JOC The Journal of Organic Chemistry

Article

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Alkynylated Phenazines: Synthesis, Characterization, and Metal-Binding Properties of Their Bis-Triazolyl Cycloadducts

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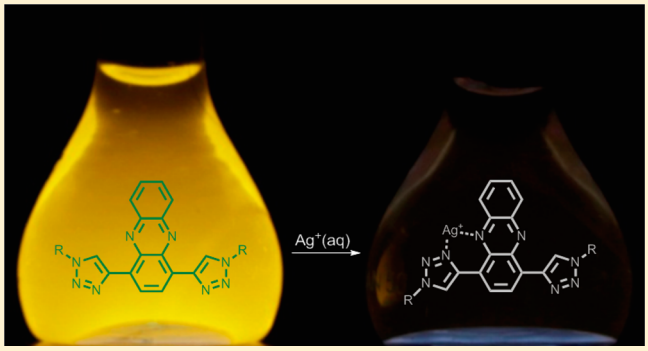
Supporting Information

ABSTRACT: We have synthesized a series of ethynylated phenazines and their bis-triazolyl cycloadducts to serve as metal ion sensors. Binding of metal ions is achieved through coordination to the phenazine nitrogen atom and the triazole ring. To allow metal sensing in aqueous solution, the triazole units are substituted with water-soluble ethylene glycol chains. These phenazine cycloadducts exhibit a selective affinity for binding silver ions. Examination of the halogenated analogues reveals a lowering of the band gap and the corresponding bathochromic shifts in the absorption and emission spectra. The electron-withdrawing properties of these halogens also result in significantly decreased metal-binding activity of the phenazine cycloadducts.



INTRODUCTION

The redox properties of phenazine and its derivatives have garnered some interest, finding use in biofuel cells,[1] solar cells,[2] and OLEDs,[3−5] but an even more attractive aspect of phenazines is their role in pharmaceutical applications. They are biosynthesized by bacteria, and many possess broad-spectrum antifungal and antibiotic activity,[6−8] as well as the capacity for DNA intercalation.[9,10] Sensing schemes involving water-soluble phenazine-based dyes include electrochemical detection of biological molecules[11,12] and colorimetric pH sensing.[13] Less attention has been paid to phenazines themselves, though they have demonstrated the ability to bind silver,[14] and their peralkynylated counterparts have also shown an affinity for binding metals.[15]

We decided to further investigate the metal-binding properties of alkynylated phenazine derivatives. The ethynyl functional group can be transformed via the alkyne−azide 1,3-dipolar cycloaddition pioneered by Huisgen.[16,17] Since the discovery of Cu(I) as a catalyst for this reaction,[18,19] this "click" chemistry has flourished,[20−23] appearing in bioconjugation,[24,25] polymer and materials chemistry,[26−32] and organic synthesis.[33] With regards to heteroaromatic molecules, the triazole ring influences the electronic properties,[34,35] and its electron-donating ability can be used to bind metal ions.[36,37]

Functionalization of the phenazine core with a sufficiently hydrophilic azide produces a water-soluble fluorophore suitable for metal ion detection. We previously reported water-soluble metal sensors with benzo- and naphthothiadiazole at their core, synthesized by the addition of triethylene glycol substituted azides to the alkynylated thiadiazoles.[38] The hydrophilic arms provide water solubility, while the triazole moiety forms an efficient binding pocket with the nitrogen of the thiadiazole. Introduction of a branched ethylene glycol side chain on the triazole should further improve the solubility in water, as well as the quantum efficiency of the fluorophore, thanks to its aggregation-suppressing ability.[39]

Some fluorescence-based silver ion sensors are known,[40−45] but with the exception of the recent Pt-containing polyfluorene,[42] they do not work in water. THF or ethanol is used, which is not optimal and also avoids the thorny issues of the preservation of fluorescence in water and the competition of water as a ligand. Here, we report on a series of ethynylated phenazines, and the successful application of the silver ion sensing capabilities of their triazolyl cycloadducts in water.

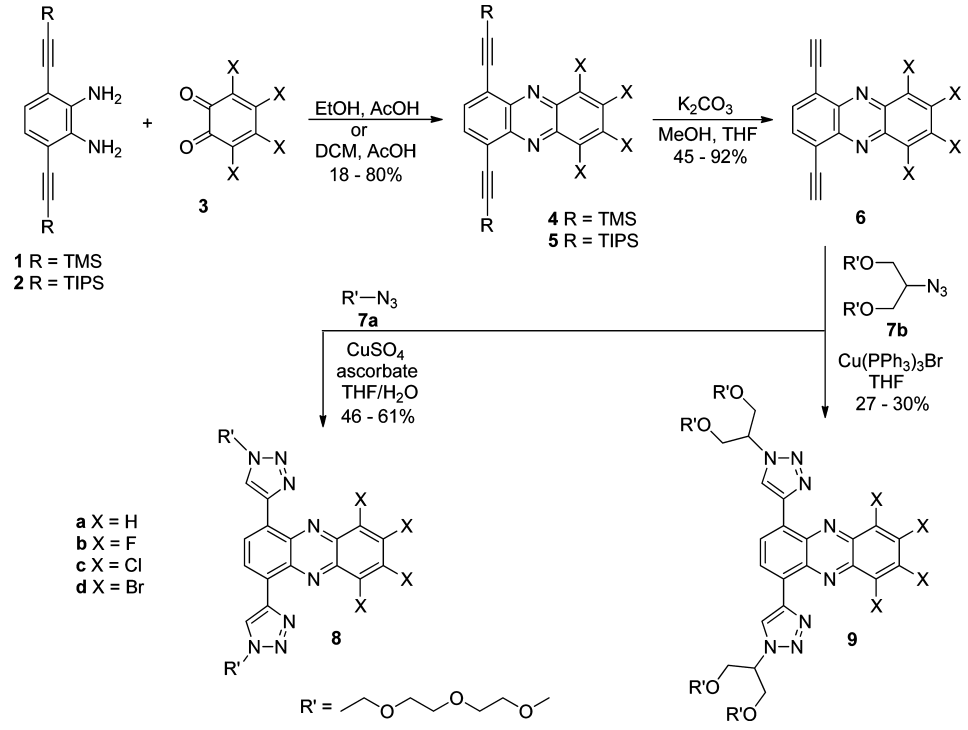
RESULTS AND DISCUSSION

The synthesis of the alkynylated phenazines and their corresponding cycloadducts is shown in Scheme 1. Alkynylated phenazines **4a−d** and **5a−d** were synthesized via condensation of **1** or **2** with **3a−d**. Ethanol was used as a solvent, but in the case of the fluorinated compounds, nucleophilic solvents had to

Received: June 25, 2012
Published: August 15, 2012

   dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479−7486

Scheme 1. Synthesis of Cycloadducts 8 and 9



be avoided, as they undergo substitution side reactions at the fluorinated carbons.

From the trimethylsilyl-protected phenazine core **4a–c**, deprotection with potassium carbonate gave **6a–c**. To avoid degradation of **6**, reaction with either **7a** or **7b** was carried out immediately to give **8** or **9**. The targets **9a,b** were obtained in 27–30% yield, while the TEG-substituted **8a,c** formed in 46–61% yield. The poor yields for this well-known reaction prompted us to vary the conditions slightly. Water has been postulated as an ideal solvent for the stabilization of copper acetylide intermediates,[46] but the presence of water as cosolvent had no effect on our reaction, though it is necessary when using $CuSO_4$ as catalyst. Performing the reaction at elevated temperatures (50 °C) did not improve the yield, nor did variation of the copper catalyst ($Cu(PPh_3)_3Br$ or $CuSO_4$/ascorbate). Due to the reactive nature of the ethynylated species **6**, a one-pot deprotection/cycloaddition reaction would be ideal; however, such attempts turned out to be less reliable overall and, in the best case, resulted in a similar yield.

Figure 1 shows the absorption spectra of the bis-ethynylphenazines **5a–c** and **6a–c**. The TMS- and TIPS-protected compounds show very similar absorption spectra, with less distinct local maxima for the TMS-protected series (similar to the broad spectra of **5b**). Halogen substitution causes red shifts which increase upon descending the group. The same effect is seen in the emission profiles (Figure 2), with the exception of the bromine-substituted phenazine, which is nonemissive. The heavy-atom effect of the bromine leads to a decrease of the fluorescence quantum yield of **5d**. The optical properties of **5a–d** are summarized in Table 1 and are consistent with the previously reported properties of halogenated azaacenes[47] and pentacenes.[48]

To gain further insight into the spectral properties of these compounds, we performed quantum chemical calculations. The calculated energies of the frontier orbitals and a comparison of the experimental and calculated band gaps are recorded in

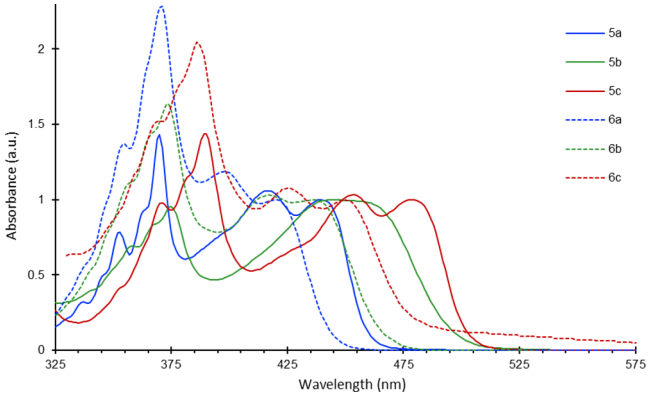


Figure 1. Absorption spectra of **5a–c** and **6a–c** in dichloromethane.

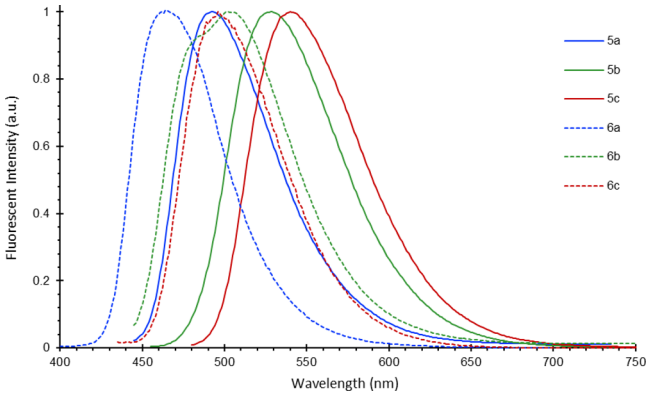


Figure 2. Emission spectra of **5a–c** and **6a–c** in dichloromethane.

Table 2. Upon chlorination of the alkynylated phenazine, the LUMO is stabilized by 0.49 eV, whereas the HOMO is stabilized by only 0.30 eV. This results in a lowering of the optical gap by 0.19 eV, which agrees closely with the

dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479–7486

Table 1. Photophysical Properties Recorded for Compounds 5a–d in DCM

compd	abs λ_{max} (nm)	em λ_{max} (nm)	Stokes shift (cm^{-1})	Φ_f (±0.1)	τ_f (ns)
5a	416	492	3710	0.02	0.37
5b	443	528	3630	0.50	10
5c	451	540	3650	0.11	2.5
5d	453	n/a	n/a	n/a	n/a

Table 2. Calculated and Experimental HOMO–LUMO Gaps (Gas Phase)

compd	HOMO (eV)[a]	LUMO (eV)[a]	calcd gap (eV)	exptl gap (eV)[b]
6a	−6.24	−3.11	3.13	2.96
6b	−6.60	−3.60	3.00	2.85
6c	−6.54	−3.60	2.94	2.76
9a[c]	−5.81	−3.01	2.80	2.76
9b[c]	−6.13	−3.51	2.62	2.59
8c[c]	−6.10	−3.56	2.54	2.53

[a]Calculated by SPARTAN 10 using the B3LYP method with the 6-311++G** basis set. [b]Acquired from the λ_{max} of absorption. [c]Triazole substituent approximated by a methyl group.

experimentally observed change of 0.20 eV. From the visual representations of the frontier molecular orbitals (Figure 3a), it is apparent that the coefficients of the HOMO on the halogenated ring are smaller than those of the LUMO. Therefore, the stabilizing effect of halogenation is greater for the LUMO than for the HOMO, resulting in the observed bathochromic shifts. This effect is seen to a greater extent in the cycloaddition products, where the HOMOs are located almost exclusively on the triazole-containing axis, resulting in even greater bathochromic shifts upon halogenation.

What is the conformation of the triazole unit with respect to the phenazine ring? Quantum chemical calculations always give the rotamer, in which the C–H group is close to the N unit of the phenazine nucleus, and never the one in which the bidentate binding pocket is formed. We calculated the internal rotation around the C–C bond that connects the phenazine with the triazole rings (Figure 3b, B3LYP/6-311++G**). The rotamer forming the binding pocket is ca. 9 kcal mol^{-1} higher in energy. The reason for the energy difference is probably the mutual electrostatic repulsion of the two adjacent electron pairs of the participating heterocyclic nitrogens (Figure 3b,c). Upon the coordination of silver ions the binding pocket forms through rotation. We have calculated the structure of the Ag^+ complex of a simplified model (Figure 3d, B3LYP/6-31G**) in the absence of further ligands. The silver ion forces the ligand into a conformation that accommodates the cation optimally. This conformation is not planar but has a torsion angle of around 40°. Additionally, one can see that in the optimized structure the distance of the triazole nitrogen to the silver cation is 2.24 Å, while the distance to the phenazine nitrogen is 2.35 Å. Upon fluorination of the unsubstituted part of the

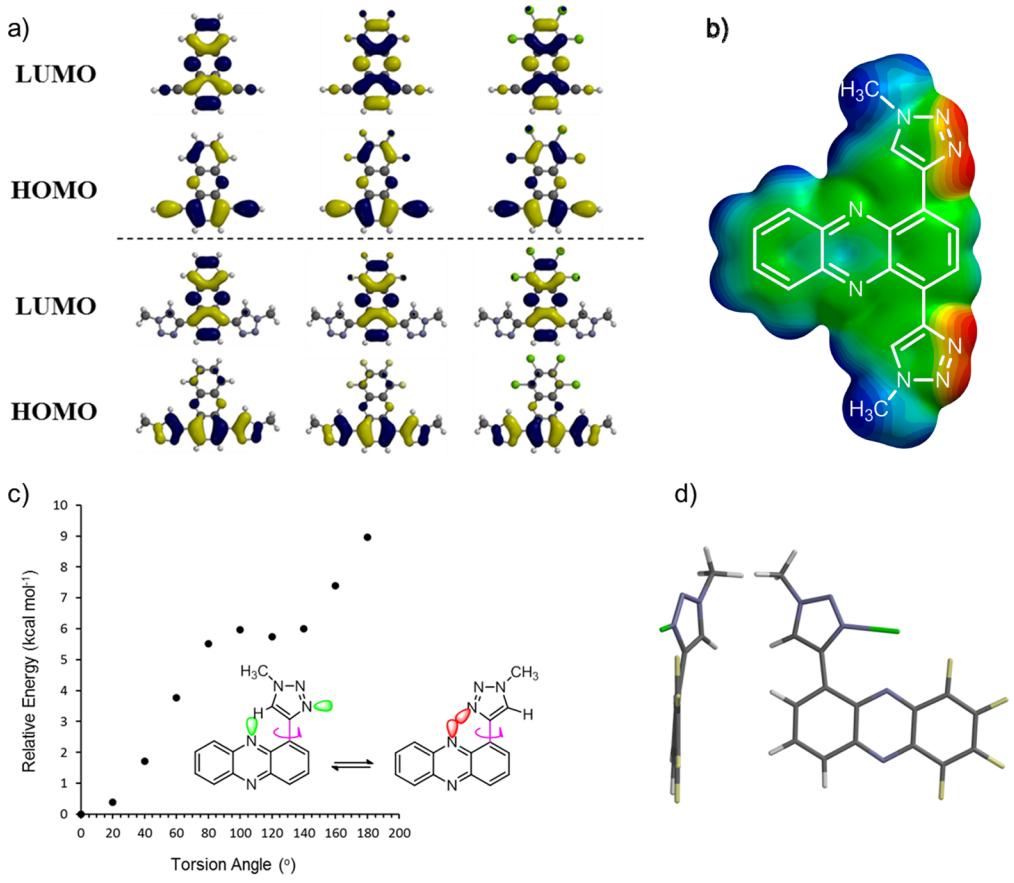


Figure 3. (a) Frontier orbitals for **6a–c** (top) and simplified models of **9a–c** (bottom). (b) Electrostatic potential map highlighting the localization of electron density on the nitrogen atoms, particularly those of the triazole ring. (c) Rotational profile of a simplified model of **8a** and **9a**. The left conformation (green) displays the lowest relative energy. The other conformation is 8.96 kcal mol^{-1} higher in energy. (d) Simplified model of **8b** and **9b** showing the predicted conformation when binding to Ag^+.

dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479–7486

phenazine, the geometry changes and the Ag−triazole distance is reduced to 2.21 Å, while the distance to the now much more electron poor phenazine is increased to 2.45 Å. As a consequence of the geometrical change the torsion angle is now only 35°. While these are only gas-phase calculations without added ligands or counterions, they are supported by 2D ^{1}H−^{1}H NOESY NMR (see the Supporting Information). In the absence of silver, the predicted rotamer is observed, with no interaction between the triazole hydrogen and the aromatic hydrogen (at the 2- or 3-position). After addition of silver ion, there is a clear interaction between these hydrogen atoms, made possible through the rotation of the triazole ring.

Figure 4 shows the absorption spectra of **9a,b** and **8c** in both water and dichloromethane. Though these compounds are

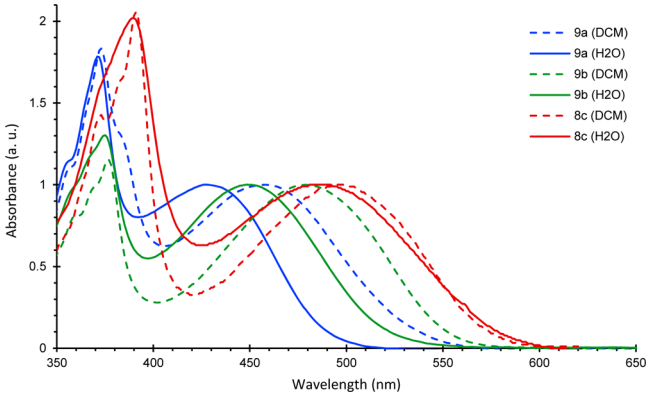


Figure 4. Absorption spectra of the cycloadducts **9a,b** and **8c** in water and dichloromethane.

soluble in both solvents, there is a considerable hypsochromic shift in the absorption profiles when going from organic to aqueous solvent, as much as 30 nm. This trend exists to a varying degree in each of the cycloadducts. The reverse occurs in the emission spectra (Figure 5), with aqueous solvent

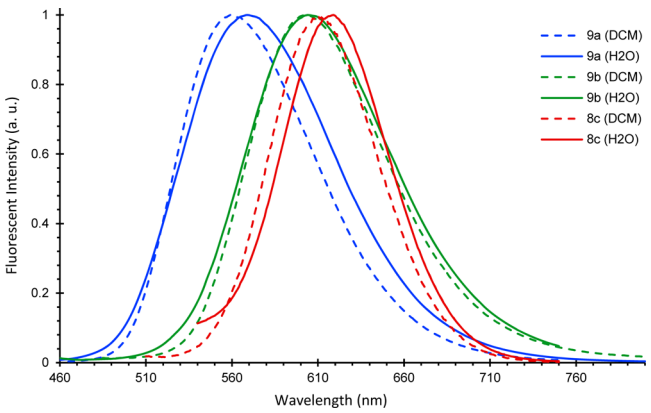


Figure 5. Fluorescence spectra of the cycloadducts **9a,b** and **8c** in water and dichloromethane.

inducing either a bathochromic shift or none at all. A large Stokes shift results in water. Variation of the water-soluble triazole substituent does not have any appreciable effect on the absorption or emission. The spectra of **8a** are nearly identical with those of **9a** and are therefore not shown.

The phenazine cycloadducts (Table 3) possess rather long lifetimes (greater than 10 ns in organic solvents). It is unclear how much this is due to the phenazine core. The radiative rate of phenazine is very low; the dominant decay pathway from the excited singlet states is intersystem crossing to the triplet states.[49,50] The low quantum yield of the alkynylated phenazine **5a** indicates that nonradiative decay is still efficient. Further substitution of the phenazine ring (with halogens or triazole rings) increases the quantum yield, as well as the lifetime (Table 1). The cycloadducts **8** and **9** have even longer lifetimes, suggesting that the triazole rings modulate the photophysical properties of the molecules.

The ready solubility of the bis-triazolylphenazine adducts in water and the acceptable quantum yield of **9a** allow the examination of its metal binding properties in aqueous solution. Screened metals include Na^+, K^+, Li^+, Ag^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Hg^{2+}, Cd^{2+}, and Pb^{2+}. The halogenated fluorophores showed little if any response to metal ions. These are apparently so electron-poor as to preclude efficient metal binding in water. For the unsubstituted phenazine cycloadducts **8a** and **9a**, only minimal quenching upon exposure to Cu^{2+} and Hg^{2+} was observed. As seen in Figure 6, the fluorescence quenching by Ag^+ was pronounced, indicating that these compounds may serve as fluorescent sensors for silver ions.

Due to the increasing prevalence of silver in industrial applications, and its toxicity, the U.S. Environmental Protection Agency has set a secondary maximum contaminant level of 0.1 mg/L for silver.[51] As a result, there exists a desire for sensitive and selective methods of silver ion detection in aqueous media. As fluorescent sensors, the phenazine cycloadducts possess attractive properties. Their Stokes shifts are quite large (>5000 cm^{-1}), allowing the excitation wavelength to be far removed from the emission wavelength. The auxochromic effect of the triazole units pushes the luminescence of these compounds from the blue-green region to the yellow and beyond, allowing cellular background fluorescence to be easily filtered out. The lifetimes are also relatively long, enabling such techniques as time-gated detection, though the lifetimes are lower in water than in dichloromethane.

Titrations of **8a** and **9a** with $AgNO_3$ were performed to determine the strength of the binding. Significant deviation from linearity occurred when the data were fitted to the typical Stern−Volmer equation. The data however could be fitted well by eq 1,[52−54] where ΔI is the change in fluorescent intensity,

$$\Delta I = \frac{\alpha}{2}\left\{\left([F] + [Q] + \frac{1}{k}\right) \pm \sqrt{\left([F] + [Q] + \frac{1}{k}\right)^2 - 4[F][Q]}\right\} \quad (1)$$

[F] is the concentration of the fluorophore, [Q] is the concentration of the quencher, and α is a constant. The binding constant K can be extracted from eq 1 using a nonlinear least-squares curve fitting. The titration curve is shown in Figure 7. The data agree with a 1:1 binding ratio, which is also supported by ^{1}H−^{1}H NOESY NMR (see the Supporting Information). The binding constant for silver(I) was determined to be log K = 3.75 ± 0.09 for **8a** and log K = 2.84 ± 0.02 for **9a**.

Previous evidence that phenazine[14] and peralkynylated phenazine[15] are able to bind silver begs the question of whether the triazole is necessary for the binding event. We investigated the interaction of bare phenazine and alkynylated

dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479−7486

Table 3. Photophysical Data for 8 and 9

	abs λ_{max} (nm)		em λ_{max} (nm)		Stokes shift (cm^{-1})		Φ_f (±0.1)		τ_f (ns)	
compd	DCM	H_2O	DCM	H_2O	DCM	H_2O	DCM	H_2O	DCM	H_2O
8a	450	433	559	573	4333	5643	0.31	0.01	19	1.7
9a	458	428	559	569	3945	5790	0.27	0.04	19	4.0
9b	479	448	603	604	4293	5765	0.04	<0.01	7.9	4.5
8c	496	486	610	619	3768	4421	0.06	<0.01[a]	16	6.8[a]

[a]Determined in MeOH/H_2O.

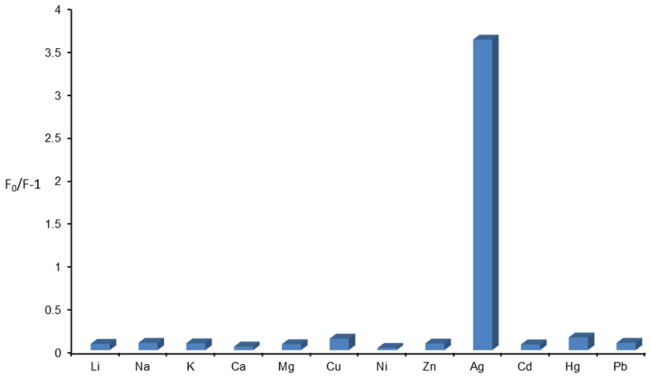


Figure 6. Relative fluorescence quenching of **9a** by metal ions in water.

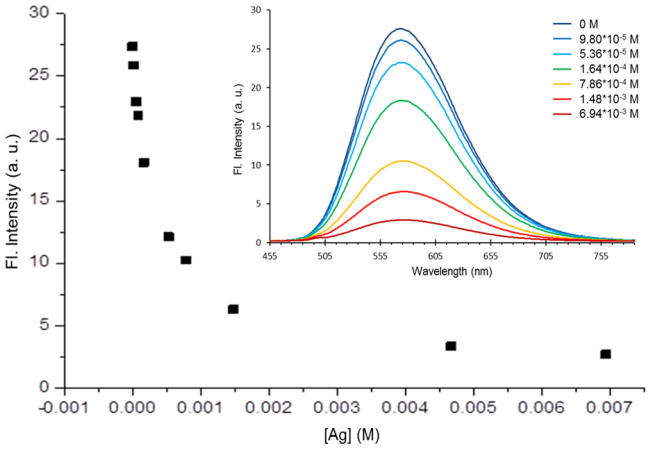


Figure 7. Representative titration (inset) and binding curve of **8a**.

phenazine **5a** with silver ions. Titrations of the three different phenazine compounds (including the cycloadduct **8a**) were performed in ethanol, which provides sufficient solubility and is somewhat comparable to water. Complex formation between silver ion and phenazine itself was observed only at excess concentrations of silver (>10^5 equiv), and no binding constant could be extracted. The binding constant for **8a** was determined to be log K = 3.44 ± 0.05, similar to the result obtained in water, while the value for **5a** was significantly lower (log K = 2.70 ± 0.02). The participation of the triazole ring serves to strengthen the binding affinity toward silver ions, though it is not strictly necessary. The selectivity of the phenazine cycloadducts for silver ion stems from the phenazine, and adjustment of the electronic properties of the phenazine core leads to changes in the metal-binding activity. The more electron-poor halogen-substituted phenazine compounds are unable to bind metal ions, despite the presence of the triazole. Interestingly, the cycloadduct **8a** is more sensitive to Ag(I) than **9a**. This suggests that the ethylene glycol side chains interfere with the binding of silver in some way, but the exact nature of this interaction is not clear.

CONCLUSION

Water-soluble bis-triazolyl cycloadducts were synthesized from hitherto unknown alkynylated phenazines to serve as selective silver ion sensors. Halogenation of the phenazine core lowers the band gap of these materials and also diminishes the capacity for metal binding. The properties of these phenazine cycloadducts and their selectivity for silver ions make them promising aqueous fluorescent sensors for silver ions, while the known biological activity of phenazine derivatives hints that these water-soluble phenazine cycloadducts may yet prove useful in other areas.

EXPERIMENTAL SECTION

Quantum yield measurements were measured relative to an appropriate standard (quinine sulfate in dilute sulfuric acid or fluorescein in dilute sodium hydroxide solution). Time-correlated single photon counting lifetime measurements were made with a pulsed laser diode.

3,6-Bis((trimethylsilyl)ethynyl)benzene-1,2-diamine (1). 4,7-Bis((trimethylsilyl)ethynyl)benzo[*c*][1,2,5]thiadiazole[55−57] (5.19 g, 15.8 mmol) and dry THF (50 mL) were placed in an oven-dried Schlenk flask, which was purged with nitrogen gas and cooled to 0 °C. Lithium aluminum hydride (1.50 g, 39.5 mmol) was slowly added to the reaction mixture over a period of 30 min. The reaction mixture was then stirred for 30 min under nitrogen, at which point it was slowly quenched with saturated aqueous NH_4Cl (30 mL) at 0 °C. The resulting product was extracted with diethyl ether (3 × 200 mL) and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (9/1 hexanes/Et_2O) gave compound **1** as an air-sensitive yellow solid (4.31 g, 14.3 mmol, 91% yield). Mp: 140−144 °C. IR (cm^{-1}): 3425, 3420, 3335, 3075, 2956, 2897, 2788, 2142, 1616, 1608, 1451, 1411, 1247, 1245, 1184, 1123. ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 2H), 3.94 (s, 4H), 0.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 122.4, 110.0, 102.1, 101.3, 0.4. HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{24}N_2Si_2$ 300.1478, found 300.1472.

3,6-Bis((triisopropylsilyl)ethynyl)benzene-1,2-diamine (2). 4,7-Bis((triisopropylsilyl)ethynyl)benzo[*c*][1,2,5]thiadiazole[55−57] (3.26 g, 6.56 mmol) and dry THF (50 mL) were placed in an oven-dried Schlenk flask, which was purged with nitrogen gas and cooled to 0 °C. Lithium aluminum hydride (0.622 g, 16.4 mmol) was slowly added to the reaction mixture over a period of 30 min. The reaction mixture was then stirred for 12 h under nitrogen, at which point it was slowly quenched with saturated aqueous NH_4Cl (30 mL) at 0 °C. The resulting product was extracted with diethyl ether (3 × 200 mL) and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (9/1 hexanes/Et_2O) gave compound **2** as an air-sensitive light yellow solid (2.92 g, 6.23 mmol, 95% yield). Mp: 127−129 °C. IR (cm^{-1}): 3436, 3328, 3070, 2954, 2862, 2715, 2611, 2140, 1612, 1481, 1269, 1384, 1361, 1253, 1184. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 3.97 (s, 4H), 1.14 (s, 42H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 122.5,

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110.3, 104.0, 97.5, 19.1, 11.6. HRMS (EI): m/z $[M]^+$ calcd for $C_{28}H_{48}N_2Si_2$ 468.3356, found 468.3359.

General Procedure 1. The diamine (**1** or **2**) was added to a solution of **3** in EtOH (10 mL) or DCM (50 mL), along with AcOH (3 mL). The reaction mixture was stirred overnight (~16 h). The solution was then extracted with saturated aqueous $NaHCO_3$ (50 mL) and DCM (2 × 50 mL). The organic fractions were collected and dried over sodium sulfate, the solvent was removed under reduced pressure, and the product was purified by silica gel chromatography.

1,4-Bis((trimethylsilyl)ethynyl)phenazine (4a). The *o*-benzoquinone was freshly prepared by stirring a solution of catechol (1.10 g, 9.98 mmol) in $CHCl_3$ (200 mL) into a solution of $K_2Cr_2O_7$ (5.88 g, 20.0 mmol) in 1 M H_2SO_4 (100 mL). After stirring for 10 min at room temperature, the organic fraction was collected, the solvent was removed under reduced pressure, and the benzoquinone was reacted with **1** (1.00 g, 3.33 mmol) according to general procedure 1, using EtOH as solvent. The reaction mixture was heated to 40 °C and stirred overnight at this temperature. Purification by silica gel chromatography (3/1 hexanes/DCM) gave the product **4a** as a yellow solid (780 mg, 2.09 mmol, 63%). Mp: 166−168 °C. IR (cm^{-1}): 3089, 3040, 2963, 2954, 2897, 2152, 1919, 1518, 1473, 1406, 1281, 1138, 1118, 1025. ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, J = 3.4 Hz, J = 6.7 Hz, 2H), 7.95 (s, 2H), 7.83 (dd, J = 3.4 Hz, J = 6.7 Hz, 2H), 0.35 (s, 18H). ^{13}C NMR (100 MHz in $CDCl_3$): δ 143.6, 143.0, 134.4, 131.2, 130.3, 124.3, 104.2, 101.6, 0.1. HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{24}N_2Si_2$ 372.1478, found 372.1488.

1,2,3,4-Tetrafluoro-6,9-bis((trimethylsilyl)ethynyl)phenazine (4b). The tetrafluoro-*o*-quinone was freshly prepared before use according to a previously published procedure.[58] **1** (1.10 g, 3.66 mmol) and **3b** (2.00 g, 11.1 mmol) were reacted according to general procedure 1, using DCM as solvent. The reaction mixture was heated to reflux and stirred overnight at this temperature. Purification by silica gel chromatography (10/1 hexanes/DCM) yielded **4b** as a yellow solid (292 mg, 0.657 mmol, 18%). Mp: 207−210 °C. IR (cm^{-1}): 2957, 2901, 2853, 2153, 1675, 1595, 1536, 1485, 1341, 1245, 1073, 833, 755, 686, 625, 464. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 2H), 0.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 135.7, 124.5, 106.3, 100.5, 1.4 (the carbons next to the fluorine atoms could not be identified). ^{19}F NMR (300 MHz, $CDCl_3$): δ −149.61 (dd, J = 16.2 Hz, J = 3.6 Hz, 2F), −150.34 (dd, J = 15.0 Hz, J = 3.0 Hz, 2F). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{21}F_4N_2Si_2$ 445.1174, found 445.1180.

1,2,3,4-Tetrachloro-6,9-bis((trimethylsilyl)ethynyl)-phenazine (4c). **1** (0.600 g, 2.00 mmol) and **3c** (0.982 g, 3.99 mmol) were reacted according to general procedure 1, using EtOH as solvent. The reaction mixture was heated to 40 °C and stirred overnight at this temperature. Purification by silica gel chromatography (20/1 hexanes/DCM) yielded **4c** as a yellow solid (819 mg, 1.60 mmol, 80%). Mp: 201−203 °C. IR (KBr, cm^{-1}): 2958, 2899, 2152, 1573, 1551, 1488, 1454, 1371, 1245, 1132, 1050. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 2H), 0.36 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 138.7, 135.4, 135.1, 132.2, 124.3, 105.8, 100.2, −0.1. HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{20}Cl_4N_2Si_2$ 507.9919, found 507.9918.

1,2,3,4-Tetrabromo-6,9-bis((trimethylsilyl)ethynyl)-phenazine (4d). **1** (0.300 g, 0.998 mmol) and compound **3d** (0.846 g, 2.00 mmol) were reacted according to general procedure 1. The reaction mixture was heated to 40 °C and stirred overnight at this temperature. Purification by silica gel chromatography (hexanes) yielded **4d** as a yellow solid (303 mg, 0.440 mmol, 48%). Mp: 137 °C dec. IR (cm^{-1}): 2958, 2925, 2899, 2852, 2153, 1893, 1573, 1446, 1359, 1254, 1247, 1099, 1044. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H), 0.38 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 145.0, 140.5, 137.1, 133.9, 129.2, 110.8, 105.5, 5.1. HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{20}Br_4N_2Si_2$ 683.7899, found 683.7895.

1,4-Bis((triisopropylsilyl)ethynyl)phenazine (5a). The *o*-benzoquinone was freshly prepared by stirring a solution of catechol (0.692 g, 6.40 mmol) in $CHCl_3$ (200 mL) into a solution of $K_2Cr_2O_7$ (3.76 g, 12.8 mmol) in 1 M H_2SO_4 (100 mL). After the mixture was stirred for 10 min at room temperature, the organic fraction was collected, the solvent was removed under reduced pressure, and the benzoquinone was reacted with **2** (1.00 g, 2.13 mmol) according to general procedure 1, using EtOH as solvent. The reaction mixture was heated to reflux and stirred overnight. Purification by silica gel chromatography (3/1 hexanes/DCM) gave the product **5a** as a yellow solid (0.480 g, 0.887 mmol, 42%). Mp: 96−98 °C. IR (cm^{-1}): 3062, 2962, 2864, 2756, 2723, 2154, 1946, 1886, 1568, 1521, 1461, 1409, 1257, 1118. ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (dd, J = 3.4 Hz, J = 6.7 Hz, 2H), 7.94 (s, 2H), 7.84 (dd, J = 3.4 Hz, J = 6.7 Hz, 2H), 1.26 (s, 42H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 143.8, 133.9, 131.2, 130.5, 124.8, 104.0, 101.0, 19.2, 11.9. HRMS (EI): m/z $[M]^+$ calcd for $C_{34}H_{48}N_2Si_2$ 540.3356, found 540.3354.

1,2,3,4-Tetrafluoro-6,9-bis((triisopropylsilyl)ethynyl)-phenazine (5b). The tetrafluoro-*o*-quinone was freshly prepared before use, according to a previously published procedure.[58] **2** (0.500 g, 1.07 mmol) and **3b** (0.576 g, 3.20 mmol) were reacted according to general procedure 1, using DCM as solvent. The reaction mixture was heated to reflux and stirred overnight. Purification by silica gel chromatography (10/1 hexanes/DCM) yielded **5b** as a yellow solid (152 mg, 0.248 mmol, 23%). Mp: 107−108 °C. IR (cm^{-1}): 2939, 2891, 2864, 2159, 1675, 1595, 1536, 1480, 1341, 1260, 1076, 993, 881, 809, 678, 453. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 2H), 1.24 (s, 42H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 135.5, 124.8, 102.8, 102.6, 19.0, 11.8 (the carbons next to the fluorine atoms could not be identified). ^{19}F NMR (300 MHz, $CDCl_3$): δ −148.80 (dd, J = 15.0 Hz, J = 3.0 Hz, 2F), −149.91 (dd, J = 16.2 Hz, J = 3.6 Hz, 2F). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{34}H_{45}F_4N_2Si_2$ 613.3052, found 613.3067.

1,2,3,4-Tetrachloro-6,9-bis((triisopropylsilyl)ethynyl)-phenazine (5c). **2** (0.200 g, 0.427 mmol) and **3c** (0.115 g, 0.469 mmol) were reacted according to general procedure 1, using EtOH as solvent. The reaction mixture was heated to reflux and stirred overnight. Purification by silica gel chromatography (20/1 hexanes/DCM) yielded **5c** as a yellow solid (54.0 mg, 0.0796 mmol, 19%). Mp: 100−102 °C. IR (cm^{-1}): 2964, 2866, 2725, 2156, 1949, 1458, 1369, 1263, 1107, 1031. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 2H), 1.21 (s, 42H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 138.8, 135.9, 133.7, 132.2, 124.5, 102.4, 102.0, 18.8, 11.4. HRMS (EI): m/z $[M]^+$ calcd for $C_{34}H_{44}Cl_4N_2Si_2$ 676.1797, found 676.1776.

1,2,3,4-Tetrabromo-6,9-bis((triisopropylsilyl)ethynyl)-phenazine (5d). **2** (0.200 g, 0.427 mmol) and **3d** (0.271 g, 0.640 mmol) were reacted according to general procedure 1. The reaction mixture was heated to reflux and stirred overnight. Purification by silica gel chromatography (hexanes) yielded **5d** as a yellow solid (65.0 mg, 0.0759 mmol, 18%). Mp: 107 °C dec. IR (cm^{-1}): 2941, 2891, 2864, 2725, 2150, 1892, 1701, 1573, 1463, 1448, 1359, 1269, 1126. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 1.21 (s, 42H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 139.9, 136.1, 131.7, 128.7, 124.3, 102.5, 101.8, 18.8, 11.4. HRMS (EI): m/z $[M]^+$ calcd for $C_{34}H_{44}Br_4N_2Si_2$ 851.9777, found 851.9739.

1,4-Diethynylphenazine (6a). **4a** (0.186 g, 0.499 mmol) was dissolved in 1/1 THF/MeOH (20 mL), to which K_2CO_3 (0.190 g, 4.99 mmol) was added. The solution was stirred for 30 min at room temperature. The product mixture was then poured over H_2O (50 mL) and extracted with DCM (2 × 50 mL). The resulting solution was dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (10/1 hexanes/EtOAc) gave **6a** as a yellow solid (0.105 g, 0.460 mmol, 92%). Mp: 80 °C dec. IR (cm^{-1}): 3298, 3270, 3232, 3205, 2101, 1521, 1473, 1334, 1112, 1034. ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 8.01 (s, 2H), 7.87 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 3.76 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.2, 134.9, 131.7, 130.4, 124.0, 86.1, 80.6. HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_8N_2$ 228.0687, found 228.0690.

1,2,3,4-Tetrafluoro-6,9-diethynylphenazine (6b). **4b** (59 mg, 0.13 mmol) was dissolved in THF (10 mL), to which K_2CO_3 (0.18 g, 1.3 mmol) was added. The solution was stirred for 2 h at room temperature. The reaction did not go to completion, and no progress was seen after 2 h or even after 24 h. The product mixture was then poured over H_2O (50 mL) and extracted with DCM (2 × 50 mL). The resulting solution was dried over sodium sulfate, and the solvent

dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479−7486

was removed under reduced pressure. Purification by silica gel chromatography (20/1 hexanes/EtOAc) gave **6b** as a yellow solid (0.018 g, 0.060 mmol, 45%). Mp: 51 °C dec. IR (cm^{-1}): 3263, 2955, 2923, 2356, 2036, 1615, 1489, 1261, 1069, 800. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 2H), 3.79 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 136.4, 124.2, 87.3, 79.4 (the carbons next to the fluorine atoms could not be identified). ^{19}F NMR (400 MHz): δ −148.80 (dd, J = 16.2 Hz, J = 3.6 Hz, 2F), −149.91 (dd, J = 15 Hz, J = 3.0 Hz, 2F). HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{16}H_5N_2F_4$ 301.0383, found 301.0419.

1,2,3,4-Tetrachloro-6,9-diethynylphenazine (6c). **4c** (0.200 g, 0.392 mmol) was dissolved in 1/1 THF/MeOH (20 mL), to which K_2CO_3 (0.542 g, 3.92 mmol) was added. The solution was stirred for 30 min at room temperature. The product mixture was then poured over H_2O (50 mL) and extracted with DCM (2 × 50 mL). The resulting solution was dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (20/1 hexanes/EtOAc) gave **6c** as a yellow solid (0.119 g, 0.325 mmol, 83%). Mp: 40 °C dec. IR (cm^{-1}): 3269, 2958, 2954, 2924, 2109, 1727, 1549, 1454, 1368, 1287, 1247, 1051, 1039. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 2H), 3.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 138.9, 136.1, 135.4, 132.1, 124.0, 86.8, 79.2. HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_4Cl_4N_2$ 363.9129, found 363.9133.

1-Azido-2-(2-(2-methoxyethoxy)ethoxy)ethane (7a). 2-(2-(2-Methoxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate[59] (12.9 g, 40.5 mmol) and NaN_3 (5.27 g, 81.0 mmol) were stirred into 1/1 H_2O/MeOH (100 mL). The reaction mixture was heated to reflux and stirred overnight (16 h). The reaction mixture was cooled and extracted with DCM (2 × 70 mL). The organic fractions were collected and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (1/1 hexanes/EtOAc) gave **7a** as a pale yellow oil (6.76 g, 35.7 mmol, 88%). IR (cm^{-1}): 2872, 2097, 1453, 1284, 1106, 934, 851. ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (m, 8 H), 3.55 (m, 2H), 3.38 (t, J = 5.1 Hz, 2H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.0, 70.8, 70.8, 70.7, 70.1, 59.1, 50.8.

13-Azido-2,5,8,11,15,18,21,24-octaoxapentacosane (7b). 2,5,8,11,15,18,21,24-Octaoxapentacosan-13-yl 4-methylbenzenesulfonate[59] (8.90 g, 16.5 mmol) and NaN_3 (5.37, 82.6 mmol) were stirred into 4/1 H_2O/EtOH (250 mL). The reaction mixture was heated to reflux and stirred for 2 days. The reaction mixture was cooled and extracted with DCM (3 × 75 mL). The organic fractions were collected and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (EtOAc) gave **7b** as a pale yellow oil (6.2 g, 15 mmol, 92%). IR (cm^{-1}): 2866, 2092, 1455, 1269, 1098, 849, 731. ^1H NMR (300 MHz, $CDCl_3$): δ 3.48−3.35 (m, 29H), 3.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.67, 70.64, 70.38, 70.35, 70.28, 70.24, 60.3, 58.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{35}N_3O_8Na$ 432.2316, found 432.2319.

1,4-Bis(1-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)phenazine (8a). **6a** (0.300 g, 1.31 mmol) and **7a** (0.746 g, 3.94 mmol) were dissolved in a 5/1 THF/H_2O solution (20 mL) and deoxygenated via the freeze−pump−thaw method (3×). Under a flow of nitrogen, $CuSO_4{\cdot}5H_2O$ (0.820 g, 3.29 mmol) and sodium ascorbate (0.651 g, 3.29 mmol) were added, and the reaction mixture was then sealed and stirred overnight at room temperature. The crude mixture was then filtered through Celite with DCM, and the solvent was dried with sodium sulfate and removed in vacuo. The product **8a** was purified via silica gel flash chromatography (DCM, followed by EtOAc) and isolated as an orange oil (487 mg, 0.803 mmol, 61%). IR (cm^{-1}): 2942, 2921, 2871, 2783, 2772, 2739, 2739, 1751, 1653, 1647, 1558, 1447, 1430, 1352, 1332, 1229, 1108, 1098, 1064, 1030. ^1H NMR (300 MHz, $CDCl_3$): δ 9.20 (s, 2H), 8.96 (s, 2H), 8.32 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 7.88 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 4.74 (t, J = 5.4 Hz, 4H), 4.04 (t, J = 5.4 Hz, 4H), 3.68 (m, 8H), 3.57 (m, 9H), 3.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 142.0, 140.2, 130.5, 129.6, 128.6, 128.0, 126.4, 71.78, 70.77, 70.53, 70.50, 69.74, 58.9, 50.4. HRMS (EI): m/z $[M]^+$ calcd for $C_{30}H_{38}N_8O_6$ 606.2914, found 606.2903.

1,2,3,4-Tetrachloro-6,9-bis(1-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)phenazine (8c). **6c** (0.080 g, 0.22 mmol) and **7a** (0.12 g, 0.66 mmol) were dissolved in a 5/1 THF/H_2O solution (20 mL) and deoxygenated via the freeze−pump−thaw method (3×). Under a flow of nitrgoen, $CuSO_4{\cdot}5H_2O$ (0.14 g, 0.55 mmol) and sodium ascorbate (0.11 g, 0.55 mmol) were added, and the reaction mixture was then sealed and stirred overnight at room temperature. The crude mixture was then filtered through Celite with DCM, and the solvent was dried with sodium sulfate and removed in vacuo. The product **8c** was purified via silica gel flash chromatography (DCM followed by EtOAc) and isolated as a red oil (75 mg, 0.10 mmol, 46%). IR (cm^{-1}): 2904, 2883, 2869, 2854, 1734, 1653, 1558, 1457, 1374, 1252, 1108, 1099. ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 2H), 8.98 (s, 2H), 4.70 (t, 4H), 4.00 (t, 4H), 3.64 (m, 8H), 3.49 (m, 8H), 3.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 138.9, 136.4, 134.3, 131.4, 129.5, 128.2, 126.3, 71.86, 70.77, 70.56, 69.58, 59.0, 50.5. HRMS (EI): m/z $[M]^+$ calcd for $C_{30}H_{34}Cl_4N_8O_6$ 742.1355, found 742.1333.

1,4-Bis(1-(2,5,8,11,15,18,21,24-octaoxapentacosan-13-yl)-1*H*-1,2,3-triazol-4-yl)phenazine (9a). **6a** (48 mg, 0.21 mmol) and **7b** (190 mg, 0.46 mmol) were stirred together in H_2O (1 mL) and THF (5 mL). The solution was then deoxygenated via the freeze−pump−thaw method (3×). Under a flow of nitrogen, $Cu(PPh_3)_3Br$ (0.020 g, 0.021 mmol) was added. The reaction mixture was then sealed under an inert atmosphere and stirred at 50 °C for 2 days. The reaction mixture was then extracted with saturated aqueous NH_4Cl (25 mL) and DCM (5 × 25 mL), the organic fractions were collected and dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (gradient elution, EtOAc → 20/1 EtOAc/MeOH → 10/1 EtOAc/MeOH) gave **9a** as an orange oil (66 mg, 0.063 mmol, 30%). IR (cm^{-1}): 2870, 1717, 1584, 1435, 1218, 1095, 851, 767. ^1H NMR (300 MHz, $CDCl_3$): δ 9.27 (s, 2H), 9.00 (s, 2H), 8.32 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 7.89 (dd, J = 10.2 Hz, J = 3.3 Hz, 2H), 5.09 (p, J = 6.0 Hz, 2H), 4.09 (d, J = 6.3 Hz, 8H), 3.70−3.40 (m, 48H), 3.30 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 142.5, 140.8, 130.9, 130.1, 129.1, 128.6, 126.1, 72.15, 71.31, 70.88, 70.85, 70.76, 70.75, 70.63, 61.3, 59.3. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{50}H_{79}N_8O_{16}$ 1047.5609, found 1047.5618.

6,9-Bis(1-(2,5,8,11,15,18,21,24-octaoxapentacosan-13-yl)-1*H*-1,2,3-triazol-4-yl)-1,2,3,4-tetrafluorophenazine (9b). **6b** (18 mg, 0.060 mmol) and **7b** (61 mg, 0.15 mmol) were stirred together in H_2O (1 mL) and THF (5 mL). The solution was then deoxygenated via the freeze−pump−thaw method (3×). Under a flow of nitrogen, $Cu(PPh_3)_3Br$ (0.011 g, 0.012 mmol) was added. The reaction mixture was then sealed under an inert atmosphere and stirred at 50 °C for 2 days. The reaction mixture was then extracted with saturated aqueous NH_4Cl (25 mL) and DCM (5 × 25 mL), the organic fractions were collected and dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (gradient elution, EtOAc → 20/1 EtOAc/MeOH → 10/1 EtOAc/MeOH) gave **9b** as a red oil (18 mg, 0.016 mmol, 27%). IR (cm^{-1}): 2923, 2856, 1737, 1456, 1260, 1092, 198, 464. ^1H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 2H), 9.15 (s, 2H), 5.11 (p, J = 6.0 Hz, 2H), 4.09 (d, J = 6.3 Hz, 8H), 3.70−3.55 (m, 41H), 3.48 (m, 8H), 3.33 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 140.4, 130.3, 129.3, 126.0, 72.22, 71.36, 70.93, 70.91, 70.81, 70.59, 61.4, 59.3 (the carbons next to the fluorine atoms could not be identified). ^{19}F NMR (400 MHz, $CDCl_3$): δ −150.88 (dd, J = 16.2 Hz, J = 3.6 Hz, 2F), −152.06 (dd, J = 15.0 Hz, J = 3.0 Hz, 2F). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{50}H_{75}F_4N_8O_{16}$ 1119.5232, found 1119.5230.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra and tables giving Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/jo3012978 | J. Org. Chem. 2012, 77, 7479−7486

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Notes

The authors declare no competing financial interest.

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