CHAPTER 3

POLYMER SUPPORTED REAGENTS : SYNTHESIS OF PHENACYL ESTERS OF PHENOXYACETIC ACIDS

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ABSTRACT :

Polymer supported nucleophilic reagents has been prepared by treatment of sodium salt of phenoxyacetic acids with Amberlite IRA-400 (Cl^-) a macroreticular anion-exchange resin containing quaternary ammonium group. Phenacyl esters were readily obtained by the reaction of this reagent with phenacyl bromide under mild reaction conditions with quantitative yields and purity.

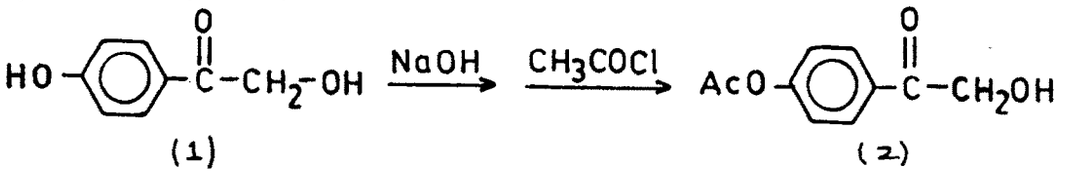
Kinetic studies of the reaction of phenacyl bromide with substituted phenoxyacetate ions revealed that, the phenoxyacetate ions are much weak nucleophiles than benzoate ions. The polymer support seems to cause high anionic activation of the held phenoxyacetate anion leading to the fast, clean and complete reaction. The importance of the procedure embodied here lies in the ease, simplicity and regeneration of the resin used.

INTRODUCTION :

The selection of protecting group is an important step in synthetic methodology. When a chemical reaction is to be carried out selectively at one reaction site in a multifunctional compound, other reactive site must be temporarily blocked. Many protecting groups have been and are being, developed for this purpose. A protecting group must fulfil a number of requirements. It must react selectively in good

yield to give a protected substrate that is stable to projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack regenerated functional group. The protective group should form crystalline derivative that can be easily separated from side products associated with its formation or cleavage. The protecting group should have a minimum of additional functionality to avoid further sites of reaction.

Since a few protective groups can not satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed. In early syntheses the chemist chose a standard derivative known to be stable to the subsequent reactions. In a synthesis of collistephin chloride the phenolic -OH group in (1) is selectively protected as an acetate[1]. In the presence of silver ion the aliphatic hydroxyl group in (2) displaced the bromide ion in bromo-glucoside. In the final step the acetate group was removed by basic hydrolysis.



(1) (2)

Other classical methods of cleavage include acidic hydrolysis (eq. 1), reduction (eq. 2) and oxidation (eq. 3).

$$ArO-R \longrightarrow ArOH \quad \text{---- (1)}$$

$$RO-CH_2Ph \longrightarrow ROH \quad \text{----- (2)}$$

$$RNH-CHO \longrightarrow [RNHCOOH] \longrightarrow RNH_2 \quad \text{---- (3)}$$

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Some of the original work in carbohydrate area in particular reveals extensive protection of carbonyl and hydroxyl groups. For example, a cyclic diacetonide of glucose was selectively cleaved to monoacetonide[2]. A more recent summary[3] describes the selective protection of primary and secondary hydroxyl groups of gentiobiose.

More satisfactory protective groups and more effective methods for the formation and cleavage of the protected compounds were developed as the more complicated structures were synthesized. At first tetrahydropyranyl acetal was prepared[4], by an acid catalysed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild hydrolysis, but formation of this acetal introduces a new chiral centre. Formation of 4-methoxytetrahydropyranyl acetal[5] eliminates this problem.

Catalytic hydrogenolysis of O-benzyl protective group is a mild, selective method introduced by Bergmann and Zervas[6] to cleave a benzyl carbomate ($>NCO - OCH_2C_6H_5 \longrightarrow >NH$) prepared to protect an amino group during synthesis.

Three selective methods to remove protective groups are receiving much attension : "assisted", electrolytic and photolytic removal. The examples illustrating "assisted" removal of protecting groups are : (i) a stable allyl group can be converted to a labile vinyl ether group (eq. 4)[7], (ii) a β haloethoxy (eq. 5)[8] or a β silyl ethoxy (eq. 6)[9]

derivative is cleaved by attack at the β-substituent.

$$RCOCH_2CH=CH_2 \xrightarrow{{}^{-}OBu^{t}} [RCOCH=CHCH_3] \xrightarrow{H_3O^{+}} ROH \quad ---(4)$$

$$RO\text{-}CH_2\text{-}CCl_3 + Zn \longrightarrow RO^{-} + CH_2=CCl_2 \quad ----(5)$$

$$ROCH_2CH_2SiMe_3 \xrightarrow{F^{-}} RO^{-} + CH_2=CH_2 + FSiMe_3 \quad -----(6)$$

R=alkyl, aryl , R'CO-, R'NHCO—

Removal of protecting group by electrolytic oxidation or reduction can be very satisfactory, a review artical by Mairanovsky[10] discusses electrochemical removal of protective groups[11].

Photolytic cleavage reactions of o-nitrobenzyl, phenacyl and nitrophenyl sulfenyl derivatives takes place in high yield on irradiation of the compound for few hours at 254-350 nm[12-13].

One widely used method of formation of protected compounds involves polymer supported reagents[14-17] with the advantage of simple workup by filtration and automated syntheses, especially of polypeptides. Polymer supported reagents are used to protect terminal -COOH group as a polymer bound ester (RCOOR'-(P)) during peptide syntheses[14]; to protect primary alcohols as P -trityl ethers[18]; and to protect 1,2 and 1,3-diol as P -phenyl boronates[19]. Monoprotection of symetrical dialdehydes and diacid chlorides has been reported[16], some diprotection occurs with diols and diamines[16].

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Protection of carboxyl group :

The carboxyl group is present in a number of compounds of biological and synthetic interest. In peptide syntheses a terminal carboxyl group in an amino acid is either protected so that coupling can occur at α-amino group or converted to activated ester so that coupling will occur at carboxyl group. To effect selective protection when a side chain carboxyl group is present, an amino acid can be treated with formaldehyde to form a 5-oxo-1,3-oxozolidine. Macrolide precursors are often converted to activate esters to facilitate lactonization.

Some new methods of formation and some new methods of cleavage are given below :

New Methods of Formation :

(1) $RCOOH + R'X \xrightarrow[25\text{-}80^{\circ},\ 1\text{-}10\ h]{DBU,\ C_6H_6} RCOOR'$, 70-95 %

RCOOH = alkyl, aryl, hindered acids

R' = Et, n- and s-Bu, CH_3SCH_2 ...

X = Cl, Br, I

This reaction also proceeds well in acetonitrile, allowing lower temperatures (25°) and shorter times.

(2) $RCOOH + R'OH \xrightarrow[25^{\circ},\ 1\text{-}24\ h,\ 70\text{-}95\ \%]{DCC/DMAP,\ Et_2O} RCOOR'$

DMAP = 4-dimethylaminopyridine

RCOOH = alkyl, aryl, α-amino, hindered acids

R' = Et, t-Bu, Ph, $PhCH_2$, aryl

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(3) $\underset{\text{NHPG}}{\text{RCHCOOH}} \xrightarrow[\text{pH 7}]{Cs_2CO_3} \xrightarrow[\text{6 h}]{\text{R'X, DMF}} \underset{\text{NHPG}}{\text{RCHCOOR'}}$

R' = Me, 80 %; $PhCH_2$, 70-90 %; o-$NO_2C_6H_4CH_2$, 90 %; p-$MeOC_6H_4CH_2$, 70 %; Ph_3C, 40-60 %; t-Bu, 14 %; PhCOCH(Me), 80 %; N-phthalimidomethyl, 80 % yield.

A study of relative rates of this reaction indicates that Cs^+ K^+ Na^+ Li^+; I^- Br^- Cl^-; HMPA DMSO DMF.

(4) $\underset{\text{NHPG}}{\text{RCHCOOH}} + \text{R'X} \xrightarrow[25^\circ,\ 24\ \text{h},\ 90\text{-}95\ \%]{NaHCO_3/DMF} \underset{\text{NHPG}}{\text{RCHCOOR'}}$

R' = Et, n-Bu, s-Bu

X = Br, I

(5) $\underset{\text{NHPG}}{\text{RCHCOOH}} + \text{R'X} \xrightarrow[25^\circ,\ 3\text{-}24\ \text{h},\ 70\text{-}95\ \%\ \text{phase transfer reaction}]{(C_8H_{17})_3N^+MeCl^-,\ \text{aq}\ NaHCO_3/CH_2Cl_2} \underset{\text{NHPG}}{\text{RCHCOOR'}}$

(6) $\text{RCOOH} + R'_3O^+BF_4^- \xrightarrow[20^\circ,\ 1\text{-}24\ \text{h}]{EtN\text{-}i\text{-}Pr_2,\ CH_2Cl_2} \text{RCOOR'},\ 70\text{-}95\ \%$

RCOOH = hindered acids

R' = Me, Et

(7) $\text{RCOOH} + Me_2NCH(OR')_2 \xrightarrow[1\text{-}36\ \text{h}]{25\text{-}80^\circ} \text{RCOOR'},\ 80\text{-}95\ \%$

RCOOH = Ph, 2,4,6-$Me_3C_5H_2$-, N-protected amino acids

R' = Me, Et, $PhCH_2$, s-Bu

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(8) $RCOOH + R'OH \xrightarrow[0\text{-}20^{\circ},\ 24\ h]{R''NC} RCOOR'$, 36-98 %

RCOOH = amino, dicarboxylic acids; ≠ PhCOOH

R' = Me, Et, t-Bu

R" = t-Bu

(9) $RCOOH + R'OH \xrightarrow[25^{\circ},\ 12\ h,\ 75\text{-}80\ \%]{Ph_3P(OSO_2CF_3)_2,\ CH_2Cl_2} RCOOR'$

R = aryl

R' = Et

New Methods of Cleavage :

(1) $RCOOR' + Nu^- \xrightarrow{\text{aprotic solvent}} RCOOH$

Nu^- = LiS-n-Pr: HMPA, 25°, 1 h, ca. quant yield

Nu^- = NaSePh: HMPA-THF, reflux, 7 h, 90-100 % yield

Nu^- = LiCl: DMF or Py, reflux, 1-18 h, 60-90 % yield

Nu^- = KO-t-Bu: DMSO, 50-100°, 1-24 h, 65-95 % yield

Nu^- = NaCN (for decarboxylation of malonic esters):
DMSO, 160°, 4 h, 70-80 %

(2) $RCOOR' + Me_3SiCl \xrightarrow[\text{reflux, 5-35 h}]{NaI,\ CH_3CN} RCOOH$, 70-90 %

RCOOH = alkyl, aryl, hindered acids

R' = Me, Et, i-Pr, t-Bu, $PhCH_2$

(3) $RCOOR' + KO_2 \xrightarrow[25^{\circ},\ 8\text{-}72\ h]{18\text{-crown-}6,C_6H_6} RCOOH$, 80-95 %

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Potassium superoxide cleaves hindered esters of hindered acids; it does not cleave amides.

(4) $RCOOR' + KO\text{-}t\text{-}Bu/H_2O \xrightarrow[80\text{-}100\ \%]{25^\circ,\ 2\text{-}48\ h} RCOOH$

1 eq 8 eq 2 eq

RCOOH = Ph, aryl, hindered acids

R' = Me, t-Bu, alkyl

"Anhydrous hydroxide" also cleaves tertiary amides.

(5) $\underset{NHPG}{RCHCOOR'} + BBr_3 \xrightarrow[-10^\circ,\ 1\ h\ -\ 25^\circ,\ 2h]{CH_2Cl_2} \underset{NH_2}{RCHCOOH},\ 60\text{-}85\ \%$

R' = Me, Et, t-Bu, $PhCH_2$

PG = $-COOCH_2Ph$, -COO-t-Bu; OMe, OEt, O-t-Bu, OCH_2Ph side chain ethers

(6) $RCOOR' + AlX_3 + R''SH \xrightarrow[70\text{-}95\ \%]{25^\circ,\ 5\text{-}50\ h} RCOOH$

R = Ph, steroid side chain, ...

R' = Me, Et, $PhCH_2$

R" = Et, $HO(CH_2)_2$-

X = Cl, Br

Phenacyl esters serve very well for synthetic purposes because a phenacyl ester is much more readily cleaved by nucleophiles than other esters. Phenacyl esters are stable to acidic hydrolysis e.g. con HCl; HBr/HOAc[20]; 50 % CF_3COOH/CH_2Cl_2, HF, $0^\circ C$, 1 hr[21]. They are formed by reaction of acid

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with phenacyl bromide in presence of base[20-21] and can be cleaved by treatment with Zn/HOAc or H_2/Pd-C[20,22]. Under basic coupling conditions an aspartyl peptide that has a β-phenacyl ester is converted to succinimide[23].

In a penicillin synthesis the carboxyl group was protected as a p-bromophenacyl ester that was cleaved by nucleophilic displacement. Hydrogenolysis of benzyl ester was difficult, perhaps because of catalyst poisoning by sulpher, Basic hydrolysis of methyl or ethyl ester lead to attack β-lactum ring[24].

α-Methylphenacyl ester and p-methoxyphenacyl esters can be cleaved by irradiation, has been also reported[25].

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PRESENT WORK :

Phenacyl esters are generally used as protecting groups[22]. Hendrickson had reported earlier that the phenacyl esters can be synthesized according to traditional methods[26] which can be plagued by slow reaction times[26], hydrolysis of alkylating agents, low yields of product and contamination of product with starting alkylating reagent. Durst[27] overcame some of these problems by carrying out the reaction with the potassium salt of the acid in the presence of dicyclohexyl-18-crown-6 under reflux and Clarke[28] utilized potassium fluoride in glacial acetic acid for the preparation of phenacyl esters.

Kinetic studies revealed that phenoxyacetate ions are much weaker nucleophiles than benzoate ions[29], thus making the formation of their esters with phenacyl bromide still more difficult. The synthesis of phenacyl esters of phenoxyacetic acid has many uses in organic chemistry. The majority of these derivatives are solids and as such they provide a useful means of characterising phenoxyacetic acids. Sodium salt of phenoxyacetic acid with Amberlite IRA-400 (Cl^-) forms the polymer supported phenoxyacetate anion. This on treatment with phenacyl bromide in suitable solvent forms phenacyl ester. The products were obtained in higher yields and purity. The reactions were performed at room temperature (25^oC). The esterification proceed in nonpolar as well as polar solvents. Hydrophobic and hydrophilic solvents are equally effective

indicating that microenvironment of the resin is almost independent of the medium.

Reaction :

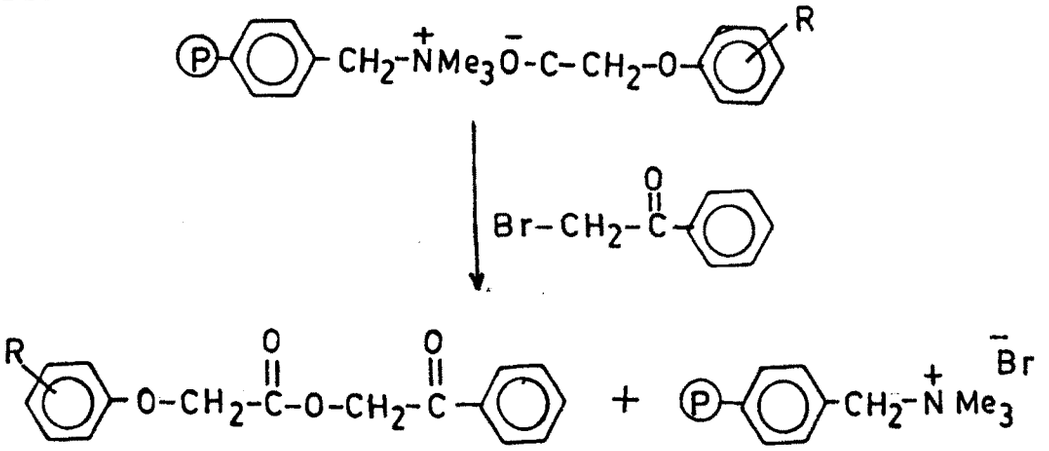

Table - Phenacyl Esters of substituted phenoxyacetic acids.

Anion	Reaction period (hr)	Yield (%)	m p ^{o}C
$C_6H_5 \cdot OCH_2COO^-$	8	95	65
$CH_3C_6H_4 \cdot OCH_2COO^-$ (m)	8	98	64
$CH_3 \cdot C_6H_4 \cdot OCH_2COO^-$ (p)	8	97	94
$CH_3 \cdot C_6H_4 \cdot OCH_2COO^-$ (o)	8	95	59
$Cl \cdot C_6H_4 \cdot OCH_2COO^-$ (p)	6	95	86
$Cl \cdot C_6H_4 \cdot OCH_2COO^-$ (o)	6	95	62
α-Naphthoxyacetate	4	96	117
β-Naphthoxyacetate	4	98	118

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EXPERIMENTAL :

General :

Benzene (BDH), Methanol (BDH), redistilled ethanol, 1,2 dimethoxyethane (SISCO) were commercially available and distilled before use. Phenoxyacetic acids were prepared according to the procedure given in the 'Text book of Organic Chemistry' by A.I.Vogel. Phenacyl bromide was prepared by method of Rather and Reid[30]. PMR spectra were recorded on 90 MHZ Perkin Elmer Spectrometer.

General procedure for preparation of polymer supported phenoxyacetate anion :

Commercial strongly basic anion exchange resin in the chloride form [Amberlite IRA-400 (Cl^-)] packed in a column was washed with 0.25 N aqueous sodium salt of phenoxyacetic acid (prepared by dissolving 25 m mol of phenoxyacetic acid in 100 ml 0.25 N NaOH) until complete removal of chloride ion. The resin was then successively washed with water, alcohol and ether. Finally dried in vacuo at 50°c over P_2O_5 for 10 hr. The exchange capacity was determined by passing 1 M sodium chloride solution (100 ml) through the resin (0.3 g) in a column. The amount of phenoxyacetate anion in the eluent was titrated with 0.01 N hydrochloric acid using methyl orange as an indicator. The exchange capacity found to be 0.8 - 1.00 m mol of phenoxyacetic acid/g of dry resin.

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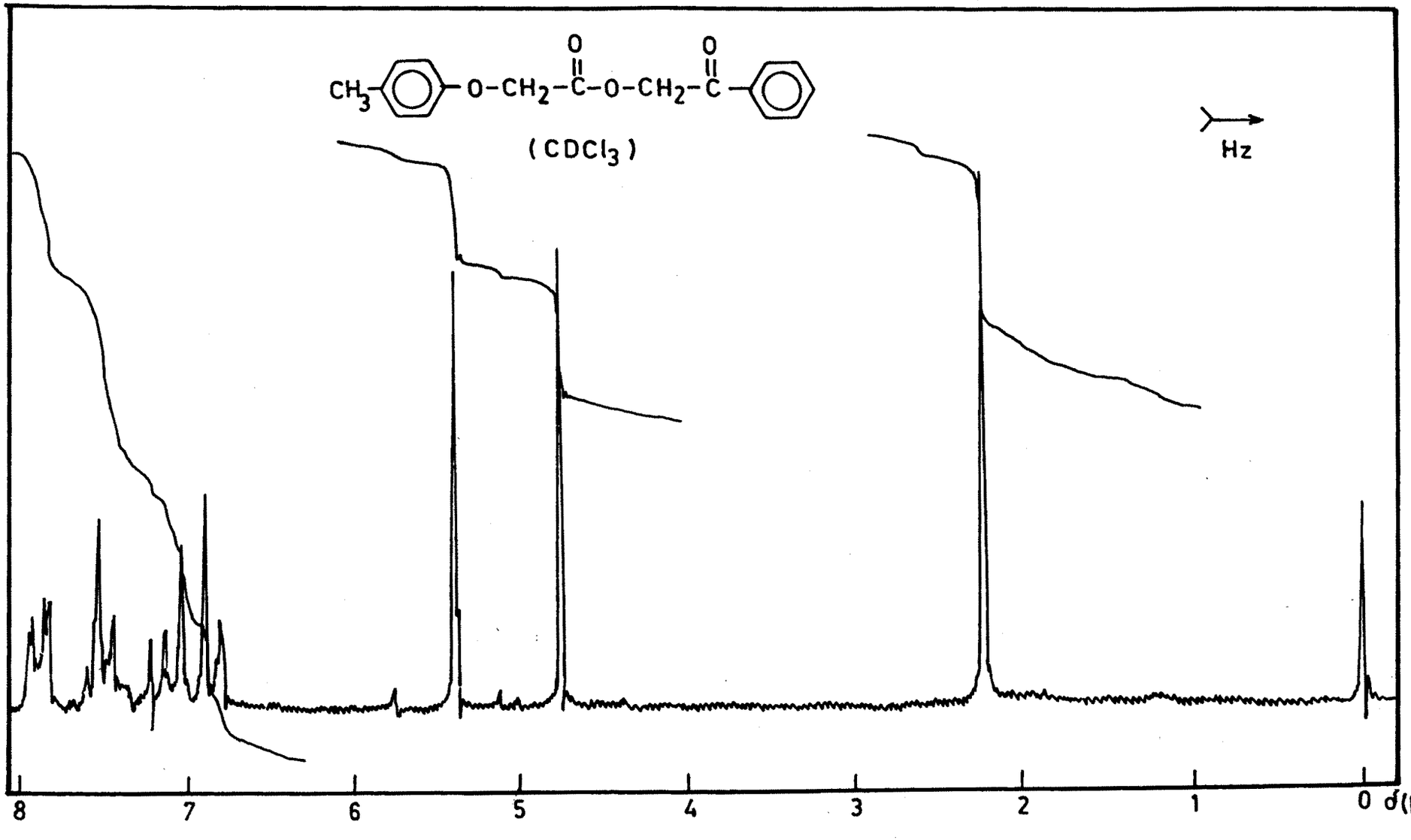
General procedure for preparation of phenacyl esters of phenoxyacetic acids :

Polymer supported phenoxyacetic acid anion (5 m mol) was added to the phenacyl bromide (5 m mol) in ethanol (15 ml). The mixture was then stirred at room temperature. The reaction was monitered by TLC. After completion of reaction, the resin was filtered off, washed with some more quantity of solvent so as to remove adsorbed product. Evaporation of the solvent furnished the phenacyl esters in quantitative yields and purity (Table).

The products were characterised by PMR, IR and TLC.

Some illustrative PMR spectra of phenacyl esters of phenoxyacetic acids are given just after experimental part.



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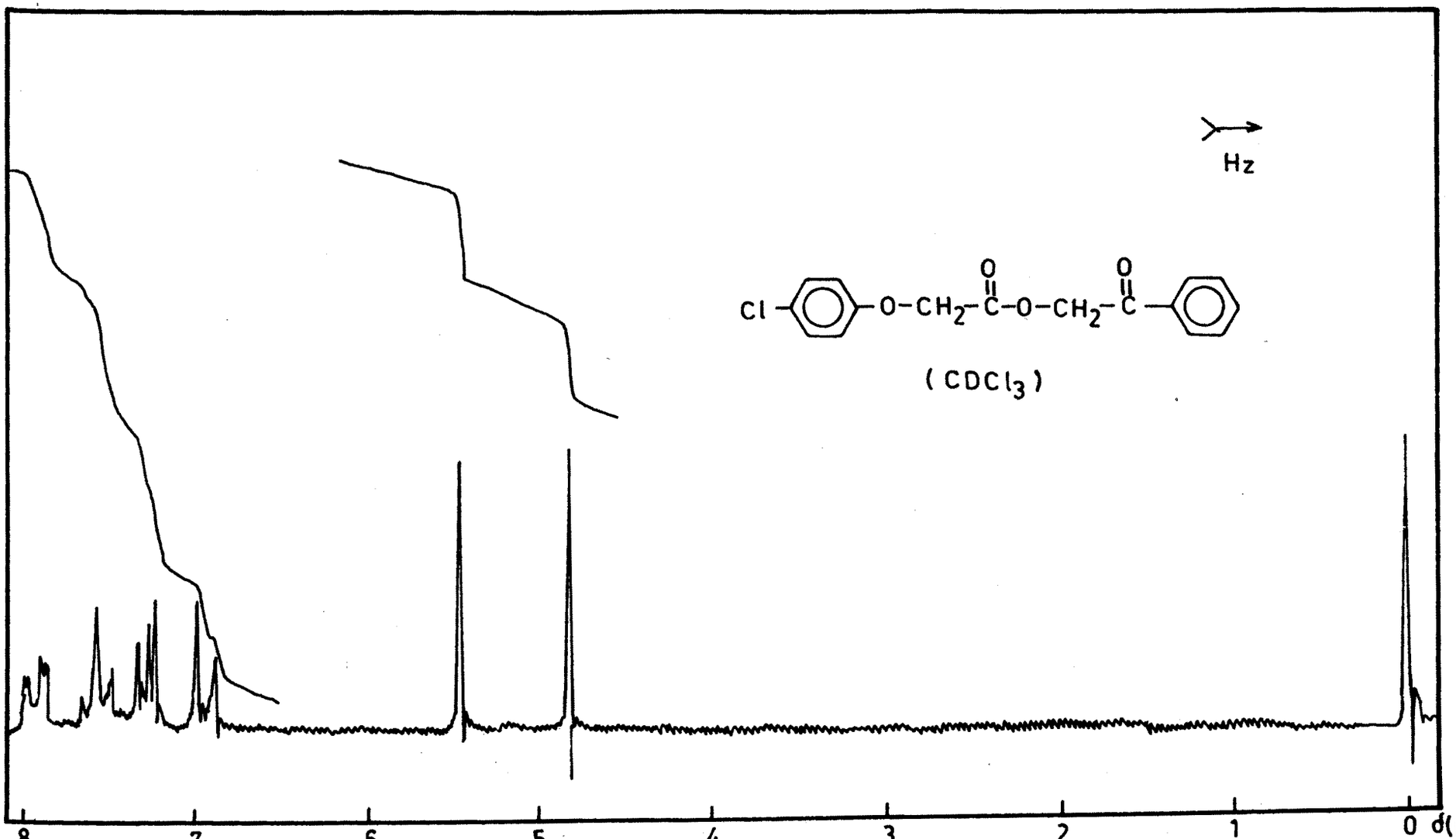
Hz
Cl
O-CH2-C-O-CH2-C
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(CDCl3)
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7
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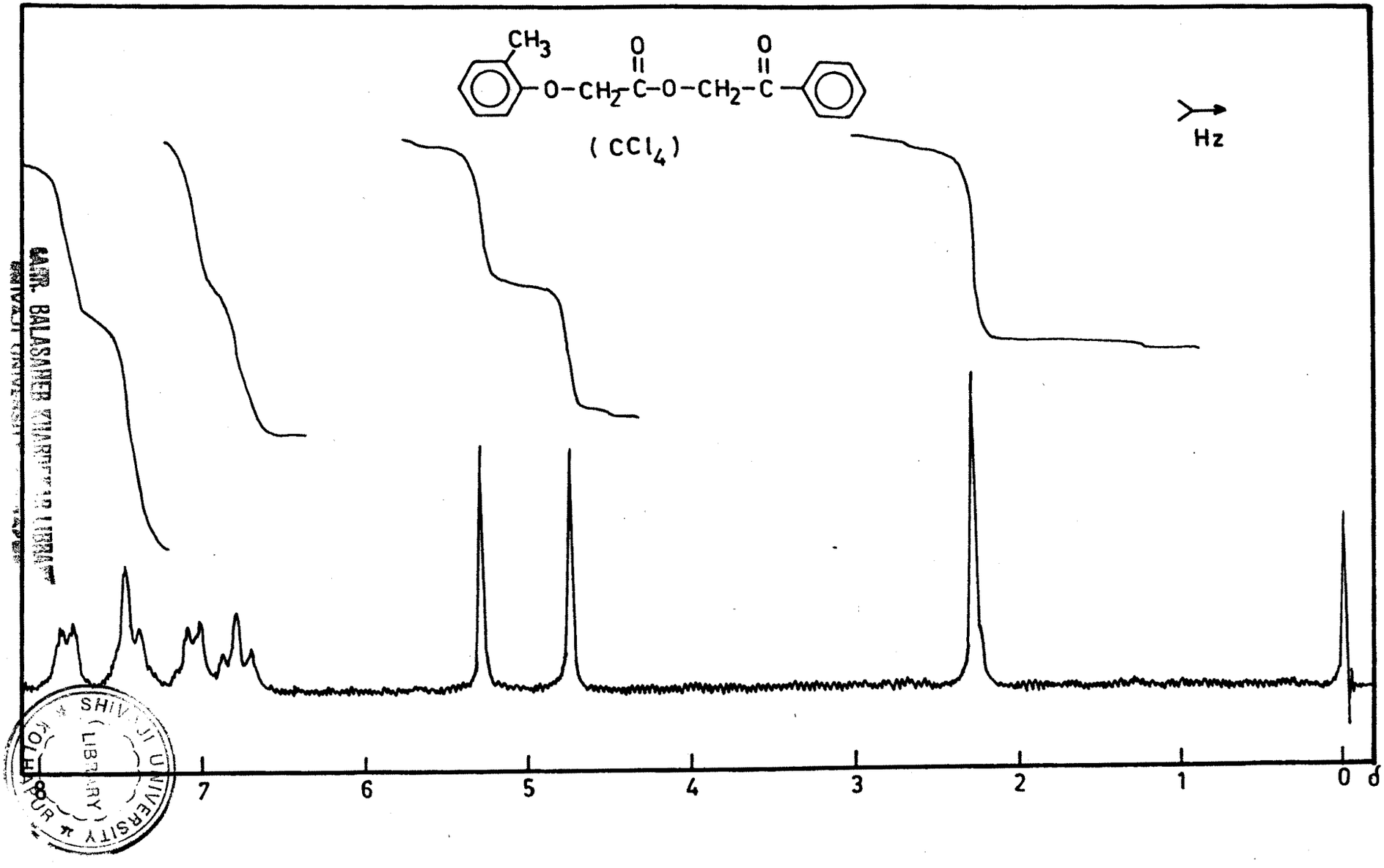

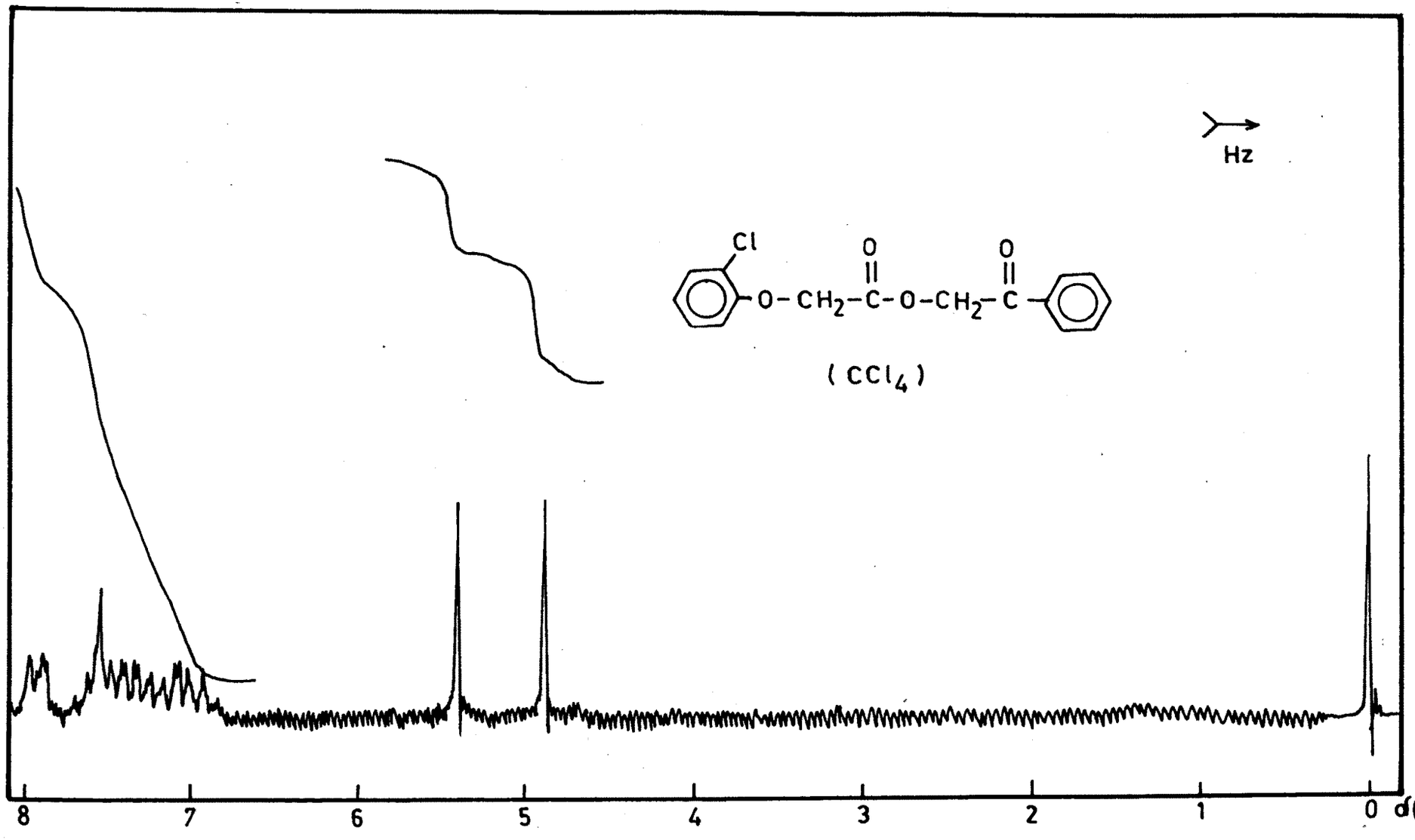
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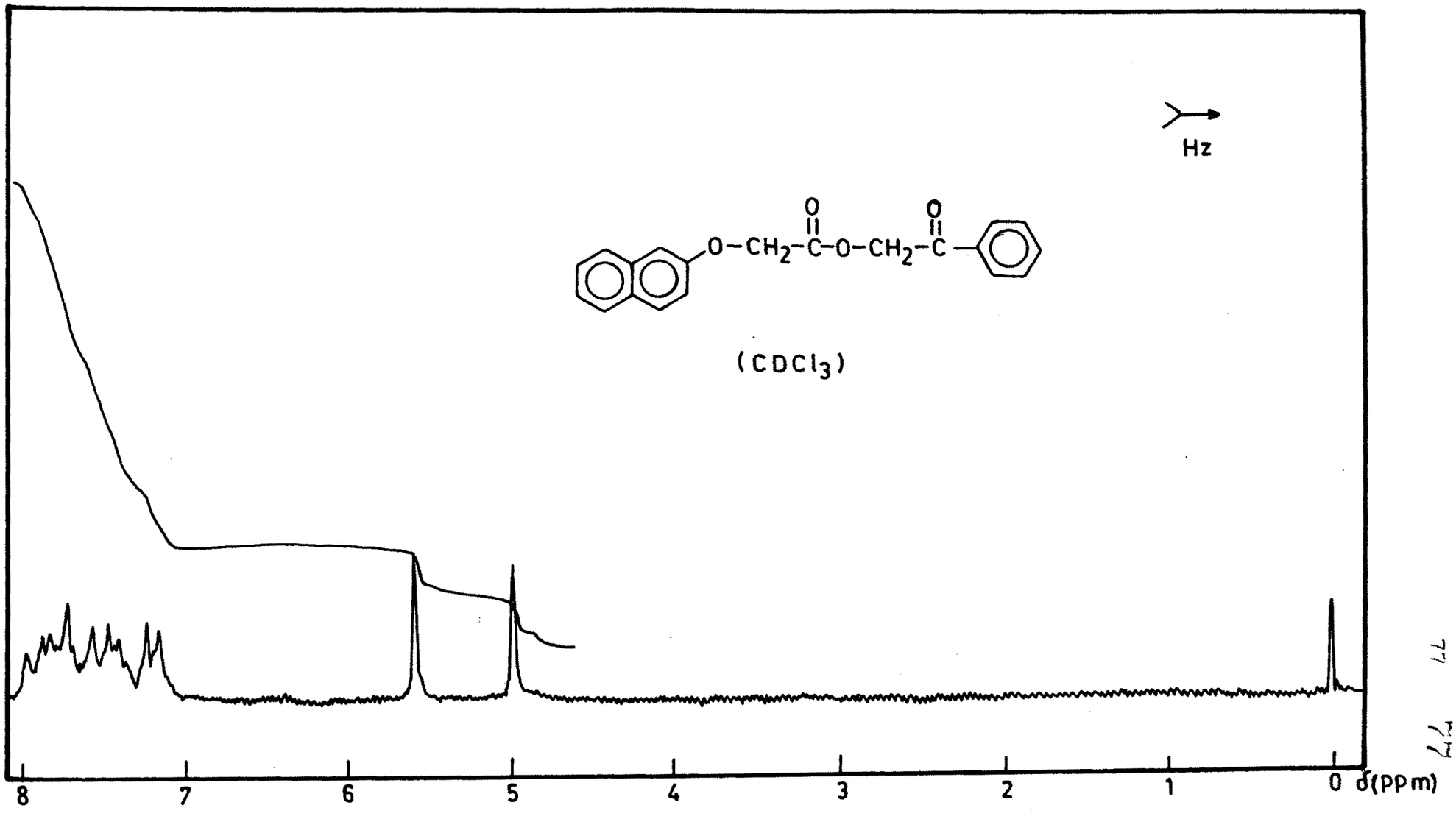
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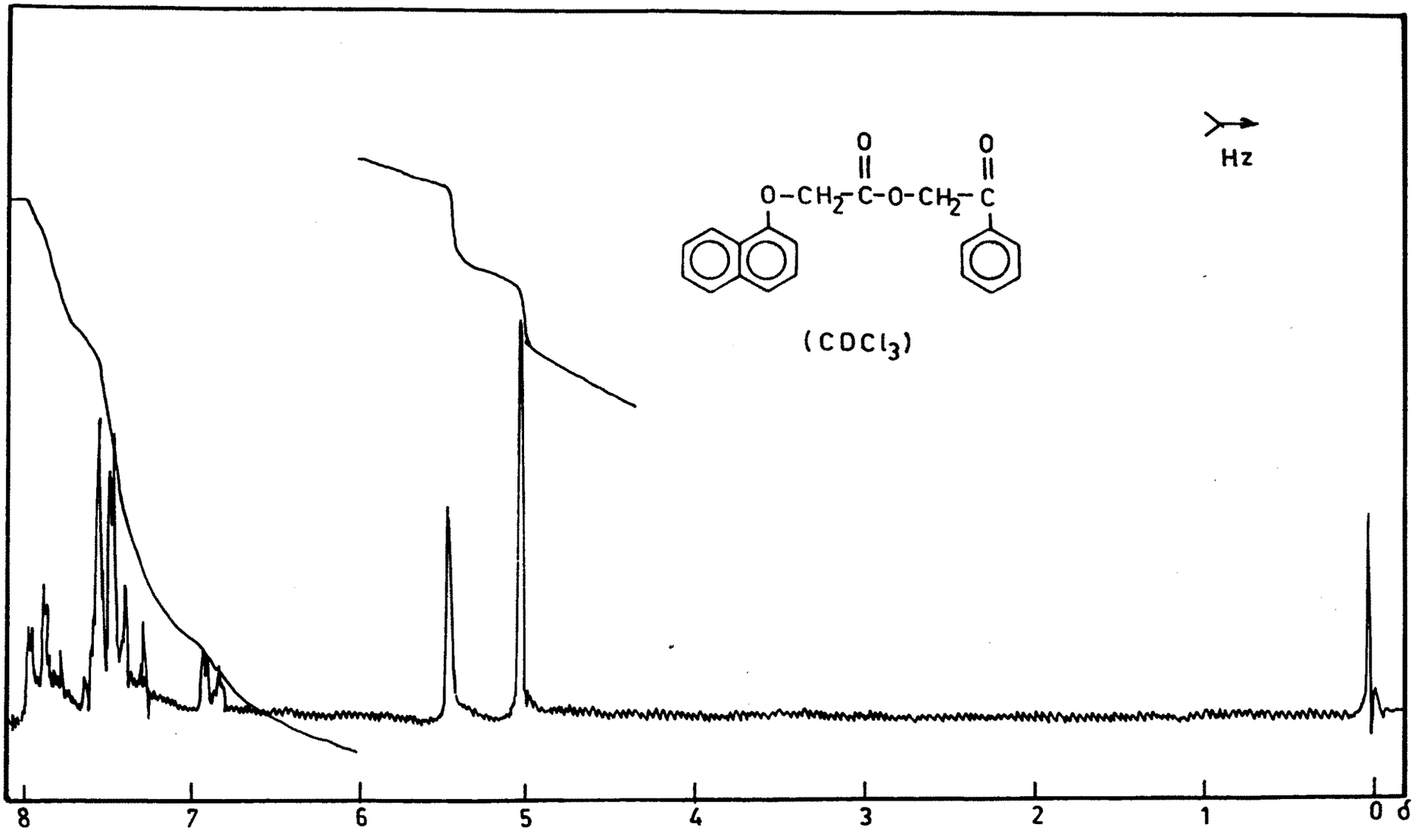
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Hz
(CDCl3)
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