Synthesis and optoelectronic properties of 2,6-bis(2-anilinoethynyl)pyridine scaffolds†

Jeffrey M. Engle, **Calden N. Carroll**, **Darren W. Johnson**[*], and **Michael M. Haley**[*]
Department of Chemistry and Materials Science Institute, University of Oregon, Eugene, Oregon, 97403-1253, USA.

Abstract

A series of sixteen bisphenylureas based on a 2,6-bis(2-anilinoethynyl)pyridine scaffold have been synthesized for use as potential anion sensors. Prior work with one of these receptors revealed a distinct fluorescence response in the presence of a suitable anion source with specificity towards chloride anion. This study demonstrates that the fluorescent properties of these receptors can be tuned through the systematic variation of the pendant functional groups.

Introduction

Supramolecular anion sensors have received considerable attention in recent years, specifically those displaying a colorimetric and/or fluorescence response in the presence of specific anions.[1–7] A typical design motif for these sensors takes advantage of non-covalent interactions such as electrostatics,[8–10] hydrogen bonding,[11–13] anion-π,[14–16] and hydrophilicity/hydrophobicity. [17–20] To obtain a colorimetric and/or fluorescent outcome, a fluorophore unit is often appended to the sensor scaffold, which changes its fluorescent response upon a binding event; however, the pendant fluorophores are often bulky and exhibit a limited range of responses.[21] An alternative approach would be to functionalize a fluorophore backbone with typical anion binding motifs.[22–24] This would eliminate the need for a receptor to have a pendant fluorophore and could allow for greater tunability of both fluorescence response and binding strength.

The 2,6-bis(arylethynyl)pyridine scaffold has found utility in numerous areas of chemistry. The inherent properties of such ethynylpyridines (conjugation, absorption/emission, pH-dependent speciation, metal binding capability, rigidity, *etc.*),[25–27] have been exploited for applications such as liquid crystals,[28] lightemitting materials,[29] rotaxane-type structures,[30] molecular magnets,[31] antiangiogenic activity,[32] polymer composites[33] and coordination complexes.[24,34,35] In contrast, the supramolecular chemistry of 2,6-bis(arylethynyl)pyridines has received little attention, perhaps in part due to the scarcity of uniting the fields of molecule/ion recognition with the synthesis of highly-conjugated, carbon-rich materials.

haley@uoregon.edu; dwj@uoregon.edu; Fax: +1 541-346-0487; Tel: +1 541-346-0456.

Most of the host/guest studies reported have focused on exploiting the pyridine lone pair to bind metal ions[22] or organoiodides.[3] Alternatively, we hypothesized that the unique absorption/emission properties in tandem with the structural rigidity of (arylethynyl)pyridines aptly positions them to function as small molecule or ion receptors. Moreover, we envisioned that the 2,6-bis(arylethynyl)pyridine scaffold and its derivatives would serve as a versatile building block for the development of receptor molecules that target a variety of guests depending on the protonation state of the pyridine and the style of functional group appended to the arylethynyl unit.[36]

Our initial studies focused on sulfonamide derivatives of 2,6-bis(2-aniloethynyl)pyridine to form an anion binding cavity (*e.g.*, **1**, Fig. 1). To our delight, this class of receptors showed the remarkable propensity of forming 2 + 2 dimers with either water, halides or both depending on the protonation state of the receptor.[37] Subsequent studies examined urea derivatives such as **2** (Fig. 1), which possessed much simpler solution speciation with halides, as the two urea binding groups obviate the need for higher order aggregates to form to satisfy the anion's hydrogen bonding preference. Crystallographic data indeed showed that the urea receptors formed a 1 : 1 complex with chloride starting from TFA-protonated **2** (R = H).[35] More importantly, the urea derivatives exhibited switchable fluorescent and colorimetric responses upon protonation. For example, the *p*-methoxy derivative of **2** displayed an "on-off" fluorescence behavior in the presence of chloride, while the *p*-nitro derivative exhibited an "off-on" fluorescence behavior in organic solvents.[34] The magnitude of the fluorescence event was dictated by the anion, resulting in a rare, fully organic "turn-on" fluorescent sensor for chloride, which typically quenches fluorescence. While the cause of this behavior is still under investigation, it would be desirable to tune these systems so that the "turn on" behavior could be observed even in competitive solvents such as DMSO or water. To achieve this goal we describe herein the synthesis of a small library of sixteen different 2,6-bis(2-aniloethynyl)pyridine bisureas (**2–5/a–d**). We also report an exhaustive study of their absorption and emission profiles in CH_3CN, and ultimately show that a similar "turn-on" behaviour can be observed even in relatively polar solvents.

Results and discussion

To obtain a full range of electron-poor and electron-rich scaffolds, we examined 2,6-bis(2-aniloethynyl)pyridine derivatives functionalized with *tert*-butyl (**6**), carboethoxy (**7**), trifluoromethyl (**8**), and methoxy (**9**) groups located at the 4-position on the aniline rings, to be consistent with our previous studies. Each derivative was synthesized *via* a twofold Sonogashira cross-coupling reaction between the respective 4-functionalized-2-ethynylanilines with 2,6-dibromopyridine as shown in Scheme 1; thus, protodesilylation of known anilines **10–13**[38,39] in basic MeOH (EtOH for **11**) followed by cross-coupling afforded the 2,6-bis(2-aniloethynyl)pyridine cores **6–9** in good to excellent yield. Each of these derivatives was then reacted with 4-methoxyphenyl isocyanate (**a**), 4-nitrophenyl isocyanate (**b**), phenyl isocyanate (**c**) and pentafluorophenyl isocyanate (**d**) to furnish the sixteen bisureas **2–5/a–d**.

Interestingly, the purification and characterization of some of these compounds proved problematic. First, the yields for reactions with **7** and **8** were in general considerably lower

than those of their electron-rich counterparts, **6** and **9** (Table 1). This was anticipated since the aniline nitrogens on **7** and **8** should be less nucleophilic due to the presence of the *para*-substituted electron-withdrawing groups. However, these bisureas were accompanied by myriad side products, as revealed by TLC analysis. In the case of **4d**, a small amount of a 2-quinazolinone derivative was isolated along with the desired bisurea; the X-ray crystal structure of this unanticipated material and discussion of its formation are given in the Supporting Information[†].

Second, the ^{1}H NMR spectra of certain bisureas were unexpectedly complex. For example, the proton spectrum of **3d** (which appears as one spot by thin layer chromatography) is shown on the bottom of Fig. 2a; however, when this same compound is prepared as the TFA salt, the spectrum simplifies to afford the anticipated set of resonances (Fig. 2a top). Interestingly, when TFA is added to **3d** while in solution, the ^{1}H NMR spectrum does not resolve, suggesting the presence of a kinetically stable aggregate. This behaviour was observed more often in scaffolds containing electron-withdrawing units at R and/or R′, which is an indication that the urea pK_as are lowered, leading to increased hydrogen bond donor ability. Clearly, protonation and addition of an anionic guest to **3d** breaks up the self-association/ aggregation, leading to the simplified ^{1}H NMR spectrum; therefore, compounds **2–5/a–d** were isolated as their corresponding trifluoroacetic acid (TFA) salts.

Another unusual problem was encountered while attempting to determine binding constants and stoichiometries of some of the bisureas with various tetrabutylammonium salts. For example, the ^{1}H NMR titration of **3d** with tetrabutylammonium chloride is shown in Fig. 2b. During the course of the titration the ^{1}H NMR spectra go from sharp and resolved prior to the addition of chloride to completely obscured at approximately one equiv. of chloride. At the half equivalent point visible aggregate is present in the NMR tube, but remarkably, upon addition of excess chloride the host goes back into solution and the ^{1}H NMR spectra resolve.

The most likely explanation for the observed phenomena is an equilibrium involving aggregation in solution. This behavior was observed more often in scaffolds containing electron-withdrawing units at R and/or R′, which is an indication that when the urea pK_as are lowered, hydrogen bond donor ability increases and aggregation increases. This phenomenon prevented the accurate determination of binding constants for this class of sensors, but it can clearly be seen that there is a strong propensity for these molecules to form complexes/aggregates in the presence of a suitable anionic guest.

This hypothesized self-aggregation in solution can also be observed in the X-ray crystal structure of **2b**.[40] In the solid-state a solvent water molecule resides inside the molecular cavity of **2b**, forming two solvent O_w–H…N, N–H…O_w hydrogen bonds and one bridging intermolecular O_w–H…O H-bond (Fig. 3 left). The molecules are also joined together by three N–H…O H-bonds between the $-NO_2$ group in one molecule and NH groups in another one. In the crystal structure the molecules assemble into 1-D molecular strips that form layers perpendicular to the *b* axis (Fig. 3 right). Even in the case of such a complex

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[†]Electronic supplementary information (ESI) available: synthetic procedures and spectral data for **2–9**; discussion of and X-ray data for the 2-quinazolinone derivative. CCDC reference number 844848. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc00975g

molecular shape, all H atoms that can form H-bonds are involved in intra-and intermolecular H-bonds in the crystal structure, providing another example of the Hamilton rule.[41]

With the library of compounds now in hand, we examined the absorption and emission properties of the bisureas as well as those of the scaffold cores. Given that an ideal anion sensor is one that is capable of functioning in polar media, such as DMSO, H_2O or CH_3CN, all UV-vis and fluorescence studies were performed in CH_3CN solutions. Fig. 4 shows the absorption spectra for the bis(arylethynyl)pyridines **6–9**. Depending on the electronic nature of the substituents attached to these cores a red or blue shift in absorption is observed. For example, the trifluoromethyl substituted core **8** has a blue-shifted absorbance compared to the *tert*-butyl substituted core **6**, while the methoxy substituted core **9** is red-shifted. This same red and blue shifting behavior is seen in the corresponding emission spectra (Fig. 4). The electron-withdrawn cores are blue shifted and the electron rich cores are red shifted. One interesting phenomenon occurs in the case of the methoxy-substituted core **9**. It contains two distinct fluorescence bands, which are likely the result of dual emission from one species in solution.

The photoluminescence quantum yield (PLQY) for each of the four ethynylpyridines followed the trend in which the most electron rich cores had the lowest PLQY and the most electron poor cores had the highest PLQY (Table 2).

The neutral bisureas of each core were investigated in a similar manner. Fig. 5 shows the UV-vis spectra for the *tert*-butyl derivatives **2a–d**. Interestingly, the substituted phenyl ureas had virtually no effect on the resulting UV-vis λ_{max} indicating that the ethynylpyridine cores are primarily responsible for the observed adsorption behavior of the bisurea scaffolds.

The neutral bisurea scaffolds were also investigated with respect to their fluorescence, with careful attention paid to those scaffolds containing electron withdrawing R and R′ groups (*e.g.* **3b, 3d, 4b**, and **4d**). Given that an ideal sensor is one that would go from an "off" state to an "on" state, we were primarily interested in electron withdrawing scaffolds that were nonemissive in their unbound state. Based on these criteria, compound **3d** was further scrutinized with respect to its ability to sense chloride, whereas **4d** was not studied further due to its tendency to decompose into the 2-quinazolinone byproduct described in the Supporting Information[†].

Gratifyingly, compound **3d** exhibits a fluorescence "off to on" response in the presence of chloride despite being in a polar MeCN solvent (Fig. 6). Although compound **3d** is not soluble in water, these results provide evidence that this particular ethynylpyridine scaffold can be tuned to exhibit a fluorescence response even in the presence of a highly competitive/polar solvent. Further studies will focus on determining the exact cause of this fluorescence and will aim to exhibit this same response in an aqueous solvent system.

Conclusion

The inherently fluorescent ethynylpyridine scaffolds presented herein can be tuned to exhibit either a red or blue shifted fluorescence response depending on the electron donating or withdrawing ability of the pendant functional groups. Similarly, the hydrogen bonding

behavior of the bisurea scaffolds is highly dependent on the pendant functional groups. NMR spectroscopic and solid state structural studies indicate that without a suitable guest these receptors hydrogen bond strongly with themselves, suggesting that these sensors could allow for larger binding constants for anionic guests and potentially greater selectivity. The simple derivatization of this class of receptors allows for a "turn-on" fluorescence response to analytes in increasingly polar solvents, a feature often lacking in small molecule organic anion probes.[24]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and References

1. Gunnlaugsson T, Glynn M, Tocci GM, Kruger PE, Pfeffer FM. Coord. Chem. Rev. 2006; 250:3094.

2. Amendola V, Esteban-Gomez D, Fabbrizzi L, Licchelli M. Acc. Chem. Res. 2006; 39:343. [PubMed: 16700533]

3. Beer PD, Gale PA. Angew. Chem., Int. Ed. 2001; 40:486.

4. Holliday BJ, Mirkin CA. Angew. Chem., Int. Ed. 2001; 40:2022.

5. Anslyn, EV.; Dougherty, DA. Modern Physical Organic Chemistry. University Science; 2005. illustrated edition.

6. Bianchi, A.; Bowman-James, K.; García-Espana, E. Supramolecular Chemistry of Anions. 1st edn. Wiley-VCH; 1997.

7. Sessler, JL.; Gale, PA.; Cho, W-S. Anion Receptor Chemistry. Cambridge: Royal Society of Chemistry; p. 1-26.

8. Savage PB, Holmgren SK, Gellman SH. J. Am. Chem. Soc. 1993; 115:7900.

9. Savage PB, Holmgren SK, Gellman SH. J. Am. Chem. Soc. 1994; 116:4069.

10. Schmidtchen FP. Angew. Chem., Int. Ed. Engl. 1977; 16:720.

11. Kelly TR, Kim MH. J. Am. Chem. Soc. 1994; 116:7072.

12. Bühlmann P, Nishizawa S, Xiao KP, Umezawa Y. Tetrahedron. 1997; 53:1647.

13. Andrievsky A, Ahuis F, Sessler JL, Vögtle F, Gudat D, Moini M. J. Am. Chem. Soc. 1998; 120:9712.

14. Schottel BL, Chifotides HT, Dunbar KR. Chem. Soc. Rev. 2008; 37:68. [PubMed: 18197334]

15. Quiñonero D, Garau C, Rotger C, Frontera A, Ballester P, Costa A, Deyà PM. Angew. Chem., Int. Ed. 2002; 41:3389.

16. Berryman OB, Bryantsev VS, Stay DP, Johnson DW, Hay BP. J. Am. Chem. Soc. 2007; 129:48. [PubMed: 17199282]

17. Inoue Y, Hakushi T, Liu Y, Tong L, Shen B, Jin D. J. Am. Chem. Soc. 1993; 115:475.

18. Steed JW, Juneja RK, Atwood JL. Angew. Chem., Int. Ed. Engl. 1995; 33:2456.

19. Steed JW, Johnson CP, Juneja RK, Atwood JL, Burkhalter RS. Supramol. Chem. 1996; 6:235.

20. Staffilani M, Hancock KSB, Steed JW, Holman KT, Atwood JL, Juneja RK, Burkhalter RS. J. Am. Chem. Soc. 1997; 119:6324.

21. Lavis LD, Raines RT. ACS Chem. Biol. 2008; 3:142. [PubMed: 18355003]

22. Basabe-Desmonts L, Reinhoudt DN, Crego-Calama M. Chem. Soc. Rev. 2007; 36:993. [PubMed: 17534482]

23. de Silva AP, Gunaratne HQN, Gunnlaugsson T, Huxley AJM, McCoy CP, Rademacher JT, Rice TE. Chem. Rev. 1997; 97:1515. [PubMed: 11851458]

24. Carroll CN, Naleway JJ, Haley MM, Johnson DW. Chem. Soc. Rev. 2010; 39:3875. [PubMed: 20820467]

25. Spitler EL, McClintock SP, Haley MM. J. Org. Chem. 2007; 72:6692. [PubMed: 17685654]

26. Spitler EL, Shirtcliff LD, Haley MM. J. Org. Chem. 2006; 72:86. [PubMed: 17194085]

27. Zucchero AJ, McGrier PL, Bunz UHF. Acc. Chem. Res. 2009; 43:397. [PubMed: 19961212]

28. Karchava AV, Maksimova FV, Yurovskaya MA. Chem. Heterocycl. Compd. 1994; 30:1195.

29. Yamaguchi Y, Kobayashi S, Wakamiya T, Matsubara Y, Yoshida Z. Angew. Chem., Int. Ed. 2005; 44:7040.

30. Abe H, Takashima S, Yamamoto T, Inouye M. Chem. Commun. 2009:2121.

31. Rajadurai C, Ivanova A, Enkelmann V, Baumgarten M. J. Org. Chem. 2003; 68:9907. [PubMed: 14682682]

32. Ahn CM, Shin W-S, Bum Woo H, Lee S, Lee H-W. Bioorg. Med. Chem. Lett. 2004; 14:3893. [PubMed: 15225692]

33. Holmes BT, Deb P, Pennington WT, Hanks TW. J. Polym. Res. 2005; 13:133.

34. Carroll CN, Coombs BA, McClintock SP, Johnson CA II, Berryman OB, Johnson DW, Haley MM. Chem. Commun. 2011; 47:5539.

35. Carroll CN, Berryman OB, Johnson CA II, Zakharov LN, Haley MM, Johnson DW. Chem. Commun. 2009:2520.

36. Engle JM, Lakshminarayanan PS, Carroll CN, Zakharov LN, Haley MM, Johnson DW. Cryst. Growth Des. 2011; 11:5144.

37. Berryman OB, Johnson CA II, Zakharov LN, Haley MM, Johnson DW. Angew. Chem., Int. Ed. 2008; 47:117.

38. Kimball DB, Weakley TJR, Haley MM. J. Org. Chem. 2002; 67:6395. [PubMed: 12201760]

39. McClintock SP, Forster N, Herges R, Haley MM. J. Org. Chem. 2009; 74:6631. [PubMed: 19642649]

40. Crystal data for **2b**: $C_{44}H_{42}Cl_3N_7O_7$, $M_r = 887.20$, $0.21 \times 0.14 \times 0.02$ mm, monoclinic, $P2_1/c$, $a = 9.5229(13)$ Å, $b = 39.529(5)$ Å, $c = 11.6647(16)$ Å, $\beta = 98.282(3)°$, $V = 4345(1)$ Å^3, $Z = \rho_{calcd} = 1.356$ g cm^{-1}, $\mu = 0.270$ mm^{-1}, $2\theta_{max} = 50.00°$, $T = 173(2)$ K, 41736 measured reflections, 7661 independent reflections [$R_{int} = 0.0927$], 538 independent refined parameters, $R_1 = 0.0808$, w$R_2 = 0.1968$ (with $I > 2\sigma(I)$), $R_1 = 0.1361$, w$R_2 = 0.2255$ (all data), GOF = 0.996, max/min residual electron density $+0.418/-0.316$ e Å^{-3}. CCDC 844848 contains the supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

41. Hamilton, W. Benjamin, WA. Hydrogen bonding in solids: methods of molecular structure determination. New York: Amsterdam; 1968.
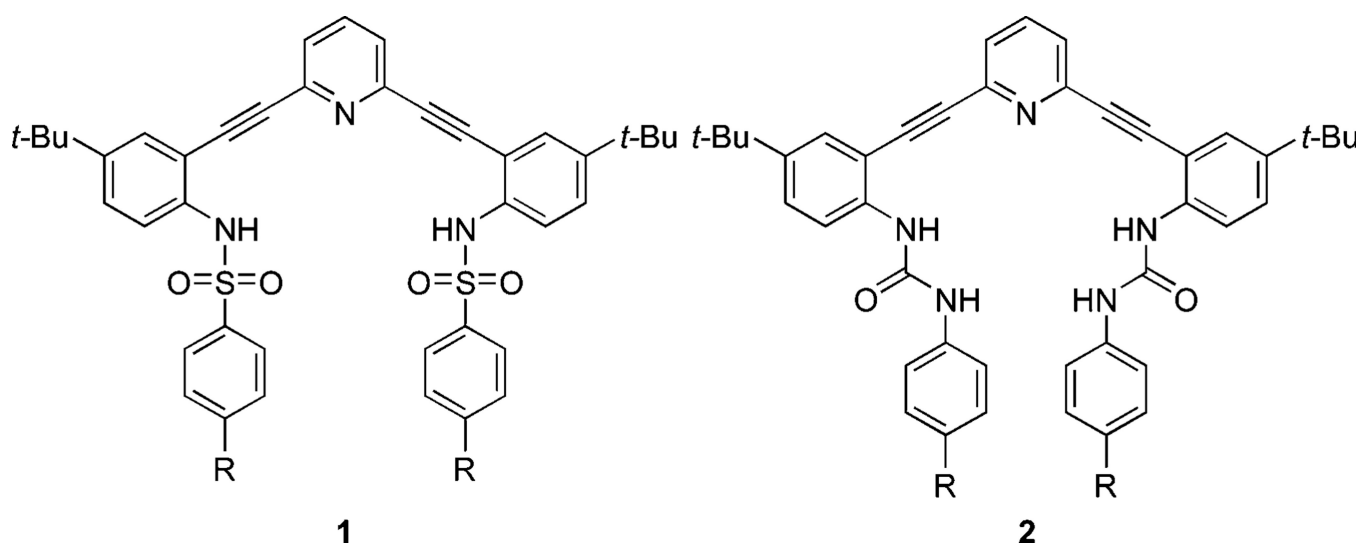
Fig. 1.
Sulfonamide-based (**1**) and urea-based (**2**) anion sensors.
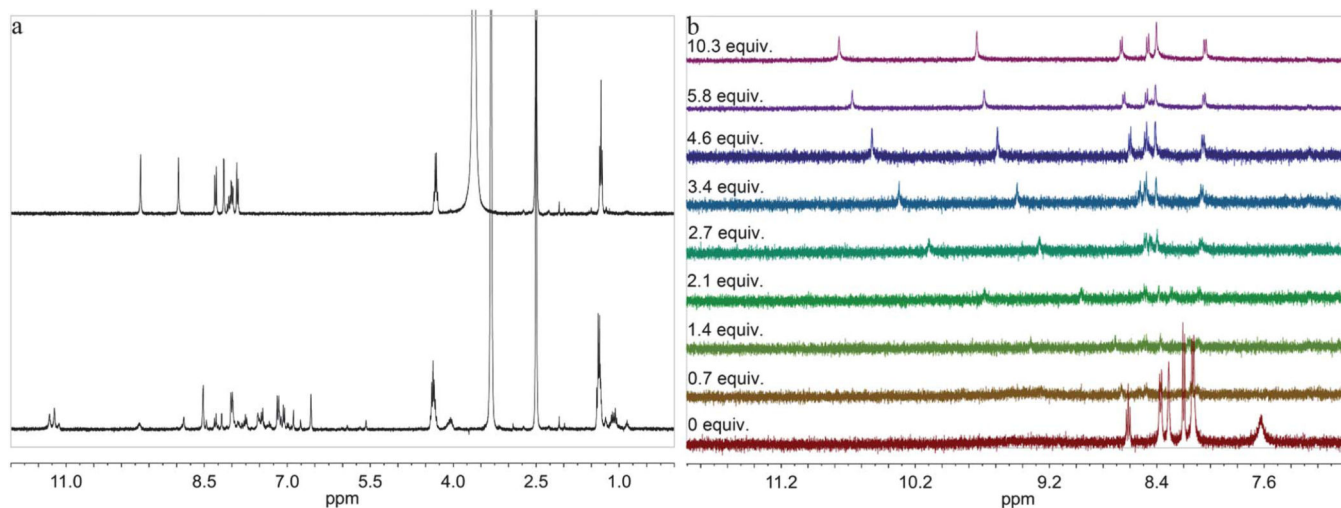
Fig. 2.
(a) ^{1}H NMR spectrum of the **3d·TFA** salt (top) in DMSO-d6 compared to the ^{1}H NMR of **3d** in its neutral state (bottom). When TFA is added to **3d** while in solution the ^{1}H NMR spectrum does not resolve, suggesting the presence of a kinetically stable aggregate. (b) ^{1}H NMR titration of **3d** with Bu$_4$NCl in CD$_3$CN. The ^{1}H NMR titration shows resolved peaks prior to addition of Bu$_4$NCl, but upon addition of *ca*. one equivalent Bu$_4$NCl the sample forms insoluble aggregates. Upon addition of excess Bu$_4$NCl the aggregation appears to dissipate and the ^{1}H NMR spectra resolve.
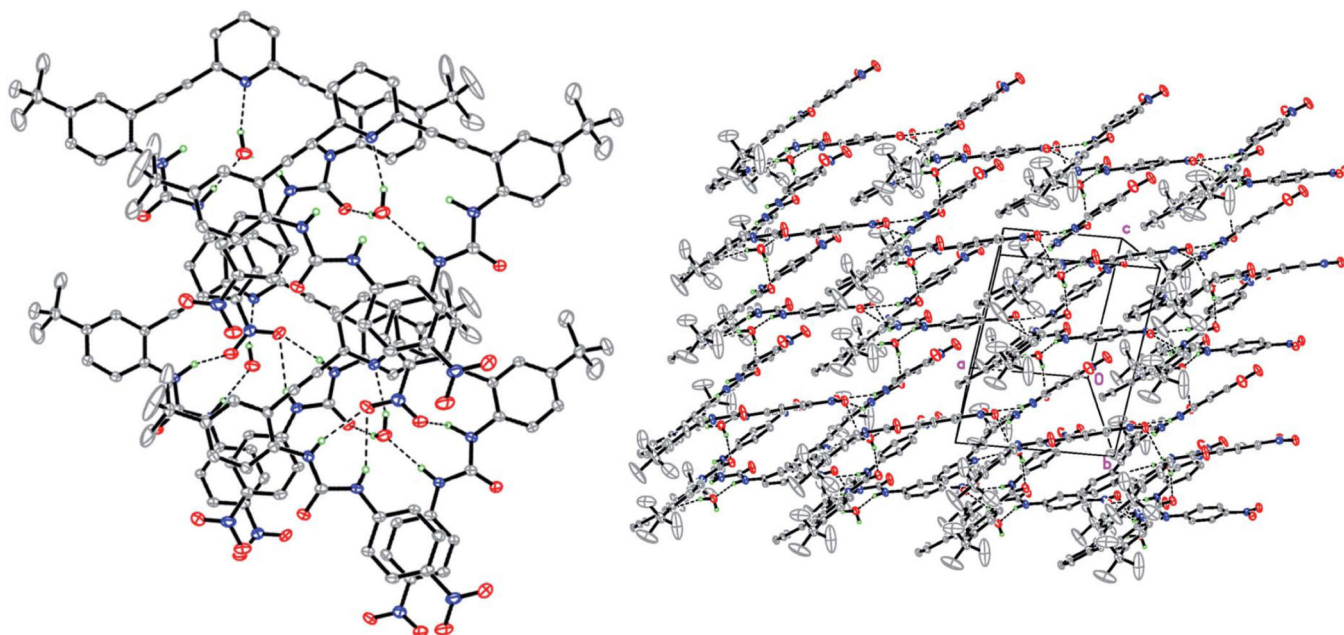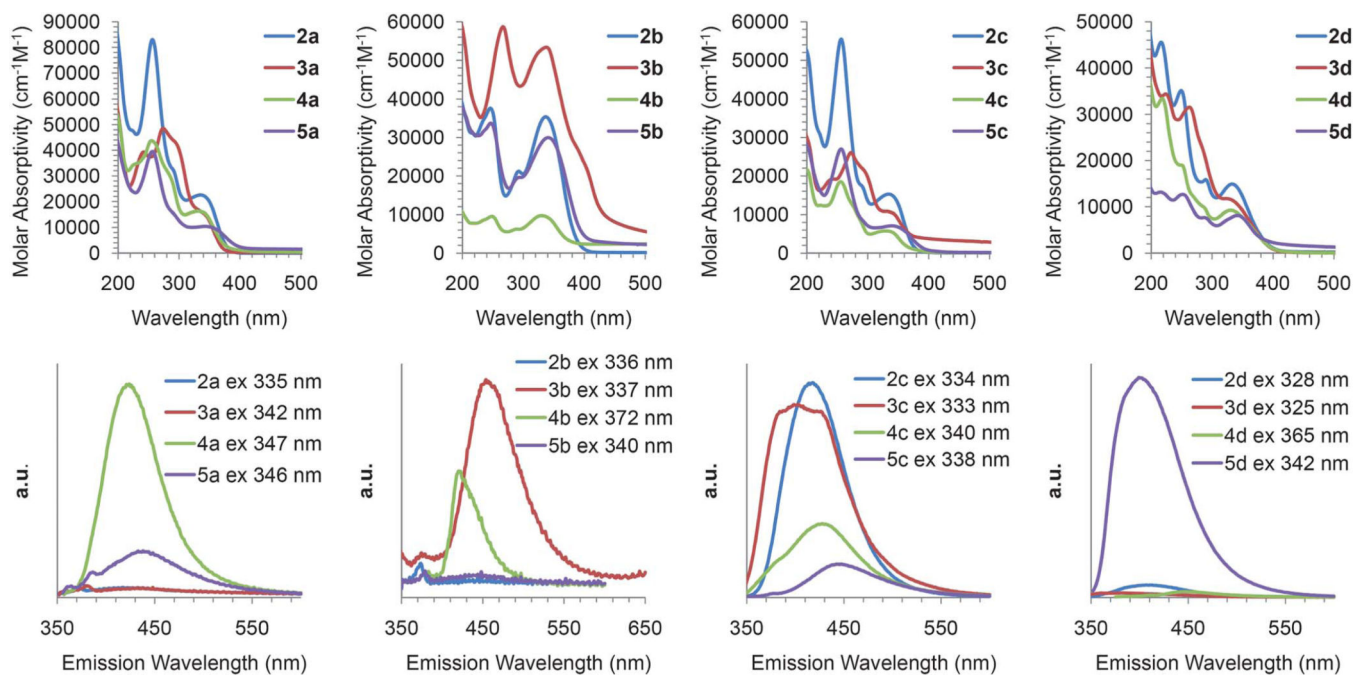
Fig. 3.
X-ray crystal structure of **2b**–top view (left) and side view (right); ellipsoids drawn at the 30% probability level.
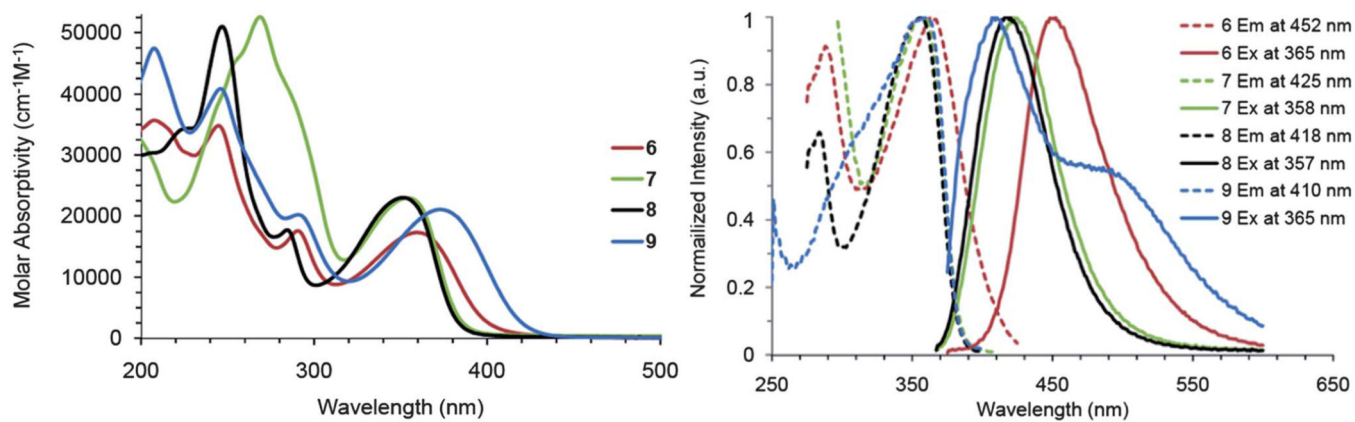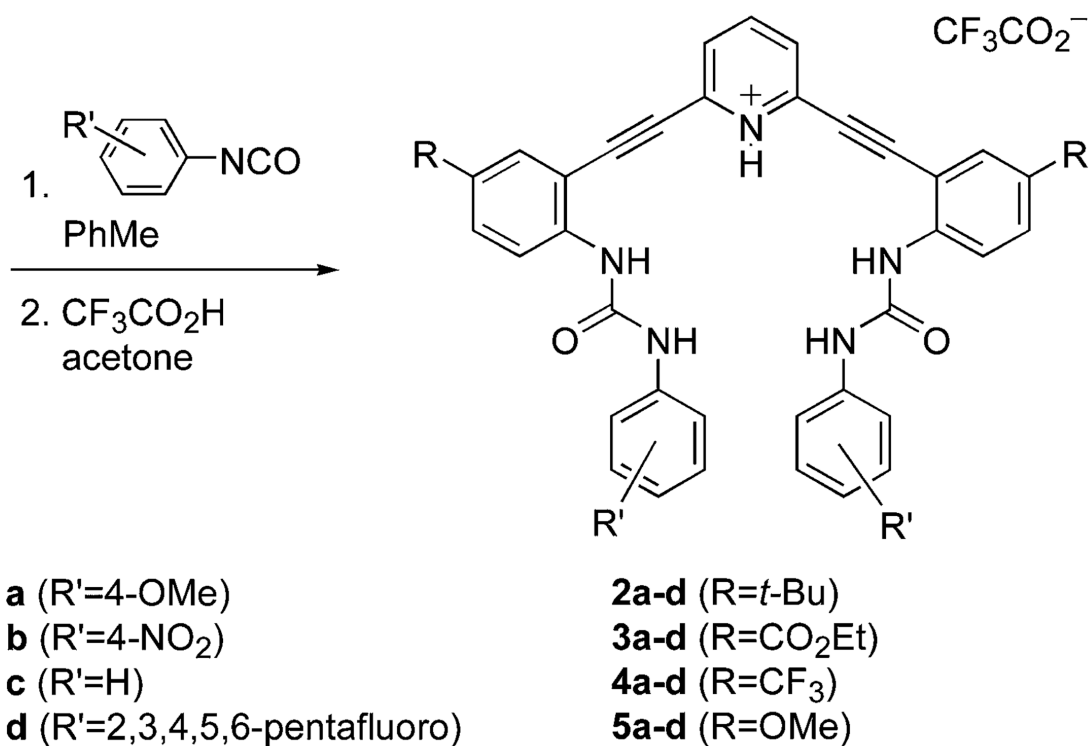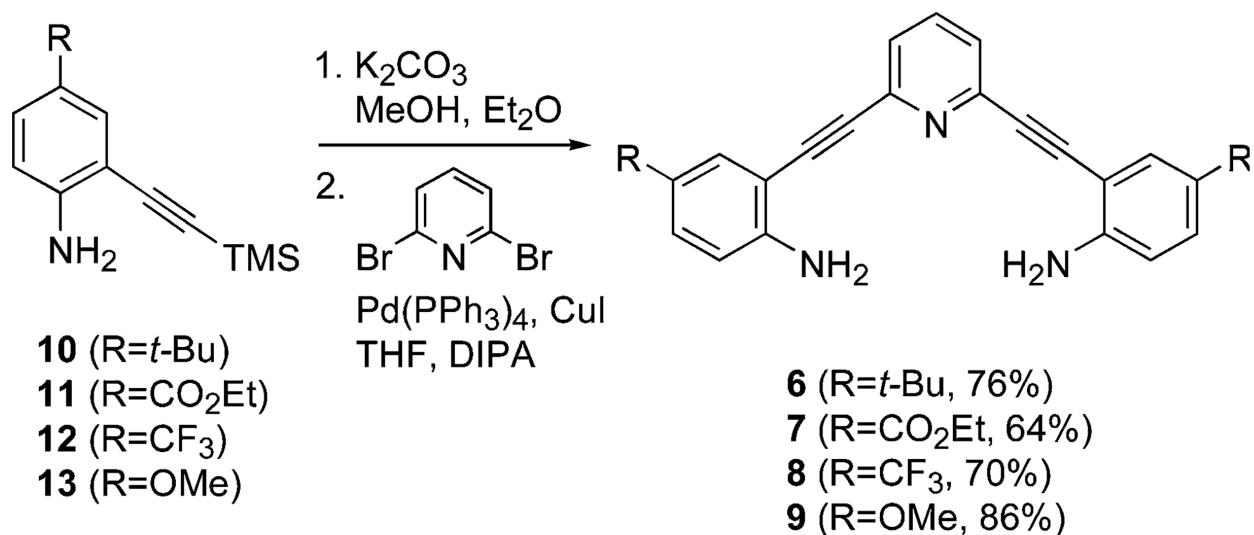
Fig. 4.
Electronic absorption (left) and excitation/emission (right) spectra of ethynylpyridine cores
6–9.

Fig. 5.
Electronic absorption spectra of **2a–5a** (top left), **2b–5b** (top middle-left), **2c–5c** (top middle-right), and **2d–5d** (top right) followed by fluorescence spectra of **2a–5a** (bottom left), **2b–5b** (bottom middle-left), **2c–5c** (bottom middle-right), and **2d–5d** (bottom right).
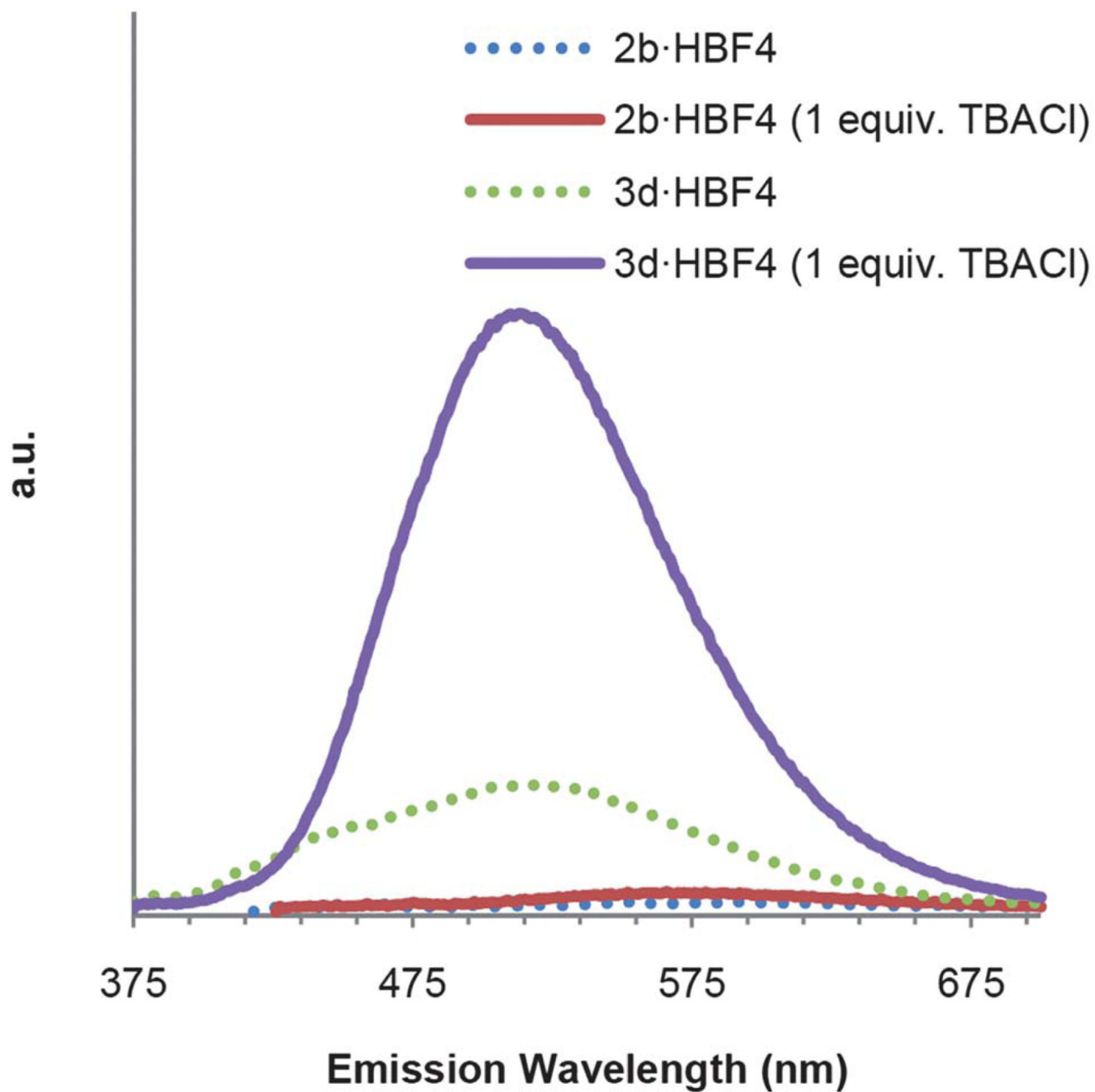
Fig. 6.
Emission spectra of **2b·HBF$_4$** and **3d·HBF$_4$** before addition of TBACl (dotted lines) and
after addition of TBACl. Compound **2b·HBF$_4$** was excited at 416 nm, and compound
3d·HBF$_4$ was excited at 365 nm.

1. K₂CO₃
MeOH, Et₂O

2. [2,6-dibromopyridine]
Pd(PPh₃)₄, CuI
THF, DIPA

10 (R=*t*-Bu)
11 (R=CO₂Et)
12 (R=CF₃)
13 (R=OMe)

6 (R=*t*-Bu, 76%)
7 (R=CO₂Et, 64%)
8 (R=CF₃, 70%)
9 (R=OMe, 86%)

1. [R'-aryl-NCO]
PhMe

2. CF₃CO₂H
acetone

CF₃CO₂⁻

a (R'=4-OMe)
b (R'=4-NO₂)
c (R'=H)
d (R'=2,3,4,5,6-pentafluoro)

2a-d (R=*t*-Bu)
3a-d (R=CO₂Et)
4a-d (R=CF₃)
5a-d (R=OMe)

Scheme 1.
Synthesis of sixteen differentially substituted 2,6-ethynylpyridine bisphenylurea scaffolds.

Table 1

Yields for **2–5/a–d**

	R	R′	Yield
2a	t-Bu	4-OMe	93%
2b	t-Bu	4-NO$_2$	93%
2c	t-Bu	H	92%
2d	t-Bu	2,3,4,5,6-pentafluoro	81%
3a	CO$_2$Et	4-OMe	57%
3b	CO$_2$Et	4-NO$_2$	30%
3c	CO$_2$Et	H	26%
3d	CO$_2$Et	2,3,4,5,6-pentafluoro	76%
4a	CF$_3$	4-OMe	16%
4b	CF$_3$	4-NO$_2$	34%
4c	CF$_3$	H	37%
4d	CF$_3$	2,3,4,5,6-pentafluoro	75%
5a	OMe	4-OMe	64%
5b	OMe	4-NO$_2$	86%
5c	OMe	H	61%
5d	OMe	2,3,4,5,6-pentafluoro	71%

Table 2

PLQY and Stokes Shifts for 6–9 in MeCN

	R	Stokes shift (cm^{-1})	Quantum yield
6	t-Bu	5270	0.6%
7	CO$_2$Et	4290	1.2%
8	CF$_3$	4090	1.1%
9	OMe	2890, 3150	0.1%