

## The Design and Synthesis of Pyrazine Ligands Suitable for Molecular Weaving with Octahedral Metal Ions

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### ABSTRACT

**Pyrazine-2-carboxylic Acid(pyridine-2-ylmethyl)amide** and **2,4-di(n(pyridalmethyl)formamide)pyrazine**, two new ligands designed to require a weaving topology around octahedral metal ions have been synthesized in high yield and characterized. These new ligands utilize the nitrogens in pyridines and pyrazines in their structures to produce poly-dentate binding sites for coordinating to metals producing multiple crossovers with the goal of forcing over/under repeats in metal complexes. Characterization of the ligands was achieved by Mass Spectroscopy,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, mp, IR spectroscopy and Elemental analysis.

Keywords: *Molecular Weaving, oligomeric pyridine, pyrazine, supramolecular chemistry.*

### INTRODUCTION

Molecular Weaving is a goal of synthetic chemists that would allow them to manipulate molecules in the same way that one would weave a piece of fabric. The molecules are designed to bow in and out as a thread would in and out of a loom. Coordination chemistry is a field of chemistry in which individually recognizable organic molecules are bound to metal ions by the energetically favorable sharing of electron pairs from heteroatoms to the metal ions.

With the goal of a ligand with two distinct poly-dentate sites that rigidly alternated sides of the ligand we proposed to coordinate pyridine and pyrazine to achieve weaving using their nitrogens in the rings to designate the sites desired. The metal ions would organize, or anchor, the ligand into the proper orientation.

Coordination compounds are defined as compounds formed by the binding of simpler, yet distinct, molecules by non-covalent bonds. A covalent bond shares one electron from each atom; whereas in the coordinate bond both electrons are from one atom. Another field, supra-molecular chemistry, shares in definition the use of non-covalent bonds in the interactions of molecules. These possible interactions include but are not limited to hydrogen bonding,  $\pi$ - $\pi$  and metal-ligand interactions.

Another non-covalent bond that is central to the ultimate outcome of our proposed course is the mechanical bond. This isn't a bond in the sense of shared electrons but rather a physical constraint as a knot in a piece of rope as it wraps around itself or a chain that is composed of linked rings.

Examples of mechanical bonds occur in the supramolecular chemistry of Stoddart(1995) and Sanvage(1990) Figure 1. these, and other chemists successful in making complex molecules containing mechanical bonds often use a template strategy to achieve the mechanical bond. In the template, one

component (the anchor) organizes the other component (the turn) prior to the covalent bond formation occurring to "trap" the molecules in a mechanical bond. A similar strategy using a metal ions as the anchor and linear nitrogen-bearing organic ligands as the turn might be used to weave as in figure 2.

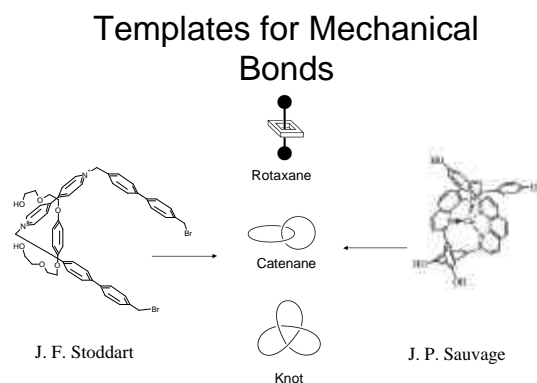


Figure 1.

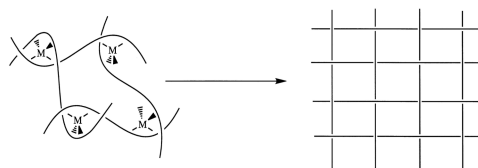


Figure 2. Molecular Weaving Scheme

## MATERIALS AND METHODS

All chemicals and materials were purchased from Aldrich Chemical Co. and used as received. One exception is 2,3-pyrazinecarboxylic acid which was synthesized by Robert Ullom from 2,3-dimethylpyrazine according to the literature (Fleischer *et. al.*, 1972).

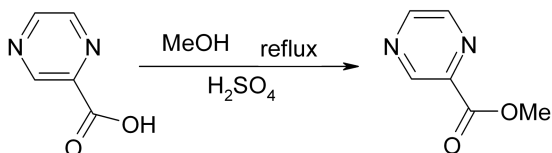


Figure 3.

### 2-Pyrazinemethylester (1)

2-Pyrazinemethylester was prepared by dissolving 2-pyrazinecarboxylic acid (10.2959g, 0.0829 mol) into 100mL of methanol and 1.4 mL of H<sub>2</sub>SO<sub>4</sub>. This solution was then refluxed for 15 hrs producing a yellow/gold solution as the acid dissolved (Fleischer *et. al.*, 1972). The resulting solution was evaporated down to 25 mL and made neutral by slowly adding solid NaHCO<sub>3</sub> and then adding a 5% solution of the same until neutrality was achieved. The compound was then extracted with 6-400 mL portions of ether and dried over NaSO<sub>4</sub> overnight. The solution was filtered with coarse filter paper and the solvent was dried and a yellow oil remained. The resulting oil was then dissolved into a 1% methanol/CH<sub>2</sub>Cl<sub>2</sub> and the eluent was passed through a silica column. The solvent was reduced and cooled producing yellow crystals (7.56g, 0.055 mol, 66% yield).

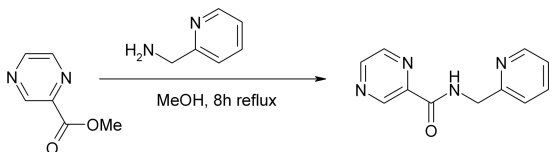


Figure 4.

### Pyrazine-2-carboxylic Acid(pyridine-2-ylmethyl)amide (2)

Pyrazine-2-carboxylic Acid(pyridine-2-ylmethyl)amide was prepared by dissolving 2-pyrazinemethylester (3.254g, 0.0235 mol) into 15 mL of methanol and adding 2-aminomethylpyridine (3.05g, 0.0283 mol) with an additional 7.5 mL of methanol. The solution was refluxed overnight and then dried down to an off-white powder (Cati, *et. al.*2004). Excess 2-aminomethylpyridine was removed by vacuum while heating in water bath (3 hrs). The resulting product was dissolved in a minimal amount of warmed solvent and then cooled

to produce colorless crystals (3.95g, 0.0185 mol, 79%).

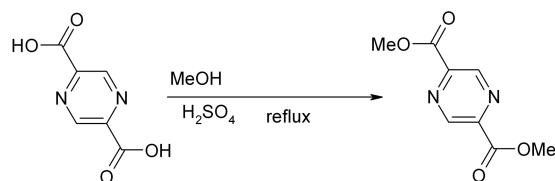


Figure 5.

### 2,3-Pyrazinedimethylester (3)

2,3-Pyrazinedimethylester was prepared by dissolving 2,3-Pyrazinedicarboxylic acid (4.9578g, 0.0295m) into 50 mL methanol. While stirring 0.07 mL of concentrated H<sub>2</sub>SO<sub>4</sub> was added slowly. The solution was left to reflux for 12 hours after which a white precipitate formed on the stir bar (Fleischer *et. al.*, 1972). This was physically broken up via glass rod. An additional 0.05 mL H<sub>2</sub>SO<sub>4</sub> was added 18.5 hours later. White precipitate remained 24 hours later and an additional 50 mL ethanol and 0.05 H<sub>2</sub>SO<sub>4</sub> was added to the solution and the reflux was increased for 18 hours. The solution was made neutral with NaHCO<sub>3</sub>, extracted with 7-25mL portions of CHCl<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. CHCl<sub>3</sub> was removed to yield 2,3-Pyrazinedimethylester (4.96g, 0.025m, 86% yield).

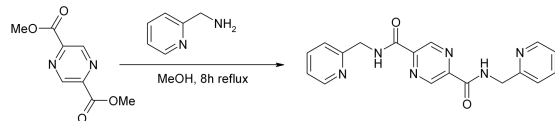


Figure 6.

### 2,4-di(n(pyridalmethyl)formamide)pyrazine (4)

2,4-di(n(pyridalmethyl)formamide)pyrazine was prepared by dissolving 2,3-Pyrazinedimethylester (4.162g, 0.021m) into 30mL of MeOH. To the solution 2-(aminomethyl)pyridine (5.68g, 0.052m) was added and the resulting solution was refluxed for 8 hours (Cati, *et. al.*2004). A white precipitate formed and was isolated via frit, and rinsed with MeOH to yield 2,4-di(n(pyridalmethyl)formamide)pyrazine ( 7.12g, .02m, 95% yield).

## RESULTS and DISCUSSION

The goal of this work was to design and synthesize pyrazine based ligands whose structure ensures binding to the octahedral metal ions in a weaving fashion. Pyrazine was chosen as the core unit because its two nitrogens are rigidly confined to opposite sides of the aromatic ring. Octahedral metal

ions often bind a linear tridentate ligand in a meridional fashion. We reasoned that two such ligands would provide an octahedral geometry around the metal ion and provide the crossover that is required in weaving.

Thus we designed ligand 2 as a test case to examine if the donor set we decided to use would actually provide the geometry we wanted. These complexes wouldn't be woven, but determine if weaving is possible.

The next step was to design 2 tridentate sites into the ligand with the binding sites rigidly constrained to opposite sides of the ligand system. We don't want more than three donors of this ligand on any one metal so that we can bind multiple ligands around a metal ion.

The choice of pyrazine is necessary to ensure that the "the arms" of the ligand don't complex the same metal which is impossible if pyrazine itself is involved in the complexation. Pyridine was chosen as the terminal groups for two reasons. 1) It is planer and aromatic which should help with the rigidity and stabilization by  $\pi$ - $\pi$  bonding in the woven complex., 2) because we eventually plan to extend these ligand systems beyond two binding sites, which will involve changing the pyridines to pyridines. The chemistry of these heteraromatics is similar, which should help us as we develop the larger systems.

Amide nitrogens as the connecting units between pyridine and pyrazine also have multiple advantages,

1. These functional groups have been used in similar ligands providing us with a background in similar synthesis.
2. Flexibility in synthetic routes due to the fact that amide chemistry is well known and relatively simple.
3. The deprotonated nitrogen provides us with a negative charge, which should increase the stability of the proposed complex.
4. The  $\pi$ -bond of the amide functional group provides rigidity and further potential  $\pi$ - $\pi$  interactions to encourage formation of the woven structure desired.

Results of the ligand synthesis were quite pleasing. The proposed routes to the ligands worked as expected and the yields as well as the purity were quite high. Below the reactions are listed along with the results and characterization.

### Synthesis (1) 2-Pyrazinemethylester

The yield for this step was consistently 66%.  $^{13}\text{C}$  NMR shows carbon atoms in six peaks in as expected and in the proper intensities and positions in the field. The  $^1\text{H}$  NMR also gives the expected peaks in the intensities and positions in the field. GC/Mass Spec shows a strong peak at  $m/z=139$  while the molecule MW is 138.1. IR spectroscopy was measured in the range of  $400\text{-}4000\text{ cm}^{-1}$ . Peaks were observed at  $1717$  and  $1142\text{ cm}^{-1}$  representing

the ester and carbon-oxygen bond respectively (Silverstien *et. al.* 1991). The melting point was found to be  $58^\circ\text{C}$ .

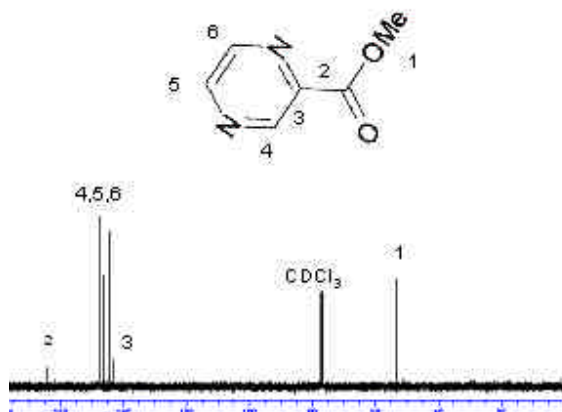


Figure 7.  $^{13}\text{C}$  NMR of (1)

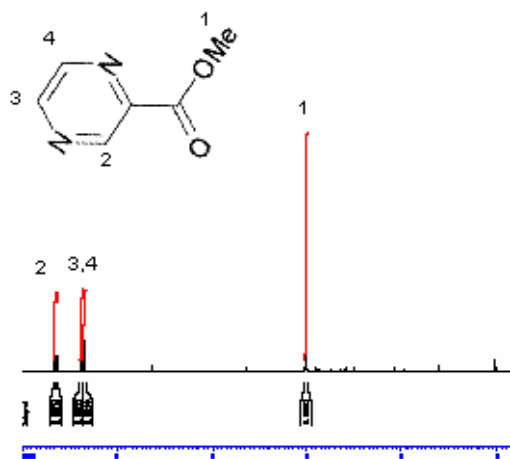


Figure 8.  $^1\text{H}$  NMR of (1)

### Synthesis (2) Pyrazine-2-carboxylic Acid(pyridine-2-ylmethyl)amide

The yield on this step was 79%. Previous attempts at this synthesis yielded darker yellow compound that showed strong peaks on GC/Mass spec indicating excess amino pyridine was present. We were successful at removing this impurity by drying the product under vacuum. The  $^{13}\text{C}$  NMR spectrum shows six peaks of proper strength and placement in the field.  $^1\text{H}$  NMR also confirms the presence of all protons as predicted. GC/Mass Spec shows strong

peak at  $m/z=215.1$  while the molecule is mw of 213.22 g/mol. IR spectroscopy measuring in the 400-4000  $\text{cm}^{-1}$  range showed peaks of 346.93 and 1669.00  $\text{cm}^{-1}$  indicating N-H stretching and carbonyl/amid respectively (Silverstien *et. al.* 1991). The melting point was found at 69°C. The theoretical elemental analysis for  $\text{C}_{11}\text{N}_4\text{H}_{10}\text{O}$  is C, 61.67%; N, 24.14%; H, 4.59%. Experimental analysis found these to be C, 61.88%; N, 23.99%; H, 4.47%.

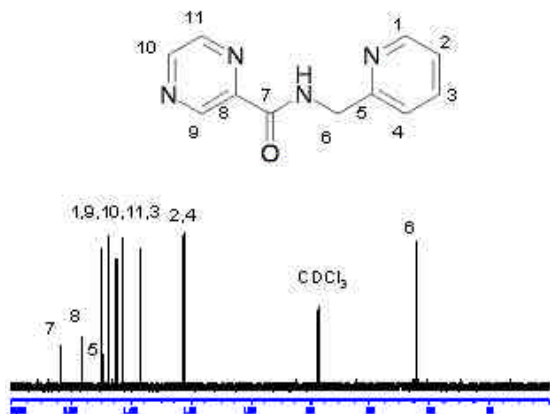


Figure 9.  $^{13}\text{C}$  NMR of (2)

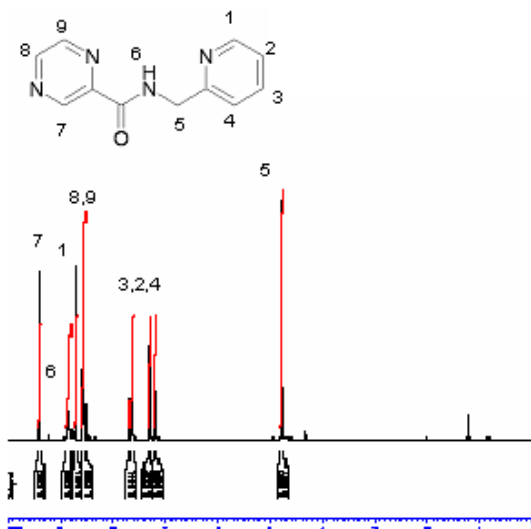


Figure 10.  $^1\text{H}$  NMR of (2)

#### Synthesis (3) 2,3-Pyrazinedimethylester

A yield of 85% was obtained on this synthesis.  $^{13}\text{C}$  NMR shows four peaks of proper strength and placement in the field.  $^1\text{H}$  NMR confirms the presence of all protons predicted. Mass spectroscopy shows a strong peak at 197  $m/z$  corresponding with the molecular weight of 196.164  $m/g$ . IR spectroscopy shows peaks at 1720, a series of peaks from

2961.44-3077.74, and 3425.71  $\text{cm}^{-1}$  representing the aldehyde, C-H bonds in the aromatic and the N-H respectively (Silverstien *et. al.* 1991). Melting point was found to be 168°C. Theoretical elemental analysis for  $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$  is C, 48.98%; H, 4.10%; N, 14.28%. Experimental analysis found these to be C, 48.97%; H, 4.23%; N, 14.21%.

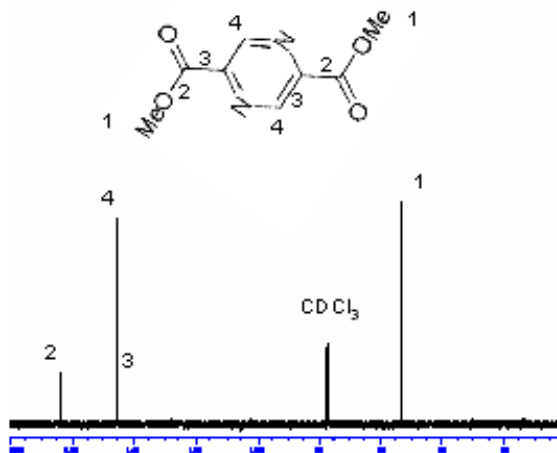


Figure 11.  $^{13}\text{C}$  NMR of (3)

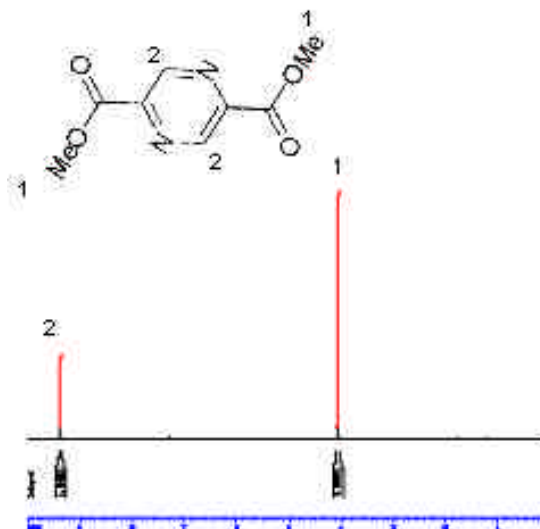


Figure 12.  $^1\text{H}$  NMR of (3)

#### Synthesis (4) 2,4-di(n(pyridalmethyl)formamide) pyrazine

A yield of 81% was obtained on this synthesis.  $^{13}\text{C}$  NMR shows nine peaks at the proper strengths and placement in the field.  $^1\text{H}$  confirms the presence of all protons predicted. Mass spectroscopy showed a strong peak at 349.1 correlating with the weight of the ligand at 348.33  $m/g$ . IR spectroscopy yielded

peaks at 1681, a series from 2919-3052 and 3333 representing the carbonyl, C-H stretch in the aromatics and the N-H stretch respectively (Silverstien *et. al.* 1991). The melting point was found to be 206°C. Theoretical elemental analysis for C<sub>18</sub>H<sub>16</sub>O<sub>2</sub>N<sub>6</sub> is C, 62.05%; N, 24.30%; H, 4.63%. Experimental analysis found these to be C, 61.88%; N, 23.99%; H, 4.47%.

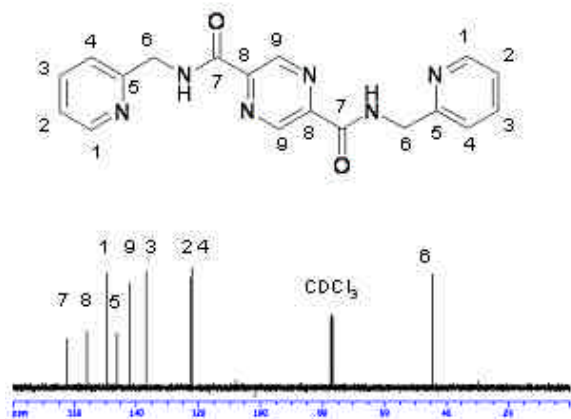


Figure 13. <sup>13</sup>C NMR of (4)

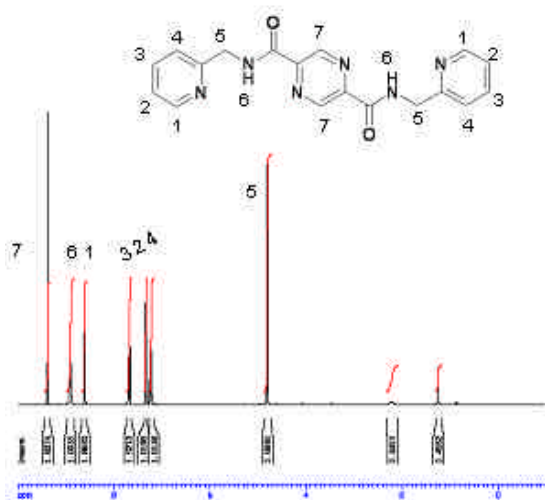


Figure 14. <sup>1</sup>H NMR of (4)

In conclusion potential octahedral ion binding weaving ligands were prepared by simple reactions in high yield and purity. Their structures have been unequivocally characterized.

#### ACKNOWLEDGEMENTS

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