NMR Study of Pyridine based Tripodal Rheniumtricarbonyl Complexes (NMR and X-ray)


Technetium-99m and Rhenium (188/186) in radiopharmaceuticals:

99m−Tc is the most commonly used radio nuclide in radiopharmaceutical imaging and a very wide range of its complexes have been investigated. The similar moieties of Tc and Re offer a tremendous opportunity to study 99m−Tc containing drugs using non-radioactive 188Re. Tridentate ligands are known to be critical for maintaining the cationic nature and have a significant impact on the bio-distribution characteristics of the 99m−Tc/188Re tripodal complexes.1 When appropriate ligands coordinate to 99m−Tc(CO)3 or 188Re(CO)3 via the three pyridine rings (i.e. Complex 2), the uncoordinated apex ligand can then be functionalised as the target vehicle. Suitable complexes of this type can potentially be used for both diagnostic and therapeutic applications (see Table 1), therefore it is essential to understand the fundamental chemistry of these complexes. We have previously shown that the N-acetylated 1,1,1-tris(pyridin-2-yl)methylamine2 (R=COCH3) forms a clean lipophilic 99m−Tc-tripodal complex3, like structure 2 [R = NHCOCH3], but Tc was used instead of Re. We have now established that the nature of the metal complexes formed when such ligands react with [Re(CO)3Br] depends on the nature of the N-substituent and the reaction conditions.4,5

Complex syntheses:

We have successfully prepared a range of pyridine based tripodal Rheniumtricarbonyl complexes (both cationic and neutral) using Rhenium pentacarbonyl bromide and substituted trispyridine ligands in toluene (Fig. 1). Many of the initially formed Re(II) complexes (i.e. 2a) underwent HBr elimination and further rearrangement to give the neutral complexes (i.e. 3).

The structure of the initially formed ionic complex 2a was confirmed by NMR studies showing all three pyridine signals are all magnetically equivalent. The subsequent loss of hydrogen bromide led to the formation of the neutral complex (tpmbaRe(CO)3). This clearly suggests that ligand tpmba 2 (R = COPh), initially coordinates to the Rhenium via its three pyridine rings to give the cationic complex 2a, but due to its instability, it subsequently rearranged to give neutral complex 3.

As expected, the NMR spectra of complex 3 showed the chemical shifts of the non-coordinated pyridine to be significantly different from those of the two coordinated rings, which were magnetically equivalent. However, using the help of COSY/HSQC, more careful NMR analysis of the 1H NMR spectrum still failed to locate any signals that could contribute to the 3H protons on the two coordinated pyridine rings in 3. The clue came from the substantial broadening of carbon resonances associated with the coordinated pyridine rings observed in the 13C-NMR of the complex 3, which suggested the presence of an NMR exchange process. This was then confirmed by acquiring both the 1H and 13C NMR spectra of 3 in d2-DMSO at higher temperatures. At 371 K, a broad signal corresponding to the two protons at the 3H positions became visible at 6.8, 8.4 ppm using a 270 MHz spectrometer. The dramatic broadening of these 3H proton resonances at modest temperatures, points to the origin of these effects as being due to the restricted rotation of the uncoordinated pyridine ring. In NMR solution state, the rotating py−ring will ensure the 3H protons in the coordinated py−rings to experience the alternating effects of the nitrogen lone pair and this proposal is supported by the Single X−ray crystal structure (Fig.2) where it shows the close proximity between the two 3H protons and uncoordinated nitrogen.

Since we observed unusual 3H proton disappearance in 1H-NMR analysis of complex 3, we were interested to investigate whether the presence of a benzyl (CH2) substituent (instead of NH2) on the amine group in the type of complex would also result in some restricted rotation of the uncoordinated py−ring.

As expected, the slow rotation of the uncoordinated pyridine ring had again influenced the 3H proton in the coordinated ring of this complex 4, showing a similar broadening feature in its 1H NMR spectrum. However, only one of the 3H proton was affected (6.8 ppm). This is due to the presence of the asymmetric nature raised from the tetrahedral nitrogen, meaning the three py−rings are now chemically and magnetically nonequivalent. Hence, three sets of chemical shifts corresponding to each py−ring are observed (see spectrum), particularly for those protons at the 3H positions (6.7, 7.8, 8.17 and 8.80 ppm).

Moreover, the N−H proton shows significant coupling to one of the benzyl protons (JNH = 8 Hz), but not the other suggesting that the dihedral angle to the later benzyl proton is approaching 90° (Fig.3)

NMR study of neutral complex (tpmba)Re(CO)3.

NMR study of ionic complex [tbpba]Re(CO)3 ClBr.

NMR studies of other prepared Re(0) tripodal carbonyl complexes:

Along with many other Rheniumtricarbonyl complexes, (bpmab)Re(CO)3, 5 and (Ph-bpmab)Re(CO)3, 6 were also prepared. NMR and X-ray studies of their structures shows no sign of restricted rotation of the apog substituent and no broadening effect was observed in their 1H NMR spectra.

Table 1

<table>
<thead>
<tr>
<th>Applications</th>
<th>Diagnostic examinations</th>
<th>Therapeutic treatments to target locations</th>
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</thead>
<tbody>
<tr>
<td>Emissions</td>
<td>y−ray</td>
<td>β−ray</td>
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<tr>
<td>Generators</td>
<td>Transportable</td>
<td>Mo/Re/CoTC</td>
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<td>Half life (t1/2)</td>
<td>Optimun 6 hours</td>
<td>17 hours 186Re; 90 hours 188Re</td>
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References:


188Re/186Re NMR Spectra: At various temperatures were recorded on Bruker Avance 300, 500, and 900 MHz and test 270 MHz spectrometers. 1H NMR spectra in d2-DMSO were referenced to the residual CD2D2 signal at 2.50 ppm.

Acknowledgments:

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Figures:

Figure 1 shows the structural results of complex 3 prepared for presentation.

Figures 2-3 show the chemical structures for complexes 2a, 3 and 4 respectively.