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Phenol-containing bis(oxazolines): synthesis and fluorescence sensing of amines

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Abstract—The fluorescence sensing of primary amines as their neutral forms has been studied with bis(oxazolinyl)phenols (Me-BOP, Ph-BOP), which are efficiently synthesized starting from mesitylene in six steps and in overall 12–22% yields. The BOP sensors showed fluorescence enhancement toward butylamine and several arylethylamines, whereas they showed fluorescence quenching toward secondary and branched amines. The opposite fluorescence behavior is explained by an increased conformational restriction at the excited state, at which a proton transfer complex between the host and guest forms that is stabilized in a tripodal hydrogen bonding mode. This is the first example in which fluorescence enhancement is observed in amine sensing with phenolic fluorophores. Enantiomeric α-chiral organoamines were also sensed with different fluorescent intensity changes by Ph-BOP, complementing the previous tris(oxazolines) that sense enantiomeric α-chiral organoammonium ions.

1. Introduction

Among various sensing techniques available for clinical, biological, and environmental analyses, fluorescence sensing has advantages of high sensitivity and compatibility for the online and real-time analyses.[1] Amines are an important class of biologically active compounds among those to be sensed by fluorescence analysis. Amines as their neutral forms are generally sensed with fluorescence sensors based on binol or other phenolic fluorophores, mostly in the fluorescence quenching mode.[1f,2] In some cases, amines are sensed as their ammonium salts, which results in the fluorescence enhancement through the photo-induced electron-transfer mechanism.[3] Recently, we have introduced novel tris(oxazoline) receptors **1**, which selectively recognize certain organoammonium ions and also show unusual chiral discrimination toward α-, β-, and α,β-chiral organoammonium ions (Fig. 1).[4] Interestingly, the receptors also sense organoammonium ions with fluorescence enhancement.[4d] The enhancement was attributed to the conformational restriction of the tripodal ligands upon guest binding. As an extension of this novel sensing mechanism, we were interested in an analogous tripodal system that may recognize organoamines in their neutral forms. Thus, we designed a phenol-containing bis(oxazoline) system such as **2** (Fig. 1), in which the acidic hydroxyl group is expected to act as a hydrogen bond donor toward amine guests. With this hydrogen bond donor together with the two oxazoline hydrogen bond

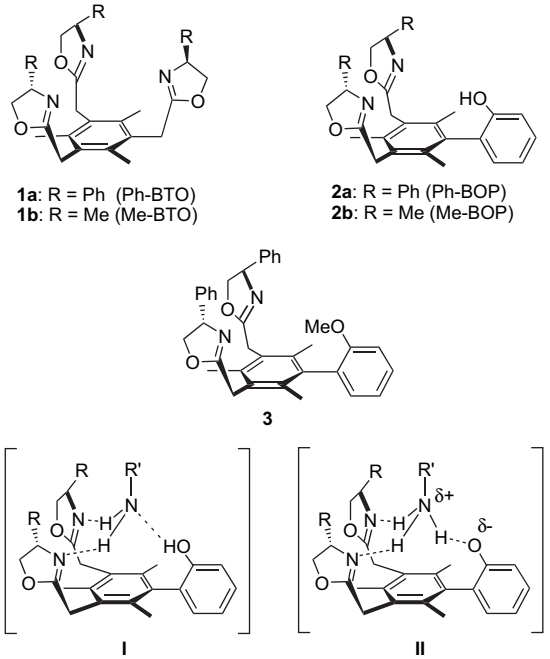

Figure 1. Structures of tripodal oxazolines **1**, phenol-containing bis(oxazolines) **2**, their amine inclusion complexes **I** (at the ground state) and **II** (at the excited state), and a reference compound **3**.

Keywords: Amine sensing; Fluorescence sensors; Hydrogen bonding; Chiral sensing.
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acceptors, the new receptors may recognize an amine guest in a tripodal hydrogen bonding mode, which is reminiscent of the tripodal hydrogen bonding between tris(oxazolines) **1** and organoammonium ions. The recognition of amines by the phenol-containing receptors **2** in the tripodal fashion is expected to generate a proton transfer complex such as **II** at the excited state, because the phenol at the excited state becomes much more acidic than its ground state (phenol: pK_a^*=4.1 vs pK_a=9.0).[5] Thus, the proton transfer complex is supposed to be conformationally more rigid compared to its ground state complex **I**. Therefore, the receptor's fluorescence property is expected to change upon guest binding, hopefully to a fluorescence enhancement mode. Described herein are an efficient synthesis of bis(oxazolinyl)phenols (BOPs) **2** and an investigation of their fluorescence behavior toward various organoamines.

2. Results and discussion

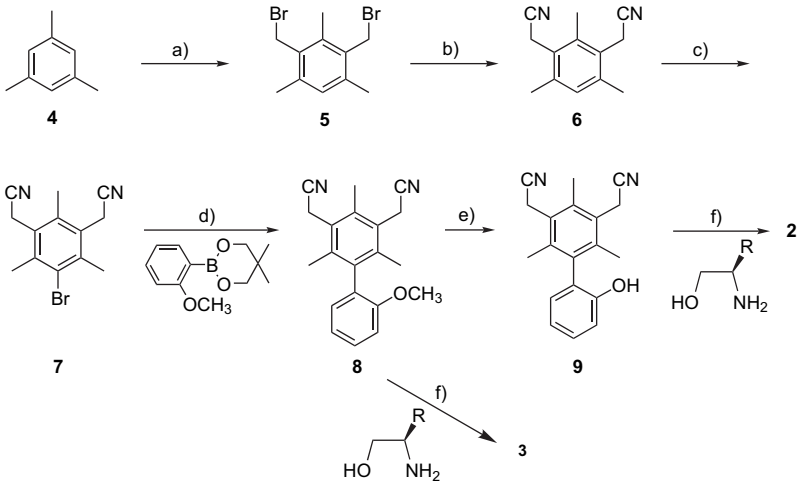
2.1. Synthesis

Our synthetic efforts started from commercially available mesitylene. A controlled bromomethylation of mesitylene with paraformaldehyde and HBr in acetic acid[6] and subsequent nucleophilic substitution of the resulting bis(bromomethyl) compound **5** by cyanide afforded the bis(nitrile) compound **6**. Bromination of this compound with $Me_3(PhCH_2)NBr_3/ZnCl_2$[7] gave the bromo compound **7**. It is worth mentioning that attempts to prepare **7** directly from 2-bromomesitylene via the above sequence, namely bromomethylation and substitution, failed as the bromomethylation of 2-bromomesitylene stopped at the mono-bromomethylated stage even under severe reaction conditions. This could be probably owing to the deactivating effects of the bromine and bromomethyl group toward the electrophilic substitution on the benzene ring. Next, the Suzuki coupling[8] was employed to construct the carbon–carbon bond of the biphenyl core. Thus, the coupling of **7** with 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane[9] yielded methyl ether **8**, which on subsequent deprotection with BBr_3 afforded **9**. Finally, the oxazoline ring was constructed by double condensation of amino alcohols with nitrile group of **9** in the presence of cadmium acetate as a mild Lewis acid catalyst[10] to afford the BOP sensors **2** (Scheme 1).

2.2. Fluorescence studies

The UV–vis spectra of Ph-BOP **2a** in acetonitrile showed absorption maxima at 196 and 276 nm at 0.1 mM concentration. The fluorescence emission spectra displayed emission of the biphenyl nucleus at λ_{max}=300 nm when excited at 276 nm. Similarly, Me-BOP **2b** showed absorption maxima at 276 nm and the fluorescence emission at λ_{max}=305 nm when excited at 275 nm in acetonitrile (at 0.1 mM concentration). The emission wavelengths observed were shorter than that of *o*-phenylphenol[11] because little conjugation is expected between the two phenyl rings.

When Ph-BOP **2a** (0.1 mM in CH_3CN) was titrated with increasing amount of 2-(3,4-dimethoxy)phenylethylamine (**Am4**) as a guest at 25 °C, about 2-fold increase in the fluorescence intensity of the sensor was observed (Fig. 2a). This is an interesting result because so far fluorescence sensing of amines with phenol- or binaphthol-derived sensors resulted in fluorescence quenching rather than enhancement.[1f] Also, amines are efficient fluorescence quenchers of most unsubstituted aromatic hydrocarbon fluorophores such as anthracene, perylene, and carbazole.[1b] The fluorescence enhancement was further confirmed by titrating Ph-BOP **2a** with a non-fluorescent guest such as butylamine (Fig. 2b). Similarly, Me-BOP **2b** also gave a fluorescence enhancement upon titrating with butylamine (Fig. 2c). Although the enhancement is not large, as far as we know, this is the first example of neutral amine sensing with phenol-containing sensors in the fluorescent enhancement mode. We evaluated other amine guests that have different structural features, which are listed in Figure 3. The guests such as 2-phenylethylamine (**Am1**), 4-methoxyphenylethylamine (**Am3**), and tryptamine (**Am5**) also exhibited fluorescence enhancement. It should be noted that in the case of the guests containing aromatic fluorophores such as **Am1** and **Am3**–**Am5**, the fluorescence from the guest itself overlapped



Scheme 1. Synthesis of compounds **2** and **3**. Reagents and conditions: (a) paraformaldehyde, 30% HBr in AcOH, AcOH, 80 °C, 5 h, 95%; (b) NaCN, MeOH/H_2O (5:2), reflux, 5 h, 76%; (c) $Me_3(PhCH_2)NBr_3$, $ZnCl_2$, AcOH, 70 °C, 6 h, 75%; (d) 5 mol % $Pd(PPh_3)_4$, K_3PO_4, DMF, 100 °C, 24 h, 86%; (e) BBr_3, CH_2Cl_2, 25 °C, 48 h, 76%; (f) $Cd(OAc)_2$, PhCl, reflux, 96 h, 58% (R=Ph, **2a**), 32% (R=Me, **2b**), 55% (R=Ph, **3**).

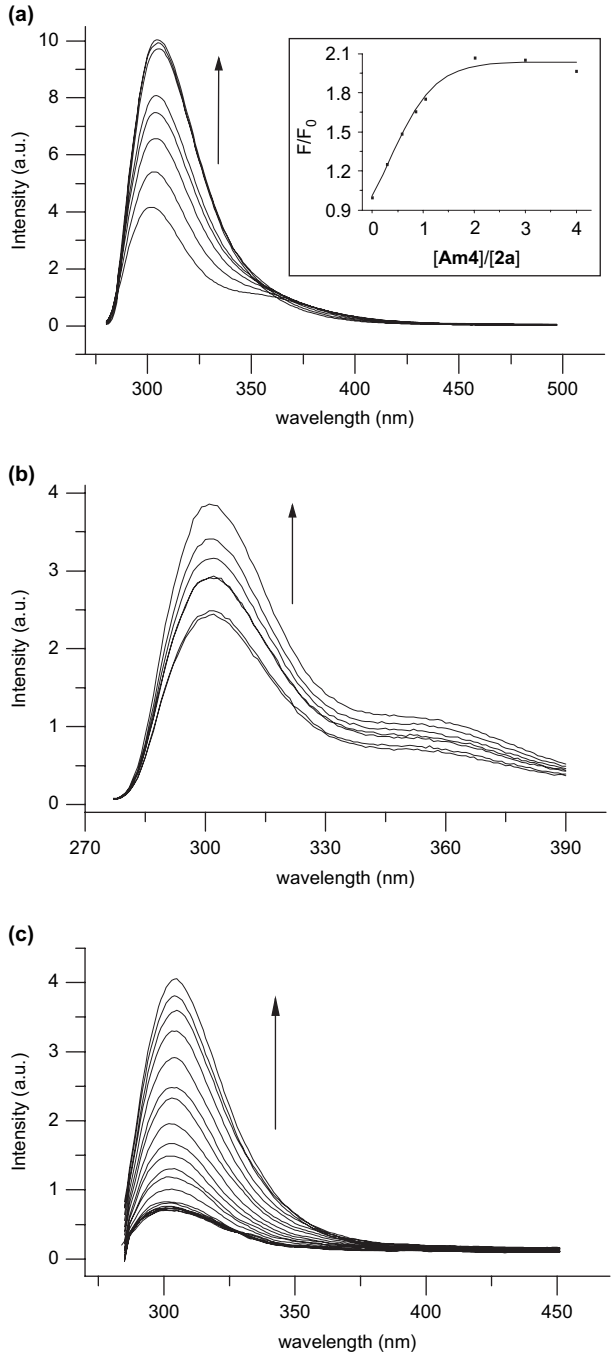


Figure 2. Fluorescence changes measured in CH_3CN at λ_{ex}=276 nm: (a) titration of Ph-BOP **2a** (0.1 mM) with **Am4** (0.0–4.0 equiv from the bottom) (inset: dependence of fluorescence intensity (F/F_0) depending on the ratio [**Am4**]/[**2a**]); (b) titration of Ph-BOP **2a** (0.1 mM) with **Am2** (0.0–6.2 equiv from the bottom); (c) titration of Me-BOP **2b** (0.1 mM) with **Am2** (0.0–10 equiv from the bottom) with λ_{ex}=275 nm.

with that of the host–guest complex. However, the fluorescence enhancement due to the complexation was apparent, as inferred from a non-linear increase of the fluorescence intensity in the plot of F/F_0 versus $[G]_0/[H]_0$ (Fig. 4). The fluorescence intensity increases rather rapidly up to the equivalent point and then slows down upon titration of **2a** with **Am1**, which can be interpreted in this way: at the initial stage, the fluorescence increase results from both the host–guest complex and guest, while in the later stage, the increase is mainly due to the guest added.

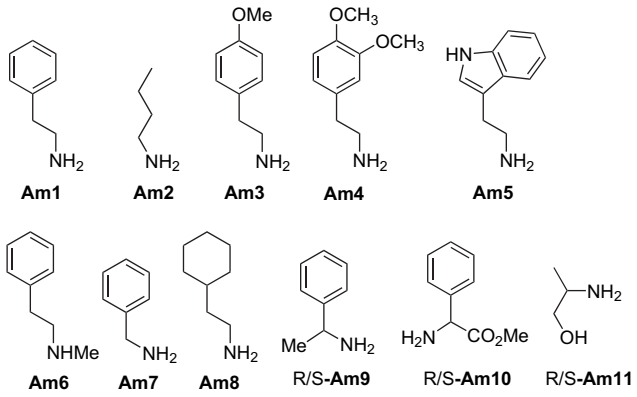


Figure 3. Chemical structures of the amine guests studied.

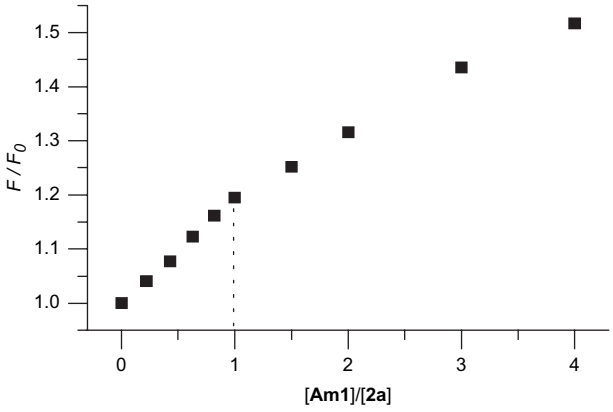


Figure 4. A plot of F/F_0 versus [**Am1**]/[**2a**].

In contrast to the β-arylethylamine or butylamine guests (**Am1**–**Am5**), interestingly, fluorescence quenching was observed for other types of guests such as **Am6**–**Am11**. For example, titrations of Ph-BOP **2a** with **Am6** resulted in fluorescence quenching (Fig. 5), and a similar level of quenching was observed in the case of other guests. How can we rationalize such an opposite result depending on the guests? We suppose that the fluorescence enhancement or quenching observed is dependent on the guest's binding affinity, which is related to the fluorescence enhancement mechanism. Previously we have shown that the ammonium

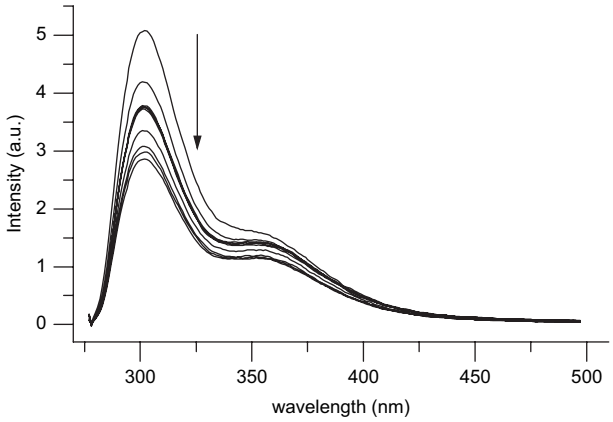


Figure 5. Fluorescence changes upon titration of Ph-BOP **2a** (0.1 mM) with **Am6** (0.0–6.0 equiv from the top) in acetonitrile at λ_{ex}=276 nm.

ions of linear primary amines **Am1**–**Am5** are bound more strongly to the tris(oxazoline) receptors **1** than those of branched or secondary amines **Am6**–**Am11**, because the former guests experience less steric strain from the host's 4-oxazolinyl substituents (Ph or Me in the case of Ph-BTO and Me-BTO, respectively) in the inclusion complexes than the latter guests.[4] Similarly, the steric strain between BOPs **2** and the guests can be expected under the tripodal hydrogen bonding mode (Fig. 6), and under this reasoning, we can expect that BOPs **2** would experience less steric strain in binding the linear organoamines than the others such as the branched guests. In the case of the secondary amines such as **Am6**, BOPs **2** cannot form the tripodal hydrogen bonding suggested. The molecular interactions between Ph-BOP **2a** and amines have been studied by ^{1}H NMR titrations. Although the binding induced chemical shifts were small, certain proton peaks (particularly, the oxazoline ring protons) shifted to downfield upon guest binding ($\Delta\delta$=0.025 ppm when 2 equiv of **Am1** were added).

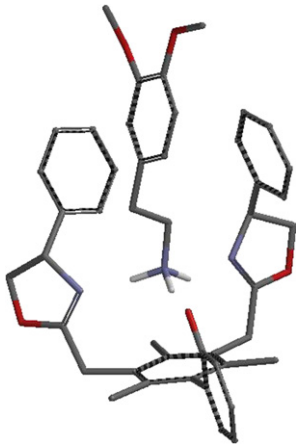


Figure 6. An energy minimized structure of the inclusion complex between Ph-BOP **2a** and **Am4**.

As noted above, the acidity of the phenolic ligand would increase at the excited state and thus proton transfer complexes would form when the receptors bind amines. The proton transfer complexes should be tighter and thus conformationally more rigid than the host–guest complexes at the ground state. This enhanced conformational restriction is believed to contribute to the fluorescence enhancement observed. Such an explanation is based on the tripodal hydrogen bonding mode between the host and guest. When the tripodal hydrogen bonding is not strong enough, we may not expect the enforced conformational restriction and thus little fluorescence enhancement would result. Instead, we may observe fluorescence quenching because generally amines are fluorescence quenchers toward the phenol-based fluorophores. In this way, the observed fluorescence behavior of BOPs toward the amines can be explained.

To get a better understanding for the structural factors that are responsible for the fluorescence enhancement observed, we further examined the fluorescence behavior with reference compounds. We performed the fluorescence titration of **Am1** with the reference compound **3**, in which the phenolic hydroxyl group is protected as its methyl ether, under otherwise identical conditions. As expected, fluorescence quenching was observed in this case upon increasing the amount of **Am1** (Fig. 7a), which indicates that the hydroxyl group in BOPs **2** is essential for the fluorescence enhancement. As discussed above, the hydroxyl group of Ph-BOP **2a** and an amine guest form a proton transfer complex at the excited state, which is stabilized through the hydrogen bonding by the oxazoline ligands. When the hydroxyl group is blocked, no such proton transfer complex would form, and thus no fluorescence enhancement is expected, as observed in the case of **3**.

A direct and straightforward consequence of our presumption should be that phenol **9**, in which two oxazoline ligands are replaced by nitrile groups, should show fluorescence quenching toward amines, as the nitrile groups cannot act as hydrogen bond acceptors to stabilize the host–guest complex. Indeed, fluorescence quenching was observed when phenol **9** was titrated with **Am1** under otherwise identical conditions (Fig. 7b).

These observations clearly augment our presumption to be true and also highlight the key role of the oxazoline ligands in the fluorescence enhancement observed for amines **Am1**–**Am5**. Moreover, the absorption spectra measured during the titration of Ph-BOP **2a** with **Am1** showed no appreciable change, which indicates that the enhanced fluorescence is not due to an increased absorption.

The fluorescence enhancement resulting from the conformational restriction alone, however, seems to be moderate, such as a few times enhancement as observed previously by us.[4d] In this conformational restriction model, the hydrogen bonding interactions are also believed to reduce the charge

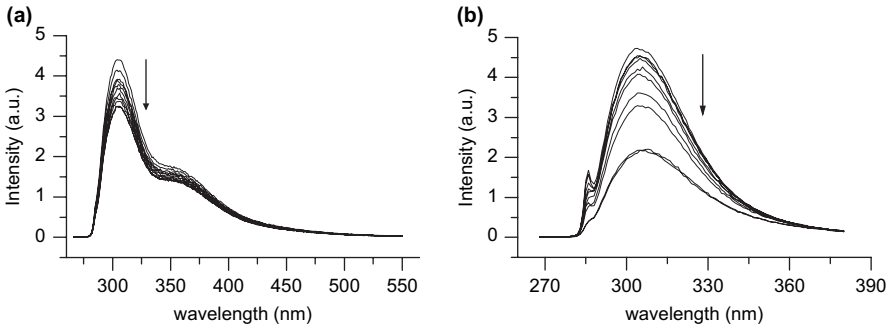


Figure 7. Fluorescence changes measured in CH_3CN: (a) titration of reference compound **3** (0.1 mM) with **Am1** (0.0–4.2 equiv from the top) at λ_{ex}=284 nm; (b) titration of phenol **9** (1.0 mM) with **Am1** (0–10 equiv from the top) at λ_{ex}=287 nm.

separation of the excited state host–guest complex, thereby suppressing some possible quenching processes.[12] At this point, it is premature to speculate on the nature of the host–guest complex at the excited state, but it is certain that the degree of the proton transfer between the phenolic host and an amine is reduced by the 'backside' hydrogen bonding provided by the two oxazoline ligands, which results in the fluorescence modulation of the phenolic fluorophore toward amines, from quenching to enhancement, as observed for the amines **Am1**–**Am5**.

The association constants for the complex formation of Ph-BOP **2a** with some amine guests can be obtained from the observed fluorescence data. On the assumption that host **2a** (H) and a guest amine (G) interact in a 1:1 fashion, the non-linear least squares fit[13] by the following equation[14] gives the association constants K_{11},

$$F/F_0 - (k_G/k_H)[G] = 1 + (k_{11}/k_H)K_{11}[G]/\{1 + K_{11}[G]\}$$

where F_0 is the fluorescence intensity of free host and F is the observed fluorescence intensity during titration, which can be expressed as $F=k_G[G]+k_H[H]+k_{11}[HG]$. The k_G/k_H value can be obtained by measuring concentration-dependent fluorescence changes for the guest and host separately under the same conditions. Association constants thus obtained were in the range of 10^2–10^3 M^{-1} (Table 1), which are much less than that obtained with tris(oxazoline) receptors **1** ($\log K_{11}=6.65$ M^{-1} for *n*-$BuNH_3^+$, determined by UV–vis titration).[4a] This is not an unexpected result because

Table 1. Association constants K_{11} and Stern–Volmer constants K_{SV} determined from the fluorescence titration of Ph-BOP **2a** with the amines in acetonitrile at 25 °C

	Am1	**Am2**	**Am3**	**Am4**	**Am5**
K_{11} (M^{-1})	2100	330	2440	3200	7490
	Am6	**Am7**	**Am8**	(*R*)-**Am9**	(*S*)-**Am9**
K_{SV} (M^{-1})	1290	930	1080	1290	770

neutral hydrogen bonding in the case of BOPs **2** should be much weaker than the charged hydrogen bonding between an ammonium ion and BTOs **1**. The association data indicate that the fluorescence enhancement is related to the association constant: as in the case of the tris(oxazoline) receptor Ph-BTO **1**, the β-aryl-substituted linear amine guests (**Am1** and **Am3**–**Am5**), which show larger fluorescence enhancement compared to an aliphatic guest **Am2**, also gave larger association constants. In the case of amine guests **Am6**–**Am10**, which are believed to have poor binding affinities, we were not able to determine meaningful association constants due to large errors in the non-linear regression process. Instead, the Stern–Volmer constants were obtained for these weakly binding amine guests, which showed linear relationships for the equation: $F_0/F=1+K_{SV}[G]$.[1b]

2.3. Enantio-discrimination

We reasoned that Ph-BOP **2a** might discriminate α-chiral amines because the two phenyl-substituted oxazolines could provide a pseudo-C_2-symmetric chiral environment toward α-substituents of α-chiral amines. The steric interactions between the oxazolinyl phenyl substituents and the guest's α-substituents would be different between the enantiomers, which would lead to different fluorescence properties, as we pointed out above in the cases of different achiral amines. Indeed, we were able to observe substantial differences in the fluorescence behavior between the enantiomeric α-chiral amines examined. For example, when Ph-BOP **2a** was titrated with each of the enantiomeric α-methylbenzylamines (**Am9**), fluorescence quenching resulted in both cases but with different magnitude. Plots of F/F_0 depending on [**Am9**]/[**2a**] values for each of the enantiomeric guests show significant differences in the F/F_0 values between the enantiomers (Fig. 8). Similarly, the other two guests also showed different fluorescence quenching behaviors depending on enantiomeric guests.

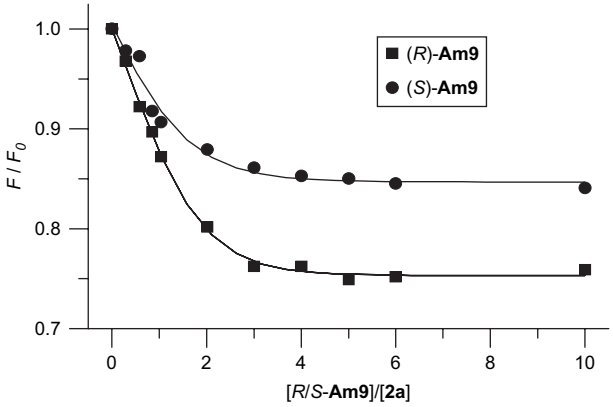


Figure 8. A plot of F/F_0 versus [**Am9**]/[**2a**] depending on the enantiomeric guest.

Therefore, Ph-BOP **2a** can be used as a fluorescence sensor for the monitoring of enantiomeric purity of certain amines in their neutral forms, which complements the enantiomeric sensing of α-chiral organoammonium ions by its tris(oxazoline) analogue **1a**.

3. Conclusion

In conclusion, we have synthesized the phenol-containing bis(oxazolines) as novel fluorescence sensors toward primary amines. The sensors showed fluorescence enhancement toward some linear primary amines and fluorescence quenching toward branched and secondary amines. The observed fluorescence enhancement is ascribed to the conformational restriction and modulation of charge separation of the excited state host–guest complex through hydrogen bonding by the well-directed oxazoline ligands. Although the observed fluorescence enhancement is moderate, it should be noted that this is the first example of amine sensing by phenolic fluorophores in the fluorescence enhancement mode. We have also shown that Ph-BOP **2a** is capable of enantio-discriminating α-chiral amines and thus may be useful for the determination of their enantiomeric purities. A further study on the structure modification of the present system toward a colorimetric sensor of amines is underway.

4. Experimental

4.1. General

2,4-Bis(bromomethyl)-1,3,5-trimethylbenzene,[6] 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane,[9] and benzyl(trimethyl)ammonium tribromide[7] were prepared according to the literature procedures. All other chemicals were commercially available and used without further purification. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. Unless otherwise mentioned, all NMR spectra were recorded in $CDCl_3$ solution containing tetramethylsilane as internal standard. Chemical shifts are reported in δ unit. For column chromatography silica gel of 230–400 mesh was used. Fluorescence spectra were recorded on Photon Technical International Fluorescence system. Fluorescence experiments were carried out in 10-mm quartz cuvette at room temperature. Fluorescence titrations were performed at 0.1 mM concentration and the required guest solutions (10–30 mM) are prepared from appropriate amount of amines in 0.1 mM host solution. Both excitation and emission slit widths were 2 nm.

4.1.1. [(3-Cyanomethyl-2,4,6-trimethyl)phenyl]acetonitrile (6). A mixture of 2,4-bis-(bromomethyl)-1,3,5-trimethylbenzene (**5**) (3.06 g, 10 mmol), sodium cyanide (1.47 g, 30 mmol) in water (20 mL) and methanol (50 mL) was refluxed for 5 h. The solvent was evaporated and diluted with cold water (100 mL) to give the product as a precipitate, which was filtered and washed with water (1.5 g, 76%). An analytically pure sample was obtained by recrystallization from dichloromethane/hexane: R_f=0.3 (dichloromethane/hexane=4/1); mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.3 (s, 6H), 2.4 (s, 3H), 3.7 (s, 4H), 7.0 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 16.5, 18.4, 117.3, 126.5, 131.1, 135.6, 136.9; MS (EI) *m/z* 198.10 (M^+); HRMS calcd for $C_{13}H_{14}N_2$ (M^+) required 198.1157, found 198.1155. Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.84; H, 7.20; N, 13.89.

4.1.2. [(3-Bromo-5-cyanomethyl-2,4,6-trimethyl)phenyl]acetonitrile (7). To a suspension of bis(nitrile) **6** (0.99 g, 5.0 mmol) in AcOH (1.7 mL) were charged benzyl(trimethyl)ammonium tribromide (1.47 g, 5 mmol) and zinc chloride (0.75 g, 5.5 mmol). The resulting mixture was stirred at 70 °C for 5 h, and then cooled and poured into crushed ice containing 5% sodium hydrogen sulfate. The precipitate was filtered, washed with excess water, and recrystallized from ethyl acetate/hexane to yield **7** (1.05 g, 76%) as white needles: R_f=0.3 (dichloromethane); mp 185 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.4 (s, 6H), 2.6 (s, 3H), 3.8 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 20.5, 22.3, 117.3, 128.4, 128.7, 135.0, 138.0; MS (EI) *m/z* 276.13 (M^+), 278.12 (M^++2); HRMS calcd for $C_{13}H_{13}BrN_2$ (M^+) required 276.0262, found 276.0262. Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 55.84; H, 4.68; N, 10.05.

4.1.3. [(5-Cyanomethyl-2′-methoxy-2,4,6-trimethyl)biphenyl-3-yl]acetonitrile (8). A mixture of bromide **7** (0.28 g, 1.0 mmol), 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane (0.60 g, 2.75 mmol), $Pd(PPh_3)_4$ (0.05 g, 5 mol %), and K_3PO_4 (1.16 g, 5.5 mmol) in DMF (5 mL) was stirred at 100 °C for 24 h. The resulting mixture was filtered through Celite, washed with hot ethyl acetate, and then the filtrate was concentrated to yield a black residue. Purification by column chromatography gave **8** (0.26 g, 86%): mp 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.0 (s, 6H), 2.1 (s, 3H), 3.7 (s, 7H), 7.0–7.1 (m, 3H), 7.3–7.4 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 18.7, 19.6, 56.1, 111.6, 118.2, 121.6, 126.9, 129.7, 130.0, 131.4, 135.0, 136.6, 139.0, 157.1; MS (EI) *m/z* 304.21 (M^+); HRMS calcd for $C_{20}H_{20}N_2O$ (M^+) required 304.1576, found 304.1580. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.48; H, 6.61; N, 9.30.

4.1.4. [(5-Cyanomethyl-2′-hydroxy-2,4,6-trimethyl)biphenyl-3-yl]acetonitrile (9). To a solution of **8** (0.3 g, 1.0 mmol) in dichloromethane was charged $BF_3\cdot OEt_2$ (8.0 mL, 8.0 mmol) (1.0 M in dichloromethane) at 0 °C, and the mixture was allowed to stir at room temperature for 48 h. An aqueous workup and subsequent purification by column chromatography gave **9** (0.22 g, 76%); mp 202 °C. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.1 (s, 6H), 2.5 (s, 3H), 3.8 (s, 4H), 6.9–7.0 (m, 3H), 7.28–7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 18.5, 19.7, 116.4, 117.7, 121.9, 127.3, 128.1, 130.2, 130.8, 136.3, 136.4, 137.7; MS (EI) *m/z* 290.19 (M^+); HRMS calcd for $C_{19}H_{18}N_2O$ (M^+) required 290.1419, found 290.1420. Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 76.75; H, 6.19; N, 9.68.

4.1.5. [2′,4′,6′-Trimethyl-3′,5′-bis(4-phenyl-4,5-dihydrooxazol-2-yl)methyl]biphenyl-2-ol (Ph-BOP, 2a). A mixture of bis(nitrile) **9** (0.29 g, 1.0 mmol), (*S*)-(+)-2-phenylglycinol (0.54 g, 4.0 mmol), and $Cd(OAc)_2$ (0.013 g, 0.25 mmol) in chlorobenzene was refluxed for 4 days while a mild stream of nitrogen was bubbled through the reaction mixture. Evaporation of the solvent gave a black residue, which was purified by column chromatography (gradient elution: 10%→60% ethyl acetate in hexane) to give **2a** (0.3 g, 58%): mp 90 °C; $[\alpha]_D^{25}$ +87.3 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.05 (s, 3H), 2.08 (s, 3H), 2.4 (s, 3H), 3.8 (s, 4H), 4.0–4.1 (m, 2H), 4.6–4.7 (m, 2H), 5.0–5.1 (m, 2H), 6.9–7.0 (m, 4H), 7.1–7.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.1, 18.0, 19.0, 29.9, 69.3, 69.4, 75.2, 75.5, 116.2, 120.1, 126.5, 127.6, 127.7, 128.1, 128.8, 128.89, 128.93, 130.2, 131.1, 135.3, 136.5, 142.3, 142.5, 154.1, 167.7; MS (EI) *m/z* 530.39 (M^+); HRMS calcd for $C_{35}H_{34}N_2O_3$ (M^+) required 530.2569, found 530.2560. Anal. Calcd for $C_{35}H_{34}N_2O_3$: C, 79.22; H, 6.46; N, 5.28. Found: C, 77.07; H, 6.69; N, 5.18.

4.1.6. [2′,4′,6′-Trimethyl-3′,5′-bis(4-methyl-4,5-dihydrooxazol-2-yl)methyl]biphenyl-2-ol (Me-BOP, 2b). Prepared from **9** as above in 32% yield: mp 133 °C; $[\alpha]_D^{25}$ +11.2 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 1.2 (q, 6H), 2.0 (s, 6H), 2.3 (s, 3H), 3.7 (s, 4H), 3.78–3.83 (m, 2H), 4.07–4.12 (m, 2H), 4.3–4.4 (m, 2H), 6.9–7.0 (m, 3H), 7.2–7.4 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.2, 18.3, 18.4, 22.17, 22.2, 30.3, 61.7, 61.8, 75.0, 116.7, 120.5, 128.7, 129.4, 130.7, 131.69, 131.73, 136.8, 154.7, 166.6; MS (EI) *m/z* 406.27 (M^+); HRMS calcd for $C_{25}H_{30}N_2O_3$ (M^+) required 406.2256, found 406.2253. Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 69.94; H, 7.67; N, 6.77.

4.1.7. {[3,5-Bis(4-phenyl-4,5-dihydrooxazol-2-yl)-methyl]-2′-methoxy-2,4,6-trimethyl}biphenyl (3). Prepared from **8** similarly as above in 55% yield: mp 93 °C; $[\alpha]_D^{25}$ +74.37 (*c* 0.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.06 (s, 3H), 2.07 (s, 3H), 2.6 (s, 3H), 3.7 (s, 3H), 3.9 (s, 4H), 4.0–4.1 (m, 2H), 4.56–4.62 (m, 2H), 5.1–5.2 (m, 2H), 7.0–7.1 (m, 4H), 7.0–7.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.4, 18.3, 30.3, 55.6, 69.7, 75.0, 110.9, 120.8, 126.8, 126.9, 127.3, 127.6, 128.1, 128.5, 128.8, 129.1, 130.3, 131.1, 131.3, 135.4, 136.1, 137.1, 142.8, 156.9, 167.4; MS (EI) *m*/*z* 545.25 (M^++1); HRMS calcd for $C_{36}H_{36}N_2O_3$ (M^+) required 544.2726, found 544.2729. Anal. Calcd for $C_{36}H_{36}N_2O_3$: C, 79.38; H, 6.66; N, 5.14. Found: C, 79.23; H, 6.57; N, 5.13.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.060.

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