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Helical Aromatic Foldamers Functioning as a Fluorescence Turn-on Probe for Anions

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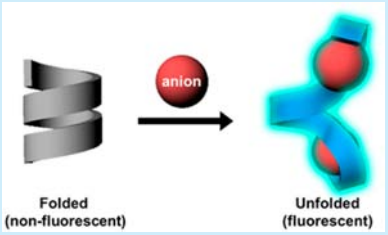
Supporting Information

ABSTRACT: Indolocarbazole-pyridine hybrid foldamers are strongly fluorescent in an extended random conformation, but the fluorescence is completely quenched upon folding to a helical conformation due to the compact stacking between aryl planes in the backbone. Anion binding disturbs the helical conformation, thus regenerating the fluorescence of the foldamers. This unique property has been utilized to develop a fluorescence turn-on probe for anions such as sulfate and fluoride.

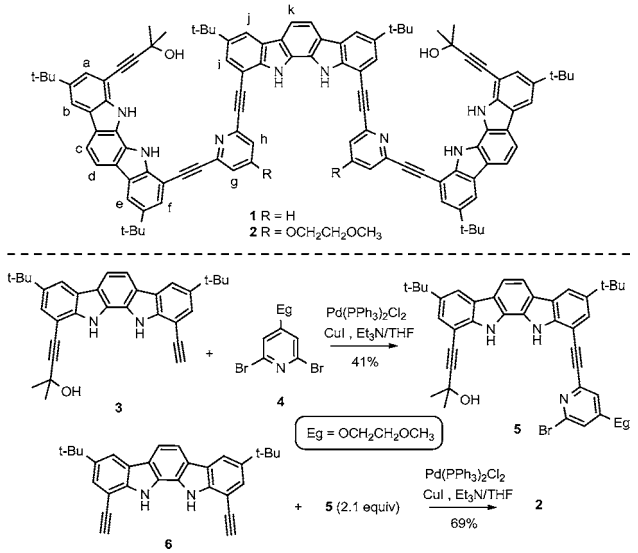


In recent years, anions have emerged as a key research subject in the field of supramolecular chemistry due to the growing recognition of their crucial roles in chemical, biological, and environmental systems. A large variety of synthetic molecules have been described that interact with anions to generate optical or electrochemical signals, thus functioning as molecular probes for anions.[1] In most cases, the signals upon anion binding result from the electronic perturbation of synthetic molecules by hydrogen-bond formation or chemical reactions. It was also described that the fluorescence "turn-on" signals could be produced by the modulation of the assembly and disassembly of small organic molecules and polymers.[2]

Foldamers are synthetic oligomers that tend to adopt well-defined secondary structures.[3] Among them, we have been interested in the aromatic helical foldamers that are responsive to external stimuli to develop molecular switches and smart materials.[4,5] When folded into a helical conformation, the aromatic foldamers display considerable changes in the absorption and emission properties due to the π-stacking of the backbone aromatic planes. We envisioned that these unique features could be implemented in the development of molecular probes for anions that would disrupt π-stacked arrays in the helical foldamers. In this study, we, for the first time, describe a foldamer-based molecular probe for anions using indolocarbazole−pyridine hybrid foldamers **1** and **2**, which are strongly fluorescent when unfolded, but the fluorescence is completely quenched upon folding to a helical conformation. Anions such as fluoride and sulfate effectively disturb the folding conformation to regenerate the fluorescence of the foldamers, functioning as "turn-on" fluorescence probes for the anions.

The synthesis of compound **1** was described previously.[6a] The synthesis of foldamer **2** is outlined in Scheme 1. Sonogashira coupling reaction[7] of a 1:1 mixture of compound **3**[6a] and **4** gave compound **5** (41%), which in turn was reacted with compound **6**[6a] to afford foldamer **2** in 69% yield. All new

Scheme 1. Synthesis of Foldamer 2



compounds were fully characterized as detailed in the Supporting Information. The folding features of foldamers **1** and **2** were first revealed in the solid state by single-crystal X-ray diffraction. As shown in Figure 1, foldamer **2** adopted a helical structure of two turns which were tightly stacked together with an average interplanar distance of 3.4 Å. The two helical enantiomers, right- (*P*) and left-handed (*M*) helices, were alternatively stacked to afford a racemic crystal (Figure S12). The indolocarbazole NH protons and pyridyl nitrogen atoms were all converged inward into the internal cavity wherein two water molecules were occupied by hydrogen bonds.

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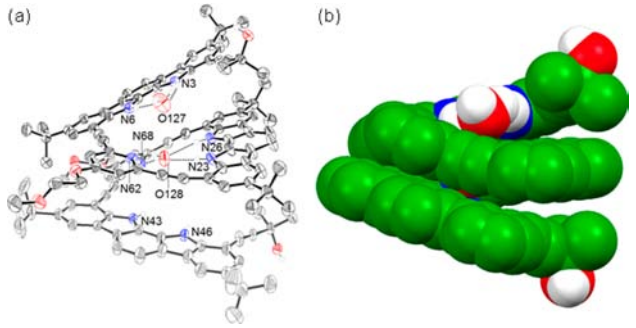

Figure 1. (a) ORTEP (50% probability) and (b) space-filling (CPK) views of X-ray crystal structures of **2**. Two water molecules are entrapped in the helical cavity of **2** by multiple hydrogen bonds with the indolocarbazole NHs and pyridine nitrogen atoms. The CH hydrogen atoms are omitted for clarity.

In solution, the folding properties of foldamers **1** and **2** strongly depend on the nature of solvents. As described previously,[6] foldamer **1** folded to a helical conformation in nonpolar solvents including wet CD_2Cl_2, $CDCl_3$, and toluene-d_8 but existed in extended random conformations in polar solvents such as DMSO-d_6 and acetone-d_6. Likewise, foldamer **2** also showed the same folding features in solution as evidenced by ^{1}H NMR and fluorescence spectroscopy. As shown Figure 2c, the ^{1}H NMR aromatic signals of **2** were

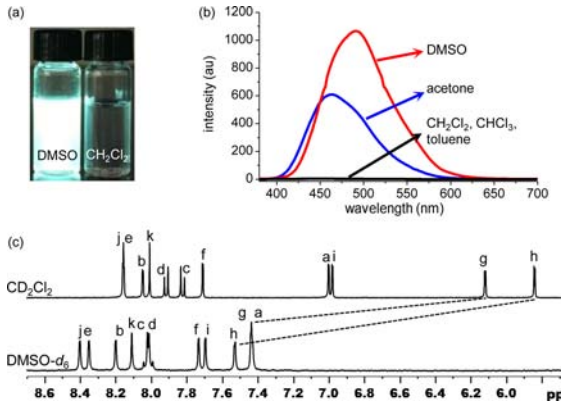

Figure 2. (a) Photograph of **2** (1.0×10^{-5} M) upon illumination with a UV lamp (~365 nm), (b) fluorescence spectra of **2** (2.0×10^{-6} M) in various wet solvents, and (c) partial ^{1}H NMR spectra of **2** (1.0×10^{-3} M) in DMSO-d_6 and water-saturated CD_2Cl_2.

considerably shifted upfield in water-saturated CD_2Cl_2 compared to that in DMSO-d_6. In particular, the pyridine signals displayed the most pronounced shifts; two signals H^g and H^h appeared at 7.43 and 7.53 in DMSO-d_6 but they were dramatically shifted to 6.12 and 5.84 ppm in water-saturated CD_2Cl_2, respectively. These characteristic upfield shifts strongly support that foldamer **2** adopts a helical conformation with compact stacking between the backbone aryl planes in water-saturated CD_2Cl_2, which is consistent with the X-ray crystal structure.

In addition, the emission properties of foldamers **1** and **2** were sensitive to the nature of solvents (Figure 2a,b and Figure S4). The foldamers were essentially nonfluorescent in wet CH_2Cl_2, $CHCl_3$, and toluene. This fluorescence quenching[8] supports the stacked arrangement of indolocarbazoles and pyridines in **1** and **2** as a result of the helical folding. In sharp contrast, the foldamers were strongly fluorescent in DMSO and acetone, which contain good hydrogen bond acceptors with β scales of 0.76 and 0.43, respectively.[9] These solvents tend to form strong hydrogen bonds with the indolocarbazole NH protons in foldamers **1** and **2**, which should be all desolvated for the helical folding because the in situ generated internal cavity is too small to accommodate these solvents. As a consequence, foldamers **1** and **2** existed in unfolded random conformations and thus were fluorescent in DMSO and acetone.

In this context, we hypothesized that anion binding to the foldamers might also disturb their helical folding to turn on the fluorescence. We added anions as tetrabutylammonium salts to a water-saturated CH_2Cl_2 solution containing **1** or **2** (Figure 3).

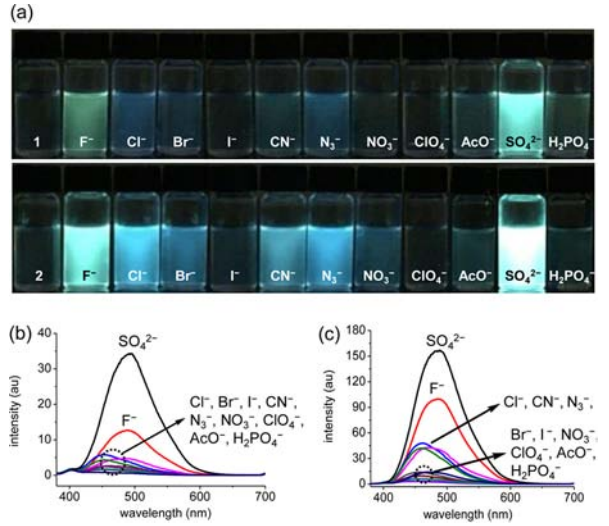

Figure 3. (a) Photographs of **1** (above) and **2** (below) (1.0×10^{-5} M) upon illumination with a UV lamp (~365 nm); emission spectra of (b) **1** (2.0×10^{-6} M) and (c) **2** (2.0×10^{-6} M) in the absence and presence of anions (5 equiv) in water-saturated CH_2Cl_2.

Two trends were apparent. First, sulfate and fluoride ions were the most efficient in regenerating the fluorescence of **1** and **2**. This can possibly be attributed to the formation of strong hydrogen bonds between the anions and foldamers. Second, the anion-induced fluorescence enhancement of **2** was much larger than that of **1**. In foldamer **1**, a greenish fluorescence (λ_{max} = ~490 nm) was clearly visible only in the presence of sulfate and fluoride ions, while a bright blue-colored fluorescence (λ_{max} = ~460 nm) was additionally seen with **2** in the presence of other anions such as chloride, cyanide, and azide ions under the same conditions. Foldamer-based anion probes of this kind are highly attractive and useful because anion binding leads to the fluorescence "turn-on" from the completely nonfluorescent state.

^{1}H NMR studies demonstrated that anion binding altered the helically folded conformation of the foldamer, which might be responsible for the fluorescence recovery. As a representative example, foldamer **2** adopted a helix of two turns in wet CD_2Cl_2, and therefore, ^{1}H NMR aromatic signals were significantly shifted upfield as mentioned earlier. Upon addition of sulfate ion, most aromatic signals in **2** were noticeably shifted downfield (Figure 4b and Figures S1 and S2), implying that the stacked helical arrangement of the aromatic rings is broken. In particular, one of the two pyridine signals CH^g was greatly shifted from 6.12 to 8.27 ppm, which was much greater than

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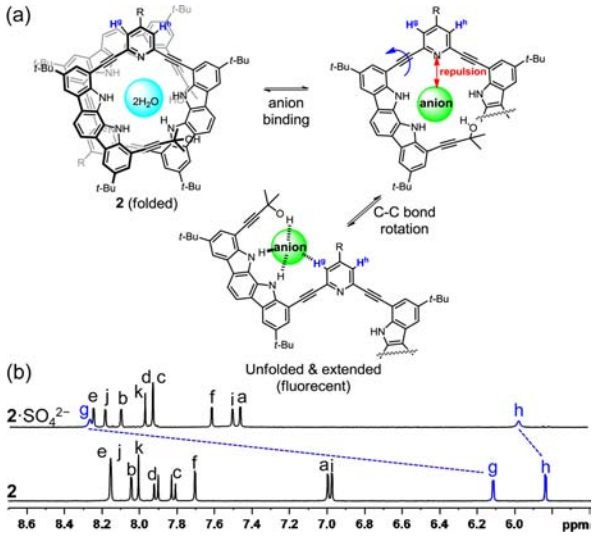

Figure 4. (a) Possible unfolding process of helical foldamers upon anion binding and (b) partial ^{1}H NMR spectra of **2** (1.0×10^{-3} M) in the absence (bottom) and presence (above) of $(TBA)_2SO_4$ (5 equiv) in water-saturated CD_2Cl_2.

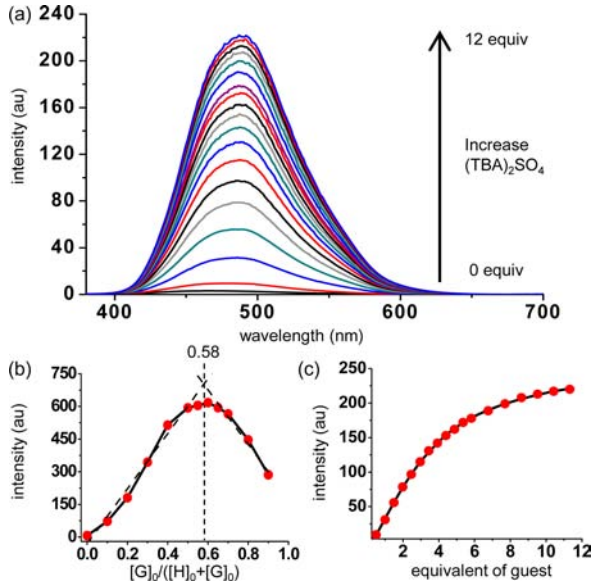

Figure 5. (a) Fluorescence spectral changes of **2** (5.0×10^{-6} M in 1% (v/v) CH_3OH/water-saturated CH_2Cl_2) with increasing the amount of $(TBA)_2SO_4$; (b) Job plot; (c) titration curves at 490 nm (dot: experimental, line: theoretical).

the magnitude ($\Delta\delta$ = 0.1−0.5 ppm) of the downfield shifts observed for other aromatic protons. This result clearly indicates the formation of the CH^g···anion hydrogen bond as shown in Figure 4a. When an anion binds to the helical cavity through hydrogen bonding with NHs and OH, repulsive interaction between the bound anion and the pyridine nitrogen is present. To avoid this repulsion, the ethynyl bond should be rotated. As the consequence, the CH^g hydrogen atom can simultaneously participate in the hydrogen bond with the same anion. In turn, the foldamer becomes unfolded and becomes fluorescent upon anion binding. Furthermore, electron-donating ethylene glycol (Eg) substituents in foldamer **2** are expected to increase the electron density in the pyridyl nitrogen, which may facilitate the unfolding upon anion binding due to the stronger repulsive interactions.

Next, we determined the association constants of **2** with three representative anions, F^-, Cl^-, and SO_4^{2-} as tetrabutylammonium salts. The maximum values on the Job plots were observed at 0.58−0.70 of [anion]/([anion] + [**2**]) (Figure 5b and Figures S6b and S7b), suggesting that 1:2 (**2**/anion) binding modes are predominant under the conditions.[10] Titration experiments were conducted with fluorescence spectroscopy at 25 °C in 1% MeOH/water-saturated CH_2Cl_2, and titration curves were analyzed by a nonlinear squares fitting method (Figure 5 and Figures S6 and S7).[11] As summarized in Table 1, foldamer **2** bound most strongly the sulfate ion with the binding constants, log K_1 = 5.25 and log K_1K_2 = log β = 10.23. Decreased binding affinities were observed with fluoride and chloride ions. To confirm the validity of these values, we also conducted the ^{1}H NMR titrations of compound **5** forming only 1:1 complexes with anions (Figures S8−10). The association constants (log K) of compound **5** were comparable to those (log K_1 or (log β)/2) of foldamer **2**. It should be noted that, in addition to the downfield shifts of NH and OH signals, the pyridine CH hydrogen of **5** was largely shifted downfield during the titrations, as in the case of foldamer **2**. The complexation-induced shifts of all these signals gave identical association constants within experimental error, implying that these signals participate in the same binding event.

Table 1. Association Constants[a] of 2 and 5 for Anions at 24 °C in 1% MeOH/Water-Saturated CH_2Cl_2

	2		5
	log K_1	log β	log K
Cl^-	4.31 ± 0.01	7.76 ± 0.02	4.14 ± 0.05
F^-	4.62 ± 0.68	7.92 ± 0.03	4.10 ± 0.05
SO_4^{2-}	5.25 ± 0.05	10.23 ± 0.10	4.75 ± 0.09

[a]Anions were used as tetrabutylammonium salts, and titration experiments were carried out using fluorescence spectroscopy for **2** and ^{1}H NMR spectroscopy for **5** (see the Supporting Information)

Finally, we investigated whether the sulfate complex of **1** could refold to a helical conformation when the pyridine rings in **1** were protonated. In such a case, strong hydrogen bonds might form between the protonated pyridines and the bound sulfate ion, instead of the original repulsion exerted in the helical conformation of the neutral form. To examine this possibility, we added perchloric acid to a fluorescent, water-saturated CH_2Cl_2 solution containing **1** and sulfate ions. The resulting solution became nonfluorescent (Figure 6a). Next, when tetrabutylammonium hydroxide was added, the solution became fluorescent again. This on-and-off fluorescence switching, modulated by acid−base chemistry as described here,[12] should be attributed to the repetitive alteration of folding and unfolding conformations. Moreover, this refolding into a compact helical conformation due to the protonation was confirmed in the X-ray crystal structure of complex **1**·$2H^+ \supset SO_4^{2-}$ (Figure 6b and Figure S11). The sulfate ion was situated in the middle of the helical cavity through eight hydrogen bonds, six with the indolocarbazole NHs and two with the protonated pyridinium NHs.

In conclusion, we have demonstrated for the first time that aromatic helical foldamers can function as fluorescence "turn-on" probes for anions. The helically folded indolocarbazole−pyridine foldamers are nonfluorescent but become fluorescent upon binding anions such as fluoride and sulfate which disturb the helical conformations with compact aromatic stacking. It

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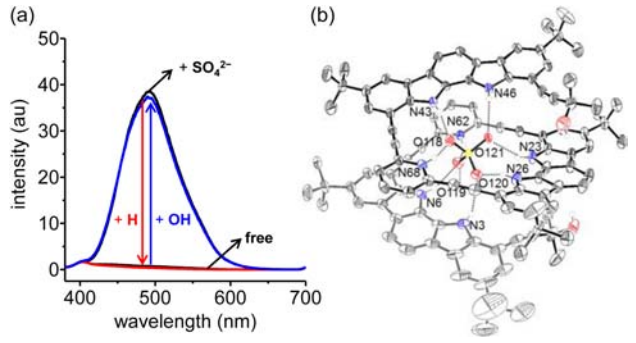

Figure 6. (a) Fluorescence on−off switching of the sulfate complex of **1** (2.0×10^{-6} M) in water-saturated CH_2Cl_2 that was reversibly controlled by addition of perchloric acid and tetrabutylammonium hydroxide and (b) X-ray crystal structure of complex $\mathbf{1}{\cdot}2H^+{\supset}SO_4^{2-}$.

has been also proven that the reversible switching of on and off fluorescence can be achieved by controlling the folding and unfolding states.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02156.

Syntheses and characterizations of new compounds, NMR studies, fluorescence studies, binding studies, and X-ray crystallographic data for $\mathbf{2}{\supset}2H_2O$ and $\mathbf{1}{\cdot}2H^+{\supset}SO_4^{2}$ (PDF)

Crystallographic data for $\mathbf{2}{\supset}2H_2O$ (CIF)

Crystallographic data for $\mathbf{1}{\cdot}2H^+{\supset}SO_4^{2}$ (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For books and recent reviews, see: (a) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry: Monograph in Supramolecular Chemistry*; RSC: Cambridge, UK, 2006. (b) *Anion Recognition in Supramolecular Chemistry, Topics in Heterocyclic Chemistry*; Gale, P. A., Dehaen, W., Eds.; Springer: Berlin, 2010; Vol. *24*. (c) Ballester, P. *Acc. Chem. Res.* **2013**, *46*, 874. (d) Cametti, M.; Rissanen, K. *Chem. Soc. Rev.* **2013**, *42*, 2016. (e) Santos-Figueroa, L. E.; Moragues, M. E.; Climent, E.; Agostini, A.; Martínez-Máñez, R.; Sancenón, F. *Chem. Soc. Rev.* **2013**, *42*, 3489. (f) Kim, S. K.; Sessler, J. L. *Acc. Chem. Res.* **2014**, *47*, 2525. (g) Zhou, Y.; Zhang, J. F.; Yoon, J. *Chem. Rev.* **2014**, *114*, 5511. (h) Cai, J.; Sessler, J. L. *Chem. Soc. Rev.* **2014**, *43*, 6198. (i) Evans, N. H.; Beer, P. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11716. (j) Gale, P. A.; Caltagirone, C. *Chem. Soc. Rev.* **2015**, *44*, 4212. (k) Busschaert, N.; Caltagirone, C.; Van Rossom, W.; Gale, P. A. *Chem. Rev.* **2015**, *115*, 8038.

(2) (a) Rajamalli, P.; Prasad, E. *Org. Lett.* **2011**, *13*, 3714. (b) Sakai, R.; Nagai, A.; Tago, Y.; Sato, S.-i.; Nishimura, Y.; Arai, T.; Satoh, T.; Kakuchi, T. *Macromolecules* **2012**, *45*, 4122. (c) Ji, X.; Yao, Y.; Li, J.; Yan, X.; Huang, F. *J. Am. Chem. Soc.* **2013**, *135*, 74. (d) Foster, J. A.; Edkins, R. M.; Cameron, G. J.; Colgin, N.; Fucke, K.; Ridgeway, S.; Crawford, A. G.; Marder, T. B.; Beeby, A.; Cobb, S. L.; Steed, J. W. *Chem. - Eur. J.* **2014**, *20*, 279. (e) Watt, M. M.; Engle, J. M.; Fairley, K. C.; Robitshek, T. E.; Haley, M. M.; Johnson, D. W. *Org. Biomol. Chem.* **2015**, *13*, 4266.

(3) For reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (c) *Foldamers: Structure, Properties, and Applications*; Hecht, S., Huc, I., Eds.; Wiley-VCH: Weinheim, 2007. (d) Guichard, G.; Huc, I. *Chem. Commun.* **2011**, *47*, 5933. (e) Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. *Chem. Rev.* **2012**, *112*, 5271.

(4) (a) Juwarker, H.; Suk, J.-m.; Jeong, K.-S. *Chem. Soc. Rev.* **2009**, *38*, 3316. (b) Juwarker, H.; Jeong, K.-S. *Chem. Soc. Rev.* **2010**, *39*, 3664.

(5) (a) Lee, S.; Flood, A. H. *J. Phys. Org. Chem.* **2013**, *26*, 79. (b) Zhang, D.-W.; Zhao, X.; Li, Z.-T. *Acc. Chem. Res.* **2014**, *47*, 1961. (c) Shigeno, M.; Kushida, Y.; Yamaguchi, M. *Chem. Commun.* **2016**, *52*, 4955. (d) Yu, Z.; Hecht, S. *Chem. Commun.* **2016**, *52*, 6639. (e) Barboiu, M.; Stadler, A.-M.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2016**, *55*, 4130.

(6) (a) Jeon, H.-G.; Jung, J. Y.; Kang, P.; Choi, M.-G.; Jeong, K.-S. *J. Am. Chem. Soc.* **2016**, *138*, 92. (b) Kim, J. S.; Jeon, H.-G.; Jeong, K.-S. *Chem. Commun.* **2016**, *52*, 3406.

(7) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: Weinheim, 1997; Chapter 5, pp 203−229. (b) Zhang, J.; Pesak, D. J.; Ludwick, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4227. (c) Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165.

(8) (a) Lahiri, S.; Thompson, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 11315. (b) Caldwell, S. T.; Cooke, G.; Hewage, S. G.; Mabruk, S.; Rabani, G.; Rotello, V.; Smith, B. O.; Subramani, C.; Woisel, P. *Chem. Commun.* **2008**, 4126. (c) Zhu, N.; Hu, W.; Han, S.; Wang, Q.; Zhao, D. *Org. Lett.* **2008**, *10*, 4283. (d) Xu, Z.; Singh, N. J.; Lim, J.; Pan, J.; Kim, H. N.; Park, S.; Kim, K. S.; Yoon, J. *J. Am. Chem. Soc.* **2009**, *131*, 15528. (e) Nandwana, V.; Samuel, I.; Cooke, G.; Rotello, V. M. *Acc. Chem. Res.* **2013**, *46*, 1000.

(9) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: Sausalito, CA, 2006; p 147.

(10) Ulatowski, F.; Dąbrowa, K.; Bałakier, T.; Jurczak, J. *J. Org. Chem.* **2016**, *81*, 1746. We cannot completely rule out the formation 1:3 (**2**/anion) binding mode at higher concentrations.

(11) (a) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311. (b) Fielding, L. *Tetrahedron* **2000**, *56*, 6151. (c) Thordarson, P. *Chem. Soc. Rev.* **2011**, *40*, 1305.

(12) (a) Ma, G.; Müller, A. M.; Bardeen, C. J.; Cheng, Q. *Adv. Mater.* **2006**, *18*, 55. (b) Chen, L.; Di, J.; Cao, C.; Zhao, Y.; Ma, Y.; Luo, J.; Wen, Y.; Song, W.; Song, Y.; Jiang, L. *Chem. Commun.* **2011**, *47*, 2850. (c) Jordan, L. M.; Boyle, P. D.; Sargent, A. L.; Allen, W. E. *J. Org. Chem.* **2010**, *75*, 8450. (d) Carroll, C. N.; Coombs, B. A.; McClintock, S. P.; Johnson, C. A., II; Berryman, O. B.; Johnson, D. W.; Haley, M. M. *Chem. Commun.* **2011**, *47*, 5539. (e) Zhou, K.; Wang, Y.; Huang, X.; Luby-Phelps, K.; Sumer, B. D.; Gao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6109. (f) Sun, C.; Ren, C.; Wei, Y.; Qin, B.; Zeng, H. *Chem. Commun.* **2013**, *49*, 5307. (g) Sun, C.; Liu, Y.; Liu, J.; Lu, Y.-J.; Yu, L.; Zhang, K.; Zeng, H. *J. Org. Chem.* **2014**, *79*, 2963.

DOI: 10.1021/acs.orglett.6b02156
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