Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXI, No. 2

SYNTHESIS OF DEUTERATED POLYETHYLENE GLYCOLS

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SUMMARY

The synthesis of polyethylene glycols [α-Hydro-ω-hydroxy-poly(oxy-1,2-ethanediyl)-d_x], deuterated in the chain, up to the length of the chain of 20 carbons was achieved by reaction of ethylene glycol-d_4 with iodine as catalyst.

Key words: deuterated polyethylene glycols, tetraethylene glycol-d_{16}, hexaethylene glycol-d_{22}, octaethylene glycol-d_{30}

INTRODUCTION

Essentially there are two principles of synthesis in the preparation of polyethylene glycols:

1. Polycondensation of a low polyethylene glycol with water-removing methods (1).
2. Synthesis of two low polyethylene glycols, whose contrary ends of chains are protected and whose reaction sites are occupied with relatively easy reacting substances (2-7).

Both methods lead to the synthesis of polyethylene glycols (2), especially tetraethylene glycol, hexaethylene glycol and octaethylene glycol. Because of the necessity to use relatively easily available deuterated starting chemicals in this work the first principle of synthesis is applied.

Perry and Hibbert (1) heated ethylene glycol for 4 hours to 190 °C (463 K), using 0,3 mass per cent of iodine as condensation catalyst. In this way they received a mixture of diethylene glycol, triethylene glycol, tetraethylene glycol and pen-

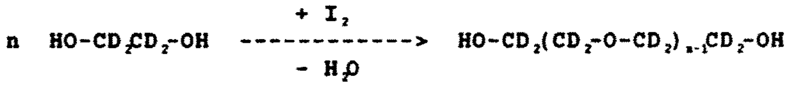
0362–4803/92/020091–04$05.00

Received 30 September, 1991
Revised 22 October, 1991

taethylene glycol which were separated by fractional distillation.

This work describes a modification of the synthesis (1) by longer reaction time and stepwise addition of iodine during reaction. Using deuterated starting chemicals the desired compounds could be prepared in the following way:

POLYETHYLENE GLYCOL-D$_x$ SYNTHESIS SCHEME



$$n\ HO\text{-}CD_2CD_2\text{-}OH \xrightarrow[-\ H_2O]{+\ I_2} HO\text{-}CD_2(CD_2\text{-}O\text{-}CD_2)_{n-1}CD_2\text{-}OH$$

(1) (2)

Deuterated polyethylene glycols are used in physical basic research, especially in research on the yield of lipids.

EXPERIMENTAL

The deuterated starting chemical in the synthesis of (2) was ethylene glycol-d_4 (1) with a content of deuterium of 99,4 atom per cent. Condensation of (1) with 1,2 per cent of iodine took place in a three neck flask by heating for 22 hours to a temperature of 190 °C (463 K). During the condensation reaction water was removed continuously by distillation. The final mixture contained diethylene glycol-d_8 (3), triethylene glycol-d_{12} (4), tetraethylene glycol-d_{16} (5), pentaethylene glycol-d_{20} (6), hexaethylene glycol-d_{24} (7) and heptaethylene glycol-d_{28} (8). By contrast an increased quantity of iodine and longer reaction time leads to additional formation of (7) and (8).

(2) was prepared by following fractionation using an effective separating distilling apparatus [fraction (1) to (6)] which operated under reduced pressure. An additional mercury vapour pump enabled a very high vacuum [fraction (7) and (8)]. The pressure was then measured by means of a McLeod gauge. In Table 1 are represented the pertinent yields and in Table 2 several analytical characteristics. Mass spectrometric analysis showed that there was no detectable reduction of the deuterium content during the polycondensation reaction.

The polycondensation of (1) should be continued to yield longer chains. Therefore (1) was condensed under the same conditions (22 hours, 190 °C), then heated with 1,2 per cent of iodine for

Table 1. Practical characteristics of the deuterated polyethylene glycols

compound	formula	yield I	yield II	boiling point	pressure
		[%]	[%]	[°C]	[mm Hg]
(1)	$C_2D_4H_2O_2$	20,6[a]	4,9[a]	51- 52	1
(3)	$C_4D_8H_2O_3$	24,2	9,1	88- 90	1
(4)	$C_6D_{12}H_2O_4$	15,0	7,4	108-112	1
(5)	$C_8D_{16}H_2O_5$	7,8	7,2	132-135	1
(6)	$C_{10}D_{20}H_2O_6$	4,3	4,4	156-163	1
(7)	$C_{12}D_{24}H_2O_7$	3,8	6,7	175-180	0,01
(8)	$C_{14}D_{28}H_2O_8$	1,5	4,1	202-205	0,01
(9)	$C_{16}D_{32}H_2O_9$	-	1,7	220-225	0,01
(10)	$C_{18}D_{36}H_2O_{10}$	-	0,8	235-238	0,01
(11)	$C_{20}D_{40}H_2O_{11}$	-	2,5	255-260	0,01

[a] recovered starting substance

Table 2. Analytical characteristics of the deuterated polyethylene glycols

compound	¹H-n.m.r. Δδ (ppm)[a]	¹H-n.m.r.		molecular weight	mass spectrometric analysis[c]
		calculated[b]	found[b]		
(1)	1,7	-	-	66	-
(3)	1,4	0,024	0,029	114	82
(4)	1,0	0,036	0,046	162	130
(5)	0,8	0,048	0,048	210	178
(6)	0,7	0,060	0,067	258	226
(7)	0,6	0,072	0,078	306	274
(8)	0,5	0,084	0,104	354	322
(9)	0,4	0,096	0,143	402	370
(10)	-	-	-	450	418
(11)	-	-	-	498	466

[a] $\Delta\delta = \delta_{OH\text{-}signal} - \delta_{internal\ CH_2\text{-}signal}$

[b] integral ratio CH_2-signal versus OH-signal

[c] greatest fragment peak in the spectrum

a further 22 hours and finally heated with 0,2 per cent of iodine for 8 hours to a temperature of 190 °C (463 K) repeatedly. The results of this modification of synthesis prove, that additional to (2) there were formed octaethylene glycol-d_{32} (9), nonaethylene glycol-d_{36} (10) and decaethylene glycol-d_{40} (11). The characteristics are represented in Table 1 (yield II) and in Table 2.

Additional deuterated polyethylene glycols with a higher degree of polycondensation were formed too, but they could not be separated with the current apparatus.

It was difficult to prove the identity of each isolated polyethylene glycol with the accessible analytical methods under the given conditions (Table 2). The difference between OH- and internal CH_2- signal in the ^1H- n.m.r.- spectrum decreases with higher molecular weights, the integral ratio between OH- and CH_2- signals is a characteristic of each member of the polyethylene glycol series and was compared with the calculated ratio.

Polyethylene glycols do not possess a molecular peak in the mass spectrum, because they are splitting the group CD_2O as the smallest fragment (8). So the separated substances are characterized by the highest mass spectrometric fragment peak.

There were no specific differences in the i.r. spectra of each member of the polyethylene glycols (6).

All typical peaks of the ^1H- n.m.r., mass spectrometric and i.r. spectroscopic analyses of the deuterated polyethylene glycols could be detected.

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