Deuterium labelling studies with aliphatic amines

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Aliphatic amines have been labelled at α- and β-positions with deuterium using platinum-D₂O. The deuterated amines have been examined by proton and deuterium NMR spectroscopy.

During the past few decades labelling of organic molecules by incorporation of deuterium and tritium has become a widely useful technique in organic, physical as well as in biochemistry. The use of deuterated drugs has proved to be of immense value in the study of the mechanism of drug action and in elucidating metabolic and biosynthetic pathways. There are several good methods available for deuterium labelling of organic compounds and many of them are also used for tritium labelling.

Deuterium and tritium labelling of aliphatic compounds by exchange methods using metal catalyst is difficult although platinum is a good catalyst for exchange labelling of aromatic compounds. This is due to the easy formation of π-complex between the metal and the aromatic ring, which then gets converted into σ-complex (Pt-C bond). The decomposition of this complex with a suitable isotope source (D₂O/HTO, D₂T₂ etc.) yields the labelled compound. It was noticed that alkyl chains in aromatic compounds get labelled extensively and for that migration of platinum from the aromatic nucleus to the aliphatic chain has been proposed. Deuterium labelling of aliphatic alcohols and ethers by exchange using platinum catalyst is difficult. However, nitrogen being more basic than oxygen, it was thought that organic bases would complex with platinum and the molecule will get labelled in the same way as the aliphatic chain of an alkyl aromatics. Initial work in this regard was done using tritiated water and platinum for labelling of triethylamine, the tritium NMR of which showed label at the α- and β-positions. Encouraged with this result, we decided to undertake deuterium labelling of aliphatic amines in the presence of platinum as catalyst and D₂O as the isotope source.

The platinum catalyst was prepared freshly from platinum chloride by reduction with sodium borohydride. The catalyst, the amine and deuterium oxide were heated in a sealed tube at 110-20°C for 70 hr. The deuterated amines obtained were analysed by ¹H and ²H NMR spectroscopy. The relative amounts of deuterium incorporation for various amines has been given in Table I.

It is clear from proton NMR that the α-position of amine gets extensively labelled, the β-position to a small extent while other positions are negligibly labelled. It was difficult to determine whether all the positions of amines get labelled from proton NMR, hence, proton decoupled deuterium NMR spectra of some of the samples were recorded at 2H MHz (270 MHz for proton). The relative deuterium incorporations at the α- and β-positions observed from ²H NMR are given in Table II. The incorporation by ²H NMR is more reliable although there is good agreement in the results by both the methods.

Experimental Section

Platinum chloride (J & M), D₂O and sodium borohydride (E-Merck), n-butylamine and n-hexylamine (Riedel), di-n-butylamine and n-hexylamine (BDH) and tri-n-butylamine (SRL) were

| Table I—Deuterium incorporation in aliphatic amines by ¹H NMR spectroscopy |
|---|---|---|
| Sr. No. | Amine | % of Deuterium at α-position | β-position |
| 1 | n-Butylamine | 82 | 21 |
| 2 | Di-n-butylamine | 73 | 25 |
| 3 | Tri-n-butylamine | 74 | very little |
| 4 | n-Hexylamine | 62 | 36 |
| 5 | n-Heptylamine | 71 | 42 |

| Table II—Relative deuterium incorporation at α- and β-positions by ²H NMR spectroscopy |
|---|---|---|
| Sr. No. | Amine | % of Deuterium incorporation at α-position | β-position |
| 1 | Di-n-butylamine | 75 | 25 |
| 2 | Tri-n-butylamine | 83.3 | 16.7 |
| 3 | n-Hexylamine | 59.37 | 40.63 |
used. All the amines were distilled just before use. 

\(^1\)H NMR spectra were recorded on a Varian XL-100 while \(^2\)H NMR spectra on a Bruker (270 MHz) instrument.

Preparation of platinum catalyst. To a well stirred solution of platinum chloride (1g, 3.76 mmoles) in distilled water (200 mL) was added sodium borohydride (1.8 g, 47.59 mmoles) in small lots during 20 min. The solution was stirred for about 10 min and the precipitate of platinum was allowed to settle down. The supernatent liquid was decanted and the precipitate was washed with distilled water (\(3 \times 5 \text{ mL}\)) and with D\(_2\)O (\(3 \times 0.5 \text{ mL}\)). Most of the aqueous part was removed by centrifugation and the residue used for labelling of amines.

Deuterium labelling of aliphatic amines. General procedure. To a freshly distilled solution of amine (6.84 mmoles) and D\(_2\)O (0.5 mL, 22.5 mmoles) in a glass tube was added the platinum catalyst (\(~0.079 \text{ g}\)) and the tube was sealed. It was then heated in a paraffin bath at 110-20\(^\circ\)C for 70 hr. The cooled sample tubes were carefully opened, respective amine was dissolved in methylene chloride and the catalyst removed by centrifugation. The residue was repeatedly washed with methylene chloride and combined organic extract was dried over anhyd. sodium sulphate. Removal of solvent followed by short path distillation gave the deuterated amine. Following deuterated amines have been prepared. The NMR spectra of non-deuterated and deuterated amines were recorded at the same concentration under identical conditions to compare integrations for the calculation of \(^2\)D incorporation.

\(n\)-Butylamine (Deuterated): \(^1\)H NMR (CDCl\(_3\)) : 0.92 (3H, t, J=7 Hz, CH\(_3\)CH\(_2\)), 1.36 (3.16H, bs, CH\(_2\)-CH\(_2\)-CH\(_2\)-NH\(_2\)), \(\beta\)-CH\(_2\) being 21% deuterated), 2.7 (0.36H, bs, CH\(_3\)-NH\(_2\)), \(\alpha\)-CH\(_2\) being 82% deuterated).

Di-\(n\)-butylamine (Deuterated): \(^1\)H NMR (CDCl\(_3\)) : 0.94 (6H, t, J=7 Hz, 2xCH\(_3\)), 1.38 (6H, bs, (CH\(_2\)-CH\(_2\)), \(\beta\)-CH\(_2\) being 25% deuterated), 2.4 (1.08H, bs, CH\(_3\)-NH-CH\(_3\)), \(\alpha\)-CH\(_2\) being 73% deuterated). \(^2\)H NMR (CHCl\(_3\), 41.44 MHz, Reference D\(_2\)O): Relative labelling at \(\alpha\)- and \(\beta\)- positions being 75% and 25%, respectively.

Tri-\(n\)-butylamine (Deuterated): \(^1\)H NMR (CDCl\(_3\)) : 0.94 (9H, d, J=7 Hz, 3xCH\(_3\)), 1.38 (12H, brm, (CH\(_2\)-CH\(_2\)), difficult to calculate the % of deuterium labelling at \(\beta\)-position), 2.38 (1.56H, bs, N-(CH\(_2\))\(_3\), \(\alpha\)-CH\(_2\) being 74% labelled). \(^2\)H NMR (CHCl\(_3\), Reference D\(_2\)O): Relative labelling at \(\alpha\)- and \(\beta\)-positions being 83.3% and 16.7%, respectively.

\(n\)-Hexylamine (Deuterated): \(^1\)H NMR (CDCl\(_3\)) : 0.92 (3H, t, J=7 Hz, -CH\(_3\)), 1.34 (5.12H, brm, -(CH\(_2\))\(_4\), \(\beta\)-CH\(_2\) being 36% deuterated), 2.5 (0.76H, two broad singlets, CH\(_2\)-NH\(_2\)), \(\alpha\)-CH\(_2\) being 62% deuterated); \(^2\)H NMR (CHCl\(_3\), Reference D\(_2\)O): Relative labelling at \(\alpha\)- and \(\beta\)-positions being 59.37% and 40.62%, respectively.

\(n\)-Heptylamine (Deuterated): \(^1\)H NMR (CDCl\(_3\)) : 0.92 (3H, t, J=7 Hz, -CH\(_3\)), 1.32 (5.8H, bs, -(CH\(_2\))\(_4\), \(\beta\)-CH\(_2\) being 42% deuterated), 2.5 (0.58H, two broad singlets, CH\(_2\)-NH\(_2\)), \(\alpha\)-CH\(_2\) being 71% deuterated).

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References