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Development of Dpa-based imidazole zinc anion receptors

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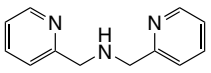
Abstract—A synthetic route for a new, phenolic Dpa-based aza ligand is presented and its chelation with zinc ions and imidazole were studied using UV/vis and mass spectrometry. A bathochromic shift of 30 nm was observed for the 2*Zn complex of the ligand in UV/vis zinc titration experiments. The mass spectrum indicated formation of an imidazole anion zinc chelate complex.

Di-(2-picolyl)amines (Dpa) **1** are well-known tridentate ligands capable of donating three electron pairs to a cationic metal centre. The Dpa geometry and its conformational flexibility gives this ligand a strong affinity for biologically interesting Zn^{2+} and Cu^{2+} ions, while the tridentate amine-metal chelation still leaves anionic coordination places free for counter ions. It has been recently demonstrated that bimetallic phenol-bridged double Dpa chelates can function in molecular recognition of anionic species, for example, phosphate,[1] pyrophosphate[2] or phospholipid[3] anions.

During our research on sequence directed protein recognition, we required access to new chromophoric ligand



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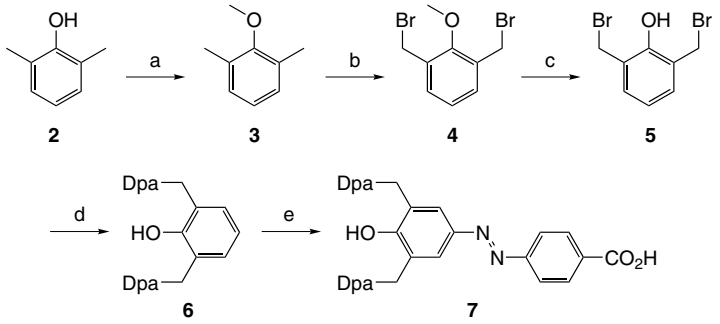
structures that can bind two zinc ions to form a receptor for imidazole anion coordination. Herein we report the synthesis of a new Dpa aza chelate and demonstrate the formation of a coordination complex with zinc ions and imidazole as evidenced by mass spectrometry.

The synthesis of **7** is illustrated in Scheme 1. Phenol **2** was etherified with methyl iodide and product **3**[4] was then brominated under Wohl–Ziegler conditions.[5,6] Demethylation of **4** with boron tribromide afforded **5**.[7]



Scheme 1. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 72 h, 88%; (b) NBS, AIBN, CCl_4, reflux, 2 h, 43%; (c) BBr_3, CH_2Cl_2, −78 °C → rt, 3 h, 89%; (d) Dpa, K_2CO_3, DMF, rt, 51%; (e) NaOH, *p*-aminobenzoic acid, HCl, $NaNO_2$, 0 °C, 34%.

Keywords: Dpa; Zinc; Chelation.
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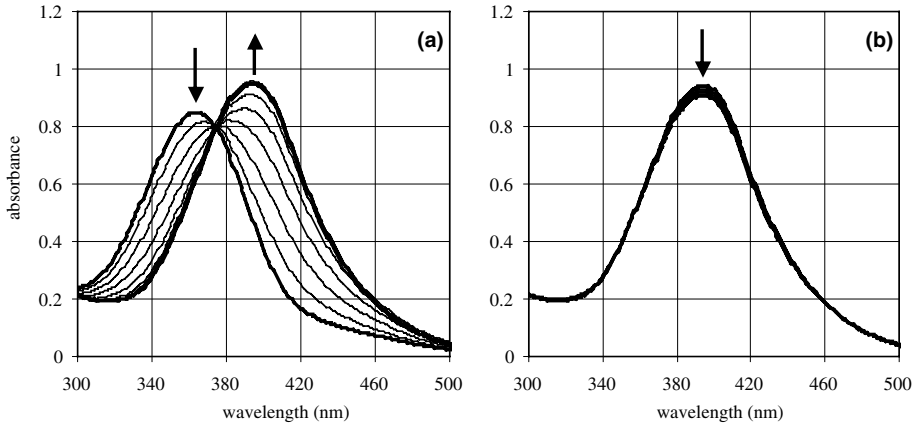

Figure 1. UV/vis spectra of the titration measurements. (a) Titration of the zinc acetate to chelate **7** solution (0.1 μM solution in MeOH). (b) Titration of the imidazole to 2Zn-chelate **7**-complex (0.1 μM solution in MeOH). In both cases titration was performed in 0.1 equiv steps from 0 to 1 equiv.

Substitution of the bromines with Dpa under basic conditions gave **6** in 51% yield after chromatographic purification.[8] Due to the strong chelation tendency of the Dpa substituted molecules their chromatographic purification was tedious leading to modest yields. To conclude the synthesis of **7**, *para*-amino benzoic acid was first treated with hydrochloric acid and sodium nitrite to convert the amino group to a diazonium function, which was then reacted with phenol **6** in water under basic conditions to give the target **7**.[9] Compound **7** was obtained in its zwitterionic form and purified with reverse-phase chromatography.

The ability of compound **7** to chelate zinc ions and further, an imidazole, was monitored by UV/vis spectroscopy. The UV/vis spectrum showed that the absorption wavelength shifted 30 nm from 367 nm to 397 nm when zinc ions were chelated with the ligand **7** (Fig. 1a). Subsequent zinc chelate titration with imidazole caused only some lowering of the absorbance (Fig. 1b). The UV/vis titration measurements indicated that **7** strongly chelates zinc ions, but zinc complex coordination with imidazole was only moderately visible.

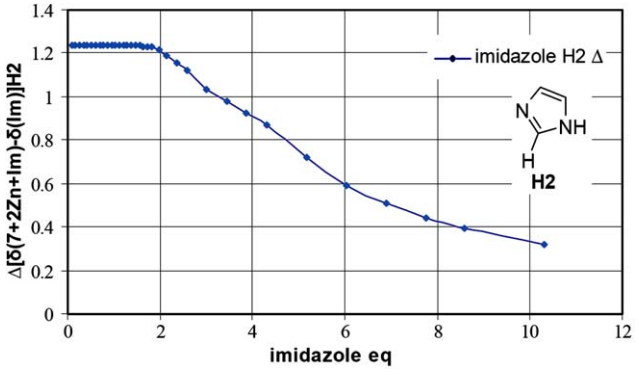

Figure 2. The ^{1}H NMR titration curve of 2*Zn(NO_3)$_2$ chelate **7** titrated against imidazole in CD_3OD (♦). The monitored δH-value belongs to the imidazole proton H2. The calculated curve $\Delta[\delta(7+2Zn+Im) - \delta(Im)]H2$ shows the difference between chelated and free imidazole (7.67 ppm).

Because the imidazole UV/vis titration experiments did not give explicit data on complexation phenomenon, the 2Zn-chelate **7** was additionally titrated against imidazole whilst monitoring the imidazole H2 chemical shift in the ^{1}H NMR (Fig. 2). The 2Zn **7** chelate caused a 1.24 downfield shift compared to free imidazole. The shift was constant up to 2 equiv of imidazole, which implies that imidazoles are strongly complexed. A distinctive feature was that upon titration continual precipitation was observed in the range of 1.0–2.0 equiv of imidazole addition. This suggests salt formation with the acid group and, on the other hand, implies that imidazole is first complexed with 2Zn ligand. Dapporto et al. earlier reported a ^{1}H NMR imidazole the 2Zn chelate complexation study for a phenolic amine ligand.[10] The observed imidazole H2 downfield shift was 0.7 ppm for 1:1 imidazole ligand systems (2Zn) measured in CD_3OD.

The positive ionisation electrospray mass spectrum of the UV/vis sample shows that an imidazole anion-zinc-chelate **7**-complex (Im^-•2Zn•**7**-complex) was formed (Fig. 3). The observed mass pattern of 881, 883 and 885 is characteristic for double zinc chelate isotopes. The main peak (883) fits perfectly for the combined mass of the Im^-•2Zn•**7**Na^+ cluster. It is also worth noting that unchelated and zinc chelated ions were not detected. The mass peak at 951 most likely arises from a molecular cluster involving acid salt formation with a second imidazole (Im^-•2Zn•**7**•Im•Na^+).

In conclusion, a rapid synthesis of the di-Dpa phenol ligand **7** has been achieved. Ligand **7** forms a strong zinc chelate, capable of significant imidazole binding as measured by UV/vis spectroscopy and mass spectrometry. The synthesis and development of improved chromo- and fluorophoric Dpa chelates as well as dynamic NMR and molecular modelling studies of the complexes are currently underway.

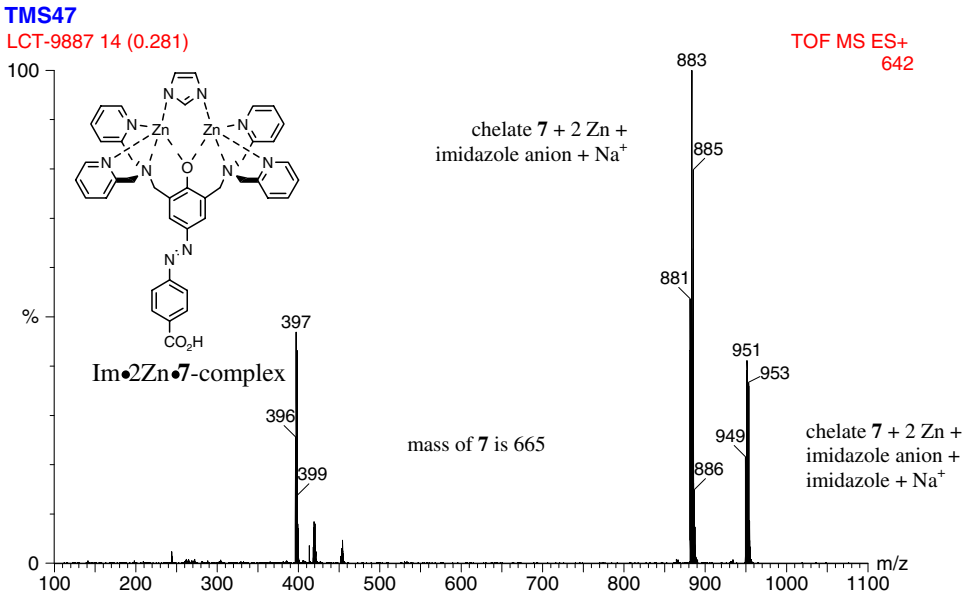

Figure 3. The mass spectrum of the Im•2Zn•7-complex.

Acknowledgements

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References and notes

1. Ojida, A.; Mito-oka, Y.; Sada, K.; Hamachi, I. *J. Am. Chem. Soc.* **2004**, *126*, 2454.
2. Lee, D. H.; Im, J. H.; Son, S. U.; Chung, Y. K.; Hong, J.-I. *J. Am. Chem. Soc.* **2003**, *125*, 7752.
3. Jiang, H.; O'Neil, E. J.; DiVittorio, K. M.; Smith, B. D. *Org. Lett.* **2005**, *7*, 3113.
4. Data for compound **3**: 2,6-dimethylphenol (8.00 g, 65.5 mmol, 100 mol %) was dissolved in acetone (100 mL) and MeI (28.0 g, 200 mmol, 305 mol %) and K_2CO_3 (18.5 g, 134 mmol, 204 mol %) were added to the solution. The reaction mixture was refluxed for three days and then the solvent was evaporated in vacuo. The residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$ (3×100 mL), brine (3×100 mL) and dried (Na_2SO_4). The solvent was evaporated giving 7.75 g (88%) of the product. R_f 0.52 (10:1 cyclohexane/EtOAc).
5. Togo, H.; Hirai, T. *Synlett* **2003**, *5*, 702.
6. Data for compound **4**: 2,6-dimethylmethoxybenzene (3.07 g, 22.5 mmol, 100 mol %) and NBS (8.24 g, 46.4 mmol, 206 mol %) were dissolved in CCl_4 (30 mL) and a few crystals of AIBN were added. The mixture was heated (+85 °C) and a few more AIBN crystals were added. After refluxing (2 h) the colour changed from yellow to white and the solution was cooled to rt. The resulting solid was filtered and the solvent evaporated in vacuo. The crude product (6.33 g, 96%) was recrystallised from EtOAc/hexane giving **4** as light yellow crystals (2.86 g, 43%). R_f 0.78 (30:1 CH_2Cl_2/MeOH); δ_H (400 MHz, $CDCl_3$): 4.03 (3H, s, OCH_3), 4.56 (4H, s, CH_2Br), 7.12 (1H, t, ArH, $J=7.6$), 7.38 (2H, d, ArH, $J=7.7$); δ_C (100 MHz, $CDCl_3$): 29.5, 62.2, 125.0, 131.9, 132.2, 156.6.
7. Data for compound **5**: boron tribromide (1.1 M CH_2Cl_2, 7.0 mL, 7.7 mmol, 151 mol %) was added to methoxybenzene **4** (1.50 g, 5.1 mmol, 100 mol %) under argon at −78 °C. After addition, the solution was allowed to warm to rt and stirring was continued for 3 h. The reaction was quenched with water (8 mL) and diluted with EtOAc (40 mL). The organic phase was washed with saturated aqueous NaCl (2×20 ml) and dried (Na_2SO_4). The solvent was removed giving a light yellow product (1.27 g, 89%). R_f 0.69 (30:1 CH_2Cl_2/MeOH); δ_H (400 MHz, $CDCl_3$): 4.57 (4H, s, $ArCH_2Br$), 6.90 (1H, t, ArH, $J=7.6$), 7.27 (2H, d, ArH, $J=7.7$); δ_C (100 MHz, $CDCl_3$): 29.3, 121.2, 125.2, 131.4, 153.4.
8. Data for compound **6**: a mixture of phenol **5** (0.94 g, 3.4 mmol, 100 mol %), Dpa (1.46 g, 7.1 mmol, 209 mol %), K_2CO_3 (0.98 g, 7.1 mmol, 209 mol %) and DMF (8.0 mL) was stirred under argon at rt for 19 h. The solution was diluted with EtOAc (30 mL), washed with water ($3\times$ 30 mL) and brine (3×30 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product (1.42 g, 82%) was purified by flash chromatography (Si_2O, ∅ 3×22 cm, 30:1–10:1 CH_2Cl_2/MeOH) giving an oily, yellow product (0.88 g, 51%); R_f 0.57 (10:1 CH_2Cl_2/MeOH); δ_H (400 MHz, $CDCl_3$): 3.83 (4H, s, $CH_2N(CH_2)_2$), 3.88 (8H, s, $CH_2N(CH_2)_2$), 6.78 (1H, t, ArH, $J=7.5$), 7.11 (4H, t, C_5H_4N, $J=6.0$), 7.23 (2H, d, ArH, $J=7.5$), 7.50 (4H, d, C_5H_4N, $J=7.8$), 7.59 (4H, t, C_5H_4N, $J=7.6$), 8.52 (4H, t, C_5H_4N, $J=4.3$); δ_C (100 MHz, $CDCl_3$): 54.5, 59.6, 118.3, 121.8, 122.8, 123.9, 129.0, 136.4, 148.7, 155.8, 159.1; HRMS (ESI) calcd for $C_{32}H_{33}N_6O$ (M^+H) 517.2716, found 517.2715, $\Delta=0.2$ ppm.
9. Data for compound **7**: sodium nitrite (0.15 g, 1.76 mmol, 234 mol %) was dissolved in water (0.5 mL) and the solution was cooled to 0 °C (solution A). *p*-Aminobenzoic acid (0.11 g, 0.80 mmol, 106 mol %) was dissolved in HCl (10% solution, 0.70 mL) and this solution was also cooled to 0 °C (solution B). Compound **6** (0.39 g, 0.76 mmol, 100 mol %) was dissolved in NaOH (10% solution, 1.5 mL) and the solution cooled to 0 °C (solution C). Solution A was added slowly to solution B and this mixture was then added very slowly to solution C. After stirring for half an hour at 0 °C, the reaction mixture was washed with EtOAc (2×10 mL). After washing the

aqueous phase was made acidic (1 M HCl, pH ~ 5) and the crude product (0.35 g, 70%) precipitated from the solution. The product was purified by flash chromatography (LiChroprep. RP-18, ∅ 2.5 × 30 cm, 5:1–2:1 H_2O/MeCN) giving a deep red product (0.17 g, 34%). R_f 0.46 (1:1:0.02 H_2O/MeCN/TFA); δ_H (400 MHz, $CDCl_3$): 4.26 (4H, s, $CH_2N(CH_2)_2$), 4.42 (8H, s, $CH_2N(CH_2)_2$), 7.52 (4H, dt, C_5H_4N, $J = 1.3$, 6.9), 7.57 (4H, d, C_5H_4N, $J = 7.9$), 7.85 (2H, s, ArH), 7.91 (2H, d, ArH, $J = 8.5$), 7.96 (4H, dt, C_5H_4N, $J = 1.5$, 7.8), 8.18 (2H, d, ArH, $J = 8.5$), 8.67 (4H, d, C_5H_4N, $J = 4.5$); δ_C (100 MHz, $CDCl_3$): 57.0, 59.1, 123.1, 123.4, 125.5, 125.8, 128.6, 131.9, 133.5, 141.3, 146.4, 148.1, 154.9, 156.5, 169.0; HRMS (ESI) calcd for $C_{39}H_{37}N_8O_3$ (M^+H) 665.2989, found 665.2971, $\Delta = 2.7$ ppm.

10. Dapporto, P.; Formica, M.; Fusi, V.; Giorgi, L.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P. *Inorg. Chem.* **2001**, *40*, 6186.