Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXV, No. 12

DEUTERIUM LABELLING OF POLY((DIMETHYLIMINIO)ALKYLENES)

B. Westermark
Department of Chemistry, University of Helsinki
E. Hesperiankatu 4, SF-00100 Helsinki

SUMMARY

Selectively deuterated monomers for preparation of deuterated poly((dimethyliminio)propylene), poly((dimethyliminio)hexylene), and poly((dimethyliminio)decylene) have been synthesized:(2-$^2H_2$)-1,3-dibromopropane, (2,5-$^2H_2$)-1,6-dibromohexane, (1,10-$^2H_2$)-, (2,9-$^2H_2$)-, and (4,7-$^2H_2$)-1,10-dibromodecane and N,N,N',N'-tetra-($^2H_2$)-methyldecamethylenediamine. The syntheses of all dibromoalkanes involved a carboxylic acid or a carboxylic acid derivative either as starting compound or as an intermediate. (2-$^2H_2$)-1,3-Dibromopropane was synthesized from catalytically exchanged ($NaO^2H/^2H_2O$) diethylmalonate by reduction with lithium aluminium hydride and bromination with HBr. (2,5-$^2H_2$)-1,6-Dibromohexane and (2,9-$^2H_2$)-1,10-dibromodecane were prepared from base-catalytically ($NaO^2H/^2H_2O$, 160°C) exchanged sodium salts of adipic and succinic acids, respectively, followed by reduction ($LiAlH_4$) and bromination (HBr). (1,10-$^2H_2$)-1,10-Dibromodecane was prepared from succinic acid by reduction with $LiAl^2H_4$ and subsequent bromination. (4,7-$^2H_2$)-1,10-Dibromodecane was synthesized by coupling the lithiooxazoline salt of acetic acid with (2,5-$^2H_2$)-1,6-dibromohexane followed by synthetic steps analogous to those above. The synthesis of N,N,N',N'-tetra-($^2H_2$)-methyldecamethylenediamine was achieved by reductive amination between hexamethylenediamine and perdeuteroformaldehyde.

Key words: poly((dimethyliminio)alkylenes), (2-$^2H_2$)-1,3-dibromopropane, (2,5-$^2H_2$)-1,6-dibromohexane, (1,10-$^2H_2$)-1,10-dibromodecane, (2,9-$^2H_2$)-1,10-dibromodecane, (4,7-$^2H_2$)-1,10-dibromodecane, N,N,N',N'-tetra-($^2H_2$)-methyldecamethylenediamine

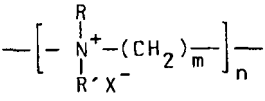
0362–4803/88/121381–11$05.50

Received March 22, 1988
Revised May 19, 1988

INTRODUCTION

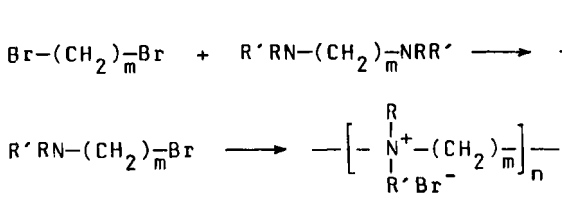
In studies of molecular dynamics ^{2}H-NMR spectroscopy has recently taken a prominent place among the NMR spectroscopic techniques /1/. However, the low natural abundance of deuterium makes a direct NMR study of this nucleus a very difficult task. In order to facilitate a ^{2}H-NMR study of the systems of interest substrates should be labelled with deuterium before the NMR measurements. Fortunately there are currently a large number of efficient methods available for the selective deuteration of a diversity of molecular positions /2/.

The present work is concerned with deuterium labelling of poly((dimethyliminio)alkylenes) (α,ω-ionenes) at several positions in the repeating units. The general stucture of the ionenes is shown below, which according to Rembaum et al. /3/ are ionic polyamines.



The ionenes are related to aliphatic biogenic amines such as putrescine, spermidine and spermine /4/. The deuterium labelling methods for the ionenes are therefore useful also for these ionic polyamines. Ionenes possess one type of exchangeable hydrogens at the carbon atoms adjacent to the quaternary ammonium nitrogens. However, due to the instability of the ionenes in solution the exchange cannot be made without a considerable degradation of the polyion chain. Furthermore the four groups adjacent to the quaternary nitrogens are about equally prone to deuterium exchange thus prohibiting any selectivity. Thus the deuterium labelling has to be performed through synthesis of the α,ω-ionenes from selectively deuterated monomers.

Ionenes are usually synthesized by polyquaternization of tetraalkyldiaminoalkanes with dibromoalkanes /5/ or from dialkylaminoalkyl bromides /6/, which are therefore used for the selective deuteration of this type of starting molecules.



Carboxylic acids are highly versatile intermediates for the synthesis of both alkyl bromides and alkyl amines in high yield. Deuterium labelling is further facilitated by some inherent chemical properties of the carboxylic acids and we therefore concentrated mainly on synthetic methods leading to labelled straight-chain 1,n-alkanedioic acids or their derivatives. A few good alternative synthetic methods for the synthesis of selectively labelled dibromoalkanes are also discussed.

In this paper we report the selective deuterium labelling of 3,3-, 6,6-, and 10,10-ionene in the following positions of the repeating units: position 2 with respect to the quaternary nitrogens for all three ionenes and further positions 1 and 4 and the methyl groups for 10,10-ionene. The synthetic procedures for the deuterated compounds do not differ significantly from well-established procedures for the protonated analogues.For such details the appropriate literature sources are referred to.

DISCUSSION

(1,n-$^2H_2$)-1,n-Dibromoalkanes

The most convenient method for the preparation of selectively 1,n-labelled 1,n-dibromoalkanes seems to be through reduction of the corresponding dicarboxylic acids or their derivatives with

lithium aluminium deuteride to diols /7a,7b/ and subsequent conversion of these to dibromides with HBr /8/. The procedures for these synthetic steps, which are analogous to those for the protonated analogues are well established.

$$RO_2C-(CH_2)_m-CO_2R \xrightarrow[THF]{LiAl^2H_4} HOC^2H_2-(CH_2)_m-C^2H_2OH \xrightarrow{HBr}$$

$$Br-C^2H_2-(CH_2)_m-C^2H_2-Br$$

The deuterated 1,n-alkanediols are stable against exchange of the deuterium atoms under the drastic conditions used in the bromination step (hot(100°) HBr,47%). For more unstable compounds the bromination can be performed for example by reaction of tri-n-alkylphosphine with carbon tetrabromide solutions of the starting diols /9/.

(2,n-1-$^2H_2$)-1,n-Dibromoalkanes

Carboxylic diacids and their derivatives are also versatile as starting compounds for dibromoalkanes labelled on the next-neighbour carbons to the bromo atoms. The acidic α-protons of dicarboxylic acid salts are exchanged by heating at 160° in ^2H_2O containing a small amount of free O^2H^-. The synthetic procedure has earlier been quite thoroughly investigated for several carboxylic acid salts /10/.

$$CH_3-(CH_2)_m-CO_2^- \ Na^+ \xrightarrow[(160^\circ)]{^2H_2O,\ O^2H^-} CH_3-(CH_2)_{m-1}-C^2H_2CO_2^- \ Na^+$$

The ((2,n-1)-$^2H_2$)-1,n-dibromoalkanes are subsequently obtained by reduction of the dicarboxylic acid to the corresponding diols and

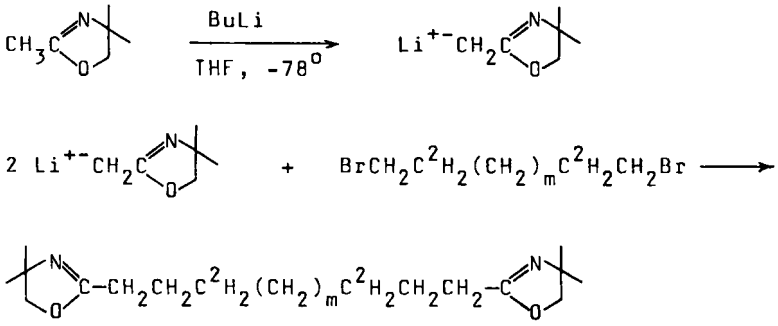
conversion of these to the dibromoalkanes.The method above is not the only possibility of synthesizing (2,n-1)-deuterated dibromoalkanes. Alternatively one could start from a straight-chain 1,m-deuterated dibromoalkane with two carbon atoms less than in that being synthesized and carboxylate the di-Grignard reagent of the latter /11/. This method is however restricted to such dibromoalkanes, which can form the Grignard reagents, i.e. there should be at least four carbon atoms in the starting dibromoalkane /12/. The same restriction with respect to the number of carbon atoms in the dibromoalkane must also be accounted for if the intermediate diol is prepared directly by Grignardation of formaldehyde /13/. The two latter methods involving the Grignardation step are useful for 1,n-labelling of straight-chain diols and dibromides with ^{13}C and ^{14}C.

(4,(n-3)-$^2H_2$)-1,n-Dibromoalkanes

Although the protons on the carbon atoms, which are more than two carbons away from the chain ends of a dicarboxylic acid, can be exchanged for deuterons with a base catalyst this cannot be done selectively. In order to deuterate such positions it is necessary to build the chain from smaller molecular fragments, which have been previously deuterated in appropriate positions.

It is well-known that the α-protons of a carboxylic acid can be made more acidic by converting the acid to its oxazoline derivative /14/. The oxazoline group is an excellent protecting group for carboxylic acids /14/ allowing the use of several useful reagents. For example the oxazoline derivatives of acetic acid can be converted to a lithium salt with butyllithium in THF /15/. This lithium salt is a very strong nucleophilic reagent and can substitute halogens of alkylhalides /15/. These properties of the lithiooxazoline derivative of acetic acid were applied in the synthesis of a (4,7-$^2H_2$)-decanedioic acid by reacting (2,5-$^2H_2$)-

1,6-dibromohexane with two moles of the former salt. The (4,7-$^2H_2$)-1,10-dibromodecane was finally obtained by analogous synthetic steps as those for the (1,10-$^2H_2$)-1,10-dibromodecane and the (2,9-$^2H_2$)-1,10-dibromodecane.



A good general alternative to obtain (4,n-3-$^2H_2$)-alkanedioic acids is to couple a (2,m-1-$^2H_2$)-labelled di-Grignard reagent with the magnesium chloride salt of 2-bromoacetic acid or alternatively a (1,m-$^2H_2$)-labelled di-Grignard reagent with magnesium chloride salt of 3-bromopropanoic acid.

Methyl-deuteration of N,N,N',N'-tetramethyldiaminoalkanes

The α,ω-ionenes are usually synthesized by polyquaternization of tetramethyldiaminoalkanes with dibromoalkanes. Consequently, methyl deuteration of these polyamines is achieved through the use of N,N,N',N'-tetra-($^2H_3$)-methyldiaminoalkanes as diaminoalkane components. At first sight it therefore appears profitable to alkylate di-$^2H_3$-methylamine with an appropriate dibromoalkane. However, it is well-known that primary or secondary amines cannot be converted directly to tertiary amines without a considerable amount of byproducts due to overalkylation. Earlier studies of alkylation reactions between dimethylamine and dibromoalkanes have shown that depending on the number of carbon atoms in the dibromoalkane either cyclic or

polymeric products (low molecular weight ionenes) are formed /16/. Such overalkylation can largely be avoided if a large excess of the starting amine is used. Such an approach for labelling is however ruled out because of high cost.

An efficient synthetic method for the direct preparation of tertiary amines from primary and secondary amines is the Eschweiler-Clarke reaction /17/. The primary or secondary amine is converted to the corresponding methyl-alkylated tertiary amine in good yield by one or two subsequent reductive aminations of formaldehyde.

$$R{-}NH_2 \xrightarrow{H_2CO,\ HCO_2H} R{-}N(CH_3)_2$$

If perdeuteroformaldehyde is used the method leads to the introduction of two deuterons per methyl group in the molecule,

$$R{-}NH_2 \xrightarrow{{}^2H_2CO,\ HCO_2H} R{-}N(C^2H_2H)_2$$

and three deuterons per methyl group if the formic acid is also deuterated. However, two deuterons per methyl group has been shown to be sufficient for most NMR applications. It has been shown that even in the solid phase methyl groups perform rapid rotations about the C-C or C-X bonds thus making the methyl deuterons equivalent /18/. An alternative for this kind of deuteration is to react the dichloride of the diacids with two moles of di-($^2H_3$)-methylamine and reduce the resulting diamide to the tertiary diamine /19/.

GENERAL SYNTHETIC PROCEDURES

In this section we outline the synthetic procedures used in the preparation of the selectively deuterated dibromoalkanes and the N,N,N',N'-tetra-($^2H_2$)-methyldecamethylenediamine. For more

details in specific synthetic steps appropriate literature sources are referred to. Modifications of the referenced procedures are emphasized however. Order of magnitude yields for the syntheses as achieved here are given. The success of the deuterations has been confirmed in terms of well-defined ^{2}H-NMR spectra of the final products.

(2-$^2H_2$)-1,3-Dibromopropane

Diethylmalonate was catalytically exchanged with deuterons in the 2-position by stirring in 0.1M O^2H^- - ^2H_2O for 12h. The mixture was then quenched with ^{2}HCl, the organic layer separated and purified by distillation. The (2-$^2H_2$)-diethylmalonate was reduced to (2-$^2H_2$)-propane-1,3-diol with lithium aluminium hydride in THF /7a/ and the diol was converted to (2-$^2H_2$)-1,3-dibromopropane with HBr(47%) /8/. The bromination with HBr was modified from the usual use of a small amount sulphuric acid as catalyst. Instead the bromination was performed in a reaction flask equipped for distillation under a slight vacuum at 100° and the excess water formed is distilled during the reaction. The water vapor together with a small amount of 1,3-dibromopropane was trapped at -10°. In order to facilitate the isolation of dibromopropane the reaction mixture was vigorously stirred with methylene chloride followed by separation of the layers. The methylene chloride layer was washed with water,saturated sodium hydrogen carbonate and again with water and finally dried over anhydrous sodium sulphate. The dibromopropane was purified by column chromatography (Merck Kieselgel 60, 70-230 mesh ASTM) with methylene chloride as eluent. Total yield ~80%.

(2,5-$^2H_2$)-1,6-Dibromohexane

1,6-Hexanedioic acid was catalytically deuterated in the 2- and 5-position with $O^2H^-/^2H_2O$ in an autoclave at 160° for 3 days

/10/. After isolation the (2,5-$^2H_2$)-1,6-hexanedioic acid was reduced with lithium aluminium hydride to the corresponding diol /7b/, which was subsequently converted to the dibromide with HBr(47%) /8/. The bromination step and the purification of the 1,6-dibromohexane was analogous to those for the 1,3-dibromopropane above. The yield was ~70%.

(1,10-$^2H_2$)-1,10-Dibromodecane

1,10-Decanedioic acid was converted to (1,10-$^2H_2$)-decane-1,10-diol by reduction with lithium aluminium deuteride in THF /7b/. The diol was subsequently converted to the dibromide with HBr(47%) /8/. The yield was ~80%.

(2,9-$^2H_2$)-1,10-Dibromodecane

The 2,9-labelled dibromodecane was synthesized in ~70% yield from 1,10-decanedioic acid analogous to that for the (2,5-$^2H_2$)-1,6- dibromohexane.

(4,7-$^2H_2$)-1,10-Dibromodecane

(2,5-$^2H_2$)-1,6-Dibromohexane was reacted with two equivalents of lithiooxazoline of acetic acid in THF (-78°C) /14,15/ and the (4,7-$^2H_2$)-1,10-decanedioxazoline was hydrolyzed to (4,7-$^2H_2$)-1,10-decanedioic acid with 3M HCl. The 4,7-labelled dibromide was subsequently obtained via reduction with lithium aluminium hydride /7b/ and conversion of the resulting diol to (4,7-$^2H_2$)-1,10-dibromodecane with HBr(47%) /8/. Overall yield was ~70%.

N,N,N,N-tetra-($^2H_2$)-methyldecamethylenediamine /17/

1 Mole decamethylenediamine was reacted with 5 moles 90% formic acid. To this reaction mixture was added 2.2 moles 35% perdeuteroformaldehyde in ^2H_2O. The resulting reaction mixture was heated under reflux at 100° for about 12h and then acidified

with HCl. Remaining formaldehyde and formic acid was evaporated, the hydrochloride taken up in water, made basic with 25% NaOH and steam distilled. The product was separated from the water by saturation with KOH and finally dried over KOH. Overall yield was ~85%.

ACKNOWLEDGEMENT

Financial support from the Academy of Finland is gratefully acknowledged.

REFERENCES

1. H.W. Spiess, Adv.Polym.Sci. 66, 23(1985)

2. A.F.Thomas, Deuterium Labeling In Organic Chemistry, Meredith, New York 1971

3. A. Rembaum, W. Baumgartner, A. Eisenberg, J. Polym. Sci., Part B6, 159(1968)

4. R.J.Bergeron, Acc.Chem.Res. 19, 105(1986)

5. A. Rembaum, H. Noguchi, Macromolecules 5, 261(1972)

6. M.R. Lehman, D.D. Thompson, C.S. Marvel, J. Amer. Chem. Soc. 55,1977(1933)

7a. R.F.Nystrom, W.G.Brown, J.Amer.Chem.Soc. 69, 1197 (1947)

7b. R.F. Nystrom, W.G. Brown, J. Amer. Chem.Soc. 69, 2548(1947)

8. O. Kamm, C.S. Marvel, Org. Synth., Coll. Vol.1, 25(1941)

9. J.Hooz, S.S.H.Gilani, Can.J.Chem. 46, 86(1968)

10. J.G. Atkinson, J.J. Csakvary, G.T. Herbert, R. S. Stuart, J. Amer. Chem. Soc. 90, 498(1968)

11. Houben-Weyl, Band 13, Teil 2a, p.247

12. Houben-Weyl, Band 13, Teil 2a, p.97

13. W.J.Gensler,P.T.Manos,I.Ruks, J.Org.Chem.33, 3408(1968)

14. A.I.Meyers, D.J.Temple, D.Haidukewych, E.D.Mihelich, J.Org.Chem. 39, 2787(1974)

15. A.I.Meyers, D.L.Temple, R.L.Nolen, E.D.Mihelich, J.Org.Chem. 39, 2778(1974)

16. A.Rembaum, H.Noguchi, Macromolecules 5, 253(1972)

17. H.T.Clarke, H.B.Gillespie, S.Z. Weisshaus, J.Amer.Chem.Soc. 55, 4751(1933)

18. L.W.Jelinski, C.E.Sullivan, D.A.Torchia, Nature 284, 531 (1980)

19. H.C. Brown, P.Heim, J.Org.Chem. 38, 912(1973)