Fluorescent chemosensor for reactive organohalides in micellar solution with an example of autocatalysis†‡

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Received (in Cambridge, UK) 16th January 2009, Accepted 18th February 2009
First published as an Advance Article on the web 12th March 2009
DOI: 10.1039/b900963a

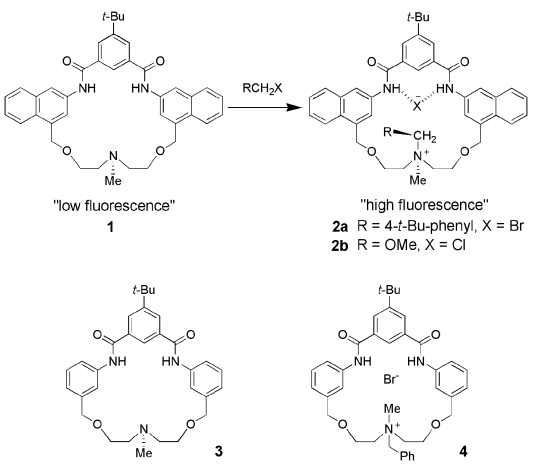
***N*-Alkylation of a fluorescent macrocyclic amine in aqueous micellar solution produces enhanced emission; the reaction with chloromethyl methyl ether exhibits autocatalysis.**

Recently we reported that macrocycle **1** can act as a fluorescent chemosensor for reactive organohalides including some that are known to be carcinogens.[1] The sensing effect is due to an accelerated *N*-alkylation reaction that produces a quaternary ammonium product, **2**, which exhibits diminished PET quenching of the naphthalene fluorophores (Scheme 1). Previous mechanistic studies with the non-fluorescent parent **3** have shown that the macrocycle accelerates the *N*-alkylation reaction by forming a non-covalent pre-reaction complex that undergoes a rapid S_N2 reaction inside the macrocyclic cavity, with the two amide NH groups activating the halide leaving group.[2] This enzyme-like enhancement effect is inhibited by polar solvents which act as competitive inhibitors. Sensor **1** is not effective in homogeneous aqueous solution, which is a practical limitation since many, but not all,[3] of the eventual applications involve aqueous biological or environmental samples.[4] One of the simplest ways to overcome this technical problem is to incorporate the sensor inside micelles, which have relatively dry and non-polar interiors.[5] Here, we demonstrate that fluorescent macrocycle **1** can sense the presence of reactive organohalides in micellar solution, and thus act as a dosimeter for these dangerous alkylation agents.[6]

Previous work with parent **3** uncovered very high reactivity with benzyl bromides.[2b] Furthermore, the *N*-alkylation products have a propensity to form aggregrates in non-polar solvents. This aggregation is readily envisioned by inspecting the X-ray crystal structure of previously unreported ion-pair **4**, formed by reaction of parent **3** with benzyl bromide (Fig. 1).§

Our first goal was to determine if the reactivity and signal response with sensor **1** changed as we moved from organic solvent to aqueous micelles. Therefore, we examined the alkylation of **1** with 4-*tert*-butylbenzyl bromide. As shown in Fig. 2a, treatment of **1** with a ten-fold excess of 4-*tert*-butylbenzyl bromide in *tert*-butylmethyl ether solvent produced a moderate fluorescence increase and also an intense excimer emission band at 520 nm, presumably due to self-aggregation of the ion-pair product **2a**. Shown in Fig. 2b is the change in fluorescence emission when the same reaction is repeated in an aqueous micellar solution composed of Tween 20, a neutral polyethylene glycol surfactant with cmc of 6×10^{-5} at 21 °C. There is a substantial fluorescence enhancement but no emerging excimer band indicating that the ion-pair product does not self-aggregate in micellar solution. In both solvent systems the reaction exhibited pseudo first-order kinetics with the reaction rate about 1.5 times faster in the organic solvent (second-order rate constants are 3×10^3 M^{-1} h^{-1} and 5×10^3 M^{-1} h^{-1}, respectively).

We next examined the reaction of **1** with the potent alkylating agent chloromethyl methyl ether to produce ion-pair **2b**.¶ In organic solvent, a rapid pseudo first-order reaction is observed with the same emerging excimer band as in Fig. 2a.[1] In contrast, the *N*-alkylation reaction in micellar solution generated a strong, four-fold increase in fluorescence intensity with no excimer band (Fig. 3a). Furthermore, there was a very distinct change in reaction kinetics to a sigmoidal profile (curve A in Fig. 3b). This biphasic kinetic feature is a signature of autocatalysis,[7] and this conclusion was confirmed with curves B and C, which show that the induction period disappeared when the same reaction was repeated with small amounts (0.1 and 0.2 molar equivalents) of the product **2b** present at time zero. In contrast, the presence of simple lipophilic quaternary ammonium salts such as **6** had no effect on the sigmoidal kinetic profile. This suggests that the autocatalysis is not produced by any reaction-induced change in micelle charge or structure, but rather it is due to the cationic macrocyclic component in product **2b** acting as a Lewis acid catalyst. This explanation implies that ion-pair **2b** is less aggregated in micelles than organic solvent and better able to activate the electrophilic chloromethyl methyl ether. Independent evidence for decreased aggregation in micelles was



Scheme 1

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† This article is dedicated to Professor Seiji Shinkai, on the occasion of his 65th birthday.

‡ CCDC 716932. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b900963a

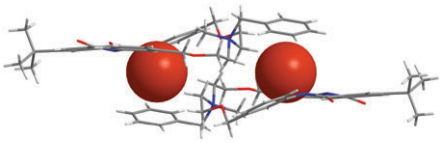


Fig. 1 X-Ray structure of **4** which packs in the unit cell as a cofacial dimer of ion-pairs. The two bromide anions are shown as spheres.

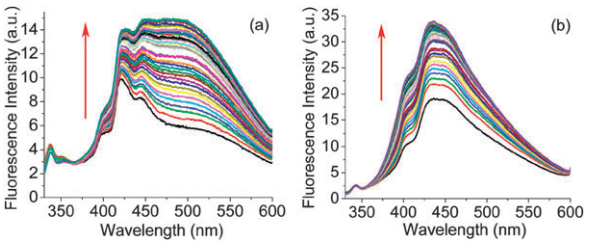


Fig. 2 Change in fluorescence emission (ex: 306 nm) for sensor **1** (20 μM) after treatment with 4-*tert*-butylbenzyl bromide (200 μM) at 25 °C in, (a) *tert*-butylmethyl ether, and (b) aqueous micellar solution (800 μM, Tween 20).

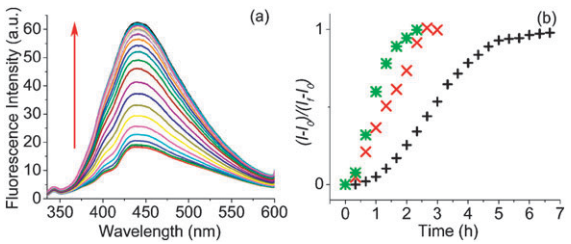
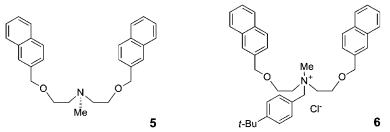


Fig. 3 (a) Change in fluorescence emission (ex: 306 nm) for sensor **1** (20 μM) in micellar solution (800 μM, Tween 20) after treatment with chloromethyl methyl ether (200 μM) at 25 °C, (b) change in fluorescence emission (440 nm) for the same reaction but in the presence of 0.0 (curve A: +), 0.1 (curve B: ×) and 0.2 (curve C: *) molar equivalents of the product **2b** at time zero.

gained by a control experiment that monitored the change in fluorescence when sensor **1** was treated with HCl to produce the ion-pair **1**·$\mathbf{H^+Cl^-}$. In organic solvent, this titration produced a fluorescence enhancement due to protonation of the tertiary amine and, concomitantly, a strong excimer emission (Fig. 4a).[1] However, in micellar solution there was only an increase in monomeric fluorescence and no excimer band (Fig. 4b).



It seems that the appearance of product **2b** induces a change in the micellar reaction mechanism. We propose that the early stage of *N*-alkylation reaction occurs within the non-polar interior of the micelle and proceeds by the S_N2 mechanism that has been previously elucidated and described in the introduction section.[2] In weakly polar organic solvent , the ion-pair product, **2b**, is tightly associated, aggregated, and relatively inert. However, in micelles there is some deaggregation which

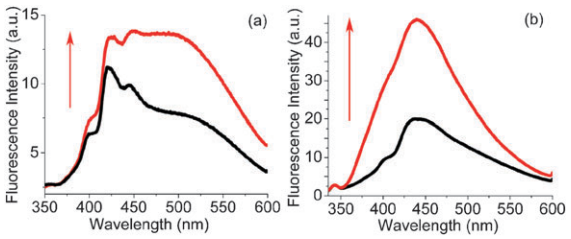


Fig. 4 (a) Change in fluorescence emission (ex: 306 nm) for sensor **1** (10 μM) with excess HCl in *tert*-butylmethyl ether, (b) sensor **1** (20 μM) with excess HCl in micellar solution (800 μM, Tween 20).

allows the cationic macrocycle component in **2b** to activate the chloromethyl methyl ether for nucleophilic attack by another molecule of **1**. Additional studies are needed to fully test all aspects of this hypothesis and to learn why the autocatalytic effect is absent when the organohalide is 4-*tert*-butylbenzyl bromide. In any case, we have demonstrated that fluorescent macrocycle **1** can act as a dosimeter for reactive organohalides in aqueous micellar solution, a significant step towards the utilization of this novel class of chemosensors for practical application.

This work was supported by the ACS-PRF (USA). The X-ray crystal data were acquired and analyzed by B. Noll, A. Oliver and K. Stanger, and we are grateful for their technical expertise.

Notes and references

§ Crystal data for $C_{38}H_{44}BrN_3O_4$ (**4**): M_r = 686.67; triclinic; $P\bar{1}$; a = 9.2525(2) Å; b = 12.9343(3) Å; c = 14.9171(4) Å; α = 89.0162(16)°; β = 74.4480(15)°; γ = 76.6934(15)°; V = 1671.77(7) Å^3; Z = 2; T = 100(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 1.274 mm^{-1}; d_{calc} = 1.364g cm^{-3}; 60 507 reflections collected; 11 155 unique (R_{int} = 0.0484); giving R_1 = 0.0473, wR_2 = 0.1208 for 8973 data with [$I > 2\sigma(I)$] and R_1 = 0.0645, wR_2 = 0.1300 for all 11 155 data.

¶ The identities of products **2a** and **2b** were confirmed by standard NMR and mass spectrometric methods. These compounds were stable in the micellar solution, as judged by TLC analysis. The importance of the macrocyclic structure of **1** was confirmed with control experiments that monitored the reaction of fluorescent acyclic tertiary amine **5** with chloromethyl methyl ether in both organic solvent and aqueous Tween 20 micelles. In both cases, the reactivity of **5**, as judged by the rate of fluorescence increase, was many orders of magnitude slower than **1**.

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