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Structural parameters of Zn(II) complexes of 8-hydroxyquinoline-based tripodal ligands affect fluorescence quantum yield

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ABSTRACT

Tripodal ligands containing 8-hydroxyquinoline moieties have been reported with strong binding but perplexing fluorescence properties. Herein we describe the synthesis, photophysical properties and structural characterization of three 8-hydroxyquinoline-based fluorescent Zn(II) probes. Incorporation of the chromophore into a tripodal scaffold resulted in femtomolar sensitivity to the analyte. All three ligands were determined to bind Zn(II) in a 1:1 metal–ligand stoichiometry. Strong zinc affinity was complemented by more than 10-fold fluorescence turn-on. An X-ray crystallographic study revealed very different ligand geometries in the zinc complexes that may influence their spectroscopic behavior.

1. Introduction

Development of novel analytical tools for studying biological functions of zinc has been a focus of many research groups during the past decade. This work has yielded a variety of sensors that have already proven to be valuable tools in addition to the classical fluorescent zinc reporter, TSQ [1]. In particular, fluorescein-based ligands have been utilized to study synaptically released Zn^{2+} in hippocampal specimens [2]. Ratiometric imaging on the cellular level has been performed using compounds containing benzoxazole and benzimidazole reporter groups [3], as well as fluorescently labeled carbonic anhydrase-based biosensors [4]. Many of the recently developed zinc imaging tools have been aimed at studying neurobiology of this otherwise spectroscopically silent metal. Hence, the majority of the sensors reported have zinc affinities that fall within subnanomolar to millimolar range, which is relevant to this field. Stronger zinc chelators are far less common. Nevertheless, several reports describe cellular systems in which Zn(II) regulation occurs on a sub-picomolar level, requiring more sensitive probes [4,5].

Previous work from this and other laboratories described the use of tripodal N_4-ligands as chelation enhanced fluorescent chemosensors for Zn^{2+} [6] and other ions. The reported compounds were structurally related to the ligand tris(2-pyridylmethyl)amine (TPA) which is known for strong binding of divalent metal ions [7]. Compounds **1**, **2** and **3**, shown in Scheme 1, contain this same ligand scaffold structure, except that either one or two arms have been modified to contain the elements of 8-hydroxyquinaldine (8-HQ), a well known chromophore and an established analytical tool for zinc chelation. The ligand 8-HQ is a classic chelating agent used for a variety of purposes [8]. It forms a 2:1 ligand–Zn(II) complex with binding affinity of $\log\beta_2 = 16.76$ ($\log K_1 = 8.66$, $\log K_2 = 8.1$) [9]. However, the geometry of binding shown by 2:1 8-HQ:Zn(II) complexes is quite different from that shown by 1:1 TPA:Zn(II) complexes.

Part of the interest in these particular compounds relates to behavior described in earlier studies. We published a preliminary report finding compound **3** to show good fluorescence enhancement upon Zn^{2+} chelation [10]. Compound **2** was prepared by Aoki et al. [11] and found to be quenched by Zn^{2+} under different conditions. A compound similar to **2** (lacking the sulfonamide substituent) was shown by Xue et al. [12] to be unresponsive to Zn. Therefore, we report here new compound **1** alongside structural and optical characterization of compounds **2** and **3** in an effort to gain insight into the confusing behavior of these probes.

2. Experimental

2.1. Reagents and methods

All solvents and reagents were purchased from commercial sources and used as received. Solvents used for spectroscopic measurements were HPLC grade. UV–Vis spectra were acquired on an Agilent 8453 UV–Vis spectrometer. NMR spectra were obtained on Bruker AVANCE 400 MHz spectrometers. Mass spectra were recorded on Agilent 1100 Series LC-MSD VL MS spectrometer. Melt-

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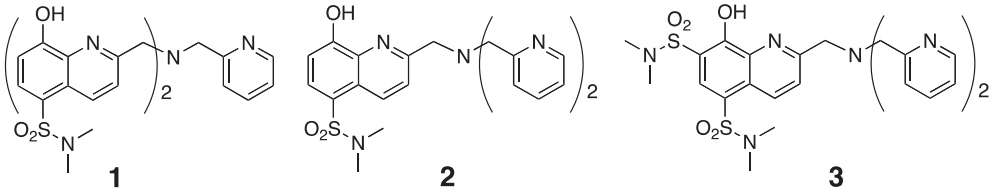

Scheme 1. Fluorescent ligands described in this paper.

ing points were taken in open tubes in a MelTemp II capillary melting point apparatus. Elemental analysis was performed by Quantitative Technologies, Inc. (Whitehouse, NJ). X-ray structures were determined at the X-ray crystallography laboratory, University of Minnesota (Minneapolis, MN).

2.2. Synthesis of the complexes

2.2.1. Synthesis of 8-methoxymethoxy-2-methyl-quinoline-5-(N,N-dimethyl)sulfonamide (**6**)

Compound **5** (3.65 g, 13.7 mmol) [13] was combined with K_2CO_3 (5.68 g, 41.12 mmol) in dry DMF (40 mL) and stirred at room temperature under argon for 1 h. The mixture was cooled to 0 °C and chloromethylmethyl ether (3.31 g, 41.12 mmol) was added dropwise. The reaction mixture was stirred for 4 h at 0 °C under argon. The reaction was quenched by addition of water (5 mL). The solvent was evaporated under high vacuum and the crude product was partitioned between H_2O (50 mL) and CH_2Cl_2 (3 × 100 mL). The organic fractions were combined and concentrated. The title product was obtained by silica column chromatography. The product was eluted using a 1:1 mixture of EtOAc and hexanes. R_f = 0.21 (silica, 1:1 EtOAc/hexanes). The title product is a light yellow solid. Yield = 2.7 g (64%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.96 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 5.56 (s, 2H), 3.58 (s, 3H), 2.80 (s, 3H), 2.76 (s, 6H). GCMS calc. for [M+H$^+$] 311.1, found 311. *Anal.* Calc. for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85; N, 9.03. Found: C, 54.14; H, 5.72; N, 8.95%.

2.2.2. Synthesis of 8-methoxymethoxy-quinoline-5-(N,N-dimethyl)sulfonamide-2-carbaldehyde (**7**)

Anhydrous 1,4-dioxane (40 mL) was added to **6** (1.2 g, 3.87 mmol), SeO_2 (0.43 g, 3.87 mmol) and crushed molecular sieves (2 g). The reaction mixture was refluxed for 3 h under argon. The solution turned deep red and then black. After 3 h, the solution was cooled to room temperature and filtered through a bed of Celite. The Celite was washed with 1,4-dioxane (80 mL). The solvent was evaporated and the crude product was redissolved in CH_2Cl_2 (200 mL). This solution was washed with brine (25 mL) and water (25 mL) and dried with Na_2SO_4. CH_2Cl_2 was evaporated under reduced pressure. The title product was obtained by silica column chromatography (EtOAc:hexanes in a 1:1 ratio). R_f = 0.38 (silica, 1:1 EtOAc/hexanes). The pure product is a yellow oil. Yield = 0.752 g (60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.29 (s, 1H), 9.24 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 5.61 (s, 2H), 3.61 (s, 3H), 2.80 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.04, 157.94, 151.64, 140.19, 135.37, 134.39, 128.11, 125.33, 119.09, 110.68, 95.50, 57.01, 37.39. ESI-MS: calc. for [M + H$^+$] 325.08, found 325.3. *Anal.* Calc. for $C_{14}H_{16}N_2O_5S$: C, 51.84; H, 4.97; N, 8.64. Found: C, 51.77; H, 4.84; N, 8.54%.

2.2.3. Synthesis of 8-methoxymethoxy-quinoline-5-(N,N-dimethyl)sulfonamide-2-methanol (8)

Compound **7** (0.7 g, 2.15 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2:EtOH (8 mL of each) and cooled to 0 °C. Meanwhile, $NaBH_4$ (81.2 mg, 2.15 mmol) was dissolved in absolute EtOH (8 mL). The $NaBH_4$ solution was added dropwise and the resulting mixture was stirred at 0 °C for 10 min. The reaction was quenched by the addition of water (5 mL). The reaction mixture was diluted with ethyl ether (100 mL) and washed twice with water (30 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The title product was obtained by silica column chromatography (CH_2Cl_2:MeOH in a 95:5 ratio). R_f = 0.45 (silica, 95:5 CH_2Cl_2/MeOH). The title product is a light yellow solid. Yield = 0.66 g (93%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.11 (d, J = 8.7 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 5.52 (s, 2H), 4.99 (s, 2H), 3.60 (s, 3H), 2.79 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.20, 156.83, 139.12, 134.52, 131.52, 125.49, 124.81, 120.37, 110.31, 95.19, 64.47, 56.78, 37.35. ESI-MS: calc. for [M+H$^+$] 327.09, found 327.2. *Anal.* Calc. for $C_{14}H_{18}N_2O_5S$ + 0.5 EtOAc: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.99; H, 5.75; N, 7.62%.

2.2.4. Synthesis of 2-bromomethyl-8-methoxymethoxy-quinoline-5-(N,N-dimethyl)sulfonamide (**9**)

Anhydrous CH_2Cl_2 (10 mL) was added to NBS (0.409 g, 2.3 mmol) and cooled to 0 °C under argon. Dimethyl sulfide (202 μL, 2.76 mmol) was added dropwise. After stirring for 10 min. at 0 °C the solution became milky white. The solution was cooled to −15 °C and **8** (0.5 g, 1.53 mmol), dissolved in anhydrous CH_2Cl_2 (5 mL), was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 4 h. The reaction mixture was diluted with ethyl ether (100 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over K_2CO_3 and concentrated under reduced pressure. The title product was obtained by silica column chromatography (EtOAc:hexanes in a 1:1 ratio). R_f = 0.4 (silica, 1:1 EtOAc/hexanes). The title product is a brown solid. Yield = 0.334 g (56%). ^{1}H NMR ($CDCl_3$) δ 9.1 (d, J = 8.9 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 5.59 (s, 2H), 4.79 (s, 2H), 3.6 (s, 3H), 2.81 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 157.08, 156.62, 139.93, 134.89, 132.12, 125.21, 124.7, 123.12, 110.48, 95.28, 56.8, 37.31, 33.97. MALDI: calc. for [M+H$^+$] 389.01 and 391.01, found 389 and 291. *Anal.* Calc. for $C_{14}H_{17}BrN_2O_4S$ + 1/3CH_3CN: C, 43.72; H, 4.50; N, 8.11. Found: C, 43.79; H, 4.21; N, 7.80%.

2.2.5. Synthesis of N,N′-Bis-(8-hydroxyquinoline-5-(N,N-dimethyl)sulfonamide-2-methyl)-pyridin-2-ylmethyl-amine (**1**)

Compound **9** (0.52 g, 1.34 mmol) was added to sodium bicarbonate (0.561 g, 6.68 mmol) in dry DMF under argon. The mixture was cooled to 0 °C and 2-aminomethyl pyridine (0.048 g, 0.445 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 10 h. The DMF was evaporated under high vacuum and the product was redissolved in EtOAc (100 mL) and washed with H_2O (25 mL). The title product was obtained by silica column chromatography (CH_3Cl:MeOH in a 98:2 ratio). R_f = 0.23 (silica, 95:5 CH_2Cl_2/MeOH). The title product is a light green solid. Yield = 0.29 g (30.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 8.97 Hz, 2H), 8.38 (d, J = 9.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 5.1 Hz, 1H), 7.71(t, J = 9.2 Hz, 1H), 7.38 (d,