Exchange of H Atoms for Deuterium and Tritium in Cyclic N-Nitrosamines

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The exchange of α protons for deuterium or tritium in di-N-nitrosohomopiperazine and in di-N-nitroso-2,6-dimethylpiperazine is described. It is shown that an exchange in bifunctional N-nitrosamines occurs in all acidic positions, even in those which are sterically hindered. In addition, it is demonstrated that α protons will also exchange for tritium in ²H₂O enriched H₂O, using KOH.

It has been demonstrated by different types of reactions that the α protons in N-nitrosamines exhibit an acidic character and can for this reason be exchanged for deuterium with a large excess of D₂O/NaOD.

It was therefore of interest to find out, a) whether a similar exchange could be carried out in cyclic, bifunctional nitrosamines and b) whether tritium could be introduced with a substoichiometric amount of ³H₂O in H₂O, using KOH as catalyst.

Here we report our investigations on the KOH catalyzed exchange of α protons in di-N-nitrosohomopiperazine 1 and in di-N-nitroso-2,6-dimethylpiperazine 2 for deuterium and tritium.

The substrates 1 or 2 were dissolved in hot ethanol (50 mg/0.2 ml) in a 5 ml round bottomed flask. Powdered KOH (50 mg) and D₂O (0.2 ml) or H₂O, enriched with ³H₂O (1 Ci/0.2 ml), were added and the stoppered flask was heated to 90 °C for about 16 h. After cooling, the mixture was taken up in CH₂Cl₂ (20 ml), dried over Na₂SO₄, concentrated to 0.5 ml, and the residue chromatographed on a silica gel column (30 cm × 2.5 cm) which was eluted with CH₂Cl₂/ether/a-hexane (10/7/5). The identities of the isolated labelled compounds were confirmed by thin layer chromatography against authentic unlabelled compounds and by mass spectrometry.

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The number of protons exchanged for deuterium was determined by mass spectrometry. The total exchange rate was 64% for 1 and 51% for 2. The distribution of the deuterium atoms is shown in Fig. 1.

Fig. 1. Distribution of deuterium atoms in di-N-nitrosohomopiperazine 1 and di-N-nitroso-2,6-dimethylpiperazine 2.

Tritium content in the exchanged products was determined by scintillation counting in INSTA GEL (Packard Instr. Comp., Downers Grove, III., USA). After exchange with 1 Ci ³H₂O 666 µCi/mg were obtained for tritiated 1 and 693 µCi/mg for tritiated 2.

The following conclusions can be drawn from the given results:

1) Deuterium atoms were introduced in all positions α to the N-nitroso groups of bifunctional cyclic N-nitrosamines. The yield of fully exchanged 1 is higher (4.1%) than in 2 (0.5%; cf. Fig. 1).

2) The distribution of the deuterium atoms differs in the two compounds (cf. Fig. 1); for compound 1 a smaller amount of exchange is found at low levels (0; 1 and 2 deuterium atoms) compared to the exchange at high levels (6; 7 and 8 deuterium atoms). The maximum frequency is found at 5 deuterium atoms. Compound 2 shows nearly a symmetrical distribution with the maximum in the median position. It can be assumed that the observed difference in deuterium incorporation into compounds 1 and 2 might be due to reduced acidity of α protons by the +1 effect of the substituent methyl groups. Furthermore, the methyl substituents restrict the free transition of conformers which seems to complicate the exchange.

3) It is possible to introduce both deuterium or tritium atoms into cyclic di-N-nitrosamines. The exchange for tritium can be effectively achieved even with substoichiometric amounts of reacting agent.

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