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One-pot metal templated synthesis for the preparation of 2-quinoxalinol salen metal complexes

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ABSTRACT

Metal complexes of 2-quinoxalinol salen (salqu) ligands can be prepared in a one-pot metal templated synthesis resulting in significantly enhanced yields than if the ligand were prepared and isolated prior to introducing the metal for complexation. Using this method, 12 salqu metal complexes have been prepared and characterized from +2 metal ions.

One-pot multicomponent syntheses have received increasing attention of late, because they not only address fundamental principles of synthetic efficiency and reaction design [1–3], but they also expand the possibilities for extending one-pot reactions into combinatorial and solid-phase methods [3,4]. This presents a new way of thinking about "greener" chemistry by allowing for the reduction of synthetic steps, purification solvents, and wastes. A one-pot metal templated strategy for the preparation of metal complexes for use in applications offers the distinct advantages of reduced environmental impacts and easier procedures for workup.

Salen or salph complexes have been used widely in applications for everything from catalysts to molecular recognition. For example, salen Cu, Mn, or Ru complexes have been used as catalysts in the catalytic oxidation of secondary amines [5], as the basis for enantioselective catalysts [6], and as catalysts for ring-opening metathesis [7]. Uranyl (UO_2^{2+}) salophen complexes have been used in molecular recognition studies [8–10]. In addition, salen Mn complexes can act as catalytic scavengers of hydrogen peroxide and have been demonstrated to have a degree of cytoprotectivity [11].

Symmetric and unsymmetric 2-quinoxolinol salen ligands (abbreviated *salqu, e.g.* 3) have been synthesized for use in catalysis using solution phase and combinatorial strategies [12,13]. A disadvantage of this reaction scheme was an extended reaction time required to obtain the optimal yields. Metal complexes of this series of ligands were then prepared by a standard proton transfer procedure [14]. Because applications in solid-phase extraction and catalysts of salqu metal complexes have been developed [15,16], it was thought that it would to be advantageous to find a more efficient, economical method to prepare salqu metal complexes. Here, a one-pot synthetic method based on a metal template synthesis to access salqu metal complexes will be introduced. With this method, 12 salqu metal complexes have been synthesized from diamino-2-quinoxalinol (**1**, Scheme 1) in significantly higher yields in a shorter time than when the ligand is isolated and purified prior to complexation.

Previously, to prepare the salqu metal complexes, two steps were required. The first being the preparation of salqu ligands followed by preparation of the salqu metal complex. In the synthesis of symmetric salqu ligands, the final optimized conditions required that the diamino-2-quinoxalinol intermediate **1** be reacted with 10 equiv. of the desired salicylaldhyde derivatives (**2**) at reflux temperature in methanol for 48 h [12]. The ligand must then be isolated prior to the addition of the metal to prepare the metal complex, resulting in yields around 60.0%. Metal complexes are then prepared from a reaction of the salqu ligand (**3**) with 1.2 equiv. of the desired metal acetate at reflux temperature in either DMF or DCM with MeOH reacted for 2–12 h [14]. The final yields for this step are around 85.0%, resulting in an overall yield for both reactions close to 50%.

Using a metal templating strategy for a one-pot synthetic method, the diamino-2-quinoxalinol intermediate **1** is reacted with 2.1 equiv. of the salicylaldhyde derivative (**2**) and 1.1 equiv. of metal acetate is added directly to the reaction mixture. This also does not require a mixed solvent system, only methanol is used. The mixture was then heated to reflux temperature and allowed to react for 6 h. After the reaction was determined to be complete,

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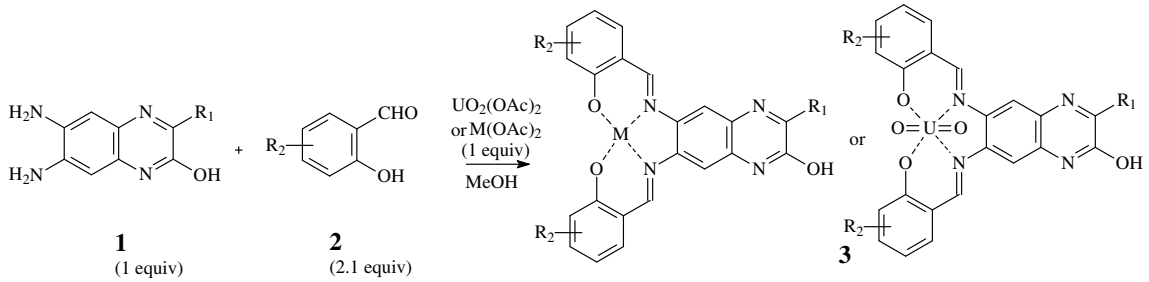

Scheme 1. Method for a one-pot synthesis of salqu metal complexes.

Table 1
Salqu metal complexes synthesized using a one-pot metal templated method.

	$[M]^{2+}$	R_1	R_2	Yield
3a	Cu^{2+}		3,5-di-*tert*-butyl	72.8
3b	Cu^{2+}		H	80.0
3c	Mn^{2+}		3,5-di-*tert*-butyl	76.5
3d	Co^{2+}		3,5-di-*tert*-butyl	69.4
3e	Ni^{2+}		3,5-di-*tert*-butyl	62.7
3f	UO_2^{2+}		3-OH	84.5
3g	UO_2^{2+}		3,5-di-*tert*-butyl	62.0
3h	UO_2^{2+}		H	61.2
3i	UO_2^{2+}		3,5-di-*tert*-butyl	65.3
3j	UO_2^{2+}		H	63.4
3k	UO_2^{2+}		H	67.0
3l	UO_2^{2+}		H	69.8

a large quantity of red or black solid was found to precipitate from solution. The precipitates were filtered and washed with ethanol five times. The solids were dried to obtain salqu metal complexes with purity greater than 95% (purity was identified by NMR and TLC.) Yields were found to range from 60% to 85%. The results are listed in Table 1.

The IR spectral results are indicative of metal complexation. Broad peaks in free ligands seen around 3400 cm^{-1} (3400–3448 cm^{-1}) are indicative of the presence of the hydroxyl groups on the free ligand. These broad signals are seen to be absent in the Cu, Mn, Co, Ni, and UO_2 metal complexes indicating the formation of the metal complex with these oxygens. Coordination through the phenolic hydroxyl unit in the salicylaldehyde coordination site can also be shown a shift in the C–O band for the metal complexes between 1199 and 1213 cm^{-1} as compared to the sharp peak in the free ligands (1263–1276 cm^{-1}) [18]. (**3j** is lower 1146 cm^{-1} although there is not a peak seen as in the range characteristic of the C–O stretch in the starting material.)

The spectra of the free ligands have peaks around 1654–1658 cm^{-1} for the carbon–nitrogen imine stretch. This is seen to shift to 1599–1620 cm^{-1} (**3f–3l**) for the uranyl complexes and is indicative of coordinated imine nitrogens [16,17]. This peak is seen at 1616–1614 cm^{-1} in the Ni^{2+} and Co^{2+} complexes, and in the Cu^{2+} complex (**3b**) but is not as well defined in the Mn^{2+}or in the Cu^{2+} (**3a**) in which the metal may not be strongly coordinating to the imines. Bands around 900 cm^{-1} (897–903 cm^{-1}) seen in the uranyl complexes (**3f–3l**) are due to the asymmetric and symmetric UO_2 stretching characteristic of linear uranyl ion in the complex [17].

In the ^1H NMR spectra of the uranyl (UO_2^{2+}) complexes, a significant shift in the imine CH=N proton is observed in the uranyl metal complexes (9.5–9.8 ppm for **3f–3l**) as compared to the free ligands (8.9–9.3 ppm). This is indicative of the imine nitrogen lone pairs coordinating to the metal center. In a similar fashion, there are three hydroxyl peaks in the ^1H NMR spectra of the free ligands (12.1–13.3 ppm) while in the uranyl (UO_2^{2+}) complexes, only one from the quinoxolinol hydroxyl group remains (12.6–12.7 ppm for **3f**, **3h**, and **3j–3l**, 12.2–12.3 ppm for **3g** and **3i**). (The slight difference seen in the data for **3g** is presumably due to the difference in solvation of the more subsituted and is comparable to **3i**.)

The advantages of the one-pot synthetic method for preparing salqu metal complexes are the shortened reaction time from more than 2 days to 6 h and improved final yields from less than 50.0% to over 60–85%. This also allows us to simplify the procedure and to conserve the amounts of the salicylaldhyde derivatives (2) used while avoiding the use of the more troublesome solvent DMF. This method could be a method for synthesis of these complexes using combinatorial methods because of the simple procedure and high yields.

In conclusion, a one-pot methodology based on a metal templating synthesis using +2 metal ions to more easily and rapidly prepare salqu metal complexes is an efficient method to prepare these metal complexes. With this method, several salqu metal complexes have been synthesized and identified. This will be a more convenient synthetic method in exploring the use of such metal complexes. In the future, a new salqu metal complex library will be prepared in this way.

General procedure and data

All amino acid methyl esters, DFDNB, HCl (37%) and aldehydes were purchased from Acros. Ammonium hydroxide (5.0 N), palladium on carbon (wet, 5%) were purchased from Aldrich. Starting materials were used as received. All organic solvents were purchased from Fisher Scientific and were used directly for synthesis. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) or Bruker

AV 400 spectrometer (operated at 400 and 100 MHz, respectively). Chemical shifts are reported as δ values (ppm). The solvents used are indicted in the experimental details. Electrospray ionization mass spectrometry was performed on a Micromass QTOF mass spectrometer (Waters Corp, Milford MA). Direct probe samples were on a VG-70S mass spectrometer (Waters Corp, Milford MA). Reaction progress was monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Aluminum silica gel 60-F254 precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. IR spectroscopic data were collected using a SHIM-SDZU Inc. IR, Prestige-21 Fourier Transform Infrared Spectrophotometer and KBr solid samples.

To a 5 ml methanol solution of intermediate **1** (0.05 mmol), 2.1 equiv. of the desired salicylaldehyde derivatives (e.g., **2** 0.105 mmol) and 1.1 equiv. of metal acetate (0.055 mmol) are added. The mixture was heated to reflux temperature with stirring and allowed to react for 6 h. At this time, a dark red or black solid precipitates out, indicating the completion of the reaction. The precipitates were filtered from the reaction solution. They were then washed with ethanol five times. Finally, the solids were dried under high vacuum.

3a: IR: 3067, 2955, 1661, 1586, 1528, 1491, 1416, 1377, 1260, 1209, 1173, 1130 cm^{-1}. MS: 760.0 (M+H); HRMS: found (760.3413); calc. (760.3422).

3b: IR: 3510, 3392, 1655, 1605, 1587, 1560, 1526, 1499, 1442, 1382, 1331, 1200, 1178, 1151 cm^{-1}. MS: 536.1 (M+H); HRMS: found (536.0912); calc. (536.0909).

3c: IR: 3385, 3248, 3208, 2955, 2911, 1670, 1582, 1532, 1462, 1416, 1317, 1248, 1177, 1130 cm^{-1}. MS: 751.3 (M+H); HRMS: found (751.3420); calc. (751.3429).

3d: IR: 3066, 2957, 1665, 1614, 1572, 1524, 1501, 1462, 1410, 1256, 1180, 1128 cm^{-1}. MS: 755.3 (M+H); HRMS: found (755.3369); calc. (755.3372).

3e: IR: 3067, 2955, 2870, 1665, 1616, 1584, 1533, 1598, 1464, 1414, 1379, 1260, 1182, 1130 cm^{-1}. MS: 755.3 (M+H); HRMS: found (755.3461); calc. 755.3471.

3f: ^{1}H NMR (400 MHz DMSO-d^6): δ 4.22 (s, 2H), 6.54–8.67 (m, 13H), 9.55 (s, 1H), 9.71 (s, 1H), 11.77 (bs, 1H), 11.82 (bs, 1H), 12.69 (bs, 1H). ^{13}C NMR: 160.2, 159.4, 155.0, 137.8, 132.8, 132.0, 129.7, 128.9, 126.9, 126.3, 124.1, 124.0, 123.9, 119.5, 117.1, 106.3, 42.0. IR: 3397, 3337, 2965, 1657, 1620, 1582, 1545, 1491, 1445, 1204, 903 cm^{-1}. MS: 816.2 (M+H+CH_3CN); HRMS: found (816.2178); cal (816.2183).

3g: ^{1}H NMR (400 MHz DMSO-d^6): δ 1.19 (s, 18H), 1.64 (s, 18H), 4.11 (s, 2H), 7.09–7.63 (m, 10H), 7.70(s, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 12.18 (bs, 1H). ^{13}C NMR: 173.3, 173.0, 171.2, 165.1, 153.8, 148.8, 144.6, 144.3, 143.5, 142.0, 137.1, 135.9, 134.2, 133.1, 131.3, 128.9, 123.3, 110.6, 42.0, 40.3, 38.6, 36.3, 35.1. IR: 3433, 2957, 1655, 1620, 1383, 1283, 1229, 1153, 937, 760 cm^{-1}. MS: 967.4 (M+H); HRMS: found (967.4514); calc. (967.4524).

3h: ^{1}H NMR (400 MHz DMSO-d^6): δ 4.20 (s, 2H), 6.73–6.77 (t, 2H), 7.00–7.04 (t, 2H), 7.24–7.88 (m, 10H), 8.12(s, 1H), 9.60 (s, 1H), 9.76 (s, 1H), 12.67 (bs, 1H). ^{13}C NMR: 170.8, 170.2, 168.0, 167.3, 161.3, 155.0, 148.9, 143.6, 137.8, 137.3, 136.5, 132.8, 129.7, 128.9, 126.9, 124.8, 121.4, 121.0, 119.5, 117.4, 106.3, 42.3. IR: 3397, 3337, 2965, 1657, 1620, 1582, 1545, 1491, 1445, 1204, 1144, 1040 cm^{-1}. MS: 784.0 (M+H+CH3CN); HRMS: found (784.2280); calc. (784.2285).

3i: ^{1}H NMR (400 MHz DMSO-d^6): δ 1.22 (d, 6H), 1.26 (s, 18H), 1.69 (s, 18H), 3.50 (m, 1H), 7.26–7.80 (m, 6H), 9.30 (s, 1H), 9.46 (s, 1H), 12.28 (bs, 1H). ^{13}C NMR: 173.3, 172.6, 153.4, 148.6, 144.6, 144.4, 143.3, 136.8, 135.7, 134.4, 128.9, 123.3, 110.4, 40.4, 38.6, 36.4, 35.1, 25.1. IR: 3444, 2958, 1710, 1666, 1587, 1423, 1371, 1224, 898 cm^{-1}. MS: 919.2 (M+H); HRMS: found (919.4514); calc. (919.4524).

3j: ^{1}H NMR (400 MHz DMSO-d^6): δ 1.28 (d, 6H), 3.56 (m, 1H), 6.74–8.17 (m, 10H), 9.61 (s, 1H), 9.81 (s, 1H), 12.58 (bs, 1H). ^{13}C NMR: 170.8, 170.2, 170.0, 167.9, 166.6, 154.6, 148.3, 143.5, 137.2, 136.5, 132.5, 131.9, 124.8, 124.6, 121.4, 121.0, 119.4, 117.4, 106.2, 30.5, 20.6. IR: 3406, 2966, 1654, 1602, 1539, 1463, 1400, 1384, 1145, 898 cm^{-1}. MS: 736.2 (M+H); HRMS: found (736.2280); calc. (736.2285).

3k: ^{1}H NMR (400 MHz DMSO-d^6): δ 1.00 (d, 6H), 2.28 (m, 1H), 2.74 (d, 2H), 6.75 (t, 2H), 7.03 (t, 2H), 7.44 (s, 1H), 7.65 (m, 2H), 7.87 (t, 2H), 8.19 (s, 1H), 9.61 (s, 1H), 9.78 (s, 1H), 12.54 (bs, 1H). ^{13}C NMR: 170.8, 170.2, 162.3, 155.2, 148.3, 143.4, 137.2, 136.5, 132.6, 132.0, 124.8, 124.6, 121.4, 121.1, 119.3, 117.4, 106.2, 42.1, 26.8, 23.1. IR: 3395, 2927, 1637, 1606, 1539, 1463, 1435, 1383, 1282, 937 cm^{-1}. MS: 709.2 (M+H); HRMS: found (709.2167); calc. (709.2176).

3l: ^{1}H NMR (400 MHz DMSO-d^6): δ 2.15 (s, 3H), 2.96 (t, 2H), 3.16 (t, 2H), 6.75 (t, 2H), 7.03 (t, 2H), 7.46 (s, 1H), 7.66 (m, 2H), 7.87 (t, 2H), 8.19 (s, 1H), 9.62 (s, 1H), 9.78 (s, 1H), 12.64 (bs, 1H).). ^{13}C NMR: 170.8, 170.2, 168.0, 167.2, 161.1, 155.0, 148.5, 143.5, 137.3, 136.5, 132.7, 131.2, 124.7, 121.4, 121.0, 119.4, 117.5, 106.3, 33.3, 30.5, 15.2. IR: 3395, 2927, 1637, 1606, 1539, 1463, 1435, 1383, 1282, 937 cm^{-1}. IR: 3408, 1655, 1637, 1601, 1583, 1537, 1464, 1440, 1382, 1300, 1199, 1150, 897, 760 cm^{-1}. MS: 768.2 (M+H); HRMS: found (768.2013); calc. (768.2006).

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