CHAPTER 2

BOROHYDRIDE REDUCING AGENT DERIVED FROM ANION EXCHANGE RESIN : SELECTIVE REDUCTION OF α,β-UNSATURATED CARBONYL COMPOUNDS

CHAPTER II

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ABSTRACT

Borohydride exchange resin (BER) was obtained by treatment of Amberlite IRA-400 with aqueous solution of sodium borohydride. The BER exhibited selectivity in the reduction of α,β-unsaturated carbonyl compounds such as cinnamaldehyde, benzal acetone, benzalacetophenone, citral, crotonaldehydes etc. to the corresponding unsaturated alcohols in high yields. The reaction may be performed in aprotic solvents such as ether or benzene without significant variation in yield, although longer reaction times are required. The reaction rate seems to be dependent on the structure of the substrate and on the substrate to BER ratio. The rate of reduction with BER are found to be slower than $NaBH_4$ adsorbed on alumina, suggesting greater selectivity of BER.

Introduction

A serious shortcoming of catalytic hydrogenation, the inability to reduce selectively the carbonyl function of ketones,

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acids, esters, and amides in the presence of carbon-carbon double bonds, has led to the widespread use of certain complex metal hydrides[1] for the reductions of carbonyl groups. Most reductions of carbonyl and other functional groups are now done with reagents that transfer a hydride ion from a group III atom. The numerous reagents of this type that have become available provide a considerable degree of selectivity and steriochemical control. Sodium borohydride and lithium aluminium hyride are not only the most familiar examples, but also indicate the range in selectivity possible with hydride reducing agents. Sodium borohydride is a mild reducing agent, reducing only aldehydes and ketones rapidly. Lithium aluminium hydride is one of the most powerful hydride-transfer agents, it will reduce ketones, esters, acids and even amides quite rapidly. The reactivity of these reagents, along with that of several other related reducing agents, is summarized in Table 1.

The anions of the two complex hydrides can be regarded as derived from lithium or sodium hydride and either aluminium hydride or borone.

$$\mathrm{LiH} + \mathrm{AlH_3} \longrightarrow \mathrm{Li^+}\ \mathrm{AlH_4^-}$$

$$\mathrm{NaH} + \mathrm{BH_3} \longrightarrow \mathrm{Na^+}\ \mathrm{BH_4^-}$$

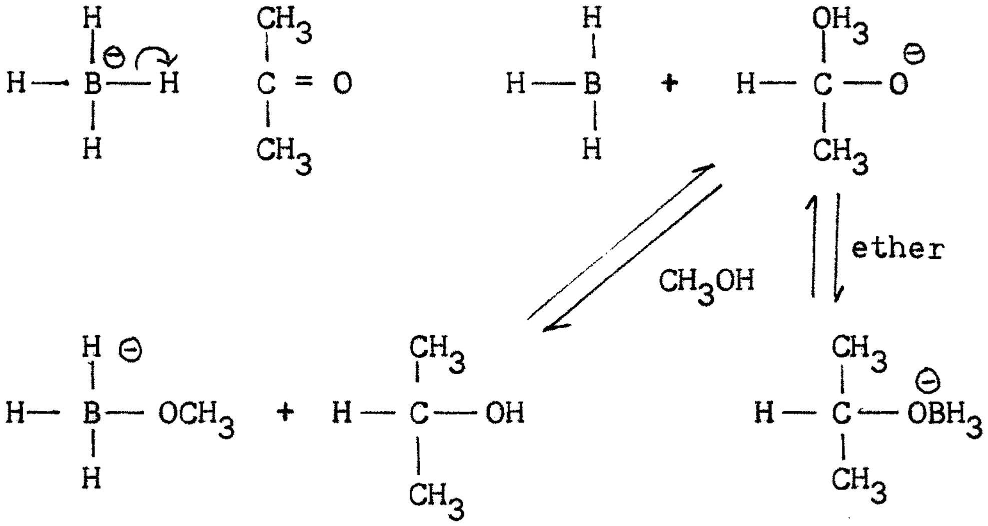
These anions are nucleophilic reagents and as such they normally attack polarised multiple bonds such as $C = O$ or $C \equiv N$ by transfer of hydride ion to the more positive atom. They do not usually react with isolated carbon-carbon double or triple bonds.

Table 1

Reactivity of Hydride-Transfer Reducing Agents

Reducing Agent	Usual products					
	Acyl chloride	Aldehyde	Ketone	Ester	Acid	Amide
$NaBH_4$	alcohol	alcohol	alcohol	-	-	-
$LiAlH_4$	alcohol	alcohol	alcohol	alcohol	alcohol	amine
Li Al(t.Buol$_3$H	aldehyde	alcohol	alcohol	very slow	-	aldehyde
AlH_3	alcohol	alcohol	alcohol	alcohol	alcohol	amine
B_2H_6	-	alcohol	alcohol	-	alcohol	amine
$[(CH_3)_2CH\text{-}\overset{CH_3}{CH}]_2BH$	-	alcohol	alcohol	-	-	aldehyde
$[(CH_3)_2CH\ CH_2]_2AlH$	-	alcohol	alcohol	aldehyde	-	aldehyde

Thus reduction of acetone with sodium borohydride proceeds as in scheme 1.

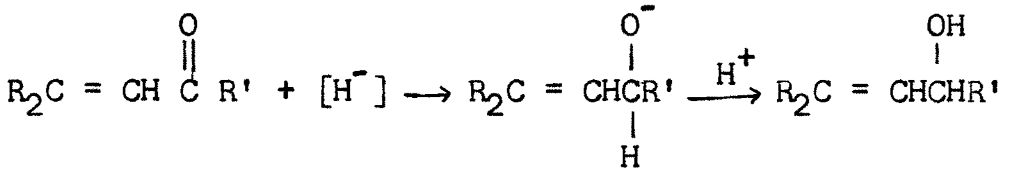


In aprotic solvents the alkoxyborohydride is formed, but in hydroxylic solvents reaction with the solvent may occur to give the alcohol directly. With both reagents all four hydrogen atoms may be used for reduction, being transferred in a stepwise process as illustrated for reduction of a ketone.

The hydride reduction of α,β-unsaturated carbonyl compounds can take one of two courses. Initial reaction at the carbonyl group gives allylic alcohols (scheme 2). Usually, no further reduction takes place, since the unconjugated carbon-carbon double bond, an enolate is produced. In protic solvents, this can lead to the carbonyl compounds, which can, in turn, be reduced, resulting ultimately in the saturated alcohol (scheme 3). For this reason, it is fairly common to find both saturated and unsaturated alcohols from $NaBH_4$ or $LiAlH_4$ reduction of conjugated unsaturated ketones[2].

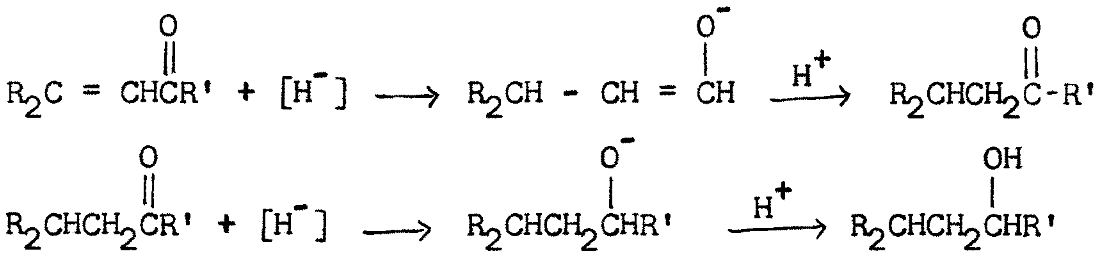
The extent of reduction to the saturated alcohol is usually greater with $NaBH_4$ than with $LiAlH_4$.

Scheme 2



$$R_2C = CH\overset{O}{\overset{\|}{C}}R' + [H^-] \longrightarrow R_2C = CH\underset{H}{\overset{O^-}{C}}R' \xrightarrow{H^+} R_2C = CH\overset{OH}{C}HR'$$

Scheme 3



$$R_2C = CH\overset{O}{\overset{\|}{C}}R' + [H^-] \longrightarrow R_2CH - CH = \overset{O^-}{C}H \xrightarrow{H^+} R_2CHCH_2\overset{O}{\overset{\|}{C}}-R'$$

$$R_2CHCH_2\overset{O}{\overset{\|}{C}}R' + [H^-] \longrightarrow R_2CHCH_2\overset{O^-}{C}HR' \xrightarrow{H^+} R_2CHCH_2\overset{OH}{C}HR'$$

Sodium borohydride reduction of carbon-carbon double bonds has been observed in conjugated esters[3], nitroalkenes[4] and enol acetates[5]. These examples are apparently widely regarded as exceptions to the general rule that double bonds are inert to sodium borohydride. In connection with study requiring allylic alcohols, the sodium borohydride procedure was applied to 2-cyclohexenone. A very substantial percentage of the product was the fully reduced cyclohexanol. Examination of the literature revealed several similar reports[6-10] of conjugated ketone double bond reduction, all of which involved substituted cyclohexenones. Although the number of specific examples of enone complete reduction exceeds those where only the carbonyl group is affected, the former are still viewed as abnormal[10].

In cases where the reduction of an α,β-unsaturated ketone to an allytic alcohol without double bond reduction is desired, changes in reaction conditions with lithium aluminium hydride, such as the use of short reaction times and relatively low temperatures[11,12] or the use of a slurry of this metal hydride in a nonbasic solvent such as benzene[13], may be beneficial. However, a far more satisfactory solution is the use of either aluminium hydride or diisobutylaluminium hydride as the reducing agent[14]. The results obtained from reduction of 2-cyclopentenon with a number of metal hydride reagents are indicated in the scheme 4 and Table 2.

Scheme 4

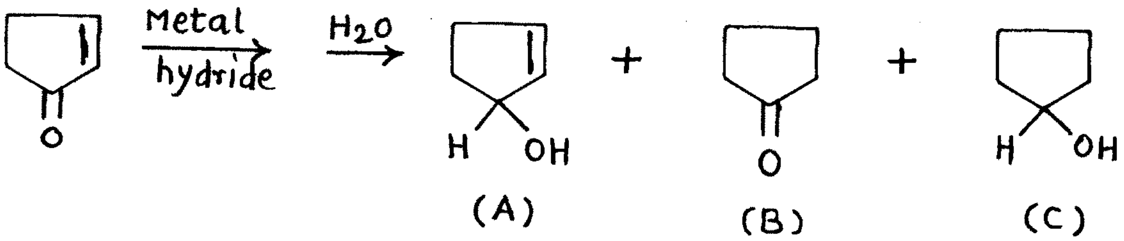


Table 2 :

Reducing agent	Product composition %		
	A	B	C
$LiAlH_4$, $(C_2H_5)_2O$, 10°	85	15	-
$LiAlH_4$, THF, 0°	14	2	84
$LiAlH(OCH_3)_3$, THF, 0°	91	-	9
$LiAlH[OC(CH_3)_3]_3$, THF, 0°	-	11	89
$NaBH_4$, C_2H_5OH	-	-	100

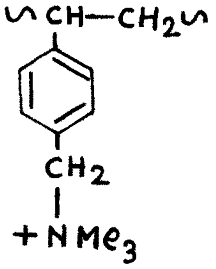
Reduction with lithium aluminium hydride aluminium chloride (3:1) also provides an excellent route from α,β-unsaturated carbonyl compounds to unsaturated alcohols which are difficult to prepare with lithium aluminium hydride alone because of competing reduction of the olefinic double bond. The effective reagent is thought to be aluminium hydride formed in situ from lithium aluminium and aluminium chloride.

$$C_6H_5CH{=}CHCO_2C_2H_5 \xrightarrow[\text{ether}]{3LiAlH_4\text{-}AlCl_3} C_6H_5CH{=}CH.CH_2OH$$

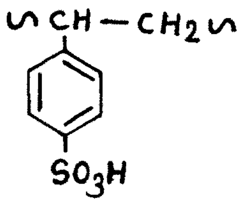
It has been found that reagents supported on insoluble polymers have acquired popularity in the last ten to fifteen years and have already found wide applications in various fields, particularly for solving problems in organic synthesis[15].

The most common strongly basic anion-exchange resins are crosslinked polystyrenes containing quatarnary ammonium groups (1). The desired anions may be bound to these polymers either by (i) displacing a relatively weakly bound anion, or (ii) treating the hydroxide form of the resin with the acid corresponding to the anion. The latter is usually the method of choice when the desired anion is only weakly bound. The order of affinities quoted for some strongly basic anion-exchange resins is as follows[16].

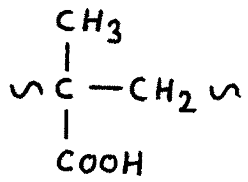
$I^- > C_6H_5O^- > Br^- > CN^- > NO_2^- > Cl^- > IO_3^- > CH_3COO^- > OH^- > F^-$



(1)



(2)



(3)

The common cation-exchange resins contain either benzenesulphonic acid groups (2) or aliphatic carboxylic acid groups (3). The desired cations may be bound to these either (i) by treating the acid form of resin with the appropriate metal hydroxide or (ii) by displacing a weakly bound cation. The order of affinities quoted for some cation-exchange resins is as follows[18].

strongly acidic : $Ni^{2+} > Cu^{2+} > Co^{2+} > Mn^{2+} > Ag^{+} > Na^{+} > H^{+}$

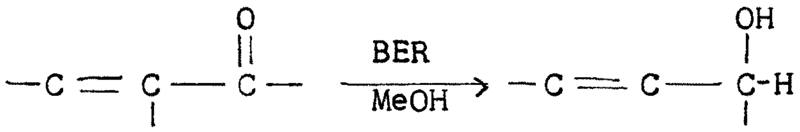
weakly acidic : $H^{+} \gg Ag^{+} > Na^{+}$.

Borohydride exchange resin (BER) was obtained by treatment of Amberlite IRA-400 with aqueous solution of $NaBH_4$ in 1977 by Gibson and Baily and used in ethanol to reduce benzaldehyde to benzyl alcohol[17]. The reaction was, however, much slower than that using sodium borohydride. BER has been used in solvent purification, generation of volatile metal hydrides and reduction of metal ions and some aldehyde[18]. The BER exhibited a high chemoselectivity not only between aldehydes and ketones but also between ketones[19]. Now we wish to report that BER shows selectivity in the reduction of α,β-unsaturated alcohols in high yields.

PRESENT WORK

Selective Reduction of α,β-Unsaturated Carbonyl Compounds

The selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding unsaturated alcohols is a frequent synthetic problem. In recent years various reagents have been developed for such selective reductions[11-13,20], but they have several disadvantages such as complex reaction work-up, low yields etc. The selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding unsaturated alcohols with borohydride exchange resin (BER) prepared from Amberlite IRA-400 is reported in the following pages and is found to be more efficient than with the other reagents.



$$-C=\underset{|}{C}-\overset{\overset{O}{\|}}{C}-\ \xrightarrow[\text{MeOH}]{\text{BER}}\ -C=C-\underset{|}{\overset{\overset{OH}{|}}{C}}\text{-H}$$

The BER reductions are studied to investigate (i) the effect of BER/substrate ratio, (ii) the solvent effect, (iii) the effect of substrate structure and (iv) the effect of anion exchange resin. The rate of reduction with BER is compared with $NaBH_4$ adsorbed on alumina.

Effect of BER/substrate ratio :

BER shows selectivity in the reduction of α,β-unsaturated carbonyl compounds to the corresponding unsaturated alcohols in high yields. The reaction rate is found to be dependent on the

BER to the substrate ratio as summarised in Table 1. It is found that rate of reduction increases with increase of BER to substrate ratio, however, the yields generally remain unaffected.

Table 1

Reduction of α,β-unsaturated carbonyl compound with BER in Methanol (20 ml) at 25° C.

Entry	Carbonyl compound 1 m mol	BER/mmol of g substrate	Time hr	Yield %
1	Cinnamaldehyde	0.3	2.0	99.0
2	Cinnamaldehyde	0.5	1.5	99.0
3	Cinnamaldehyde	1.0	0.25	99.0
4	Cinnamaldehyde	2.0	0.10	99.0

Solvent Effect

The $NaBH_4$ is generally be used in hydroxylic media. Reactions can be carried out in aprotic solvents by using $NaBH_4$ adsorbed on alumina[21] and silica gel[22]. Now we wish to report that the BER is a practically useful alternative. We have shown that BER can be used in a range of solvents, including aprotic solvents, to reduce various α,β-unsaturated carbonyl compounds to the corresponding unsaturated alcohols without significant variation in yields although longer reaction times are required.

The reduction of α,β-unsaturated carbonyl compounds is performed in aprotic solvents such as ether or benzene without significant variation in yields although longer reaction times are required as summarised in Table 2.

Table 2

Reduction of α,β-unsaturated carbonyl compounds with BER at 25°C

Entry	Carbonyl compound (a)	Solvent	Time hr	Yield %
1	Cinnamaldehyde	Methanol	1.50	99.0
2	Cinnamaldehyde	Dichlorobenzene	4.00	99.0
3	Cinnamaldehyde	Benzene	60.00	99.0
4	Cinnamaldehyde	Ether	48.00	99.0
5	Cinnamaldehyde	Ethanol	3.00	99.0

(a) BER used 0.5 gm/mmol substrate.

Effect of substrate structure :

Besides selectivity in the reduction, it is also observed that the rates of reduction of different carbonyl compounds are different with BER. Therefore by using BER specific reductions can be carried at room temperature and method has immense synthetic potential.

The reduction rates also found to be dependent on the structure of substrate as BER reduces the α,β-unsaturated aldehydes much faster than ketones. The reduction of a unhindered ketone, benzalacetone is much faster than hindered ketone, benzalacetophenone (Table 3) and this could be explained on steric effect.

Table 3

Reduction of α,β-Unsaturated Carbonyl Compounds with BER at 25^{o} C in 20 ml methanol.

Entry	Carbonyl compound (a)	Time hr	Yield %
1	Cinnamaldehyde	1.50	99.0
2	Benzalacetone	4.00	99.0
3	Benzalacetophenone	28.00	89.00
4	Benzalacetylacetone	4.00	93.0
5	Dibenzalacetone	4.00	90.0
6	Citral	3.00	90.0
7	Crotonaldehyde	0.25^{b}	85.0

(a) BER used 0.5 g/mmol substrate.

(b) One m mol substrate in 10 ml methanol + 10 ml water.

Effect of anion exchange resin :

It is also observed that the rate of reduction also depend upon the type of resin used. The reticular resin Amberlyst A26 shows more reactivity than the linear resin Amberlite IRA-400 (Table 4). These results are interesting in that the more porous beads (Amberlite IRA-400) are less reactive than the less porous beads (Amberlyst A-26).

Table 4

Reduction of α,β-unsaturated carbonyl compounds with BER at 25°C

Entry	Carbonyl compound	BER used	Time hr	Yield %
1	Cinnamaldehyde	Amberlite IRA-400	1.5	99.0
2	Cinnamaldehyde	Amberlyst A-26	0.5	99.0

The lower rates of reaction of the BER suggest that they may possess greater selectivity than $NaBH_4$ e.g. the rate of reduction may depend on the chain length of aliphatic ketones as observed for olefin hydrogenation using resin-bound catalysts[17]. The rates of reduction with BER are found to be slower than $NaBH_4$ adsorbed on alimina suggesting greater selectivity of BER[21].

The BER has significant advantages over other hydride systems. Thus, simple separation of the reagent by filtration or decantation gives the solution of a pure product essentially free from a boron moiety[18]. The resin could be used repeatedly, since it can be regenerated to its initial activity by treating with a solution of $NaBH_4$.

EXPERIMENTAL

General

Cinnamaldehyde (BDH), citral (BDH), $NaBH_4$ (BDH), crotonaldehyde (BDH), Benzal acetone (High purity Chemical Ltd.), were commercially available and distilled before use. Amberlite IRA-400 and Amberlyst A-26 resins are markated by Rohm and Haas Ltd. The reaction solvents were reagent grade and unless indicated otherwise, were not specially dried. Benzal acetophenone, Benzal acetyl acetone and Dibenzal acetone were prepared according to the procedures given in the 'Text book of Organic Chemistry' by I.A. Vogel. I.R. Spectra were recorded on Perkin-Elmer Infracord and P.M.R. on 90 MHZ Spectrometer. Purity was checked by GLC AIMIL DUAL column gas chromatograph model 5500 series on carbowax 10 % chromosorb-W-column.

General procedure for the preparation of BER

20 gms of wet chloride-form resin (Amberlite IRA-400 anion exchange resin) was slurry packed with 100 ml sintered glass funnel, mounted on a filtering flask. Then, 200 ml of aqueous $NaBH_4$ solution (0.5 M) was slowly passed through the resin over a period of 60 minutes. The resulting resin was washed with distilled water thoroughly until free from excess of $NaBH_4$. The borohydride exchange resin was then dried in vacuo at 65° C for 2 hours. The dried resin was analysed for borohydride content by hydrogen evolution on acidification

with 0.8 N HCl and the average capacity of BER was found to be 2,5 mmol of BH_4^- per gram. The dried resin was stored under nitrogen at room temperature and the hydride content was found to be constant over 6 weeks.

General procedure for the reduction of α,β-unsaturated carbonyl compounds :

A solution of a carbonyl compound (1 mmol) in methanol (20 ml) was added to the BER (0.5 g) with constant stirring. After completion of the reaction the resin was removed by filtration and distillation of the solvent furnished the corresponding alcohol in high yield. The products were characterised by NMR and IR and the purity was checked by GC. The resin could be used repeatedly, since it could be regenerated to its initial activity by treating with a solution of $NaBH_4$.

The products were charactarized by IR, NMR and GC analysis and by comparison with authentic samples. Some illustrative spectra of reduction products are given just after the experimental part.

Fig 1 - IR of cinnamyl alcohol

Fig 2 - NMR of cinnamyl alcohol

Fig 3 - IR of 4-phenyl 3-buten-2-ol

Fig 4 - NMR of 4-phenyl 3-buten-2-ol

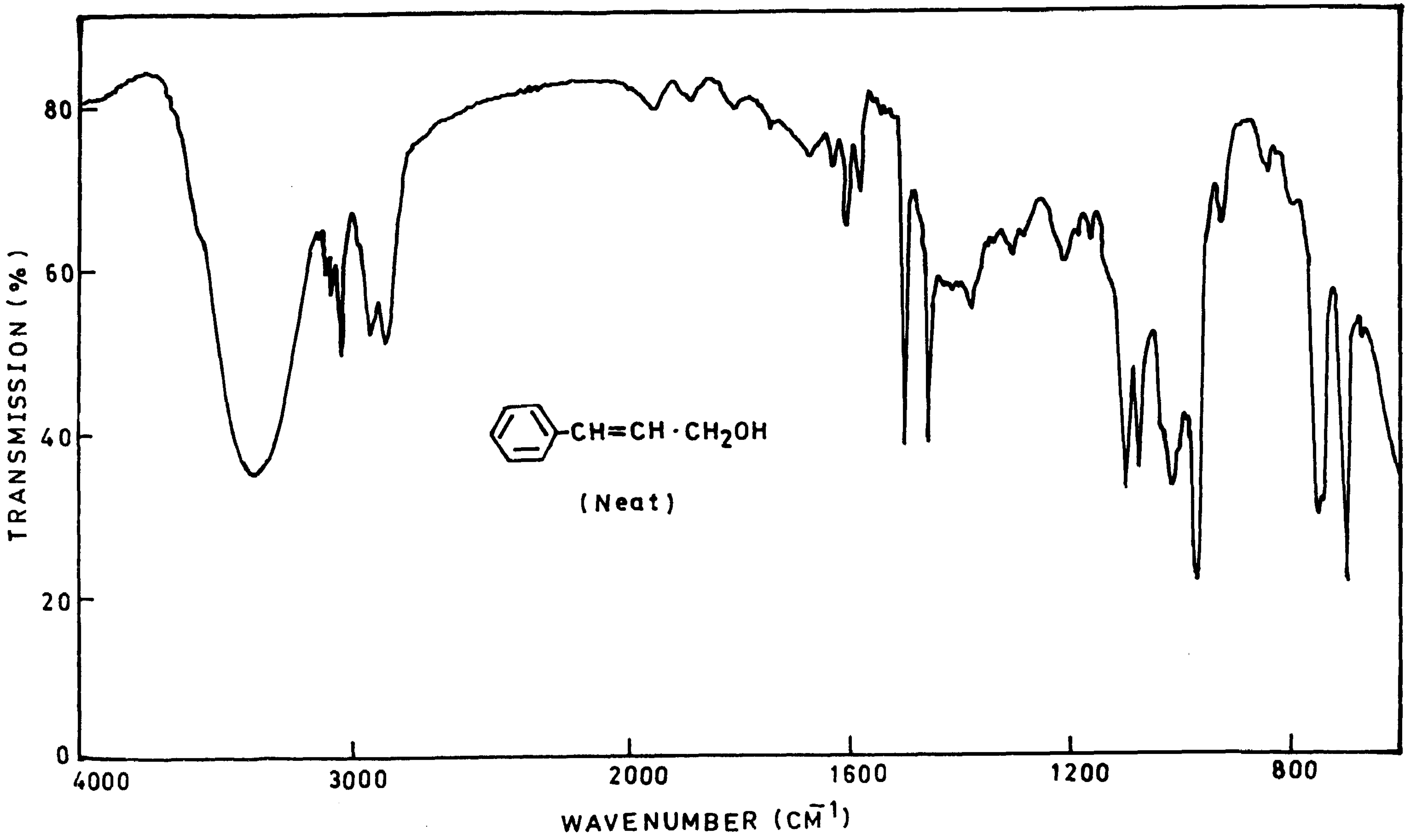

TRANSMISSION (%)
80
60
40
20
0
4000
3000
2000
1600
1200
800
WAVENUMBER (CM̄¹)
CH=CH·CH₂OH
(Neat)

Fig. 1

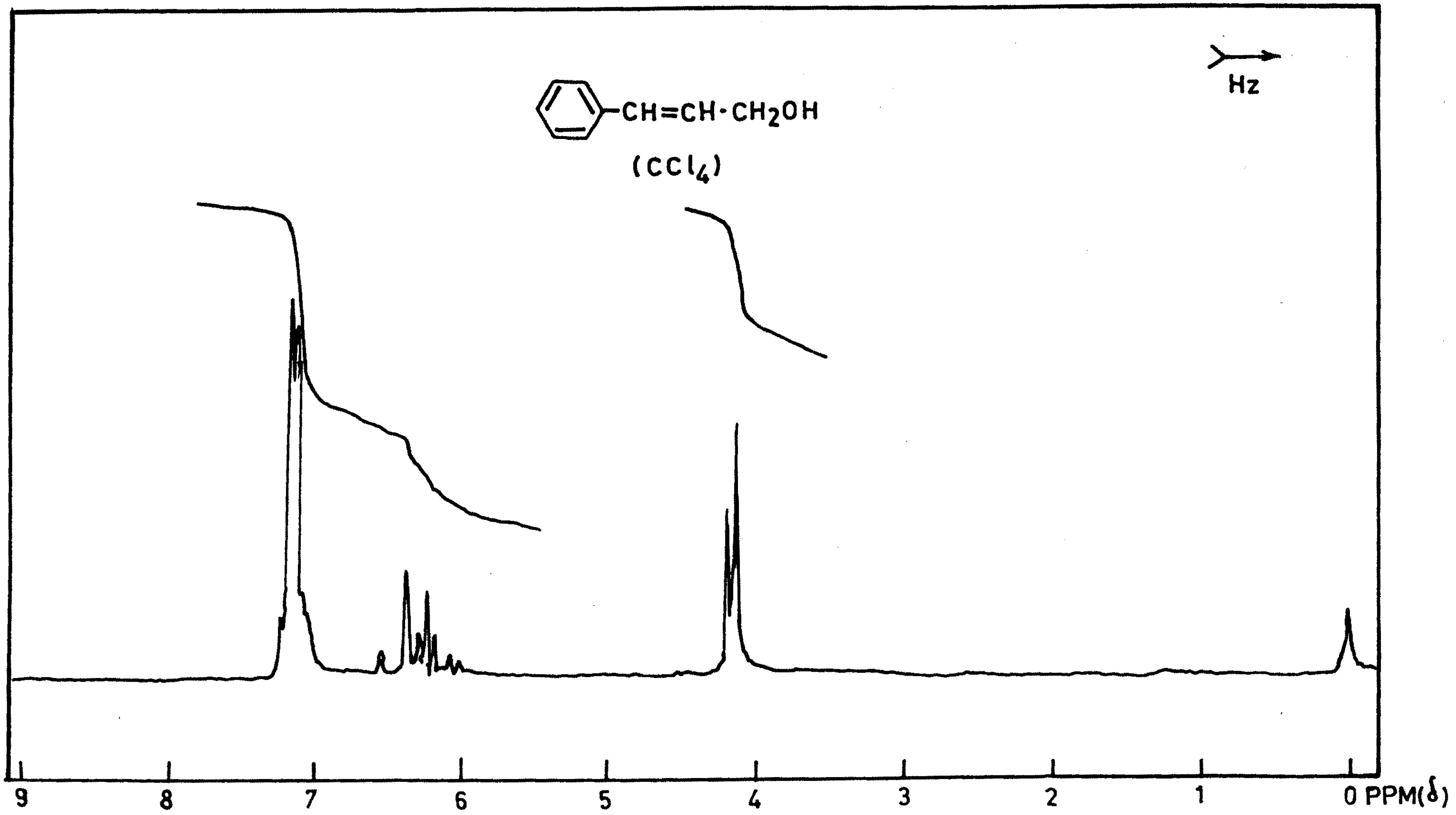


Fig. 2

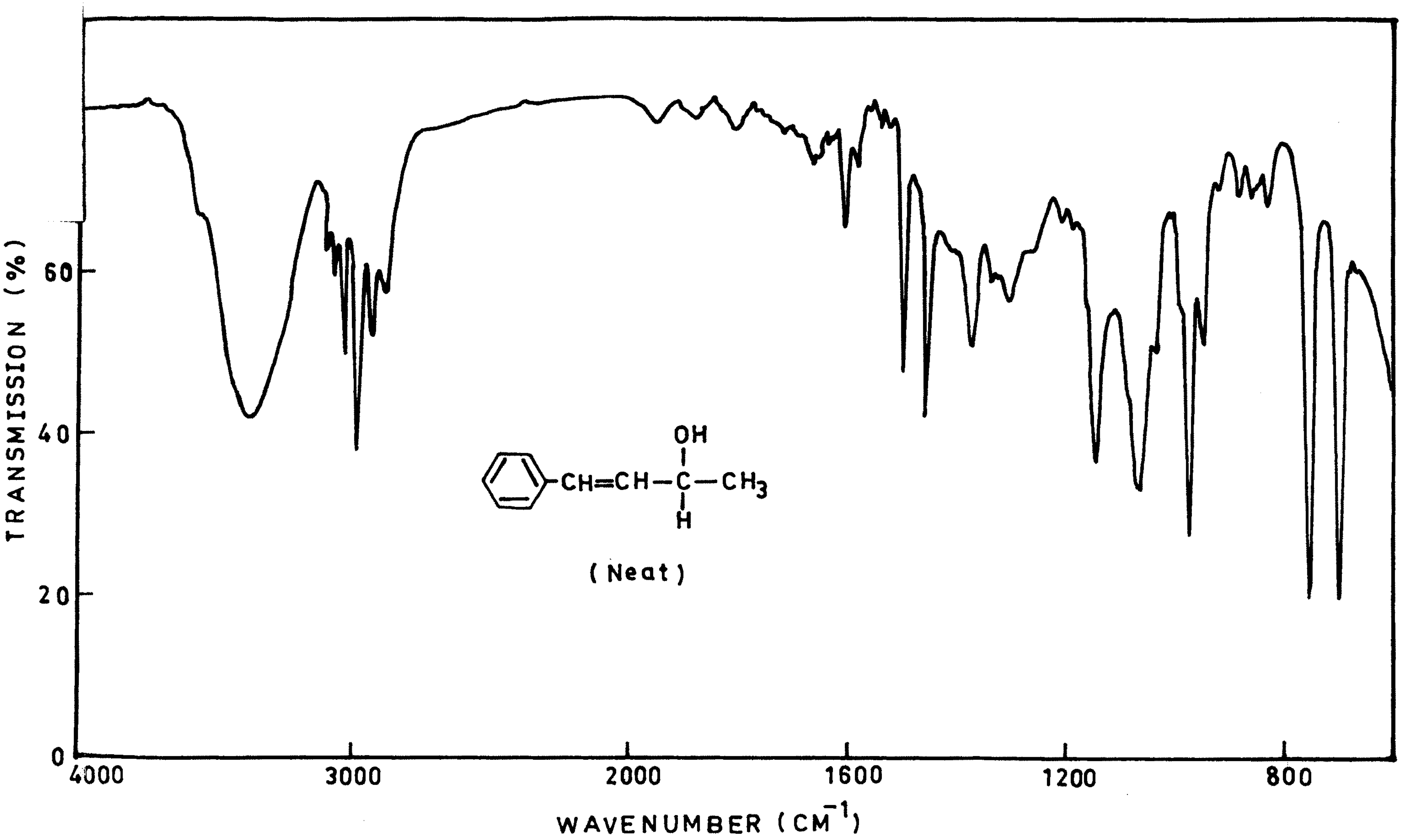

TRANSMISSION (%)
0
20
40
60
4000
3000
2000
1600
1200
800
WAVENUMBER (CM^{-1})
OH
CH=CH—C—CH$_3$
H
(Neat)

Fig. 3

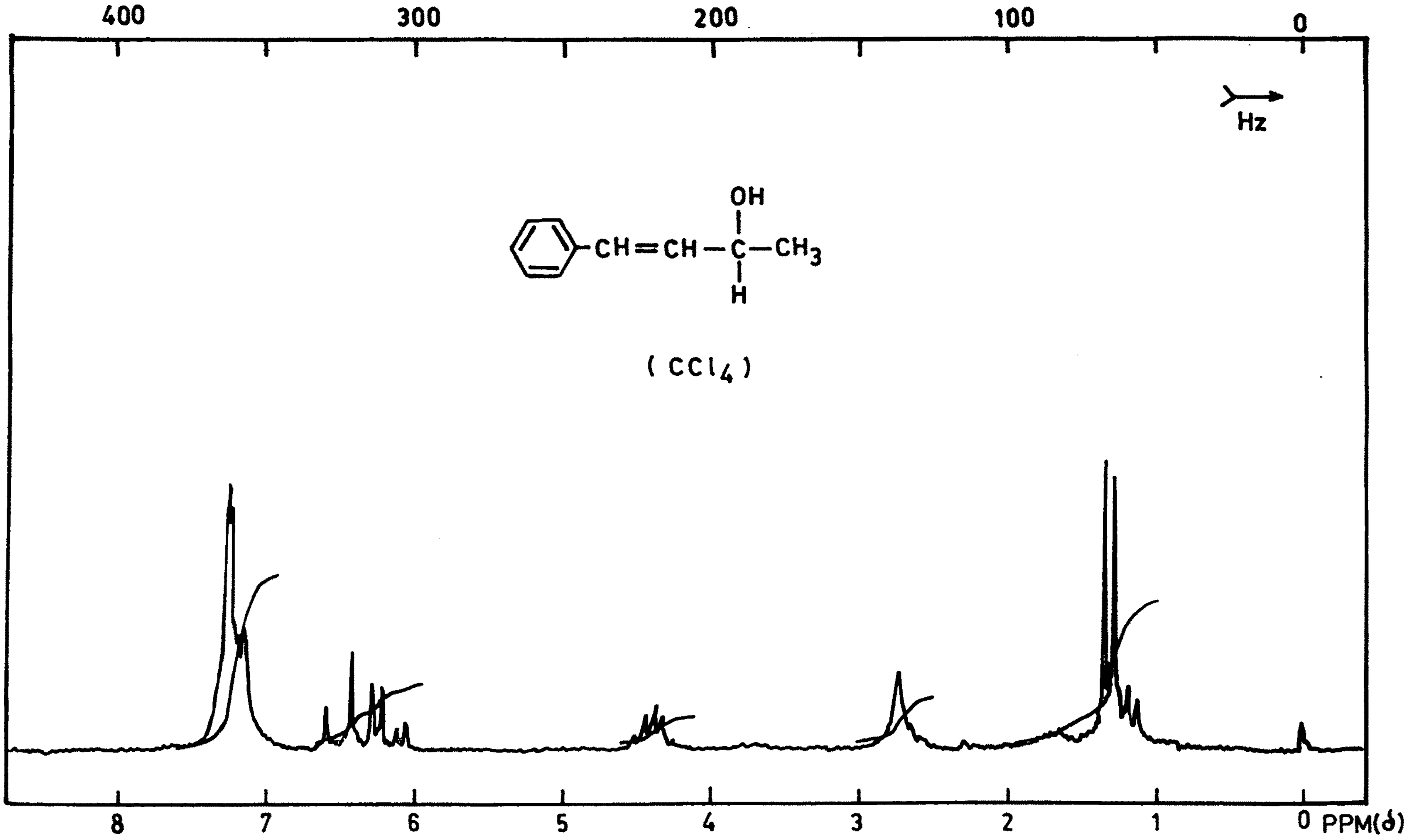


Fig. 4

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