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Clarification of a misconception in the BINOL-based fluorescent sensors: synthesis and study of major-groove BINOL-amino alcohols†

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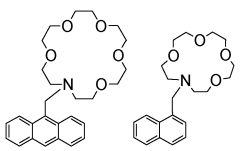
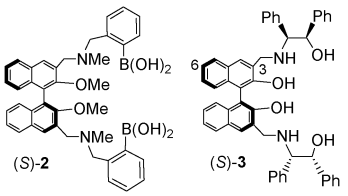
The major-groove BINOL-amino alcohol (*S*)-6 shows greatly enhanced fluorescence over the minor-groove one (*S*)-3. The study of a series of the major-groove BINOL-amino alcohol compounds demonstrates that the commonly accepted acid inhibition of the PET fluorescence quenching of aryl-amine compounds is not involved in the BINOL-amine sensors.

The photo-induced electron transfer (PET) from a nitrogen atom to an adjacent aromatic fluorophore has been extensively used in the design of fluorescent sensors for metal cations, pH, carbohydrates, carboxylic acids and other species.[1] As represented by compounds **1a** and **1b**, the attachment of the azacrown ether unit to the anthracene and naphthalene rings has quenched their fluorescence *via* PET. Binding of the azacrown ether rings with an alkaline metal cation or an acid proton makes the lone pair electron of the nitrogen unavailable for PET, generating significant fluorescence enhancement.[2] The fluorescence quenching *via* the electron transfer process can be determined by the oxidation potentials of the donor and acceptor.[3] For a tertiary amine donor [$E(D/D^+) \approx 0.9$ V *vs.* SCE, 1.1 V *vs.* NHE][4a] or a secondary amine donor [$E(D/D^+) \approx 1.1$ V *vs.* SCE, 1.3 *vs.* NHE][4a] in the presence of an alkyl naphthalene acceptor [$E(A/A^+) \approx 1.5$ V *vs.* Ag/AgCl, 1.7 V *vs.* NHE],[4b] the reaction is thus exothermic and favorable. However, if 1-naphthol [$E(A/A^+) \approx 0.8$ V *vs.* Ag/AgCl, 1.0 V *vs.* NHE][4b] or 2-naphthol [$E(A/A^+) \approx 0.9$ V *vs.* Ag/AgCl, 1.1 V *vs.* NHE][4b] is used as the acceptor, the electron transfer from amines should be endothermic and unfavorable.

In spite of the above thermodynamic argument, the acid-suppressed PET was proposed previously to account for the fluorescence enhancement of the 1,1′-bi-2-naphthol



(BINOL)-amine-based fluorescent sensors such as (*S*)-**2**[5a] and (*S*)-**3**[5b] in the presence of various substrates. Because of the extensive activity in the development of the BINOL-based fluorescent sensors, this misconception propagates continuously. Herein, we present an experimental study on a series of BINOL-amino alcohol derivatives to clarify the role of PET in the fluorescent recognition conducted by the BINOL derivatives.



Recently, we reported that when a solution of (*S*)-**3** was treated with (*S*)-mandelic acid (MA), a white precipitate was produced accompanied with a large fluorescence enhancement.[5b] In contrast, no precipitate formed in the presence of (*R*)-MA and also only very small change in fluorescence was observed. In order to probe the origin of the unusually large fluorescence enhancement observed for the interaction of (*S*)-**3** with (*S*)-MA and to develop new enantioselective fluorescent sensors,[6] the structural analogs of (*S*)-**3** are prepared and studied. As shown in Scheme 1, compound (*S*)-**6** was obtained by moving the minor groove 3,3′-amino alcohol units of (*S*)-**3** to the major groove. Bromination of (*S*)-BINOL followed by protection of the hydroxyl groups with MOM gave (*S*)-**4**.[7a] Treatment of (*S*)-**4** with ^{n}BuLi followed by addition of DMF and then hydrolysis generated the 6,6′-diformylBINOL (*S*)-**5**.[7b] Reductive amination of (*S*)-**5** by reaction with (1*R*,2*S*)-2-amino-1,2-diphenylethanol and $NaBH_4$ produced (*S*)-**6**.[7c] The ^{1}H NMR spectrum of (*S*)-**6** in $CDCl_3$ shows two doublets at δ 3.62 (d, J = 13.6 Hz, 2H) and 3.77 (d, J = 13.6 Hz, 2H) for the diastereotopic methylene protons on the amino alcohol units of this compound. The difference between these two signals ($\Delta\delta$) is 0.15, significantly smaller than that of its minor-groove

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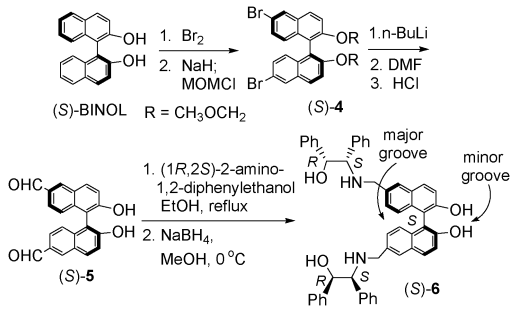

Scheme 1 Synthesis of (*S*)-**6**.

analog (*S*)-**3** ($\Delta\delta$ = 0.32). In (*S*)-**3**, there should be intramolecular hydrogen bonding between the nitrogens of the amino alcohol units and the central BINOL hydroxyl protons. This should restrict the rotation of each methylene group generating more different environment for the two protons. Moving the amino alcohol units to the major groove in (*S*)-**6** removes this type of intramolecular hydrogen bonding and allows the methylene groups to freely rotate around the C–C single bonds, leading to the much smaller chemical shift difference for the proton signals. There is also a large difference in optical rotation between (*S*)-**6** and (*S*)-**3**. The specific optical rotation, $[\alpha]_D$, of (*S*)-**6** is +92.1 (c = 0.36, CH_2Cl_2) which is the opposite of that of the specific optical rotation of (*S*)-**3** {$[\alpha]_D$ = −24.5 (c = 1.15, CH_2Cl_2)}. Thus, these two molecules should have very different stereo conformation even though the configurations of their BINOL and amino alcohol units are the same.

A dramatic fluorescence enhancement was observed going from (*S*)-**3** to (*S*)-**6** as shown in Fig. 1 (over 30 fold). Compound (*S*)-**3** shows dual emission at λ_{em} = 439, *ca.* 370 (sh.) nm, but the major-groove isomer (*S*)-**6** gives only the short wavelength emission at λ_{em} = 379 nm with little long wavelength emission. The dramatic fluorescence enhancement observed at the short wavelength emission from (*S*)-**3** to (*S*)-**6** could be attributed to the removal of the intramolecular hydrogen bonding between the BINOL hydroxyl protons of (*S*)-**3** and the amine nitrogens. According to the study of Iwanek and Mattay on the fluorescence quenching of BINOL with amines,[8a] the greatly quenched fluorescence of (*S*)-**3** could arise from the radiationless decay of the excited intramolecularly hydrogen bonded compound as well as the formation of a weakly fluorescent compound, such as **A*** shown in Fig. 1, generated from the excited state intramolecular proton transfer. The weak emission signals of these species might overlap with the excimer emission[9] of (*S*)-**3** at the long wavelength. The BINOL hydroxyl groups in (*S*)-**6** cannot form the corresponding intramolecular complexes, leading to its much greater fluorescence than (*S*)-**3**.

To further understand the fluorescence property of (*S*)-**6**, we have compared its fluorescence spectrum with that of the unsubstituted (*S*)-BINOL. As shown in Fig. 2, *very little difference in fluorescence intensity between these two molecules is observed*. The estimated fluorescence quantum yields (Φ_F) of (*S*)-**6** and (*S*)-BINOL in benzene are 6% and 2% respectively by using quinine sulfate as the standard. That is, *the nitrogen atoms of the amino alcohol units in* (*S*)-**6** *provide no PET fluorescence quenching in contrast to that proposed previously*.[5]

To determine the contribution of the intramolecular hydrogen bonding between the nitrogen atom and the adjacent hydroxyl proton in each of the amino alcohol units of (*S*)-**6**, we have methylated the amino alcohol hydroxyl groups to give compound (*S*)-**7** (Fig. 3). No significant difference between the fluorescence intensity of (*S*)-**7** and (*S*)-**6** was observed (Fig. 2). The fluorescence quantum yield of (*S*)-**7** is estimated to be 6%. Therefore, both (*S*)-**6** and (*S*)-**7** do not exhibit the PET fluorescence quenching by the adjacent nitrogen atoms.

In order to explore the effect of the BINOL hydroxyl groups of these sensors, the methoxylmethylated compound (*S*)-**8** is prepared (Fig. 3). This compound shows greatly enhanced fluorescence over (*S*)-BINOL, (*S*)-**6** and (*S*)-**7**, but very similar to the methylated (*S*)-BINOL, (*S*)-**9** (Fig. 2). The much weaker fluorescence of (*S*)-BINOL, (*S*)-**6** and (*S*)-**7** than (*S*)-**8** could be accounted for by the excited state dissociation of their more acidic BINOL hydroxyl protons to generate the weakly fluorescent species,[8] though this proton dissociation is much less efficient than that in (*S*)-**3** due to its intramolecular hydrogen bonds. Alkylation of the BINOL units in (*S*)-**8** and (*S*)-**9** shuts down the excited state proton dissociation, generating the large fluorescence enhancement. The fluorescence quantum yields of (*S*)-**8** and (*S*)-**9** in benzene are estimated to be 49% and 65% respectively. Compound (*S*)-**10** where both the BINOL hydroxyl groups and the aminoalcohol hydroxyl groups are alkylated (Fig. 3). Its fluorescence quantum yield is 46%, close to that of (*S*)-**8**. Thus, the nitrogen atoms in (*S*)-**8** and (*S*)-**10** do not provide the generally observed large PET quenching in the naphthalene-amine-based sensors.

The interaction of (*S*)-**6** with the (*R*)- and (*S*)-enantiomers of MA was studied. When a clear solution of (*S*)-**6** (2.0×10^{-4} M, benzene/0.4% DME) was treated with (*S*)-MA (1.0×10^{-3}–5.0×10^{-3} M), a white suspension was generated. Under the same conditions, when (*S*)-**6** was treated with (*R*)-MA, a "semi-transparent" precipitate was generated. Both precipitates were collected by filtration. ^{1}H NMR analysis

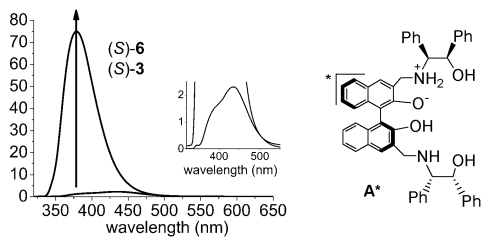

Fig. 1 Fluorescence spectra of (*S*)-**6** and (*S*)-**3** in benzene at 1.0×10^{-4} M (λ_{ex} = 341 nm, slit: 5.0/5.0 nm).

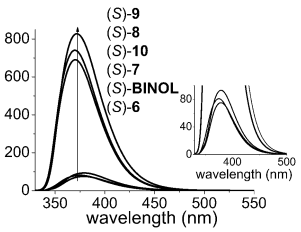

Fig. 2 Fluorescence spectra of compounds (*S*)-BINOL, (*S*)-**6**, (*S*)-**7**, (*S*)-**8**, (*S*)-**9** and (*S*)-**10** in benzene at 1.0×10^{-4} M (λ_{ex} = 341 nm, slit: 5.0/5.0 nm).

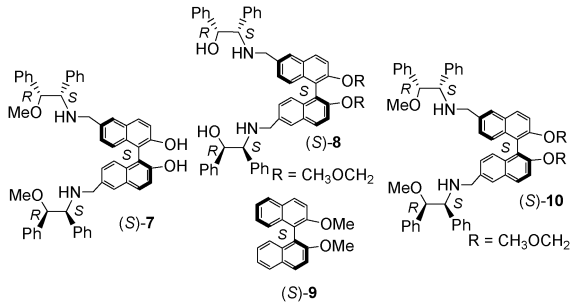

Fig. 3 Structures of various BINOL-derivatives.

showed 1 : 3 ratio between (*S*)-**6** and (*S*)-MA or (*R*)-MA in the precipitate.

The fluorescence spectra of (*S*)-**6** in the presence of (*S*)- and (*R*)-MA were measured. The suspension of (*S*)-**6** with (*R*)-MA exhibited large fluorescence enhancement but that of (*S*)-**6** with (*S*)-MA showed almost no change in intensity (Fig. 4). Thus, the fluorescence responses of (*S*)-**6** towards the enantiomers of MA are highly enantioselective with I_R/I_S = 6.8 (Fig. 4a).[6,10] The intermolecular complex of (*S*)-**6** + (*R*)-MA might be structurally more rigid than that of (*S*)-**6** + (*S*)-MA, giving rise to the much greater fluorescence. The enantioselectivity of the major-groove BINOL molecule (*S*)-**6** is opposite to that of its minor-groove analog (*S*)-**3** where (*S*)-MA causes large fluorescence enhancement but (*R*)-MA doesn't. Thus, the sensor-substrate bindings in (*S*)-**3** and (*S*)-**6** are very different. The unobserved fluorescence enhancement of (*S*)-**3** or (*S*)-**6** in the presence of the chirality-mis-matched MA also demonstrates that merely protonating the nitrogen atoms in the BINOL-amine sensors cannot enhance the fluorescence and there is no acid-suppressed PET with the use of these sensors.

In summary, we have incorporated amino alcohol units to the major groove of BINOL to construct new chiral fluorescent sensors. Fluorescent study of these compounds has clarified a previous misconception: *The commonly accepted acid inhibition of the PET fluorescence quenching in the aryl-amine sensors is not involved in the fluorescent responses of the BINOL-amine based sensors at all*! This is consistent with the thermodynamic argument on the basis of the oxidation potentials of the amine donors and the naphthol acceptors. The introduction of a hydroxyl group to naphthalene has significantly decreased its oxidation potential and makes the electron-transfer to its excited state from an amine unfavorable. The greatly enhanced fluorescence of (*S*)-**3** and (*S*)-**6** in the presence of the chirality-matched MA should be due to the formation of the structurally much more rigid fluorephores upon acid complexation, the suppressed excited state proton transfer and the isolation of the fluorophores in the solid state. This work has provided a better understanding for the mechanism of the fluorescence response of the BINOL-based sensors.

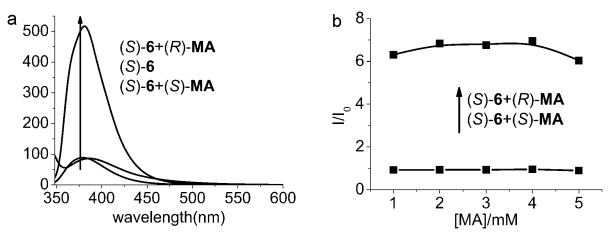

Fig. 4 (a) Fluorescence spectra of (*S*)-**6** (2.0×10^{-4} M) with (*R*)- and (*S*)-MA at 4.0×10^{-3} M. (b) Fluorescence responses of (*S*)-**6** (2.0×10^{-4} M) at 381 nm toward (*R*)- and (*S*)-MA at various concentrations. (Solvent: benzene containing 0.4% DME. λ_{exc} = 341 nm, slit: 5.0/5.0 nm).

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