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One-Pot Synthesis of Coumarin-Based Oxazabicyclic and Oxazatricyclic Compounds and Their Fluorescence Redox Switching Properties

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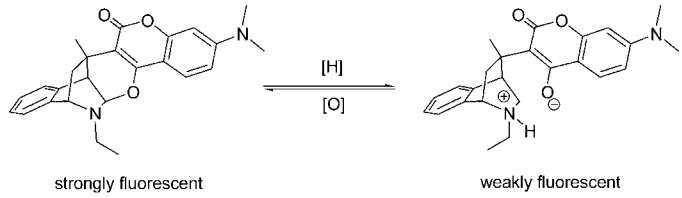
ABSTRACT



An oxazabicycle and an oxazatricycle were efficiently synthesized by coupling of coumarins and *N*-alkylquinolium or isoquinolium salt to investigate their fluorescence redox-switching properties. Chemical reduction of the strongly fluorescent oxazabicycle and oxazatricycle results in the ring-opened products with a distinct decrease in emission intensity. Both resulting ring-opened species can be swiftly reverted to the original ring-closed forms by oxidation.

Partly owing to the increasing interest in molecular electronics and photonics,[1] the properties of molecules or ions which can be switched from one configuration to another by an external perturbation have received much attention in the past two decades. Particular interest is devoted to molecular switches whose emission properties are controlled by redox potential, as they could find application in biochemical and biophysical investigations.[2] Most molecular fluorescent switching systems operating via a redox couple, consist of a metal-centered redox couple[3] or a luminescent ion core encircled by a macrocyclic receptor.[4] Recently, an "all-organic" donor−acceptor system and chemical and electrochemical fluorescent switches were developed by covalently connecting a fluorophore (the donor, i.e., aminonaphthalene) and an active redox switch (the acceptor, i.e., quinone/hydroquinone) with a conjugated or unconjugated spacer.[5] The fluorescence emission of the donors can be reversibly quenched depending upon the oxidation state of the acceptors.

However, a number of the reported organic fluorescent switching systems suffer from a lack of comparable stability in the reduced forms; i.e., they tend to slowly revert to the oxidized form, which substantially limits their practical applications. For instance, the commonly seen redox-active unit hydroquinone in the donor−acceptor switches is gradually reoxidized back to the corresponding quinone by

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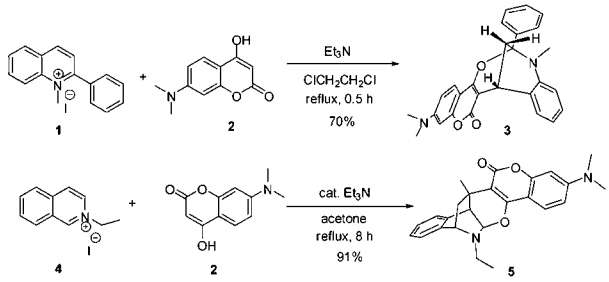
standing in the open air for several hours.[6] Perhaps because of this air-sensitive property, few X-ray crystal structures of the reduced form of all-organic fluorescence redox switches were reported in the literature.[7] Thus, development of a redox-active subunit (the control unit) which can exist in two different oxidation states with comparable stability (a bistable system) remains a major challenge in the field of molecular switches.

In this paper, we report the synthesis and investigation of the switching behavior of two novel heterocyclic systems containing a coumarin moiety as the fluorescence active unit and an oxazabicyclic or oxazatricyclic moiety as the redox-active fragment. Chemical studies show that this coumarin-containing two-component system behaves as a molecular switch whose emission can be controlled by ring-opening and ring-closing of the oxazatricyclic moiety. Most importantly, both oxidized and reduced forms of these molecular switches are relatively stable and can be characterized by single-crystal X-ray diffraction analysis.

Scheme 1 describes the preparation of the oxazabicycle **3** and oxazatricycle **5**. The oxazabicycle **3** was realized by

Scheme 1



coupling of *N*-methyl-2-phenylquinolium iodide (**1**) and 7-dimethylamino-4-hydroxycoumarin (**2**) in the presence of triethylamine in 1,2-dichloroethane under reflux conditions in 70% yield. Compound **1** was prepared by refluxing 2-phenylquinoline with methyl iodide in benzene. Compound **2** was prepared by the previous reported procedure.[8]

The oxazatricycle **5** was easily accessed via a multicomponent reaction (MCR) of *N*-ethylisoquinolium iodide (**4**), **2**, and excess acetone in the presence of a catalytic amount of triethylamine under reflux conditions in 91% yield. *N*-Ethylisoquinolium iodide (**4**) was prepared by refluxing isoquinoline with ethyl iodide in benzene. The molecular structures of **3** and **5** were elucidated by X-ray crystallography as shown in Figure 1,[9] which clearly revealed the

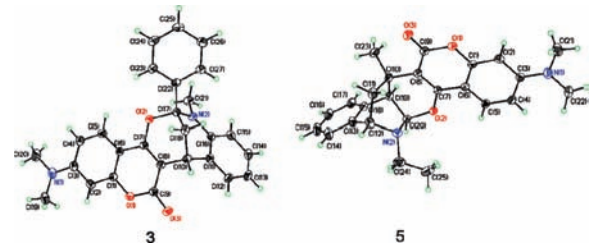
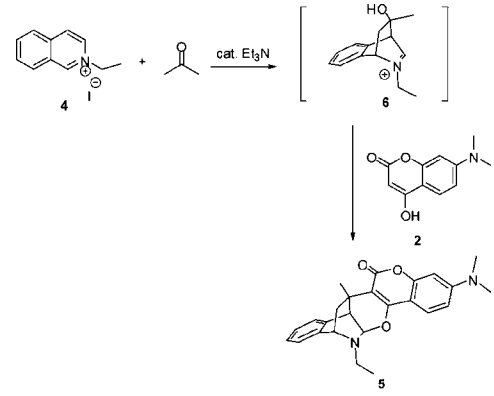


Figure 1. X-ray crystal structures of the oxazabicycle **3** and oxazatricycle **5**.

rigid oxazabicyclic and oxazatricyclic skeletons, respectively. The mechanism for the formation of **3** presumably involved a nucleophilic attack of coumarin **2** to the 4-position of **1** to yield the initial coupling product, followed by the subsequent intramolecular cyclization reaction to afford the oxazabicycle **3**. A similar Lewis acid mediated coupling of 4-hydroxycoumarin and 2-phenylflavylium salt to generate the corresponding dioxabicyclic compound has been previously reported.[10]

Scheme 2 depicts the proposed mechanism for the formation of **5**. It began with an equilibrium-driven, inverse-

Scheme 2



electron-demand aza-Diels−Alder reaction of acetone enolate and isoquinolinium salt to give the iminium-containing cycloadduct **6**.[11] The second step involved a nonequilibrium trapping of **6** with **2** to afford the target oxazatricycle **5**. In addition to forming three C−C bonds and one C−O bond in the final product, this MCR was found to be highly

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(9) Crystallographic data (excluding structure factors) for **3**, **5**, **7**,and **8** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-727190, -27191, -00825, and -700826, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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regiospecific and stereoselective, creating a tricyclic system that contains four chiral centers.[12]

The oxazabicycle **3** emitted strong fluorescence in both hexane and toluene and was highly solvent-dependent. The emission intensity decreased as the solvent polarity increased. External perturbation with a reducing agent by addition of sodium borohydride to **3** in methanol caused the ring-opening of the oxazabicyclic moiety and yielded the weakly fluorescent amino alcohol **7**, whose crystal structure is shown in Figure 2.[9]

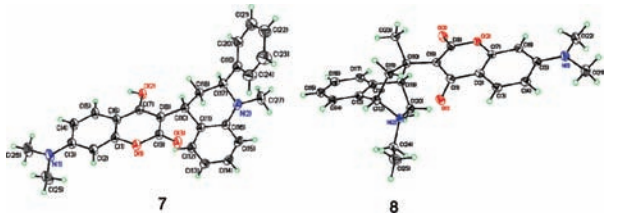
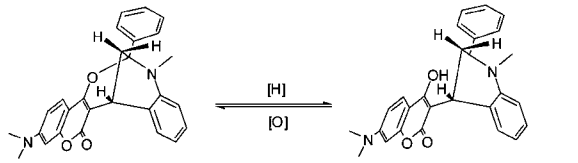


Figure 2. X-ray crystal structures of the oxazabicycle **7** and oxazatricycle **8**.

The resulting reduced **7** was weakly fluorescent in most of organic solvents except in hexane, which had the fluorescence quantum yield of 0.255. Compound **7** can be swiftly reverted to **3** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation in methylene chloride at room temperature. Scheme 3 shows the redox switch between the

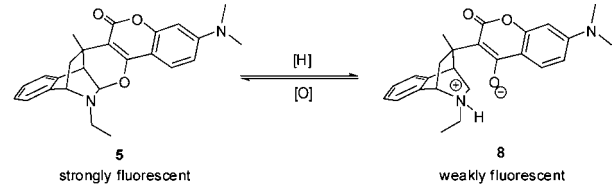
Scheme 3



ring-closed oxazabicycle **3** and ring-opened amino alcohol **7**. The repeated redox switching between **3** and **7**, however, resulted in the formation of a minor red byproduct, presumably due to the aromatization of tetrahydroquinoline moiety of **7** to the corresponding quinolium derivative. Theoretically, this undesired aromatization reaction can be prevented by introduction of *gem*-dimethyl groups to the methylene carbon of the heterocyclic moiety on **3**.

The oxazatricycle **5** also emitted strong fluorescence in various solvents but was solvent-independent. Addition of sodium borohydride to **5** in methanol induced the ring-opening of the oxazatricyclic moiety followed by the intramolecular hydrogen transfer from the 4-hydroxycoumarin group to the nearby tertiary amine to generate the weakly fluorescent zwitterionic species **8**. Note that this intramolecular hydrogen-transfer reaction was not observed for amino alcohol **7** because the aniline moiety of **7** is much less basic than the tertiary amine of **8**. Since the protonated ammonium moiety is less susceptible to oxidation in the air, the reduced **8** is quite stable at room temperature. It can be recrystallized and then subjected to single X-ray diffraction analysis. The crystal structure of zwitterion **8**, shown in Figure 2,[9] indicated that the positive charge mainly located on the ammonium cation (N2) and the negative charge partially delocalized on the 1,3-dicarbonyl structure of the 4-hydroxycoumarin fragment with the C(1)−O(1) bond length [1.294(2) Å] longer than the C(8)−O(3) bond length [1.222(2) Å]. The distance between the ammonium hydrogen and O(1) oxygen was measured to be 1.549 Å, which is much longer than the N(2)−H bond length [1.06(3) Å]. This observation, along with the detection of a downfield ammonium proton absorption peak at 16.62 ppm on ^{1}H NMR spectra, provided solid evidence to support the zwitterionic structure of **8**. Similar to the amino alcohol **7**, the fluorescent emission of the reduced **8** can also be instantly switched on by DDQ oxidation. Scheme 4 shows the redox switch

Scheme 4



between the ring-closed oxazatricycle **5** and ring-opened zwitterion **8**. The redox process between **5** and **8** was repeated more than 10 times without the appearance of detectable byproducts on TLC plates.

Figures 3 and 4 show the bar graphs of the fluorescence quantum yields (Φ_f) of **3**, **7** and **5**, **8** in different solvents,

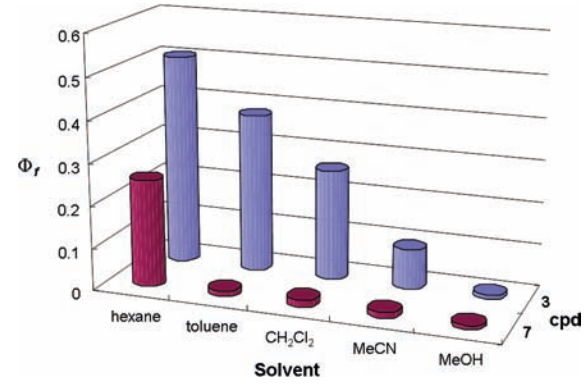


Figure 3. Fluorescence quantum yields of **3** and **7** in different solvents.

(12) A library of 17 oxazatricycles with various substituents was prepared via this MCR for biological activity evaluation. The results will be reported elsewhere.

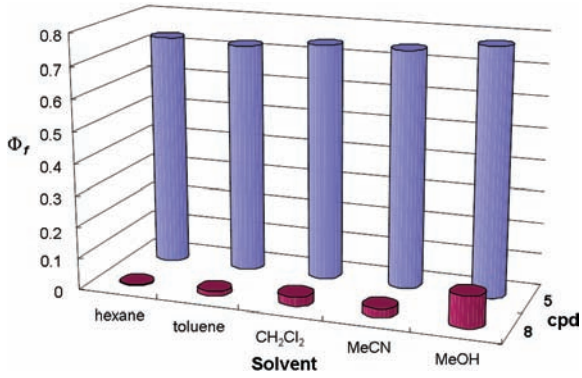


Figure 4. Fluorescence quantum yields of **5** and **8** in different solvents.

respectively. (The detailed fluorescence parameters of compounds **2**, **3**, **7**, **5**, and **8** are listed in the Supporting Information.) The parent fluorophore **2** was strongly fluorescent in methanol, and the emission was solvent-dependent. When the coumarin fluorophore was connected to a rigid bicyclic ring as in the oxazabicycle **3**, the emission remained intense in nonpolar solvents but gradually decreased as the solvent polarity increased. After reduction, the intrinsic fluorescence of the coumarin in the ring-opened amino alcohol **7** was found to be partially quenched by the adjacent amine group in most of the solvents. Apparently, a more flexible conformation upon ring-opening of **3** might also contribute a certain role in quenching the fluorescence of **7**.

Interestingly, when the coumarin fluorophore was connected to a rigid oxazatricyclic ring as in the oxazatricycle **5**, the emission remained intense but no longer solvent-dependent, which might be attributed to the absence of the 4-hydroxyl hydrogen atom at the coumarin moiety. After chemical reduction, the intrinsic fluorescence of the coumarin in the ring-opened zwitterion **8** was substantially quenched by the excess electrons on the negative charge oxygen atom at the 4-position of coumarin moiety, presumably via the internal charge-transfer mechanism.[13] It is worth mentioning that the fluorescence intensity of the oxidized **5** is found to be up to 180-fold stronger than that of the reduced **8** in hexane (see Figure 4).

Although the fluorescence quenching mechanisms of these two heterocycles merit further investigations, the fact that the highly fluorescent oxazatricycle **5** can be swiftly interconverted to the corresponding weakly fluorescent ring-opened form **8** by redox reaction suggests that the oxazatricyclic moiety may have the potential to function as a molecular switching scaffold. To the best of our knowledge, this work represents the first example of a bistable, heterotricyclic ring-controlled fluorescence molecular switch, which we believe may lead to future development of the fluorescence redox switches with novel molecular structures.

In summary, two novel reversible fluorescence redox switches containing a coumarin moiety as the fluorescence active unit and an oxazacyclic moiety as the redox active fragment were efficiently synthesized and characterized. We have demonstrated that the emission of the fluorophore of the oxazatricycle **5** can be controlled by $NaBH_4$-induced ring-opening and DDQ-mediated ring-closing of the heterocyclic moiety. This work provides a new molecular scaffold for design of reversible, all-organic, bistable fluorescence redox switches. Further modifications of **8** by introducing appropriate substituents at the nitrogen atom to function as a potential chemosensor for metal ion detections are in progress.

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Supporting Information Available: Synthesis of compounds **3**, **5**, **7**, and **8**, experimental details, and additional spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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