STEREOCHEMISTRY OF REDUCTIVE DEHALOGENATION WITH DEUTERIUM GAS

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SUMMARY

The stereochemistry of reductive debromination and deiodination of 4-haloprolines and 2- or 7-bromocholesterols with $^2H_2$ catalyzed by Pd was investigated using ^2H NMR. The reactions are stereoselective but not stereospecific.

Keywords: deuteration, L-proline, cholesterol, ^2H NMR

INTRODUCTION

Tritium or deuterium can be introduced into organic molecules with $^3H_2$ or $^2H_2$ and a catalyst using alkenes or haloalkanes as substrates. The stereochemistry of this reaction in cycloalkenes has been thoroughly investigated[1], especially by the application of ^3H NMR. Less is known about the reaction with halocycloalkanes. Gut and Uskovic[2] studied the dehalogenation of 7-bromosteroids such as 7α-bromocholesterol acetate (Fig. 1, 1) with $^2H_2$. On the basis of chemical degradation reactions they concluded that the reaction proceeded with retention, but experiments with tritium and analysis with ^3H NMR[1] indicated that the reaction is not stereospecific.

Recently Römer et al[3] synthesized [2-^{2}H]- and [2-^{3}H]-cholesterol from 2α- or 2β-bromocholesterol (Fig. 1, 2,3). Based on chemical degradation they claimed that the reaction proceeded with retention. To test whether reductive debromination indeed proceeds

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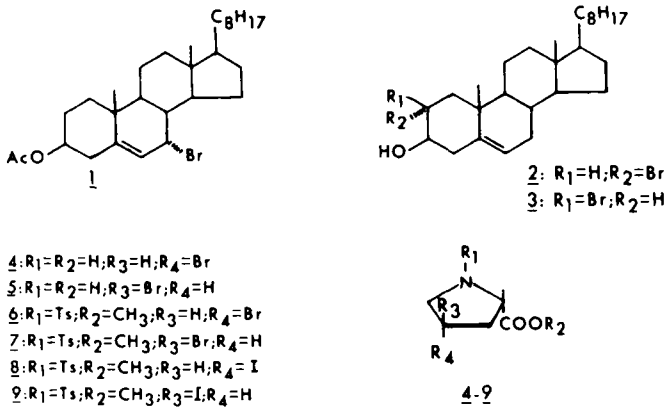


Figure 1.

with retention we reinvestigated the reductive debromination of 1-3 using ^{2}H NMR for analysis of the labelled products. Since we are interested in a short synthesis for [4-trans-^{3}H]proline[4] we also investigated the dehalogenation of some 4-halo-L-proline derivatives (Fig. 1, 4-9).

EXPERIMENTAL

^{1}H NMR spectra were recorded at 200 MHz on a Bruker WP200 or 360 MHz on a AM360 NMR spectrometer. ^{2}H NMR spectra were measured on the Bruker AM360 operating at 55,28 MHz. Chemical shifts are given in ppm with respect to TMS. Mass spectra were recorded on a Varian MAT 311-A (EI and DCI) or a HP 5995A GC-MS combination (EI). TLC scan plates were scanned with a Camag TLC scanner at 235 nm.

7-α-bromocholesterol acetate (1)[5]

^{1}H NMR ($C^{2}HCl_3$): δ =3,85 (H_3); 4,62 (H_7) and 5,60 (H_6); mass spectrum (EI): m/z=426 (5% ($(M-HBr)^+$); m/z=366 (100% $(M-HBr-HOAc)^+$).

2-α-bromocholesterol (2)[3]

^{1}H NMR ($C^{2}HCl_3$): δ =4,70 (H_2); 3,35 (H_3); 5,43 (H_6); mass spectrum (EI): m/z=464/466 (45%, M^+); m/z=385 (70%, $(M-Br)^+$); m/z=384 (100%, $(M-HBr)^+$).

2-β-bromocholesterol (3)[3]

^1H NMR (C^2HCl_3): δ =4,20 (H_2); 3,60 (H_3); 5,43 (H_6); mass spectrum (EI): m/z=464/466 (30%, M^+); m/z=384 (22%, $(M-HBr)^+$); m/z=367 (30%, $(M-Br-H_2O)^+$).

cis-4-bromo-L-proline (4)[6]

^1H NMR (^2H_2O): δ =4,40 (H_2), 2,70 and 2,95 ($2xH_3$); mass spectrum (DCI/NH_3): m/z=194/196 (30%, MH^+); m/z=211/213 (15%, $(M+NH_4)^+$).

trans-4-bromo-L-proline (5)[6]

^1H NMR (^2H_2O): δ =4,55 (H_4); 2,60 and 2,80 ($2xH_3$); mass spectrum (DCI/NH_3): m/z=194/196 (35%, MH^+); m/z=211/213 (18%, $(M+NH_4)^+$) According to ^1H NMR the compound contained 5% of the corresponding cis-isomer (4).

N-tosyl-4cis-bromo-L-proline methyl ester (6) and N-tosyl-4--trans-bromo-L-proline methyl ester (7) were prepared by refluxing a solution of N,O-ditosyl-trans-4-hydroxyl-L-proline-methyl ester (10; 1 gram) in acetone (100 ml) with LiBr (4 gram) for 48 hours. After evaporation of the acetone, the residue was extracted with dichloromethane and this extract was chromatographed over silica gel (mobile phase n-hexane/ethyl acetate, 3:1 v/v) yielding apart from starting material (18% yield) pure cis (6) and trans-bromide (7); both in a yield of 300 mg (36%) as colourless crystals.

cis-bromide (6)

^1H NMR (C^2HCl_3): δ =4,00 (H_4); 2,45 and 2,75 (H_3); mass spectrum (EI): m/z=302 and 304 (30%, $(M-COOCH_3)^+$); m/z=91 (100%, $(C_7H_7^+$)

trans bromide (7)

^1H NMR (C^2HCl_3): δ =4,40 (H_4); 2,45 (H_3); mass spectrum (EI): m/z=302 and 304 (30%, $(M-COOCH_3$); m/z=91 (100%, $(C_7H_7)^+$)

N-tosyl-4-cis-iodo-L-proline methyl ester (8) and N-tosyl-4-trans-iodo-L-proline methyl ester (9) were prepared by refluxing a solution of N,O-ditosyl-trans-4-hydroxy-L-proline methyl ester ((10, 1 gram) in acetone (100 ml) with NaI (4 g) for 48 hours. After evaporation of the acetone, the residue was extracted with dichloromethane and this extract was chromatographed over silica gel (mobile phase n-hexane/ethyl acetate, 3:1 v/v) yielding apart from starting material (43% yield) pure cis (8) and trans-iodide (9); yields 160 mg (17%) and 300 mg (32%) respectively; both colourless crystals.

cis-iodide (8)

^{1}H NMR (C^2HCl_3): δ=3,75 (H_4); 2,40 and 2,80 (H_3); mass spectrum (EI): m/z=350 (61%, $(M-COOCH_3)^+$); m/z=91 (100%, $(C_7H_7)^+$)

trans-iodide (9)

^{1}H NMR (C^2HCl_3): δ =4,30 (H_4); 2,45 (H_3); mass spectrum (EI): m/z=350 (54%, $(M-COOCH_3)^+$); m/z=91 (100%; $(C_7H_7)^+$)

Deuteration reactions

The deuteration reactions were carried out under a pressure of 20-40 cm H_2O ($\sim 10^5$ Pa). The substrate was dissolved in a concentration of 10 mg/ml (for solvents see Table I) while the same amount of catalyst was used. After removal of the catalyst over hyflo and evaporation of the solvent in vacuo the deuterated products were isolated by preparative TLC on silica gel for cholesterol-acetate using n-hexane/ethyl acetate (95:5, v/v) for cholesterols n-hexane/ethyl acetate (6:4, v/v) for L-prolines n-butanol/acetic acid/water (4:1:1, v/v) and for N-tosyl-L-proline methyl esters n-hexane/ethyl acetate (6:4, v/v) as mobile phase.

RESULTS

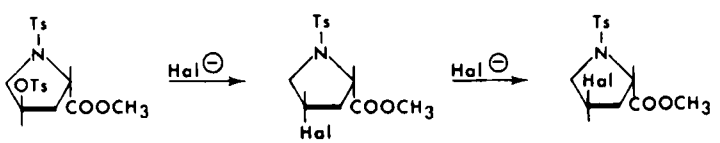
Synthesis of starting materials

The substrates for the reductive dehalogenation were synthesized

according to the literature: 2α- and 2β-bromocholesterol 2,3 were prepared from cholesterol as described by Römer et al[3], 7-α-bromocholesterol acetate (1) from cholesterol as described by Gut and Uskovic[2]) and cis and trans-4-bromo-L-proline (4,5) from L-proline as described by Wieland et al.[6]. The N-tosyl-4-halo-L-proline-methyl esters (6-9) were prepared by reaction of N-O-ditosyl-4-trans-hydroxyl-L-proline methylester (10) with sodium iodide or lithium bromide (Fig. 2) while the cis and trans products were isolated by chromatography. All compounds had a chemical purity of ≥98% except for 4-trans-bromo-L-proline (5)[7], which contained about 5% of the corresponding cis isomer (4).

Deuteration reactions

The deuteration reactions were carried out with deuterium gas under low pressure (10^5 Pa). The conditions are summarized in Table I. The deuteration reactions were followed by TLC and after completion of the reaction the products were isolated by chromatography and analyzed by ^1H NMR and ^2H mass spectrometry. The assignment of the resonances of the protons/deuterons in cholesterol was done using ^1H-^1H correlation NMR spectroscopy[8]: for N-tosyl-L-proline-methyl ester the signals were assigned in analogy with other 4-substituted-N-tosyl-L-proline-methyl esters, viz. δH_4-cis > than δH_4-trans[9] (see Fig.3). In the case of the L-prolines the difference between δH_4-trans and δH_4cis is too small (0,02 ppm[10]) to be used in ^2H NMR and for this reason we tosylated the prolines (with tosylchloride in NaOH[11]) resulting in a larger difference between H_4-trans and H_4-cis (again δH_4-cis > δH_4-trans).



10 6,8 7,9

Figure 2

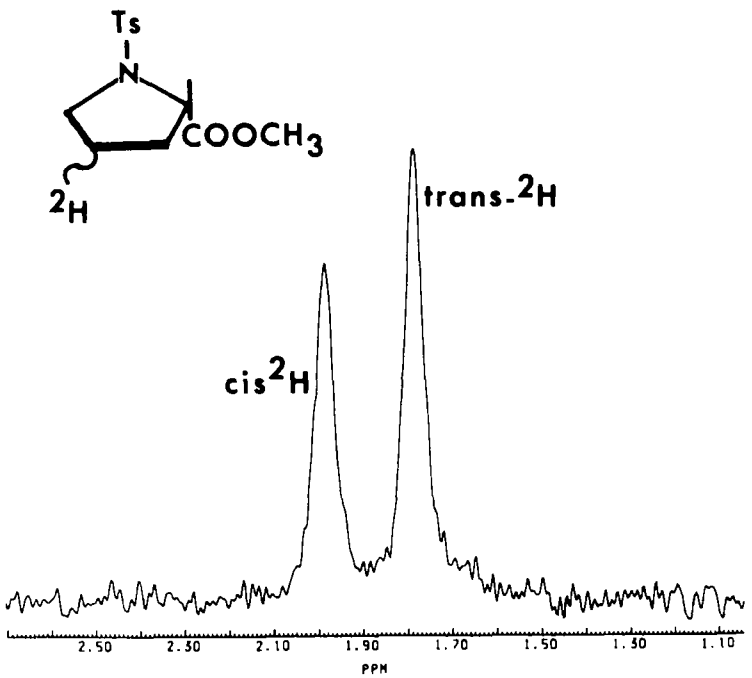


Figure 3: ^{2}H-NMR ($C^{1}HCl_3$) spectrum of N-tosyl-4-deutero-L--proline methyl ester formed upon reductive deiodination of N-tosyl-4-cis-iodo-L-proline methyl ester (8). (After 105 minutes).

A possible complication of reductive dehalogenation is isomerisation of the starting material under influence of the halide released. For the N-tosyl-4-bromo-L-proline methyl esters, the 4-bromo-L-prolines and the 2-bromocholesterol no (<2,5%) isomerisation was observed (using TLC or HPLC). For 7α-bromocholesterol a number of side products (about 5, depending on the catalyst) were formed; no attempts were made to isolate and identify these products.

With the N-tosyl-4-iodoproline methyl esters (8,9) a clear isomerisation was observed (see Fig.3). The results of this reaction are given in Fig. 4a,b. Since we measured the ^{2}H-distribution and the total amount of reduced material at different times it was possible to extrapolate the values for the reductive

Table I: Deuteration of the different halo-substrates

Substrate	Solvent	Catalyst	Reaction time	Position of ^{2}H in product
1	ethyl acetate	Pd/C (10%)	2 hours	50% α ; 50% β
	ethyl acetate	$Pd/CaCO_3$ (10%)	5 hours	50% α ; 50% β
	dioxane/triethyl amine (9:1, v/v)	Pd/C (10%)	5 hours	33% α ; 67% β
2	dioxane/ethanol/aq NaOH (1 N) (10:3:2, v/v)	Pd/C (10%)	1,5 hours	90% α ; 10% β
3	dioxane/ethanol/aq.NaOH (0,5 N) (20:1:1, v/v)	Pd/C (10%) Pd/C (10%)	1,5 hours	80% α ; 20% β
4	DMF/H_2O (9:1, v/v)	Pd/C (10%)	2 hours	50% cis ; 50% trans
5	DMF/H_2O (9:1, v/v)	Pd/C (10%)	2 hours	30% cis ; 70% trans
6	dioxane/triethyl amine	Pd/C (10%)	2 hours	50% cis ; 50% trans
7	dioxane/triethyl amine	Pd/C (10%)	2 hours	33% cis ; 67% trans
8	dioxane/triethyl amine	Pd/C (10%)	1,5 hours	33% cis ; 67% trans*
9	dioxane/triethyl amine	Pd/C (10%)	1,5 hours	10% cis ; 90% trans*

* extrapolate to t=0 hours

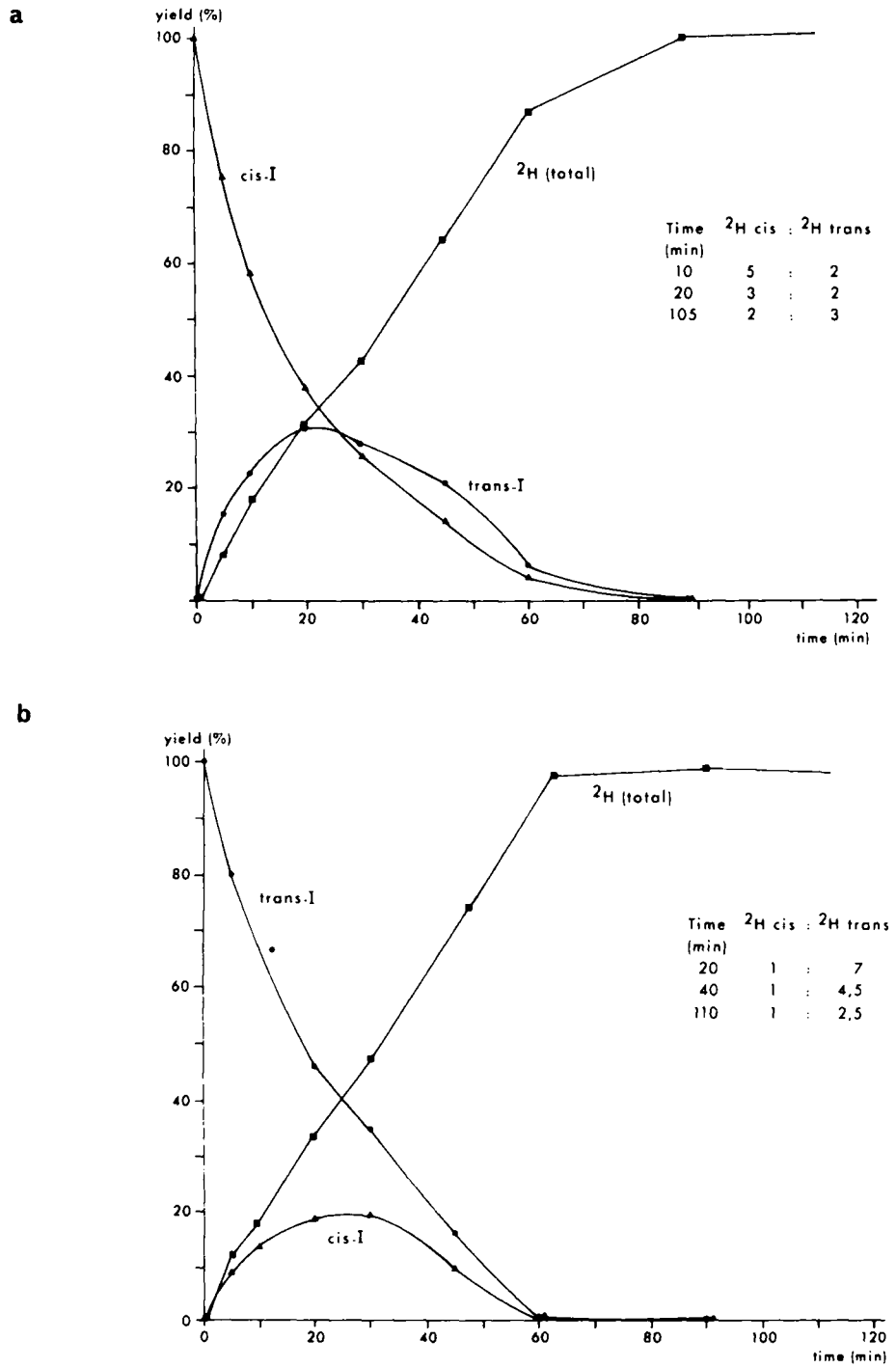


Figure 4: a: reductive deiodination of N-tosyl-4-cis-iodo-L-proline methyl ester (8)
b: reductive deiodination of N-tosyl-4-trans-iodo-L-proline methyl ester (9)

dehalogenation for the pure 4-trans and 4-cis-iodomaterials [15] (values at t=0); these are included in Table I.

The results of the deuteration reactions are given in Table I. With the 2-bromocholesterols (2,3), 4-bromo-L-prolines (4,5) and N-tosyl-4-iodo-L-proline methyl esters (8,9) deuterium was only incorporated at the original position of the halogen atom. With 7-α-bromo-cholesterol acetate (1) apart from incorporation at position 7 deuterium was also incorporated at positions 4α and 4β in agreement with the results found by Gut et al[2] and Al Rawi et al[1] while with Pd/C using ethyl acetate as solvent incorporation at other positions was observed.

With N-tosyl-4-bromo-L-proline methyl esters (6,7) incorporation into the methyl group of the N-tosyl group was also observed (^2H NMR δ 2,30 and mass spectrum enhanced ratio m/z=92/m/z=91); as expected for such an exchange-reaction the deuterium content of the tosyl group increased with increasing reaction time.

DISCUSSION

The results presented in Table I indicate that with the exception of the N-tosyl-4-cis-iodo-L-proline methyl ester, reductive dehalogenation is not stereospecific. The ratio observed for 7-bromo-cholesterol is in agreement with the literature for tritium[12] but not for the results obtained with chemical degradation[2]. The ratio α-^2H/β-^2H in the deuterated cholesterols formed by reduction of the 2-bromocholesterols is more or less independent of the configuration of the starting material, in complete contradiction to the results found by Römer et al[3] with chemical degradation. This illustrates the danger of such chemical degradation reactions; with the availability of high resolution NMR instruments such methods should no longer be applied.

For the prolines the situation is different. Stereoselectivity but no stereospecificity is obtained with the bromides; the distribution is independent of the presence of protecting groups.

For the iododerivatives stereospecificity is possible but isomerisation levels off this process during the reductive dehalogenation. Altman and Silberman[13] have investigated the stereochemistry of 4-tritio-L-proline prepared by reductive deiodination of 4-iodo-L-proline[14]; they found a ratio 4-cis-^{3}H/4-trans-^{3}H of 1:5; this is in agreement with the results obtained for the N-tosyl-methylesters.

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7. Since we omitted the removal of N-benzyloxycarbonyl-trans-4-hydroxy-L-proline on reduction of the 4-oxo compound our 4-trans-bromo-L-proline methylester contained 5% of the corresponding cis-isomer.
8. COSY experiments (Hellema, J.R. and Wagenaars, G., unpublished results) indicated the following ^{1}H or ^{2}H chemical shifts: 2α: =1,85; 2β: =1,50; 4α or 4β: =2,25; 7β: =2,00; 7α: =1,55.
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14. The stereochemistry of the starting material used in reference 13 is not specified.
15. Parameter estimates were obtained by repetitive simulation; due to the complex nature of the system (7 reactions) and the relatively limited data non-linear least squares regression analysis was not feasible.