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3,2-Hydroxypyridinone (3,2-HOPO) vinyl sulfonamide and acrylamide linkers: aza-Michael addition reactions and the preparation of poly-HOPO chelators

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ABSTRACT

The HOPO vinyl sulfonamide **3** and the corresponding HOPO acrylamide **10** were easily prepared by short synthetic sequences. Investigation of the aza-Michael reactions of these linkers showed that they proceed at a higher rate in solvent systems containing water. The scope and limits of the aza-Michael reactions of **3** and **10** were examined. Reagents **3** and **10** reacted cleanly with piperazine to give the corresponding adducts which were deprotected to give the di-HOPO ligands **7** and **16**. Reaction of HOPO acrylamide **10** with 1,4,7-triazacyclononane gave the tris-adduct **17** which was deprotected to give the desired tris-HOPO ligand **18**. Overall, the aza-Michael reactions of **3** and **10** appear to be governed not only by the solvent but also by the nature of the amine and the solubility of the reaction intermediates.

There has been considerable interest in the synthesis, coordination chemistry, and biological applications of hydroxypyridinone (HOPO) ligand systems.[1] Tris-HOPO chelators have been shown to form strong complexes with hard metal ions such as iron, gadolinium, and gallium. A recent review on hydroxypyridinones as 'privileged' structures for the design of medicinal drugs has been published.[2] 3,4-HOPO chelators have been extensively examined for the treatment of iron overload diseases[3] and cancer treatment.[4] Another review[5] discusses the use of HOPO chelators as contrast agents in magnetic resonance imaging (MRI), a hot area of research.[6] HOPO chelators have been attached to dendrimers[7] and viral capsids.[8] HOPO complexes of gallium (III) isotopes are also being investigated for positron emission tomography (PET) applications.[9]

The sulfonamide moiety is present in a wide array of drugs that range from sulfa antibiotics to Viagra and Celebrex.[10] Sulfonamides have been used clinically to treat diseases like glaucoma, macular edema, diverse neuromuscular disorders, and fungal infections. They have also been used in cancer treatment.[11] Sulfonamide derivatives are known to be inhibitors of carbonic anhydrase[12] and matrix metalloproteinases.[13]

Given the importance of both the HOPO ligand and the sulfonamide bond, synthetic methodology to access molecules that incorporate both these features are lacking. This could be due to the fact that in comparison to the corresponding amides, non-aryl sulfonamide systems are more difficult to prepare. The traditional method for synthesizing sulfonamides is by reacting ammonia, primary or secondary amines with the desired sulfonyl chloride. Aromatic sulfonyl chlorides are often directly synthesized by chlorosulfonylation and many are commercially available. However, aliphatic sulfonyl chlorides are not as easily accessed though they can be prepared from the corresponding sulfonate salts. Recently, some alternate routes for accessing aliphatic sulfonamides have been published.[14] A popular method involves the conversion of thiols to a sulfonic acid chloride using oxidative chlorination followed by in situ coupling with amines.[15]

In this paper, we disclose a convenient and convergent procedure for the incorporation of HOPO ligands onto various amine platforms using aza-Michael reactions of a new vinyl sulfonamide-HOPO reagent. The choice of primary sulfonamide in the linker is relevant as it provides a site for H-bonding, metal ion[11b] or anion bonding,[16] and permits subsequent attachment to another group via N-alkylation. Our interest in this area was further stimulated by recent disclosures on vinyl sulfonamide reagents which have been shown to be valuable 'linchpins' in diversity-oriented synthesis as they undergo aza-Michael, Heck, and RCM reactions.[17] We also report the results of the aza-Michael reaction of the corresponding HOPO acrylamide, which allows access to amide analogs for comparison purposes.

Our study began with the preparation of the HOPO vinyl sulfonamide reagent **3**. It was also decided to prepare the simpler and more easily accessible sulfonamide **1** to conduct some model studies on reactivity. Using a modification of a procedure reported by Li et al.,[18] the synthesis of vinylsulfonamide **1** was accomplished, in a one-pot reaction, from commercially available 2-chloro-

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ethanesulfonyl chloride. In our hands, the most convenient procedure involved the addition of chloroethanesulfonyl chloride to a solution of amylamine in dichloromethane in the presence of triethylamine at room temperature (Scheme 1). After aqueous work-up and chromatographic purification, vinyl sulfonamide **1** was isolated in good yields. Similar reaction of HOPO amine **2**,[19] with chloroethanesulfonyl chloride gave HOPO vinyl sulfonamide reagent **3** in 63% yield after purification.[20]

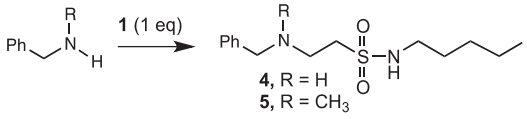
The aza-Michael addition of vinylsulfonamide **1** with a primary amine was first examined. The desired addition showed little progress when a 1:1 mixture of benzyl amine with the vinylsulfonamide reagent **1** in acetonitrile was stirred at room temperature for 8 days. However, better results were observed when excess benzyl amine (4 equiv) was used in this reaction (85% yield over 8 days at rt). When a 1:1 mixture of benzyl amine and **1** was refluxed in acetonitrile for 3 days, the desired adduct **4** was isolated in 75% yield (Table 1, entry 1).

From our initial studies, it was clear that under traditional conditions, aza-Michael addition reactions of primary amines to the vinyl sulfonamide were slow. Our observation is not unique as there are reports in the literature that primary vinyl sulfonamides are not particularly reactive in aza-Michael reactions. This has been ascribed to deprotonation of the acidic sulfonamide proton to some degree reducing the reagent's electrophilicity.[21] In one study that examined the Michael addition of 2-phenylethanethiol to representative vinyl sulfonyl Michael acceptors, the sulfonamide analog was found to be the least reactive while the phenyl vinyl sulfonate ester was the most reactive.[21] In another study, it was found that no aza-Michael addition occurred in the absence of Lewis acids in both solution and solid phase, when excess 4-furoylpiperazine was contacted with vinyl sulfonamides on solid support or in corresponding model studies.[22] It became imperative to identify more favorable conditions for the aza-Michael addition reactions of amines/polyamines with reagent **1**.

Recently, several publications have appeared on the rate enhancement of Michael addition reactions in the presence of water.[23] Importantly, Naidu et al reported a dramatic increase in both the rate and yields in the Michael addition of amines and thiols to dehydroalanine amides upon using THF:water or methanol:water as the solvent.[24] A similar rate enhancement was observed in the aza-Michael addition of cyclam to phenyl vinyl sulfone and phenyl vinyl sulfoxide when water was added to the reaction mixture.[25] However, in the case of vinyl sulfonamides, it was not known if there is any rate acceleration of the aza-Michael addition in the presence of water in the solvent system. We decided to examine whether the inclusion of water in the solvent system could favorably impact the addition of amines to vinyl sulfonamides.

Given the lack of aqueous solubility of sulfonamide **1**, we decided that mixed solvents such as THF:water or methanol:water may be more appropriate for our reaction.[24] Indeed, this proved to be correct. In the aza-Michael addition of benzyl amine (1 equiv) to vinyl sulfonamide **1** (1 equiv) we observed a significant increase in the rate of reaction, when the reaction was run in a 2:3 mixture of methanol/water for 18 hours. Adduct **4** was formed in 62% yield (Table 1, entry 2). When the same reaction was run in a solution of THF/water, the rate enhancement was significantly less but the reaction did proceed at room temperature and a higher yield of the adduct was isolated after 4 days (entry 3).

Table 1
Reactions of vinyl sulfonamide **1** with amines

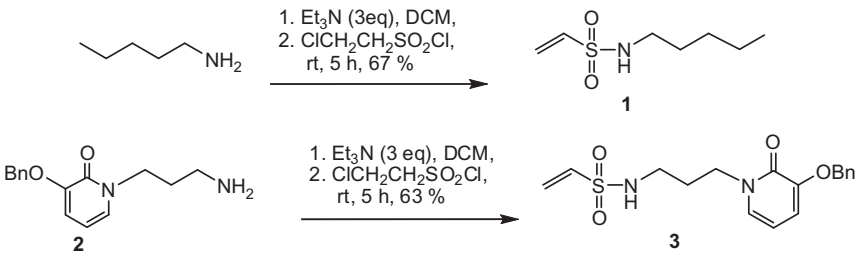


Entry	R	Solvent	Temp	Time	Yield[a] (%)
1	H	CH_3CN	Reflux	3 d	75
2	H	2:3 MeOH:H_2O	rt	18 h	62
3	H	2:3 THF:H_2O	rt	4 d	87
4	CH_3	CH_3CN	Reflux	3 d	79
5	CH_3	2:3 THF:H_2O	rt	18 h	83

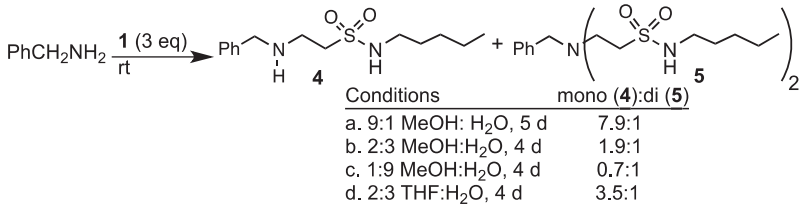
[a] Isolated yield after work-up. TLC was homogeneous.

N-Methyl benzyl amine was used as a model to understand the reactivity of secondary amines with **1**. When a 1:1 mixture of the amine and **1** was refluxed in acetonitrile for 3 days, sulfonamide **5** was isolated in 79% yield (entry 4). When a mixture of water and THF was used as the solvent, the same reaction gave an 83% yield of the product after only 18 hours (entry 5). The precise explanation for the rate enhancement observed in Michael additions in aqueous solutions is unknown.[26] Various factors such as hydrogen bonding and/or hydrophobic effects have been invoked as potential contributors to the rate enhancement. Further, in the case of sulfonamides, solubility of both starting materials and products in the reaction medium appear to impact the progress of the reaction.

From the literature, aza-Michael reactions of primary amines in aqueous solvent systems have been reported to give monoalkylation only[23c] or mixtures of mono and di-adducts.[27] Hence, it was not clear whether the reaction of vinyl sulfonamide **1** with a primary amine (benzyl amine) could be controlled to obtain the di-adduct selectively and in good yields. A number of reaction conditions were examined for this purpose using a three to one stoichiometric ratio of vinyl sulfonamide **1** to benzyl amine (Scheme 2). In all cases, we obtained product mixtures with varying ratios of the mono to di, with the mono usually being the major product. These reactions could easily be monitored by ^{1}H NMR analysis. The benzyl protons of the mono and di-adducts have well differentiated chemical shifts, δ 3.80 and 3.69, respectively, and could be easily integrated to obtain the ratio of the mono to di in the crude products.



Scheme 1.



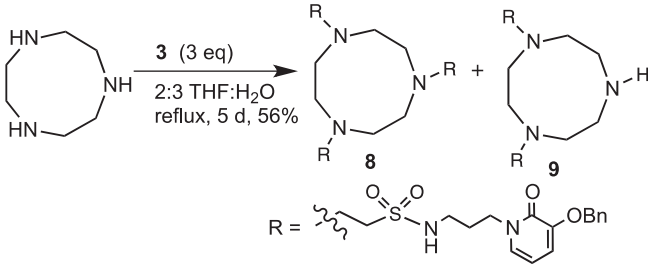
Scheme 2.

With the useful information obtained from our model studies with vinyl sulfonamide **1**, we began to explore the aza-Michael reaction of the HOPO vinylsulfonamide **3**, for the preparation of sulfonamide-linked HOPO chelators. Of particular interest to us was the reaction of **3** with azacyclic polyamines. The syntheses of chelators in which the HOPO ligands have been appended to piperazine and 1,4,7-triazacyclononane have been reported and they have been shown to be strong chelators of iron.[28]

Based on our results, we expected that secondary amines would undergo efficient aza-Michael addition with **3**. We were particularly optimistic with piperazine as our substrate, since it is known that cyclic amines react more readily with various Michael acceptors than their acyclic analogs.[29] When piperazine was reacted with sulfonamide **3** (2.1 equiv) in refluxing acetonitrile, the rate of addition was slow (8 days) but the sulfonamide-linked bisHOPO compound **6** was obtained in 48% yield. However, when the same reaction was run in 2:3 THF/water at room temperature for 1 day, the product **6** was isolated in excellent yield after chromatographic purification (Scheme 3).[30] Clearly, the addition of water improved both the yield and rate of the reaction in this case. Deprotection of **6** using 1:1 HBr/acetic acid gave the sulfonamide-linked bisHOPO chelator **7** as the hydrobromide salt in 92% yield after lyophilization.[31]

The successful reaction of HOPO vinyl sulfonamide **3** with piperazine encouraged us to explore the corresponding reaction of sulfonamide **3** with 1,4,7-triazacyclononane. When triazacyclononane was stirred with 3 equiv of vinyl sulfonamide **3** in 2:3 THF/water it was observed that there was very little product formation after 1 day at rt. Subsequently, the reaction mixture was refluxed for 5 days adding THF as necessary to maintain homogeneity. After purification by preparative TLC on alumina, the desired tris-adduct **8** was obtained in 56% yield contaminated with small amounts of the di-adduct, **9** (Scheme 4). In addition to spectral analysis, LCMS confirmed the presence of the major tris-adduct (1175, $[MH]^+$) and also the minor di-adduct (827, $[MH]^+$). Given the success of the reaction of **3** with piperazine, our results with 1,4,7-triazacyclononane were unexpected. It is clear that both the solubility of the starting materials and the intermediates play a critical role in the success of this reaction.

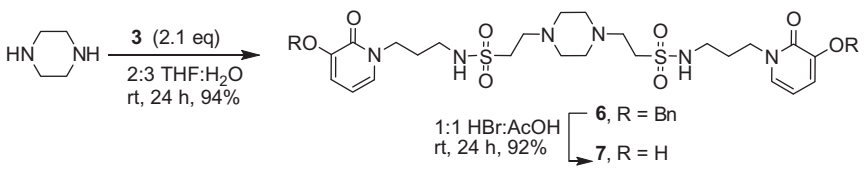
Our focus then turned to the corresponding HOPO acrylamide **10**. It was relevant to examine its reactivity with secondary amines and determine whether a similar rate of acceleration in aqueous solvents would be observed. Also the studies would provide amide analogs of the sulfonamides for comparison purposes.



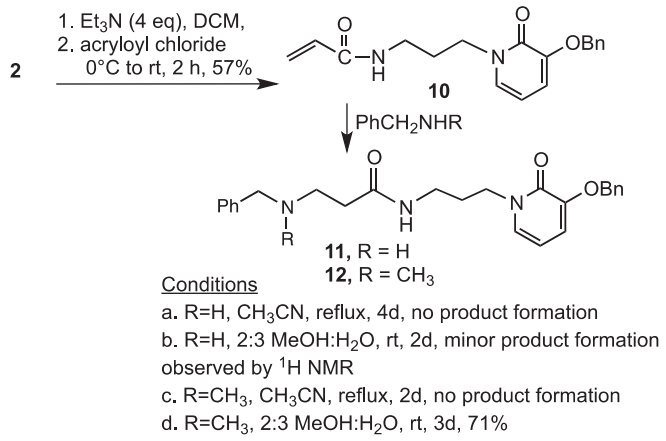
Scheme 4.

The coupling of HOPO amine, **2**, with acryloyl chloride in the presence of excess triethylamine in dichloromethane gave the HOPO acrylamide reagent **10** in 57% yield after purification (Scheme 5). The difference in reactivity between the vinyl sulfonamide **1** and HOPO acrylamide **10** became quickly apparent, in the reaction of **10** with benzyl amine. No significant product formation was observed when benzyl amine (1 equiv) was refluxed with **10** (1 equiv) for 3 days in acetonitrile. Minor adduct formation was observed by proton NMR analysis when this reaction was conducted in 2:3 methanol/water for 2 days at room temperature. In contrast to the reaction with **1,** when a 1:1 mixture of *N*-methylbenzyl amine and HOPO acrylamide **10** was refluxed in acetonitrile for 2 days, no product formation was observed. However, when the same reaction was carried out in 2:3 methanol/water at room temperature for 3 days, the aza-Michael product **12** was isolated in 71% yield after chromatographic purification. Though the reaction was slow, the use of methanol/water as a solvent did result in good yields of **12**.

The difference in reactivity of the HOPO acrylamide **10** with benzyl amine and *N*-methyl benzyl amine was surprising. To further establish the difference in reactivity (primary vs secondary amine), the reagent **10** (1 equiv) was reacted with *N*-methylethylenediamine (5 equiv) in 2:3 methanol/water. After 1 day, only the mono adduct, **13**, from addition at the secondary amine, was isolated in 86% yield after column chromatography (Scheme 6). The secondary amine shows a surprising selectivity over the primary amine for addition to **10** and there is no obvious explanation for this unexpected behavior. It has been reported[23d] that secondary amines undergo aza-Michael additions in higher yields than primary amines though no competitive studies like ours have been published. It is likely that both the solubility and the steric and hydrophobic nature of the amine are key factors that affect the rate



Scheme 3.



Scheme 5.

of this reaction. When *N*,*N*′-dimethyl ethylenediamine was treated with **10** (2 equiv) in methanol/water for 3 days, the dialkylated product **14** was isolated in 53% yield after purification.

The aza-Michael addition of acrylamide-HOPO reagent **10** with piperazine was also examined (Scheme 7). Treatment of piperazine with acrylamide **10** (2 equiv) in methanol/water for 3 days gave the desired dialkylated product **15** in 87% yield after purification. Deprotection of the benzyl groups using HBr/acetic acid gave the water-soluble amide linked bisHOPO chelator **16** as the hydrobromide salt in good yield.[32] The reaction of 1,4,7-triazacyclononane with HOPO acrylamide **10** (3 equiv) in methanol/water was slow but gave the tris-HOPO product **17** in good yield after purification (Scheme 7). In contrast to the corresponding vinyl sulfonamide addition, this reaction goes to completion. Deprotection using HBr/acetic acid gave the water-soluble tris-HOPO chelator **18** as the hydrobromide salt in good yield.[33]

In conclusion, the aza-Michael reaction of vinyl sulfonamides has received little attention as a synthetic tool. In this Letter, the aza-Michael reaction of vinyl sulfonamide **1** was shown to be very slow in refluxing acetonitrile but occurs more rapidly in aqueous solvent systems (e.g., THF/water or methanol/water). This finding is consistent with the rate of acceleration observed in the presence of water in aza-Michael addition studies of various acrylate derivatives. Both benzyl amine and *N*-methyl benzyl amine gave good yields of the desired mono adducts with **1**. In contrast, the reaction of benzyl amine with excess sulfonamide **1** could not be controlled to give only the di-adduct. Piperazine undergoes efficient addition with vinyl sulfonamide **3** to give the di-adduct **6** in good yields. However, our results from the reaction of **3** with 1,4,7-triazacyclononane suggest that solubility considerations of the intermediates may play a role in driving this reaction to completion. In contrast to HOPO vinyl sulfonamide **3**, the corresponding HOPO acrylamide, **10**, appears to be less reactive under comparable conditions with both primary and secondary amines. However, the higher reactivity of **10** with secondary amines over primary amines is clearly seen in its reaction with *N*-methyl ethylenediamine, which reacts preferentially at the secondary amine site. In spite of its reduced reactivity, reagent **10** does add efficiently to secondary amines including piperazine. The reaction of HOPO acrylamide **10** with 1,4,7-triazacyclononane does proceed, albeit slowly, to give the desired tris-adduct **17** in good yields. Overall, the aza-Michael reactions appear to be governed not only by the solvent but by the nature of the amine and the solubility of the reaction intermediates. While HOPO vinyl sulfonamide **3** does react more readily than acrylamide **10**, its use to prepare poly-HOPO derivatives from the corresponding polyamines may be limited due to solubility considerations. Finally, this work resulted in the successful synthesis of a new bis-3,2-HOPO sulfonamide chelator **7** and its amide analog **16**. We also prepared tris-3,2-HOPO amide linked chelator **18** to demonstrate the potential applicability of our new methodology. The usefulness of reagents **3** and **10** in Heck and metathesis reactions, which can further enhance the value of these new linkers, remains to be examined.

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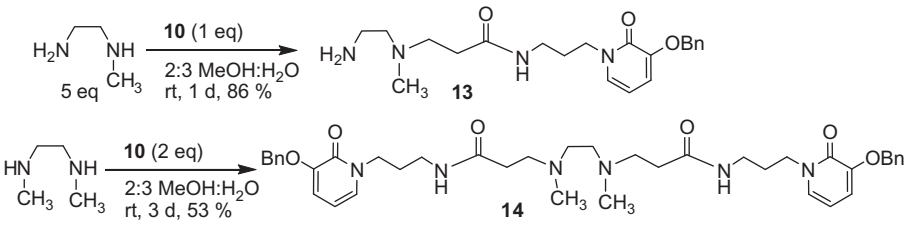
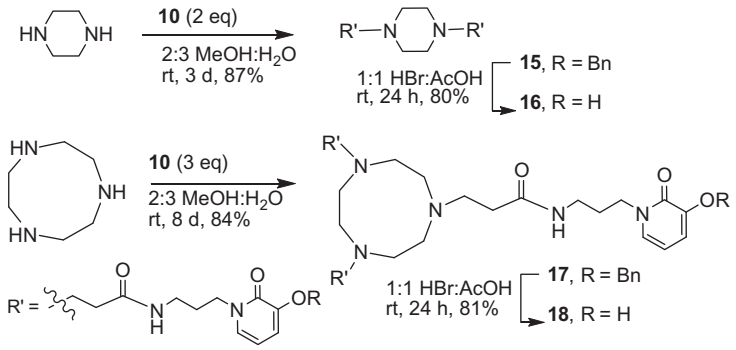


Scheme 6.



Scheme 7.

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20. *Synthesis of HOPO vinylsulfonamide* ***3***: 2-Chloroethanesulfonyl chloride (0.242 g, 1.49 mmol) was added to a solution of triethylamine (0.46 mL, 4.46 mmol) and HOPO amine **2** (0.461 g, 1.78 mmol) in dichloromethane (6 mL) at rt and the solution stirred for 5 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 1 M HCl (10 mL), saturated $NaHCO_3$ (2 × 15 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude product was purified by radial chromatography to give **3** (0.328 g, 63%) as a viscous oil: IR (neat) 3168, 1651, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.33 (m, 5H), 6.89 (dd, J = 1.4, 6.9 Hz, 1H), 6.67 (dd, J = 1.6, 7.5 Hz, 1H), 6.58 (dd, J = 8.7, 16.8 Hz, 1H), 6.19 (d, J = 16.4 Hz, 1H), 6.10 (t, J = 7.1 Hz, 1H), 6.01 (t, J = 6.4 Hz, 1H), 5.85 (d, J = 10.2 Hz, 1H), 5.12 (s, 2H), 4.13 (t, J = 6.0 Hz, 2H), 2.96 (q, J = 6.1 Hz, 2H), 1.96 (quin, J = 5.9 Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 158.4, 148.5, 136.2, 135.9, 128.8, 128.4, 127.9, 127.2, 125.6, 115.7, 105.5, 70.6, 46.1, 39.2, 29.8; Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.24; H, 5.47; N, 7.84.
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30. *Synthesis of disulfonamide* ***6***. To a solution of HOPO vinyl sulfonamide **3** (0.050 g, 0.143 mmol) in 2:3 THF/H_2O (5 mL) was added piperazine (0.006 g, 0.068 mmol) and the solution stirred at rt for 24 h. The solvent was removed in vacuo and the resulting residue was extracted into dichloromethane (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The crude product was purified by radial chromatography to give **6** (0.051 g, 94%) as a white solid: mp 46–48 °C; IR (KBr) 3435, 1650, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (quin, J = 6.1 Hz, 4H), 2.46 (br s, 8H), 2.81 (t, J = 7.0 Hz, 4H), 3.13–3.04 (m, 8H), 4.09 (t, J = 6.2 Hz, 4H), 5.09 (s, 4H), 6.10 (t, J = 7.1 Hz, 4H), 6.68 (dd, J = 1.6, 7.4 Hz, 2H), 6.91 (dd, J = 1.7, 6.8 Hz, 2H), 7.43–7.30 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.5, 39.5, 49.0, 46.2, 52.1, 52.7, 70.7, 105.4, 115.7, 127.3, 128.0, 128.5, 128.8, 136.0, 148.7, 158.5. Anal. Calcd for $C_{38}H_{50}N_6O_8S_2{\cdot}H_2O$: C, 56.98; H, 6.54; N, 10.49. Found: C, 56.95; H, 6.12; N, 10.09.
31. *Synthesis of diHOPO* ***7***. A solution of 1:1 48% HBr/AcOH (3 mL) was added to protected HOPO sulfonamide **6** (0.051 g, 0.065 mmol) and the solution stirred at rt for 18 h. The solvent was removed in vacuo. The residue was washed with $CHCl_3$ (2 × 5 mL), and EtOAc (2 × 5 mL). The washed product was dissolved in nanopure water and lyopholized to give the diHOPO **7** (0.046 g, 92%) as a white solid: mp 92–94 °C (dec); IR (KBr) 3368, 3119, 2532, 1674, 1583 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.02 (quin, J = 6.7 Hz, 4H), 3.16 (t, J = 6.7 Hz, 4H), 3.67–3.47 (m, 16H), 4.10 (t, J = 6.9 Hz, 4H), 6.39 (t, J = 7.2 Hz, 2H), 7.00 (dd, J = 1.8, 7.3 Hz, 2H), 7.19 (dd, J = 1.6, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 29.7, 40.7, 46.9, 48.2, 50.2, 51.4, 109.3, 119.4, 130.1, 146.1, 159.3. Anal. Calcd for $C_{24}H_{38}N_6O_8S_2{\cdot}3HBr{\cdot}3H_2O$: C, 32.05; H, 5.27; N, 9.34. Found: C, 31.90; H, 5.14; N, 9.32.
32. *Bis-HOPO* ***16***. Mp 105–110 °C; IR (KBr) 3251, 1645, 1613, 1557 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.60–1.73 (quin, 4H), 2.49 (t, J = 5.5 Hz, 4H), 2.81 (t, J = 6.24 Hz, 4H), 3.27 (t, J = 6.22 Hz, 4H), 3.52 (br s, 8H), 3.90 (t, J = 6.96 Hz, 4H), 6.27 (t, J = 6.96 Hz, 2H), 6.79 (d, J = 7.32 Hz, 2H), 7.14 (d, J = 6.24 Hz, 2H); ^{13}C NMR (50 MHz, D_2O) δ 27.8, 29.3, 36.22, 47.1, 48.7, 52.8, 108.9, 118.8, 129.0, 145.3, 158.2, 170.6. Anal. Calcd for $C_{26}H_{38}N_6O_6{\cdot}3HBr{\cdot}2.5H_2O$: C, 38.16; H, 5.66; N, 10.27. Found: C, 38.02; H, 5.30; N, 9.97.
33. *Tris-HOPO* ***18***. Mp 60–65 °C; IR (KBr) 3391, 1651, 1550 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.81–1.91 (m, 6H), 2.67 (t, J = 6.45 Hz, 6H), 3.13 (t, J = 6.75 Hz, 6H), 3.39–3.44 (m, 18H), 3.94 (t, J = 7.05 Hz, 6H), 6.29 (t, J = 7.32 Hz, 3H), 6.91 (dd, J = 1.77, 7.62 Hz, 3H), 7.09 (dd, J = 1.77, 7.05 Hz, 3H); ^{13}C NMR (50 MHz, D_2O) δ 27.8, 29.6, 36.5, 47.6, 49.3, 53.2, 108.4, 118.3, 129.0, 145.3, 158.1, 172.7. Anal. Calcd for $C_{39}H_{57}N_9O{\cdot}5HBr$: C, 39.02; H, 5.21; N, 10.50. Found: C, 39.18; H, 5.44; N, 10.32.