

# A Study of Nickel-Catalyzed Coupling Reactions by Electropray Ionization Mass Spectrometry

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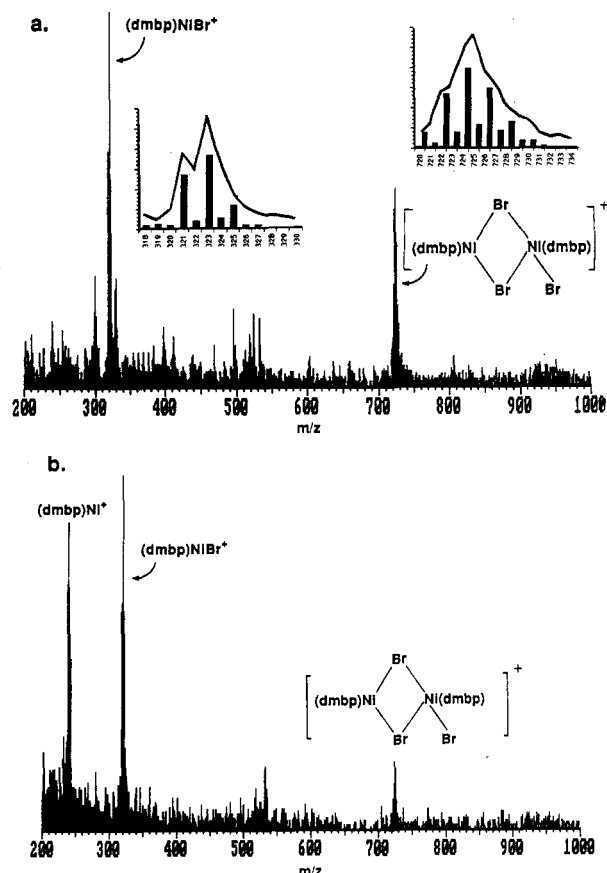
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**Summary:** ESI-MS was used to characterize Ni(III) complexes formed during the Raney nickel-catalyzed coupling of 2-bromo-6-methylpyridine (1). This paper shows that the intermediate Ni(III) complex of 6,6'-dimethyl-2,2'-bipyridine (3) may be dimeric. For the related mixed-coupling reaction of 2-bromo-6-methylpyridine (1) and 2-bromo-pyridine (5), as many as eight intermediates corresponding to all possible complexes of 2,2'-bipyridine (7), 6-methyl-2,2'-bipyridine (6), and 6,6'-dimethyl-2,2'-bipyridine (3) were detected. An interesting discovery was the reduction of Ni(III) to Ni(I) during ESI-MS at increased repeller voltages.

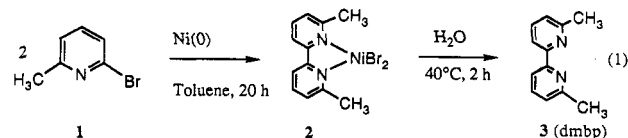
A recent advance in mass spectrometry, electropray ionization (ESI), has revolutionized the analysis of high mass biopolymers.<sup>1</sup> Less well developed are applications of ESI to smaller molecules.<sup>2</sup> This exceedingly mild ionization technique allows determination of ion masses (molecular ions) with almost no fragmentation by direct injection of a solution of ions into the MS. We have been exploring<sup>3</sup> applications of ESI to organic and organometallic chemistry and report herein a study of Ni-bipyridyl complexes. While bipyridyl complexes have been characterized using other MS techniques such as FAB,<sup>4</sup> it is known that the FAB matrix plays a significant role in the ionization and that both molecular ions as well as fragments are observed. ESI on the other hand usually shows only molecular ions and can be used to study solution chemistry in a variety of organic solvents (acetonitrile, methanol, or THF).

Transition metals such as Cu, Ni, and Pd have been widely used for diaryl coupling reactions.<sup>5</sup> Recently, during a study on syntheses of bipyridyl-transition metal complexes,<sup>6</sup> we carried out a Raney nickel coupling reaction for the synthesis of 6,6'-dimethyl-2,2'-bipyridine (3). This approach was recently reported by Breitmaier,<sup>7</sup> who



**Figure 1.** (a) ESI-MS spectrum of the intermediate 2 (eq 1) in CH<sub>3</sub>CN (low repeller voltage = 20 V) (dmbp)NiBr<sup>+</sup> (322), [(dmbp)NiBr<sub>2</sub>Ni(dmbp)Br]<sup>+</sup> (724). Insets show calculated (bar graph) and observed (curve) data for ions (C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>-NiBr<sup>+</sup>) and (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>Ni<sub>2</sub>Br<sub>3</sub><sup>+</sup>), respectively (cf. ref 9). (b) ESI-MS spectrum of the intermediate 2 (eq 1) in CH<sub>3</sub>CN (high repeller voltage = 50 V) (dmbp)Ni<sup>+</sup> (242), (dmbp)NiBr<sup>+</sup> (322), [(dmbp)NiBr<sub>2</sub>Ni(dmbp)Br]<sup>+</sup> (724).

reported coupling 2-bromo-6-methylpyridine (1) in the presence of Ni(0) to generate the nickel(III) complex 2, which was isolated and characterized by microanalysis (eq 1). Hydrolysis of complex 2 gave 6,6'-dimethyl-2,2'-



bipyridine in 65% overall yield. With the help of ESI-MS,<sup>8</sup> we were able to examine the structure of the intermediate complex 2.

Complex 2 was dissolved in acetonitrile at a concentration of about 10<sup>-4</sup> M and infused at 5 μL/min into our

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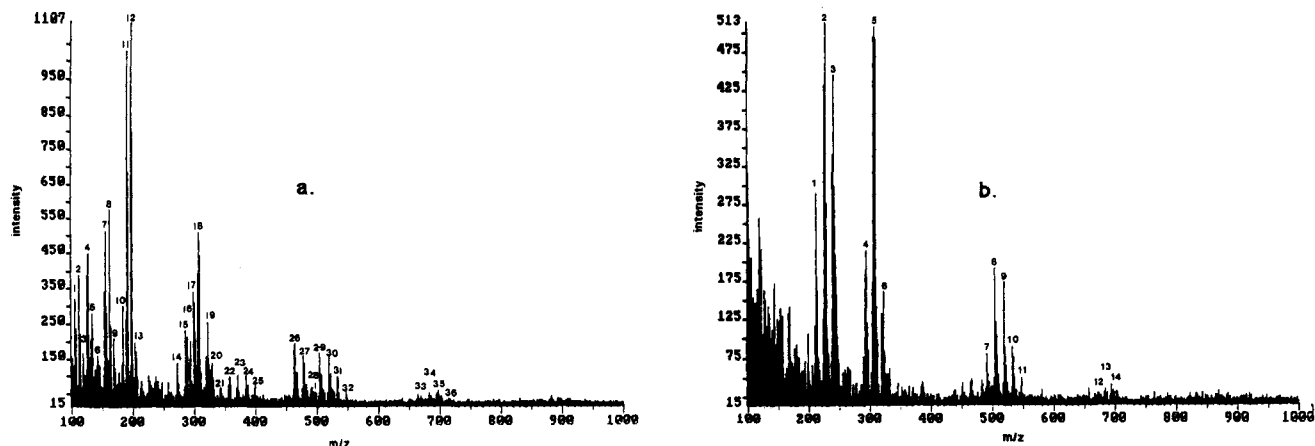
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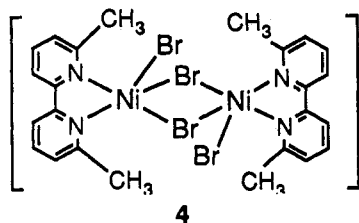
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**Figure 2.** (a) ESI-MS spectrum of the mixed complexes (eq 2) in CH<sub>3</sub>CN (low repeller voltage = 20 V): 1 (bpy)Ni<sup>2+</sup> (107), 2 (mbp)Ni<sup>2+</sup> (114), 3 (dmbp)Ni<sup>2+</sup> (121), 4 [(bpy)(CH<sub>3</sub>CN)Ni]<sup>2+</sup> (128), 5 [(mbp)(CH<sub>3</sub>CN)Ni]<sup>2+</sup> (135), 6 [(dmbp)(CH<sub>3</sub>CN)Ni]<sup>2+</sup> (142), 7 (bpy + H)<sup>+</sup> (157), 8 unknown (164), 9 (mbp + H)<sup>+</sup> (171), 10 (dmbp + H)<sup>+</sup> (185), 11 [(bpy)(mbp)Ni]<sup>2+</sup> (192), 12 [(mbp)<sub>2</sub>Ni]<sup>2+</sup> (199), 13 [(mbp)(dmbp)Ni]<sup>2+</sup> (206), 14 [(dmbp)NiBr<sub>2</sub>Ni(CH<sub>3</sub>CN)<sub>2</sub>]<sup>2+</sup> (271), 15 unknown (288), 16 [(bpy)NiBr<sub>2</sub>-Ni(bpy)]<sup>2+</sup> or [(bpy)NiBr]<sup>+</sup> (294), 17 [(bpy)NiBr<sub>2</sub>Ni(mbp)]<sup>2+</sup> (301), 18 [(mbp)NiBr<sub>2</sub>Ni(mbp)]<sup>2+</sup> or [(mbp)NiBr]<sup>+</sup> (308), 19 [(dmbp)NiBr<sub>2</sub>Ni(dmbp)]<sup>2+</sup> or [(dmbp)NiBr]<sup>+</sup> (322), 20 [(bpy)(CH<sub>3</sub>CN)NiBr<sub>2</sub>Ni(bpy)(CH<sub>3</sub>CN)]<sup>2+</sup> (335), 21 [(bpy)(CH<sub>3</sub>CN)-NiBr<sub>2</sub>Ni(mbp)(CH<sub>3</sub>CN)]<sup>2+</sup> (342), 22 [(mbp)(CH<sub>3</sub>CN)NiBr<sub>2</sub>Ni(dmbp)(CH<sub>3</sub>CN)]<sup>2+</sup> (356), 23 [(bpy)<sub>2</sub>NiBr<sub>2</sub>Ni(bpy)]<sup>2+</sup> (372), 24 [(bpy)(mbp)NiBr<sub>2</sub>Ni(mby)]<sup>2+</sup> (386), 25 [(bpy)(dmbp)NiBr<sub>2</sub>Ni(dmbp)]<sup>2+</sup> (400), 26 [(bpy)(mbp)NiBr]<sup>+</sup> (464), 27 [(mbp)<sub>2</sub>NiBr]<sup>+</sup> (478), 28 [(mbp)(dmbp)NiBr]<sup>+</sup> (492), 29 [(dmbp)<sub>2</sub>NiBr]<sup>+</sup> (506), 30 [(mbp)<sub>2</sub>NiBr-CH<sub>3</sub>CN]<sup>+</sup> (519), 31 [(mbp)(dmbp)NiBr-CH<sub>3</sub>-CN]<sup>+</sup> (533), 32 [(dmbp)<sub>2</sub>NiBr-CH<sub>3</sub>CN]<sup>+</sup> (547), 33 [(bpy)NiBr<sub>2</sub>Ni(bpy)Br]<sup>+</sup> (668), 34 [(bpy)NiBr<sub>2</sub>(mbp)Br]<sup>+</sup> (682), 35 [(mbp)NiBr<sub>2</sub>-Ni(mbp)Br]<sup>+</sup> (696), 36 [(mbp)NiBr<sub>2</sub>Ni(dmbp)Br]<sup>+</sup> (710). (b) ESI-MS spectrum of the mixed complexes (eq 2) in CH<sub>3</sub>CN (high repeller voltage = 50 V): 1 (bpy)Ni<sup>+</sup> (214), 2 (mbp)Ni<sup>+</sup> (228), 3 (dmbp)Ni<sup>+</sup> (294), 4 (bpy)NiBr<sup>+</sup> (294), 5 (mbp)NiBr<sup>+</sup> (308), 6 (dmbp)NiBr<sup>+</sup> (322), 7 (mbp)(dmbp)NiBr<sup>+</sup> (492), 8 (dmbp)<sub>2</sub>NiBr<sup>+</sup> (506), 9 [(mbp)<sub>2</sub>NiBr(CH<sub>3</sub>CN)]<sup>+</sup> (519), 10 [(mbp)(dmbp)-NiBr(CH<sub>3</sub>CN)]<sup>+</sup> (533), 11 [(dmbp)<sub>2</sub>NiBr(CH<sub>3</sub>CN)]<sup>+</sup> (547), 12 [(bpy)NiBr<sub>2</sub>Ni(bpy)Br]<sup>+</sup> (668), 13 [(bpy)NiBr<sub>2</sub>Ni(mbp)Br]<sup>+</sup> (682), 14 [(mbp)NiBr<sub>2</sub>Ni(mbp)Br]<sup>+</sup> (696).

quadrupole ESI-MS to provide the spectrum shown in Figure 1a. A major peak centered at  $m/z = 724$  (low-resolution data, see ref 9) suggests that the product is the dimeric complex 4. The 724 ion corresponds to [(dmbp)<sub>2</sub>Ni<sub>2</sub>Br<sub>3</sub>]<sup>+</sup> (loss of Br<sup>-</sup> from 4).<sup>10,11</sup> A base peak



centered at  $m/z 322$  corresponding to [(dmbp)NiBr]<sup>+</sup> (loss of Br<sup>-</sup> from monomer 2 or via fragmentation of 4) was also

(8) General experimental details and conditions for ESI-MS are reported in ref 6 and involves injection of ~5  $\mu\text{L}/\text{min}$  of a  $10^{-4}$  M acetonitrile solution of the complex for 2–5 min during data collection. Spectra shown consumed less than 50  $\mu\text{g}$  of material. For this study we used needle voltage = 2.2 kV, ESI chamber temp = 55  $^{\circ}\text{C}$ , flow rate = 5  $\mu\text{L}/\text{min}$ , repeller voltage = 20 V, nozzle voltage = 200 V, lens temp = 120  $^{\circ}\text{C}$ , block temp = 250  $^{\circ}\text{C}$ .

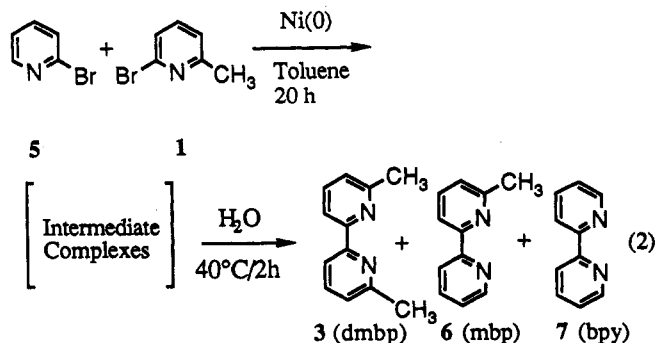
(9) Because only low-resolution spectra<sup>10</sup> are reported here, all  $m/e$  values are calculated using an average mass for bromine of 80 and nickel as 58. Insets in Figure 1a show theoretical isotope patterns calculated using MacSpec from Spire Software.

(10) Electrospray ionization sources are most readily adapted to low-resolution quadrupole MS instruments due to design requirements for operation of an atmospheric pressure source with high-resolution magnetic sector instruments whose analyzer operates at very low pressures. In addition, the high voltages of magnetic sector instruments also create technical difficulties.<sup>11</sup> The instrument used in this study was a Vestec<sup>12</sup> Model ES-200 quadrupole with a 2000 amu mass range operating at a resolution of 200. Most of our data does not resolve the <sup>79</sup>Br (50%), <sup>81</sup>Br (50%), <sup>58</sup>Ni (68%), and <sup>60</sup>Ni (26%) isotope patterns which would of course be observable at higher resolutions. Figure 1a shows calculated and observed patterns for [(dmbp)NiBr]<sup>+</sup> (cf. ref 9).

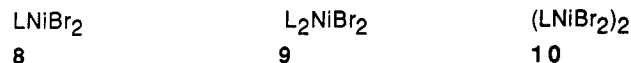
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seen. Although ESI-MS usually only shows molecular ions, fragmentation may be induced by the technique of collision-induced dissociation (CID) in the high-pressure source. It is known, that when the MS repeller voltage (normally about 20 V) is raised, ions spend more time in the high-pressure region of the source and fragmentation is sometimes observed. Under high repeller voltage (50 V) the ESI-MS spectrum of complex 4 (Figure 1b) shows a decrease in the dimeric ion with a new ion appearing at  $m/z = 242$ . This corresponds to reduction of Ni[II] to Ni[I] producing [(dmbp)Ni]<sup>+</sup>.

Since we were interested in the synthesis of *unsymmetrical* bipyridines and the coupling mechanism involves the intermediacy of a mixed pyridine complexes, we examined the selectivity of this reaction in a *mixed-coupling* reaction. On the basis of the pathway in eq 1, one might have expected three complexes analogous to 2. Using stoichiometric amounts of 2-bromopyridine 5 and 2-bromo-6-methylpyridine 1, the coupling reaction was run under the same conditions as above and the intermediate complexes isolated. Hydrolysis gave bipyridines 3 and 6 in a ratio of about 1:1 (eq 2). Only a trace of 7 was detected by NMR of the crude product. ESI-MS analysis



of intermediate complexes from the mixed-coupling reaction, however (Figure 2a), shows more than the expected three intermediate complexes. Although the spectrum appears complicated, all the peaks are derived from the possible complexes 8, 9, and 10. One notices immediately

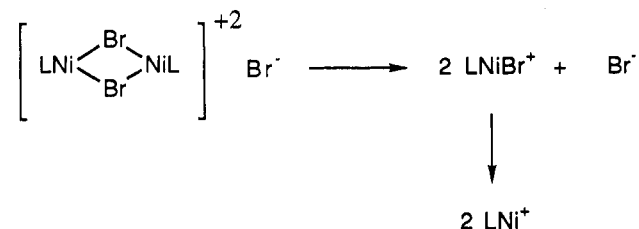


the cluster of dimer peaks (33–36 in Figure 2a) is much less intense than in the case of pure [(dmbp)NiBr<sub>2</sub>]<sub>2</sub>. Peaks 33–36 show dimers for several combinations of dmbp, mbp, and bpy in (LNiBr<sub>2</sub>)<sub>2</sub>. More interesting are small doubly charged dimer ions (peaks 16–19 in Figure 2a). These ions may be assigned to 4 of the 5 possible combinations of dmbp, mbp, and bpy; however, observation of peak 17 (*m/z* = 301) proves that the ion is a doubly charged dimer ion [(bpy)NiBr<sub>2</sub>Ni(mbp)]<sup>2+</sup> and not a singly charged monomer [LNiBr]<sup>+</sup>. Smaller amounts of dimers may be due to the more favorable formation of L<sub>2</sub>NiBr<sub>2</sub> species (peaks 11 and 12) with less-hindered ligands.<sup>13</sup>

Again, when high MS repeller voltage (50 V) is employed, the ESI-MS spectrum of the mixed complex changes (Figure 2b). At high repeller voltage a reduction of Ni[II] to Ni[I] again occurs during the electrospray ionization process.<sup>15</sup>

The acetonitrile solvent, a poorer donor compared to bipyridines, appears in several ions. In the case of complexes where the total number of valence electrons is greater than 18 (i.e. peaks 30–32), the appearance of a

solvent molecule might be evidence of incomplete desolvation in the ESI process.<sup>4d</sup>



The reduction process needs to be further investigated, although the same phenomenon has been observed in fast atom bombardment spectra.<sup>16</sup> Since the Ni[II]/Ni[I] redox chemistry is not well developed,<sup>17</sup> ESI could prove useful in this area.

In conclusion, we have shown that ESI-MS is useful for studying reactions involving metal ions. We also point out that ESI represents a unique method for determination of the masses of ionic materials *in solution*, including ions resulting from noncovalent interactions.<sup>18a,b</sup> ESI is also the mildest of the "soft" ionization techniques. No energy bombardment of the sample is needed to produce ions. Other ionization methods are termed "energy sudden" techniques and apply energy to the sample, i.e. hot atoms as in FAB or a high-energy laser in laser desorption. Since primarily molecular ions are observed, quite complex mixtures of transition metal complexes can be determined easily and structural information deduced using CID at high repeller voltages. Further studies are in progress and will be reported in due course.

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