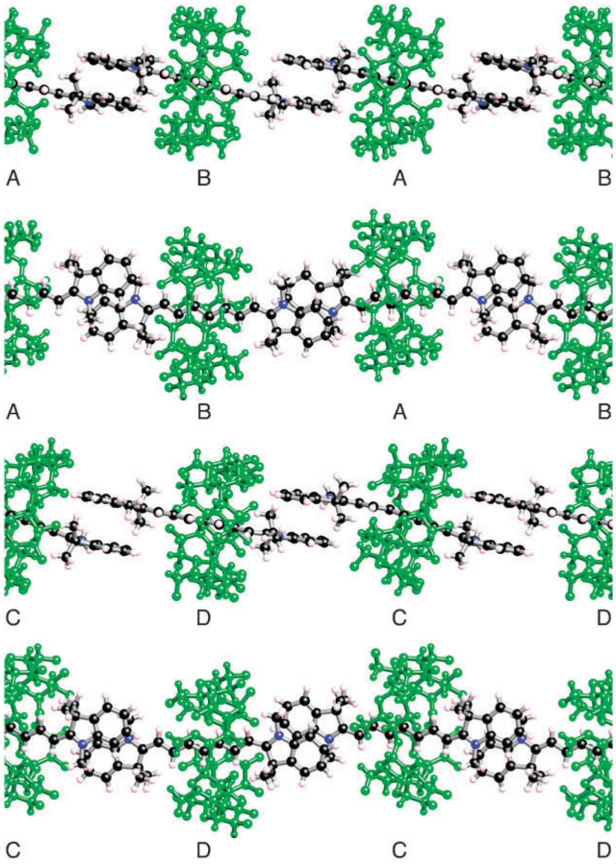

Fig. 2 Two orthogonal views of the two strands, ABAB and CDCD, of rotaxane molecules in the crystal structure of **1**⊂α-CD·PF$_6$. The four rotaxane molecules in the asymmetric unit are labelled A–D (α-CD in green; PF$_6$ anions and water molecules omitted for clarity).

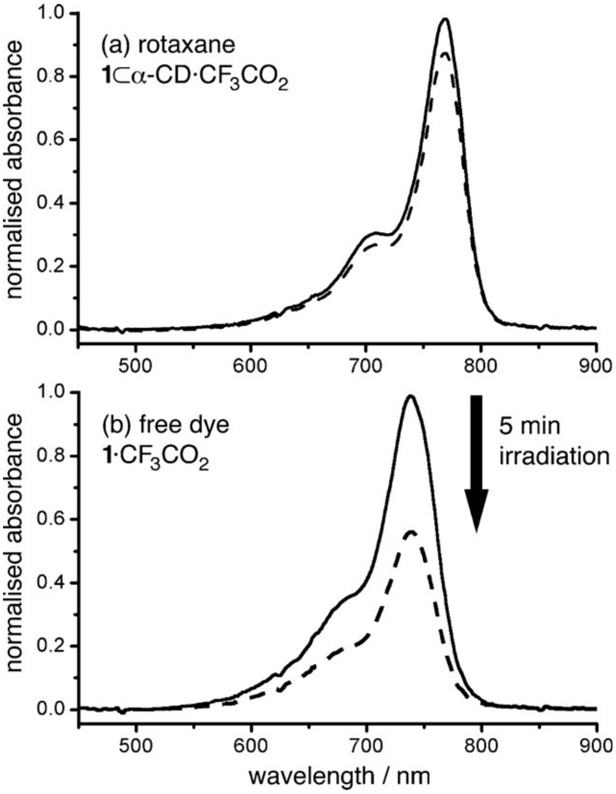

Fig. 3 Absorption spectra of air-saturated aqueous solutions of rotaxane **1**⊂α-CD·CF$_3$CO$_2$ (a) and free dye **1**·CF$_3$CO$_2$ (b) before (plain) and after (dashed) laser irradiation at 752 nm in air-saturated water for 5 min under identical conditions, showing the faster photobleaching of the free dye.

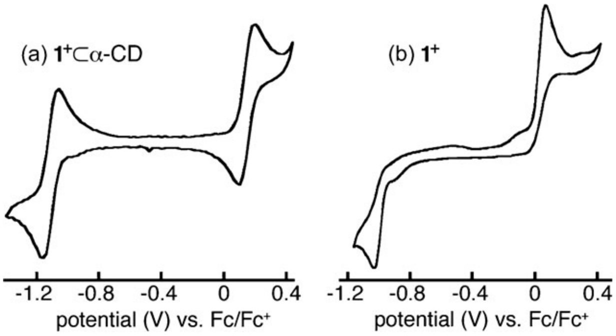

Fig. 4 Cyclic voltammagrams of rotaxane **1**⊂α-CD·PF$_6$ and free dye **1**·PF$_6$, in DMSO (both 1.0 mM in DMSO with 0.10 M Bu$_4$NPF$_6$, scan rate 2.0 mV s^{-1}). The oxidation and reduction potentials, from square-wave voltammetry, are +0.16 V and −1.16 V for **1**$^+$⊂α-CD, and +0.04 V and −1.09 V for **1**$^+$, all relative to internal ferrocene (Fc/Fc$^+$).

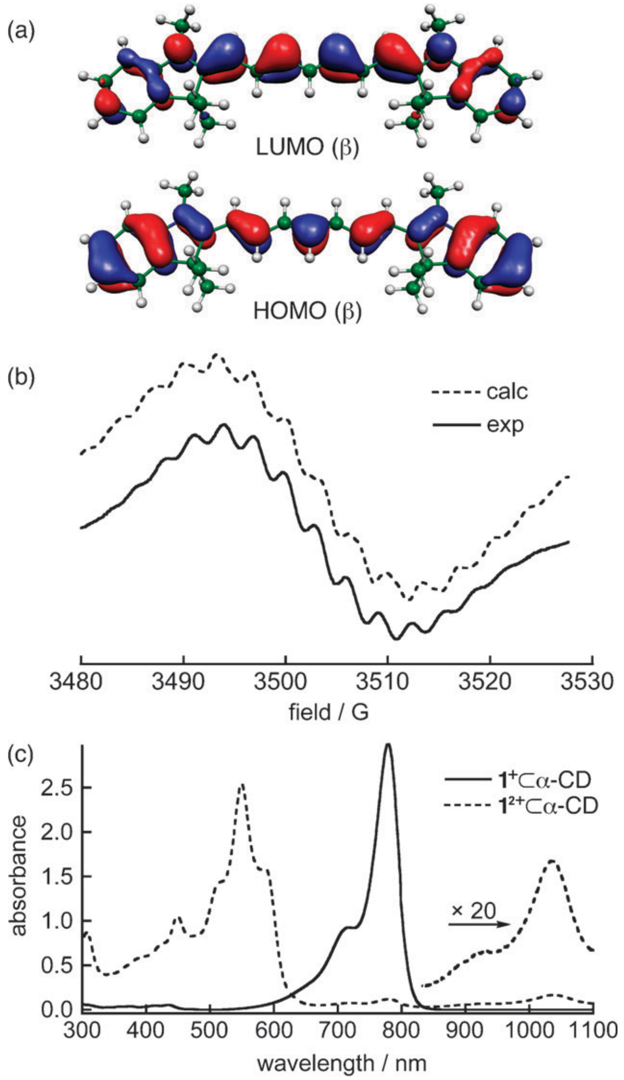

Fig. 5 (a) Representations of the HOMO(β) and LUMO(β) of the $\mathbf{1}^{2+}$ radical dication, calculated at the spin-unrestricted UB3LP/6-31G** level. TD-DFT calculations predict a first optical transition ($D_0 \rightarrow D_1$) for this radical at 954 nm (oscillator strength f = 0.2), primarily involving HOMO(β) → LUMO(β) excitation. (b) Experimental ESR spectrum of the radical dication $\mathbf{1}^{2+}\subset\alpha$-CD from oxidation of $\mathbf{1}\subset\alpha$-CD·PF$_6$ with ceric ammonium nitrate compared to a calculated spectrum using DFT coupling constants scaled by a factor of 0.9, and (c) UV-vis-NIR spectra of $\mathbf{1}\subset\alpha$-CD·PF$_6$ in DMSO before and after addition of one equivalent of ceric ammonium nitrate.

cleanly reversible, even at slow scan rates, whereas that of the free dye shows the irreversible oxidation and reduction typical of extended cyanine dyes[10] (Fig. 4).

The kinetic chemical stability of the oxidised and reduced radicals of the rotaxane makes it possible to prepare these radicals by chemical oxidation in solution. Fig. 5 shows the ESR and UV-vis-NIR absorption spectrum of the radical dication generated by chemical oxidation of $\mathbf{1}\subset\alpha$-CD·PF$_6$ with ceric ammonium nitrate; the corresponding $\mathbf{1}$·PF$_6$ decomposes under the same conditions. The optical spectrum is broadly consistent with those of previously reported cyanine radical dications, which have been stabilised by covalent modification of the polymethine bridge.[11] TD-DFT calculations indicate that the NIR band of the radical dication observed at 1047 nm can be assigned to a transition between the HOMO(β) and LUMO(β) orbitals shown in Fig. 5a (where β denotes the spin direction). The identity of the dication radical $\mathbf{1}^{2+}\subset\alpha$-CD is further supported by the ESR spectrum, which resembles that predicted by DFT calculations (Fig. 5b).

In summary, we report a practical gram-scale synthesis of a simple cyanine dye rotaxane. The crystal structure of this rotaxane shows that the cyclodextrin is tightly clasped around the centre of the dye, explaining the kinetic chemical stability of its oxidised and reduced radicals. Rotaxane formation is a promising general approach to improving the chemical stability of polymethine dyes, and preliminary results indicate that this strategy can be used to stabilise longer versions of **1** with $(CH)_9$ and $(CH)_{11}$ polymethine bridges. Rotaxane formation increases the water-solubility of the dye, which may be useful for medical applications.[3] The threaded α-cyclodextrin macrocycle, with 18 OH groups, can also be viewed as a hub for further functionalisation of the dye.

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Notes and references

‡ Crystal data: $C_{260}H_{298}F_{24}N_8O_{134}P_4$, M = 6259.01, Z = 2, monoclinic, space group $P2_1$, a = 24.8064(4) Å, b = 20.5004(3) Å, c = 30.7944(5) Å, β = 94.643(1)°, U = 15 608.8(4) Å^3, T = 120(2) K, μ = 0.135 mm^{-1}; of 271 130 reflections measured, 79 886 were independent (R_{int} = 0.06). Number of reflections with Fredel's Law is 42 692. R_{Final} = 0.1752 (18 317 reflections with $I > 3\sigma(I)$) and wR = 0.1892. CCDC 661299.†

§ The reduced fluorescence efficiency of $\mathbf{1}\subset\alpha$-CD, compared with **1**, is probably due to an increased rate of nonradiative internal conversion.[5a]

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