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9-Benzylidene-9*H*-fluorene Derivatives Linked to Monoaza-15-crown-5: Synthesis and Metal Ion Sensing

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Two kinds of novel styryl chemosensory 2-FMNC and 3-FMNC, were designed and synthesized by an apporiate introduction of 9-benzylidene-9*H*-fluorene group as fluorophore with the aim at avoiding photoisomerisation. These 9-benzylidene-9*H*-fluorene derivatives showed the similar selectivity and sensitivity upon addition of metal ions. The sensitivity of FMNC to alkaline earth metal ions was $Ba^{2+} > Sr^{2+} > Ca^{2+} \approx Mg^{2+}$.

Keywords 15-aza-5-crown ether, 9-benzylidene-9*H*-fluorene, alkaline earth metal ion

Introduction

A lot of direct sensing schemes have been described using fluorescent chemosensory molecules (fluoroionophores) whose optical properties changed upon direct binding of the cation. The photophysics and photochemistry of fluorophore linked to crown ether is an area of growing interest.[1-4] A number of these styryl derivatives linked to crown ether were reported to have high fluorescence quantum efficiency and selectivity for the metal ions.[5-10] However, photophysical properties of these styryl compounds will be worst affected due to conversion of the *trans* isomer into the *cis* isomer during the radiation of light.[11]

In the search for stable and efficient styryl chemosensory, we found 9-benzylidene-9*H*-fluorene, a kind of styryl derivative, was a suitable candidate for fluorophore because it would not occur isomerization during the radiation of light due to the symmetry property of double bond in molecular structure. This led us to synthesize a new styryl molecule 13-(2-(9*H*-fluoren-9-ylidene)methyl)-4-nitrophenyl)-1,4,7,10-tetraoxa-3-azacyclopentadecane (2-FMNC). For comparison, 13-(2-(9*H*-fluoren-9-ylidene)methyl)-4-nitrophenyl)-1,4,7,10-tetraoxa-3-azacyclopentadecane (3-FMNC) was also targeted.

Experimental

Materials

Solvents and reagents used in the synthesis of chemosensors 2-FMNC and 3-FMNC were purchased from Aladdin Reagent Company or Alfa Aesar Company and used without further purification.

Synthesis of 2-FMNC

Process for preparation of 5-nitro-2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl) benzaldehyde (3a) Under N_2 protection, $Pd(CH_3COO)_2$ (10 mg), *o*-phenanthroline (11 mg) and aza-15-crown-5 (0.24 g, 1.10 mmol) were added to a stirred hexamethylphosphamide solution of 2-chloro-5-nitrobenzaldehyde (0.2 g, 1.10 mmol). The reaction mixture was immersed in 80 ℃ oil bath and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with 20 mL CH_2Cl_2, washed with water, dried over Na_2SO_4, and the solvent was removed on vacuum. The residue was purified by chromatography on silica gel, eluting with EtOAc-petroleum ether (1∶1, volume ratio), to afford yellow oil.[12] Yield 52%. ^1H NMR ($CDCl_3$, 400 MHz) δ: 10.06 (s, 1 H), 8.59 (s, 1H), 8.22 (d, J=9.2 Hz, 1H), 7.25—7.27 (m, 1H), 3.77—3.79 (m, 4H), 3.63—3.71 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 188.8, 157.0, 139.7, 129.0, 128.6, 125, 118.9, 77.3, 77.0, 76.7, 71.2, 70.7, 70.4, 69.2, 55.1; MS *m/z*: 368.2. Anal. calcd for $C_{17}H_{24}N_2O_7$: C 55.43, H 6.57, N 7.60; found C 55.48, H 6.72, N 7.67.

Process for preparation of 13-(2-(9*H*-fluoren-9-ylidene)methyl)-4-nitrophenyl)-1,4,7,10-tetraoxa-3-azacyclopentadecane (2-FMNC) Compound **3a** (0.160 g, 0.43 mmol) was added to a solution of triphenylphosponiumfluorenylide (0.188 g, 0.43 mmol) in 5 mL of chloroform. After heating the orange solution under reflux for 3 h, the solvent was evaporated on the steam bath. The residual oil was purified by chromatography on silica gel, eluting with EtOAc-petroleum

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ether (1 ∶ 1, volume ratio), to afford orange product, m.p. 170 ℃, yield 45%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.48 (s, 1H), 8.20 (d, J=8.9 Hz, 1H), 7.81—7.56 (m, 3H), 7.55 (d, J=7.7 Hz, 1H), 7.44—7.10 (m, 6H), 3.57—3.67 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.6, 141.7, 139.9, 139.3, 139.1, 136.7, 136.2, 135.9, 129.0, 128.5, 128.3, 127.1 (2C), 126.8, 126.8, 125.0, 124.6, 124.1, 120.4, 120, 119.7, 117.3, 77.3, 77.0, 76.7, 71.1, 54.0; MS *m*/*z*: 516.4. Anal. calcd for $C_{30}H_{32}N_2O_6$: C 69.75, H 6.24, N 5.42; found C 69.14, H 6.31, N 5.36.

Synthesis of 3-FMNC

Process for preparation of 9-(5-chloro-2-nitrobenzylidene)-9*H*-fluorene (3b) 3-Chloro-6-nitrobenzaldehyde (0.418 g, 2.26 mmol) was added into a solution of triphenylphosponium fluorenylide (1.006 g, 2.36 mmol) in 12 mL of chloroform. After heating the orange solution under reflux for 3 h, the solvent was evaporated on the steam bath. The residual oil was purified by chromatography on silica gel, eluting with EtOAc-petroleum ether (1 ∶ 1, volume ratio) to afford yellow powder, m.p. 173 ℃, yield 46%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.26 (d, J=8.8 Hz, 1H), 7.83 (d, J=7.4 Hz, 1H), 7.78—7.71 (m, 3H), 7.59 (dd, J=1.8, 8.8 Hz, 1H), 7.43—7.34 (m, 3H), 7.28 (s, 1H), 7.05—6.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.1, 141.8, 139.8, 138.7, 137.9, 135.7, 134.7, 132.4, 129.3, 129.1, 127.4, 126.9, 126.5, 124.0, 121.1, 120.8, 120.1, 119.7. MS *m*/*z*: 333.1. Anal. calcd for $C_{20}H_{12}ClNO_2$: C 71.97, H 3.62, N 4.20; found C 72.03, H 3.68, N 4.35.

Process for preparation of 13-(2-(9*H*-fluoren-9-ylidene)methyl)-4-nitrophenyl)-1,4,7,10-tetraoxa-3-azacyclopentadecane (3-FMNC) To a stirred hexamethylphosphamide solution of 9-(5-chloro-2-nitrobenzylidene)-9*H*-fluorene (1.024 g, 3.10 mmol), CuI (33.9 mg) and *o*-phenanthroline (28.8 mg) were added, aza-15-crown-5 (0.7075 g, 3.23 mmol) was added in under N_2 protection. The reaction mixture was immersed in 80 ℃ oil bath and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with 100 mL CH_2Cl_2, washed with water, dried over Na_2SO_4, and solvent was removed on vacuum. The residue was purified by chromatography on silica gel, eluting with EtOAc-petroleum ether (1 ∶ 1, volume ratio), to afford yellow solid power (0.56 g), m.p. 120 ℃, yield 34 %; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.31 (d, J=9.4 Hz, 1H), 7.97 (s, 1H), 7.89 (d, J=6.6 Hz, 1H), 7.71—7.72 (m, 2H), 7.18—7.41 (m, 4H), 6.99—7.05 (m, 1H), 6.78 (d, J=6.9 Hz, 2H), 3.58—3.73 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.5, 141.5, 139.3, 139.2, 136.5, 135.8, 135.3, 128.4, 128.1, 127.1, 126.5, 126.2, 124.5, 120.7, 119.8, 119.5, 113.5, 110.9, 77.28, 76.97, 76.65, 71.21, 70.29, 70.06, 68.25, 53.00. MS *m*/*z*: 516.4. Anal. calcd for $C_{30}H_{32}N_2O_6$: C 69.75, H 6.24, N 5.42; found C 69.88, H 6.51, N 5.47.

Method

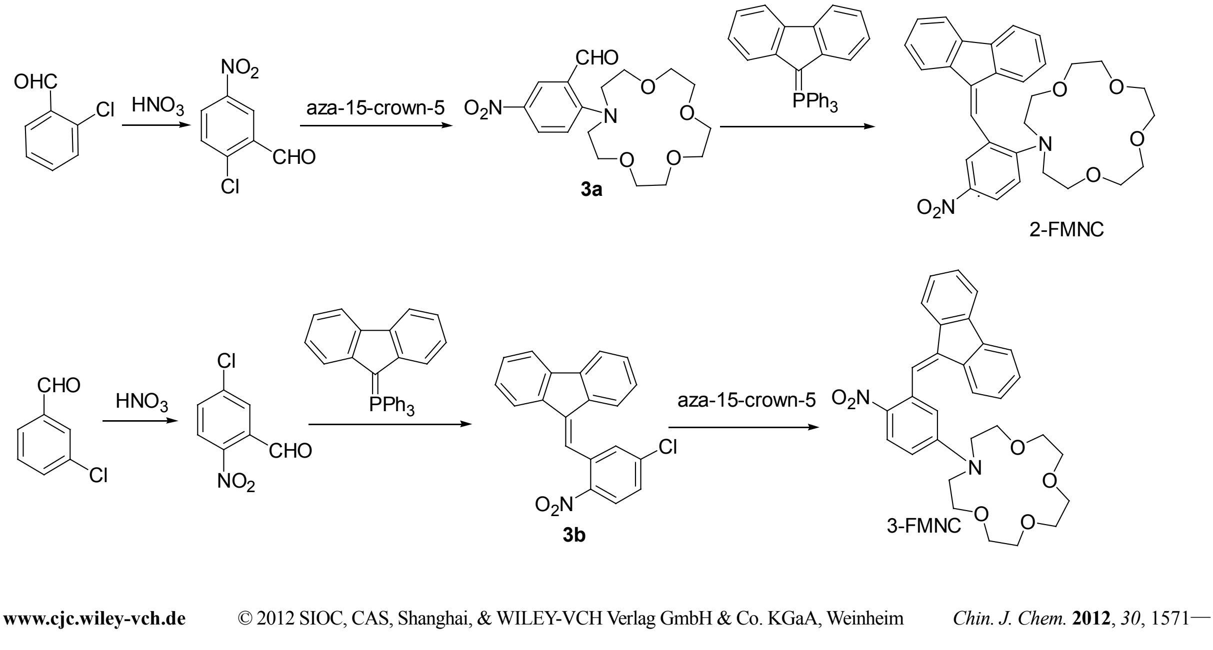
Absorption spectra were recorded on a Lambda 25 spectrophotometer under the control of a Pentium PC running the manufacturer-supplied software package. Fluorescence spectra were obtained on a Perkin-Elmer LS55 luminescence spectrometer with 10 nm excitation and emission slit widths, excitation at 378 nm. All solutions of fluorescent chemosensory were prepared in spectroscopic grade acetonitrile without special efforts to exclude water or air. Fluorescence titrations were carried out with metal ion aqueous solutions (2.1×10^{-6} mol•L^{-1}) to acetonitrile solution of compound FMNC (2.1×10^{-6} mol•L^{-1}).

Results and Discussion

The stability of 2-FMNC and 3-FMNC to the radaition

As we known, stilbene would occur *trans-cis*

Scheme 1 Synthetic routes for chemosensory 2-FMNC and 3-FMNC



isomerization under the radiation of light since the torsion of double bond became easy in the excited state.[11] Although the compounds of FMNC we designed contained a double bond, they did not give isomers since in the case of a molecule containing a double bond, for example, WXC=CYZ (W, X, Y and Z are substituting groups on the double bond), isomerization would not exist where W=X or Y=Z.

The experiment also demonstrated that FMNC were very stable in solution that repetitive absorption spectra showed almost no change under ambient light for several days. Instead, the literature reported some of the styryl compounds linked to azacrown showed a partial conversion of the *trans* isomer into the *cis* isomer in a short period.[13]

The selectivity of 2-FMNC and 3-FMNC to metal ions

2-FMNC and 3-FMNC displayed very weak fluorescence in solution. The selectivity of the probes 2-FMNC and 3-FMNC towards metal ions were tested upon addition of metal ions (50 equiv.), as shown in Figure 1. Nearly no fluorescence intensity changes were observed in emission spectra with Na^+, K^+, Cd^{2+}, Mg^{2+}, Mn^{2+}, Hg^{2+} and Li^+. However, under identical conditions, fluorescence intensities were greatly enhanced in the presence of alkaline earth metal ions such as Ca^{2+}, Sr^{2+} and Ba^{2+}, especially for Ba^{2+}. The relative fluorescence intensity of 2-FMNC and 3-FMNC reached to 41, and 34.8 respectively, which was about three times of that of the Sr^{2+} and much more than that of the Ca^{2+}. As a result of all above, we have come to the conclusion that the substituting position on benzene nucleus had slightly effect on selectivity and sensitivity of chemosensory molecules. The experiment results indicated that alkaline earth metal ions with the larger atomic weight would cause the stronger fluorescence enhancement of FMNC.

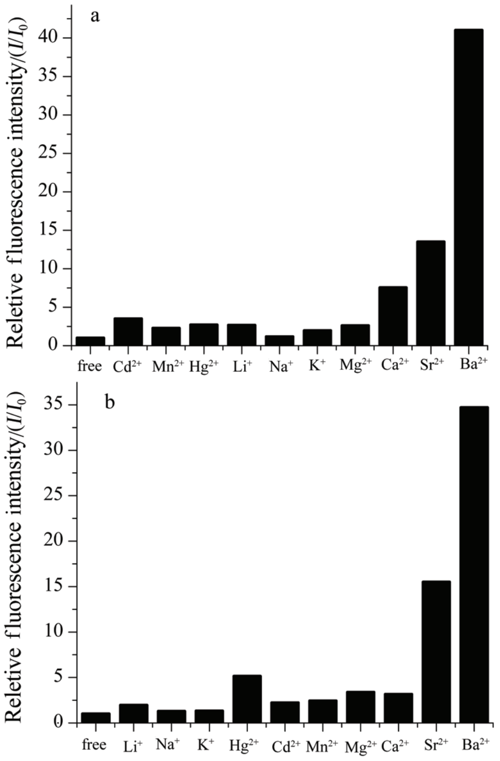


Figure 1 The relative fluorescence enhancement intensity of (2.1×10^{-6} mol•L^{-1}) in acetonitrile at room temperature upon addition of various metal cations; excitation at 392 nm; The concentration of metal cations (4.2×10^{-3} mol•L^{-1}) was 50 equiv. to compound. (a) 2-FMNC; (b) 3-FMNC.

The observed variations in the FMN-crown emission spectrum with cations were believed to be due to hindering process of photoinduced electron transfer (PET) between the aza group and fluorophore, coordination of the alkali earth ion to the oxygens and nitrogen atom of the crown raised the one-electron oxidation potential of the crown, effectively shutting down photoinduced electron transfer to the excited fluorophore.[14]

As mentioned above, the largest fluorescence enhancement was observed upon addition of Ba^{2+}, next Sr^{2+}, Ca^{2+} and Mg^{2+} were least. The results were hardly explained because the cavity size of the crown was more suitable for Ca^{2+}. We assumed that the heavy cations were also difficult for photoejection since photorelease of cations from a “cage” was possible by photoinduced irreversible changes in the chemical structure of a chelator.[15,16] The rate of photorelease of some cations from complexes of crowned styryl derivatives found to be slower for the Ca^{2+} complex than for the Li^+ complex, was reported (see Figure 2).[17] Sr^{2+} in acetonitrile was also found to exhibit the same trends as reported and much slower than that of Ca^{2+}.[18] All these gave supports for our assumption.

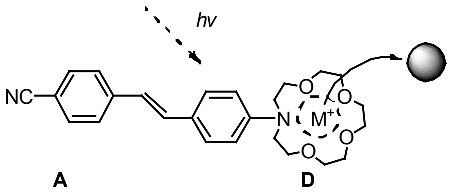


Figure 2 Photorelease of cation from a “cage” of styryl derivatives.

The fluorescence titration of FMNC with Ba^{2+} and Sr^{2+}

Figure 3 showed the results of fluorescence titration of FMNC with Ba^{2+}. When excited at 378 nm, the fluorescence emission intensity around 420 nm was quite weak in the absence of Ba^{2+} ion in acetonitrile (Off-state). However, emission intensity created remarkably enhancement (On-state) on changing the concentration of Ba^{2+} from 0 to 200 μmol•L^{-1}. Similar ‘Off-On’ behaviour was also observed in the presence of Sr^{2+} (Figure S9). The equilibrium constant for the formation of [ML] from the interaction of FMNC and metal ion could be calculated from the plot $I_0/[I-I_0]$ vs.

1/[M] using the Benesi-Hildebrand equation.[19] For example, the K_{sv} of Ba^{2+} with 2-FMNC was 4.30×10^5, but that of Sr^{2+} was 7.17×10^3.

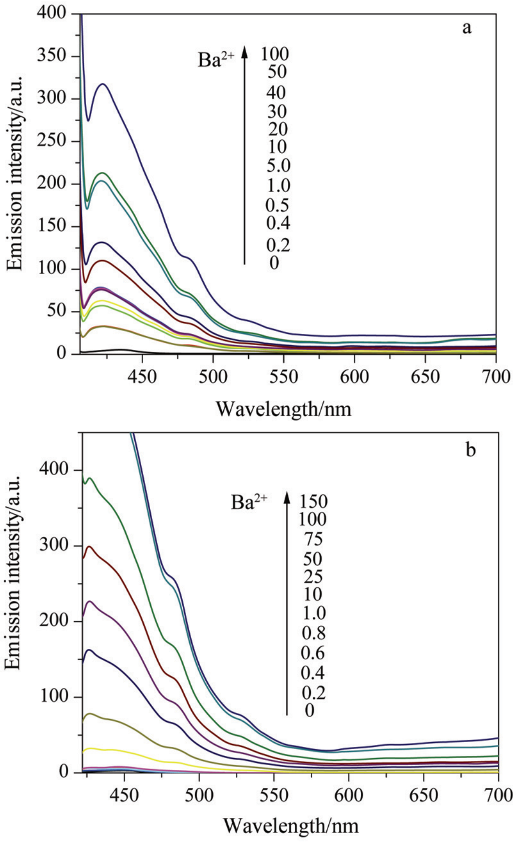


Figure 3 (a) Fluorescence spectra (λ_{ex}=389 nm) of FMNC (2.1×10^{-6} mol•L^{-1}) upon the titration of Ba^{2+} (0—100 equiv.) in acetonitrile solution. (a) 2-FMNC; (b) 3-FMNC.

The UV-vis absorption titration of FMNC with Ba^{2+} and Sr^{2+}

The UV-vis absorption spectra of 2-FMNC and its titration with Ba^{2+} were measured in acetonitrile (Figure S10 (a)). 2-FMNC exhibited its lowest energy absorption at 230 and 380 nm, which gradually increased in intensity and did not shift in wavelength with the sequential addition of Ba^{2+} ion. This also proved that the fluorescence 'on-off' of FMNC was due to the PET process. The 2-FMNC and Sr^{2+} complex had the similar UV-Vis absorption spectra except the slight intensity difference (Figure S10 (b)).

Conclusions

To avoid photoisomerisation of chemosensory, two new styryl molecules, 2-FMNC and 3-FMNC, were designed and synthesized by an apporiate introduction of 9-benzylidene-9*H*-fluorene group as fluorophore. The experiment results showed that 2-FMNC and 3-FMNC have the similar response to alkaline earth metal ions. The sensitivity of FMNC to alkaline earth metal ions ($Ba^{2+}>Sr^{2+}>Ca^{2+}\approx Mg^{2+}$) revealed that the larger size and atomic weight of alkaline earth metal ion led to a better fit to aza-15-crown-5.

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