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Fluorescence of some tri- and tetra-dentate pyrazol-derived stable ligands

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Abstract A new class of tripodal N-ligands have been prepared under mild conditions by reaction of *N*-hydroxymethyl-3,5-dimethylpyrazole with 2-furylmethylamine; 2-pyridylmethylamine; 4-nitrobenzaldehyde hydrazone and (E)-1-((anthracen-9-yl)methylene)hydrazine in a double equimolar ratio (2:1). The tripodal ligands were characterized by IR, ^{1}H-, and ^{13}C-NMR, microanalysis, and mass spectrometry. The fluorescence properties of the ligands were analyzed.

Keywords Tripodal N-ligands · Substituted hydrazones · Pyrazol · Fluorescence

Introduction

Metal complexes with suitable fluorescent ligands are useful models for various medicinal applications, i.e., analysis, imaging and detection. Interest in designing and using chelators as anti-tumor agents has grown with the evidence that cancer cells generally require more copper and iron for their growth and metabolism than normal resting cells [1–3]. Studies on desferrioxamine (DFO), a hexadentate chelator, have recognized its potential for the treatment of iron overload and, in turn, for retarding tumor growth [2]. However, its short plasma half-life and poor oral activity limits its usefulness and has led to the exploration of new chelators. Several

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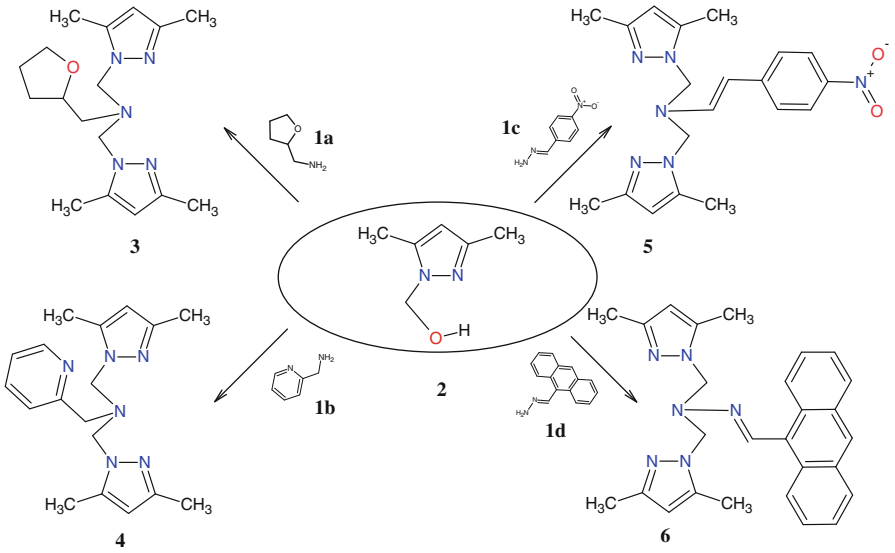

Scheme 1 Synthesis of armed tripodal N-ligands **3–6**

classes of promising bi- and tridentate molecules have been developed, including desferrithicin derivatives, *O*-trensox, thiosemicarbazones, hydroxypyridinones, and bis-hydroxyphenyltriazoles [4]. Tridentate chelators in general have been more effective than bidentate chelators due to their higher metal binding affinity [5]. A major problem lies with the toxicity of many of the compounds.

Polydentate pyrazol compounds are well-known ligands for transition metal ions in the building of polynuclear complexes as models for bioinorganic systems [6, 7] as well as for the discovery of new catalyst precursors [8]. We are currently studying the synthesis and coordination of tridentate nitrogen ligands, such as *N*,*N*-bis-[(3,5-dimethyl-1-pyrazolyl)methyl]alkylamines [9, 10]. There is now current interest to gain insight into the coordination behavior of larger ligand systems containing multiple pyrazol nitrogen-coordinating sites and a delocalized π-conjugated spacer such as an aryldiammine.

In continuation of our previous study [9, 11], we report in the present study on the synthesis of a class of polydentate ligands containing two pyrazol rings leading a functionalized chelating group or a fluorophore with the general topology shown in Scheme 1. We therefore describe here for the first time two new fluorescent tridentate compounds.

Results and discussion

On the basis of our initial study for the synthesis of tripodal N-ligands [9, 11], the new polydentate ligands **3–6** were prepared by reaction of (3,5-dimethyl-1*H*-pyrazol-1-yl)methanol **2** with 2-tetrahydrofurylmethylamine **1a** or 2-pyridylmethylamine **1b**, 4-nitrobenzaldehyde hydrazone **1c** and (E)-1-(anthracen-9-yl)methylene)hydrazone

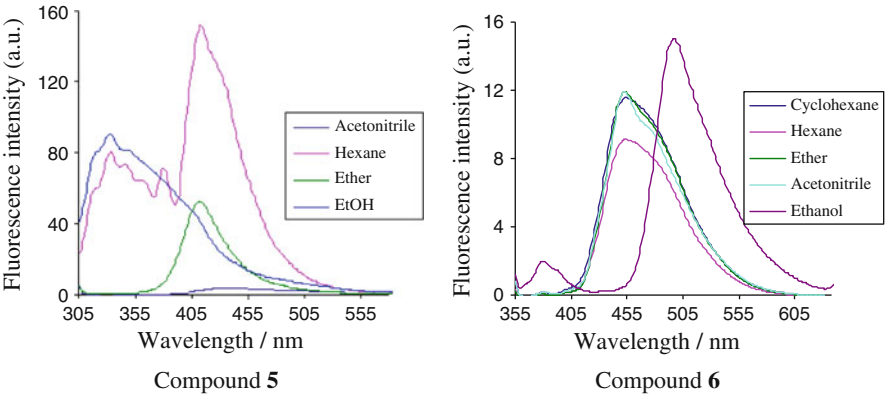

Fig. 1 Fluorescence spectra of compound (**5** and **6**) (10^{-5} M) in the presence of various solvents with an excitation of 250 and 350 nm, respectively

1d, respectively, under mild conditions (room temperature), using anhydrous acetonitrile as solvent (Scheme 1).

The initial reaction of aldehyde precursor with hydrazine in CH_2Cl_2/ethanol mixture at room temperature produced hydrazone derivatives **1c** and **1d**. The compounds **3**–**6** were isolated after 5 days of stirring at room temperature in good yield. The condensation reaction is very slow but very selective at room temperature, and, after 4–5 days of stirring at room temperature, the derivatives **3**–**6** were isolated.

Compounds **5** and **6**, containing an extended delocalized π-system, are able to exhibit fluorescence properties. In contrast, the fluorescence is inhibited in **3** and **4** when the central aromatic part is replaced by a tetrahydrofuran-2-yl-methyl or 2-pyridin-methyl group, respectively. Representative emission spectra for **5** and **6** are reported in Fig. 1.

The two compounds exhibit the same absorption profile: intense and structured bands between 400 and 500 nm. The molecular absorption coefficients are quite large and the bathochromic shift is consistent with a better delocalization in the π-conjugated system of **5** as compared to **6**. Luminescence is observed for both compounds; modification of the substituents (anthracenyl vs. 4-nitrophenyl) only induces a modulation of the quantum yield efficiency. Thus, the two tridentate ligands **5** and **6**, better described by their hydrazinium limit, form similar extended p-conjugated systems as they present similar absorption and fluorescence properties (Fig. 2).

Conclusion

The synthesis of new fluorescent tridentate compounds **5** and **6** is relatively flexible and clean. Their synthesis from aromatic aldehydes could certainly be generalized for the access of a variety of π-conjugated aromatic amines and hydrazones.

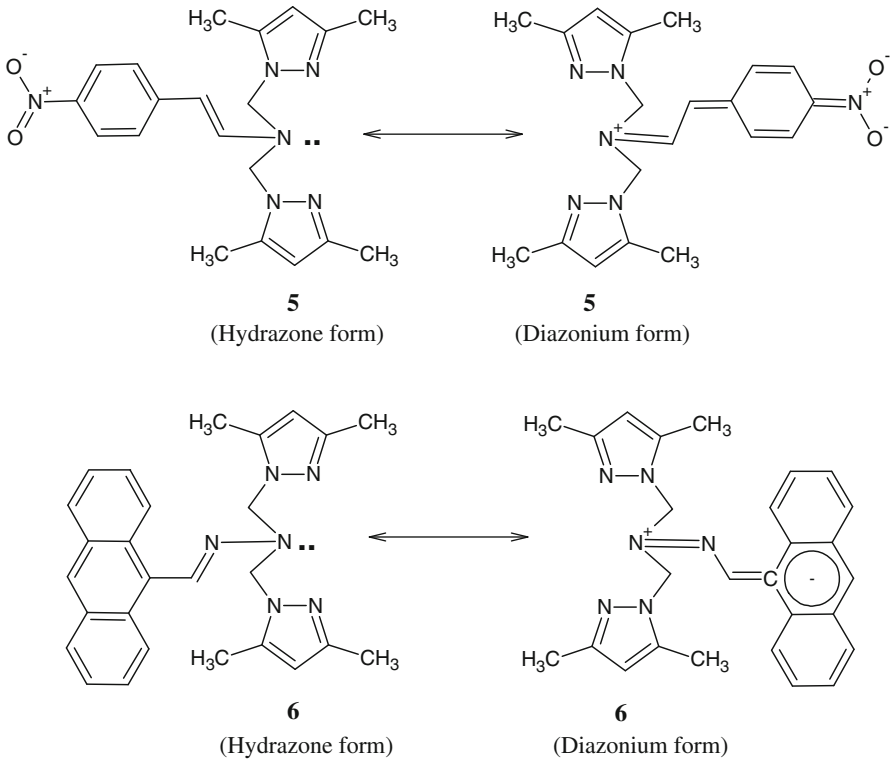

Fig. 2 Delocalized pi-system in the case of ligands **5** and **6**

Experimental

General methods

Infrared spectra were recorded on a PYE Unicam SP3-300 spectrometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (250 MHz) using TMS as internal standard. Chemical shifts are reported downfield from the standard in ppm. The FAB mass spectra were obtained on a NERMANG R10-LOC instrument. For the chemical ionization (DCI/NH_3/CH_3), the compounds were dissolved in DMSO or MeOH and dispersed in a matrix solution, currently 3-nitrobenzyl (MNBA) or glycerol (GLY). Elemental analyses were performed by the Service Central d'Analyse du CNRS LCC (Toulouse). Fluorescence experiments were performed in dilute organic solvents (ca. 10^{-5} mol l^{-1}) using a PTI spectrometer. Fluorescence quantum yields were measured on non-degassed samples at room temperature. A solution of quinine sulfate in H_2SO_4 was used as the standard for the quantum yield measurement ($\phi = 0.546$ for $\lambda = 365$ nm). Refraction index has been performed.

Synthesis of compounds (**1a**–**1d**)

Chemicals were purchased from commercial sources and used as received with the exception of MeCN, which was distilled over CaH_2. Starting compounds **1c** and **1d** were prepared according to routine literature procedures. Reactions were monitored by thin-layer chromatography, using aluminum sheets coated with silica.

*4-Nitrobenzaldehyde hydrazone (**1c**)*

p-Nitobenzaldehyde **1** (4.1 g, 82 mmol) dissolved in a mixture of solvents (50 mL of dichloromethane and 20 mL of ethanol) was added dropwise to hydrazine (NH_2–NH_2) (4.1 g, 26 mmol) in ethanol (25 mL) at room temperature. The mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure. The recrystallization in hexane/dichloromethane (1/3) of the residue afforded a yellow product of **1c** (4 g) in good yield (91 %).

Melting point: 120–122 °C. TLC: Rf = 0.21 (Silica; dichloromethane/hexane, 1/2). IR (KBr) cm^{-1}: 3,423, 3,301, 3,066, 1,629, 1,594, 1,576, 1,502, 1,401, 1,317, 1,236, 1,171. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.5–7.5 (2 dd, 5H, Ph + C<u>H</u>=N); 5.9 (s, 2H, NH_2). ^{13}C NMR (250 MHz, $CDCl_3$) δ ppm: 147.37, 141.57, 139.01, 130.73, 129.42, 128.71, 126.36, 124.02, 111.66. MS (*m/z*): 165 ($[M]^{+\cdot}$, 100 %). Elemental analysis: calculated for $C_7H_7N_3O_2$: C, 50.91 %; H, 4.27 %; N, 25.44 %. Found: C, 50.71 %; H, 4.32 %; N, 25.37 %.

*(E)-1-((anthracen-9-yl)methylene)hydrazine (**1d**)*

Anthracene-9-carbaldehyde **5** (1 g, 4.85 mmol) was dissolved in a mixture of solvents (20 mL of dichloromethane and 10 mL of ethanol) and then hydrazine (NH_2–NH_2) (1 g, 20 mmol) was added dropwise at room temperature. The mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure. The recrystallization in hexane/dichloromethane (1/3) of the residue offered a yellow product in good yield (0.80 g, 80 %).

Melting point: 122–124 °C. TLC: Rf = 0.31 (Silica; ether/hexane, 3/2). IR (KBr, υ cm^{-1}): 3,368 (NH), 1,640, 1,520, 1,440, 900, 700, 650. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.5–7.8 (m, 10 H, anthracenyl + C<u>H</u>=N); 5.6 (s, 2H, NH_2). ^{13}C NMR (300 MHz, $CDCl_3$) d = 140.92, 138.90, 131.69, 129.99, 129.14, 128.94, 128.83, 128.29, 128.17, 126.74, 126.27, 125.70, 125.35, 125.31, 125.17. MS (*m/z*): 220.1 ($[M]^+$); 204.3 ($[M–NH_2]^+$); 203 ($[A_9–CN]^+$); 177 ($[A_9]^+$); 176 $[M–HCN]^+$). Elemental analysis: calculated for $C_{15}H_{12}N_2$: C, 81.79 %; H, 5.49 %; N, 12.72 %. Found: C, 81.86 %; H, 5.38 %; N, 12.64 %.

*General procedure for the synthesis of compounds **3** and **4***

The products were prepared by the addition of appropriate amine 2-C_4H_7O–CH_2–NH_2 (**1a**), and 2-C_5H_5N–CH_2–NH_2 (**1b**) to 1-(hydroxymethyl)-3,5-dimethyl pyrazole (**1**). Then, a solution of the substituted **1** (1.01 g, 8 mmol) in acetonitrile (30 mL) was added to the desired amine (4.5 mmol) and the mixture continued to

be stirred at room temperature for 4–5 days. The formed compound was precipitated by addition of cold water to acetonitrile solution, washed with hexane and dried under vacuum. Compounds **3** and **4** were obtained as white solids (65–91 % yield).

*N,N-bis[(3,5-dimethyl-1H-pyrazol-1-yl)methyl](tetrahydro-2-furanyl)methanamine **(3)*** Yellow oil. Yield (75 %). Melting point and TLC: Rf (not determined). IR (KBr, υ cm^{-1}): 2,921, 2,866, 1,555, 1,457, 1,421, 1,377. ^{1}H NMR: ($CDCl_3$; 300 - MHz) (δ ppm): 5.65 (s. 2H, pyrazol); 4.80 (s, 4H, $2NCH_2N$); 3.60 (m, 2H, CHC-$\underline{H_2}N$); 2.60 (s, 6H, $2CH_3$); 2.15 (s, 6H, $2CH_3$); 1.60 (m, 2H, C_4H_7O–); 1.15 (m, 2H, C_4H_7O–). ^{13}C NMR ($CDCl_3$; 250 MHz) δ ppm: 9.11, 11.81, 23.69, 27.52, 50.87, 64.43, 66.29, 76.27, 104.00, 138.22, 145.56. SM (IC): $[M]^+ = 317$, 302, 258, 246, 222, 205, 179, 150, 138, 125, 109 (100 %), 96.

*N,N-bis[(3,5-dimethyl-1H-pyrazol-1-yl)methyl](2-pyridinyl)methanamine **(4)*** Yield (63 %). Melting point: 60–62 °C. IR (KBr, υ cm^{-1}): 3,464, 3,114, 2,920, 1,665, 1,590, 1,570, 1,551, 1,473, 1,451. ^{1}HNMR: ($CDCl_3$; 250 MHz) δ ppm: 8.50 (m, 1H, C_5H_4N); 7.51 (m, 2H, C_5H_4N–); 7.25 (m, 1H, C_5H_4N–); 5.75 (s. 2H, pyrazol); 4.95 (s, 4H, $2NCH_2N$); 3.85 (s, 2H, C_5H_4N–$C\underline{H_2}N$); 2.60 (s, 6H, $2CH_3$); 2.15 (s, 6H, $2CH_3$). SM: $(M)^+ = 324$, 277, 258, 246, 228, 133, 121, 109 (100 %), 93, 80. ^{13}C NMR ($CDCl_3$; 250 MHz) δ (ppm): 158.59, 148.81, 147.61, 139.93, 136.43, 123.10, 122.07, 105.70, 64.99, 54.60, 13.47, 10.6 0. SM (IC): $[M]^+ = 324$, 109 (100 %). Elemental analysis: calculated for $C_{18}H_{24}N_6$: C, 66.64 %; H, 7.46 %; N, 25.90 %. Found: C, 65.16 %; H, 7.25 %; N, 23.94 %.

*General procedure for the synthesis of **5** and **6***

The products **5** and **6** were prepared by the addition of appropriate hydrazone 4-nitro-C_6H_4–CH=N–NH_2 (**1c**), or 9-$C_{14}H_9$–CH=N–NH_2 (**1d**) to *N*-hydroxymethyl-3,5-dimethyl-pyrazole **1**. To a solution of the substituted **1** (3.1 g, 25 mmol) in acetonitrile (60 mL) was added the desired hydrazone (4.5 mmol) and the mixture continued to be stirred at room temperature for 36 h. The formed compound was precipitated by addition of cold water to acetonitrile solution, washed with hexane and dried under vacuum. Compounds **5** and **6** were obtained as white solids (64–76 % yield).

*4-nitrobenzaldehyde bis[(3,5-dimethyl-1H-pyrazol-1-yl)methyl]hydrazone **(5)*** Yield (64 %). Melting point: 160–163 °C. TLC: Rf = 0.20 (silica; ether/hexane, 2/3). IR (KBr) υ cm^{-1}: 2,923, 1,597, 1,557, 1,516, 1,462, 1,421, 1,380, 1,337, 1,309, 1,249, 1,179. ^{1}H NMR (250 MHz, $CDCl_3$) d: 8.5–7.8 (m, 5 H, Ph + CH=N); 5.9 (s, 2 H, 2(=CH) of pyrazol); 5.7 (s, 4H, $2CH_2$–); 2.4 (s, 6H, $2CH_3$); 2.2 (s, 6H, $2CH_3$). ^{13}C NMR (250 MHz, $CDCl_3$) δ ppm: 148.4, 147.1, 142.3,140,135.42, 126.40, 123.92, 106.44, 65.96, 13.50, 11.25. MS (*m/z*): 381 ($[M]^+$); 286 ($[M-Pz]^+$); 272 ($[M-H_2C$–$Py]^+$); 232 $[(Pz-CH_2)_2$–$N]^+$); 147 $[O_2N$–Ph–CH=N–$H_2]^+$); 122 ($[O_2N$–$Ph]^+$); 176 ($[A_9$–$H_2]^+$); 96 ($[Pz]^+$). Elemental analysis: calculated for $C_{19}H_{23}N_7O_2$: C, 59.83 %; H, 6.08 %; N, 25.71 %. Found: C, 59.72 %; H, 6.17 %; N, 25.64 %.

1,4-dihydro-9-anthracenecarbaldehyde-bis[(3,5-dimethyl-1H-pyrazol-1-yl)meth-yl]hydrazone ***(6)*** Yield (76 %). Melting point: 156–158 °C. TLC: Rf = 0.30 (Silica; dichloromethane/hexane, 3/2). IR (KBr, υ cm^{-1}): 3,048, 2,955, 2,917, 1,677, 1,623, 1,591, 1,553, 1,520, 1,457, 1,419, 1,384, 1,369, 1,330. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.3 (s, 1H,–C<u>H</u>=N); 7.8–8.5 (m, 9H, Aromatic proton); 5.9 (s, 2 H, 2(=CH) pyrazol); 5.8 (s, 4 H, 2 NCH_2–N); 2.4 (s, 6 H, $2CH_3$); 2.3 (s, 6 H, $2CH_3$). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 148.32 (<u>C</u>=N); 140.21, 138.36, 131.5, 129.94, 128.56, 128.28, 127.82, 125.88, 125.69, 125.08, 106.12, 77.49, 77.07, 76.64, 66.38, 13.60, 11.40. MS (*m/z*): 460.5 ($[MH+Na]^{+\cdot}$, 30 %); 459.5 ($[M+Na]^{+\cdot}$, 100 %); 341.5 ($[M-Pz]^{+}$); 109.0 ($[Pz–CH_2]^{+}$). Elemental analysis: calculated for $C_{27}H_{28}N_6$: C, 74.28 %; H, 6.46 %; N, 19.25 %. Found: C, 74.12 %; H, 6.48 %; N, 19.34 %.

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