Deuteration of a Substrate to high Isotopic Purity with low Grade Heavy Water

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Received on 30th October 1967.

SUMMARY

Deuterium chemistry is still quite costly, mainly because of the high prices of deuterated compounds needed for syntheses. Furthermore, the risk of diluting isotopically the compounds prepared is considerable. These disadvantages can be alleviated, if i) the deuterium of the D-donator is exchanged efficiently, ii) highly deuterated solvents and reactants can is be prepared conveniently on a laboratory scale, and iii) compounds, which have been isotopically diluted can be reconcentrated conveniently. Fulfillments of these requirements allows for research in deuterium chemistry on a close to pilot plant scale at tolerable costs.

With this aim in mind, basic principles of batch deuterations on pilot plant scale with low grade heavy water discussed. By up-grading D_2O wastes, close to 98 % of the deuterium employed for reaction can be incorporated into the substrate.
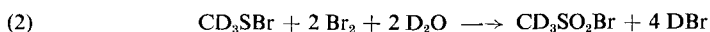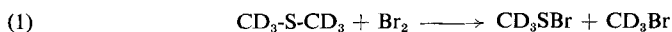
Numerous methods are known [1,2,3,4] concerning the deuteration of organic and inorganic compounds. Yet all of these methods are impracticable for pilot plant scale deuterations of a substrate to higher isotopic purity than that of the D-donor employed for reaction [23]. In this paper a convenient laboratory method is described, where the deuteration to high isotopic purity is carried out with low grade heavy water (20-99 % D_2O). Based on this method d_6-dimethyl-sulfoxyde, d_6-dimethylsulfide, d_3-methylbromide and d_4-ammoniumchloride were prepared with a purity of above 99.9 %-D. These results were achieved by deuteration with concommitant rectification.

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PRINCIPLE.

The basic principle of the method consists in running a D_2O rectification column, packed with DIXON rings, under reduced pressure (80 mm Torr). The still (Fig. 1) contains besides D_2O a suitable substrate (viz. dimethyl-sulfoxyde, ammoniumchloride) and, if necessary, an appropriate catalyst (K_2CO_3). H_2O produced by exchange of the substrate with D_2O is continuously removed by rectification. Continual removal of overhead product finally leaves in the still a highly deuterated substrate, which is in equilibrium with the surrounding heavy water.

RD REFLUX DRUM
W WASTE
R1 FLOW RATE CONTROL
SG FLOAT CHAMBER
F FLOAT
TH THERMOSTAT
V1 MAGN VALVE
SB STILL

FIG. 1. Deuteration Unit.

A batch of 1-2 kg of substrate, which must be stable against prolonged boiling with heavy water, yields in the course of the process (2-6 weeks) not more than 8-10 liters of D_2O waste; the main bulk of it having an average concentration of close to the theoretical lowest value (depending on operating conditions : appr. 70 % D_2O). For optimal controle of the deuteration process it is desirable, that the flow rate of waste D_2O is adjustable to within 10 % in the range of 5 ml/6 h (20 ml/d) and 50 ml/15 min (4.8 liter/d). An electronic controle unit (Figs. 2, 6) was constructed for the purpose of running the deu-

teration automatically. It is convenient to use, though not essential for the process. At the end of the process, the 8-10 l of waste D_2O are up-graded by rectification in the deuteration unit (Fig. 1). This leaves an ultimate waste of several liters of 1-2 % D_2O. It is thus possible to incorporate into the substrate close to 98 % of the deuterium contained in the D_2O employed for reaction.

The efficiency of the method is exemplified by the deuteration of dimethylsulfoxyde and ammoniumchloride. The scope of this method can be demonstrated by the deuteration to high isotopic purity of methylbromide, a volatile, reactive compound with three covalently bounded hydrogen atoms.

Since methylbromide can not be deuterated directly without great efforts, a round about way was chosen. First, dimethylsulfoxyde was deuterated to 99.98 %-D by rectification of heavy water, ranging in concentration between 20.5 %-99 % D_2O. Then the product was reduced with d_1-hydriodic acid (99.79 %-D) in the presence of red phosphorous [5] to d_6-dimethylsulfide (99.98 %-D). Bromine in d_1-acetic acid (99.98 %-D) cleaved the sulfide to d_3-methylbromide (99.91 %-D) and d_3-methanesulfonicacid bromide :

(1) $$CD_3\text{-}S\text{-}CD_3 + Br_2 \longrightarrow CD_3SBr + CD_3Br$$

(2) $$CD_3SBr + 2\,Br_2 + 2\,D_2O \longrightarrow CD_3SO_2Br + 4\,DBr$$

780 ml of d_1-hydrobromic acid (99.97 %-D) were obtained as byproduct. It is of interest to note, that the CH_3-group of d_1-acetic acid does not exchange its hydrogen under the experimental conditions stated below, otherwise the deutero-hydrobromic acid obtained would have shown a considerable isotopic dilution. The reduction of the sulfoxide to the sulfide may be carried out with DBr as well. The reaction is rather vigorous, though, and the yield is not quite as good. The overall yield of d_3-methylbromide, starting from d_0-dimethylsulfoxide, is close to 70 %. The scission of the CS-bond of dimethylsulfide proceedes readily with chlorine and bromine, but not with iodine. The dimethylsulfide-diiodide is reasonably stable. But when it reacts further, it shows a tendency to rearrange to iodo-dimethyl-sulfide [6, 7, 8, 9].

EXPERIMENTAL.

Rectification column.

An efficient rectification column [10, 11, 12] with appr. 170 plates can be constructed quite easily in the laboratory. A 4 m glass tube ($\varphi_i = 50$ mm) with glass joints on both ends is mounted vertically. Then a wide mesh steel cone, tip pointing upwards is inserted at the bottom end. 8 liters of clean 3 mm DIXON bronze rings (mesh : 2,700/cm²) are soaked for 24 h in hot, saturated sodiumhydroxide solution, washed alkali-free, dried, and are then dropped

through a sieve at a low rate into the column. At this point utmost care must be taken, to bring about random orientation of the DIXON rings. A second steel cone is introduced at the top end of the column to avoid dislocation of the rings during operation. Then a reflux drum RD (Fig. 1) with condenser K1, a float chamber SG, liquid return H4, vacuum pump P with pressure regulator and magnetic valve V1 are mounted as depicted in Figure 1. Finally the column is washed by refluxing with a 1 : 1 mixture of methylethylketone and water and is vakuum dried. Such a column has the following characteristics : separation parameter $\delta = 4.95.10^{-2}$; number of plates $n = 170$; (at 80 mm Torr); $n\delta = 8.5$; boil-up rate : 50 liters/d.

d_6-*Dimethylsulfoxide*, d_4-*ammoniumchloride*.

The column was evacuated to 80 mm Torr. and kept at this pressure throughout the entire operation. Then 3 liters of 20.5 % D_2O were filled into the still of 6 liters capacity. The still was fitted with four 1 KW Quickfitt heating rods. The column was flooded and then run just below the flooding point. After 3 days the concentration in the still was $c_o = 26.4$ %, that of the overhead product $c_e = 0.5$ %. ($n\delta = 4.2$). Heavy water with less than 1 % D_2O is discarded in our laboratories, because the high cost of reconcentration does not justify expenses involving upgrading such wastes. Now
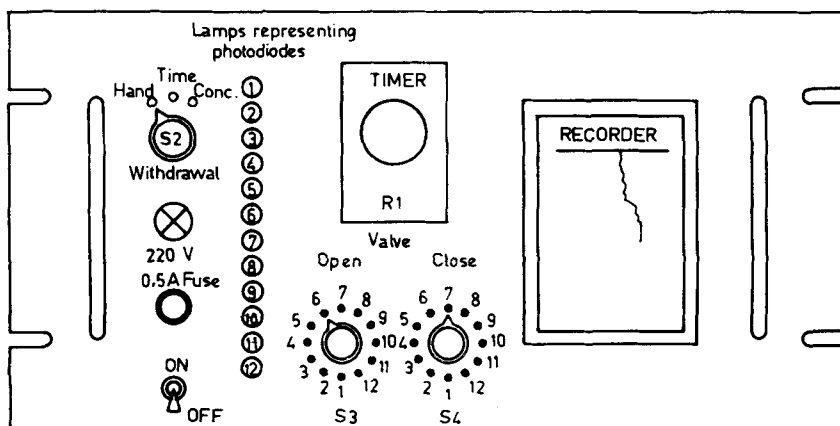

FIG. 2. Flow Rate Controle Unit : front view.

1.5 liters of freshly destilled dimethylsulfoxide and 6 g anhydrous potassium carbonate dissolved in 1 liter of 20.5 % D_2O were filled into the column over a period of 2 hours. After 24 h overhead product was withdrawn with the help of the flow rate controle unit (Figs. 2, 6). Enough D_2O of appr. 50 % was fed into the still to keep the volume constant. The concentration of the feed used

was, up to 90 % D_2O, roughly 30 % higher than the heavy water concentration in the still. Once the concentration of the overhead product has reached 90 %, a total of 500 ml of 99.2 % D_2O was gradually fed into the still and the column was subsequently run at close to equilibrium conditions, i.e. not more than 50 ml/d of overhead product are removed. Care should be taken, that the ratio of sulfoxide to water never rises above 0.4. Finally the column was operated without withdrawal for another 3 days, then as much D_2O as feasible was withdrawn from the still through the column. Air was passed into the column from the top and the still was removed quickly so as to prevent dilution of its content by water running in from the column. The product in the still was immediately transferred to a modified Thuerkauf-Baertschi Column (height : 2 m) and fractionated. The modification consists in mounting a thermostatically controlled condenser on top of the column. The rate of withdrawal of overhead product is controlled by regulating the temperature of the condenser water. In this manner very pure d_6-dimethylsulfoxide can be prepared : mp. 20.70-20.73° C, bpt. 56° C at 2 mm mercury, yield : 95 %; D-content : 99.98 %-D, D_2O (moisture) : 0.001 %. The entire operation takes approximately 15-20 days.

Likewise, 1.2 kg of ammonium chloride were deuterated by rectification. The rub-off from the Dixon rings contaminated the raw product with copper. The latter was removed conveniently by letting the hot ammoniumchloride-D_2O solution stand over zink-filings for 24 h. The high grade D_2O is destilled off and the residue sublimed. The d_4-ammoniumchloride has an isotopic purity of 99.95 %-D. Heavy metal impurities : 1 ppm copper, 20 ppm zink.

d_1-*Hydriodic acid* (99.79 %-D).

64 g (2.07 g-atoms) of dry red phosphorous were suspended in 300 g of 99.991 % D_2O. 220 g (1.73 g-atoms) of iodine were slowly added with cooling. Through a 30 cm Vigreux column 390 g (92.5 yield) of deutero-hydriodic acid (bpt. 126° C) were distilled. Density : 1.79 g/ml; 53.9 wt-% of DI; 99.79 mol-% D. [13].

d_6-*Dimethylsulfide* (99.98 %-D).

In a round-bottom flask fitted with a dropping funnel and a 30 cm Vigreux column 30 g (0.97 g-atom) of red phosphorous were suspended in a mixture of 200 g d_1-hydriodic acid (99.79 mol-%-D) and 100 g of D_2O (99.991 %). The mixture was then heated to appr. 80° C. 380 g (4.51 moles) of d_6-dimethylsulfoxyde (99.98 %-D, mp. 20.73° C) were dropped into the reaction mixture at such a rate, that the temperature of the distillate never rose above 38° C. As soon as the phosphorous was used up, an additional portion of 20 g (0.64 g-atom) was added and the reaction continued. The distilled sulfide was washed with two 50 ml portions of D_2O (99.991 %) and frac-
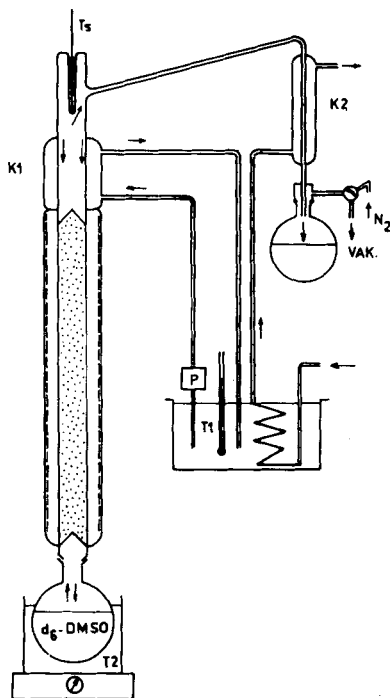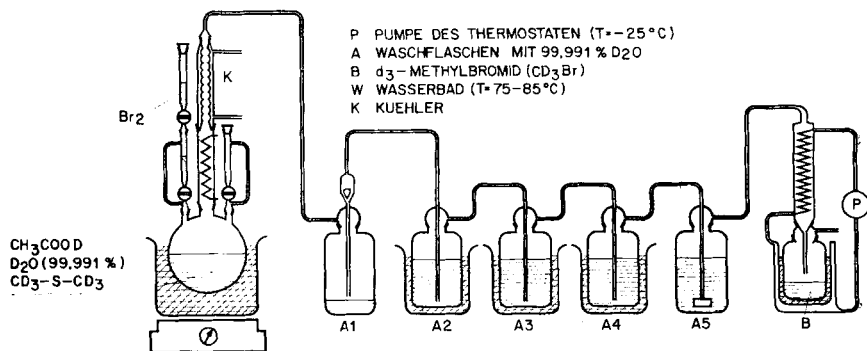
FIG. 3. Modified Thuerkauf- Baertschi column

T_1 Temperature of thermostat.
T_2 Temperature of water bath.
T_S Temperature of distilling liquid.
$K_{1,2}$ condensers.
P   pump.

FIG. 4. Apparatus for the preparation of of d_3-methylbromide.

P   pump.
A_{1-5} wash bottles containing 99,991 % D_2O.
B d_3-methylbromide at -30° C.
K   condenser.

tionated in the modified Thuerkauf-Baertschi column (Fig. 3). 260 g (84.5 % yield) of pure product (99.98 %-D, bpt. 35.5° C) were collected. A residue of 32 g, consisting mostly of impure sulfide was retained for the fractionation of the next batch of sulfide.

The reduction of the sulfide may be carried out with d_I-hydrobromic acid. After an initial latent period the reaction starts up quite vigorously. The yield is between 70-75 %.

d_3-Methylbromide (99.97 mole-%-D).

In a 2 liter round-bottom flask (see Fig. 4) 68.2 g (1 mole) of d_6-dimethyl-sulfide (99.98 %-D) were dissolved in 217 g (3.55 moles) of acetic acid-OD (99.98 %-D) [14, 15, 16, 17]. The latter was prepared by mixing equivalent amounts of pure, fractionated acetic acid anhydride with D_2O (99.991 %). The 160 g (2 g-atoms) of bromine were dropped slowly into the cooled mixture, whereupon a yellow precipitate of d_6-dimethylsulfide dibromide appeared [18, 19, 20, 21, 22, 8]. 60 g (2 moles) of D_2O (99.991 %) were added. A slow stream of dry nitrogen (P_2O_5) is passed through the apparatus to avoid sucking back of the liquid in washbottles A1-A5 (Fig. 4). The reaction mixture was then heated to 80-90° on a waterbath. An additional amount of 320 g (4 g-atoms) of bromine was now added at such a rate, that a steady stream of d_3-methyl-bromide bubbled through the last wash bottle A5. After the reaction has subsided another two portions of 68 g of d_6-dimethyl-sulfide, 60 g of D_2O, 100 g of acetic acid-OD and 480 g of bromine, were reacted as described above.

The crude methylbromide was refluxed with calciumhydride for one hour and then distilled. The product is slightly contaminated with d_9-trimethylsol-fonium bromide, but can be freed from it readily by an additional distillation. Yield : 238 g (81 %), bpt. 2° C, D-content : 99.91 mole-%-D.

780 ml of d_I-hydrobromic acid were obtained as by-product : bpt. 125° C; D-content : 99.96 %; density : 1.55 g/ml (24° C). The d_3-methanesulfonic acid in the residue was not isolated because the yield is rather low.

Operation of flow rate controle unit.

The withdrawal of overhead product of a given preset concentration is brought about by the following method. A float F swimming in the overhead product W is illuminated by a parallel ray of light. The shadow of the float falls on a sequence of twelve photodiodes. These are mounted in an aluminum block in a vertical line at a distance of 5 mm apart from oneanother. Since the density of H_2O ($d_4^{20} = 0.9982$) is different from that of D_2O ($d_4^{20} = 1.1054$), the position of the float at a given temperature is determined by the D_2O concentration of the surrounding water. This concentration decreases during rectification, as long as the dynamic equilibrium is not reached and no overhead product is removed. The float, therefore, sinks correspondingly. Now, a con-
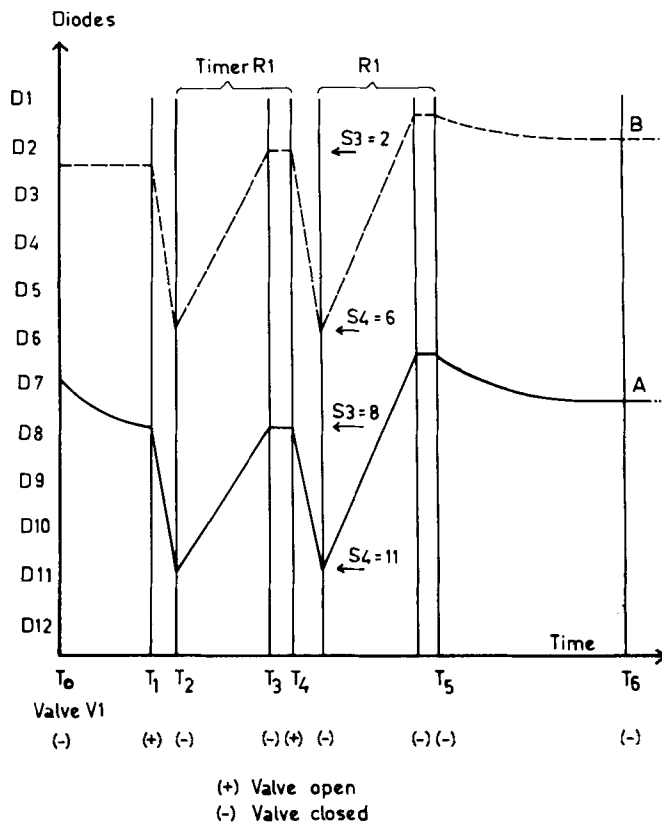
FIG. 5. Schematic movement of float during deuteration. (see also Fig. 2)

venient diode is chosen, say D8, by setting switch S3 on position 8 (Fig. 2). In the course of rectification the ray of light to D8 is intercepted by the float F $(y_{nH} = y_{S3})$* [24], valve V1 opens and the overhead product flows from container SG via stop cock H5 into the recipient W1 (Fig. 1). The float F sinks until it reaches a previously selected diode, say D11 (Fig. 2). As soon as the shadow of the float falls on D11, valve V1 closes again. Heavy water from the top end of the rectification column flows continuously from the reflux drum RD through stop cock H1 into the float vessel SG and replenishes the withdrawn quantity of D_2O. During this period F rises until SG is filled, the excess heavy water running back onto the column via stop cock H3 and H4. To ensure, that Valve V1 does not open until SG is filled to the overflow, the

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* y_{nH} = mole fraction of H_2O in overhead product; x_{oH} = mole fraction of H_2O in still; y_{S3} = mole fraction of H_2O in overhead product which is just enough to allow float F to cover the diode Di preselected with switch S3.

FIG. 6. Electronic circuit of flow rate controle unit.

electric current to the magnetic valve V1 is interrupted as soon as the diode selected by S4 lies in the shadow of F. The required length of this interruption (T_f) is controlled by timer R1. If T_f has elapsed, the process repeats itself, provided that the diode selected by S3 is not illuminated.

The heavy water concentration in the float chamber SG rises appreciably after several withdrawals, i.e. the density rises. The float comes to a stop at a position above the one chosen by S3. Valve V1 remains shut, because $y_{nH} < y_{S3}$. After y_{nH} has risen to the concentration $y_{nH} = y_{S3}$, the process of removal of overhead product repeats itself.

Finally, however, the point is reached, where y_{nH} is always smaller than y_{S3}, because the number of stages n used for rectification in the column

is not large enough to make $y_{n\mathrm{H}} \geqslant y_{\mathrm{S}3}$ (see Fig. 5, point A). The general equilibrium relationship of a binary system is expressed by the equation :

$$\frac{y_{n\mathrm{H}}}{1 - y_{n\mathrm{H}}} = e^{n.\delta} \cdot \frac{X_{o\mathrm{H}}}{1 - X_{o\mathrm{H}}}$$

In this case S3 and S4 are readjusted to higher lying diodes, say to S3 = 2 and S4 = 6 (Fig. 5, dotted line). If the condition is reached again, that $y_{n\mathrm{H}} \leqslant y_{\mathrm{S}3}$ (Fig. 5, point B), then the float can be made to sink by raising the temperature of the thermostating water. Furthermore, mechanical readjustment of the diode set and replacement of the float, by a heavier one makes it possible to carry out all above described operations at higher D_2O concentrations.

Floats are made from commercially available 50 ml brown glass vials, with necks drawn out to thin capillaries. The vials are filled with the desired amount of mercury. Such floats were used for the following D_2O concentration ranges : 15-30 %, 40-65 %, 75-80 %, 81-90 %, 90-93 %, 91-97 % and 97-99.7 %. For a rectification column with approximately 170 stages an overhead product concentration of 99.7 % D_2O indicates a concentration in the still of at least 99.9 % D_2O, provided that no H_2O seeps into the system through leaks in the fittings. The sensitivity of floats to changes in D_2O concentration and temperature varies; but it has been found useful to make the neck of the float thin enough, that it rises at concentrations above 99 % D_2O by 5 mm for each 1/100th-% rise in D_2O concentration and falls by 3 mm for each 1° C rise in temperature.

Deuterium analyses: All analyses for deuterium were carried out by NMR spectroscopy on a Varian A-60 instrument. d_6-Dimethylsulfoxyde (99.98 %-D) was taken as standard. The integrated methyl peak peaks of d_6-dimethylsulfide and d_3-methylbromide corresponded to 99.98 % and 99.91 %-D, respectively.

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n = number of stages in rectification column; α = relative volatility of H_2O and D_2O
δ = separation parametre : $\alpha = e^{n.\delta}$.

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