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Fluorescent Chemosensor for Chloroalkanes

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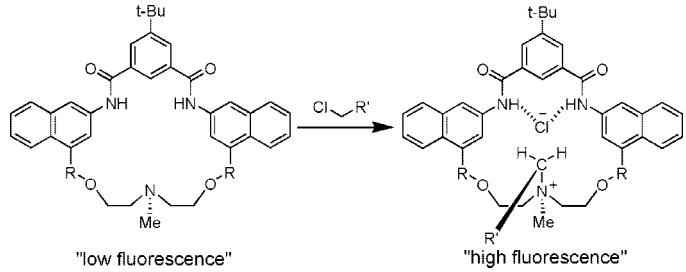
ABSTRACT



Two structurally related macrocyclic amines with naphthalene groups are shown to act as fluorescent dosimeters for reactive chloroalkanes, including the common industrial solvent dichloromethane. The macrocyclic structures contain two NH residues which greatly accelerate *N*-alkylation by activating the chloride leaving group. The chemical reaction increases fluorescence intensity by promoting excimer emission and attenuating the quenching induced by photoinduced electron transfer (PET).

Although they are known to be toxic chemicals,[1] chloroalkanes are produced in large amounts for various applications in modern society.[2] For example, dichloromethane is widely used as a solvent for extraction and synthesis,[3] and it is also a common component in paint strippers and removers.[4] The homologue, 1,2-dichloroethane, is produced in much larger amounts primarily for use as a precursor monomer for poly(vinyl chloride).[5] More reactive chloroalkanes are employed as pharmaceuticals,[6,7] insecticides,[8] and chemical warfare agents.[9] Since many of these compounds have long residence times in the environment, there is a need to develop methods of detecting and scavenging them from contaminated air and water streams.[10] This report describes a prototype fluorescent chemosensor that can detect certain types of chloroalkanes. The design is based on our recent discovery that amine macrocycle **1** attacks chloroalkanes with unusually high reactivity.[11] For example, it reacts with dichloromethane solvent to form the quaternary ammonium salt **2** with a half-life of 2 min at room temperature (Scheme 1). This is about 50000 times faster than the analogous

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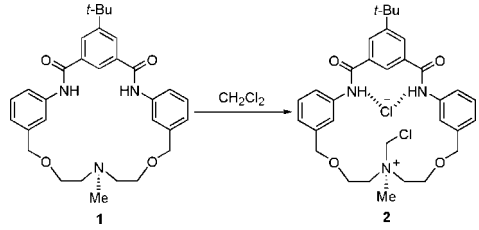
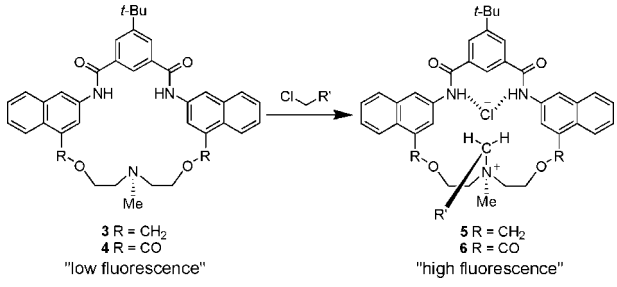
Scheme 1



alkylation reaction with control acyclic amines. Similar rate accelerations have also been measured with other types of primary chloroalkanes and detailed mechanistic studies indicate that macrocycle **1** exhibits enzyme-like properties to accelerate the bimolecular alkylation reaction.[12] Most importantly, the chloroalkane associates with the macrocycle to form a prereaction complex, which allows the two NH residues in the macrocyclic cavity to activate the chloride leaving group as the adjacent electrophilic carbon is attacked by the macrocyclic amine nitrogen. After reaction, the chloride leaving group remains strongly associated with the quaternary ammonium cation such that **2** is a contact ion pair. Furthermore, ion pair **2** has a tendency to form a cofacial aggregate in the solid state and in weakly polar solvents.[11]

Previous investigations of fluorescent sensors for haloalkanes have used fluorescent amines to react covalently and form ammonium salts.[13] The reaction leads to an increase in fluorescence intensity because it decreases quenching by photoinduced electron transfer (PET) from the lone pair on the nucleophilic amine to the attached fluorophore.[14] Herein, we describe the reactivity and fluorescence sensing properties of naphthalene containing macrocycles **3** and **4** (Scheme 2).

Scheme 2



The designs incorporate two identical naphthalene fluorophores within the macrocyclic scaffold of parent **1** in a way that does not change the number of atoms in the macrocyclic cavity. Thus, we expected to maintain the high chloroalkane reactivity due to activation by the two NH residues in the macrocyclic cavity, and also gain a fluorescent enhancement effect due to loss of PET quenching upon *N*-alkylation. The structural difference between **3** and **4** is the replacement of an electron-donating methylene unit attached to each naphthalene with a withdrawing carbonyl. As shown below, this leads to a significant change in the PET quenching response. We expected that the free base forms of **3** and **4** would exhibit low fluorescence due to PET quenching of the naphthalenes by the centrally located tertiary amine, and that fluorescent intensity would increase as the accelerated *N*-alkylation reaction occurs to give products **5** and **6**. As discussed below, an additional sensing feature is the propensity of the ion-pair products to self-associate and form aggregates that exhibit excimer emission spectra.

The synthesis of compounds **3** and **4** was achieved in straightforward fashion using methods that are described in the Supporting Information. Macrocycle **3** was obtained as single crystals, which allowed analysis by X-ray diffraction. As shown in Figure 1, the solid-state macrocyclic conformation closely matches that of parent **1** with the lone pair of the amine nitrogen pointing into the macrocyclic cavity and poised to attack an associated chloroalkane. Also shown is the unit cell packing of two cofacial macrocycles in a head to tail orientation with close overlap of the naphthalene units.

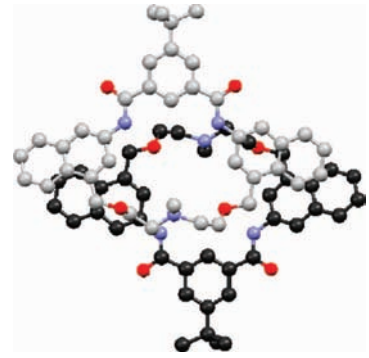


Figure 1. X-ray crystal structure of the macrocycle **3**; the unit cell packs as a cofacial dimer.

The reactivity of macrocycles **3** and **4** was first evaluated by measuring rate constants in dichloromethane solvent. NMR studies showed that the reaction products **5** and **6** (R′ = Cl) were obtained in quantitative yield, and pseudo-first-order rate constants were measured using a previously described HPLC method.[12] The second-order rate constant with **3** in dichloromethane was 2.9×10^{-4} M^{-1} s^{-1} at 25 °C, which corresponds to a half-life of about 1 min. This is approximately two times faster than the reaction of original macrocycle **1** with dichloromethane. The reaction of analogue **4** in dichloromethane is about 50 times slower with a second-order rate constant of 6.3×10^{-6} M^{-1} s^{-1} and a half-life of almost 1 h. It appears that the presence of the two electron-withdrawing carbonyl groups in **4** decreases the nucleophilicity of its attacking nitrogen.

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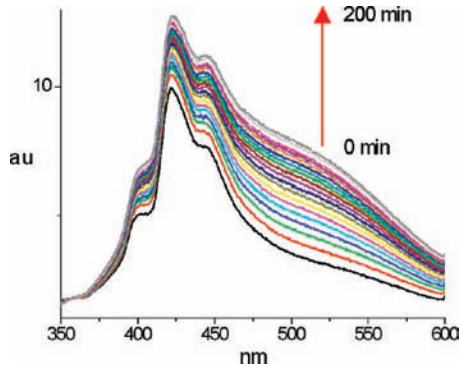

Figure 2. Change in fluorescence emission for macrocycle **3** (10 μM) in *tert*-butylmethyl ether after treatment with dichloromethane (2 mM) at 25 °C (ex: 306 nm).

Macrocycles **3** and **4** were subsequently evaluated for their abilities to sense the presence of dichloromethane in the inert solvent *tert*-butylmethyl ether. Figure 2 shows the change in fluorescence emission of **3** (10 μM) in *tert*-butylmethyl ether after addition of 2 mM of dichloromethane. Over 200 min, there was a modest enhancement of the monomer emission at 420 nm, presumably due to reaction induced inhibition of PET quenching, and a stronger enhancement of the excimer emission band at 520 nm. It appears that as the reaction progresses, the ion-pair product **5** (R′ = Cl) aggregates in the weakly polar solvent. A more dramatic change in emission spectra was obtained when **3** was treated with the more reactive chloromethyl methyl ether, a representative carcinogenic alkylating agent. As expected, the

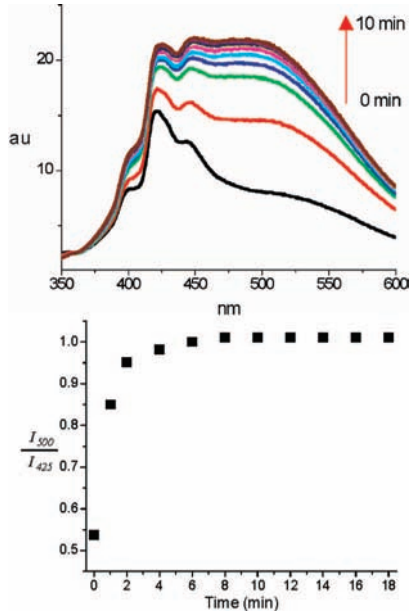

Figure 3. (Top) Change in fluorescence emission of macrocycle **3** (20 μM) in *tert*-butylmethyl ether after addition of chloromethyl methyl ether (20 μM) at 25 °C. (Bottom) Change in intensity ratio for excimer (I_{500}) divided by monomer (I_{425}) (ex: 306 nm).

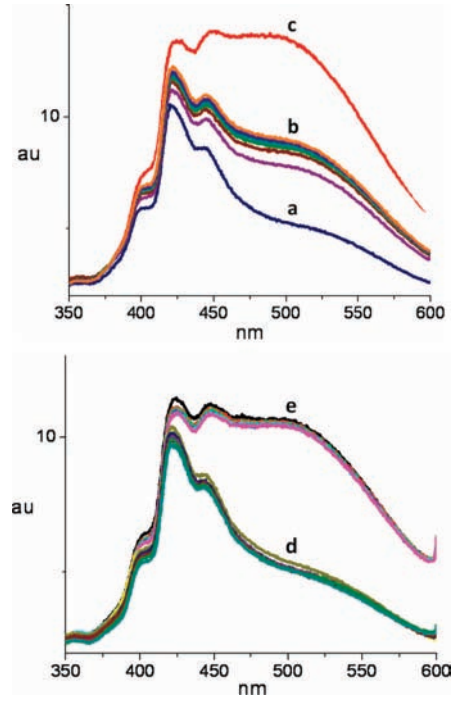

Figure 4. (Top) Fluorescence emission of: (a) macrocycle **3** (10 μM) in *tert*-butylmethyl ether, (b) after addition of TFA aliquots (up to 100 μM), and (c) subsequent single addition of tetrabutylammonium chloride (10 μM). (Bottom) Fluorescence emission of: (d) macrocycle **3** (10 μM) in *tert*-butylmethyl ether before and after addition of tetrabutylammonium chloride (100 μM) and (e) subsequent addition of TFA aliquots (up to 100 μM). T = 25 °C (ex: 306 nm).

N-alkylation reaction was much faster. For example, treatment of **3** (20 μM) with 1 molar equiv of chloromethyl methyl ether in *tert*-butylmethyl ether solvent leads to complete reaction after 10 min. Again, there is a modest increase in the monomer emission band at 420 nm, but now a much larger increase in the excimer band at 520 nm (Figure 3). Thus, compared to the previous reaction product **5** (R′ = Cl), the propensity of product **5** (R′ = OMe) to aggregate in weakly polar solvent is greater.

Further evidence that the excimer band at 520 nm is due to product self-aggregation was gained from the following titration experiments. As shown in the top of Figure 4, the fluorescence emission of macrocycle **3** (10 μM) is slightly enhanced upon protonation by trifluoroacetic acid (TFA) (100 μM) which inhibits PET quenching. A subsequent additon of tetrabutylammonium chloride (10 μM) leads to aggregation of the **3**·HCl ion pair and significant enhancement of the excimer emission band at 520 nm. Reversing the addition order produces the outcome shown in the bottom of Figure 4. As expected, adding tetrabutylammonium chloride to macrocycle **3** induces no change in fluorescence emission,[15]

(15) Even though Cl^- associates with **3** in weakly polar solvent (see citation 24 in ref 12) the data in Figure 4 indicates that it does not induce any heavy atom quenching. Furthermore, UV spectra of **3** and the product **5** are almost identical and show no evidence for charge-transfer formation.

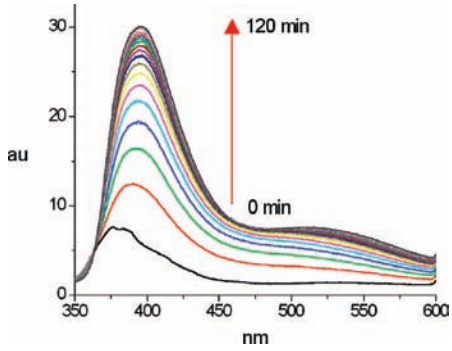

Figure 5. Change in fluorescence emission for macrocycle **4** (10 μM) in *tert*-butylmethyl ether after addition of dichloromethane (14 mM) at 25 °C (ex: 306 nm).

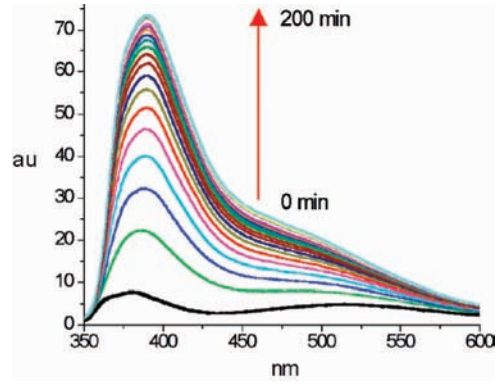

Figure 6. Change in fluorescence emission for macrocycle **4** (10 μM) in *tert*-butylmethyl ether after addition of chloromethyl methyl ether (10 μM) at 25 °C (ex: 306 nm).

but subsequent protonation by TFA induces ion-pair aggregation and excimer formation.

The naphthalene units in macrocycle **4** have a lower reduction potential due to the attached withdrawing carbonyl groups which makes quenching by PET from the central tertiary amine thermodynamically more favorable.[14] Thus, macrocycle **4** was expected to produce a stronger fluorescence response upon reaction with chloroalkanes. Indeed, treatment of **4** in *tert*-butylmethyl ether with dichloromethane (Figure 5) and the more reactive chloromethyl methyl ether (Figure 6) produced large enhancements in the monomer emission bands at 398 nm and much smaller changes in the corresponding excimer bands. The large increase in fluorescent intensity observed with this macrocycle prompted us to demonstrate fluorescent sensing by the naked eye. Shown in the Supporting Information is a comparison of three cuvettes, each containing macrocycle **4** in *tert*-butylmethyl ether. The cuvettes treated with dichloromethane or chloromethyl methyl ether are clearly brighter than the untreated control cuvette.

In summary, we have prepared macrocycles **3** and **4** and evaluated them as fluorescent dosimeters for chlorolkanes. Macrocycle **3** is the more reactive sensor, whereas macrocycle **4** gives the larger signal enhancement. Depending on the exact sensing application, either of these two prototype chemosensors may be useful for optimization within analytical devices that measure the amount of chloroalkane in polluted air. We envision a design that draws air through a nonvolatile liquid or thin film containing the chemosensor.

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Supporting Information Available: Synthetic methods, X-ray and spectral data, kinetic data, curve fittings, and naked eye detection data. This material is available free of charge via the Internet at http://pubs.acs.org.

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