CHAPTER 2

POLYMER-SUPPORTED MELDRUM'S ACID ANION : A SIMPLE AND EFFICIENT METHOD FOR BIS-ALKYLATION OF MELDRUM'S ACID

ABSTRACT

Alkylation of Meldrum's acid anion supported on Amberlite IRA-400 gave bis-alkylated products in high yields and purity.

INTRODUCTION

The reagents supported on insoluble polymers have found wide applications during last decade or so in various fields, perticularly in organic synthesis.[1] Recently Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione) (6.1) has attracted much attention as a versatile synthon[2] in organic synthesis. Our attention was focussed on Meldrum's acid by its high acidity (pKa 4.83), ease with which it undergoes a variety of reactions and the possibility that it could serve as an attractive alternative to malonic esters in organic synthesis[3,4] and it has strong tendancy to undergo bis-alkylation.[4]

The preparation of "Meldrum's acid" was reported by Meldrum in 1908 by the condensation of malonic acid with acetone in acetic anhydride containing a small amount of sulphuric acid[5] and Davidson and Bernhard assigned the correct structure[6] (6.1) to Meldrum's acid as 2,2-dimethyl-1,3-dioxan-4,6-dione.

Meldrum's acid (pKa 4.83)[7] is a strong organic acid comparable in strength to acetic acid (pKa 4.76) and is around ten pK units more acidic than acylic malonate esters. This can be explained as with dimedone (pKa 5.2)[6] on the basis of the stability of the resultant anion in which the π orbitals are rigidly held in the ideal configuration for overlap. The tautomeric properties of dimedone and Meldrum's acid are quite different, the former exists predominantly in the mono-enol form, whereas the latter is the diketo tautomer ($>$99.5%).[8] This is not surprising since esters are generally enolized to a much smaller extent than ketones.[9]

The conformation of 1,3-dioxan-4,6-dione system has been studied by n.m.r.,[10] dipole moment measurements[11] and x-ray crystallography.[12] The majority opinion favours a boat structure for 2,2,5,5-tetrasubstituted compounds. Other physical properties of the system which have been studied include u.v.,[13] i.r.,[14] mass,[15] ^{1}H-n.m.r.,[16] and ^{13}C-n.m.r.[17]

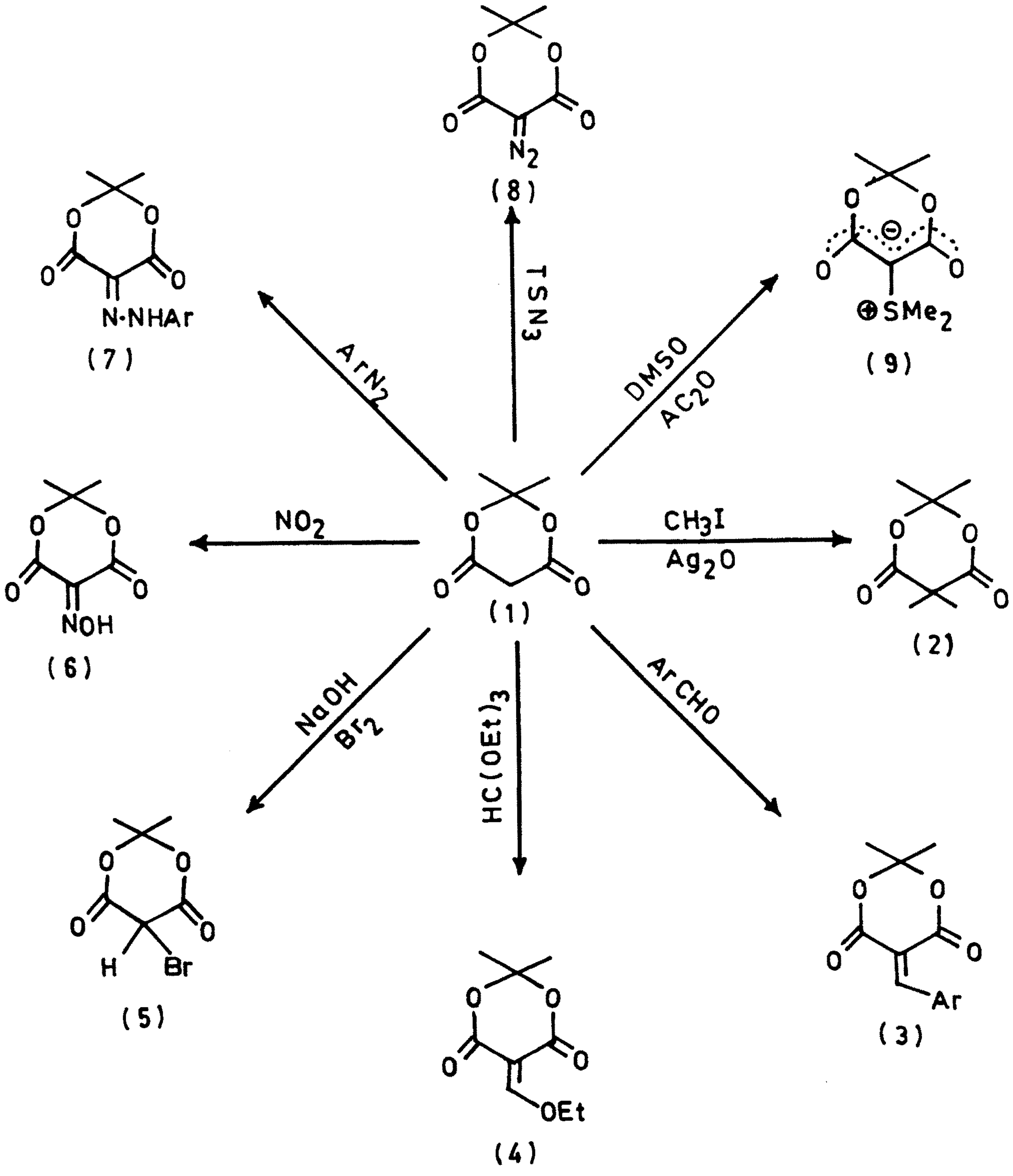
The chemistry of Meldrum's acid is dominated by its susceptibility to nucleophilic attack at positions 4 and 6 and to electrophilic attack (via the anion) at position 5. Acid or base catalysed hydrolysis leads to malonic acid.[5] Ethanolysis in the presence of hydrogen chloride leads to the malonate diester[13,20] while phenols give monoaryl esters.[18] Ketones react with Meldrum's acid by displacement of acetone to give 2,2-disubstituted-1,3-dioxan-4,6-diones,[19] which can undergo decarboxylation, as in the case of aniline[5] to give anilide. The ring also undergoes fragmentation by pyrolysis.

In contrast to these examples, the reactions of Meldrum's acid with electrophiles generally leave the ring intact. Chart 6 gives the outline of the reactions involved.

The presence of a highly reactive methylene group and easily degradable ester function in Meldrum's acid makes it an

CHART-6

Reactions with electrophiles



attractive synthon in organic syntheses. Meldrum's acid can act as a methylene synthon by hydrolysis and exhaustive decarboxylation of its derivatives. The conditions needed for certain heterocyclic systems are surprisingly mild.[21,22] Dauben's two step synthesis of δ-damascone[23] is a beautiful example of the use of strong dinophile character of methylene Meldrum's acid. Under extreme conditions, cleavage of acetone may be followed by decarboxylation to give lactams,[24] in these cases, Meldrum's acid acts as the synthetic equivalent of ketene. McNab *et al*. have reported a new synthesis of pyridazin-3-ones by the reaction of Meldrum's acid with α-dicarbonyl monohydrazones.[25]

Meldrum's acid is widely used for the preparation of α-pyrones and 2-pyridones in heterocyclic chemistry.[2] Alkylation of Meldrum's acid with ethyl *p*-(α-bromoethyl) benzoate, followed by mild hydrolysis and decarboxylation yields the half acid ester.[3] A general β-ketoester synthesis[26] has been reported from Meldrum's acid and acid chlorides. The synthesis of 4-alkylated pyridines from 4-(1-H)-pyridones has been carried out using Meldrum's acid.[21a] 4-chloroquinoline and 4-chloropyridine react with Meldrum's acid to give substituted products which can be hydrolysed and decarboxylated to yield alkyl quinolines[21b] or pyridines.[21c] Y.Osamu *et al*. have prepared 2-substituted indoles from acyl Meldrum's acid and phenyl hydroxyl amines[27] along with poor yields of isoxazoles. An improved synthesis of 1,4-dithiaspiro decan-8-one[28] has been carried out using Meldrum's acid. The Birch reduction of 4-methoxy phenol gave 4-methoxy-3-cyclohexan-1-ol. Lactone synthesis via the intramolecular alkylation of β-keto ester dianions has been reported by Weiler and co-workers[29] from acylated Meldrum's acid.

Procedures that involve the formation and subsquent reaction of anions derived from active methylene compounds constitute a very important and synthetically useful class of organic reactions. The presence of certain unsaturated functions like nitro, carbonyl, cyano, sulphone or phenyl groups at saturated carbon atoms renders any hydrogen atoms bonded to that carbon relatively acidic. The acidity of the C-H bond in these compounds, always called as active methylene compounds, is attributed to a combination of the inductive electron withdrawing ability of the unsaturated substituents and the ability of these substituents to delocalize the negative charge formed when the proton has been removed. The effectiveness of these unsaturated functions as activating groups follows the approximate order

$$NO_2 > COR > CN \approx CO_2R > SOR > Ph > R .$$

Also the presence of two such unsaturated substituents further enhance the acidity of an active methylene compound. The high acidity of Meldrum's acid (pKa = 4.83) is attributed to the stability of the resultant anion in which the π-orbitals are rigidly held in the ideal configuration for overlap.

Removal of a proton from the carbon atom alpha to a carbonyl group leads to the formation of anions, usually called enolate anions. The rate of proton abstraction is quite high in the case of 1,3-dicarbonyl compounds. A qualitative

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A

relationship exists between the rate of proton removal and the dissociation constant (pKa value) for active methylene compounds in that proton removal is usually more rapid for more acidic compounds. Methylene groups activated by a single nitro group, two or more carbonyl, ester, or cyano groups are quite acidic and may in large part to their enolate (or analogous) anions by treatment with relatively strong bases in aprotic solvents or with an anhydrous alcoholic solution of a metal oxide. The solutions of enolate anions thus obtained are allowed to react with alkyl halides or other alkylating agents. β-Diketones are sufficiently acidic so that their anions may be formed with alkali metal hydroxides or alkali metal carbonates in water, aqueous alcohol, acetone.

These reactions share a common mechanism involving base-catalysed formation of a carbanion followed by nucleophilic attack via an S_N^2 mechanism. The alkylating agent must be a suitable substrate for an S_N^2 reaction. Primary halides and sulphonates are the best substrates. Secondary system usually give poorer yields because of competition from elimination reaction. Tertiary halides or sulphonates are unsatisfactory because elimination rather than substitution occurs.[30] These reactions are important means of synthesizing a variety of ketones[31] and carboxylic acids.[32,33]

PRESENT WORK

Bis-alkylation of Meldrum's Acid

Bis-alkylated Meldrum's acids are important synthetic intermediates. They can be easily converted into malonic esters or acids, ketones and barbiturates. They have also been used for generation of ketenes. In view of the importance of bis-alkylated Meldrum's acid in pharmaceuticals, a simple and efficient method is now reported for the bis-alkylation of Meldrum's acid.

In alkylation of Meldrum's acid exhibits an overwhelming propensity to undergo bis-alkylation, despite the use of one mole proportion of alkyl halide.[32] Ott[34] has reportedthe alkylation of Meldrum's acid with methyl iodide in ether using silver oxide which is quite expensive. This gave only dimethyl-Meldrum's acid in low yield (40%). The change of solvent from ether to acetonitrile improved the yield (67%). Hedge *et al.*[32] studied the benzylation of Meldrum's acid using metal alkoxides in different solvent. The treatment of Meldrum's acid with benzyl chloride using sodium methoxide in methanol gave dibenzyl-Meldrum's acid in 19% yield, where as the reaction with sodium ethoxide in ethanol gave 16% yield of the product. The same reaction using sodium methoxide in dimethyl formamide (DMF) improved the yield to 35%. Also, the reaction of the monosodium salt of Meldrum's acid in DMF gave somewhat better yield (42%). The above procedure has been extended for the preparation of spiro compounds[32] from dibromoalkanes in low yield (30-35%). Mane and Krishna Rao[3] have reported an exceptional monoalkylation in DMF using potassium carbonate. They have also reported bis-alkylation with ethyl bromoacetate and ethyl *p*-bromomethyl benzoate. Beres *et al.*[35] have reported the preparation of diethyl Meldrum's acid in low yield from diethyl malonic acid. Recently the bis-alkylation of Meldrum's acid has been carried out by alkyl halides in dimethyl formamide (DMF) using anhydrous potassium carbonate[36] and also under phase transfer catalysed condition.[37] However, these methods involve usual tedious reaction work up. We now report the use of anion exchange resins for bis-alkylation of Meldrum's acid which combines the advantage of solid phase synthesis and anionic activation. It avoids the tedious preparation of the quaternary ammonium salt and has the advantage in terms of yields and simplicity of performance. The resin could be used repeatedly, since it can be regenerated to its initial activity by treating with a solution of hydrochloric acid.

Effect of Solvent

Bimolecular reactions between anions and uncharged species are often very much faster in dipolar aprotic than in protic solvents. Protic solvents such as alcohols, water, hydrogen fluoride, formide and ammonia are strong hydrogen bond-donors. Dipolar aprotic solvents like dimethyl formamide (DMF), dimethylacetamide (DMAC), dimethyl sulphoxide (DMSO), hexamethylphosphoramide (HMPT), acetone, 1,2-dimethoxyethane, nitromethane, nitrobenzene, acetonitrile are very weak hydrogen-bond donors. The dipolar aprotic solvents often recommended as reaction media for bimolecular reactions are DMF, DMAC, DMSO, 1,2-dimethoxyethane and acetone. Many reactions are over a million times faster in dipolar aprotic solvents (e.g.DMF) than in protic solvent of the same dielectric constant. We have used dipolar, aprotic 1,2-dimethoxyethane as solvent for bis-alkylation of Meldrum's acid which allows ready isolation of products.

Bis-alkylation

Alkylations were carried out at 80-85°C by the addition of an appropriate halide (2 molar proportion) to the polymer-supported Meldrum's acid anion (1 molar proportion) in 1,2-dimethoxyethane as solvent. Bis-alkylation of Meldrum's acid is summarised in Table 1.

Table 1. Bis-Alkylation of Meldrum's Acid

Product	Halide	Time (hr)	Yield (%)	Observed m.p. (°C)	Lit. m.p. (°C)
IIa	CH_3I	5	80.0	62	62[6]
IIb	C_2H_5I	6	78.0	41	35-37.5[35]
IIc	n-C_4HgI	7	83.0	93	92-93[36]
IId	$C_6H_5CH_2Cl$	4	89.0	233	232-234[32]
IIe	$Br-(CH_2)_4-Br$	5	85.0	85	84-85[36]

Reaction with methyl iodide gave dimethyl Meldrum's acid (7.IIa). PMR (CCl_4) showed only two singlets (Fig1) corresponding to the gem-dimethyl group (δ = 1.62) attached to the carbonyl system and gem-dimethyl group (δ=1.77) attached to the ketal group.

Alkylation of polymer-supported Meldrum's acid anion with ethyliodide gave diethyl Meldrum's acid (7.IIb). PMR (CCl_4) supported the structure assigned (Fig 2), a triplet at δ 0.97 was due to the methyl group of the ethyl chain, a singlet at 1.75 due to gem-dimethyl group and a quartet at 2.03 due to the methylene protons.

Treatment of polymer-supported Meldrum's acid anion with n-butyl iodide yielded dibutyl Meldrum's acid (7.IIc) . The PMR (CCl_4) was in agreement with the structure (Fig 3) : a triplet (J = 6 Hz) at δ 0.95 was assigned to two methyl groups of the alkyl side chain, a multiplet between 1.1 to 1.5 corresponding to eight methylene protons singlet at 1.75 due to the gem-dimethyl group and a triplet (J = 6 Hz) at 1.93 due to methylene groups attached to the ring.

The reaction of polymer-supported Meldrum's acid and benzyl chloride gave dibenzyl Meldrum's acid (7.IId). The PMR ($CDCl_3$) showed three signals indicating three groups of protons (Fig 4), a singlet at δ 3.47 due to the four benzylic protons, a peak at δ 7.17 for aromatic protons and a singlet at exceptionaly high field δ 0.67 due to the gem-dimethyl group. The high field singlet appearance (0.67) of the gem-dimethyl group suggests that the conformation of the molecule is such that the methyl groups lie in the shielding zone of the aromatic rings.

Alkylation of polymer-supported Meldrum's acid anion with 1,4-dibromobutane gave the spiro compound isopropylidene-1,1-cyclopentane dicarboxylate (7.IIe). The PMR (CCl_4) was in agreement with the structure (Fig 5); a singlet at δ 1.75 was due to gem-dimethyl group and a multiplet between 1.37 to 2.5 corresponding to eight methylene protons.

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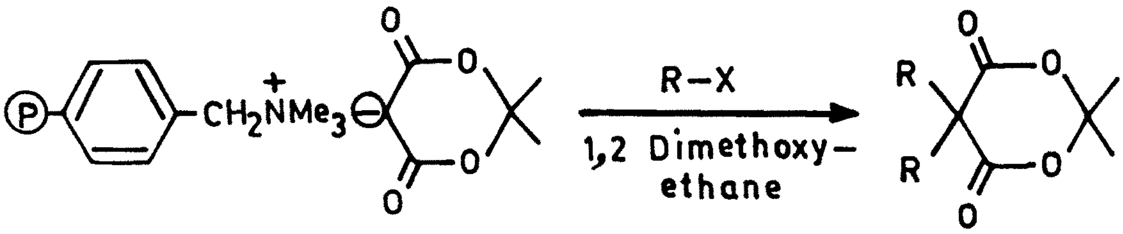
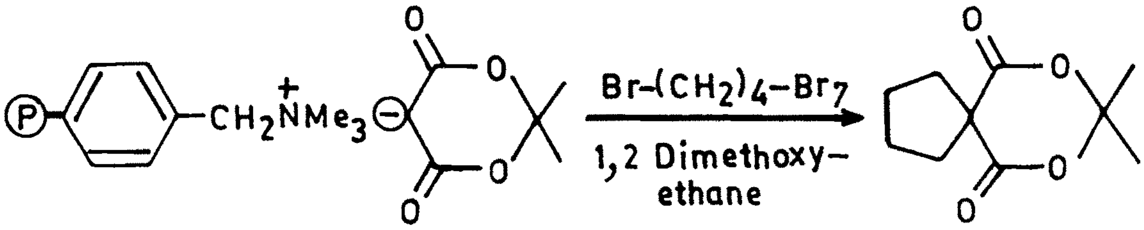


(I) (II) a-d

(a) X = I	(a) R = CH_3	(80 %)
(b) X = I	(b) R = C_2H_5	(78 %)
(c) X = I	(c) R = n-C_4H_9	(83 %)
(d) X = Cl	(d) R = $C_6H_5CH_2$	(89 %)



(I) (II) e (85 %)

EXPERIMENTAL

General

Amberlite IRA-400 (Rohm & Haas Ltd.), Methyl iodide (SRL), Ethyl iodide (Riedel), n-Butyl iodide (Fluka) and Benzyl chloride (SDS) were commercially available. 1,4-Dibromobutane was prepared according to the procedure given in the 'Text book of Organic Chemistry' by A.I.Vogel (p 280).

All the bis-alkylation reactions were performed under anhydrous conditions. 1,2-Dimethoxyethane (SISCO) was distilled before use. P.M.R. spectra were recorded on Varian T-60 Spectrometer.

Meldrum's Acid

It was prepared according to the procedure of Davidson and Bernhard.[6]

To a suspension of powdered malonic acid (52 g) in acetic anhydride (60 ml), was added, with stirring, concentrated sulphuric acid (1.5 ml). Most of the malonic acid dissolved with spontaneous cooling. To the resulting solution, acetone (40 ml) was added while cooling, to mentain the temperature between 20-25°C. The reaction mixture was allowed to stand over night in the refrigerator and the resulting crystals filtered by suction and washed three times with sufficient ice water; yield of air dried product (35 g, 49%). Recrystallization is conveniently effected without heating by dissolving the crude product (10. g) in acetone (20 ml), filtering and adding water(40 ml). The recovery is about 70%, m.p.94-95°(decomposition).

1,4-Dibromobutane

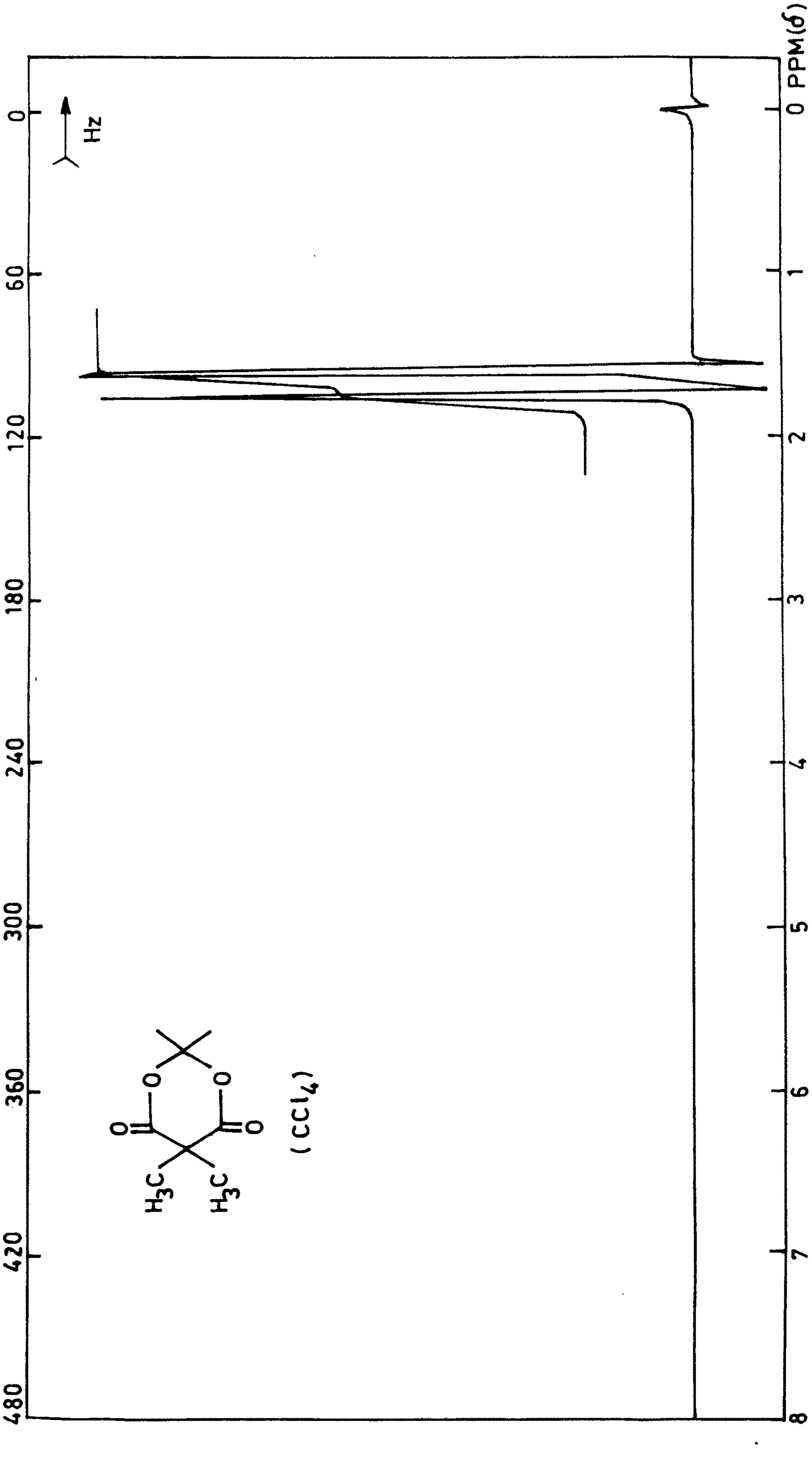
Place a mixture of 250 g (170 ml) of 48 percent hydrobromic acid and 75 g (41 ml) of concentrated sulphuric acid, in a 500 ml round bottomed flask, add 18.1 g (20.5 ml) of redistilled tetrahydrofuran (b.p. 65-66°C), attach a reflux condenser and reflux gently for 3 hours. Separate the lower layer of dibromide and wash it successively with water, 10 percent sodium carbonate solution and water, and then dry with anhydrous magnesium sulphate. It was purified by distillation b.p. 198-201°C. The yield is 40 g (21.5 ml). (Lit.[38] b.p. 200-1°C).

A General Procedure for the Preparation of Polymer-supported Meldrum's Acid Anion (I)

Commercial strongly basic anion exchange resin in the chloride form (Amberlite IRA-400 $\bar{\mathrm{Cl}}$) packed in a column is eluted with 0.25 N aqueous sodium salt of Meldrum's acid (prepared by dissolving 25 m moles of Meldrum's acid in 100 ml 0.25 N NaOH) until complete removal of chloride ion. The resin is then successively washed with water and ethanol until the excess of Meldrum's acid anion is removed ($NaNO_2$ test on acidification). The resin is finally dried in vacuo at 50°C over P_2O_5 for 10 hrs. The exchange capacity is determined by passing aqueous 1 M sodium chloride solution (100 ml) through the resin (0.3 g) in a column. The amount of Meldrum's acid anion in the eluent is titrated with 0.01 N hydrochloric acid using methyl orange as an indicator.

A General Procedure for Bis-Alkylation of Meldrum's Acid

Amberlite IRA-400 Meldrum's acid anion form (5 g, capacity 1 m mole Meldrum's acid anion/g of dry resin) in 1,2-dimethoxy ethane (10 ml) is refluxed with appropriate halide (10.01 m mole for monohalide and 5.01 m mole for dibromobutane) on water bath for 4 to 7 hrs. After completion of the reaction the resin was removed by filtration and washed with 1,2 dimethoxy ethane. The distillation of the solvent furnished the corresponding bis-alkylated product in essentially pure form with high yield. The products were characterised by PMR, IR and comparison with authentic samples.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0 PPM(δ)
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H_3C
(CCl_4)

Fig. 1

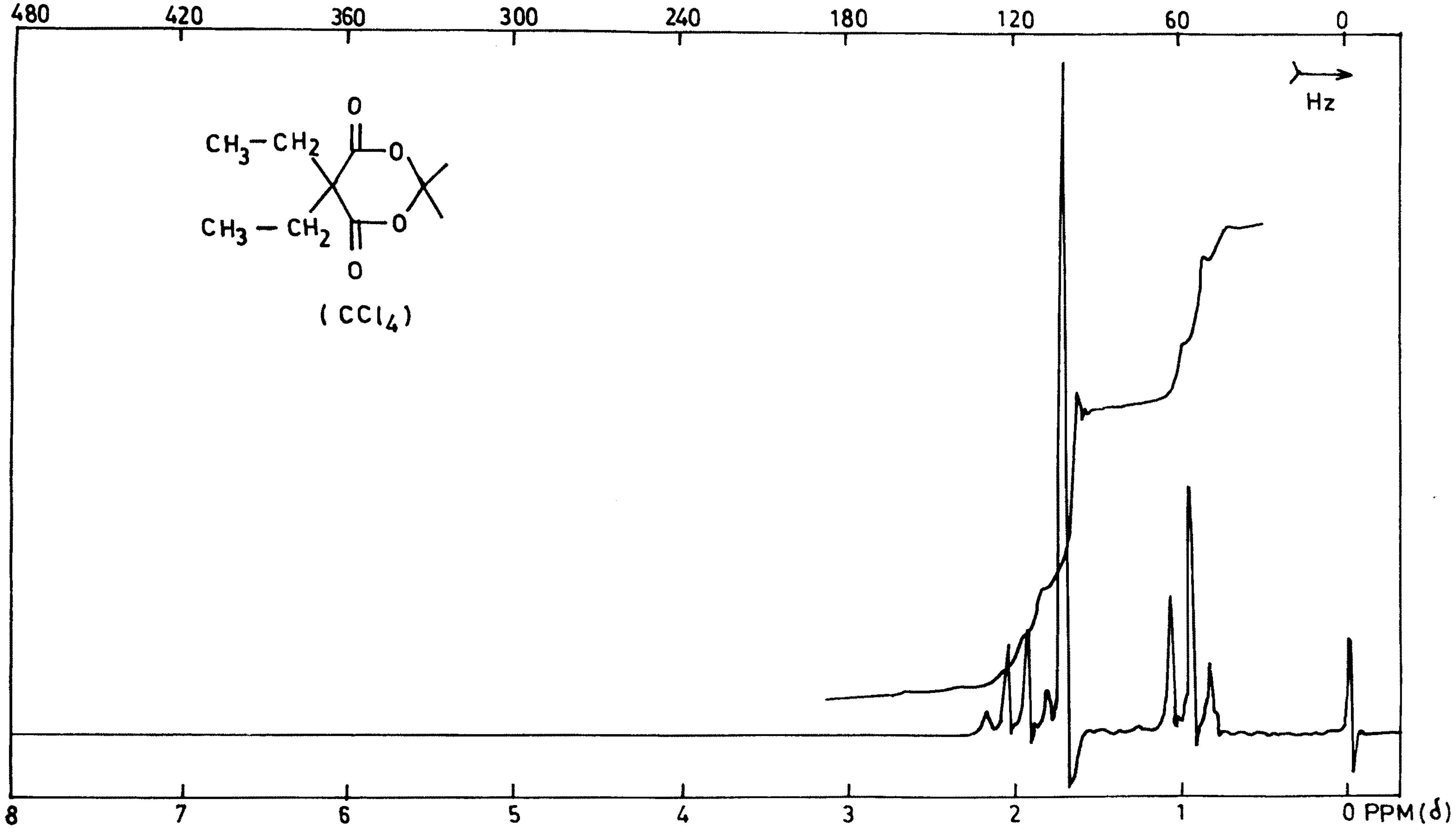
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Fig. 2

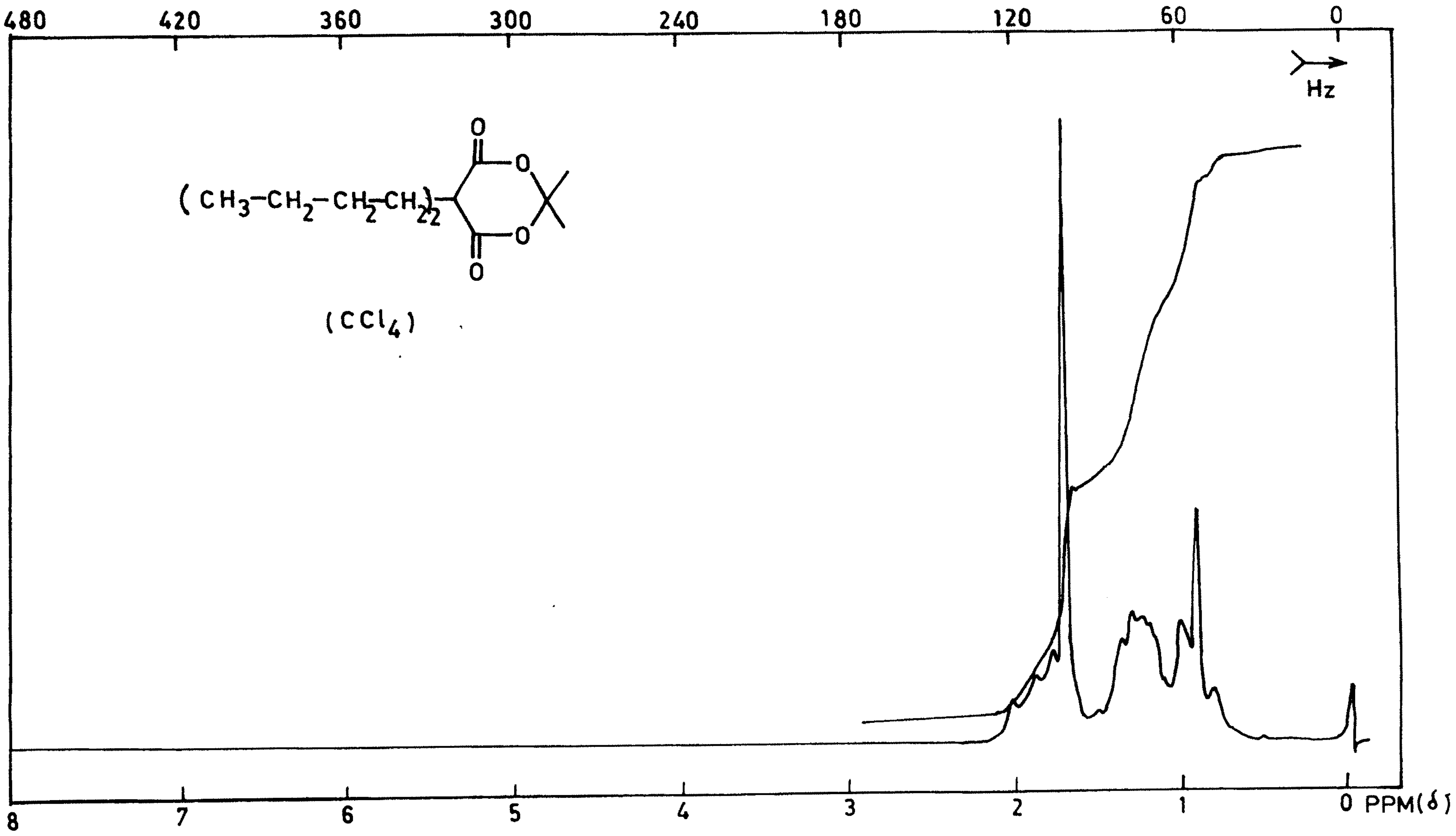
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Fig. 3

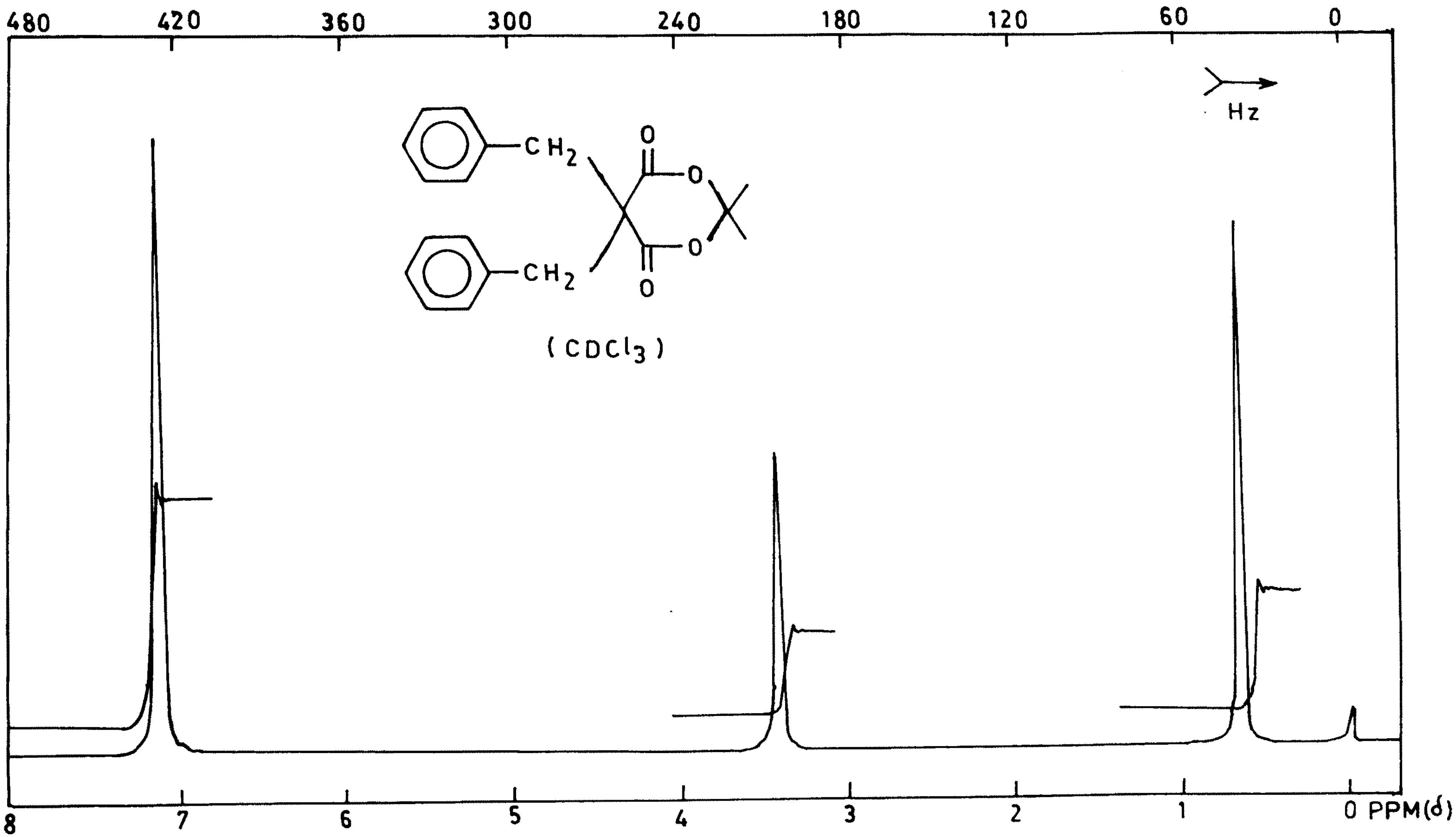
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Fig. 4

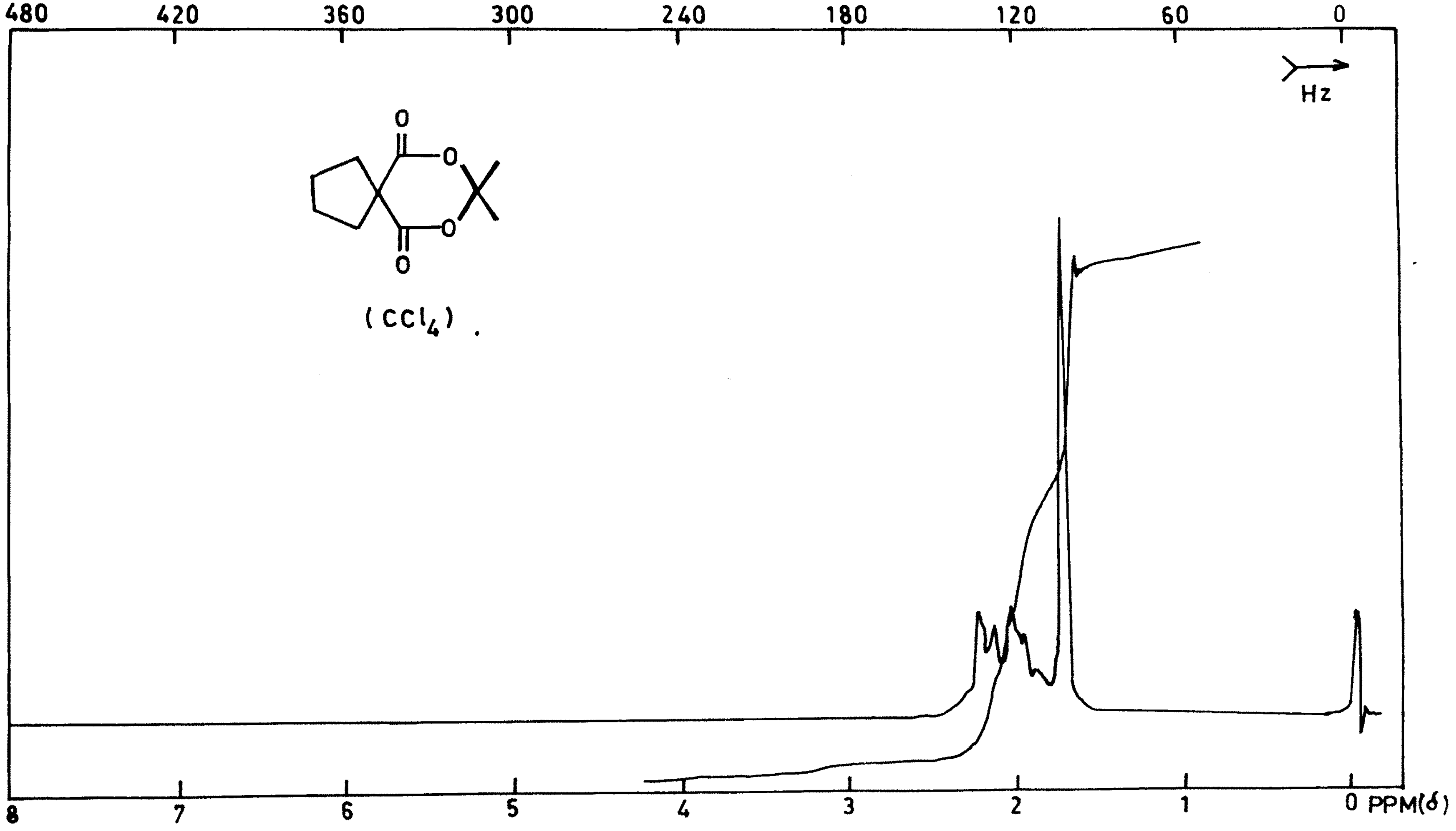

Fig. 5

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