Tetrahedron: Asymmetry Vol. 2, No. 3, pp. 187-190, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

DEUTERIUM MAGNETIC RESONANCE AS A PROBE FOR ORGANIC REACTION MECHANISMS : EPOXIDATION OF 1(3)-TOSYLGLYCEROL IS A PURE SN_2 CYCLISATION

C. Rabiller*, M. Mesbahi and F. Levayer
Faculté des Sciences et des Techniques
Laboratoire de RMN et de Réactivité Chimique - URA-CNRS 472
2 rue de la Houssinière 44072 NANTES Cedex 03
(FRANCE)

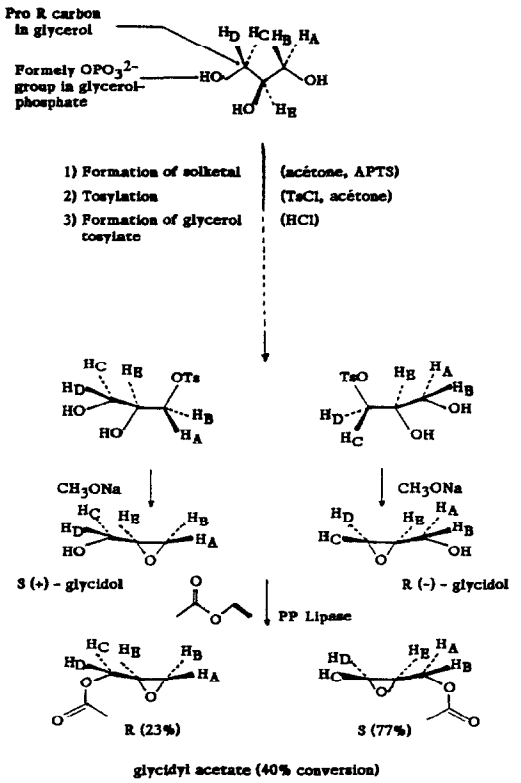
(*Received* 20 *February* 1991)

Abstract : A stereoselective deuteriation of glycerol acetonide is used to prove by means of deuterium NMR spectroscopy that the cyclisation of glycerol tosylate into glycidol is a pure SN_2 mechanism.

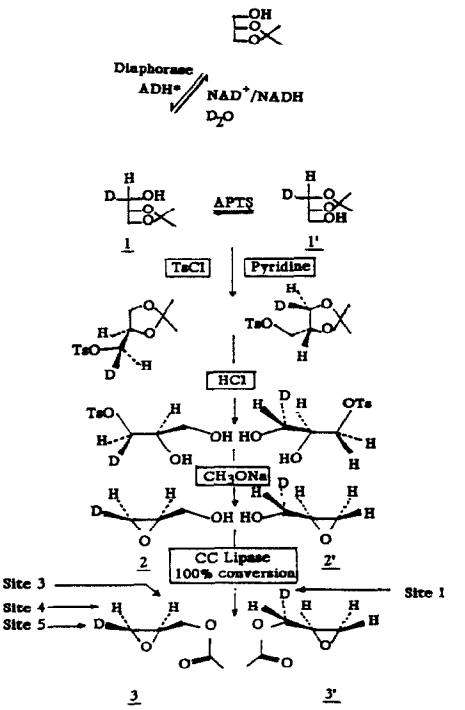
It has been proved recently in the laboratory that natural abundance deuterium NMR spectroscopy was able to afford the deuterium to proton ratio (D/H) on each site of different molecules[1,2], particularly for ethanol. The results obtained allowed us to infer the origin of different alcohols[3,4] and to determine the mechanisms of some proton transfers which are likely to occur during fermentation[5-8].

As glycerol is the second metabolite of these biotransformations, the deuterium NMR study of this compound should also provide informations concerning the biomechanical pathways[9]. Unfortunately the glycerol molecule is symetrical and the deuterium NMR spectrum appears as a broad singlet. The problem is then to find a derivative for which the five protons of the glycerol should be individualized and identified. The glycidyl acetate presents these characteritics when synthesized from glycerol according to the methodology described in scheme 1[10]. The reactions shown into this scheme suppose that the cyclisation of glycerol tosylate into glycidol is a pure SN_2 process. Such a mechanism is widely accepted for this type of reactions[11,12], but it was important to examine whether or not other mechanisms could occur and to what extend.

Thus, the intervention of a SN_1 process would mix the origin of H_A, H_B or H_D and H_C protons of glycerol (see scheme 1). The aim of this paper is to give an answer to this question by means of deuterium NMR spectroscopy. The scheme 2 describes the methodology used for this purpose. S-glycerol acetonide was obtained from D-mannitol[13,14]. The former was then partially deuterated according to a well known stereospecific enzymatic reduction procedure[15]. Equilibration of the (1R, 2R)-[1-^{2}H] acetonide 1 gave a "quasi-racemic" mixture of 1 and 1' (1R, 2S)-[1-^{2}H] acetonide[16].



Scheme 1- *Stereoselective synthesis of glycidyl acetate from glycerol*



Scheme 2- *Synthesis of a "quasi-racemic" mixture of deuterated (2R,3S)-[3-^{2}H]-2,3-epoxy-1-propyl acetate 3 and (1R,2R)-[1-^{2}H]-2,3-epoxy-1-propyl acetate 3'.*
**ADH: alcohol dehydrogenase*

If the transformation of the glycerol tosylate into glycidol is a pure SN_2 cyclisation,only the deuterated derivatives 2 : (2R, 3S)-[3-^{2}H]-2,3-epoxy propan-1-ol and 2' : (1R, 2R)-[1-^{2}H]-2,3-epoxy propan-1-ol are obtained. In this hypothesis, only the corresponding methyl esters 3 and 3' are synthesized from the non stereospecific enzymatic transesterification (100% conversion)[17].

The deuterium NMR spectra of the "quasi-racemic" 3,3' mixture then obtained and the natural abundance deuterium spectra are shown in figure 1. The presence only two peaks at $\delta = 2.48$ ppm and $\delta = 4.25$ ppm proves very clearly that the cyclisation step is purely SN_2. If not, two other peaks at $\delta = 2.65$ ppm and $\delta = 3.77$ ppm should have appeared on the spectrum.

The attribution of the methylene groups is easily deduced from the analysis of the proton NMR spectrum. Looking at, for example, the structure of S-glycidyl acetate, the following proton NMR parameters are found (see scheme 1) :

δ_C or δ_D = 2.48 or 2.66 ppm	J_{CD} = -4.8 Hz	epoxy methylenic group
δ_A or δ_B = 3.77 or 4.25 ppm	J_{AB} = -12.3 Hz	exocyclic methylenic group

Therefore, it follows that the peak at $\delta = 2.48$ ppm corresponds to compound 3 whereas the peak at $\delta = 4.25$ ppm is due 3' acetate. Furthemore, this experiment gives an unambiguous attribution of the diastereotopic protons of each methylenic carbon leading to a complete assignment of the deuterium and the proton spectra. Therefore, the ^2H chemical shifts for S-glycidyl acetate are (see scheme 1) : $\delta_A = 4.25$ ppm, $\delta_B = 3.77$ ppm, $\delta_C = 2.48$ ppm, $\delta_D = 2.66$ ppm, $\delta_E = 3.07$ ppm.(the reference used is hexamethyldisiloxane: HMDS).

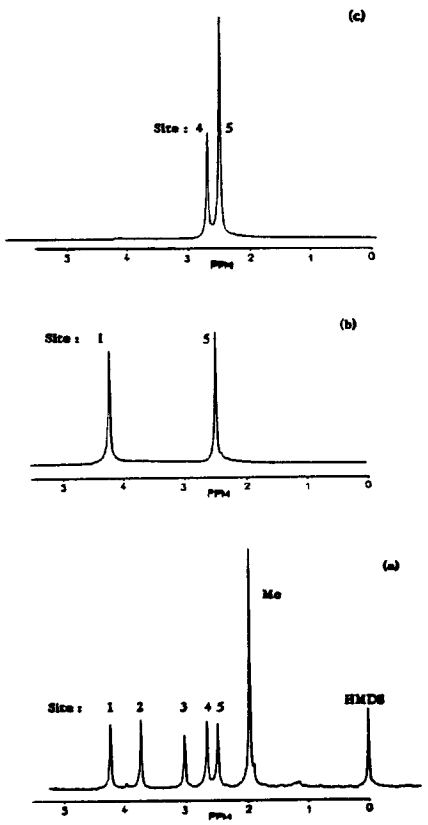
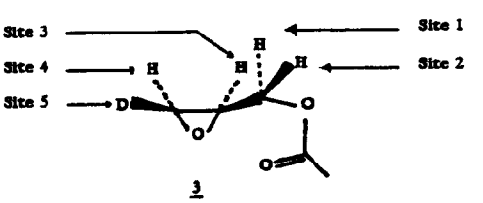


Figure 1 *:(a) Natural abundance deuterium NMR spectra of glycidyl acetate, (b) and (c) are the deuterium spectra of the mixtures of compounds 3, 3' and of 3 , 3" acetates respectively.*
**these esters were prepared from a water enriched to the 98% level.The isotopic enrichment determined from the ^1H NMR spectra of the precursor solketal was 25% in the (c) case and about 30% in the (b) case.*
**reference: hexamethyldisiloxane (HMDS),solvent: CCl_4,spectrometer : Bruker AM 400.*



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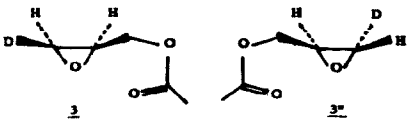
An additional proof for the total SN_2 epoxidation mechanism was afforded when using the preceding enantioselective deuterium incorporation in the racemate of the solketal.Following the reactions of scheme 2 without the APTS racemisation step of the solketal,the deuterated glycidols 2 and 2" : (2R,3S)-[3-^{2}H]-2,3-epoxy propan-1-ol respectively,should be obtained.The stereoselective transesterification with vinyl acetate as an acyl donor catalyzed by porcine pancreatic lipase (PPL) should produce a non racemic mixture of the corresponding acetates 3 and 3" (see below).



3 3"

The figure 1C shows the deuterium spectrum of this mixture when the reaction is stopped at 55% conversion.Two peaks at $\delta = 2.48$ ppm and $\delta = 2.66$ ppm are present with the relative intensity of 0.66 and 0.34.These values represent exactly the enantiomeric composition found for the acetates obtained in the same conditions from a non deuterated racemate glycidol. So it can be concluded that the absorptions at $\delta = 2.48$ and $\delta = 2.66$ ppm are due respectively to the esters 3 and 3",which were synthesized from a pure SN_2 cyclisation of the precursor glycerol tosylate.

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