

SYNTHESIS OF SOME UNSYMMETRICALLY DEUTERATED CYCLOHEXANOLS

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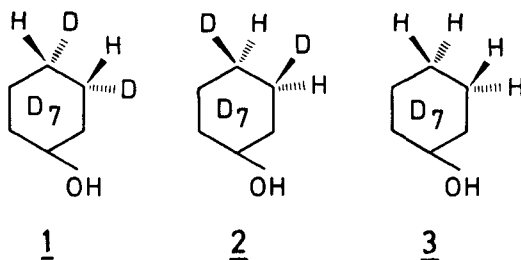
Summary

The preparations of [1,2,2,3,3,6,6-D₇]Cyclohexanol, and of two isotopomeric [1,2,2,3,4,5,5,6,6-D₉]Cyclohexanols are described. The isotopic purity of the deuterium labeled cyclohexanols is better than 90 %.

Key words: ¹H-nmr, Deuterium Labeling, Lithium Triethylborodeuteride, Cyclohexanol-d₇, Cyclohexanol-d₉.

INTRODUCTION

In connection with our NMR studies on the conformational flexibility of monosubstituted acyclic and cyclic hydrocarbons¹⁾, we considered it necessary to synthesize three asymmetrically deuterated cyclohexanols and their corresponding halides. In the past, a number of syntheses of various deuterated cyclohexanols have been published²⁾. Most of these reaction sequences are based on ring closure reactions of predeuterated molecules. The overall yield in

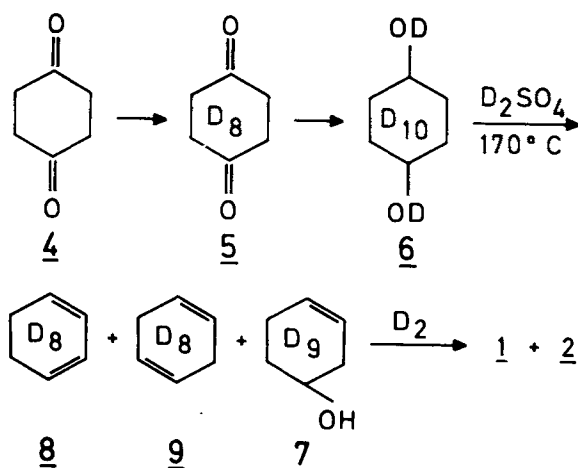


those sequences was generally small and the isotopic purity was often unsatisfactory. We want to report the efficient syntheses of the isotopomeric cyclohexanols 1, 2, and 3.

RESULTS AND DISCUSSION

The method described here starts from cyclohexanedione-1,4 4 which is fully deuterated by acid catalyzed exchange in deuterium oxide to 5 and then reduced by lithium aluminiumdeuteride to a mixture of the cis- and trans-diol 6.

Chart 1



Except for separating from inorganic material and volatile components, the diol was not purified further. Elimination of deuterium oxide from 6 was accomplished by catalytic amounts of deuterium sulfate at 170° in the absence of solvent yielding 45 % of the fully deuterated 4-hydroxy-cyclohexene 7. Considerable amounts of the isomeric deuterated cyclohexadienes 8 and 9 are formed under these conditions. 8 and 9 were identified by their glp chromatographic retention times and mass spectral data. Addition of deuterium to 7 was achieved under homogeneous phase catalysis by tris(triphenyl-

phosphine)-rhodium chloride in benzene under atmospheric pressure and at room temperature. The reaction was monitored via the disappearance of 7 by glpc.

According to the nmr spectrum (fig. 1), the product was a 1:1 mix-

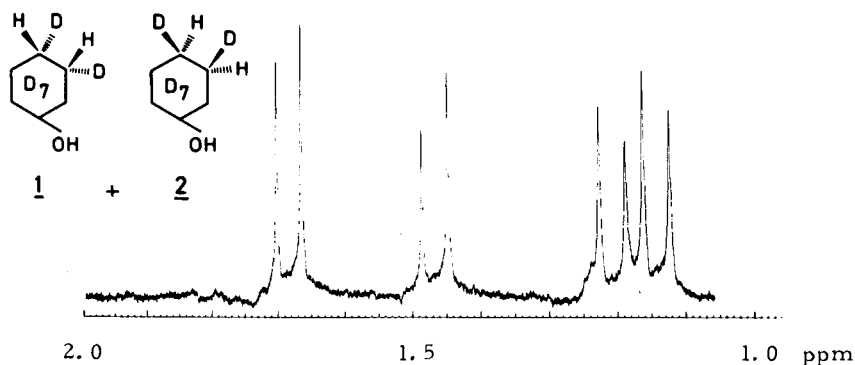
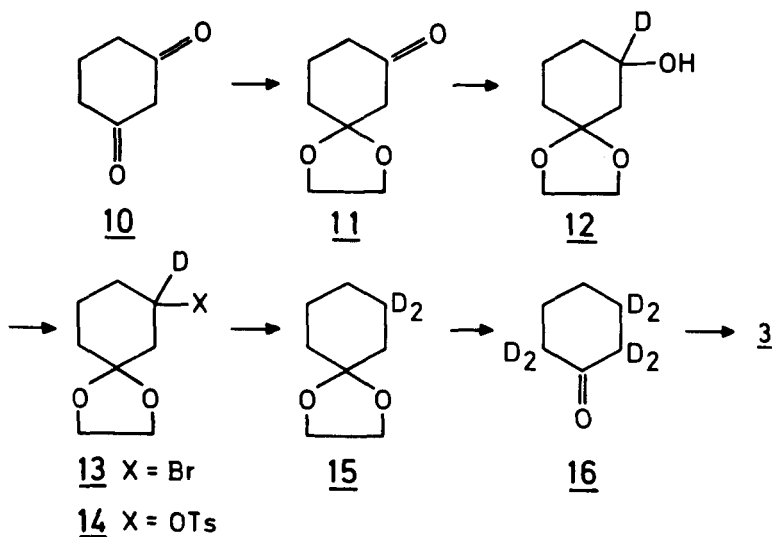


Fig. 1 100 MHz nmr spectrum of a 1:1 mixture of 1 and 2

ture of the isotopomeric cyclohexanols 1 and 2, as deuterium may add to either side of the cyclohexene double bond. The absence of additional lines in the nmr spectrum proves that no significant scrambling occurred during hydrogen addition. The overall yield of the glpc isolated mixture of the isotopomers 1 and 2 was 23.6 % based on dione 4.

The synthetic route to the cyclohexanol 3 is illustrated in chart 2. Cyclohexanedione-1,3 was converted to the mono ethylene ketal 11³⁾. In contrast to the reaction of equimolar amounts of the isomeric cyclohexanedione-1,4 and ethylene glycol yielding a mixture of di-ketal, oxo-ketal, and starting material, the reaction of 10 with ethylene glycol gives the diketal in only minor quantities. Ketone 11 was reduced by lithium aluminiumdeuteride to 3-hydroxy-cyclohexanone ethylene ketal 12.

Chart 2



There are several methods of replacing a hydroxyl group by a deuterium atom. Of these, a whole series of reactions had to be discarded because of the sensitivity of the ketal 15 to acids, the danger of scrambling the two deuterium atoms over the different ring positions, and finally the unavailability of the necessary deuterated reagents. We decided to convert the hydroxyl function to the bromide and reduce the latter by lithium triethylborodeuteride⁴⁾. In a pilot experiment a clean substitution of hydroxyl by bromide was accomplished by the triphenylphosphine - carbon tetrabromide system⁵⁾ without any detectable scrambling. Difficulties arose only when the labile bromide 13 had to be separated from triphenylphosphine oxide and excess triphenylphosphine dibromide and triphenylphosphine. However, considerable amounts of tarry material was formed when we tried to carry out the reaction and subsequent purification on a 50 to 100 mmol scale. Although the re-

duction of the bromide 13 by lithium triethylborodeuteride gave 15 in good yield, we decided to prepare the tosylate of 12 instead and reduce it to 15. Purification of tosylate 11, which seems to be also thermolabile, could be effected without extensive decomposition. Reduction to 15 gave only a 69 % yield of 15 as compared to 86 % of the bromide 13.

So far, lithium triethylborohydride had been used as a reducing agent for bromides and epoxides only⁶⁾. While the present work was in progress, two other groups reported the reduction of tosylates⁷⁾ and mesylates⁸⁾ in good yields. Though the reaction of the tosylates was reported to lead to elimination by-products, olefin formation is of only secondary importance, as the reduction accounts for over 66 % of the total conversion.

Acid catalysed hydrolysis of the ketal 15 and three additional H/D exchange cycles led to 16 which was reduced to the desired cyclohexanol 3 by lithium aluminiumdeuteride. The total yield based on ketal 11 was 39.1 %.

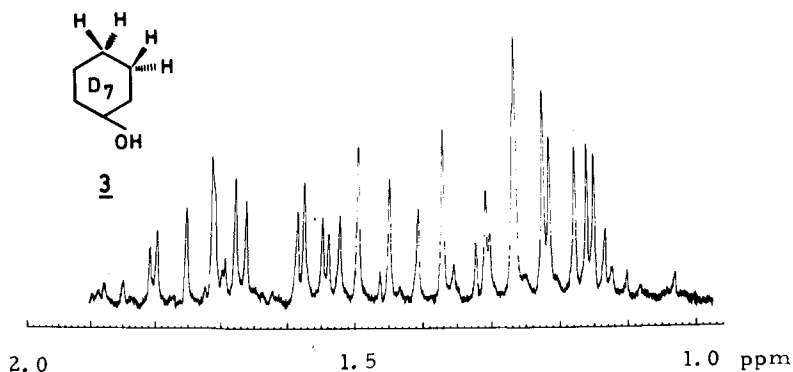


Fig. 2 100 MHz nmr spectrum of cyclohexanol-d₇ 3

The final conversion of the deuterated cyclohexanols to their halides had to avoid conditions leading to even small amounts of scrambling by-products. We used the triphenylphosphine-carbontetrahalide

systems for generating isotopically clean chlorides⁹⁾ and bromides¹⁰⁾, and N-methyl-N,N'-dicyclohexyl carbodiimidinium iodide to give unscrambled iodides¹¹⁾. If there was any small extend of scrambling at all, it is estimated to be less than 2 - 3 % by nmr spectroscopy¹²⁾.

EXPERIMENTAL

Cyclohexadione 4¹³⁾ and the cyclohexyl halides^{9,10,11)} were synthesized according to previously described procedures.

[2,2,3,3,4,4,5,5-D₈]Cyclohexane-1,4-dione 5

Cyclohexane-1,4-dione 4 (56.0 g, 500 mmol) in benzene (250 ml) was heated to reflux. A solution obtained by hydrolyzing PCl₅ (3.0 g) in deuterium oxide (60 ml, 99.7 atom % D) was added to the boiling diketone solution. The acidic deuterium oxide solution was added at the same rate as HDO/D₂O could be removed by azeotropic distillation. After the reaction was complete, all HDO/D₂O was distilled off, the reaction mixture transferred into a separating funnel, washed with two 10 ml portions of deuterium oxide. The solvent was removed in a rotary evaporator to give a red-brown residue. Purification was effected by sublimation in vacuo into a trap cooled with liquid nitrogen to give pure 5; yield : 48.1 g (80 %) M.S. (70 e.V.): m/e = 120 (M⁺), 95 % D₈, 4 % D₇.

[1,2,2,3,3,4,5,5,6,6,0,0-D₁₂]Cyclohexane-1,4-diol 6

A 2 l three-necked round-bottomed flask equipped with a teflon stirrer, dropping funnel, and a reflux condenser was flushed with dry nitrogen and charged with LiAlD₄ (4.0 g, 95 mmol) in dry tetrahydrofuran (1 l). A solution of 5 (20.0 g, 166 mmol) in dry tetrahydrofuran (150 ml) was added under vigorous agitation and after

addition was complete heated to reflux for 3 h. After cooling, excess LiAlD_4 was destroyed by adding D_2O , NaOD , and again D_2O dropwise¹⁴), filtered, and the inorganic residue washed carefully. The combined filtrates were concentrated to a few millilitres, D_2O (5 ml) and a drop of D_2SO_4 added, and the solution stirred for 1 h. Finally, all volatile components are removed in vacuo; yield : 16.4 g (77 %).

[1,2,2,3,4,5,5,6,6- D_9]Cyclohexenol-3 7

Diol 6 (16.0 g, 125 mmol) and 3 drops of 65 % D_2SO_4 in D_2O (99,5 atom % D) were heated to 170°C with magnetic agitation. The distillate consisting of a mixture of D_2O , 7, 8, and 9 was diluted with pentane and dried over Na_2SO_4 . Distillation over a 25 cm SPALTROHR column¹⁵) gave glpc pure 7; yield : 6.1 g (45 %), b.p. $67\text{-}69^\circ/15$ torr.

[1,2,2,3,4,5,5,6,6- D_9]Cyclohexanol 1 + 2

Cyclohexenol 7 (5.8 g, 55 mmol) was dissolved in dry benzene (70 ml) and degassed by bubbling a stream of dry argon through the solution. After addition of tris(triphenylphosphin)rhodium-chlorid (100 mg), the mixture was hydrogenated at a H_2 -pressure of 1 atm under vigorous stirring, until no olefin 7 could be detected by glpc (1420 ml; 63 mmol H_2). After completion of the hydrogenation reaction, all volatile components were removed under vacuo from a dark solid residue and fractionated at a SPALTROHR column; yield : 5.1 g (85 %), b.p. $84^\circ/35$ torr.

M.S. (70 e.V.): $m/e = 109$ (M^+), 95 % D_9 , 3 % D_8 , 2 % D_7 .

¹H-nmr (TMS): 2 AB signals ($\sigma_A = 1.14$ $\sigma_B = 1.67$ $\underline{J} = 3.76$ Hz)
($\sigma_A = 1.46$ $\sigma_B = 1.20$ $\underline{J} = 3.75$ Hz)

3-Hydroxy-[3-D₁]cyclohexanone ethylene ketal 12

Under an atmosphere of dry argon, oxoketal 11³⁾ (38.0 g, 250 mmol) in ether (200 ml) was added dropwise to a solution of LiAlD₄ (3.0 g, 70 mmol) in ether (400 ml) at such a rate that the reaction mixture was kept at gentle boiling. After stirring another 12 h at room temperature, the complex was decomposed by adding water and sodium hydroxide solution. The ethereal phase was separated from the inorganic salts, washed several times with ether, and the solvent removed over a 30 cm column, packed with glass helices. Rectification of the residue gave 12; yield 34.1 g (91 %),
b.p. 86-88^o/0,3-0,4 torr.
M.S. (70 e.V.): m/e = 159 (M⁺), 98 % D₁.

3-Bromo-[3-D₁]cyclohexanone ethylene ketal 13

To triphenylphosphine (26.6 g, 102 mmol) in acetonitrile (200 ml) was added bromine (16.0 g, 100 mmol) dropwise and to the resulting slightly yellow suspension the hydroxyketal 12 (15.9 g, 100 mmol) in acetonitrile (30 ml). The reaction mixture was stirred for 24 h at room temperature. After stripping off the solvent, an oily residue remained, which was extracted with ether. The ethereal layer was concentrated and stored in a refrigerator over night. The formed crystals were separated and discarded. The filtrate was completely freed from ether, and the residue subjected to a recondensation step under high vacuum. The thermolability of 13 made it necessary to cool the flask containing the raw bromide with ice water and the trap with liquid nitrogen. After 10 days, the trap contained the colorless bromide 13; yield 14.8 g (66 %).
M.S. (70 e.V.): m/e = 142 (M⁺- Br); no peak corresponding to M⁺ (m/e = 222) could be detected.

The bromide 13 had to be used immediately for further reactions. A small sample being stored for 2 days at -30^oC had decomposed to a black tarry material. .

3-Tosyloxy-[3-D₁]cyclohexane ethylene ketal 14

12 (15.9 g, 100 mmol) was reacted with toluene-4-sulfochloride in anhydrous pyridine (200 ml) at 0°C and stored in a refrigerator for 3 days. When pouring the pyridine solution into ice water (400 ml), tosylate 14 separated immediately as a crystalline white precipitate which was filtered off after 30 min, washed with water, and immediately dissolved in ether. Anhydrous magnesium sulfate was added and the ethereal solution stored in a refrigerator for 2 days. The filtered solution was concentrated in vacuo to about 75 ml. On storage at -20°C, white crystals of 14 separated; yield 27.2 g (87 %).

14 had to be stored at -30°C, as the crystals decomposed fast at room temperature.

[3,3-D₂]Cyclohexanone ethylene ketal 15

A 500 ml flat bottomed three necked flask was charged with a 1M-solution of lithium triethylborodeuteride (100 ml) in tetrahydrofuran. Under an atmosphere of dry argon, bromoketal 13 (14.2 g, 64 mmol) in tetrahydrofuran (50 ml) was slowly added. After a reaction time of 3 days at room temperature, excess reducing agent was decomposed by a few drops of deuterium oxide, until the initial gas evolution ceased, and water (200 ml) added. The main portion of tetrahydrofuran was distilled off under reduced pressure and the remaining solution extracted with three portions (30 ml) of pentane. After drying, the combined pentane extracts were distilled over a SPALTROHR column and the fraction boiling at 68-70°/20 torr was collected being pure 15; yield 7.9 g (86 %).

M.S. (70 e.V.): m/e = 144 (M⁺) 98 % D₂.

Reduction of the tosylate 14 proceeded in an analogous way except that the reaction was conducted at reflux. Yield of 15 6.4 g (69 %). M.S. (70 e.V.): $m/e = 144 (M^+)$, 98 % D_2 .

[2,2,3,3,6,6- D_6]Cyclohexanone 16

Ketal 15 (12.2 g, 85 mmol) in ether (100 ml) was hydrolyzed with a $DCl-D_3PO_4$ mixture (see above, 20 ml) over several hours under vigorous stirring to effect phase contact as efficient as possible. The ethereal layer was separated, the D_2O layer extracted with two small portions of dry ether, and the combined extracts were treated with fresh acid D_2O -solution. After three such H/D-exchange cycles, ketone 16 was isolated by distillation over a SPALTROHR column; yield 6.8 g (77 %), b.p. $85-87^\circ/80$ torr.

M.S. (70 e.V.) : $m/e = 104 (M^+)$, 92 % D_6 , 6 % D_5 , 2 % D_4 .

[1,2,2,3,3,6,6- D_7]Cyclohexanol 3

Ketone 16 (6.4 g, 61 mmol) in ether (30 ml) was added to $LiAlD_4$ (0.9 g, 21 mmol) in ether (100 ml). The reaction mixture was stirred at room temperature for another 12 h and finally decomposed with water and NaOH solution. Distillative work up gave pure alcohol 3; yield 6.1 g (93 %), b.p. $85^\circ/36$ torr.

M.S. (70 e.V.): $m/e = 107 (M^+)$, 92 % D_7 , 6 % D_6 , 2 % D_5 .

1H -nmr (TMS): $\sigma = 1.02 - 1.84$ ppm (complex, 4H)

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