Development of Alternative Technology for the Production of *meta*-Substituted Phenolic Compounds

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Summary: Development of Alternative Technology for the Production of *meta*-Substituted Phenolic Compounds

Both *m*-cresol and resorcinol are important industrial starting materials in the production of many phenolic products.

In a process similar to the one for the production of phenol, cresols are produced by reaction of toluene with propylene to give mixtures of *o*-, *m*- and *p*-isopropyltoluene. The corresponding cresols are subsequently obtained together with acetone *via* the hydroperoxides by air oxidation. Due to their close boiling points, *m*- and *p*-cresol are not separable by distillation and has to be obtained from these mixtures by elaborate adduct crystallisation, derivatization or chromatographic procedures, which results in pure synthetic *m*-cresol to be a very expensive commodity. Since it is known that *m*-cresol can be produced selectively from *o*- or *p*-toluic acid, which is readily available from the corresponding xylene, by application of Keading's Dow Phenol process, it was decided to investigate this methodology as an alternative for the synthesis of pure *m*-cresol. In order to be in a position to optimise this process, it was decided to investigate the mechanism of the reaction through the use of X-ray diffractometry, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), infrared spectrometry (IR) and MALDI-TOF mass spectrometry.

The starting point in the copper catalysed process for transforming *o*-toluic acid into *m*-cresol, has been established by X-ray diffractometry to be the formation of tetrakis(μ_2-2-

methylbenzoato)*bis*(2-methylbenzoic acid)copper(II), with the typical paddlewheel structure of Cu(II) carboxylates, when *o*-toluic acid was reacted with basic copper(II)carbonate and magnesium oxide in refluxing toluene. Apart from the expected four *o*-toluic acid entities forming the paddlewheel structure, the crystal structure also indicated another toluic acid molecule to be attached to each copper atom through the carbonyl of the carboxylic acid moiety. Extension of the X-ray crystallographic investigation to the copper salts of *p*-toluic acid, *m*-toluic acid, *p*-ethylbenzoic acid, and 2,6-dimethylbenzoic acid indicted all of these compounds, except the copper (II) salt of *p*-toluic acid, to have structures similar to that of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II). While the structure of tetrakis(μ_2-4-methyl-benzoato)*bis*(4-methylbenzoic acid)copper(II) basically also showed the paddlewheel configuration, the extra two toluic acid molecules attached to the copper atoms in the all of the other cases were absent in the structure of this compound. In this instance, interactions between an oxygen atom of one molecule and the copper of an adjacent molecule leading to an infinite "polymer" type chain along the a-axis of the crystal, was observed.

Evidence gathered from DSC, TGA, and MALDI-TOF MS investigations of the transformation of tetrakis(μ_2-2-methylbenzoato)*bis*(2-methylbenzoic acid)copper(II) into the product, suggested that this copper benzoate rearranges and cleaves into *o*-toluic acid and copper(I) 2-methyl-6-{[(2-methylphenyl)-carbonyl]oxy}benzoate at 164 °C. Decarboxylation of the latter at 249.5 °C gave *o*-toluic acid and 3-methylphenyl 2-methylbenzoate, which is hydrolysed into *o*-toluic acid and the desired product, *m*-cresol.

In contrast to the copper salt of *o*-toluic acid, which showed clear temperature differences for the different steps in the reaction process, the salt of *p*-toluic acid displayed one continuous decomposition between 160 and 260 $^{\circ}$C, thus rendering the identification of reaction intermediates at specific temperatures more or less impossible.

In a process similar to that of cresols, resorcinol is commercially produced by selective formation of *m*-diisopropylbenzene followed by oxidative cleavage of the dihydroperoxide which is obtained through aerial oxidation of the diisopropylbenzene. While this process is used globally, it is hampered by large recycle streams arising from poor *o/p* selectivity during the alkylation of benzene as well as the limitation of low conversion (20%) in the oxidation step due to the explosivity of the hydroperoxide intermediate. Since it has been demonstrated that the Diels-Alder reaction could be applied to the synthesis of *p*-cresol from isoprene and vinyl acetate, application of this methodology to the synthesis of resorcinol, was subsequently investigated.

Danishefsky's diene (*trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene), with the appropriate functional groups already trapped in the required enolic form, was selected as model substrate for the preliminary experiments with model dienophiles, methyl vinyl ketone and butyl acrylate and the novel *cis*- and *trans*-products, 4-acetyl-3-methoxycyclohexanone and butyl 2-methoxy-4-oxocyclo-hexanecarboxylate, obtained, albeit in low yields (7.49 and 6.59 % and 7.53 and 9.66 % respectively). When the reaction was extended to the more relevant methyl propiolate as dienophile, no direct Diels-Alder products could, however, be isolated and only methyl 4-hydroxybenzoate

and methyl 4-{[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]oxy}benzoate were isolated from the reaction mixture in 5.51 and 5.74 % yields respectively. The formation of the *p*-hydroxybenzoate is explicable in terms of methanol elimination from the primary Diels-Alder product, while it is clear that the second product originates from conjugate addition of the formed hydroxybenzoate to methyl propiolate. While seemingly negative, the last Diels-Alder reaction, however, showed that the envisaged methodology could in principle be used for the preparation of resorcinol, but that care would have to be taken in order to avoid unwanted methanol release. If Chan's diene [1,3-*bis*-(trimethylsilyloxy)-1-methoxy-1,3-butadiene] or an equivalent to it, could be used in a Diels-Alder reaction with an acrylate, the tendency towards methanol elimination might, however, be advantageous as it might lead to the mono-silylated resorcinol derivative in a single step. The viability of this Diels-Alder strategy towards the synthesis of resorcinol will form part of a future investigation.

While negative from the point view of methodology for the synthesis of resorcinol, the Diels-Alder reaction between methyl propiolate and Danishefsky's diene represents a new catalytic process for the preparation of methyl 4-hydroxybenzoate. This compound is widely used as a preservative in food, cosmetics and pharmaceuticals, while its free acid form (*p*-hydroxybenzoic acid), which is produced by Kolbe-Schmidt carboxylation of potassium phenolate with carbon dioxide, finds application in the liquid crystal industry.

Opsomming: Die Ontwikkeling van Alternatiewe Tegnologie vir die Produksie van *meta*-gesubstitueerde Fenoliese Verbindings

Beide *m*-kresol en resorsinol is belangrike industriële uitgangstowwe vir die sintese van verskeie fenoliese produkte.

Kresole word in 'n proses soortgelyk aan dié vir die produksie van fenol berei deur die reaksie van tolueen met propileen om mengsels van *o*-, *m*- en *p*-isopropieltolueen te vorm. Die ooreenstemmende kresole, tesame met asetoon, word gevolglik *via* die hidroperoksiede ná lugoksidasie verkry. *m*- en *p*-Kresol se kookpunte verskil so min dat dit nie deur distillasie geskei kan word nie en skeiding van hierdie mengsels berus dus op omslagtige addukkristallisasie, derivatisering of chromatografiese prosedures, wat daartoe bydra dat suiwer sintetiese *m*-kresol 'n baie duur kommoditeit is. Aangesien dit bekend is dat *m*-kresol selektief vanaf *o*- of *p*-tolueensuur, wat geredelik beskikbaar is vanaf die ooreenstemmende xileen, berei kan word deur gebruik te maak van Keading se Dow-Fenolproses, is dit besluit om hierdie metodologie as alternatief vir die sintese van suiwer *m*-kresol te ondersoek. Ten einde hierdie proses te optimiseer, is besluit om die meganisme van die reaksie met behulp van X-straaldiffraktometrie, termogravimetriese analise (TGA), differensiële skandeerkalorimetrie (DSK), infrarooispektrometrie (IR) en MALDI-TOF massaspektrometrie te ondersoek.

X-straaldiffraktometrie het bevestig dat die beginpunt van die kopergekataliseerde proses tydens die omskakeling van *o*-toleensuur na *m*-kresol die vorming van tetrakis(μ_2-2-

metielbensoato)bis(2-metielbensoësuur)koper(II), met die tipiese wawielstruktuur van Cu(II) karboksilate, is wanneer *o*-toleensuur met basiese koper(II)karbonaat en magnesiumoksied in tolueen onder terugvloei verhit word. Buiten die verwagte vier *o*-tolueensuur entiteite wat die wawielstruktuur vorm, het die kristalstruktuur aangedui dat 'n addisionele tolueensuurmolekuul deur die karboniel van die karboksielsuurmoïeteit met elke koperatoom geassosieer is. Uitbreiding van die X-straalkristallografiese ondersoek na die kopersoute van *p*-tolueensuur, *m*-tolueensuur, *p*-etielbensoësuur en 2,6-dimetoksibensoësuur het aangedui dat, buiten vir die koper(II) sout van *p*-tolueensuur, al hierdie verbindings strukture soortgelyk aan die van tetrakis(μ_2-2-metielbensoato)bis(2-metielbensoësuur)koper(II) het. Alhoewel die struktuur van tetrakis(μ_2-4-metielbensoato)bis(4-metielbensoësuur)koper(II) basies ook die wawielkonfigurasie vertoon, is die ekstra twee tolueensuurmolekules geassosieer met die koperatome in al die ander gevalle afwesig in die struktuur van hierdie verbinding. In hierdie geval is waargeneem dat interaksies tussen 'n suurstofatoom van een molekuul en die koper van 'n aangrensende molekuul tot oneindige "polimeriese" tipe kettings langs die a-as van die kristal lei.

Getuienis uit DSK, TGA en MALDI-TOF MS ondersoeke na die omskakeling van tetrakis(μ_2-2-metielbensoato)bis(2-metielbensoësuur)koper(II) na die produk, dui daarop dat die koperbensoaat by 164 °C herrangskik en in *o*-tolueensuur en koper(I) 2-metiel-6-{[(2-metielfeniel)-karboniel]oksi}bensoaat splyt. Dekarboksilering van laasgenoemde by 249.5 °C lewer *o*-tolueensuur en 3-metielfeniel 2-metielbensoaat, wat met hidrolise *o*-tolueensuur en die verlangde produk, *m*-kresol, lewer.

In teenstelling met die kopersout van *o*-tolueensuur, wat duidelike temperatuurverskille vir die verskillende stappe in die reaksie getoon het, het die sout van *p*-tolueensuur slegs een aaneenlopende ontbinding tussen 160 en 260 °C getoon wat die identifikasie van reaksie-intermediêre by spesifieke temperature min of meer onmoontlik maak.

In 'n proses soortgelyk aan dié van kresole, word resorsinol kommersiëel berei deur die selektiewe vorming van *m*-diisopropielbenseen en die daaropvolgende oksidatiewe splyting van die dihidroperoksied verkry deur lugoksidasie van die diisopropielbenseen. Alhoewel hierdie proses wêreldwyd gebruik word, word dit beperk deur groot herwinningstrome weens die swak *o*/*p*-selektiwiteit gedurende die alkilering van benseen sowel as die lae omskakeling (20 %) in die oksidasiestap as gevolg van die plofbaarheid van die hidroperoksiedintermediêr. Aangesien dit bekend is dat die Diels-Alder reaksie vir die sintese van *p*-kresol vanaf isopreen en vinielasetaat gebruik kan word, is die toepassing van hierdie metodologie op die sintese van resorsinol dus ondersoek.

Danishefsky se dieen (*trans*-1-metoksi-3-trimetielsilieloksi-1,3-butadieen), met die toepaslike funksionele groepe alreeds in die verlangde enoliese vorm vasgevang, is as modelsubstraat vir die aanvanklike eksperimente met model dienofiele, metielvinielketoon en butielakrilaat, gekies en die tot nog toe onbekende *cis*- en *trans*-produkte, 4-asetiel-3-metoksiesikloheksanoon en butiel 2-metoksi-4-oksosikloheksaankarboksilaat, is, alhoewel in lae opbrengs (7.49 en 6.59 % en 7.53 en 9.66 %), verkry. Geen direkte Diels-Alder produkte kon egter geïsoleer word toe die reaksie uitgebrei is na die meer relevante metielpropiolaat as dienofiel nie en slegs 4-

hidroksiebensoaat en metiel 4-{[(1E)-3-metoksie-3-oxoprop-1-en-1-iel]oksi}bensoaat is in 5.51 en 5.74 % opbrengs, respektiewelik, uit die reaksiemengsel geïsoleer. Die vorming van die p-hidroksiebensoaat kan verduidelik word in terme van methanol eliminasie uit die primêre Diels-Alder produk, terwyl dit duidelik is dat die tweede produk deur gekonjugeerde addisie van die gevormde hidroksiebensoaat aan metielpropiolaat gevorm word. Alhoewel oënskynlik negatief, dui die laaste Diels-Alder reaksie daarop dat die voorgestelde tegnologie in beginsel vir die bereiding van resorsinol gebruik sal kan word, maar dat voorsorg teen ongewenste metanolvrystelling getref sal moet word. Indien Chan se dieen [1,3-bis-(trimetielsilieloksie)-1-metoksie-1,3-butadieen] of 'n ekwivalent daarvan vir die Diels-Alder reaksie met 'n akrilaat gebruik sou word, mag die neiging tot metanoleliminasie egter voordelig wees aangesien dit in 'n enkele stap die mono-gesilileerde resorsinol mag lewer. Die lewensvatbaarheid van die Diels-Alder strategie vir die sintese van resorsinol sal deel vorm van 'n toekomstige ondersoek.

Alhoewel negatief in terme van metodologie vir die sintese van resorsinol, verteenwoordig die Diels-Alder reaksie tussen metielpropiolaat en Danishefsky se dieen 'n nuwe katalitiese proses vir die bereiding van metiel 4-hidroksiebensoaat. Hierdie verbinding het wye toepassing as preserveermiddel in kos, kosmetika en farmaseutika, terwyl die vry suur (*p*-hidroksibensoësuur), wat deur die Kolbe-Schmidt karboksilering van kaliumfenolaat met koolstofdioksied gevorm word, toepassing in die vloeibare-kristal-industrie het.

Chapter 1

Literature

1. Introduction and Motivation

Meta-disubstituted phenolic compounds are industrially of great importance as starting materials in the synthesis of many commercial products. These compounds are used for the synthesis of physiologically important products such as vitamin E (**1**), anti-bacterial compounds like 4-chloro-3-methylphenol (**2**), pesticides such as Fenthion (**3**) (also known as Baytex and Lebaycid), and *m*-anisylalcohol (**4**), a common intermediate in the pharmaceutical, flavour and fragrances industries. Since many of these compounds display alkyl– and/or hydroxy substitutents which are *ortho* and *para* directing in their chemical reaction properties, the synthesis of these compounds are hampered by a lack of selectivity towards the desired regio-isomer or many protection/deprotection steps in the synthetic methodology.[1,2]
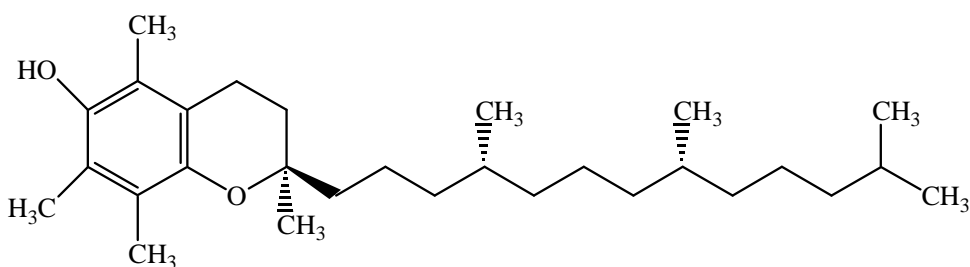
1
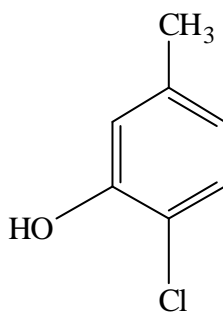
2
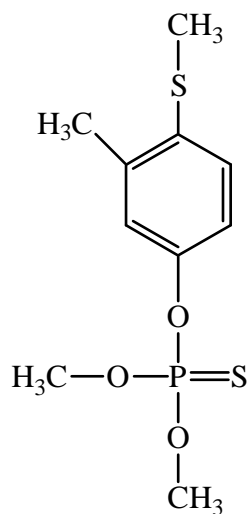
3
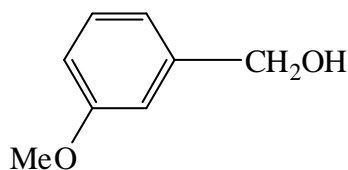
4

Meta-cresol (3-hydroxytoluene or 3-methylphenol) (**10**), for instance is produced

synthetically in a three step process comprising alkylation of toluene (**5**) with propylene

to mainly *ortho*- (**6**) and *para*-isopropyltoluene (**7**). These products are, under high

temperature conditions, isomerised to the thermodynamically more stable *m*-

isopropyltoluene (**8**), which is converted into the cresol by oxidative cleavage *via* the

tertiary hydroperoxide (**9**) (**Scheme 1.1**). Although this methodology represents a

feasible manufacturing process, the isomerisation step is equilibrium limited, which leads

to large recycle streams and the oxidation reaction is hampered by the explosivity of the

hydroperoxide, low conversions (only 20 %), large effluent streams, and the co-production of acetone, a product of low commercial value.[3]

Scheme 1.1
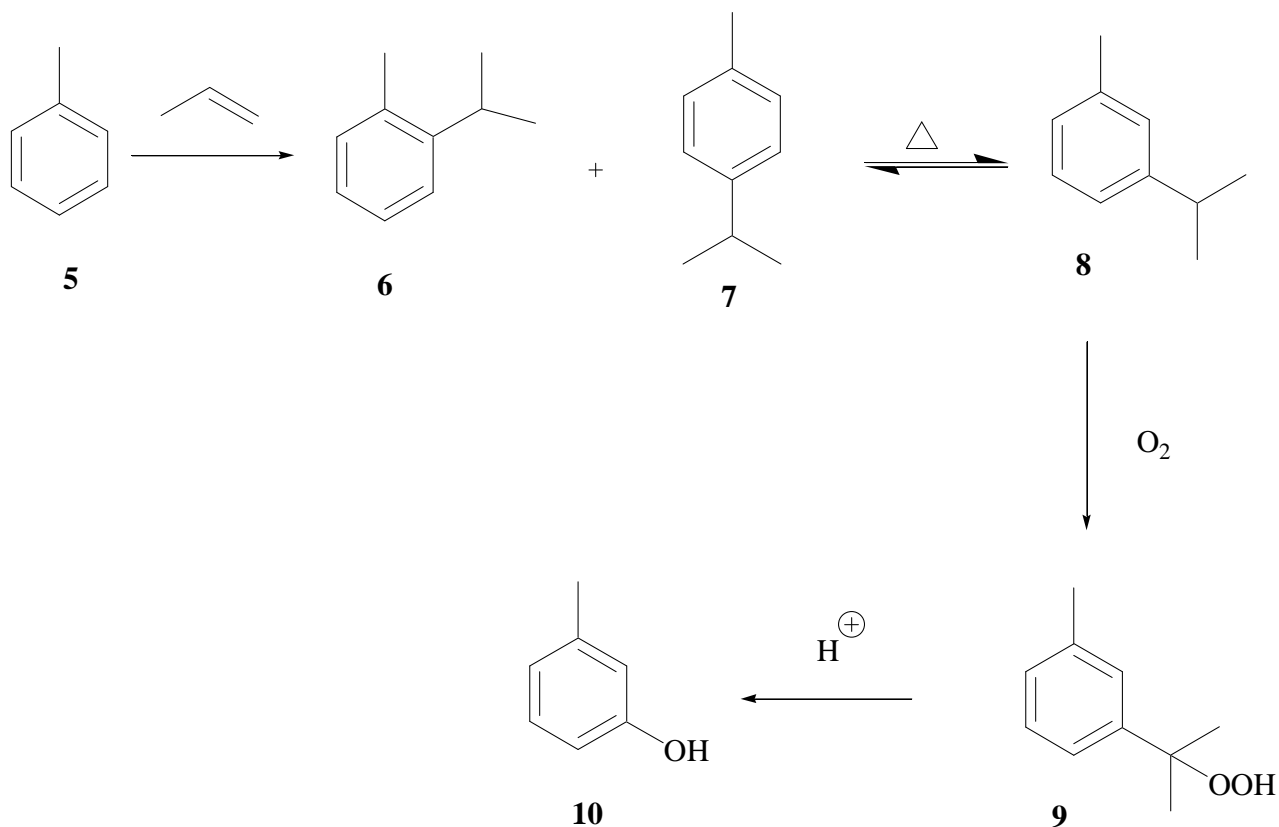
Resorcinol (1,3-dihydroxybenzene) (**14**), another important *m*-disubstituted phenolic compound, is used in the manufacturing of high-quality wood adhesives, dyes, antiseptic agents, pharmaceutical preparations and cosmetic preparations to name a few. In a process similar to that for cresols and phenol, resorcinol is mainly produced through the 1,3-diisopropylation of benzene (**11**). Again this step is complicated by the fact that the first isopropyl group is directing the second one to the *para*-position and the *p*-diisopropylated product needs to be isomerised to the thermodynamically more stable *m*-isomer (**12**). Subsequent oxidative cleavage, associated with all the problems

described for cresol production, leads to the final product together with 2 moles of acetone per mole of resorcinol (**14**) in this instance[4] (**Scheme 1.2**).

Scheme 1.2
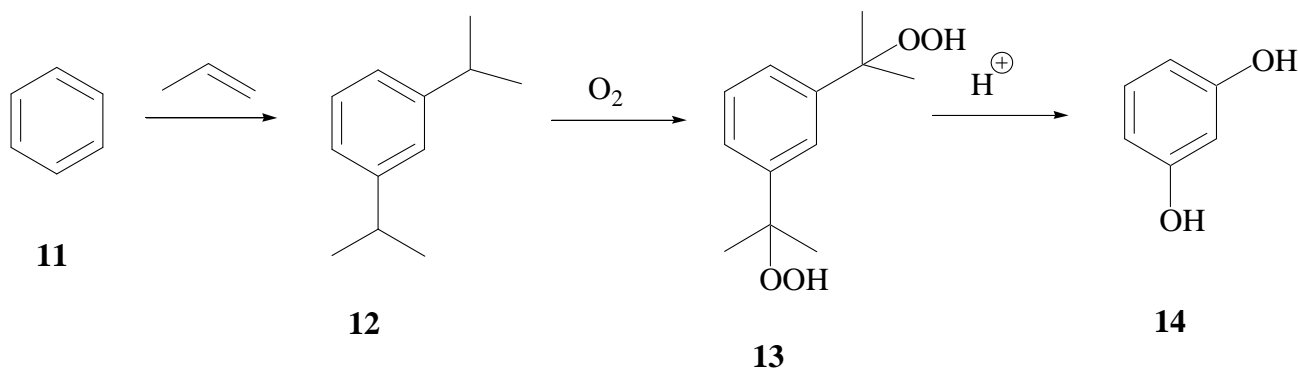
In order to circumvent the problems associated with the current *m*-cresol (**10**) and resorcinol (**14**) production processes, it was decided that an investigation into new technologies for the production of these compounds, is warranted. The newly envisaged processes should lead to *m*-cresol (**10**) and resorcinol (**14**) production through methods that start from relatively cheap raw materials, have low risk from a safety point of view, and produce no unwanted side products with minimal (if any) recycle streams.

Since Merisol (a subsidiary of Sasol) already is in the cresol business, access to this technology would put Merisol in a position where it could compete favourably with other cresol producers (especially Chinese producers) in the world economy, while access to technology for the production of resorcinol would open up a completely new market for the company.

2. Cresols

2.1 Introduction

Cresol, which is also known as methylphenol, C_7H_8O (Molecular weight = 108.14) occurs in three isomeric forms namely *o*-cresol (2-methylphenol) (**15**), *m*-cresol (3-methylphenol) (**10**) and *p*-cresol (4-methylphenol) (**16**). Mixtures of *m*- and *p*-cresol are often referred to as dicresol whereas mixtures of *o*-, *m*- and *p*-cresol are known as tri- or isocresol.[1,2] Cresylic acids can be defined as mixtures of cresols, xylenols, higher alkylated phenols, and some phenol. Cresylic acids obtained from tar are called tar acids.
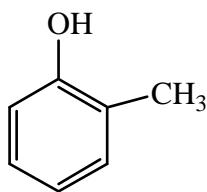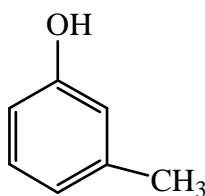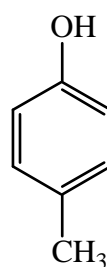
15   **10**   **16**

Cresol was first discovered in cow's urine in 1851 by Stadeler,[5] while Fairlie and Williamson found it in coal-tar creosote in 1854. In 1866 Griess managed the first synthesis of cresol by boiling diazotized toluidine. All three cresol isomers were distinguished by Engelhardt and Latschinoff for the first time in 1869.[2]

Cresols and cresol derivatives (ethers and esters) are widely distributed in nature. They are formed as metabolites of various micro-organisms and are also found in the urine of mammals. On average, humans secrete 87 mg of *p*-cresol (**16**) per day in urine.[2,6]

Various forms of cresol are also detectable in the extracts and water vapour distillates of many plants for example in jasmine flower oil, cassia flower oil, easter lily oil, camphor oil, eucalyptus oil, and ylang oil. It is also found in floral oil of *Yucca gloriosa*, in the scent of *Viola odorata*, in peppermint, and in the essential oils of several plants of the genus *Artemisia*, as well as conifers, oak wood, and sandalwood. Cresol in small amounts are also found in certain foods and drinks such as tomatoes, tomato ketchup, mushrooms, cooked asparagus, milk, certain types of cheese, butter oil, red wine, whisky, rum, cognac and other brandies as well as in raw and roasted coffee, black tea, smoked foods, tobacco, and tobacco smoke.[2,7,8]

Cresols are important chemical raw materials, which were originally obtained only from coal tar, however, after World War II they were also obtained from spent refinery caustics (*vide infra*). Since the mid-1960s, cresols have been produced synthetically on an increasing scale. Since approximately 60 % of the requirements of the United States, Europe and Japan are now provided by synthetic cresol, only about 40 % of it is met by 'natural' cresol in other words cresol obtained from coal tar and spent refinery caustics.[2]

2.2 Physical Properties

In pure form, *o*- (**15**) and *p*-cresol (**16**) are crystalline substances, while *m*-cresol (**10**) is viscous oil at room temperature. The cresols are colourless but turn yellow to brown after time and have a phenolic odour. Cresols absorb moisture from the air due to the fact that water dissolves freely in them and are themselves soluble in phenol and many organic solvents such as aliphatic alcohols, ethers, chloroform and glycerol. While less

soluble in water than in phenol, the presence of other water-soluble organic compounds such as methanol raises their solubility in water and reduces the critical solution temperature. Dissolved inorganic salts lower the water solubility of cresols.[2,9,10,11,12,13]

Cresols can be distilled with steam resulting in the formation of azeotropes with a number of compounds such as decane, 1-decene, 1-undecene, dodecane, 1,2,4,5-tetramethylbenzene, divinyl benzene, ethylene glycol, diethylene glycol, etc. to name but a few.[2,10,11,12,13]

2.3 Chemical Properties and Reactions

2.3.1 Acidity

Cresols are chemically similar to phenol. They are weak acids and dissolve in aqueous alkaline solutions to form water-stable salts known as cresolates. Thus, they can be extracted into sodium hydroxide solution from solvents that are not miscible with water. Their acidity is so low that hydrogen sulphide and carbon dioxide are able to liberate them from cresolates.[2]

2.3.2 Etherification and Esterification

The hydroxyl group of cresols can be etherified with alkyl halides, dialkyl sulfates, dialkyl carbonates, and toluene-sulfonic acid esters and react with acyl anhydrides or acyl chlorides to give cresyl esters,[2] e.g the esterifications of succinic anhydride (**17**) with *p*-cresol (**16**) to di-(*p*-cresyl) succinate (**18**) (**Scheme 2.1**), phenylacetic acid (**19**) with

phenol (**20**) and substituted phenols (**21**) (**Scheme 2.2**). 4-*tert*-Butylphenol (**23**) reacts with chloromethyl benzene (**24**) to form an ether (**Scheme 2.3**).

Scheme 2.1

Scheme 2.2

20 R = H
21 R = *o*-, *m*- or *p*-CH$_3$
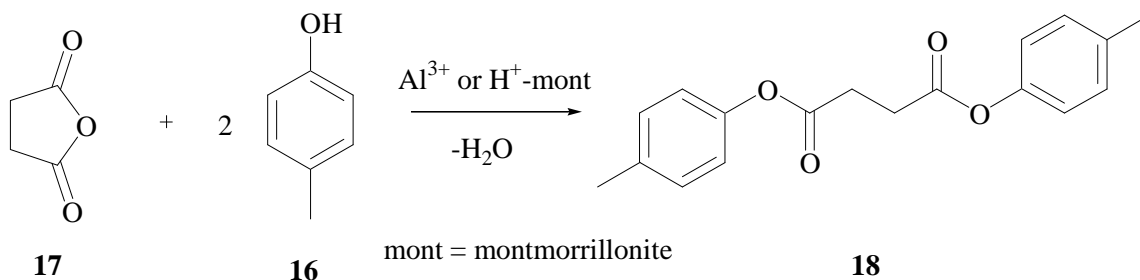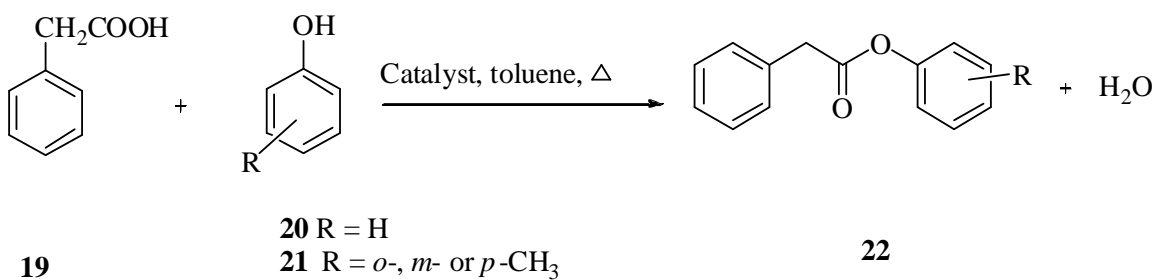
Scheme 2.3
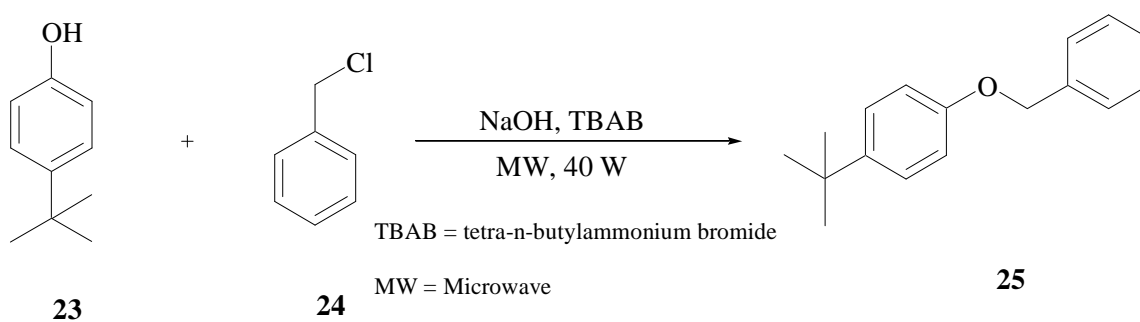
2.3.3 Substitution of the Hydroxyl Group

The OH group of cresols can be replaced by ammonia and the corresponding toluidine obtained under drastic conditions (420 $^{\circ}$C, Al_2O_3). If cresols are reacted with sulphur oxytetrafluoride at 150 $^{\circ}$C, with diphenylphosphine trichloride at 220 $^{\circ}$C or with phosphorous tribromide at 280 $^{\circ}$C, the corresponding fluoro-, chloro- or bromotoluene is obtained. The phenolic OH group is replaced by a thiobutyl group when cresols are reacted with butanethiol and hydrochloric acid. Subsequent distillation from zinc powder results in toluene.[2]

2.3.4 Hydrogenation

Toluene can also be produced from cresols by hydrogenation in the vapour phase at 300-400 $^{\circ}$C under pressure in the presence of catalysts consisting of transition metals and aluminium oxide. Hydrogenolysis over catalysts at 400-500 $^{\circ}$C or purely thermally at 500-700 $^{\circ}$C can be controlled such that cresol is mainly demethylated to phenol.[14] Hydrogenation over Raney nickel or noble-metal catalysts under less severe conditions give methylcyclohexanones or methylcyclohexanols as products.[2]

2.3.5 Oxidation

The cresols are sensitive to oxidation. Depending on the oxidizing agent, reaction conditions, and position of the methyl group, cresols are prone to oxidation reactions involving free radical mechanisms resulting in a large number of compounds such as hydroquinones, quinols, quinines, cyclic ketones, furans, dimeric and trimeric cresols and tolyl ethers.[2] With strong oxidizing agents the phenol ring can even be cleaved.

After the hydroxyl group has been protected by esterification or etherification, the methyl group can be selectively mono-, di-, or trichlorinated, or oxidised to either an aldehyde (MnO_2 or O_2) or to the carboxylic acid with acidic permanganate solution.[2] Alkali fusion of unprotected cresols in the presence of lead oxide or manganese oxide results in the production of the corresponding hydroxybenzoic acids[2]. Unlike *m*-cresol (**10**), *o*- (**15**) and *p*-cresol (**16**) can be directly oxidised with oxygen to give *o*- and *p*-hydroxybenzaldehydes when treated with methanolic sodium hydroxide in the presence of catalytic amounts of iron tetraarylporphines.[2]

2.3.6 Electrophilic Aromatic Substitution

Cresols, similar to phenols, readily undergo electrophilic aromatic substitution.[2] The substituent enters the nucleus mainly in the *o*- and/or *p*- positions relative to the hydroxyl function and thus the cresols can be nitrated even with dilute nitric acid. Nitrosation, halogenation (**Scheme 2.4**), sulphonation and alkylation occur readily. Isomerization to *m*-cresol (**10**), which is thermodynamically the most stable of the three isomers occurs if *o*- (**15**) or *p*-cresol (**16**) is heated with Friedel-Crafts catalysts such as $AlCl_3$. Hydroxy and methyl substituted benzoic acids (**28**) can be produced by the heating of dry alkali metal cresolates with CO_2 under pressure (Kolbe-Schmitt reaction)[2] (**Scheme 2.5**). In the presence of alkali, formaldehyde adds to cresols even at room temperature to form the corresponding benzyl alcohols. Condensation of these compounds under acidic conditions or at elevated temperatures leads to the formation of high-molecular mass resins. *o*-Hydroxybenzaldehydes (**29**) are the main products from the reaction of cresols with chloroform and alkali (Reimer-Tiemann synthesis)[2] (**Scheme 2.6**). Electrophilic

substitutions may sometimes be complicated by partial or substantial cessation of the reaction at the primary stage of the cyclohexadienone which is formed by the addition of the electrophile.[2] If p-cresol (16) is heated with tetrachloromethane in the presence of aluminium chloride, the main product is 4-methyl-4-trichloromethyl-2,5-cyclohexadienone (31) (Zincke-Suhl reaction) (Scheme 2.7).

Scheme 2.4

Scheme 2.5

Scheme 2.6

27   aq. NaOH, CHCl$_3$ 60°   OH CHO   20%   **29**   +   OH CHO   10%   **30**

Scheme 2.7

16   AlCl$_3$-CCl$_4$ CCl$_3$ **31**
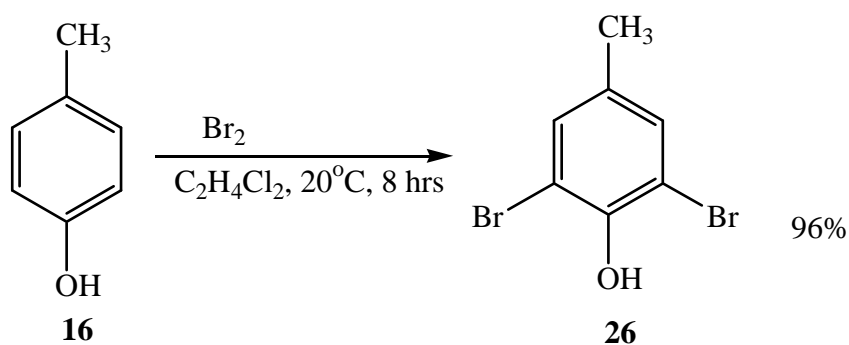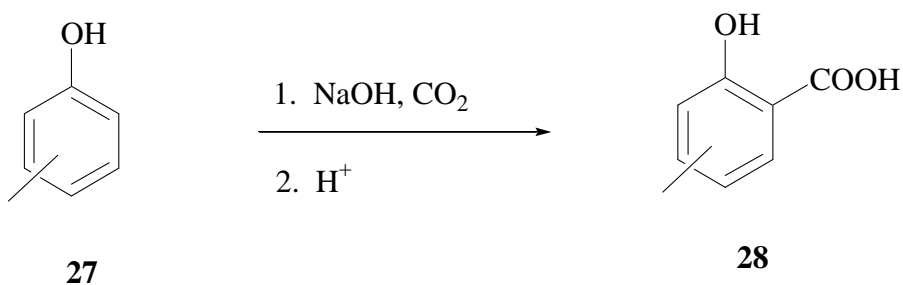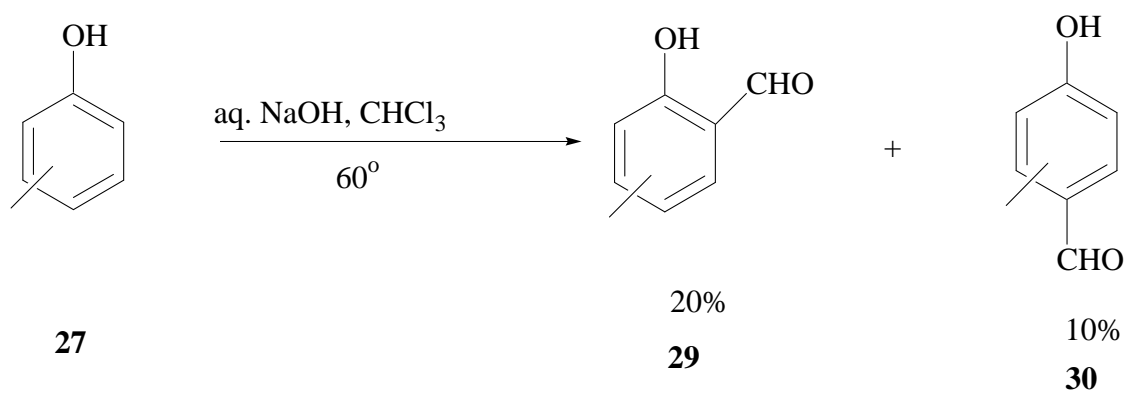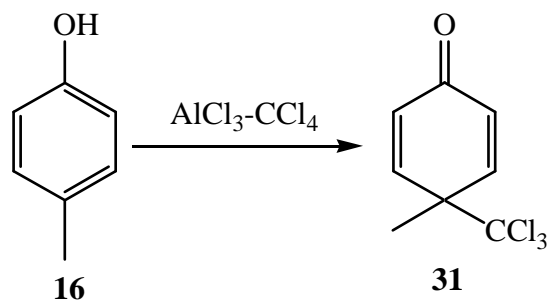
2.4 Sources of Cresols

2.4.1 Isolation from Tar Streams

Phenol, cresols, xylenols and numerous other phenols are found in the wastewater of cracking processes, tars and tar-like products formed in the thermal cracking, oxidizing thermal cracking, and hydrogenating thermal cracking of natural materials such as bituminous coal, lignite, peat, wood, lignin and other biomaterials. The yields of cresols, xylenols and other phenols as well as their quantity ratio is dependent on the process conditions, like temperature, residence time, type of reactor, and the mode of operation.[1,2]

For example, with bituminous coal, the highest yields are obtained by hydrogenation. Low-temperature carbonization gives intermediate amounts, whereas high-temperature coking produces the lowest yields. Significantly more phenol, cresols and xylenols are produced by gasification of lignin than that of bituminous coal. Small amounts of cresols, xylenols and other phenol derivatives are also formed in the catalytic and thermal cracking of petroleum fractions.[2,15]

2.4.1.1 Isolation from Coal Tars

High temperature coke-oven tar is a traditional source of tar cresols and xylenols, however this source has been declining over the past 40 years. In the United Kingdom cresols were traditionally produced from low-temperature coal tars, which were obtained in the production of smokeless fuels according to the Coalite process, but by the 1990s these tars had become far less abundantly available. The largest source of 'natural' cresols and xylenols today is provided by the liquid byproducts obtained in the Sasol

fixed bed dry bottom gasification of bituminous coal during the production of synthesis gas for the Fischer-Tropsch plants in South Africa.[2,16]

An essential source of 'natural' cresols and xylenols (approximately 5000 tonnes per annum *o*-cresol, 11 000 tonnes per annum *m/p*-cresol and 10 000 tonnes per annum xylenols) in the United States is the liquid coproducts from the Lurgi gasifiers of the Dakota Gasification Co., which gasifies lignite to synthetic natural gas.[17] When the starting material is high-temperature tar, phenols are isolated by extraction with sodium hydroxide solution or, in the Lurgi phenoraffin process from the carbolic acid that boils at 180-210 ^{o}C, from the light oil and from the filtrate of the naphthalene oil. The hydrocarbons and pyridine bases which are still present in the crude phenolate caustic are removed by steam distillation. The crude phenol is then liberated with carbon dioxide. Very often, the phenolate caustics from coking plant effluents, which contain primarily phenol and cresol and only very small amount of xylenols are incorporated.[18] Therefore, the composition of the resulting crude phenol may vary extensively. After the alkali content of the crude phenol has been lowered from approximately 2 % to approximately 0.3 % by scrubbing with water, the crude phenol is dehydrated azeotropically and rectified under vacuum into the following fractions: phenol, *o*-cresol, *m/p*-cresol mixture, xylenol and phenol tar.[2]

The isolation of cresylic acids from the liquid coproducts obtained by gasification of North Dakota lignite is possible through modifications to the known industrial processes. Further purification of cresylic acid fractions from neutral oils, tar bases, sulfur

compounds and other undesirable phenol substances can be carried out using an extractive distillation with diethylene glycol, which was developed by the Dakota Gasification Co.[17,19,20]

Companies that isolate cresols and xylenols from coal tar include Merisol (a joint venture company between Sasol and Merichem) in the United States and South Africa, Coalite Chemicals in the United Kingdom which is also in contract with Dakota Gas, Rutgers-VfT AG in Germany, DEZA Corporation in the Czech Republic, and Nippon Steel Chemical Co., Sumikin Chemical Co., Kansai Distillation Co., and ADCHEMCO Corporation in Japan.[2]

2.4.1.2 Recovery from Spent Refinery Caustics

In the United States, cresols and xylenols are also obtained from the naphtha fractions produced by catalytic and thermal cracking in the petroleum industry. These fractions contain on average approximately 0.1 % C_6-C_8 phenols. During scrubbing of the sulphur compounds contained in these fractions (hydrogen sulphides, alkyl- and arylthiols) with concentrated alkaline solutions, a process called 'sweetening', the acidic cresols and xylenols are also extracted.[2] The composition of the spent cresylate caustics fluctuates worldwide and on average they contain 20-25 % C_6-C_8 phenols and 10-15 % sulphur compounds. Until about 1990, the caustics were collected by the reprocessing firms Merichem, NorthWest Petrochemical and PMC Specialities and reprocessed in central plants by a variety of processes. NorthWest Petrochemical and PMC Specialities have, however, since then closed their operations due to competition, especially from synthetic o-cresol producers as well as increased environmental restrictions and an overall lack of

raw material. Merichem, the biggest of the three, is now the only processor of spent refinery caustics in the United States.[2]

At Northwest Petrochemical in Anacortes, Washington, the thiols in the alkaline solution were first oxidized with air to give disulfides which were then decanted as an oily layer (**Equation 1**).

$$RSNa + R'SNa + 0.5\ O_2 + H_2O \longrightarrow RSSR' + 2\ NaOH \tag{1}$$
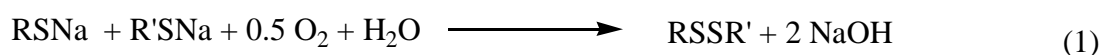
The phenols were precipitated from the aqueous alkaline phase in a packed column with a concurrent stream of carbon dioxide and then decanted. Phenols left in the carbonate-hydrogencarbonate phase were extracted into organic solvents followed by another extraction with aqueous alkali and returned to the initial column. A phenolic mixture obtained in this way might have a composition of: 20 % phenol, 18 % *o*-cresol, 22 % *m*-cresol, 9 % *p*-cresol, 28 % xylenol and 3 % higher phenols. This mixture is then separated by distillation into phenol, *o*-cresol, *m-/p*-cresol mixture and xylenols or mixtures in which particular constituents predominate.[2,21] Presumably they don't have nitrogen bases and neutral oils in this crude mixture.

The cresylics capacity at Merichem in 1996 was approximately 55 000 tonnes per annum however this figure includes phenol, the xylenols and several other alkylphenols, like *o*-ethylphenol. Merichem does not isolate cresylics exclusively from spent refinery caustics

anymore but works up cresylics from a variety of sources such as from the coal gasification plants of Dakota Gas and Sasol.[2]

In Germany different refinery techniques are used, thus the production of cresol-containing spent caustics is insufficient for economical processing, or, no spent caustics are produced at all because desulphurization is carried out differently for example by hydrotreating. In the United States also, the recovery of cresol from spent refinery caustics is receding due to refineries changing to either hydrotreating or to UOPs Merox process because of the rise in the price of sodium hydroxide. With the Merox process, substantial quantities of cresols remain in the gasoline and considerably smaller amounts of spent caustics are obtained.[2]

2.4.2 Synthetic Cresol Production

The recovery of cresols from coal tar and spent refinery caustics became insufficient to meet the rising demand. Since 1965 therefore these compounds have been increasingly produced by synthesis. The processes which are currently in use include alkali fusion of toluenesulphonates (**Scheme 2.8**), alkaline chlorotoluene hydrolysis (**Scheme 2.9**), splitting of cymene hydroperoxide (**Scheme 1.1**) and methylation of phenol in the vapour phase. The first three processes from toluene were developed from the corresponding benzene to phenol technology and are even carried out to some extent in converted plants that formerly produced phenol.[2]

Alkali fusion of toluenesulphonates (**Scheme 2.8**) is used mainly in the manufacture of *p*-cresol (**16**) and consists of four reaction steps.

The sulphonation of toluene (**Equation 2**) is usually carried out with concentrated sulphuric acid at 120-130 ^{o}C and atmospheric pressure. The sulphonic acid product mixture is neutralized with sodium sulphite and/or sodium hydroxide (**Equation 3**) and then fused with excess sodium hydroxide at 330-350 ^{o}C (**Equation 4**). Addition of water followed by acidification with sulphur dioxide/water and/or sulphuric acid (**Equation 5**) results in an aqueous phase containing crude cresol and sodium sulphite, which is returned to the neutralization unit.[2]

Scheme 2.8

$$2\ CH_3\text{-}C_6H_5 + 2\ H_2SO_4 \rightleftharpoons 2\ CH_3\text{-}C_6H_4\text{-}SO_3H + 2\ H_2O \tag{2}$$

$$2\ CH_3\text{-}C_6H_4\text{-}SO_3H + Na_2SO_3 \longrightarrow 2\ CH_3\text{-}C_6H_4\text{-}SO_3Na + H_2O + SO_2 \tag{3}$$

$$2\ CH_3\text{-}C_6H_4\text{-}SO_3Na + 4\ NaOH \longrightarrow 2\ CH_3\text{-}C_6H_4\text{-}ONa + 2\ Na_2SO_3 + 2\ H_2O \tag{4}$$

$$2\ CH_3\text{-}C_6H_4\text{-}ONa + SO_2 + H_2O \longrightarrow 2\ CH_3\text{-}C_6H_4\text{-}OH + Na_2SO_3 \tag{5}$$

$$2\ CH_3\text{-}C_6H_5 + 2\ H_2SO_4 + 4\ NaOH \longrightarrow 2\ CH_3\text{-}C_6H_4\text{-}OH + 2\ Na_2SO_3 + 4\ H_2O$$
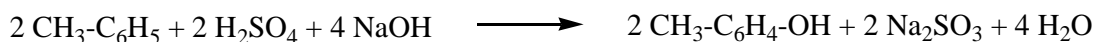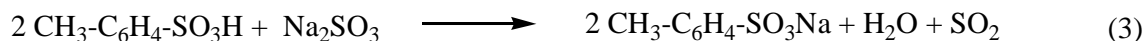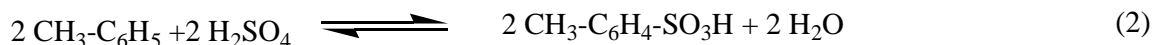
After dehydration by azeotropic distillation, the crude cresol fraction is separated by fractional distillation into phenol, *o*-cresol, *m-/p*-cresol mixture and a residue containing ditolyl sulphones, xylenols, higher phenols and other compounds. Since the sulphonation
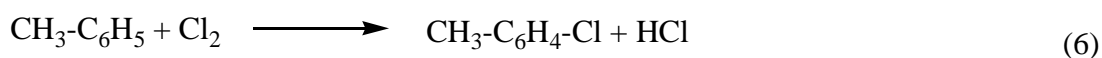
of toluene occurs mainly in the *ortho* – and *para* positions, the *p*-product, after

distillation, contains very little (*ca.* 1 %) *m*-cresol and can easily be purified further by

melt crystallization. A *p*-cresol yield of 80 % based on toluene is possible with this

process. The toluenesulphonic acid-cresol process is relatively simple with regards to the

plant required, but has the drawback of the unavoidable formation of sodium sulphite in

aqueous solution.[2]

The chlorotoluene hydrolysis process (**Scheme 2.9**) is important in the production of

cresols with a high *meta* content and is used by Bayer AG in Germany, which is the

world's largest manufacturer of synthetic cresols (more than 30 000 tonnes per annum).

In the first reaction step a mixture of *o*- and *p*-chlorotoluene in a ratio of 1:1 is produced

by chlorinating toluene with chlorine (1 : 1 mole ratio) in the presence of iron(III)chloride

and disulphur dichloride (**Equation 6**).

Scheme 2.9

$$CH_3\text{-}C_6H_5 + Cl_2 \longrightarrow CH_3\text{-}C_6H_4\text{-}Cl + HCl \tag{6}$$

$$CH_3\text{-}C_6H_4\text{-}Cl + 2\ NaOH \longrightarrow CH_3\text{-}C_6H_4\text{-}ONa + H_2O + NaCl \tag{7}$$

In the next reaction step, this mixture is treated with excess aqueous sodium hydroxide at

360-390 °C and 280-300 bar (**Equation 7**). Separation of the components is prevented by

allowing the reaction mass to flow at high velocity with frequent changes in the direction

of flow finally resulting in the reaction mixture becoming homogenous. The cresol in the

resulting sodium cresolate solution is set free by neutralization. The hydrolysis of *p*-

chlorotoluene then gives a 1:1 *m-/p*-cresol mixture and hydrolysis of *o*-chlorotoluene gives a 1:1 *o-/m*-cresol mixture. Technically pure *m*-cresol can be obtained from the latter by distilling off the *o*-cresol.[2]

The synthesis of cresols *via* cymene hydroperoxide, which is also known as the cymene-cresol process (**Scheme 1.1**) allows the production of *m*- (**10**) or *p*-cresol (**16**) from the corresponding cymenes.[3] Since steric hindrance prevents the formation of *o*-isopropyltoluene to a large extent, this process is unsuitable for the production of *o*-cresol (**15**). This process consists of three reaction steps namely toluene propylation and cymene isomerization, oxidation of the cymene to the hydroperoxide, and peroxide cleavage (**Scheme 1.1**). Cymene-cresol plants have a capacity of 22 000 tonnes per annum and have been operated in Japan by Sumitomo and Mitsui since 1969. The product obtained has a *m*- and *p*-cresol content of more than 99.5 % and a *m/p* ratio of 60:40.[2]

Synthetic *o*-cresol, and to a lesser extent 2,6-xylenol, are now produced mainly by methylation of phenol with methanol in the presence of zeolite catalysts. The reaction can be carried out in either the vapour or liquid phases and small quantities of 2,6-xylenol, which can be removed by fractionation, is co-produced.[3] Although the process consists of only one reaction step, it is based on phenol, which is relatively expensive and has the added disadvantage of several expensive purification steps.[2]

Apart from the technologies discussed above, the rising demand for cresol has stimulated the development of a number of synthetic processes, especially those that lead selectively to certain cresol isomers. These processes, i.e. Gulf oxychlorination, oxidative decarboxylation of methylbenzoic acids, Baeyer-Villiger oxidation of *p*- or *o*-methylbenzaldehyde, nucleus hydroxylation, Diels-Alder ring closure of isoprene and vinyl acetate, are, however, not yet developed to the point of industrial application.[2]
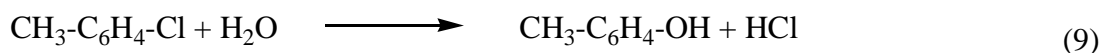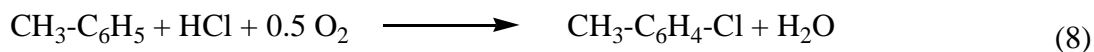
2.4.2.1 Gulf Oxychlorination

A cresol synthesis analogous to the Raschig phenol synthesis cannot be carried out satisfactorily under industrial conditions. At the temperature needed for oxychlorination in the vapour phase (**Scheme 2.10, Equation 8**), toluene is oxidized to a considerably greater extent than benzene and thus only low rates of toluene conversion are possible (**Scheme 2.10**).[2]

Gulf Research Development Co. developed a process where these disadvantages are avoided by oxychlorinating the toluene with aqueous hydrochloric acid and oxygen at a temperature of approximately 100 ^{o}C in the presence of catalytic amounts of nitric acid and a palladium or copper salt. At toluene conversion of 80 %, mainly *o*- and *p*-chlorotoluene are obtained in a 2:1 molar ratio and with a selectivity of $\geq$ 95 %. The subsequent hydrolysis of the chlorotoluene mixture is carried out in the vapour phase at 400-450 ^{o}C similar to the Raschig process but over improved catalysts such as lanthanum phosphate that may be activated with copper. At a chlorotoluene conversion of 20 %, the cresol selectivity is approximately 95 %. The isomer ratio differs from that given by the

processes already being used industrially. A large amount of *o*-cresol (**15**) is obtained in addition to *p*-cresol (**16**) with small amounts of some *m*-cresol (**10**).[2] If the hydrochloric acid liberated in the hydrolysis step (**Equation 9**) is returned to the oxychlorination reactor, the process becomes equivalent to the oxidation of toluene with oxygen.[2]

Scheme 2.10

$$CH_3\text{-}C_6H_5 + HCl + 0.5\ O_2 \longrightarrow CH_3\text{-}C_6H_4\text{-}Cl + H_2O \tag{8}$$

$$CH_3\text{-}C_6H_4\text{-}Cl + H_2O \longrightarrow CH_3\text{-}C_6H_4\text{-}OH + HCl \tag{9}$$

The Gulf oxychlorination process is equally applicable to xylenes, and is therefore also suitable for the manufacture of xylenols.[2]

2.4.2.2 Oxidative Decarboxylation of Methylbenzoic Acids

As in the Dow process for the manufacture of phenol from benzoic acid, methylbenzoic acids (**32**) are decarboxylated to cresol (**27**) when an air-steam mixture is passed through their melt at 200-240 $^{\circ}$C in the presence of copper and magnesium salts (**Scheme 2.11**).[2]

Scheme 2.11
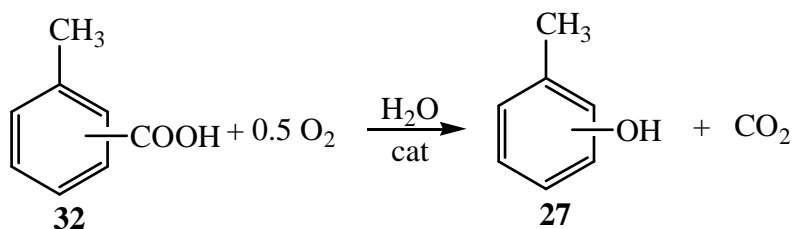
By comparison with the manufacture of phenol, the cresol process is more complex and 10-15 % less selective. This is due partly to the fact that cresols have higher boiling points and therefore optimal control of the reaction is difficult and a greater amount of tar is formed. In addition to this, the simultaneous successive oxidation of the methyl group leads to numerous byproducts.[2]

Better results are obtained when a methylbenzoic acid – steam mixture is oxidized in the vapour phase with oxygen-nitrogen mixtures over mixed catalysts at a temperature of approximately 300 °C. This process could be of interest in the manufacture of pure *m*-cresol (**10**), as only *m*-cresol (**10**) is formed from both the *ortho*- and *para*- forms of methylbenzoic acid.[2]

2.4.2.3 Baeyer-Villiger Oxidation of *p*- or *o*-Methylbenzaldehyde

This route leads to *p*-cresol (**Scheme 2.12**). Hydrogen peroxide reacts with excess formic acid (**33**) to give performic acid (**34**), which oxidizes *p*-methylbenzaldehyde (**35**) to *p*-tolyl formate (**36**), whereafter hydrolysis then leads to *p*-cresol (**16**) and formic acid (**33**).[2]

Scheme 2.12
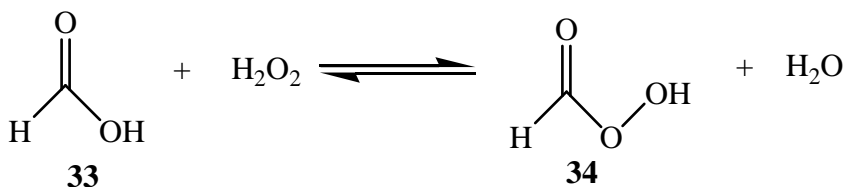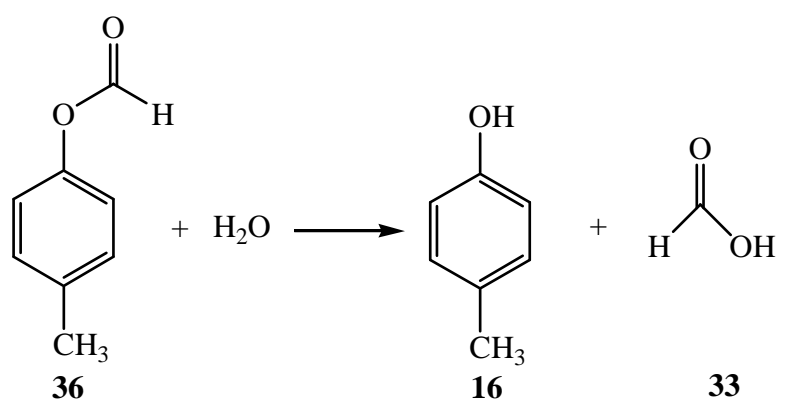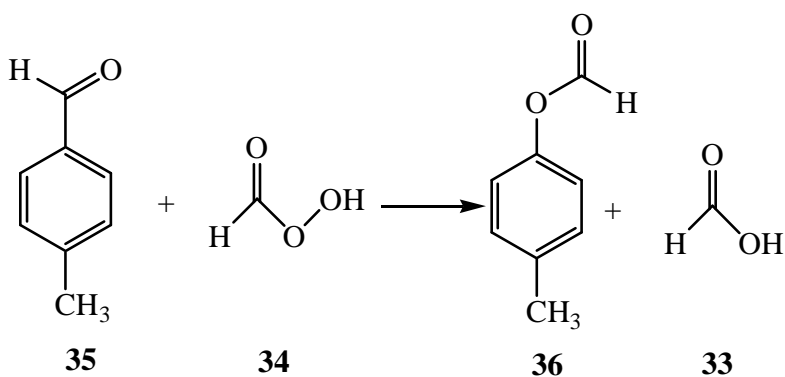
Several variants of the process have been developed with the most favourable process being invented by Mitsubishi. In this process hydrogen peroxide (1.2 mol; 90 %) is added to a mixture consisting of 1 mole of *p*-methylbenzaldehyde (**35**), 14 mole of formic acid, and approximately 10 % (4.5 mole) of water. The temperature of the mixture is maintained at 60 – 90 °C and the heat of the reaction is removed by reflux condensation under vacuum. Due to the presence of water, formate is hydrolyzed and after a reaction time of 1 h, the *p*-methylbenzaldehyde (**35**) conversion is 100 % and the *p*-cresol (**16**) yield 85 %. Instead of 90 % hydrogen peroxide, performic acid may be used or if the process is carried out in the presence of a solid acid (zeolite or ion-exchange resin), the yield rises to 90 -92 %.[2] The product is worked up by removing the formic acid by

distillation. Apart from the additional amount formed in the process, the formic acid, which has a concentration of approximately 90 % is recycled. The *p*-cresol (**16**) is then isolated from the residue, which still contains 10-20 % of high-boiling constituents.[2]

The starting material, *p*-methylbenzaldehyde (**35**), can be produced from toluene and carbon monoxide by the so-called MGC PTAL process developed by Mitsubishi. It is also used as an intermediate in the manufacture of terephthalic acid (**37**).[2]
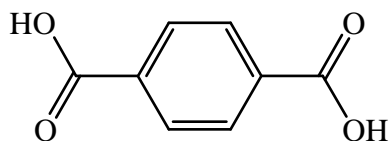
37

2.4.2.4 Ring Hydroxylation

Oxidising agents investigated to facilitate the direct hydroxylation of toluene include oxygen, hydrogen peroxide, inorganic peroxo compounds, organic peroxides and iodosyl acetate.[2]

According to Rhône-Poulenc, the most successful results so far have been obtained with 85 % hydrogen peroxide in the presence of a large amount of trifluoromethanesulphonic acid and small amounts of phosphoric acid (**Scheme 2.13**). At -20 $^{\circ}$C to -15 $^{\circ}$C and a molar ratio of H_2O_2, toluene (**5**), CF_3SO_3H, and H_3PO_4 of approximately 1:10:17:0.04, *o*-

(**15**) and *p*-cresol (**16**) are obtained in a 2:1 ratio in 80 % yield which is calculated on the basis of hydrogen peroxide at a toluene conversation of 10.6 %.

Scheme 2.13
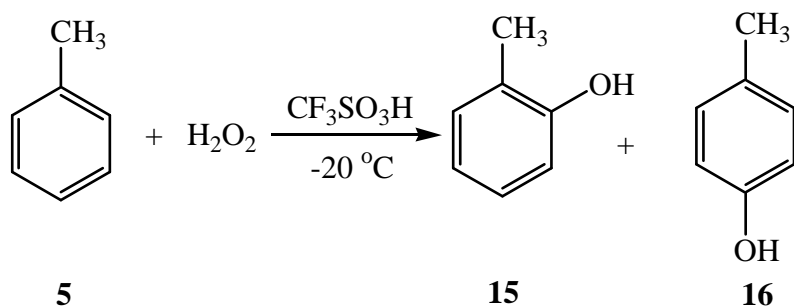
Research work carried out by UOP indicated that relatively good results could be obtained with hydrogen fluoride, which is less expensive and also easier to handle industrially than trifluoromethanesulphonic acid, in the presence of carbon dioxide. With 30 % hydrogen peroxide at 0 $^{\circ}$C and at a molar ratio of H_2O_2, toluene, HF, and CO_2 of 1:10:70:10, *o*- (**15**) and *p*-cresol (**16**) were obtained in a 2:1 ratio in 67 % yield (based on hydrogen peroxide), in addition to a small amount of *m*-cresol (**10**). Cresols can also be obtained by oxidation of toluene with N_2O in the presence of H-ZSM-5 zeolites containing Lewis acidic extra frameworks of Fe, Al or Ga. Toluene (**5**) with N_2O (molar ratio 1:3) at 350 $^{\circ}$C/ 1 bar/WHSV 1 h^{-1} on a H-[Al]ZSM-5 zeolite was oxidized to cresol with a 24 % conversion and a selectivity of approximately 27 % (molar ratio *o*- (**15**): *m*-(**10**): *p*-cresol (**16**) = 52:32:16). ICI has developed a cyclic process equivalent to the oxidation of toluene with peracetic acid, which gives yields of up to 95 % of an *o*-/*p*-cresol mixture, free of the *meta* isomer, with a cresol content of 92 %.[2]

Up to now all the processes involving nucleus hydroxylation have been unsatisfactory for various reasons. For example, the cresols must be isolated from very dilute solutions and considerable amounts of auxiliaries and unreacted starting materials must be recycled with as little waste as possible.[2]

2.4.2.5 Diels-Alder Ring Closure of Isoprene and Vinyl Acetate

p-Cresol (**16**) can be obtained selectively *via* the Diels-Alder reaction between isoprene (**38**) and vinyl acetate (**39**) in the presence of 1 % hydroquinone at 180 $^\circ$C, whereafter the formed 1-methylcyclohexen-4-yl acetate (**40**) is saponified and 1-methylcyclohexen-4-ol (**41**) dehydrogenated catalytically to p-cresol (**16**). High yields were claimed upon recycling of the starting materials (**Scheme 2.14**).[2]

Scheme 2.14
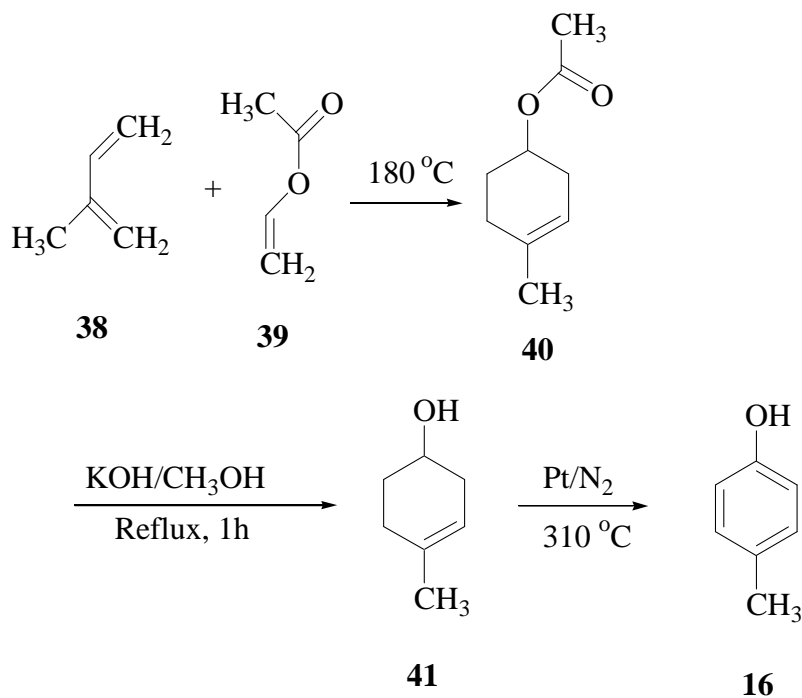
2.5 Separation and purification of cresol isomers

The isolation of individual cresol isomers, in particular *m*- (**10**) and *p*-cresols (**16**), from an isomeric mixture of cresols, has been a huge problem for cresol producers[3] world wide. Only *o*-cresol (**15**) can be separated as a pure product by distillation from mixtures of the three cresol isomers due to its lower boiling point of approximately 191 ^{o}C at atmospheric pressure[2,3] [vs 202 and 201-202 ^{o}C for *meta*- (**10**) and *para*-cresol (**16**) respectively]. Merisol has been producing approximately 3000-5000 tonnes per annum of very pure *o*-cresol (**15**) (>99 %) in this way. Some *o*-cresol (**15**) is also produced by other coal or lignite processing units.[2]

Due to the difference in their boiling points being too small for separation by distillation, *m*-cresol (**10**) (202 ^{o}C) and *p*-cresol (**16**) (201-202 ^{o}C) are obtained as a single fraction during distillation processes.[2,3,22] Since special techniques are required if these two compounds are to be separated, only three technologies are currently available for the separation of *m*- (**10**) and *p*-cresol (**16**):

Firstly, *m/p*-cresol mixtures can be separated by a butylation/debutylation process into pure *m*-cresol (**10**) with co-production of 2,6-di-*tert*-butyl-*p*-cresol (BHT) (**42**).[2] This remains, even today, the most attractive commercial method for the production of pure *m*-cresol (**10**)[3]. A possible disadvantage of this process lies in the fact that BHT (**42**) is produced as main product and thus the commercial feasibility for production of *m*-cresol (**10**) is dictated by the demand for BHT (**42**),[3] a universal antioxidant. Two distinct advantages of this process, however, lies in the fact that the *m/p* cresol feedstock is

cheaper than pure *p*-cresol (**16**) (the usual feedstock for BHT), and alkylation of the mixture renders it possible to produce either butylated *m*-cresol and/or butylated *p*-cresol or the pure *m*- (**10**) and *p*- cresols (**16**) as market demand may require.[3]
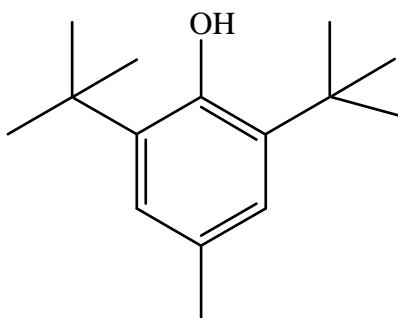
42

Secondly, since the isomers cannot be separated by distillation, direct isolation of pure *meta*- (**10**) and pure *para*-cresol (**16**) from mixtures is very tedious and expensive and only one process is currently utilised on commercial scale. This plant is based on UOP's proprietary Cresex process and is operated by Merisol at their Houston, Texas plant. Cresex, an extension of UOP's well known Sorbex process, is based on adsorption/desorption technology[3] and utilises an alkali or alkaline earth metal modified zeolite as stationary phase. The stationary phase, which can be X, A, L or ZMS-5 type zeolite or even titanium dioxide, adsorbs *p*-cresol (**16**) more strongly than *m*-cresol (**10**). *M*/*p*-Cresol mixtures can therefore be separated in an adsorption column and can be dissolved again with a suitable desorbing liquid such as an aliphatic alcohol and/or a ketone. The separation efficiency is dependent on both adsorption and desorption rates. Unlike conventional processes which only rely on differences in physical properties, adsorption can be customised to achieve a specific separation.[3]

In the third technology, the adduct crystallization process, an extraneous agent is added which leads to the creation of a solid phase even before the binary eutectic temperature of the feed components is reached. Here the extraneous agent selectively forms an adduct or an addition compound with one of the two components to be separated. The adduct can then be easily separated from the other components and thus both components can be obtained in relatively pure form.[3] Urea [$CO(NH_2)_2$], a white crystalline solid, has been used to form an adduct with *m*-cresol (**10**). The solid urea-*meta*-cresol adduct can easily be isolated from the mixture either by filtration or centrifugation, while the *p*-cresol (**16**) remains in the mother liquor. Pure *m*-cresol (**10**) is subsequently liberated from the adduct by dissolving it in hot water. Although both isomers are obtained in relatively pure form in this way, the drawback with this method is that a temperature of -10 ^{o}C to -20 ^{o}C is required for the adduct to be formed and that recoveries are poor.[3]

2.6 Uses

Cresol mixtures are highly important as solvents for synthetic resin coatings (wire enamels). The bactericidal and fungicidal properties of cresols enable them to be used as disinfectants in soap. Synthetic tanning agents of commercial importance are obtained by the condensation of formaldehyde with cresolsulphonic acids and by the sulphonation of novolaks obtained from cresols. Crude cresols are used as wood preservatives, in ore flotation and fibre treatment.[2]

m/p-Cresol mixtures free of the *o*-isomer (**15**) are used to produce neutral phosphoric acid esters which are used as fire-resistant hydraulic fluids, as additives in lubricants, as air filter oils and as flame-retardant plasticizers for PVC and other plastics.[2]

Para-cresol (**16**), either pure or mixed with *m*-cresol (**10**), is used mainly to produce 2,6-di-*tert*-butyl-*p*-cresol (BHT) (**42**), which is a nonstaining and light-resistant antioxidant with a wide range of applications including food anti-oxidants and materials applications in polyethylene/-propylene for example.[2]

m-Cresol (**10**), either in its pure form or mixed with *p*-cresol (**16**), forms a starting material for important contact insecticides such as *O,O*-dimethyl-*O*-(3-methyl-4-nitrophenyl)thionophosphoric acid (fenitrothion, Folithion, Sumithion) (**43**) and *O,O*-dimethyl-*O*-(3-methyl-4-methylthiophenyl)thionophosphoric acid ester (fenthion, Baytex, Lebaycid) (**3**).[2]


43   **3**
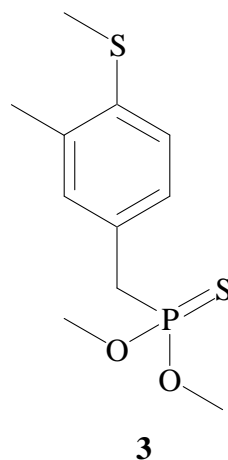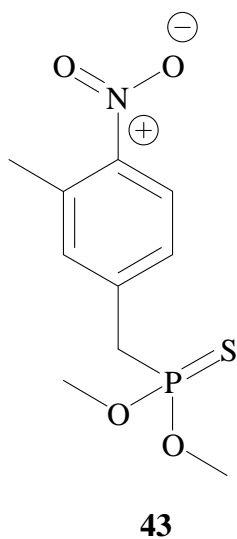
m-Cresol (**10**) is also needed in the synthesis of phenyl *m*-tolyl ether which, after oxidation with *m*-phenoxybenzaldehyde, serves as a building block in the production of insecticides of the pyrethroid type (**44**).[2]


44
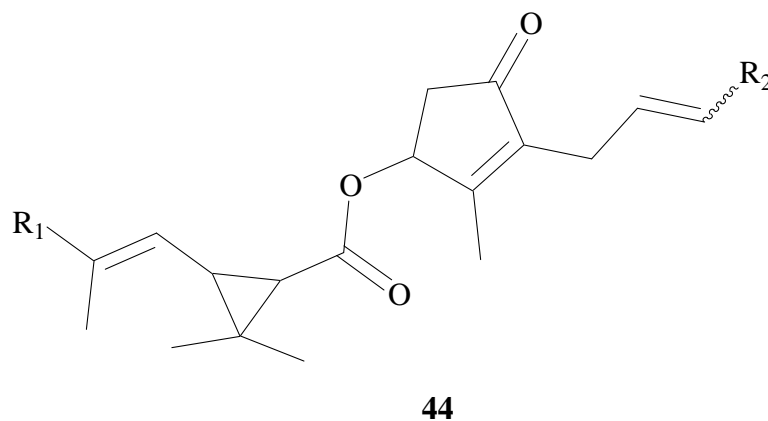
Selective methylation of pure *m*-cresol (**10**) with methanol gives 2,3,6-trimethylphenol which is an important starting material for vitamin E (**1**) synthesis. It also serves as a co-monomer for the modification of poly (phenylene oxide) resins.[2]

 Pure *m*-cresol (**10**) is furthermore important in the production of fragrance and flavour substances.[3] Its isopropylation gives thymol (**45**) from which (-)-menthol (**46**) is obtained by hydrogenation and separation of the isomers[2] (**Scheme 2.15**).

Scheme 2.15

10　　　　　　　　　　　**45**　　　　　　　　　　　**46**
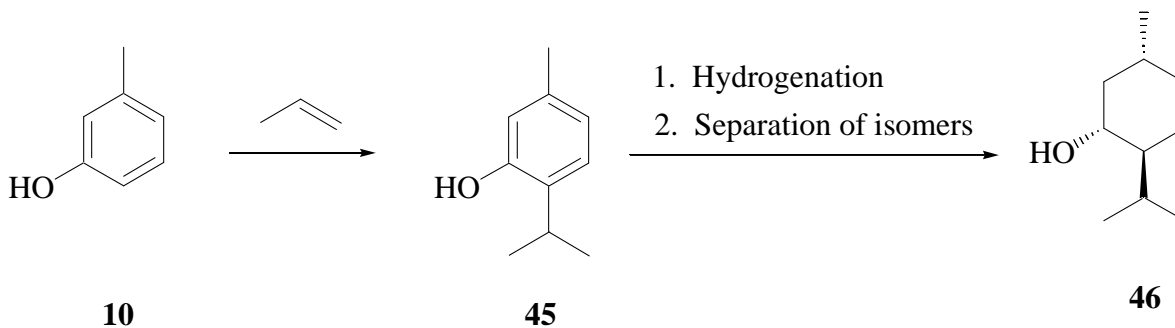
6-*Tert*-Butyl-*m*-cresol obtained by alkylation of *m*-cresol (**10**) with isobutene is used as the starting material for the perfume fixative musk ambrette. In Japan, *m*-toluidine (3-aminotoluene) is produced on demand by amination of *m*-cresol (**10**). 4-Chloro-*m*-cresol, which is obtained by selective chlorination of pure *m*-cresol (**10**) or *m*-/*p*-cresol mixtures, finds use as a disinfectant and preservative.[2] In the fragrance industry, *p*-cresol (**16**) is used to obtain *p*-cresolcarboxylic acid esters, such as *p*-cresyl acetate, *p*-cresyl phenyl acetate, and *p*-cresol methyl ether. The latter is used in the production of anisaldehyde which is an important starting material for the manufacture of 2-ethylhexyl-*p*-methoxycinnamate (**47**), a UV adsorber in sunscreen, and various other pharmaceuticals.

47
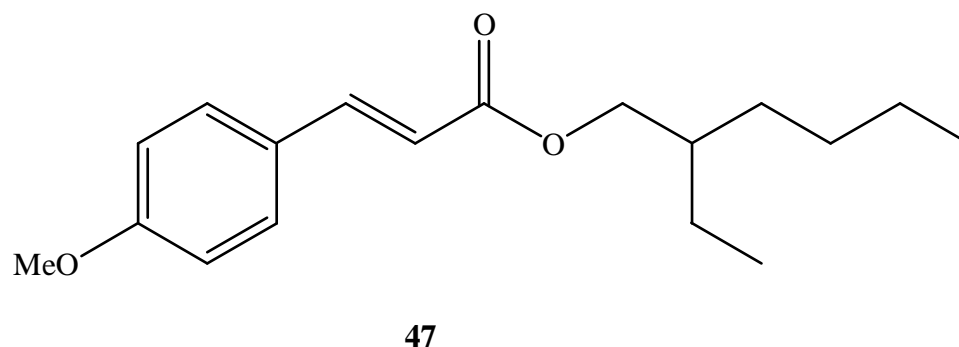
The direct oxidation of *p*-cresol gives *p*-hydroxybenzaldehyde which is either etherified to give anisaldehyde or used for the production of the aroma chemicals raspberry ketone and raspberry ketone acetate, which finds use as a pheromone of the Asian melon fly. Similar to *o*-cresol (**15**), *m*- (**10**) and *p*-cresol (**16**) are used as components of various dyes, with 2-nitro-*p*-cresol being the predominant intermediate.[2]

2,4,6-Trinitro-*m*-cresol can be used as an explosive,[1,2] whereas 2,6-dinitro-*p*-cresol (DNCP) is used as a polymerization inhibitor for styrene.[2]

Most of the *o*-cresol (**15**) manufactured in Europe is chlorinated to 4-chloro-*o*-cresol (PCOC), which is the starting material for the chlorophenoxyalkanoic acids, 4-chloro-2-methylphenoxyacetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)-propionic acid (MCPP) and *gamma*-(4-chloro-2-methylphenoxy)butyric acid (MCPB).   These compounds are important as selective herbicides. A considerably smaller proportion is nitrated to 4,6-dinitro-*o*-cresol (DNCO) which has both herbicidal and insecticidal properties and is also used as a polymerization inhibitor for the production and distillation of styrene.[2]

Highly pure *o*-cresol (**15**) is increasingly processed to epoxy-*o*-cresol novolak resins (ECN resins) especially in places like Japan. These resins are used as sealing materials for integrated circuits (chips). *o*-Cresol (**15**) of common quality is also used to modify traditional phenol-formaldehyde resins.[2]

o-Cresol (**15**) is also an important precursor of various dye intermediates of which the most important in terms of quantity is *o*-cresotinic acid (*o*-hydroxymethylbenzoic acid) produced by the Kolbe synthesis. This acid is also further used in the manufacture of pharmaceuticals and its methyl esters serve as dyeing auxiliaries.[2]

An appreciable amount of *o*-cresol (**15**) is used as a solvent either directly or after hydrogenation to 2-methylcyclohexanol or 2-methylcyclohexanone. In the form of its carbonate ester, *o*-cresol (**15**) constitutes a starting material in the synthesis of coumarin. The alkylation of *o*-cresol (**15**) with propene gives carvacrol (3-isopropyl-6-

methylphenol) (**48**) which is used as an antiseptic and in fragrances. In addition, small amounts of *o*-cresol (**15**) are alkylated with isobutene and used as starting materials in the production of various antioxidants, whereas it is also used for the production of components for thermal recording materials and for pharmaceutics, an example being the muscle relaxant Mephenesin (**2**).[2] An important field of application for technical cresol mixtures is the production of modified phenolic resins by condensation with formaldehyde.

48

2
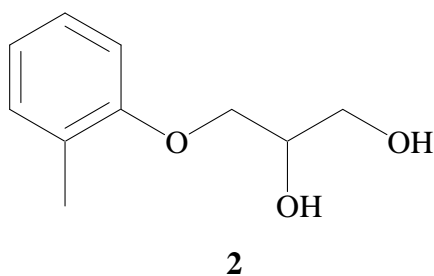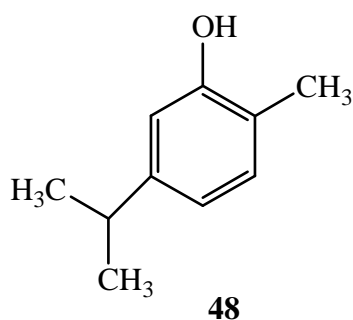
2.7 Economic Aspects

In 1998, the combined total production of cresol in the United States, Europe, Japan and South Africa was estimated to be about 175 000 tonnes of which approximately 105 000 tonnes came from synthetic producers, and approximately 70 000 tonnes from 'natural' sources.[2]

About 42 000 tonnes was produced in the United States, about 50 000 tonnes in Europe, about 58 000 tonnes in Japan and about 25 000 tonnes in South Africa. Approximately 25 % of the total output is used by the manufacturers themselves. The so-called natural cresol comes from gasification of coal, coking of coal and from spent refinery caustics in a ratio of about 50:35:15. About 45 % of the total cresol output is processed in the form of pure *o*-cresol (**15**) and pure *p*-cresol (**16**) and the rest as isomer mixtures. About 35 000-40 000 tonnes of pure *m/p*-cresol mixture was separated by the butylation/debutylation process into pure *m*-cresol (**10**) with co production of 2,6-di-tert-butyl-*p*-cresol (BHT) (**42**).[2]

The total output of cresol has diminished between 1990-2000. This is due to declining markets, the entrance of 2,6-xylenol producers into the *o*-cresol (**15**) market, the declining availability of coal tars from coking processes and of spent refinery caustics as well as increasing environmental costs which led to major industrial changes especially in the United States and Europe.[2]

3. Resorcinol

3.1 Introduction

Resorcinol (**14**), also known as 1,3-benzenediol, *meta*-benzenediol, 1,3-dihydroxybenzene, *m*-dihydroxybenzene, dioxybenzene and 3-hydroxyphenol, is a water-soluble, crystalline compound which has a faint, characteristic, aromatic odour and a taste that is sweetish at first but then becomes bitter.[4,23,24]
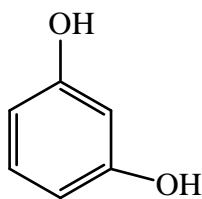
14

This compound was first obtained in 1864 by Hlasiwetz and Barth by the alkali fusion of galbadanum and asafetida resins[4,23,24] and the first syllable of the name resorcinol (**14**) is thus derived from the word resin. The structure of resorcinol (**14**) is similar to that of orcinol, 5-methyl-1,3-benzenediol, which accounts for the second part of the name. Resorcinol (**14**) does not occur in nature as such, but has been produced industrially for over 100 years.[4,23]

3.1.1 Physical Properties

Resorcinol (**14**) occurs in at least two crystalline forms. At normal pressure the α-phase is stable below approximately 71 °C whereas the β-phase is stable above that temperature

up to its melting point.[4]   Both phases exist as rhombic-pyramidal crystals but the unit cells differ in their dimensions.   The unit cells of both phases contain four resorcinol molecules. Literature data on solubilities vary widely because of the presence of these α- and β-phases. Some literature reports the solubity as 198 g of resorcinol (**14**) in 100 g of water at 50 $^{\circ}$C whereas other sources report a solubility of 371.5 g in 100 g water at 50.4 $^{\circ}$C.[4]   The density of aqueous resorcinol solutions increases approximately proportionally to the resorcinol concentration.   Resorcinol (**14**) is soluble in liquid ammonia, liquid sulphur dioxide, liquid hydrogen sulphide and pyridine.   An aqueous solution of resorcinol dissolves mannitol, sucrose, starch and cellulose as well as cresols, thymol, guaiacol, and other phenols.[4,23,24]

3.1.2 Chemical Properties

Resorcinol (**14**) can be described as a dihydric phenol and shows the typical reactivity of a phenol. Its most important reaction is with formaldehyde to form phenolic resins. The hydrogen atom *ortho* to the two *meta*-hydroxyl groups can be substituted much more easily than the other ring hydrogens. When compared to catechol and hydroquinone, resorcinol has the highest reactivity towards formaldehyde.[4,23,24]

3.1.3 Production

Resorcinol (**14**) is produced commercially in only a few specialized plants in the world where benzene is used as the main feedstock (**Scheme 3.1**). In Japan, resorcinol (**14**) is produced *via* 1,3-diisopropylbenzene (**12**) in two plants run by Sumitomo Chemical and Mitsui Petrochemical.   The United States (INDSPEC Chemical Corp) and Germany

(Hoechst) each have a single plant for the production of resorcinol *via* the classical 1,3-

benzenedisulphonic acid (**49**) route[4,23,24] (**Scheme 3.1** and **Figure 1**).[4]

Scheme 3.1
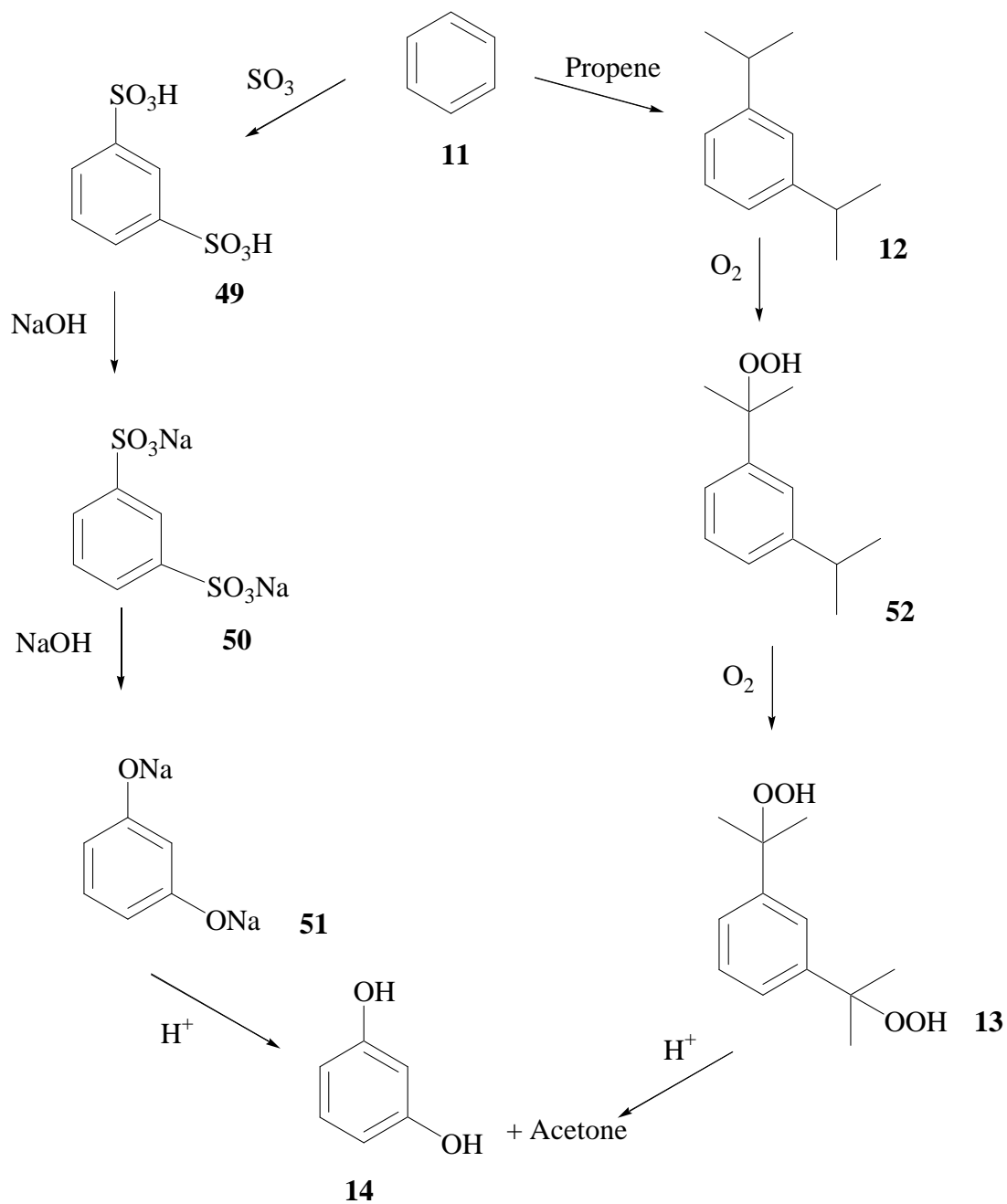
The sulphonation of benzene formerly led to the production of considerable amounts of waste, because it was carried out with mixtures of sulphuric acid and sulphur trioxide. Excess sulphuric acid was precipitated with lime (CaO) to form gypsum (CaSO$_4$·2H$_2$O) which had to be disposed of in landfills.[4]
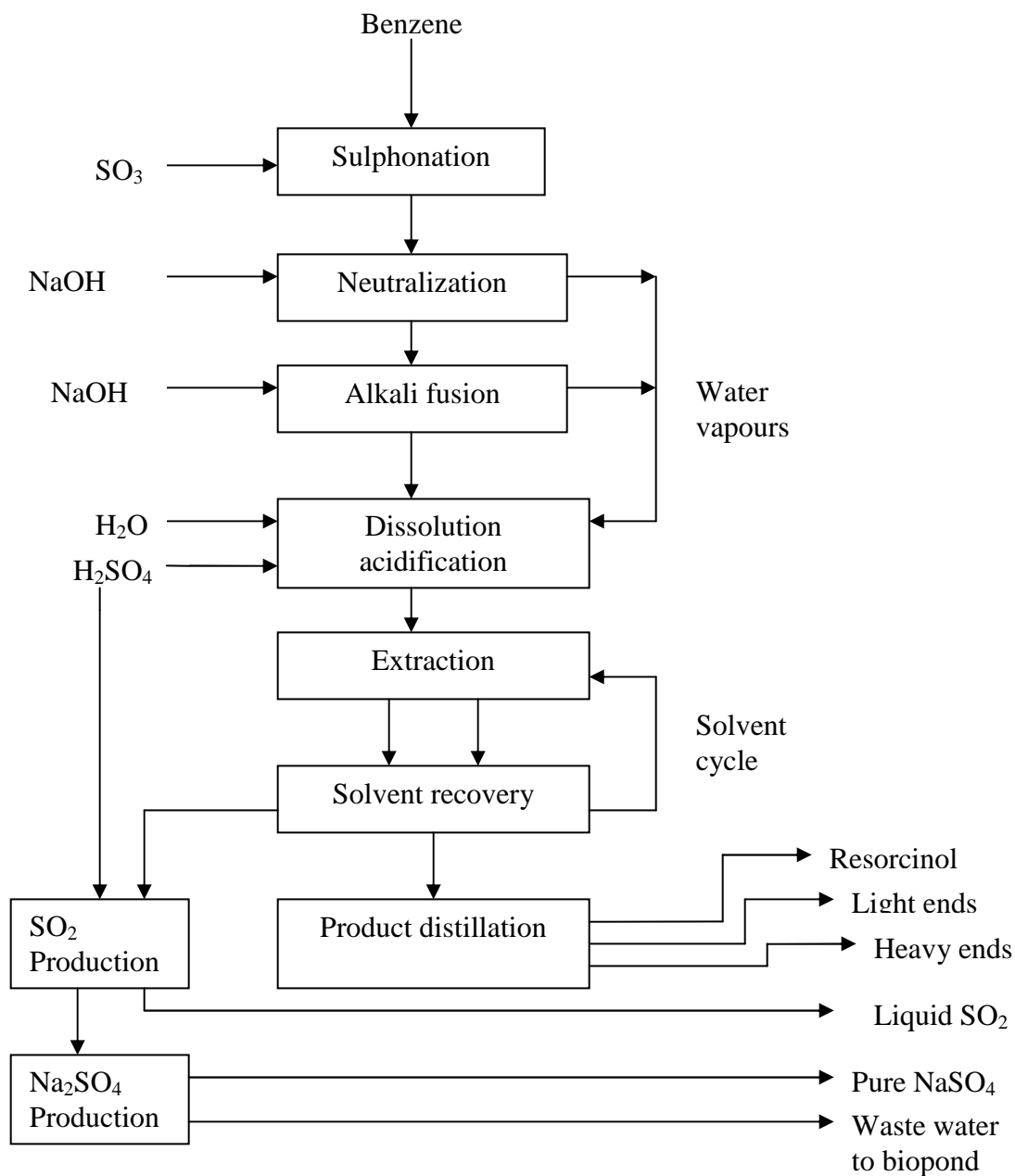
Figure 1: Resorcinol production via sulphonation

In the process variation which is currently used in Germany, the sulphonation of benzene is carried out continuously with sulphur trioxide alone so that only small amounts of sulphuric acid are present in the sulphonation mixture and the addition of lime is not required. Following neutralization with sodium sulphate, soda ash or sodium hydroxide solution, the sulphonation product disodium benzene-1,3-disulphonate (**50**) is mixed with excess sodium hydroxide and fed to an alkali fusion reactor at 320-350 $^{\circ}$C. The endothermic solid state reaction yields a white powder which consists mainly of disodium resorcinate (**51**), sodium sulphate and some excess sodium hydroxide. Depending on the method used, the product of the fusion reaction is treated with either a small or large quantity of water forming an almost saturated solution of the product. In both processes the dissolved disodium resorcinate (**51**) is then reacted with sulphur dioxide, sulphuric acid or hydrochloric acid to give resorcinol (**14**). The dissolved resorcinol (**14**) is extracted with an organic solvent with diisopropyl ether being the solvent of choice. The solvent is then distilled off and crude resorcinol (**14**) is purified further by vacuum distillation. The salt solution remaining after extraction is processed further.[4,23,24]

In the alkylation process, benzene, together with recycled benzene-cumene from the alkylation process, is alkylated with propene in the liquid phase by using an AlCl$_3$-HCl complex as a catalyst (**Scheme 3.2**).

Scheme 3.2
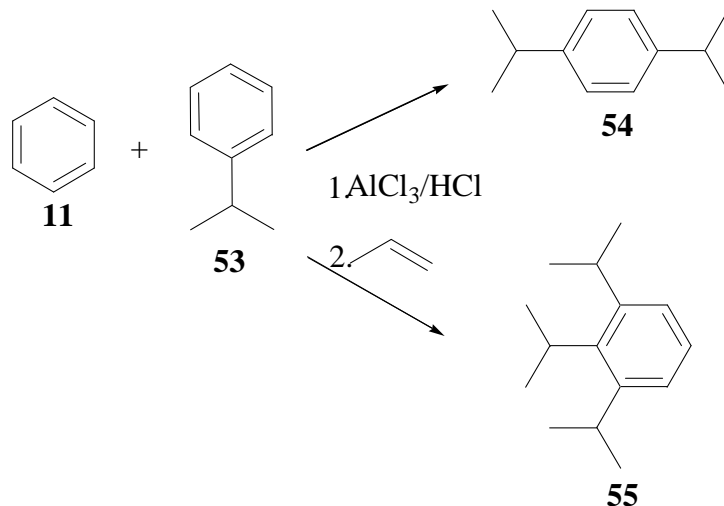
After further addition of some recycled *p*-diisopropylbenzene (*p*-DiPB) (**54**) and triisopropylbenzene (TriPB) (**55**), the alkylate is subjected to isomerization/transalkylation where most of the *p*-DiPB (**54**) and TriPB (**55**) are converted into the wanted *m*-diisopropylbenzene (*m*-DiPB) (**12**). The reaction mixture is then separated by distillation into three fractions (benzene-cumene, *m*-DiPB, and *p*-DiPB-TriPB). The subsequent air oxidation of the pure *m*-DiPB (**12**) leads to a reaction mixture containing approximately 20% of *m*-diisopropylbenzene dihydroperoxide (DHP) (**13**) and ca 35% *m*-diisopropylbenzene monohydroperoxide (MHP) (**52**), after an overall residence time of 6-8h. The heterogeneous mixture is then subjected to phase separation and the *m*-diisopropylbenzene dihydroperoxide (**13**) obtained by crystallization. The cleavage of the DHP (**13**) to resorcinol (**14**) and acetone is carried out under acid catalysis in boiling acetone with a reaction time of 30 minutes. After neutralization, acetone is distilled off at normal pressure and resorcinol (**14**) under vacuum. Further purification of

resorcinol (**14**) can be achieved by recrystallization or extraction. The overall process yield is approximately 75% based on benzene (**11**).[4,23,24]

Other processes for manufacturing resorcinol (**14**) include the one at Koppers in the United States and also at Mitsui Toatsu in Japan where a process for manufacturing resorcinol (**14**) from 1,3-diaminobenzene (**57**), which is produced by the hydrogenation of dinitrobenzene (**56**), has been developed (**Scheme 3.3**).[4]

Scheme 3.3
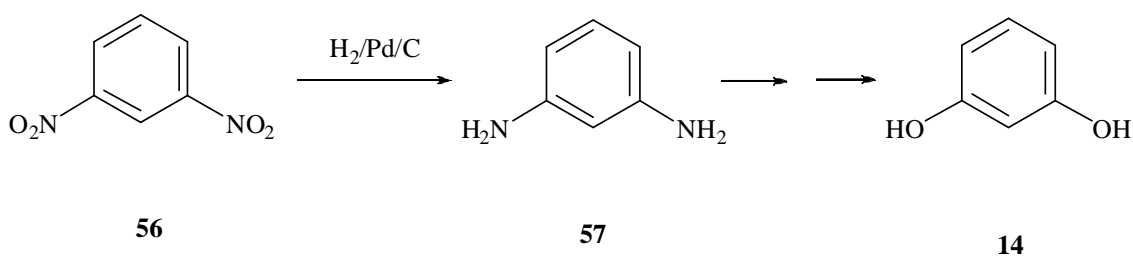
The dehydrogenation of 1,3-cyclohexanedione (**59**) to resorcinol (**14**) which was described by British Oxygen, was further developed by Hoechst in Germany to a four stage process. The starting materials are acetone and methyl acrylate or acrylonitrile (**Scheme 3.4**).[4]

Scheme 3.4
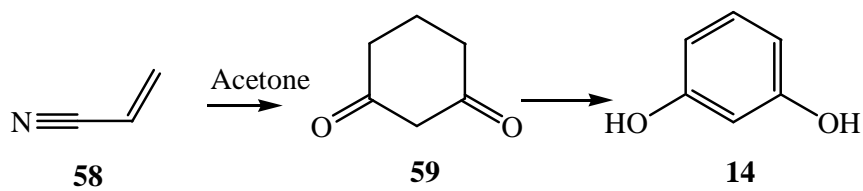
Neither process has been commercialized. The direct hydroxylation of phenol with hydrogen peroxide for example has been investigated extensively however it only yields catechol and hydroquinone.[4]

Resorcinol (**14**) should not enter rivers, lakes or groundwater. Since it is easily biodegradable, small amounts in a biological wastewater treatment plant do not pose any problems. If possible, resorcinol should be collected and returned to the producer. When resorcinol is present in the air in the form of dust, smoke or vapour, it can be removed by air scrubbing with a small amount of water in a wet filter equipped with demister.[4]
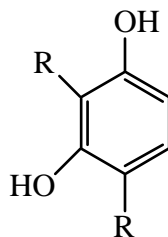
3.1.4 Reactions

The chemical reactions of resorcinol (**14**) involve both the two phenolic hydroxyl groups and the activated aromatic ring in a manner which resembles phenols. Salt or phenolate formation, esterification, etherification, amination and formation of lactones are typical reactions.

Resorcinol (**14**), in contrast to phenol (**20**), cannot be liberated from its alkali metal salts by carbon dioxide, while it can react in two tautomeric forms, the keto as well as the enol form, thus further increasing the variety of its reactions. The hydrogen atoms attached to carbon 2, 4 and 6 are doubly activated due to their location with respect to the hydroxyl groups. Resorcinol (**14**) undergoes ammonolysis with aqueous solutions of ammonium salts or amines under pressure to form *m*-aminophenol or *m*-alkylaminophenols[23] and may be partially or fully hydrogenated. It can also be halogenated, nitrated and

sulphonated to different degrees while dimercurated resorcinols can be formed by reaction with mercuric acetate.[23]

Esters of resorcinol undergo Fries rearrangement under the influence of catalysts such as Lewis acids to form phenolic ketones. Reduction of these ketones results in ring-alkylated resorcinols which are of value as pharmaceuticals. Alkylresorcinols with branched alkyl chains are obtained by the reaction of resorcinol with olefins, while Claisen rearrangement of unsaturated alkylresorcinol ethers may also lead ring-alkylated resorcinol derivatives (**60**).[23]


60 (R = CH$_3$; C$_2$H$_5$)

In a reaction which is similar to the Kolbe-Schmitt synthesis of salicylic acid from phenol, resorcinol and carbon dioxide yield β-resorcylic acid. Both the Gattermann (HCN/HCl) and Reimer-Tiemann (CHCl$_3$, NaOH) reactions may be applied to resorcinol which yield resorcylaldehydes as products (**Scheme 3.5**). Reactions with nitriles (Hoesch reaction) produce ketones (**Scheme 3.6**). Resorcinol (**14**) can couple with one to three molecules of diazonium salts (**66**) (**Scheme 3.7**).[23]
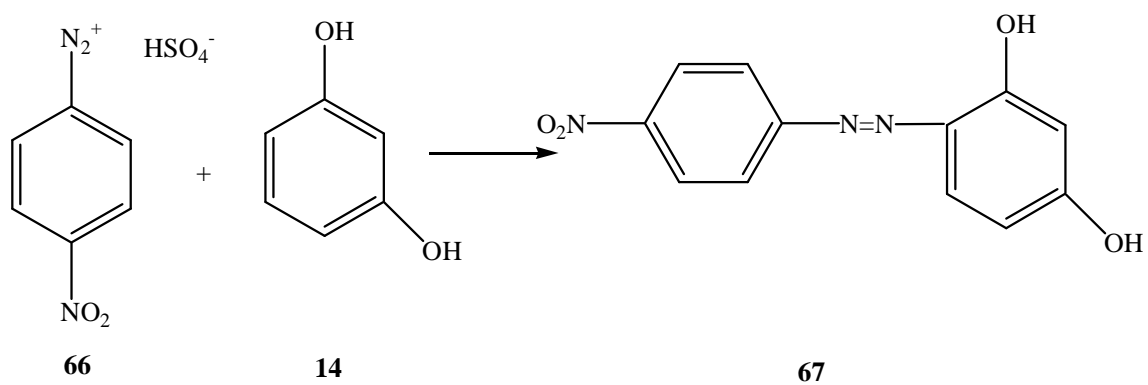
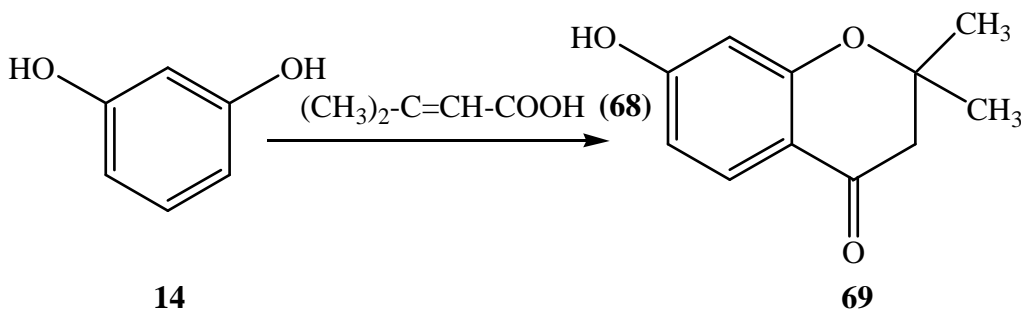**Scheme 3.5**
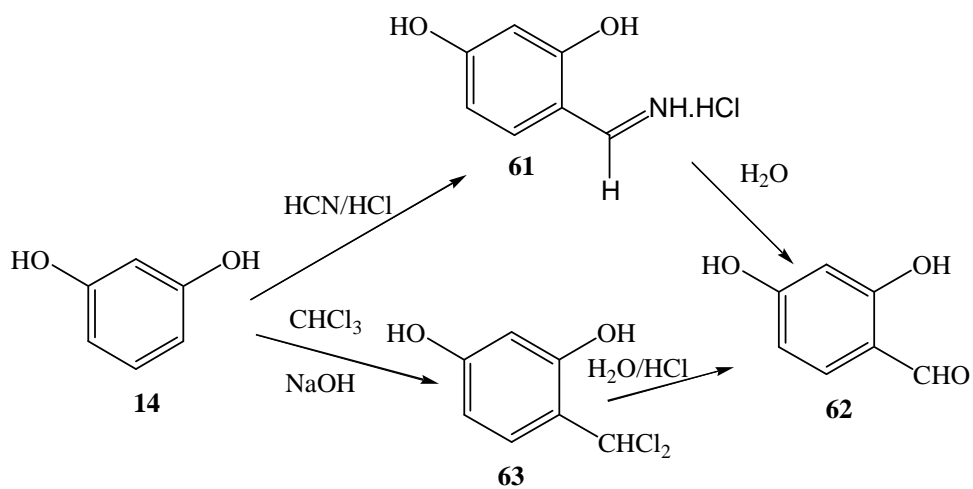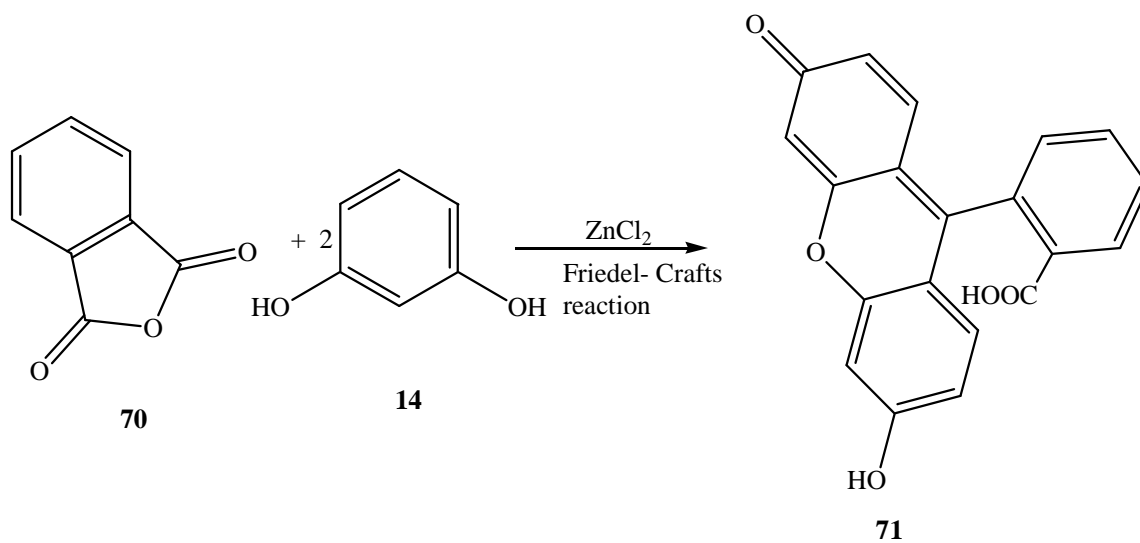

Scheme 3.6
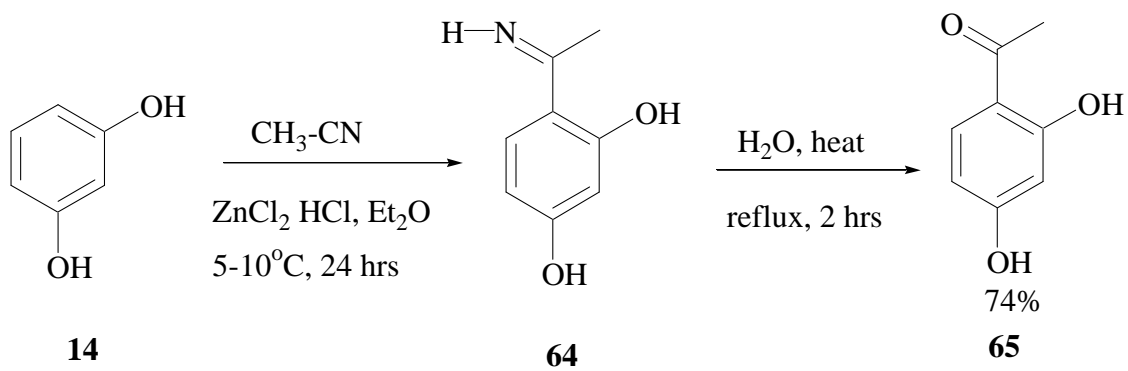
Scheme 3.7

Resorcinol (**14**) reacts with aldehydes similarly to phenol, but at significantly higher rates. In particular, the reaction with formaldehyde is of great technical importance since it leads to the formation of low-temperature-setting waterproof adhesives. Resorcinol-formaldehyde condensates have a distinct advantage over phenol-formaldehyde condensates in that they can be cured at an essentially neutral pH.[23] Resorcinol (**14**) also reacts with ketones to form complex oxygen-containing ring compounds. Condensation with unsaturated acids (**68**) gives chromanones (**69**) (**Scheme 3.8**). Reactions with phthalic anhydride (**70**) and its halogenated derivatives result in the formation of fluorescein (**71**) derivatives (**Scheme 3.9**), while epoxy derivatives of resorcinol, such as glycidyl ethers (**74**), can be prepared by the condensation of epichlorohydrin (**72**) with resorcinol (**14**) leading upon polymerization to epoxy resins (**Scheme 3.10**).[23]
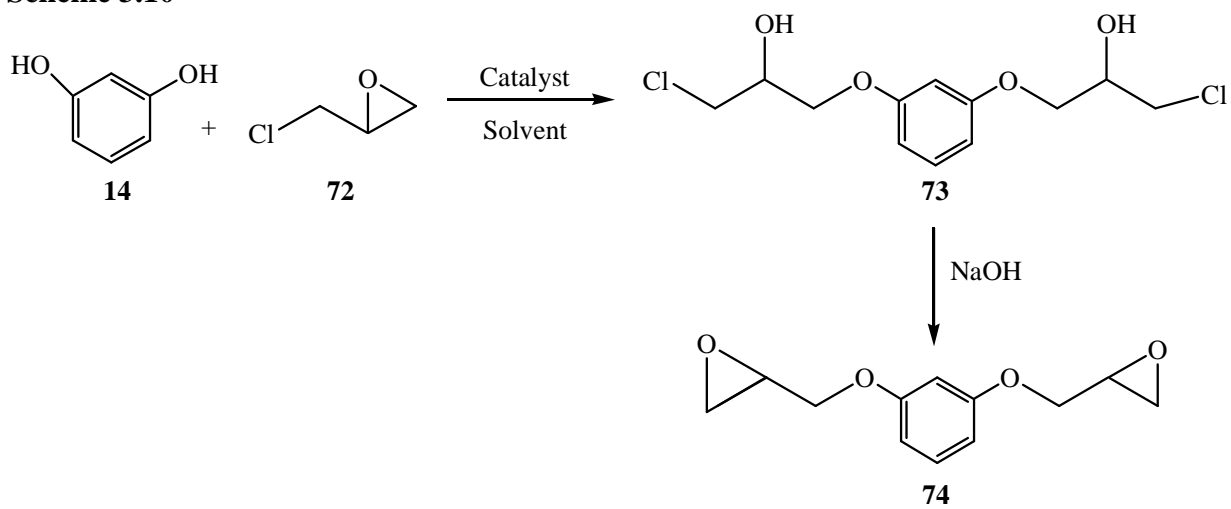
Scheme 3.8

Scheme 3.9

70 14 71

Scheme 3.10

14 72 73

NaOH

74

3.1.5 Uses

The uses for resorcinol (**14**) and its derivatives, mainly as industrial intermediates, are numerous. The primary consumer is the rubber industry whereas the second largest market for resorcinol is found in high-quality wood adhesives.[4]

Since coloured solutions or precipitates are obtained with many substances, resorcinol (**14**) and some of its derivatives are finding wide application as analytical agents, while some derivatives are also used as developers in diazo-type printing and in colour photography processes.[23] Many important dyes, in particular the eosins (**75**) and a number of azo dyes, are based on resorcinol. Resorcinol (**14**) is also used in the dyeing of furs in combination with pyrocatechol, amines and an oxidizing agent.

75
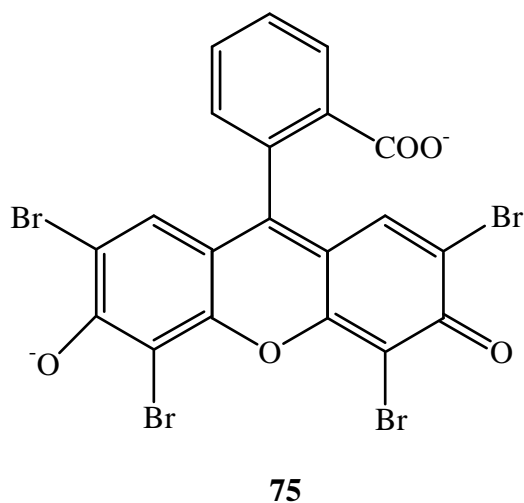
Resorcinol (**14**) also seves as an effective antioxidant and can act as a stabilizer for many halogen compounds. The lead salt of 2,4,6-trinitroresorcinol is used as a component of priming charges for the detonation of explosives.[23] The reaction of resorcinol and certain

of its derivatives with epichlorohydrin (**72**) yields glycidyl ether-type compounds (**74**) which can be cured and dried owing to the reactivity of the epoxy group and are therefore useful in special coating compositions.[23]

Being an antiseptic agent, resorcinol (**14**) is used in cosmetic preparations as well. Although it has been used internally as an intestinal antiseptic, it is mainly applied externally in the form of pastes and ointments in the treatment of skin diseases. In general, the derivatives of resorcinol are less toxic than resorcinol itself and many of them are useful in pharmaceutical preparations for example, resorcinol monoacetate and hexylresorcinol.[23] Resorcinol (**14**) is also an intermediate for the preparation of *p*-aminosalicylic acid, which has been shown to be of specific value in the treatment of tuberculosis.

Resorcinol (**14**) and particularly its mixtures and reaction products with aldehydes and quinines with or without sulphonation have been given consideration as synthetic tanning agents. The fact that it is capable of increasing the swelling of cotton fibers in alkali is of interest to the textile industry. Resorcinol (**14**) has also been used as a component in textile printing pastes.[23]

Resorcinol-formaldehyde resins have been developed for use as adhesive to cure at room temperature under neutral pH conditions without the addition of strongly acidic - or basic catalysts. Such adhesives are of special importance in the manufacture of laminated timbers, roof trusses, boat structures and laminated paper and cloth products. Other uses

for these adhesives include the inter-bonding of textile fabrics, woods, light metals, ceramic materials, plastics and elastomers. The bond obtained with such adhesives is not affected by water, is fungus- and boil- proof and does not cause degradation of the bonded materials. A special application is the bonding of textile materials to rubber as in the manufacture of tires. Other similar uses include the fabrication of belting, heavy-duty hose and rubberized textile sheeting.[23] In this regard, resorcinol (**14**) is also used for the modification of phenolic, urea and related plastics in view of the fast rate at which it is condensed and cured with formaldehyde. The addition of small quantities of resorcinol (**14**) to the resin batch or to the molding materials increases the curing rate of such resins and is claimed to yield products with great water resistance.[23]

The mono- and dibenzoates, as well as the salicylate esters and the 4-acetyl derivative of resorcinol, resacetophenone, are described as effective stabilizers of cellulose organic-ester plastic materials. The dibenzoate and the disalicylate are reported to be effective in inhibiting the embrittlement and discolouration of vinyl resins, while the mono- and diacetates have been described as useful plasticizers in the production of nitrocellulose and as solvents for nitrocellulose and cellulose acetate. Resorcinol phosphates have been described as plasticizers for cellulose plastics, while the monoacetate and monomethyl ether are recommended as solvents for the commercial extraction of lubricating-oil stocks. Resorcinol sulphophthaleins have been suggested for use as ion-exchange resins.[23]

3.1.6 Economic Aspects

During 1974, resorcinol (**14**) was produced by Koppers Co., the sole United States resorcinol manufacturer. In 1977 the United States production was estimated at 16 000 tonnes, while the Western European production amounted to 8500 tonnes. The sole Japanese manufacturer in 1975 produced an estimated 1000 tonnes of which 100 tonnes was exported. Worldwide consumption of resorcinol in 1990 was about 40 000 tonnes per annum.[4,24]

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Chapter 2

Experimental

2.1 Standard Experimental Procedures

The following general experimental techniques were used in this study.

2.1.1 Chromatographic Techniques

2.1.1.1 Thin Layer Chromatography

Qualitative thin layer chromatography (TLC) was performed on Merck aluminium sheets (silica gel 60 F_{254}, 0.25 mm). Preparative thin layer chromatography (PLC) was performed on glass plates (20 x 20 cm), covered with a layer (1.0 mm) of Kieselgel PF_{254} (100 g Kieselgel in 230 ml distilled water per 5 plates). The plates were dried at room temperature and used unactivated. The plates were loaded to a maximum of 25 mg material per plate. After development the plates were dried at room temperature in a fast stream of air and the different bands were distinguished under UV light (254 nm), scraped off and eluted with appropriate solvents.

2.1.1.2 Flash column chromatography

Silica gel 60 (0.040-0.063 mm), 230-400 mesh, ASTM from Merck was used for flash column (50 cm x 5 cm) chromatography under nitrogen pressure.

2.1.1.3 Gas chromatography

GC analysis was performed on a HP 5890 Series II Gas Chromatograph fitted with a PONA column (50 m, 0.20 i.d., 0.50 nm film thickness) at 100 °C (2 min.), where after the temperature was raised to 300 °C at a rate of 6 °C/min and kept at that temperature for a further 2 min. % Refer to relative peak area percentages.

2.1.2 Spectroscopic Methods

2.1.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

300MHz and 600MHz Bruker spectrometers were used to record NMR spectra. The solvents used were chloroform-d ($CDCl_3$) and acetone-d_6. Chemical shifts were expressed as parts per million (ppm) (δ scale) and coupling constants were measured in Hz. The following abbreviations are used:

s	singlet
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
t	triplet
m	multiplet

2.1.2.2 Mass spectrometry

High resolution mass spectra were recorded at 70eV on a VG SEQ mass spectrometer with a MASPEC II data system. MALDI-TOF spectra were collected by a Bruker Microflex LRF20 in the negative mode with the minimum laser power required to observe signals.

2.1.2.3 Infrared Analysis (IR)

Infrared spectra were recorded on a Bruker Tehsor 27 IR spectrophotometer using KBr disks.

2.1.2.4 UV/Vis spectrophotometry

A Varian Carry 50 Conc UV Visible spectrophotometer was used for spectrophotometric analysis.

2.1.3 Crystallographic characterisation of copper(II) complexes

The initial unit cell and data collections were performed on a Bruker X8 Apex II 4K Kappa CCD diffractometer using the Apex2 software package.[1] The optimum measurement method to collect more than a hemisphere of reciprocal space was predicted by COSMO.[2] Frame integration and data reduction were performed using the SAINT-Plus and XPREP[3] software packages. A multi-scan absorption correction was performed on the data using SADABS.[4] The structures were solved by the direct methods package SIR97.[5] For refinement the WinGX software package[6] incorporating SHELXL[7] were used. All non-H atoms were refined anisotropically.

H atoms were positioned geometrically and refined using a riding model with fixed C-H distances of 0.93 Å (CH) [$U_{iso}(H) = 1.2U_{eq}$], 0.97 Å (CH_2) [$U_{iso}(H) = 1.2U_{eq}$], 0.96 Å (CH_3) [$U_{iso}(H) = 1.5U_{eq}$], 0.82 Å (OH) [$U_{iso}(H) = 1.5U_{eq}$].

Molecular diagrams were drawn using the DIAMOND[8] package with a 30% thermal envelope probability for non-hydrogen atoms.

2.1.4 Microscopic observation and photographs

Crystals of the copper salts of *o*- and *p*-toluic acids were observed under an Olympus BX51 microscope and photographs were taken with a soft image system CC12 camera.

2.1.5 Differential Scanning Calorimetry (DSC)

DSC was performed on a Mettler-Toledo DSC822 in a nitrogen atmosphere.

2.1.6 Thermal Gravimetric Analysis (TGA)

Thermal changes were studied thermogravimetrically under argon at a heating rate of 10 °C using a Mettler-Toledo TGA/SDTA851e fitted with a Pfeiffer Thermostar MS.

2.2 Cresols

2.2.1 Tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (90)

o-Toluic acid (**78**) (2.52 g, 18.5 mmole), basic copper(II) carbonate (CuCO$_3$.Cu(OH)$_2$, 0.73 g, 3.3 mmole, 0.18 eq.) and magnesium oxide (0.19 g, 4.7 mmole, 0.25 eq.) were heated in refluxing toluene (30 ml) for 24 hours. The product was extracted and crystallised from diethyl ether (50 ml) to yield *tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)*[9] (**90**) as dark bluish-green cubes (1.31 g, 45.2 % yield): X-ray structure (**1**), ^{1}H NMR (300 MHz, CDCl$_3$, Plate **1a, Appendix 1)** δ_H 9.10 (s); 7.28 (s); 6.74 (s); 3.45 (s); 2.34 (s); 1.32 (s), IR (KBr, Plate **1, Appendix 2**) ν_{max}/cm^{-1} (KBr) 2929.83, 2650.09, 2534.08, 1685.09 (CO), 1614.70 (CO), 1592.73 (CO), 1568.13 (CO), 1505.55, 1455.27, 1426.99, 1392.80, 1270.89, 1195.30, 1153.35, 1091.80, 1037.59, 855.91, 789.51, 742.96, 700.24, 670.79, 565.02, 476.19, 409.90.

2.2.2 Tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (91)

p-Toluic acid (**79**) (2.52 g, 18.5 mmole), basic copper(II) carbonate (0.73 g, 3.3 mmole, 0.18 eq.) and magnesium oxide (0.19 g, 4.7 mmole, 0.26 eq.) were heated in refluxing toluene (30 ml) for 24 hours. The product was extracted and crystallised from dichloromethane (50 ml) to give *tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II)* (**91**) as light bluish-green cubes (1.24 g, 80 %). X-ray structure (**2**), IR (KBr, Plate **2**, **Appendix 2**) ν_{max}/cm^{-1} (KBr) 2964.65, 2919.04, 1680.79 (CO), 1611.26 (CO), 1563.09 (CO), 1513.50 (CO), 1412.62, 1321.29, 1285.53, 1180.95, 1116.60, 1020.56, 961.35, 840.04, 756.43, 607.15, 541.34, 468.64. .

2.2.3 *m*-Cresol (10) from *o*-toluic acid (78) (solventless)

o-Toluic acid (**78**) (21.74 g, 0.1597 moles), basic copper(II) carbonate (35.64 g, 0.1612 moles, 1.009 eq.) and magnesium oxide (1.97 g, 0.0489 moles, 0.3061 eq.) were heated to 200 ^{o}C in a round-bottomed flask fitted with a reflux condenser for 24 hours. *m*-Cresol (**10**) (10.45 g, 60.51 % yield, t_R 12.47 min) was obtained after distillation as a colourless oil: ^{1}H NMR (300MHz, CDCl$_3$, Plate **2a, Appendix 1**) δ_H 7.18 (1H, t, J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71 (2H, m, H-4, H-6); 5.81 (1H, s, OH); 2.35 (3H, s, CH$_3$), IR (KBr, Plate **3, Appendix 2**) ν_{max}/cm^{-1} (KBr) 1588.41, 1490.34, 1461.72, 1277.47, 1264.66, 1244.89, 1151.98, 925.64, 771.63, 732.22, 686.29.

2.2.4 *m*-Cresol (10) from *o*-toluic acid (78) using diphenyl ether as solvent

o-Toluic acid (**78**) (2.54 g, 18.7 mmole), basic copper(II) carbonate (0.73 g, 3.3 mmole, 0.18 eq.) and magnesium oxide (0.19 g, 4.7 mmole, 0.25 eq.) were heated in refluxing diphenyl ether (30 ml) with constant stirring. After 16 hours, the reaction

was stopped, analysed by GC. [*m*-cresol (**10**) (9.05 %, t_R 12.47 min.), *o*-toluic acid

(**78**) (6.49 %, t_R 19.6 min.), and 3-methylphenyl 2-methylbenzoate (**85**) (68 %, t_R

31.19 min.)]. Excess solvent was removed by vacuum distillation (120 ^{o}C, 16 mm

Hg), where after the distillate was purified by flash column chromatography

(hexane/EtOAc 90:10, v/v) to give *m*-cresol (**10**) as a colourless oil (R_F 0.59, 32.30

mg, 1.60 % yield). ^{1}H NMR (300MHz, CDCl$_3$, Plate **2a, Appendix 1**) δ_H 7.18 (1H, t,

J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71 (2H, m, H-4, H-6); 5.81 (1H, s,

OH); 2.35 (3H, s, CH$_3$), IR (KBr, Plate **3, Appendix 2**) ν_{max}/cm^{-1} (KBr) 1588.41,

1490.34, 1461.72, 1277.47, 1264.66, 1244.89, 1151.98, 925.64, 771.63, 732.22,

686.29.

2.2.5 *m*-Cresol (10) from *p*-toluic acid (79) in diphenyl ether

p-Toluic acid (**79**) (2.03 g, 14.9 mmole), basic copper(II) carbonate (0.15 g, 0.68

mmole, 0.046 eq.) and magnesium oxide (0.05 g, 1 mmole, 0.08 eq.) was heated to a

temperature of 230 ^{o}C in diphenyl ether (30 ml) in an oil bath with constant stirring.

The reaction was stopped after 24 hours. GC analysis indicated the reaction mixture

to contain *m*-cresol (**10**) (2.19 %, t_R 12.47 min.), *p*-toluic acid (**79**) (8.23 %, t_R 20.34

min.), and 3-methylphenyl 4-methylbenzoate (**87**) (65.70 %, t_R 35.5 min.). Excess

solvent was removed by vacuum distillation (140 ^{o}C, 16 mmHg) and diethyl ether

(150 ml) was added. The reaction mixture was then extracted into 10 % sodium

hydroxide (3 x 50 ml) and the aqueous extracts combined. Ethyl acetate (150 ml) was

added, followed by the addition of 3M HCl (40 ml) until the water layer became

acidic. The ethyl acetate layer was washed with water (2 x 100 ml), dried with

sodium sulphate and concentrated in vacuo using a rotary evaporator to give *m*-cresol

(**10**) (15.59 mg, 0.968 % yield) as a colourless oil upon distillation: ^{1}H NMR

(300MHz, CDCl$_3$, Plate **2a, Appendix 1**) δ$_H$ 7.18 (1H, t, J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71 (2H, m, H-4, H-6); 5.81 (1H, s, OH); 2.35 (3H, s, CH$_3$), IR (KBr, Plate **3, Appendix 2**) ν$_{max}$/cm^{-1} (KBr) 1588.41, 1490.34, 1461.72, 1277.47, 1264.66, 1244.89, 1151.98, 925.64, 771.63, 732.22, 686.29.

2.2.6 *m*-Cresol (10) from *p*-toluic acid (79)

p-Toluic acid (**79**) (35.08 g, 0.2577 moles), basic copper(II) carbonate (56.82 g, 0.2570 moles, 0.9973 eq.) and magnesium oxide (3.16 g, 0.0784 moles, 0.3042 eq.) were stirred at 230 °C for 32 hours, whereafter diphenyl ether (50 ml) was added and the reaction mixture refluxed. After 8 hours, more diphenyl ether (25 ml) was added. The reaction was continued for another 8 hours [*m*-cresol (**10**) (47.07 %, t$_R$ 15.0 min), *p*-toluic acid (**79**) (6.417 %, t$_R$ 20.4 min.) and 3-methylphenyl 4-methylbenzoate (**87**) (0.5545 %, t$_R$ 35.6 min.)] and distilled to give *m*-cresol (**10**) (13.23 g, 47.05 % yield) as a colourless oil: ^{1}H NMR (300MHz, CDCl$_3$, Plate **2a, Appendix 1**) δ$_H$ 7.18 (1H, t, J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71 (2H, m, H-4, H-6); 5.81 (1H, s, OH); 2.35 (3H, s, CH$_3$), IR (KBr, Plate **3, Appendix 2**) ν$_{max}$/cm^{-1} (KBr) 1588.41, 1490.34, 1461.72, 1277.47, 1264.66, 1244.89, 1151.98, 925.64, 771.63, 732.22, 686.29.

2.2.7 3-Methylphenyl 4-methylbenzoate (87)

p-Toluic acid (**79**) (1.00 g, 7.34 mmole), thionyl chloride (1.31 g, 0.8 ml, 11.0 mmole, 1.5 eq.) and dichloromethane (10 ml) were refluxed at 40 °C. After the acid had completely reacted (TLC) the solvent and HCl-gas were removed in vacuo on a rotary evaporator. Dichloromethane (10 ml) was added to the concentrate, followed by the addition of pyridine (10 ml, 0.12 mol, 16 eq.) and *m*-cresol (**10**) (166.54 mg, 1.5401

mmole, 0.210 eq.). The reaction mixture was stirred at room temperature for 2 hours, whereafter dimethyl amino pyridine (DMAP, one spatula) was added. After 12 hours, the reaction was stopped following TLC-analysis (hexane/EtOAc 80:20, v/v). Dichloromethane (50 ml) was added to the reaction mixture, which was washed with 3M HCl (3 x 40 ml), H_2O (2 x 40 ml) and saturated aq. sodium bicarbonate solution (40 ml). The dichloromethane phase was dried over sodium sulphate and the solvent removed in vacuo. The reaction mixture was thus purified by PLC (hexane/EtOAc 80:20, v/v) to give *3-methylphenyl 4-methylbenzoate* (**87**) (R_F 0.49, 126.33 mg, 12.6 %, t_R 35.99 min) as a colourless oil: ^{1}H NMR (600 MHz, Acetone-d_6, Plate **3a**) δ_H 8.07 (2H, d, J 8.13 Hz, H-2, H-6); 7.42 (2H, d, J 8.13 Hz, H-3, H-5), 7.35 (1H, t, J 7.35 Hz, H-5'); 7.14 – 7.06 (3H, m, H-2', H-4', H-6'); 2.46 (3H, s, CH_3); 2.39 (3H, s, CH_3), IR (KBr, Plate **4, Appendix 2**) ν_{max}/cm^{-1} (KBr) 1731.28 (CO), 1266.90, 1232.40, 1176.52, 1142.35, 1068.71, 1018.88, 766.88, 745.60, 684.99; MS (Plate **1**) *m/z* (EI, +ve) 226 (M[+.]), 119, 91.

2.2.8 3-Methylphenyl 2-methylbenzoate (85)

The procedure mentioned in 2.2.7 was repeated with *o*-toluic acid (**78**) (1.00 g, 7.34 mmole) instead of *p*-toluic acid to give *3-methylphenyl 2-methylbenzoate* (**85**) (R_F 0.52, 98.12 mg, 9.81 %, t_R 31.2 min) as a colourless oil: ^{1}H NMR (600 MHz, Acetone-d_6, Plate **4a**) δ_H 8.13 (1H, dd, J 1.24 Hz, J 8.52 Hz, H-6); 7.56 (1H, dt, J 1.24 Hz, 8.52 Hz, H-5); 7.42 – 7.40 (2H, m, H-3, H-4); 7.35 (1H, t, J 7.4 Hz, H-5'); 7.14 – 7.07 (3H, m, H-2', H-4', H-6'); 2.65 (3H, s, CH_3); 2.39 (3H, s, CH_3); ^{13}C NMR (Plate **4b**) δ_C 205 (C=O), 165-139 (C-1, C-2, C-1', C-3'), 132 (C-5), 131 (C-3/C-4), 130 (C-6), 129 (C-5'), 125 (C-6'/C-4'), 122 (C-2'), 118 (C-6'/C-4'), 20 (2 x CH_3); COSY Plate **4c**, HMQC Plate **4d**; IR (KBr, Plate **5. Appendix 2**) ν_{max}/cm^{-1} (KBr) 1734.27

(CO), 1224.73, 1141.39, 1043.16, 767.94, 732.60, 685.81; MS (Plate **2**) *m/z* (EI, +ve) 226 (M$^{+\cdot}$), 119, 91.

2.2.9 X-ray crystallographic characterisation of copper(II) complexes

In addition to the copper salts of *o*-toluic acid, tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**),[9] and *p*-toluic acid (**91**), salts of *m*-toluic acid (**92**), 4-ethylbenzoic acid (**94**),[10] and 2,6-dimethylbenzoic acid (**93**) were also prepared in a way similar to that of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)[9] (**90**). It should be noted though that **90** was crystallised from diethyl ether, whereas all the other complexes were crystallised from dichloromethane.. Accurate crystal structures were, however, only obtained for tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**), tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**), tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-dimethylbenzoic acid)copper(II) (**93**) and tetrakis(μ_2-4-ethylbenzoato)bis(4-ethylbenzoic acid)copper(II) (**94**) (**Table 1**).

Table 1: General crystal data and refinement parameters.

Identification code	(90)	(92)	(93)	(94)
Empirical formula	$C_{24} H_{22} Cu O_6$	$C_{48} H_{44} Cu_2 O_{12}$	$C_{61} H_{64} Cu_2 O_{12}$	$C_{54} H_{56} Cu_2 O_{12}$
Formula weight	469.96	939.91	1116.20	1024.07
Crystal system, space group	Triclinic, P1	Triclinic, P-1	Triclinic, P-1	Triclinic, P-1
Unit cell dimensions	a = 10.530(5) Å	a = 10.7268(7) Å	a = 12.8033(19) Å	a = 10.6167(5) Å
	b = 10.579(5) Å	b = 10.9500(8) Å	b = 12.8033(19) Å	b = 10.7394(7) Å
	c = 10.773(5) Å	c = 20.2381(16) Å	c = 18.724(3) Å	c = 10.8096(7) Å
	α = 109.248(5)°.	α = 81.057(4)°.	α = 89.661(5)°.	α = 81.848(3)°.
	β = 93.156(5)°.	β = 78.127(4)°.	β = 89.661(5)°.	β = 88.594(3)°.
	γ = 106.287(5)°.	γ = 66.858(3)°.	γ = 64.83°.	γ = 79.468(2)°.
Volume	1073.0(9) Å^3	2131.7(3) Å^3	2777.8(7) Å^3	1199.47(12) Å^3
Z	2	2	2	1
Density (calculated)	1.455 mg/m^3	1.464 mg/m^3	1.335 mg/m^3	1.418 mg/m^3
Absorption coefficient	1.056 mm^{-1}	1.063 mm^{-1}	0.827 mm^{-1}	0.951 mm^{-1}
F(000)	486	972	1168	534
Crystal size	0.25 x 0.08 x 0.06 mm^3	0.27 x 0.25 x 0.24 mm^3	0.51 x 0.45 x 0.37 mm^3	0.54 x 0.40 x 0.39 mm^3
Theta range for data collection / completeness for collection	2.15 to 28.00°/ 99.3%	1.03 to 25.00° / 99.5%	1.09 to 25.00°.	2.50 to 28.00°/ 99.3%
Index ranges	-13<=h<=13, -13<=k<=13, -14<=l<=14	-12<=h<=12, -13<=k<=13, -24<=l<=24	-15<=h<=15, -14<=k<=15, -22<=l<=22	-7<=h<=14, -14<=k<=14, -14<=l<=14
Reflections collected	17497	33846	20889	15971
Independent reflections	5138 [R(int) = 0.0255]	7462 [R(int) = 0.0549]	9441 [R(int) = 0.1493]	5683 [R(int) = 0.0398]
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
Max. and min. transmission	0.9394 and 0.7782	0.7845 and 0.7623	0.7494 and 0.6776	0.7080 and 0.6277
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	5138 / 0 / 284	7462 / 6 / 301	9441 / 42 / 320	5683 / 0 / 311
Goodness-of-fit on F^2	1.048	1.289	1.071	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0629	R1 = 0.1764, wR2 = 0.4297	R1 = 0.1128, wR2 = 0.2739	R1 = 0.0401, wR2 = 0.0963
R indices (all data)	R1 = 0.0302, wR2 = 0.0653	R1 = 0.2035, wR2 = 0.4569	R1 = 0.1348, wR2 = 0.2864	R1 = 0.0523, wR2 = 0.1031
Largest diff. peak and hole	0.410 and -0.326 e.Å^{-3}	2.391 and -0.798 e.Å^{-3}	1.562 and -1.409 e.Å^{-3}	0.504 and -0.367 e.Å^{-3}

2.2.10 Microscopic observation

Crystals of the copper salts of *o*- (**90**) and *p*-toluic acid (**91**) were observed under the microscope over a temperature range and photographed (**Figures 2 and 3**), (**Appendix 2**) (H = Heating up, C = Cooling down, HP = Heating up and pressing with a needle).

2.2.11 Differential Scanning Calorimetry (DSC)

2.2.11.1 *o*-Toluic acid (78)

o-Toluic acid (**78**) (5.87 mg) was subjected to two heating and cooling cycles ranging from -50 °C to 120 °C at heating and cooling rates of 10 °C/min. The third cycle and fourth cycles ranged from -50 °C to 200 °C and -50 ° to 400 °C, respectively. (**Figure 4**), (**Appendix 2**).

2.2.11.2 Tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (90)

Crystals of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) (3.67 mg) were crushed and subjected to 5 cycles of heating and cooling at rates of 10 °C/min., the first two cycles ranging from -50 ° to 200 °C, the third from -50 ° to 120 °C, the fourth from -50 ° to 220 °C and the fifth from -50 ° to 400 °C (**Figure 5**), (**Appendix 2**). The first cycle was repeated twice on fresh sample and the product analysed by ^{1}H NMR (300 MHz, Acetone-d$_6$, Plate **5a, Appendix 1**) δ_H 9.62 (s); 7.75 (m); 7.68 (m); 5.96 (s); 4.23 (m); 2.85 (d); 1.31 (m); 0.93 (m); IR (KBr, Plate **6**) ν_{max}/cm^{-1} (KBr) 3854.10, 3750.23, 3675.33, 3649.44, 3446.88, 3073.75, 3023.86, 2966.05, 2927.80, 1606.70 (CO), 1584.59 (CO), 1559.63 (CO), 1503.91, 1488.90, 1458.11, 1438.08, 1399.39, 1288.17, 1156.25, 1101.93, 1052.39, 857.26, 805.79, 787.47, 737.73, 696.38, 671.11, 563.26, 499.38, 473.18.

2.2.11.3 ***o*-Toluic acid (78) and tetrakis(μ_2-2-methylbenzoato)bis(2-methyl-benzoic acid)copper(II) (90) mixture**

A mixture of *o*-toluic acid (**78**) and tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) (2.90 mg, 5:95 m/m) were subjected to the same conditions as in 2.2.13.2. (**Figure 6**), (**Appendix 2**).

2.2.11.4 3-Methylphenyl 2-methylbenzoate (85)

3-Methylphenyl 2-methylbenzoate (**85**) (2.37 mg) were subjected to 5 cycles of cooling and heating at rates of 10 °C/min., the first two cycles ranging from 40 to -50 °C, the second from 60 to -50 °C, the third from 80 to -50 °C, the third from 240 to -50 °C and the last from 290 to -50 °C. (**Figure 7**), (**Appendix 2**). Copper(0) was subsequently added to 3-methylphenyl 2-methylbenzoate (**85**) and the DSC repeated (**Figure 8**), (**Appendix 2**).

2.2.11.5 *p*-Toluic acid (79)

p-Toluic acid (**79**) (5.87 mg) was subjected to two heating and cooling cycles ranging from -50 °C to 200 °C at heating and cooling rates of 10 °C/min. The third cycle and fourth cycles ranged from -50 °C to 260 °C and -50 °C to 400 °C, respectively. (**Figure 9**), (**Appendix 2**).

2.2.11.6 Tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (91)

Tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (**91**) (5.87 mg) was subjected to two heating and cooling cycles ranging from -50 °C to 200 °C at heating and cooling rates of 10 °C/min. The third cycle and fourth cycles ranged from -50 °C to 260 °C and -50 ° to 400 °C, respectively. (**Figure 10**), (**Appendix 2**).

2.2.12 Thermogravimetric analysis (TGA)

2.2.12.1 Tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (90)

Tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) (9.65 mg) was subjected to TGA analysis ranging from room temperature up to 500 ^{o}C and stepping at 10 ^{o}C per minute (**Figure 11**), (**Appendix 2**). *o*-Toluic acid (**78**) was thus subjected to the same conditions (**Figure 12**), (**Appendix 2**).

2.2.12.2 Tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (91)

Tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (**91**) (11.90 mg) was subjected to TGA analysis which started at room temperature and stepped at 20 ^{o}C per minute until a maximum temperature of 500 ^{o}C was obtained (**Figure 13**) (**Appendix 2**).

2.3 Diels-Alder Reactions

2.3.1 Butyl 2-methoxy-4-oxocyclohexanecarboxylate (118a and 118b)

Danishefsky's diene (**112**) (1.37 to 1.96 mmole), butyl acrylate (**114**) (187.3 mg, 1.46 mmole, 1 eq.) and toluene (2 ml) were refluxed together for up to 2 weeks. GC analysis revealed no increase in yield after 80 hours' reaction time. The reaction was thus stopped after 80 hours by removing the toluene under vacuum, where after the reaction mixture was separated by PLC (hexane/EtOAc 70:30, v/v) to give *cis*-butyl 2-methoxy-4-oxocyclohexanecarboxylate (**118a**) as a light brown oil (R$_F$ 0.3, 27.5 mg, 7.53 % yield): ^{1}H NMR (600 MHz, CDCl$_3$, Plate **6a**) δ_H 4.23-4.18 (1H, m, H-2); 4.17-4.08 (2H, m, H-1''); 3.32 (3H, s, OMe); 2.90-2.84 (1H, m, H-1); 2.80 (1H, dd, J 2.1 Hz, J 4.08 Hz, H-3); 2.49 (1H, br.d, J 2.50 Hz, H-3'); 2.47-2.44 (1H, m, H-5); 2.34-2.26 (1H, m, H-5'); 2.24-2.19 (1H, m, H-6); 2.17-2.10 (1H, m, H-6'); 1.69-1.59

(2H, m, H-2''); 1.47-1.33 (2H, m, H-3'') and 0.95 (3H, t, J 7.3 Hz, H-4''), ^{13}C NMR

Plate **6b** δ_C 209 (C=O), 173 (-COO), 79 (C-2), 64 (C-1''), 57 (OMe), 46 (C-1), 44

(C-3), 39 (C-5), 32 (C-2''), 23 (C-6), 19 (C-3''), 14 (C-4''); COSY Plate **6c**; HMQC

Plate **6d**. Another product, *trans*-butyl 2-methoxy-4-oxocyclohexanecarboxylate

(**118b**) was also formed (R_F 0.35, 35.3 mg, 9.66 % yield): ^{1}H NMR (300 MHz,

CDCl$_3$, Plate **7a**) δ_H 4.17 (2H, t, J 4.16 Hz, H-1''); 3.94-3.87 (1H, m, H-2); 3.34 (3H,

s, OMe); 2.88-2.81 (1H, m, H-1); 2.76 (1H, dd, J 1.3 Hz, J 4.19 Hz, H-3); 2.48-2.45

(1H, m, H-3'); 2.43-2.41 (1H, m, H-5); 2.38-2.29 (1H, m, H-5'); 2.22-2.12 (1H, m,

H-6); 2.03-1.91 (1H, m, H-6'); 1.70-1.61 (2H, m, H-2''); 1.47-1.34 (2H, m, H-3'')

and 0.95 (3H, t, J 7.34 Hz, H-4''), ^{13}C NMR (Plate **7b**) δ_C 208 (C=O), 174 (-COO), 79

(C-2), 66 (C-1''), 58 (OMe), 47 (C-1), 45 (C-3), 38 (C-5), 31 (C-2''), 24 (C-6), 18 (C-

3''), 14 (C-4''); COSY Plate **7c**; HMQC Plate **7d**.

2.3.2 4-Acetyl-3-methoxycyclohexanone (117a and 117b)

Danishefsky's diene (**112**) (319.9 mg, 1.857 mmole, 1.301 eq.), methyl vinyl ketone

(**113**) (100.0 mg, 1.427 mmole) and toluene (3 ml) were refluxed for 100 hours,

whereafter the reaction was stopped by evaporating the toluene in vacuo at room

temperature. PLC (hexane/EtOAc 80:20, v/v) of the reaction mixture gave *cis*-4-

acetyl-3-methoxycyclohexanone (**117a**) as a light brown oil (R_F 0.12, 18.2 mg, 7.49

% yield): ^{1}H NMR (600 MHz, CDCl$_3$, Plate **8a**) δ_H 4.22 (1H, br.s, H-3); 3.31 (3H, s,

OMe); 2.83 (1H, dd, J 1.87 Hz, J 14.98 Hz, H-2); 2.80-2.79 (1H, m, H-4); 2.53-2.51

(1H, m, H-6); 2.48-2.45 (1H, m, H-2'); 2.35-2.32 (1H, m, H-6'); 2.32-2.28 (1H, m,

H-5); 2.24 (3H, s, CH$_3$) and 2.11-2.09 (1H, m, H-5'), ^{13}C NMR (Plate **8b**) δ_C 208

(C=O), 207 (C=O), 78 (C-3), 56 (OMe), 53 (C-4), 44 (C-2), 39 (C-6), 28 (CH$_3$), 23

(C-5); COSY Plate **8c**; HMQC Plate **8d**. Another product, *trans*-4-acetyl-3-

methoxycyclohexanone (**117b**), was also isolated as a light brown oil (R_F 0.29, 16 mg, 6.59 % yield): ^{1}H NMR (600 MHz, CDCl$_3$, Plate **9a**) δ_H 3.80-3.73 (1H, m, H-3); 3.29 (3H, s, OMe); 2.97-2.91 (1H, m, H-4); 2.84 (1H, ddd, J 1.32 Hz, J 4.47 Hz, J 14.18 Hz, H-2); 2.41-2.38 (1H, m, H-2'); 2.36-2.34 (1H, m, H-6); 2.33-2.30 (1H, m, H-6'); 2.27 (3H, s, CH$_3$); 2.11-2.02 (1H, m, H-5) and 1.84-1.70 (1H, m, H-5'), ^{13}C NMR (Plate **9b**) δ_C 209 (C=O), 207 (C=O), 79 (C-3), 57 (OMe), 54 (C-4), 45 (C-2), 39 (C-6), 30 (CH$_3$), 23 (C-5); COSY Plate **9c**; HMQC Plate **9d**.

2.3.3 Diels-Alder reaction of Danishefsky's diene (112) with methyl propiolate (103)

Danishefsky's diene (**112**) (300.6 mg, 1.745 mmole), methyl propiolate (**103**) (220.1 mg, 2.618 mmole, 1.501 eq.) and toluene (2 ml) were refluxed for 26 hours, whereafter the reaction was stopped by evaporating the toluene at room temperature. The reaction mixture was separated by PLC (hexane/EtOAc 70:30, v/v). Bands 2 and 4 (R_F 0.75 and 0.42, 31.5 mg and 27.9 mg, respectively) were resubjected to PLC (hexane/DCM/EtOAc 30:65:5, v/v) to give *methyl 4-{[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]oxy}benzoate* (**120**) as white needle-like crystals (R_F 0.6, 23.6 mg, 5.74 % yield): ^{1}H NMR (300MHz, CDCl$_3$, Plate **10a**) δ_H 8.07 (2H, d, J 8.9 Hz, H-2, H-6); 7.83 (1H, d, J 12.14 Hz, H-1'); 7.12 (2H, d, J 8.9 Hz, H-3, H-5); 5.69 (1H, d, J 12.14 Hz, H-2'); 3.92 (3H, s, OMe) and 3.75 (3H, s, OMe); ^{13}C NMR (Plate **10b**) δ_C 166, 168 (2 x COOCH$_3$), 158 (C-1'), 131 (C-2/C-6), 117 (C-3/C-4), 104 (C-2'), 52, 54 (2 x OMe); and methyl 4-hydroxy benzoate (**119**), also as white needle-like crystals (R_F 0.4, 14.6 mg, 5.51 % yield): ^{1}H NMR (600MHz, Acetone-d$_6$, Plate **11a**) δ_H 7.96 (1H, s, OH); 6.72 (2H, d, J 8.8 Hz, H-2, H-6); 5.75 (2H, d, J 8.8 Hz, H-3, H-5) and 2.65 (3H, s, OMe).

2.3.4 Methyl 4-hydroxy benzoate (119)

p-Hydroxy benzoic acid (**124**) (319 mg, 2.31 mmole), *p*-toluene sulphonic acid (13 mg, 0.068 mmole, 0.029 eq.) and methanol (10 ml, 246.9 mmol, 106.9 eq.) were heated to 50 °C while stirring. The reaction was stopped after 38 hours by the addition of EtOAc (100 ml) and water (100 ml). The top layer was washed with saturated aq. sodium bicarbonate (50 ml), followed by water (2 x 100 ml) and dried over sodium sulphate. The extract was concentrated in vacuo using a rotary evaporator and separated by PLC (hexane/EtOAc 70:30, v/v) to give methyl *p*-hydroxy benzoate (**119**) as a white needle-like crystals (R_F 0.64, 114.7 mg, 32.63 % yield): ^{1}H NMR (600MHz, Acetone-d_6, Plate **11a**) δ_H 7.96 (1H, s, OH); 6.72 (2H, d, J 8.8 Hz, H-2, H-6); 5.75 (2H, d, J 8.8 Hz, H-3, H-5) and 2.65 (3H, s, OMe).

2.3.4.1 Methyl 4-{[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]oxy}benzoate (120)

Methyl *p*-hydroxy benzoate (**119**) (19 mg, 0.13 mmole), methyl propiolate (**103**) (162.5 mg, 1.933 mmole, 15 eq.), toluene (1 ml) and triethyl amine (1 drop) were refluxed together for 5 hours. The reaction mixture was thus subjected to liquid-liquid extraction with EtOAc (100 ml) and water (100 ml). The organic layer was washed with saturated aq. sodium bicarbonate (50 ml), followed by water (2 x 100 ml) and dried with sodium sulphate. The extract was concentrated in vacuo at ambient temperature and separated by PLC (hexane/EtOAc 80:20, v/v) to give *methyl 4-{[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]oxy}benzoate* (**120**) as white needle-like crystals (R_F 0.7, 6.9 mg, 23 % yield): ^{1}H NMR (300MHz, CDCl$_3$, Plate **10a**) δ_H 8.07 (2H, d, J 8.9 Hz, H-2, H-6); 7.83 (1H, d, J 12.14 Hz, H-1'); 7.12 (2H, d, J 8.9 Hz, H-3, H-5); 5.69 (1H, d, J 12.14 Hz, H-2'); 3.92 (3H, s, OMe) and 3.75 (3H, s, OMe)

All NMR spectrums can be found in Appendix 1.

All photographs of crystals, DSC, TGA, X-Ray MS and IR spectrums can be found in Appendix 2.

2.4 References

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Chapter 3

Discussion

3.1 Preparation of *m*-Cresol

3.1.1 Introduction

Cresols are important starting materials for many phenolic compounds and are currently industrially obtained from toluene (**5**) *via* a three-step process (**Scheme 3.1**). In a process similar to the one for the production of phenol, toluene is reacted with propylene (**76**) to give a mixture of *ortho-* (**6**), *meta-* (**8**) and *para*-isopropyltoluene (**7**), which is then subjected to oxidation by air and peroxide cleavage to give the corresponding cresols together with acetone. Due to their close boiling points, *meta-* (**8**) and *para*-cresol (**9**) are not separable by distillation. *m*-Cresol (**10**) is thus a very expensive starting material obtainable only after an elaborate adduct crystallisation process, derivatization or chromatography.[1,2,3]

Scheme 3.1
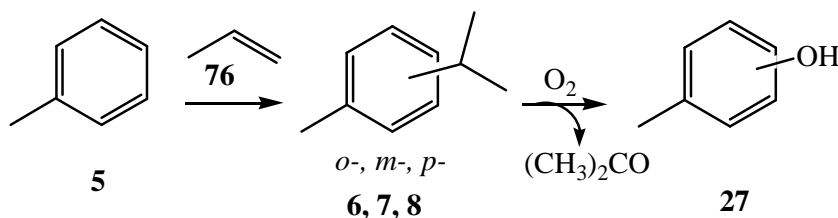
In order to circumvent the problems associated with the current cresol production process, it was decided to approach cresol production from a different angle using readily available xylenes as the primary source of carbon. If xylene (**77**) could be oxidised selectively at one methyl group only, application of the copper catalysed rearrangement as described by Kaeding in the Dow-Phenol process[4,5,6] during the mid 1960's could facilitate the desired cresol (**Scheme 3.2**) from either *ortho-* or *para*-xylene.

Scheme 3.2
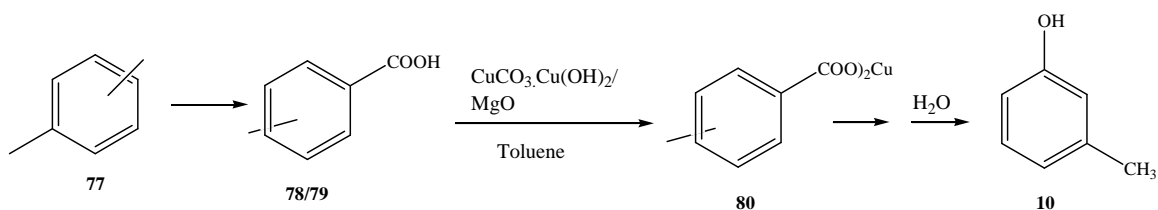
The newly envisaged process should lead to cresol production through a process that starts from a relatively cheap raw material and has a lower risk from a safety point of view, while no unwanted side products are produced and recycle streams (if any) could be minimised. Since Merisol (a subsidiary of Sasol) is in the cresol business, access to this technology would put Merisol in a position where it could compete very favourably with other cresol producers (especially Chinese producers) in the world economy and lead to an export opportunity for this company.

As the oxidation of xylenes is a well known process in the manufacture of phthalic-(**81**) and terephthalic acids (**37**) for the production of polyesters,[1] the main challenge during the current investigation would centre around the introduction of selectivity in the oxidation part of the process. Since the first carboxyl group would deactivate the ring to a large extent, it was envisaged that it should be possible to facilitate the required selective oxidation under the right conditions.

81   **37**
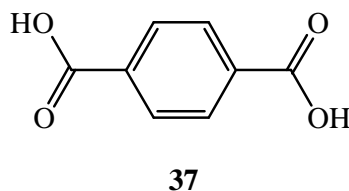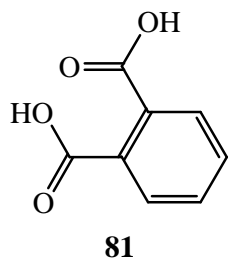
Although the second step (rearrangement of the toluic acid into cresol) (**Scheme 3.2**) has been described, the exact mechanism for the formation of phenols from copper(II)benzoates is still unknown.[7] The mechanism postulated by Keading[4,5,6] (**Scheme 3.3**) involves nucleophilic attack by a benzoate at the *ortho*-position of an adjacent benzoate, followed by decarboxylation and hydrolysis. An alternative mechanism proposed by Buijs (**Scheme 3.4**) involves electrophilic aromatic substitution by a benzoyloxy cation (**88**) on the benzoic acid or benzoate ion to form an *o*-benzoyloxybenzoic acid (**89**) which, upon decarboxylation, would give the ester and the corresponding phenol upon hydrolysis.[8,9,10]

Scheme 3.3
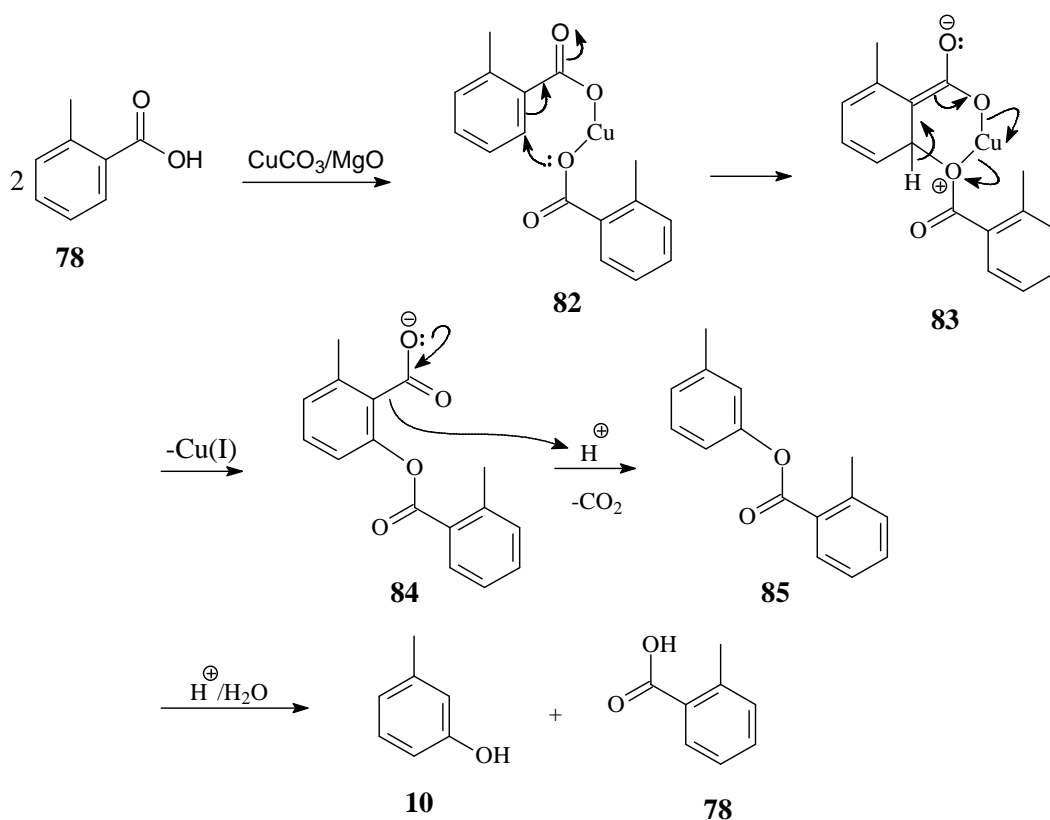
Scheme 3.4
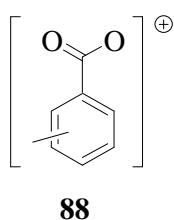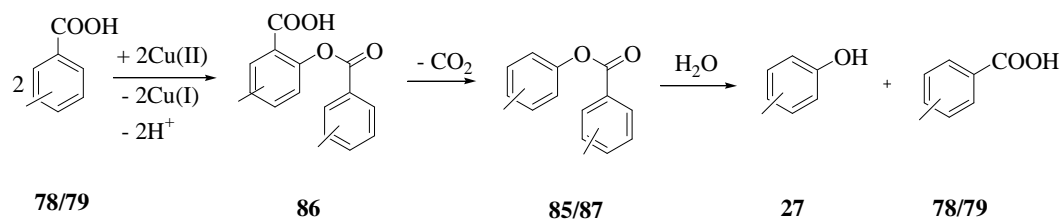
With the mechanism and limitations of the reaction not yet being determined, the aim of the current investigation was to study the reaction from a fundamental point of view in an attempt to gain a basic understanding of the reaction that would allow improvements to the process to the point where it could be turned into a viable industrially applicable technology. With the acquired basic knowledge in hand, the possibility of turning the reaction into a catalytic process, might also become feasible, since waste production cannot be tolerated in modern chemical processes.

If successful, the study would therefore contribute towards a new industrial process for cresol production that would not be complicated by the co-production of acetone, while the safety risk of explosions from the hydrogen peroxide step (in the current process) would be eliminated and waste production minimised.

3.1.2 Transformation of toluic acids into *m*-cresol

Heating *o*-toluic acid (**78**) with $CuCO_3.Cu(OH)_2$ and MgO at 200 °C for 24 hours according to Keading's method,[5] produced *m*-cresol (**10**) in 32 % yield following distillation (**Scheme 3.5**).

Scheme 3.5
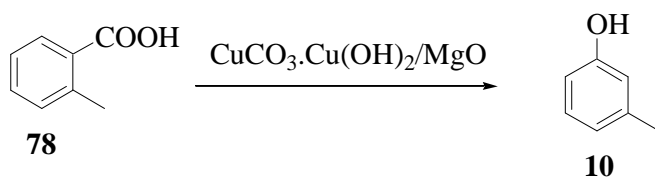
When this reaction was repeated in refluxing diphenyl ether (bp. 259 °C) for 16 hours, the major product turned out to be 3-methylphenyl 2-methylbenzoate (**85**) (68 %), whereas small quantities of *o*-toluic acid (**78**) (6.5 %) and *m*-cresol (**10**) (9.1 %) were formed (GC analysis). This result pointed towards 3-methylphenyl 2-methylbenzoate (**85**) being an intermediate in the reaction, which is also corroborated by the formation of benzoylsalicylic acid when benzoic acid is decarboxylated.[6] The identity of this novel ester was confirmed by synthesis (**Scheme 3.6**), whereas the boiling point was determined by DSC (Differential Scanning Calorimetry) to be 260 °C.

Scheme 3.6
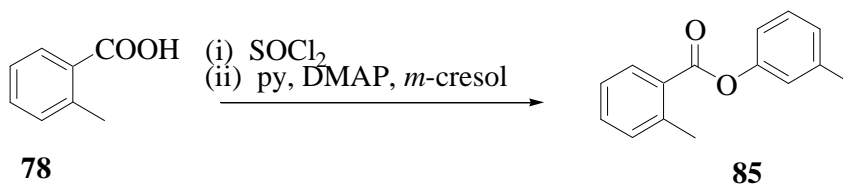
The ^{1}H NMR spectrum (Plate **4a)** of 3-methylphenyl 2-methylbenzoate (**85**) displayed the expected 8 aromatic resonances [δ 8.13 (1H, dd, J 1.24 and 8.52 Hz, H-

6), 7.56 (1H, dt, J 1.24 and J 8.52 Hz, H-5), 7.42-7.40 (2H, m, H-3 and H-4), and 7.14

-7.07 (3H, m, H-4', H-2', H-6')] together with two methyl signals at δ 2.65 and 2.39

(each 3H, each s), while the presence of the ester functionality was confirmed by a

carbon resonance at δ_C 205 in the ^{13}C NMR (Plate **4b**) as well as an ester absorption

band at 1734.27 cm^{-1} in the IR spectrum (Plate **5**). The molecular ion (*m/z* 226) could

furthermore be identified in the mass spectrum (Plate **2**).

Similar treatment of *p*-toluic acid (**79**), but at 230 $^{\circ}$C for 32 hours, produced 66 %

3-methylphenyl 4-methylbenzoate (**87**), while *m*-cresol (**10**) (2.19 %) and *p*-toluic

acid (**79**) (8.23 %) were again observed (GC analysis). The identity of

3-methylphenyl 4-methyl benzoate (**87**), an apparent intermediate in the reaction and

also a novel compound, was proven by synthesis (**Scheme 3.7**).

Scheme 3.7
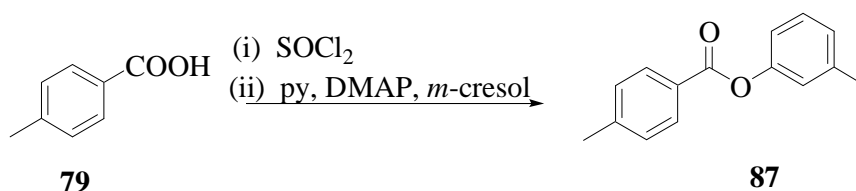
In the ^{1}H NMR spectrum (Plate **3a**) of 3-methylphenyl 4-methylbenzoate (**87**), the

appropriate aromatic resonances [H-2 and H-6 (δ 8.07, 2H, d, J 8.13 Hz), H-3 and H-5

(δ 7.42, 2H, d, J 8.13 Hz), and H-2', H-4' and H-6' (δ 7.14-7.06, 3H, m)] could easily

be distinguished, while the two methyl groups were visible at δ 2.46 and 2.39 (each

3H, each s). The structure was further confirmed by IR analysis (Plate **4**) as an ester

absorbtion band was clearly visible (v_{max} 1731.28 cm^{-1}), while the molecular ion (m/z 226) could be identified in the mass spectrum (Plate **1**).

3.1.3 Mechanistic studies

Although *m*-cresol (**10**) could be prepared successfully from both *o*- (**78**) and *p*-toluic acid (**79**) using Keading's method,[5] yields were not close to what is expected form a viable industrial process. Furthermore, Keading gave no indication as to why different temperatures were used for the different cresol isomers, while the cited paper also gave no indication as to what the required temperatures for the different steps in the mechanism (*vide supra*) would be. In order to gain a fundamental understanding of the reaction and to elucidate the mechanism and determine what the optimal temperatures for each step would be, it was decided to launch a fundamental investigation into this rearrangement reaction. Various modern analytical techniques including X-ray crystallography, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), nuclear magnetic resonance (NMR), MALDI-TOF mass spectrometry, infrared spectroscopy (IR) and microscopic observation over a temperature range, were utilised during the investigation.

3.1.3.1 Structures of copper benzoates of *o*- and *p*-toluic acids

Since Keading[5] proposed the formation of the copper salt of *o/p*-toluic acid (**78/79**) as the starting point of the reaction, our attempts at elucidating the mechanism was initiated by preparing and characterising the salts in order to have absolute clarity about the structure of the starting material. Treatment of *o*-toluic acid with basic copper(II)carbonate and MgO in refluxing toluene resulted in the formation of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) which

crystallised from ether as bluish-green cubes suitable for single crystal X-ray analysis.[11] The complex tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) crystallized in the triclinic space group P-1, (Z=2), with molecular symmetry Ci and Belsky notation as P-1, Z=1(-1):[(-1^7)].[13,14]

The centro symmetric title compound exhibited a paddlewheel structure, with four *o*-toluic acid anionic ligands forming a cage around two Cu-atoms in a syn-syn configuration. Interestingly, two more carboxylic acids moieties are apically bonded to the Cu-atoms through the carbonyl oxygen, while the acid protons are hydrogen bond to the cage carboxylate oxygens, O32---H32...O22 = 167.6° and O32...O22 = 2.6604(18) Å. Another intra-molecular H...H short contact is present at C16...O21 with C16---H16...O21 = 100.9° and C16...O21 = 2.721(2) Å.
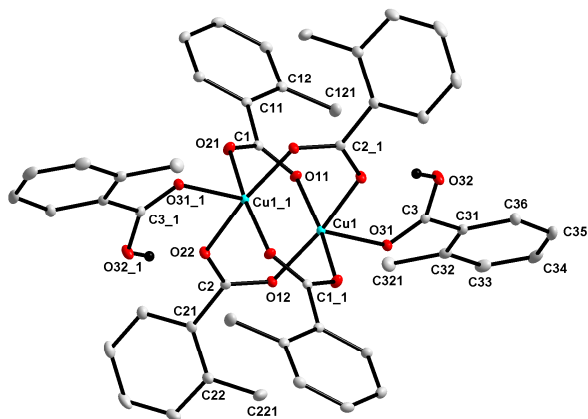
Figure 3.1: A view of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**), showing the atom-numbering scheme. Non-labelled atoms are symmetric equivalents. For the phenyl C-atoms, the first digit indicates ring number and the second digit the position of the atom in the ring.

Table 2: Selected geometric parameters (Å ,°)

Atom Pair	Bond Distance	Atom Pair	Bond Distance
Cu1-O21[i]	1.9402(12)	Cu1-Cu1[i]	2.5780(9)
Cu1-O11	1.9559(12)	C31-C3	1.485(2)
Cu1-O12	1.9585(13)	C11-C1	1.497(2)
Cu1-O22[i]	1.9900(13)	C2-C21	1.492(2)
Cu1-O31	2.1622(13)		

Symmetry codes: (i) –x+1, -y+1, -z+1

Compound (**90**) formed a puckered pseudo-hexagonal close packed layer in the (h 0 0) plane, with soft inter-molecular H...H contacts, 2.457-2.580Å.
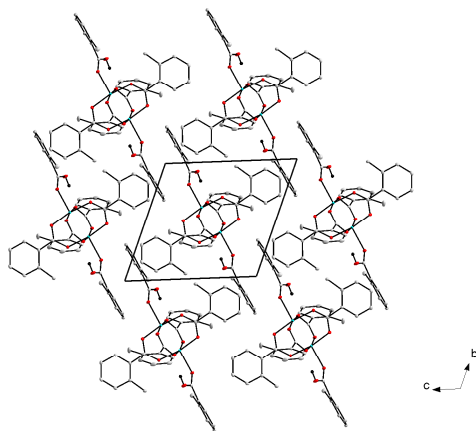
Figure 3.2: Indication of pseudo-hexagonal close packing in the (h 0 0) plane.

Similar treatment of *p*-toluic acid (**79**) gave the copper salt, which was crystallised from DCM and subjected to X-ray crystallography. The crystals of the complex tetrakis(μ_2-4-Methylbenzoato)*bis*(4-methylbenzoic acid)copper(II) (**91**) was found to be very unstable, so high quality data could not be obtained form the crystals submitted. Despite the availability of only low quality data, the structure of the complex could be elucidated and as indicated in Figure 3.3 the complex crystallized with two independent molecules in the unit-cell. Although the two independent molecules and the particular molecular packing in the unit-cell, as depicted in Figures 3.4 and 3.5, might be the result of higher symmetry, the structure could not be resolved in a space group of higher symmetry. For the purpose of this study, the data, however, confirms that four *p*-methylbenzoic acid molecules are coordinate to two copper atoms and that coppper(II) complex (**91**) clearly displays a paddlewheel configuration as was observed with the copper(II) complex of *o*-toluic acid (**90**).
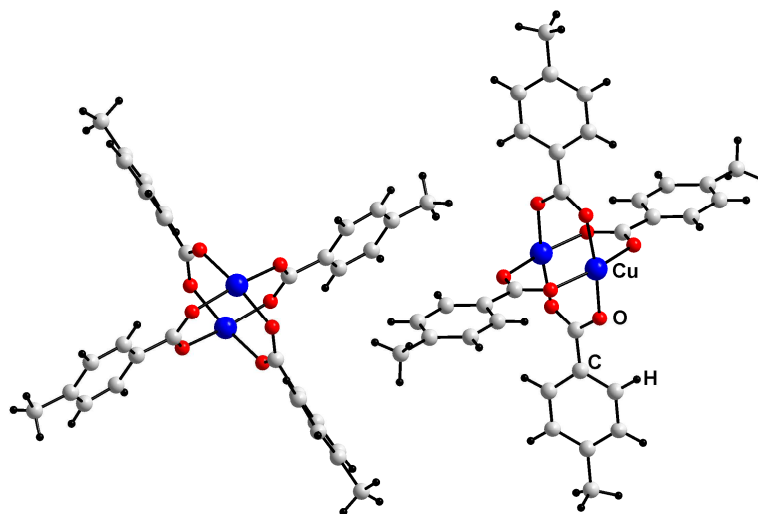
Figure 3.3: Crystal structure of tetrakis(μ_2-4-Methylbenzoato)*bis*(4-methylbenzoic acid)copper(II) (**91**).
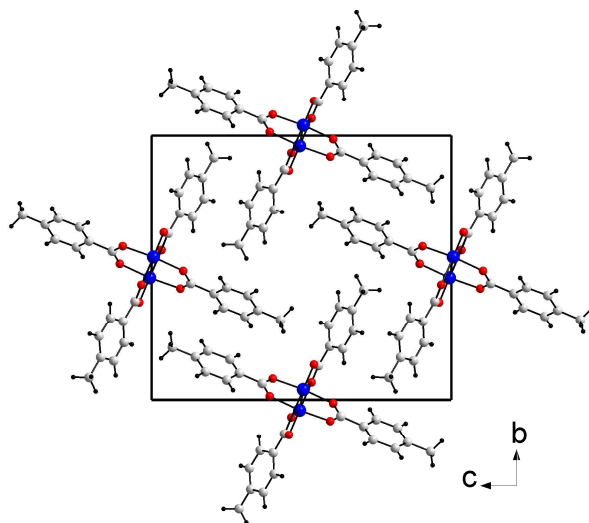
Figure 3.4: Crystal structure of tetrakis(μ_2-4-Methylbenzoato)*bis*(4-methylbenzoic acid)copper(II) (**91**) showing intermolecular contacts between neighbouring molecules.

In contrast to the structures of the other four copper complexes presented in this section, *i.e.* (**90**), (*vide supra*) and (**92**), (**94**), and (**93**) (*vide infra*), where two benzoic acid molecules are coordinated *via* the carbonyl oxygen of the carboxylic acid function to the copper atoms, the molecules of this copper(II) complex (**91**) seems to display intermolecular contacts between neighbouring molecules (**Figure 3.4**). In **Figure 3.5** this intermolecular contacts are displayed by hacked lines between an oxygen atom of one molecule and the copper atom of the neighbouring molecule to form an infinite "polymer" type chain along the a-axis.
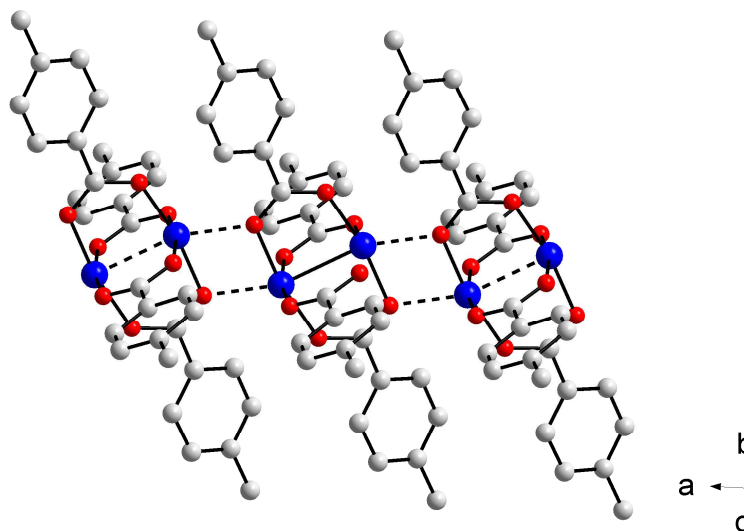
Figure 3.5: Crystal structure of tetrakis(μ_2-4-Methylbenzoato)*bis*(4-methylbenzoic acid)copper(II) (**91**) showing an "infinite" polymer type chain.

3.1.3.2 Crystal structures of other copper benzoates

Since the structures of the copper salts of *o-* and *p-*toluic acid differed quite substantially, it was decided to extend the investigation to the structures of the copper salts of other substituted benzoic acids in order to determine what the general structure of these compounds might be and if some exception to a possible general structure does exist. Copper benzoates of *m-*toluic acid, tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**), 2,6-dimethylbenzoic acid, tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-dimethylbenzoic acid)copper(II) (**93**) and 4-ethylbenzoic acid, tetrakis(μ_2-4-ethylbenzoato)bis(4-ethylbenzoic acid)copper(II) (**94**),[12] were thus also prepared in a similar way [$CuCO_3.Cu(OH_2)$/MgO in refluxing toluene], crystallised from DCM and the structures determined by X-ray crystallography to determine which of the *o-* (**90**) or *p-*toluic acid (**91**) copper salts display a typical structure.

3.1.3.2.1 Tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (92), Tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (94), Tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-di-methylbenzoic acid)copper(II) (93)

Tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**), tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (**94**), tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-di-methylbenzoic acid)copper(II) (**93**), crystallized in the triclinic space group P-1 with Z=2 for **92** and Z=1 for **94** and **93**. The molecular symmetry is Ci, with the Belsky notation P-1, Z=1(-1):[(-1^7)][13,14] for **92**, P-1, Z=2(1):[(-1^8)][13,14] for **94** and **93** (**Figure 3.6**).

.
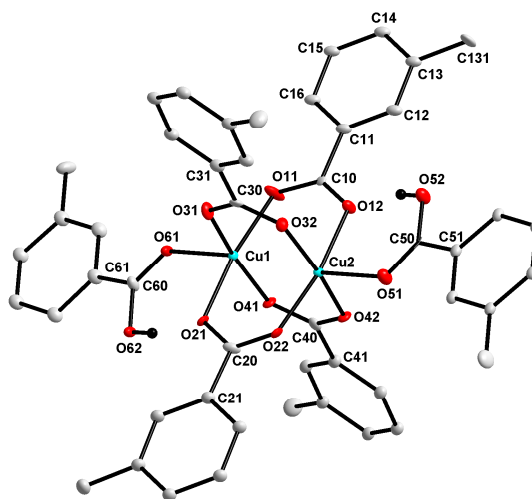
92
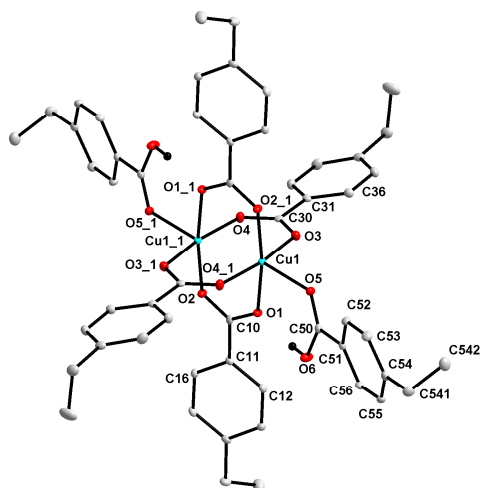
94
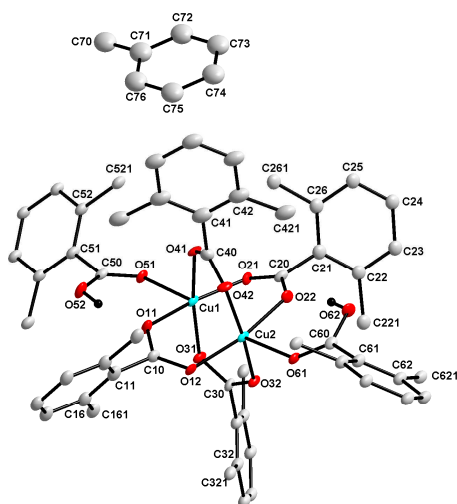
93

Figure 3.6: Views of tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**), tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (**94**) and tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-dimethylbenzoic acid)copper(II) (**93**) with the atoms numbered. Non-labelled atoms are symmetric equivalents. For the phenyl C-atoms, the first digit indicates ring number and the second digit the position of the atom in the ring.

The centro symmetric compounds each exhibits a cage-like structure. Four *m*-toluic acid, *p*-ethyl benzoic acid or 2,6-dimethylbenzoic acid anionic ligands form a cage around two Cu-atoms in a syn-syn configuration. Two more carboxylic acids are apically bonded to the Cu-atoms. The acid protons are hydrogen bonded to the cage carboxylate oxygens with O---H...O bond angles and O...O bonding distances as given in Table 6. Other geometric parameters are given in Tables 3, 4 and 5.

Table 3: Selected geometric parameters (Å ,$^\circ$) for tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**).

Atom Pair	Bond Distance	Atom Pair	Bond Distance
Cu1-O11	1.996(13)	C10-C11	1.508(18)
Cu2-O12	1.998(12)	C20-C21	1.48(2)
Cu1-O21	1.999(12)	C30-C31	1.479(16)
Cu2-O22	1.950(12)	C40-C41	1.483(17)
Cu1-O31	1.953(11)	C50-C51	1.486(15)
Cu2-O32	1.962(10)	C60-C61	1.47(2)
Cu1-O41	1.950(10)		
Cu2-O42	1.962(10)		
Cu2-O51	2.139(11)		
Cu1-O61	2.143(10)		

Table 4: Selected geometric parameters (Å ,°) for tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (**94**).

Atom Pair	Bond Distance	Atom Pair	Bond Distance
Cu1-O1	2.0040(16)	Cu1-Cu1^i	2.6047(5)
Cu1-O2	1.9593(16)	C10-C11	1.488(3)
Cu1-O3	1.9498(15)	C30-C31	1.501(3)
Cu1-O4	1.9501(16)	C50-C51	1.479(3)
Cu1-O5	2.1761(15)		

Symetry codes: (i) –x+1, -y+1, -z+1

Table 5: Selected geometric parameters (Å,°) for tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-di-methylbenzoic acid)copper(II) (**93**).

Atom Pair	Bond Distance	Atom Pair	Bond Distance
Cu1-O11	1.963(4)	C10-C11	1.468(6)
Cu2-O12	1.962(4)	C20-C21	1.457(6)
Cu1-O21	1.963(4)	C30-C31	1.493(7)
Cu2-O22	1.997(4)	C40-C41	1.467(7)
Cu1-O31	1.940(4)	C50-C51	1.494(6)
Cu2-O32	1.945(4)	C60-C61	1.475(6)
Cu1-O41	1.938(4)		
Cu2-O42	1.944(4)		
Cu1-O51	2.167(4)		
Cu2-O61	2.172(4)		

Tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**) forms a puckered pseudo-hexagonal close packed layer in the (h 0 0) plane as indicated in **Figure 3.7**, whereas tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (**94**) forms a puckered pseudo-hexagonal close packed layer in the (0 0 h) plane and tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-di-methylbenzoic acid)copper(II) (**93**) a packing layer. Soft inter-molecular C…H contacts were 2.693-2.873 Å, 2.720-2.813 Å and 2.371-2.887 Å for **92**, **94** and **93**, respectively.
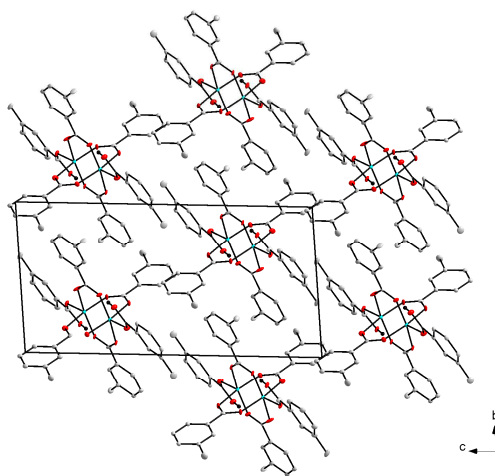
92
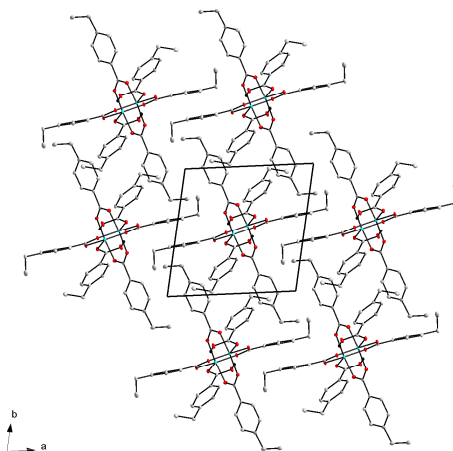
94
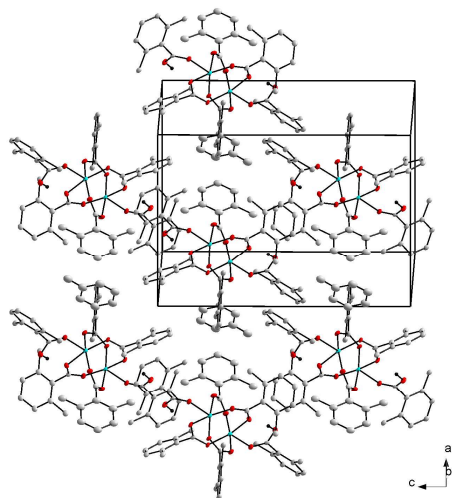
93

Figure 3.7: Packing patterns of tetrakis(μ_2-3-methylbenzoato)bis(3-methylbenzoic acid)copper(II) (**92**), tetrakis(μ_2-4-ethylbenzoato)bis(4-ethyl benzoic acid)copper(II) (**94**) and tetrakis(μ_2-2,6-dimethylbenzoato)bis(2,6-di-methylbenzoic acid)copper(II) (**93**).

When the Van der Waals radii of copper (2.32 Å) and known metallic Cu---Cu bond lengths (*ca.* 2.55 Å) are compared to the Cu---Cu separation in these structures (2.578 – 2.605 Å), one would expect the presence of weak orbital interaction. The average Cu---O bond lengths of the cage carboxylates vary between 1.956 – 1.971 Å. Each Cu atom is displaced from the basal plane of the four caged carboxylates, towards the apical O atom.

The paddlewheel seems to be the typical structure for Cu(II) benzoates as was also reported before,[10] whereas the structure of the copper salt of *p*-toluic acid (**91**) is atypical.

Table 6: Comparison of selected geometrical parameters.

	(90)	(92)	(93)	(94)
Cu…Cu	2.578 Å	2.588 Å	2.597 Å	2.605 Å
Cu-O$_{(Cage\ Carboxilate)}$ average values	1.961 Å	1.971 Å	1.956 Å	1.965 Å
Cu-O$_{(apical)}$ average values	2.162 Å	2.141 Å	2.169 Å	2.176 Å
Cu displacement from basal plane	0.171 Å	0.180 Å	0.202 Å	0.179 Å
O---H---O		167.52°, 168.38°	166.47°, 166.32°	166.79°, 166.79°
O---O		2.679 Å	2.625 – 2.639 Å	2.645 Å

3.1.3.3 Differential scanning calorimetry (DSC) and Thermal Gravimetric Analysis (TGA)

With the structures of the starting copper salts of *o*- and *p*-toluic acids (**90**) and (**91**) unambiguously determined, attention was subsequently turned towards determining the temperatures at which chemical or physical changes to the copper salts are being effected. The thermal decomposition of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) and tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (**91**) were thus investigated by DSC and TGA.

3.1.3.3.1 DSC analysis of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (90)

The first heating cycle (cycle 1) of the DSC scan of the copper salt of *o*-toluic acid, (**90**), (**Figure 3.8**) showed an endothermic transition at 164.37 °C. Upon cooling no typical accompanying crystallisation peak within 10 degrees below 164 °C was, however, observed. It could therefore be concluded that the transition at 164.37 °C represents a chemical change, rather than a phase transition.

The newly formed product from this reaction subsequently crystallised at *ca.* 78 °C upon cooling (cycle 1). From cycles 2 – 4 it is evident that the newly formed compound has a melting point of 81.6 °C and is thermally stable up to 220 °C.
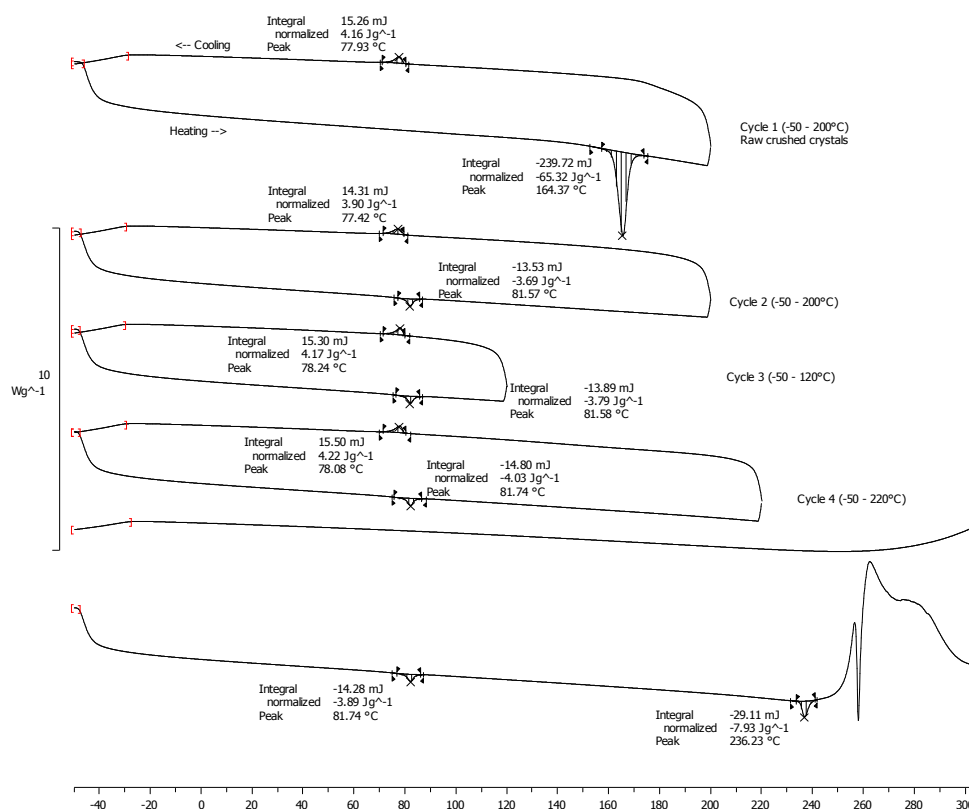
Figure 3.8: DSC scan of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) at 10 °C min^{-1}.

Since it was established that the transition at 164 °C represents a chemical rather than a physical change, the amorphous product from this transformation was subjected to a number of analytical techniques in order to determine the structure of the first intermediate in the reaction sequence. Despite the fact that both the ^{1}H NMR spectra of the starting material [tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**)] and this first intermediate product (Plates **1a** and **5a** respectively) showed poor resolution due to the paramagnetic nature of copper(II) and Cu(m), the differences in the aromatic region of these spectra [peaks between δ 7 and 8 ppm found in the spectrum of (**90**) were absent in the ^{1}H NMR spectrum of the product] clearly indicated that a chemical reaction took place during the heating cycle

of the DSC investigation. Likewise, IR-analyses confirmed tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**) and the product formed during DSC to be different as the absorption band at 1685.09 cm^{-1}, which corresponds to a carbonyl group of a carboxylic acid or carboxylate, in the IR spectrum of (**90**) [IR (Plate **1**)] was absent in the IR spectrum of the product [IR (Plate **6**)], whereas absorption bands at 1614.70, 1592.73 and 1568.13 cm^{-1} in **90** shifted slightly in the product to 1606.70, 1584.59 and 1559.63 cm^{-1}. The IR spectrum of the product furthermore didn't correspond to the IR spectra of either *o*-toluic acid (**78**) [IR (Plate **7**)] or 3-methylphenyl 2-methylbenzoate (**85**) [IR (Plate **5**)]. During the fifth cycle in **Figure 3.8**, an endothermic transition at 236 °C signals the onset of complete thermal decomposition.

While all analytical techniques utilised up to this point in the investigation clearly indicated the structure of the product from the DSC experiment to be different to that of (**90**), no conclusion as to the real structure of this product could be made. It was therefore decided to investigate the possibility that the unknown compound might be either one of two extreme possibilities, *i.e.* *o*-toluic acid itself or the ester, 3-methylphenyl 2-methylbenzoate (**85**). The DSC behaviour of these two possible compounds was therefore determined.

DSC analysis of pure *o*-toluic acid (**78**) under N$_2$ atmosphere confirmed the melting point of *o*-toluic acid (**78**) to be at 104 °C and recrystallisation to take place between 91 and 94 °C (**Figure 3.9**). No decomposition was observed during cycles 1 and 2 as the normalised enthalpies of melting (-159.20 J g^{-1} for cycle 1 and -156.82 J g^{-1} for cycle 2) as well as those for crystallisation (155.65 J g^{-1} for cycle 1 and 154.57 J g^{-1}

for cycle 2) are, within experimental error, in the same range. In cycle 4 complete

decomposition of the acid (**78**), starting after 140°C, reached a maximum at 234 °C

(**Figure 3.9**). This means that, if *o*-toluic acid (**78**) had been formed during the

pyrolysis of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**),

no recrystallization of it would have been observed after heating up to 164 °C (where

the new product formed) due to the decomposition thereof. This was proven by a

DSC analysis of a mixture of *o*-toluic acid (**78**) and tetrakis(μ_2-2-

methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) (**Figure 3.10**).
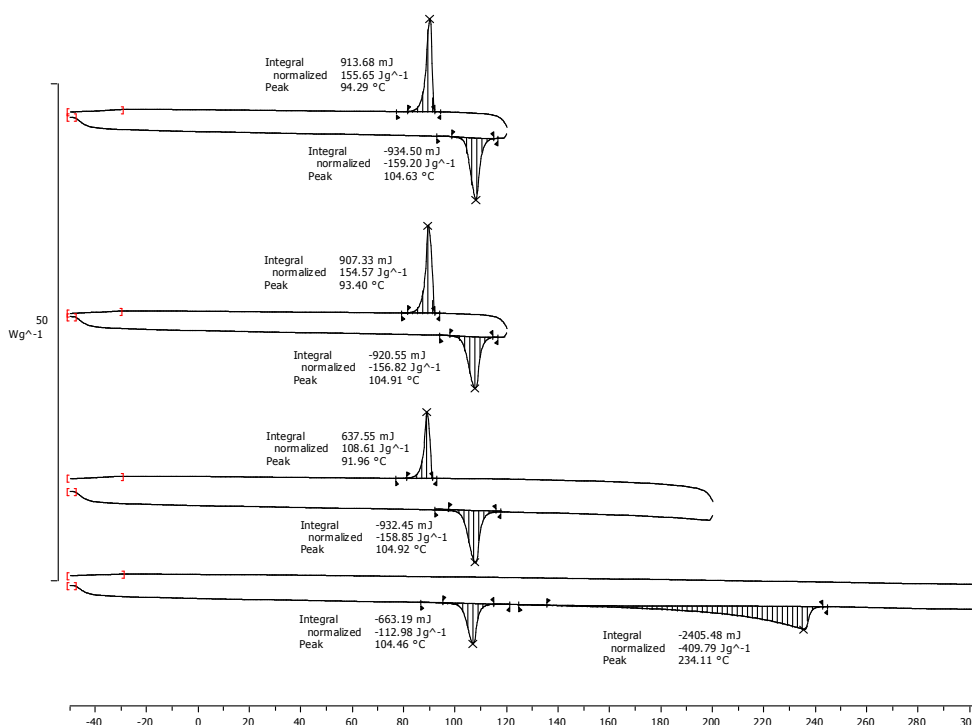
Figure 3.9: DSC scan of *o*-toluic acid (**78**) at 10°C min^{-1}.

When a mixture of *o*-toluic acid (**78**) and tetrakis(μ_2-2-methylbenzoato)bis(2-

methylbenzoic acid)copper (II) (**90**) mixture (5:95 m/m) were subjected to DSC

analysis under the same conditions, *o*-toluic acid (**78**) melted at 104.6 °C and

tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**) showed the same change at 164.37 °C as in the first DSC experiment. Upon cooling, only one product which crystallised at 78 °C similarly to that observed during the DSC analysis of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**), was observed. Further cycles were identical to those of **90 (Figure 3.10)**.
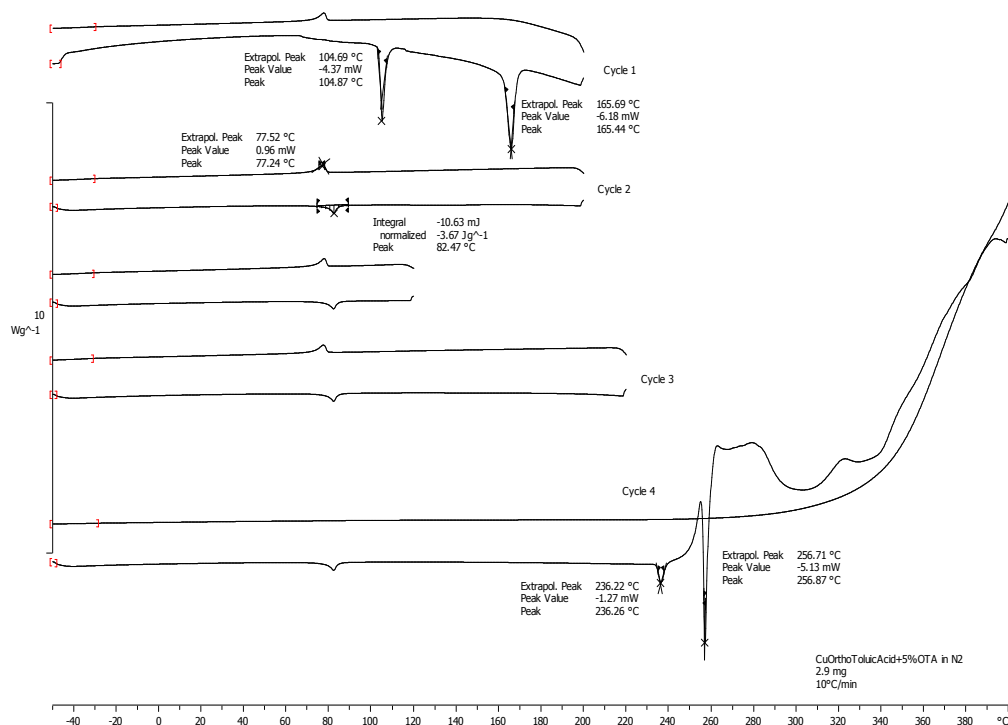
Figure 3.10: DSC scan of a mixture of *o*-toluic acid (**78**) and tetrakis(μ_2-2 methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**) at 10 °C min^{-1}.

DSC analysis of 3-methylphenyl 2-methylbenzoate (**85**) only revealed its boiling point at *ca.* 260 °C, whereas no other phase transitions or chemical changes could be observed within the investigated temperature range (**Figure 3.11**).

Sample: OrthoToluicAcidEster, 2.3700 mg

Wg^{-1} 5

Extrapol. Peak   262.37 °C
Peak Value   -6.02 mW
Peak   260.98 °C

-40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
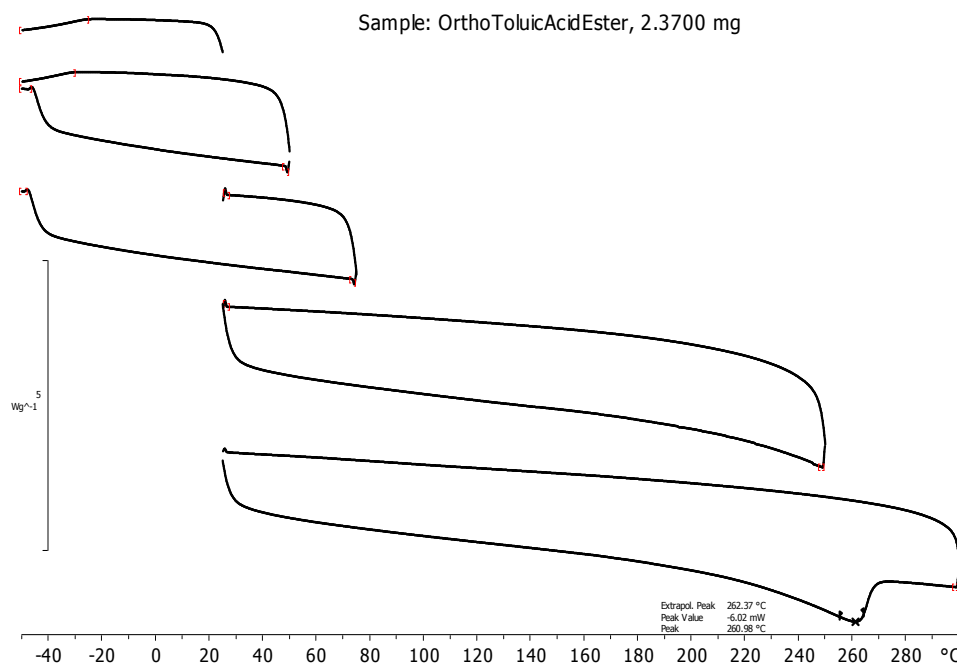
Figure 3.11: DSC analysis of 3-methylphenyl 2-methylbenzoate (**85**)

When copper(0) was added to this ester, the boiling point was elevated to *ca.* 300 ℃

as can be seen from **Figure 3.12**.

Sample: OrthoToluicAcidEsterWithCopper, 13.9800 mg

Wg^{-1} 2

Onset 240 °C

-40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
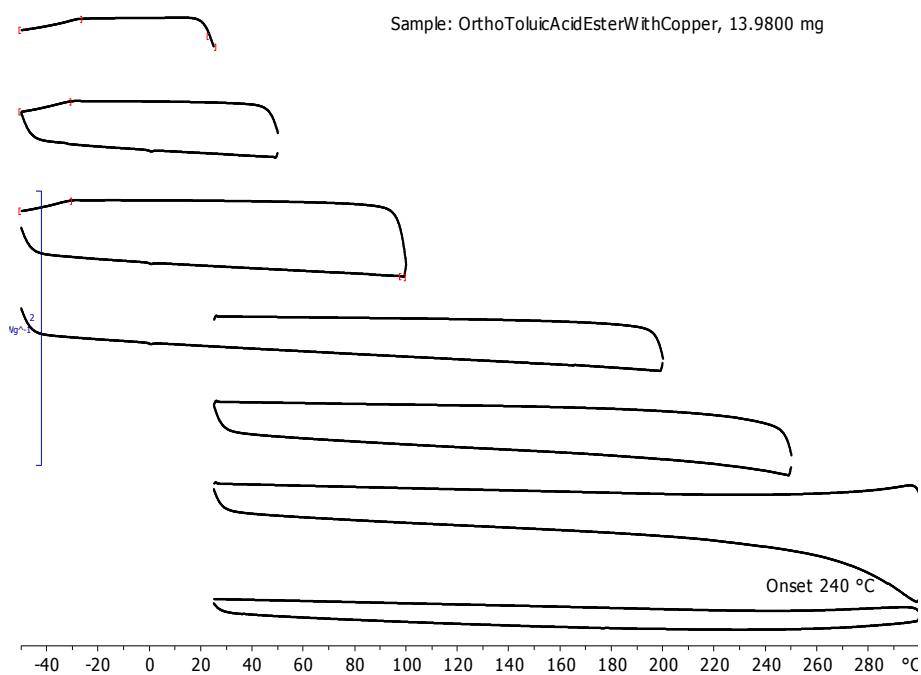
Figure 3.12: DSC analysis of 3-methylphenyl 2-methylbenzoate (**85**) with copper(0)

added.

3.1.3.3.2 TGA of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (90)

With the structure of the 164 $^{\circ}$C transformation product of (**90**) still not elucidated, it was decided to submit tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) to TGA analysis and analyse the gaseous products to be liberated, if any, by mass spectrometry. For compound (**90**), a 25 % mass loss between 140° and 200 °C with the midpoint at 164.6 °C as shown in the TGA scan in **Figure 3.13** corresponded to the chemical transition observed in cycle 1 of **Figure 3.8**. For this process the mass spectrometer detected a rise in water concentration[a]. While no water seemed to be present in the X-ray structure of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**), it has been documented that water present in crystals might be overlooked if no proper site placement is possible,[15] so this transition in the DSC cycle which was assigned to a chemical transformation might also be just a physical crystal structure change.

The solid amorphous product from the 164 $^{\circ}$C transition underwent decomposition with a 2 % mass loss at 217 °C (18 Da) and a 18.5 % mass loss at 249 °C, the latter corresponding to the loss of both carbon dioxide (44 Da) and water (18 Da), followed by further decomposition with the loss of CO, CO_2 and toluene above 250 °C in agreement with the corresponding decomposition peaks seen in cycle 5 of **Figure 3.8**. Since water, CO_2 and CO losses are not very diagnostic and could occur from any part of the molecule or a fragment of it, like liberated toluic acid, the investigation was subsequently turned to the decomposition of *o*-toluic acid.
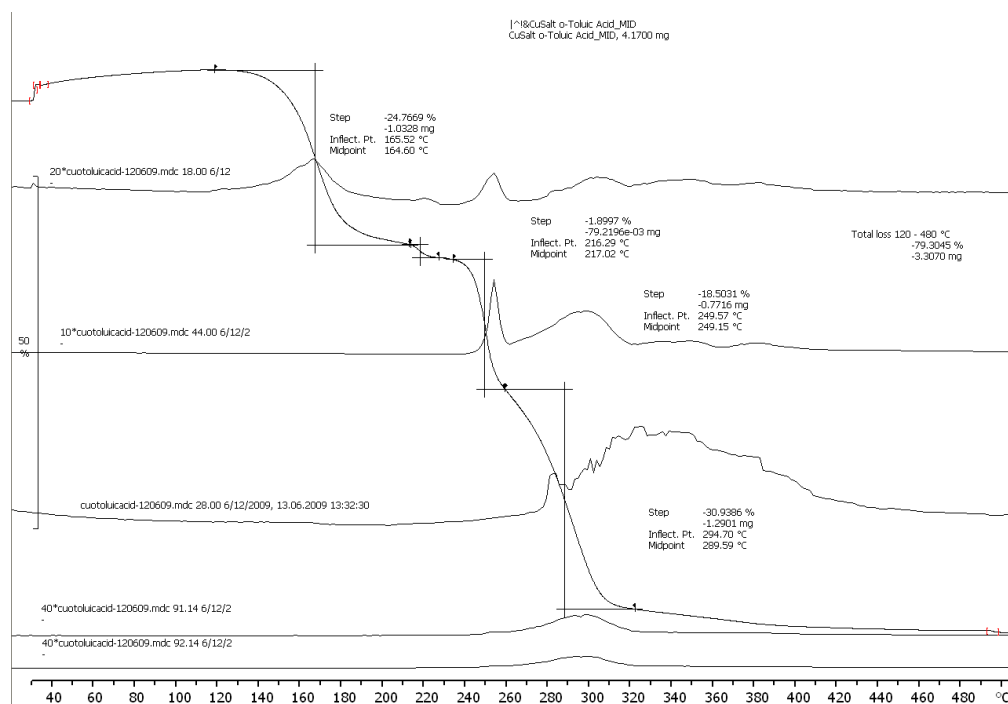
Figure 3.13: TGA scan of the copper salt of *o*-toluic acid (**90**).

For pure *o*-toluic acid (**78**), the major mass loss in the TGA scan, for which the mass spectrometer detected a rise in water concentration[a], occurred between 100 and 200 °C with the midpoint at 180 °C. Small amounts of carbon dioxide were detected at 300 °C, whereas traces of toluene were detected at 240 °C (**Figure 3.14**). This fact, taken in conjunction with the slow decomposition of *o*-toluic acid over the temperature range 160 to 240 °C observed in the DSC scan (**Figure 3.9**), rendered any conclusion as to the cause of the mass loss in the TGA of (**90**) at 249 °C and thus the structure of subsequent products and transformations, highly risky. It was therefore decided to submit solid amorphous product from the 164 °C transition of (**90**) to microscopic observation and MS analysis.

[a]It is important to note that the mass spectrometer connected to the TGA scanned only for fragments with masses of 18, 44, 28, 91 and 92 Da. The water lost might be water of crystallization.
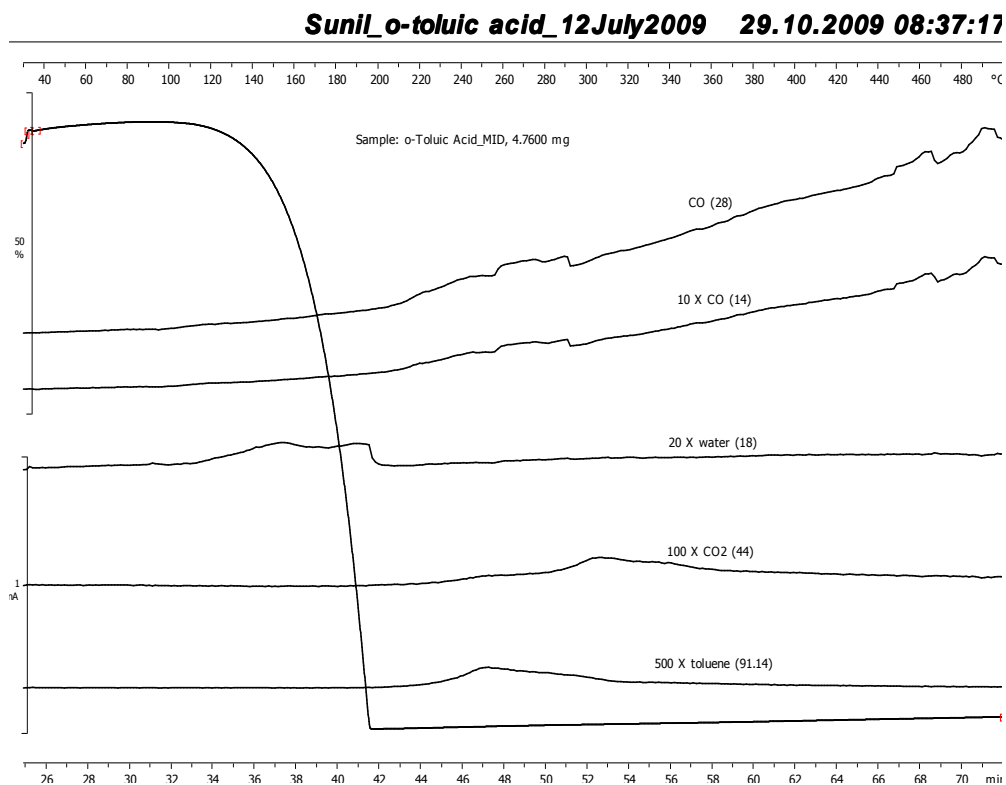
Figure 3.14: TGA scan of *o*-toluic acid (**78**).

3.1.3.4 Microscopic observations

Microscopic observations of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**) (**Figure 3.15**) confirmed decomposition of the sample between 250 $^{\circ}$C and 315 $^{\circ}$C, but no other evidence as to what happened on a molecular level could be obtained.
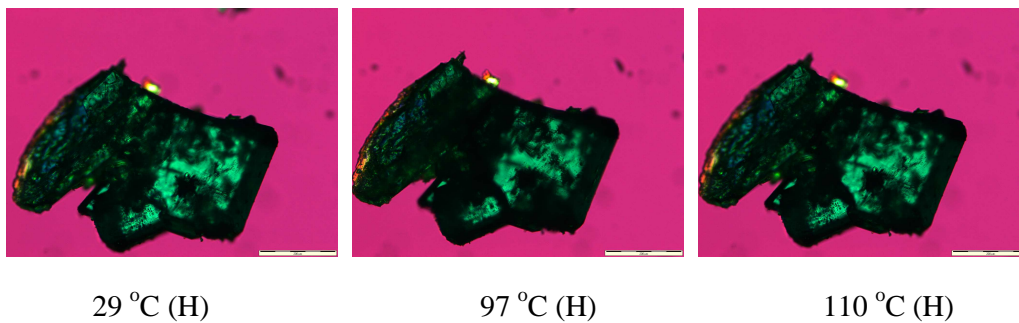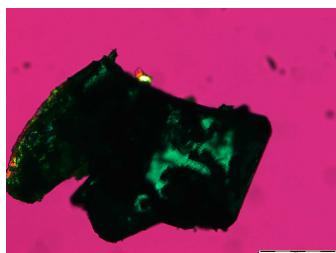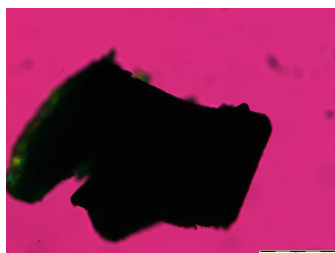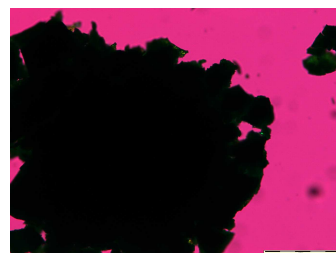
| 29 $^{\circ}$C (H) | 97 $^{\circ}$C (H) | 110 $^{\circ}$C (H) |

133 °C (H)

163 °C (H)

163 °C (HP)

180 °C (H)

70 °C (C)

50 °C (C)

30 °C (C)

28 °C (C)

75 °C (H)

105 °C (H)

160 °C (H)

190 °C (H)

200 °C (H)

210 °C (H)

220 °C (H)

235 °C (H)   250 °C (H)   275 °C (H)

285 °C (H)   300 °C (H)

(H = Heating up, C = Cooling down, HP = Heating up and pressing with a needle).
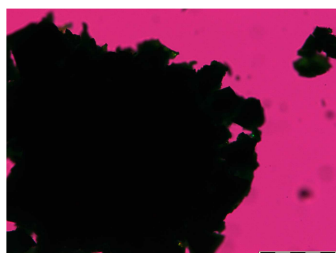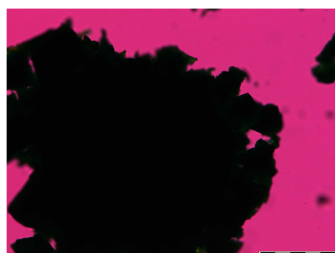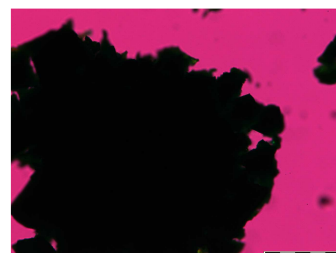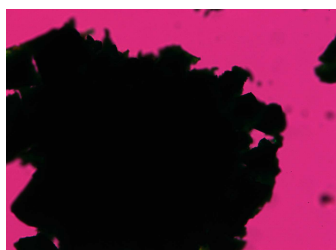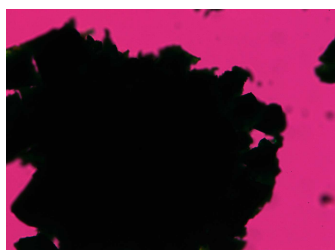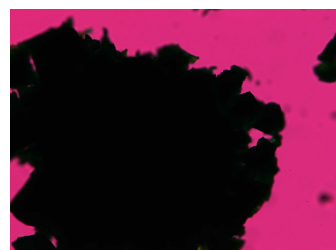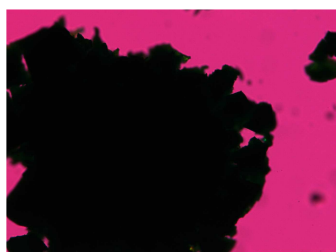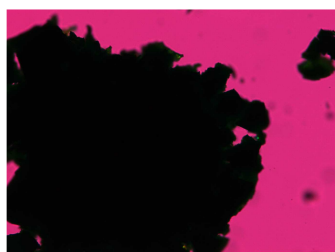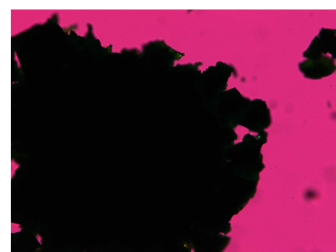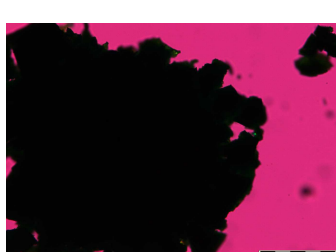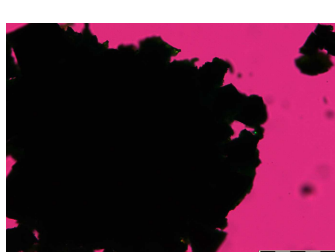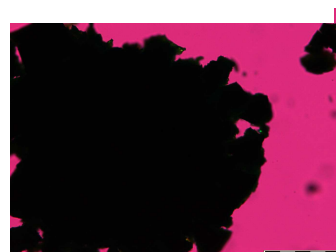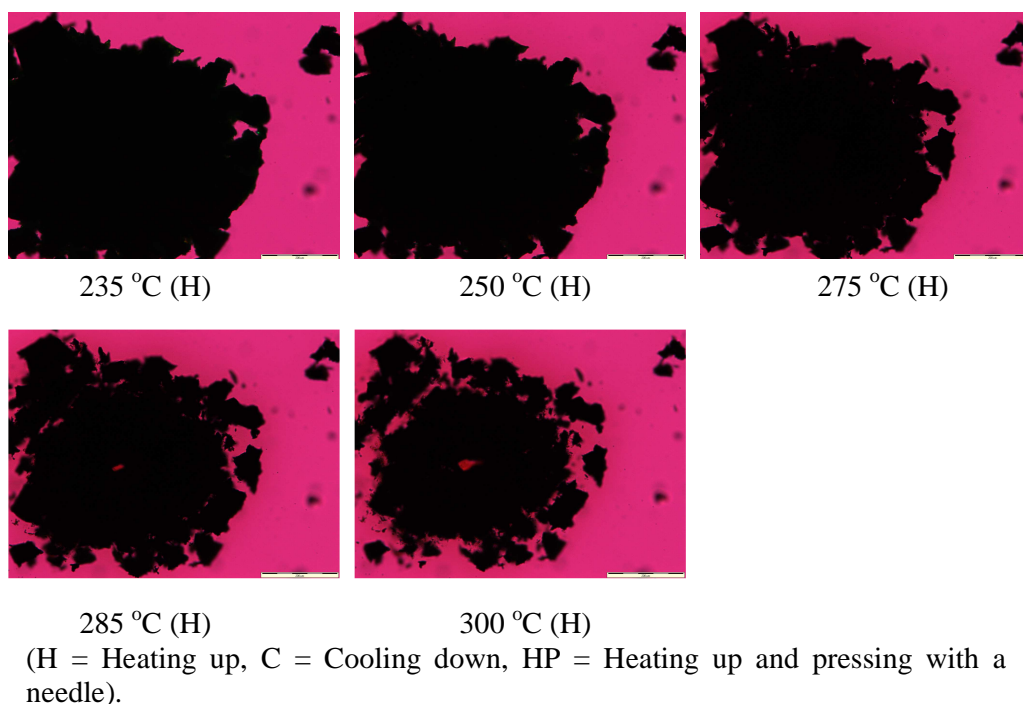
Figure 3.15: Microscopic observation of the copper salt of *o*-toluic acid (**90**).

3.1.3.5 MALDI-TOF analysis

MALDI-TOF MS analysis (in the negative mode) of the product formed after the second DSC cycle (after heating to 164 °C) on tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper (II) (**90**) indicated the presence of *o*-toluic acid (**78**) ([**71**]⁻, *m/z* 136.052) as well as a copper adduct[1] of 3-methylphenyl 2-methylbenzoate (**85**) ([**109**]⁻, *m/z* 288.645) (**Scheme 3.8**). Furthermore, a peak corresponding to the copper salt of 2-methyl-6-{[(2-methylphenyl)carbonyl]oxy}benzoic acid (**98**) ([**108**]⁻, *m/z* 332.011) was also observed. These intermediates correspond to those postulated in previous mechanisms (**Schemes 3.3 and 3.4**). Furthermore, a peak corresponding to 6-methylsalicylic acid (**100**) ([**110**]⁻, *m/z* 151.878), which can be explained by the hydrolysis of **98**, was observed. In addition to this, a peak which might be ascribed to

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[1] The formation of metallic copper from Cu(I) under similar conditions has been described by Buijs *et al.*[9]

a copper complex of toluene (**101**) was also detected at *m/z* 245.178 and is corroborated by the observed release of toluene during the TGA of tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) (**Figure 3.13**).
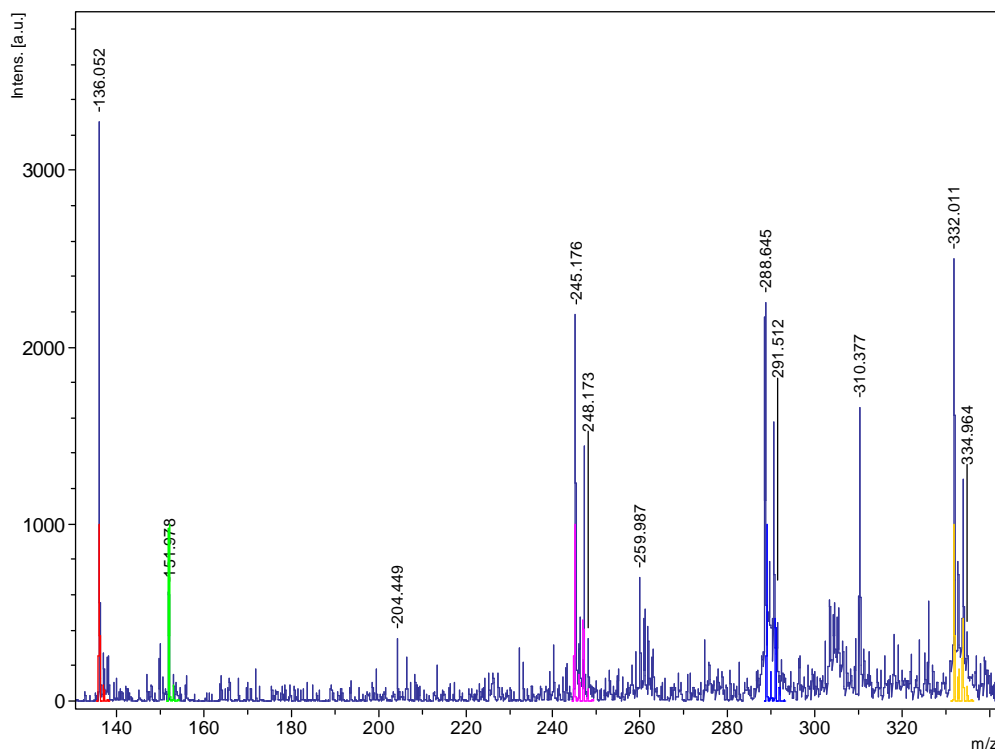
Figure 3.16: MALDI-TOF mass spectrum of the product(s) formed from tetrakis(μ_2-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II) (**90**) at 164 °C during the second DSC cycle. The coloured inserts are simulated isotope patterns corresponding to the observed peaks.

3.1.3.6 Conclusion

Considerable progress towards the elucidation of the mechanism associated with the conversion of *o*-toluic acid (**78**) to *m*-cresol (**10**) in the presence of Cu(II), together with the temperatures where these changes occur, has been made. Based on the evidence obtained in previous and the current studies, the mechanism in **Scheme 3.8**

can be proposed for this important conversion. The major chemical change at 164 °C observed in both the DSC and TGA (**Figures 3.8 and 3.14**) can be ascribed to water loss (probably from water of crystallisation), although it coming from a chemical transformation cannot be excluded at this stage. The loss of water might be accompanied by a rearrangement of tetrakis(μ_2-2-methylbenzoato)bis(2-methyl-benzoic acid)copper(II) (**90**) to intermediate (**96**) together with the cleavage of the latter into *o*-toluic acid (**78**) and copper(I) 2-methyl-6-{[(2-methyl-phenyl)carbonyl]oxy}benzoic acid[2] (**98**).

 Scheme 3.8

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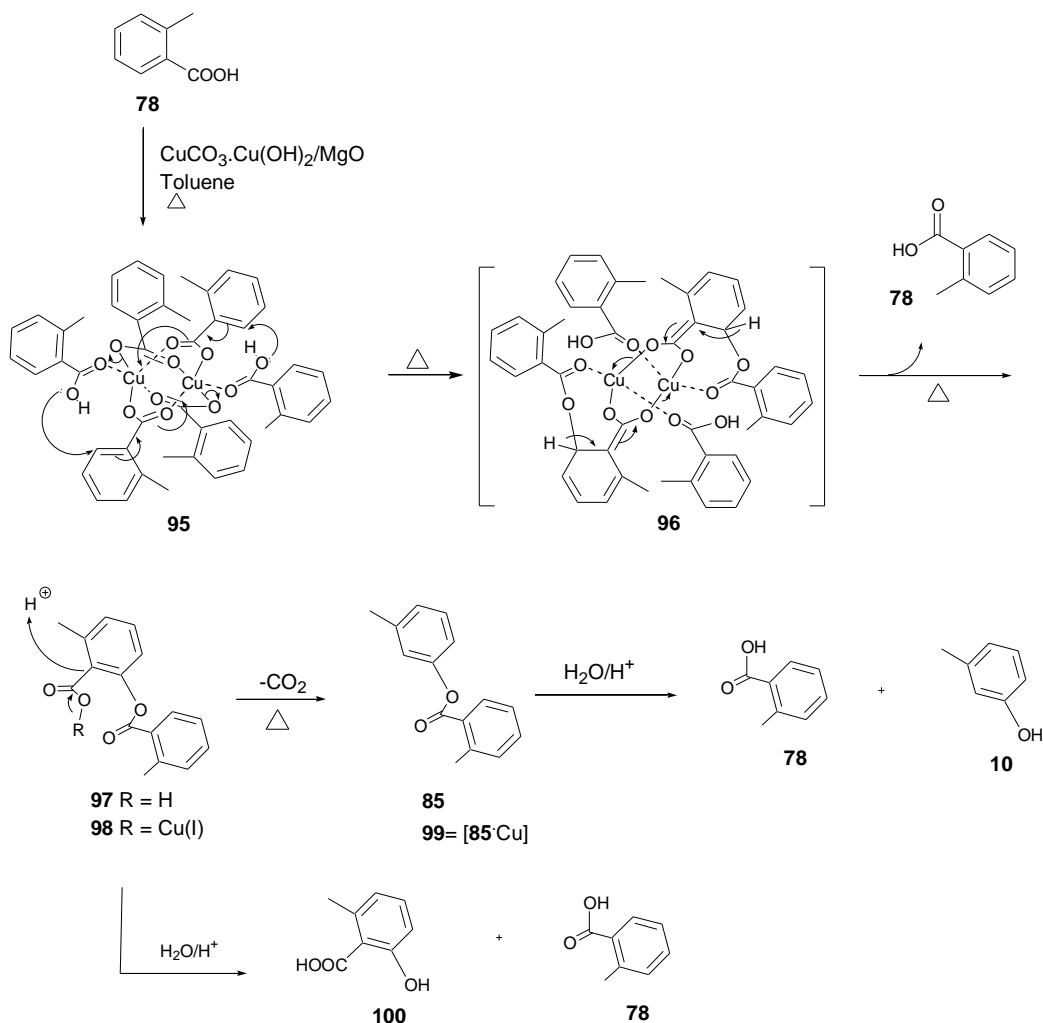
[2] The formation of Cu(I) has been reported before.[8]

The DSC amorphous product might thus be **96**, whereas the formed **78** will decompose at temperatures above 160 $^{\circ}$C. Ester **97** will be a liquid in the temperature range investigated, whereas its boiling point would most probably coincide with the onset of decomposition of the analyte. Decarboxylation has been proven to occur at 249.5 $^{\circ}$C, whereas the mass loss from 258 $^{\circ}$C observed in the TGA might correspond to *o*-toluic acid (**78**) and 3-methylphenyl 2-methylbenzoate (**85**) reaching its boiling points (258 $^{\circ}$C and *ca.* 260 $^{\circ}$C, respectively). Hydrolysis of **85** would finally yield *o*-toluic acid (**78**) and *m*-cresol (**10**).

3.1.3.7 DSC analysis of tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (91)

According to DSC analysis, the copper salt of *p*-toluic acid (**91**) melts between 176°C and 180 $^{\circ}$C as is evident from cycles 1 and 2 of its DSC scan (**Figure 3.17**). During each subsequent crystallisation (between 170 $^{\circ}$C and 173 $^{\circ}$C) the enthalpy of crystallisation is less in absolute value than its preceding enthalpy of melting ($|\Delta H_{cryst}$ = 93.4 J g$^{-1}| < |\Delta H_{melt}$ = -113.4 J g$^{-1}|$ in cycle 1 and $(|\Delta H_{cryst}$ = 57.8 J g$^{-1}| < |\Delta H_{melt}$ = -88.2 J g$^{-1}|$ in cycle 2). This clearly indicates decomposition (starting at *ca.* 160°C) during melting of the copper salt (**91**). This decomposition reaches a maximum at 221 $^{\circ}$C (cycle 4). Upon heating during cycle 5 a second decomposition is observed above 280 $^{\circ}$C.
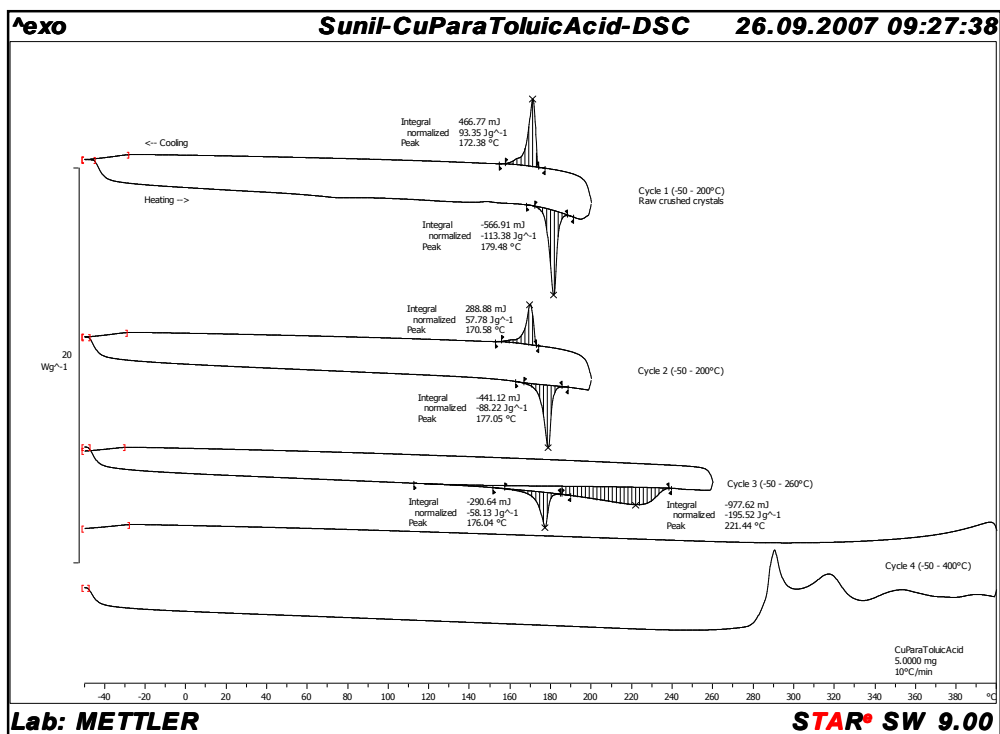
Figure 3.17: DSC scan of tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) **(91)** at 10 °C min^{-1}.

DSC analysis of pure *p*-toluic acid (**79**) under N$_2$ atmosphere confirmed the melting point to be between 180 and 180.58 °C and recrystallisation at *ca*. 177.13 – 177.16 °C. The normalised enthalpies point towards decomposition as was also encountered in the case of the copper salt of *p*-toluic acid **(91)**. In cycle 3 decomposition of the acid, started at *ca*. 150 °C reaching a maximum at 242.16 °C (**Figure 3.18**).
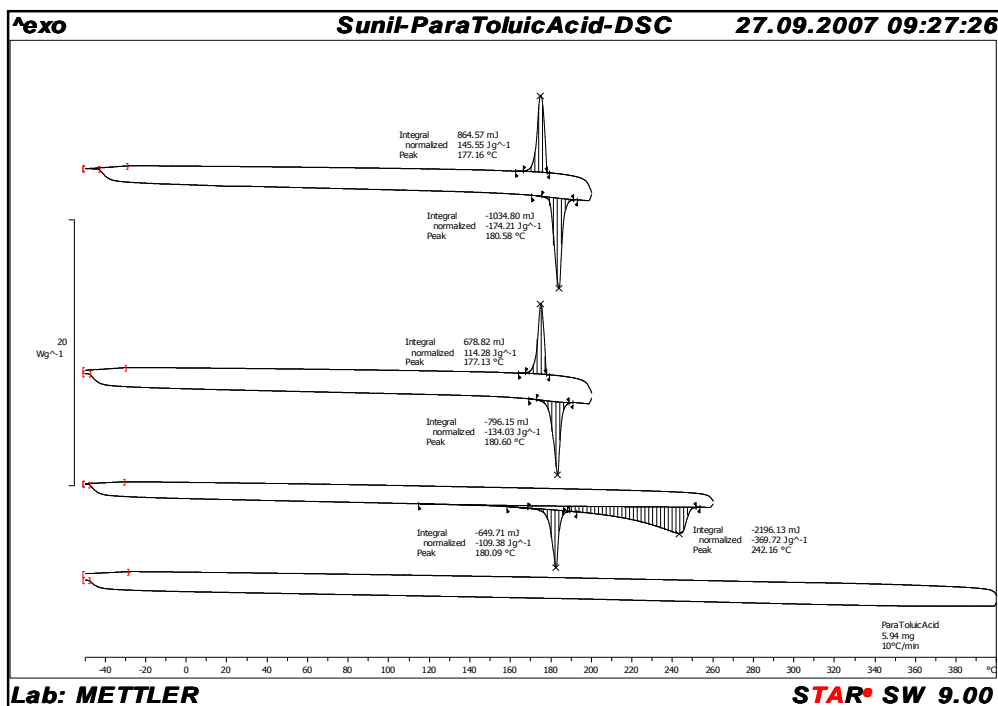
Figure 3.18: DSC scan of *p*-toluic acid (**79**) at 10 °C min^{-1}.

The irreversible transformation seen at 164 $^{\circ}$C in the DSC scan of the copper salt of *o*-toluic acid is thus not present in the salt of *p*-toluic acid, while it seems that decomposition starts somewhat earlier in the case of the *para*-isomer.

3.1.3.8 TGA of tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) (91)

In contrast to the TGA of the copper salt of *o*-toluic acid where stepwise mass losses could clearly be identified, a continuous mass loss of 90 % was observed between 160° and 260 °C for the copper salt of *p*-toluic acid (**91**) (**Figure 3.19**). This corresponds to preliminary decomposition/irreversable change during melting seen in the DSC scan of the copper salt of *p*-toluic acid (**91**) in cycle 3 of **Figure 3.18** and indicates that clear step-changes in the composition of (**91**) to the product(s) would be very difficult to identify.
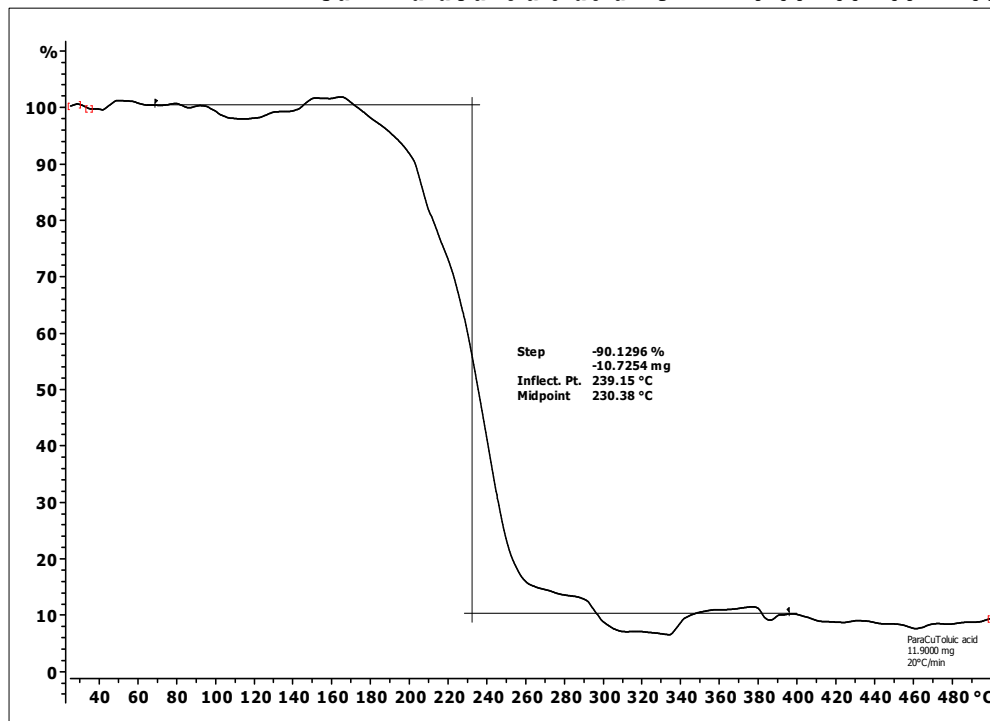
Figure 3.19: TGA scan of tetrakis(μ_2-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II) **(91).**

3.1.3.9 Microscopic observation of the copper salt of *p*-toluic acid (91)

Microscopic observations of copper salt of *p*-toluic acid (**91**) (**Figure 3.20**) confirmed that **full** decomposition of the sample occurred between 260 ^{o}C and 340 ^{o}C.
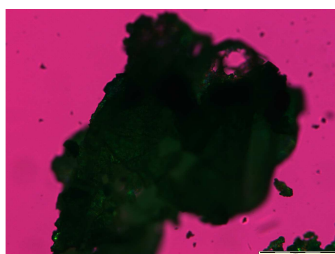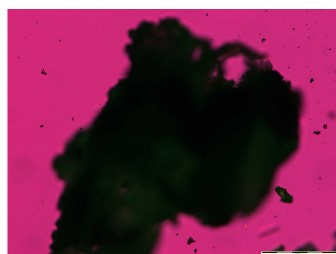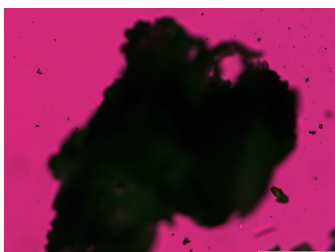

| 30 ^{o}C (H) | 70 ^{o}C (H) | 100 ^{o}C (H) |

140 °C (H)

160 °C (H)

170 °C (H)

200 °C (H)

210 °C (H)

210 °C (HP)

240 °C (H)

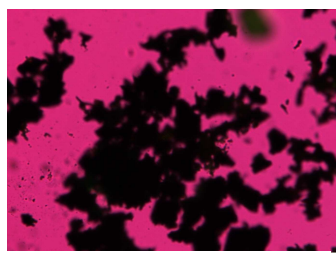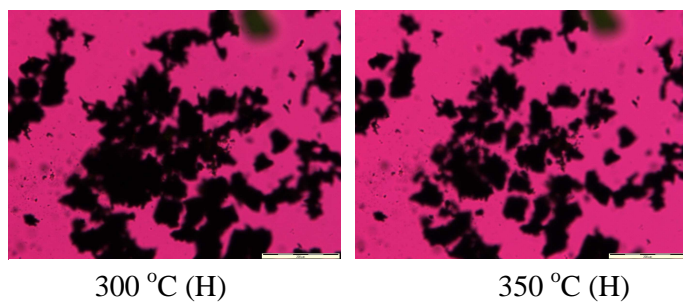140 °C (C)

80 °C (C)

27 °C (C)

240 °C (H)

280 °C (H)

300 °C (H)

350 °C (H)
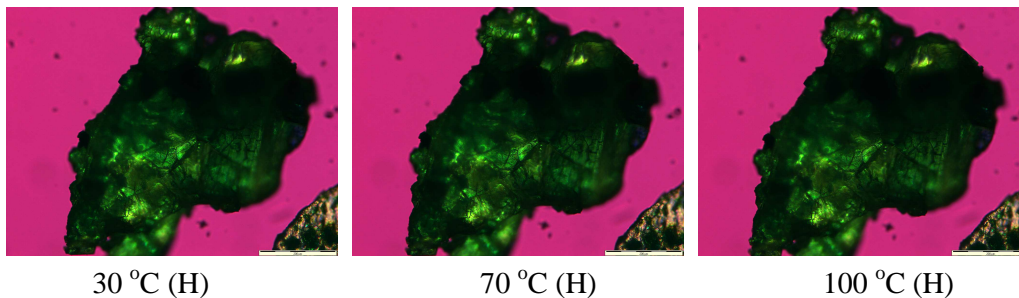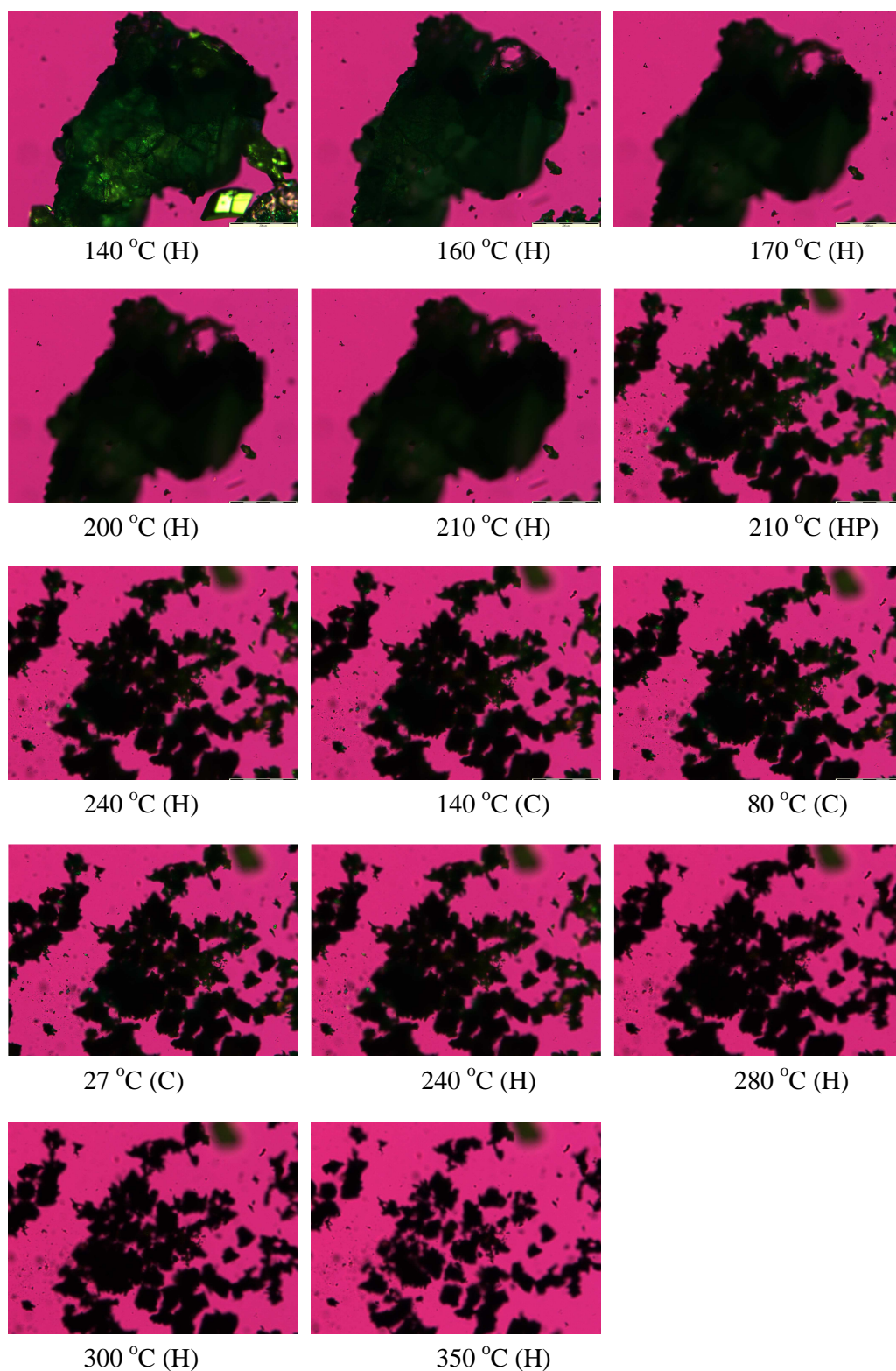
(H = Heating up, C = Cooling down, HP = Heating up and pressing with a needle).

Figure 3.20: Microscopic observation of the copper salt of *p*-toluic acid (**91**).

3.1.3.10 Conclusion

While it is clear that some differences in the temperatures of rearrangement of the copper salts of *o-* and *p*-toluic acids to the corresponding esters (**85**) and (**87**) respectively, do exist, no conclusion as to what happens at which temperature can be drawn from the data obtained for the *para*-acid, since the transformation of the copper salt of *p*-toluic acid (**91**) is to a large extent accompanied by its decomposition. Further work, like an MS investigation, might give the answer as to the mechanism of the conversion of *p*-toluic acid (**79**) into *m*-cresol (**10**).

3.2 References

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**Appendix 1
(NMR Spectrums)**

Appendix 2
(Photographs of crystals, DSC, TGA, X-Ray,
MS and IR spectrums)
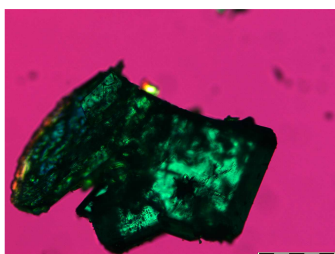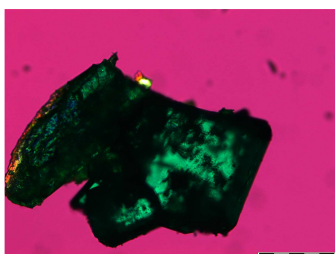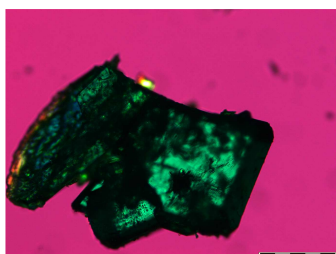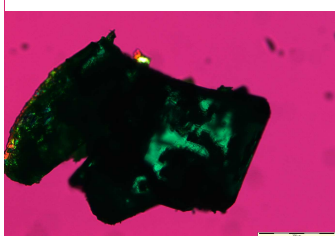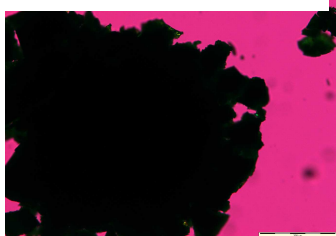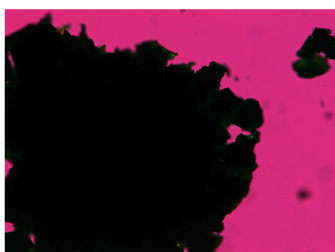
29 °C (H)   97 °C (H)   110 °C (H)

133 °C (H)   163 °C (H)   163 °C (HP)

180 °C (H)   70 °C (C)   50 °C (C)

30 °C (C)   28 °C (C)   75 °C (H)

105 °C (H)   160 °C (H)   190 °C (H)

200 °C (H)	210 °C (H)	220 °C (H)
235 °C (H)	250 °C (H)	275 °C (H)
285 °C (H)	300 °C (H)	
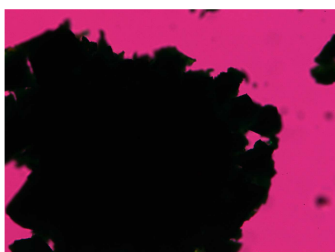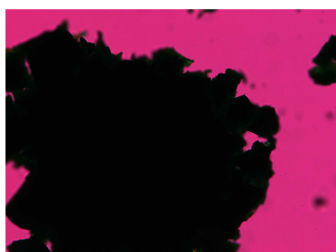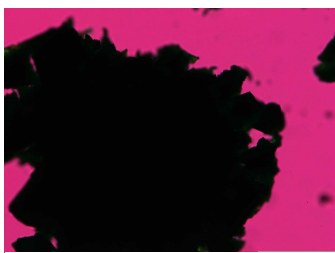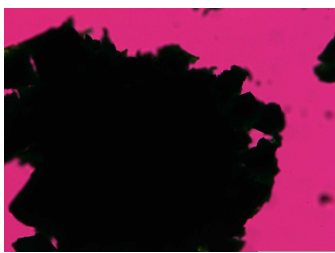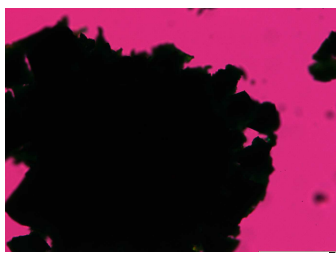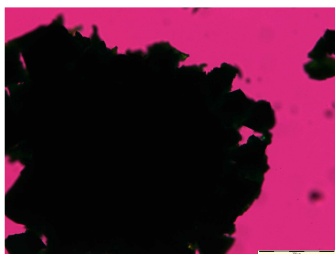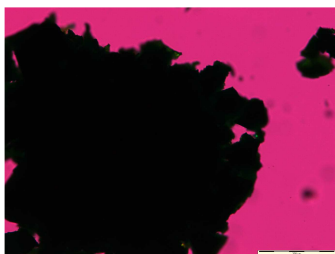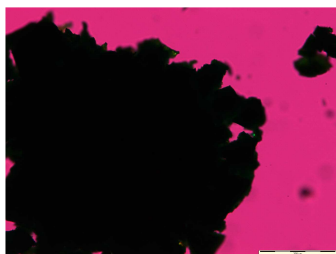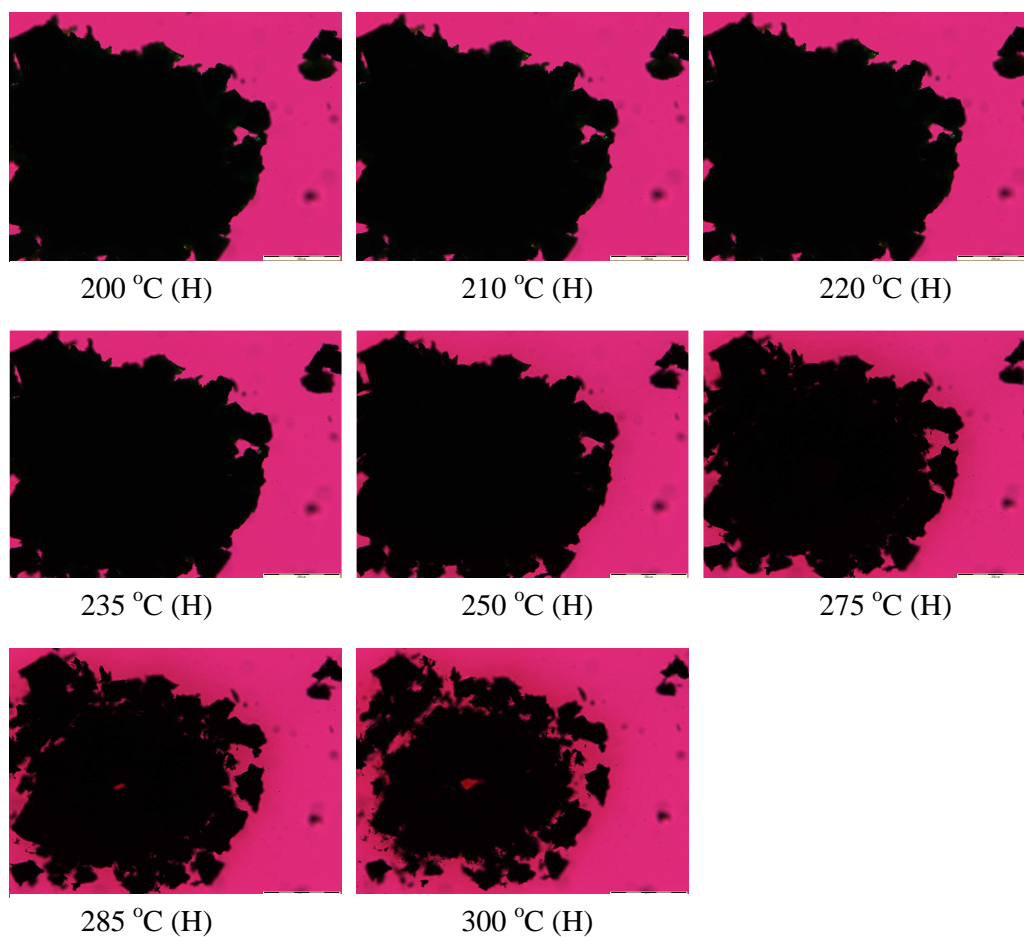
(H = Heating up, C = Cooling down, HP = Heating up and pressing with a needle).

Figure 2: Microscopic observation of *tetrakis(μ₂-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)* (**90**).
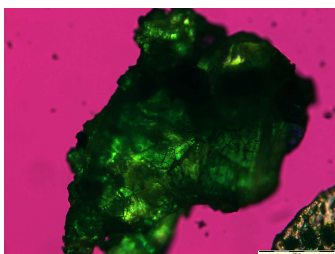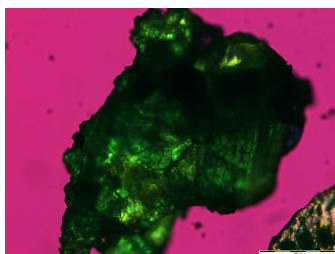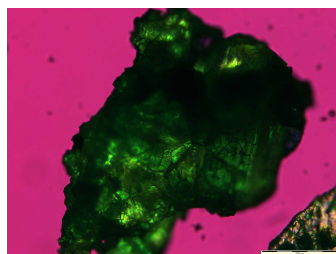
30 °C (H)	70 °C (H)	100 °C (H)
140 °C (H)	160 °C (H)	170 °C (H)
200 °C (H)	210 °C (H)	210 °C (HP)
240 °C (H)	140 °C (C)	80 °C (C)
27 °C (C)	240 °C (H)	280 °C (H)
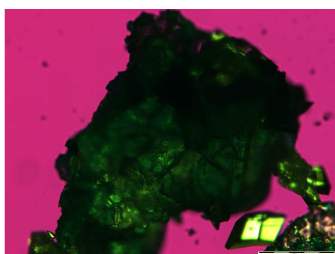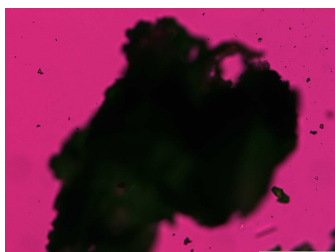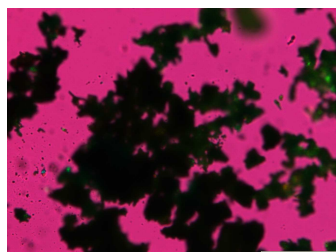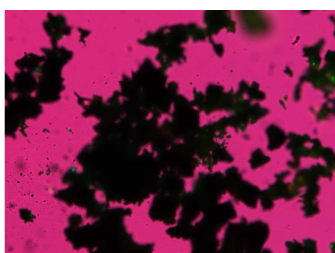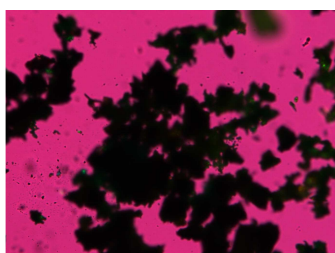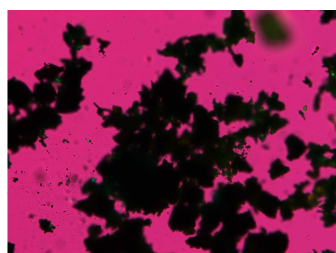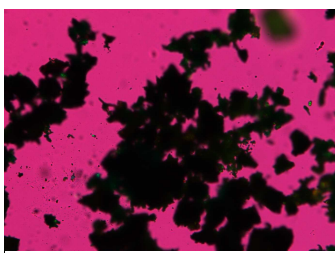
300 °C (H)	350 °C (H)

(H = Heating up, C = Cooling down, HP = Heating up and pressing with a needle).

Figure 3: Microscopic observation of *tetrakis(µ₂-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II)* (**91**).
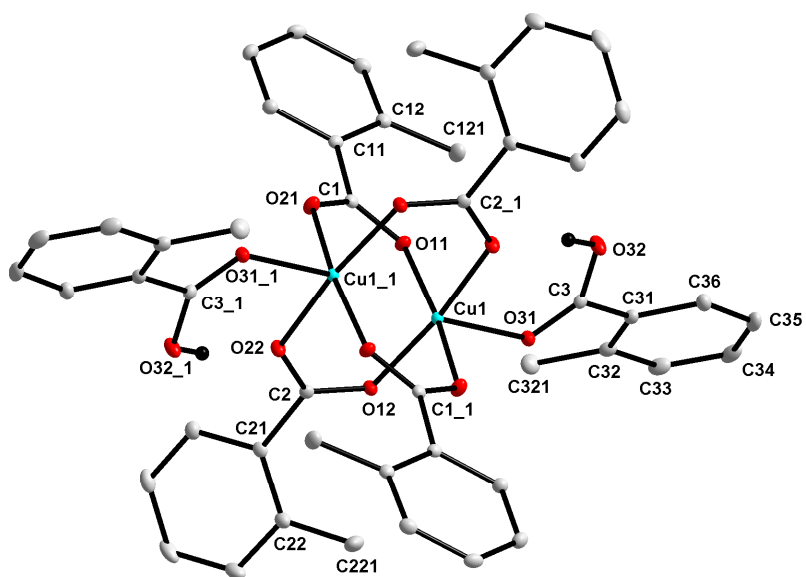
X-ray crystallography of *tetrakis(μ₂-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)* (**90**).

(**1**)
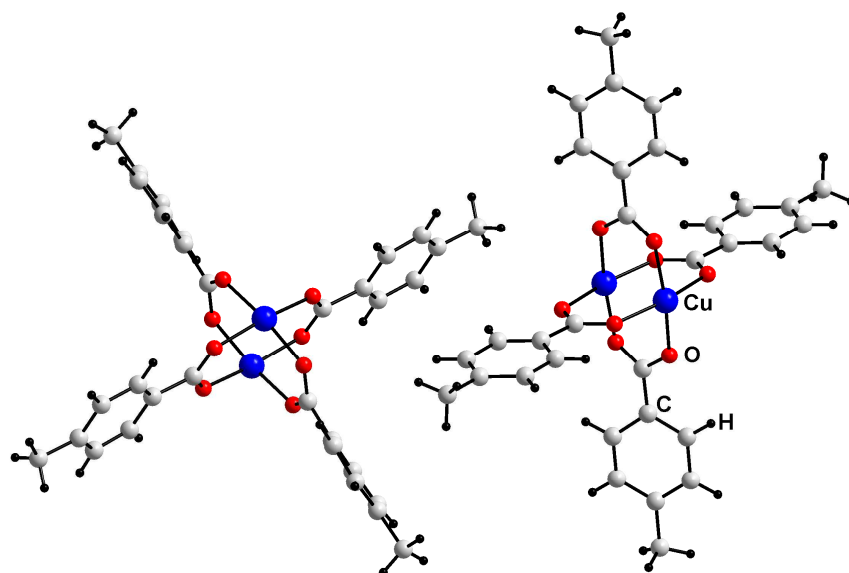
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(**91**).
(**2**)
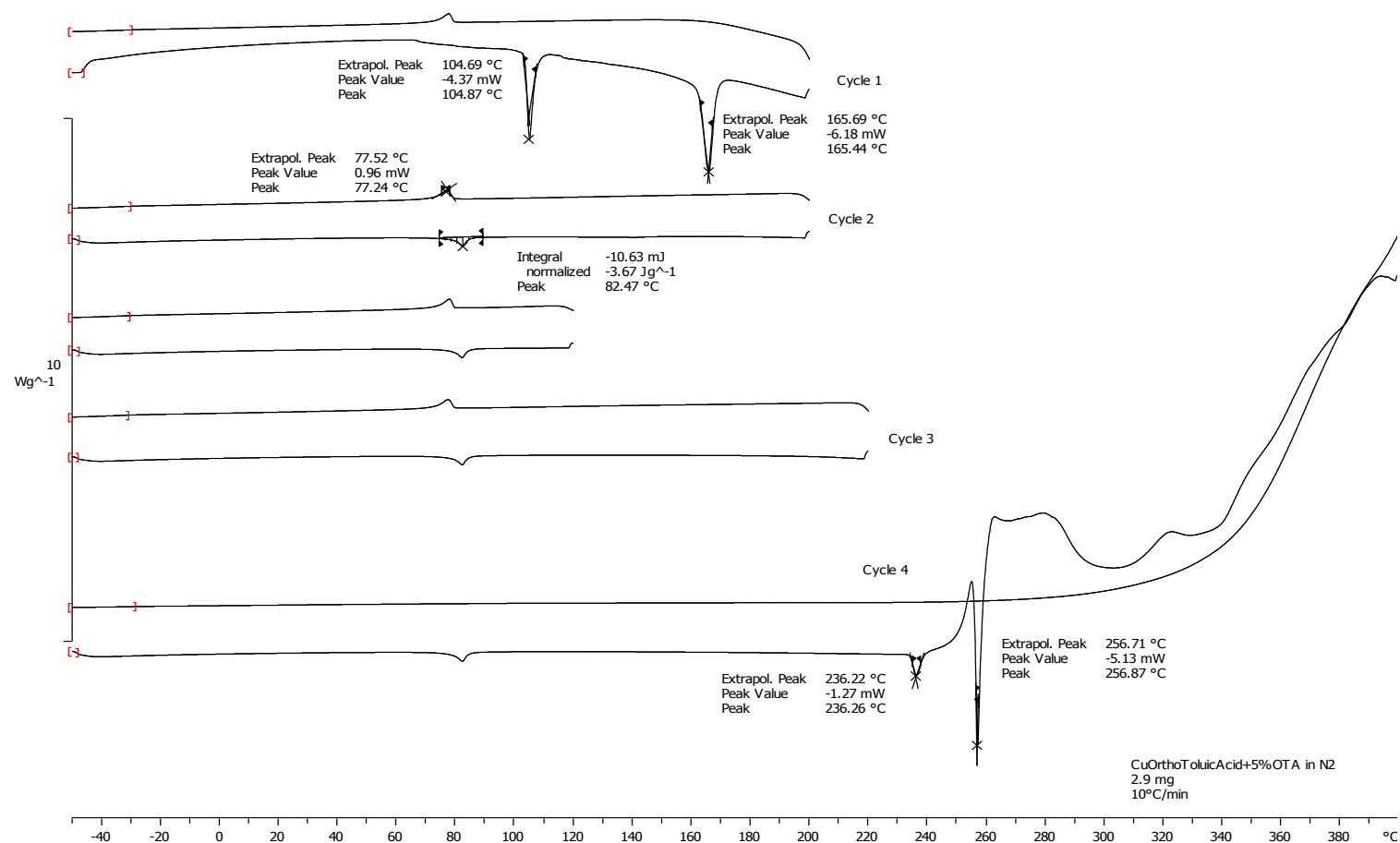
Figure 6: DSC scan of a mixture of *o*-toluic acid (**78**) and *tetrakis(μ₂-2 methylbenzoato)bis(2-methylbenzoic acid)copper (II)* (**90**) at 10 °C min⁻¹.

Sample: OrthoToluicAcidEster, 2.3700 mg

5
Wg^-1

Extrapol. Peak   262.37 °C
Peak Value   -6.02 mW
Peak   260.98 °C

-40   -20   0   20   40   60   80   100   120   140   160   180   200   220   240   260   280   °C
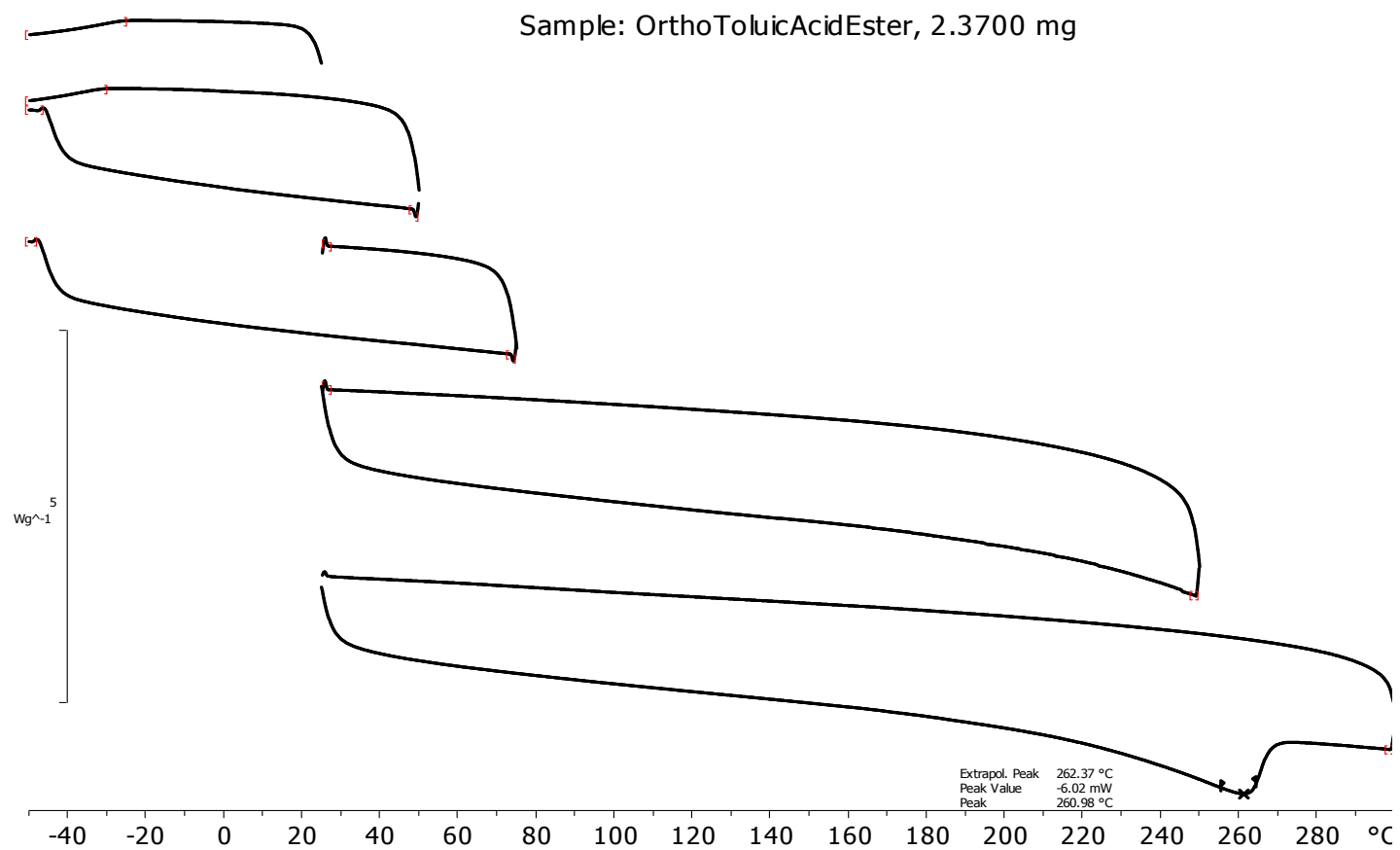
Figure 7: DSC scan of 3-methylphenyl 2-methylbenzoate (**85**).
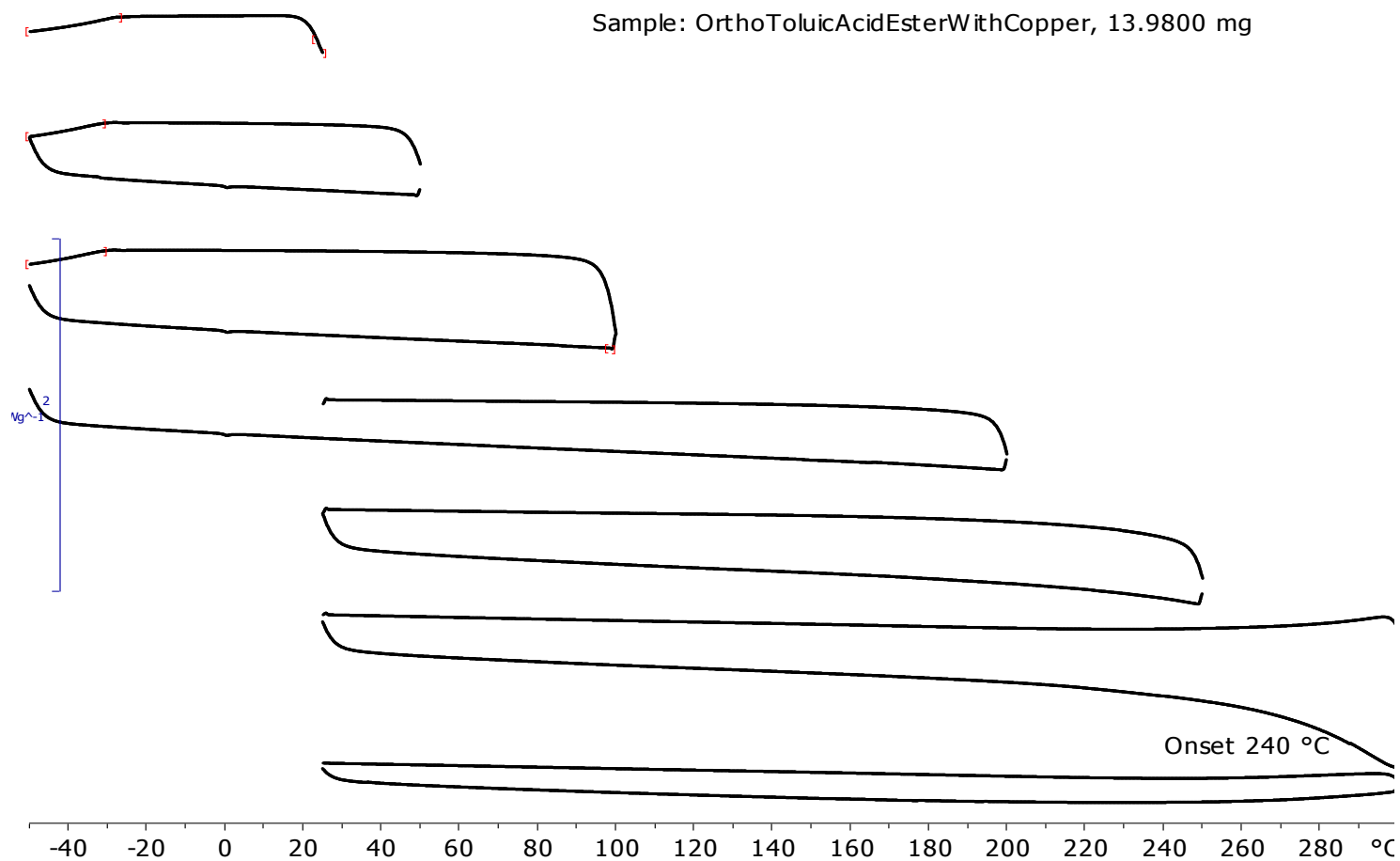
Figure 8: DSC scan of 3-methylphenyl 2-methylbenzoate (**85**) with copper (0) added.
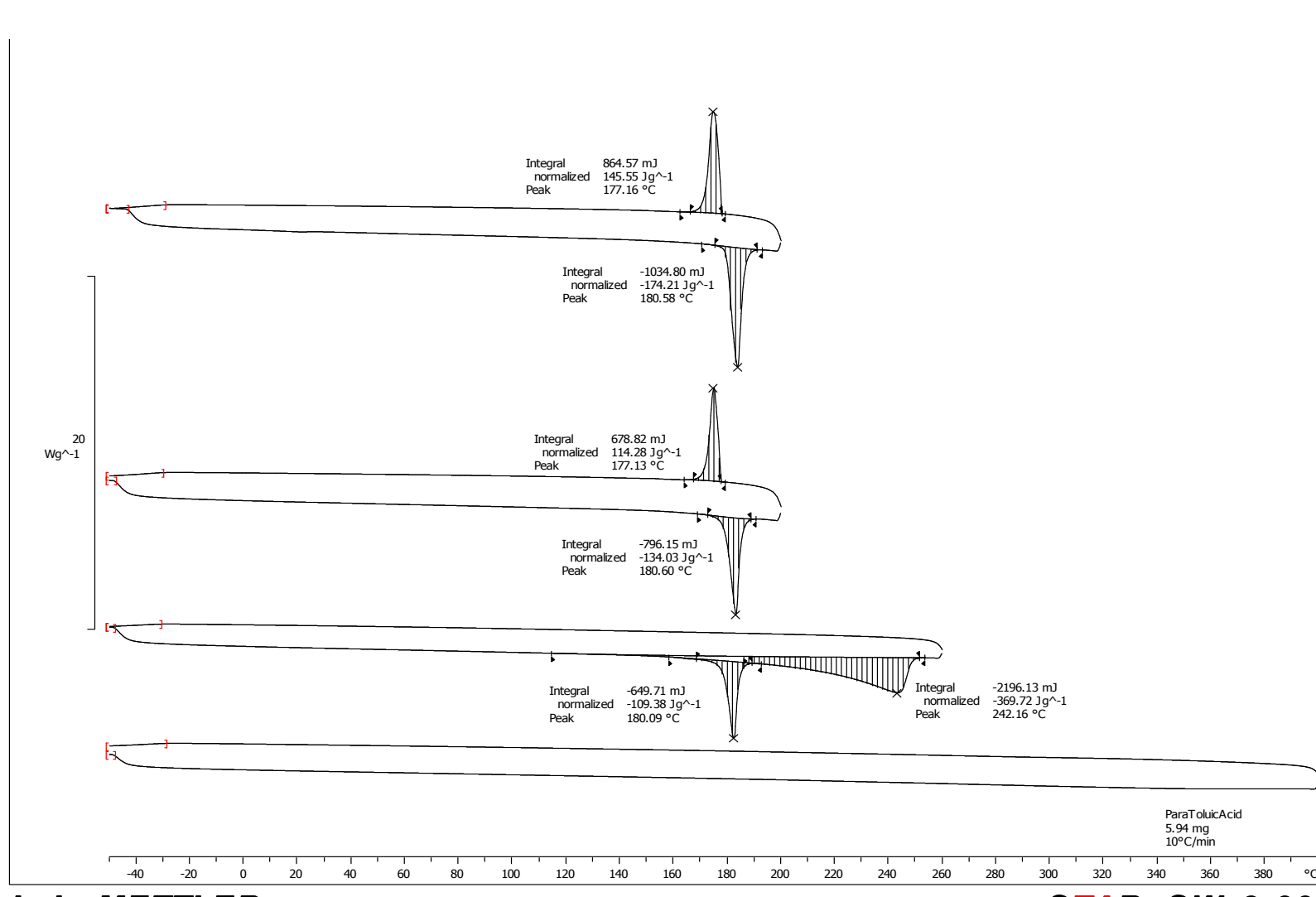
Figure 9: DSC scan of *p*-toluic acid (**79**) at 10 °C min⁻¹.
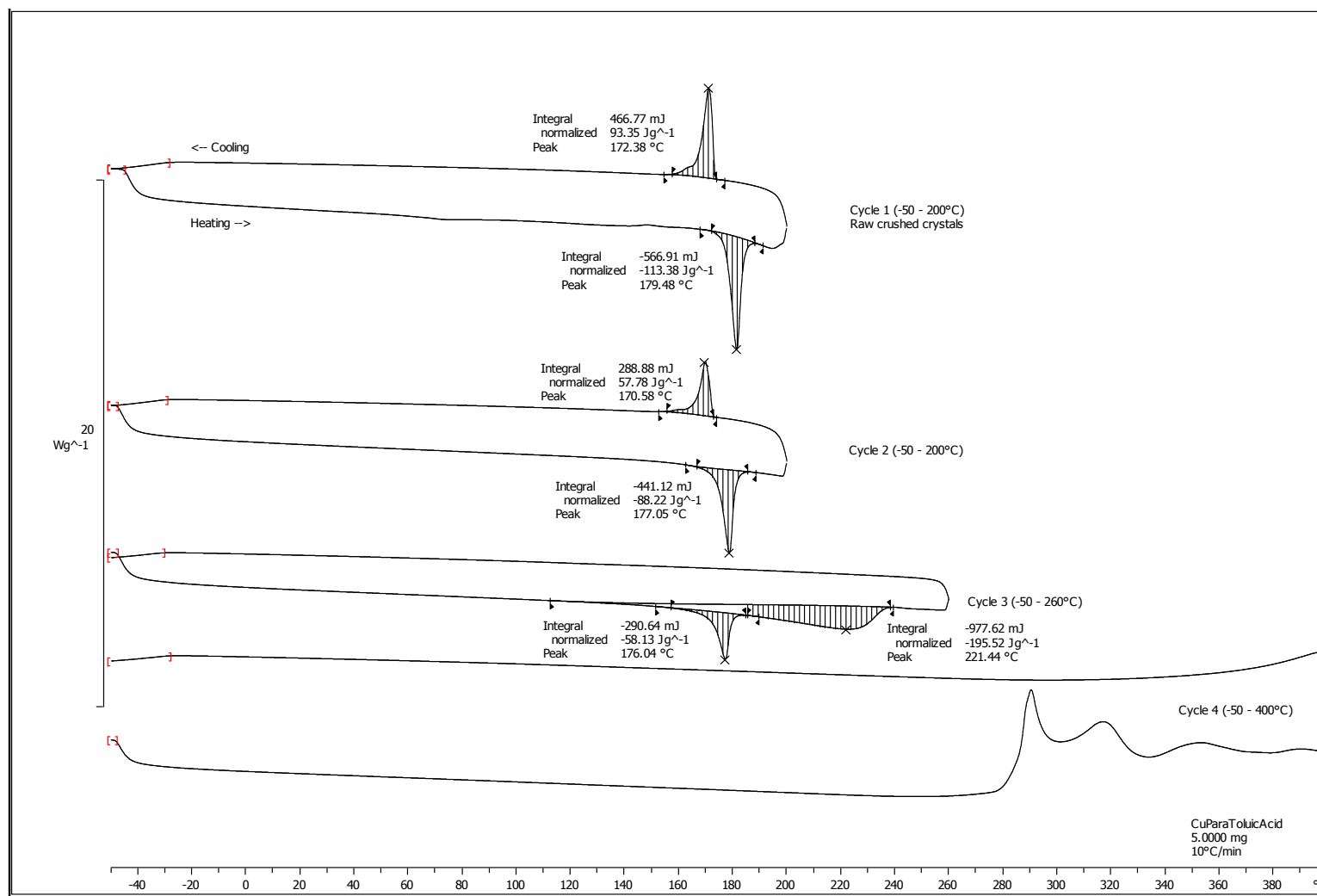
Figure 10: DSC scan of *tetrakis(μ₂-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II)* (**91**) at 10 °C
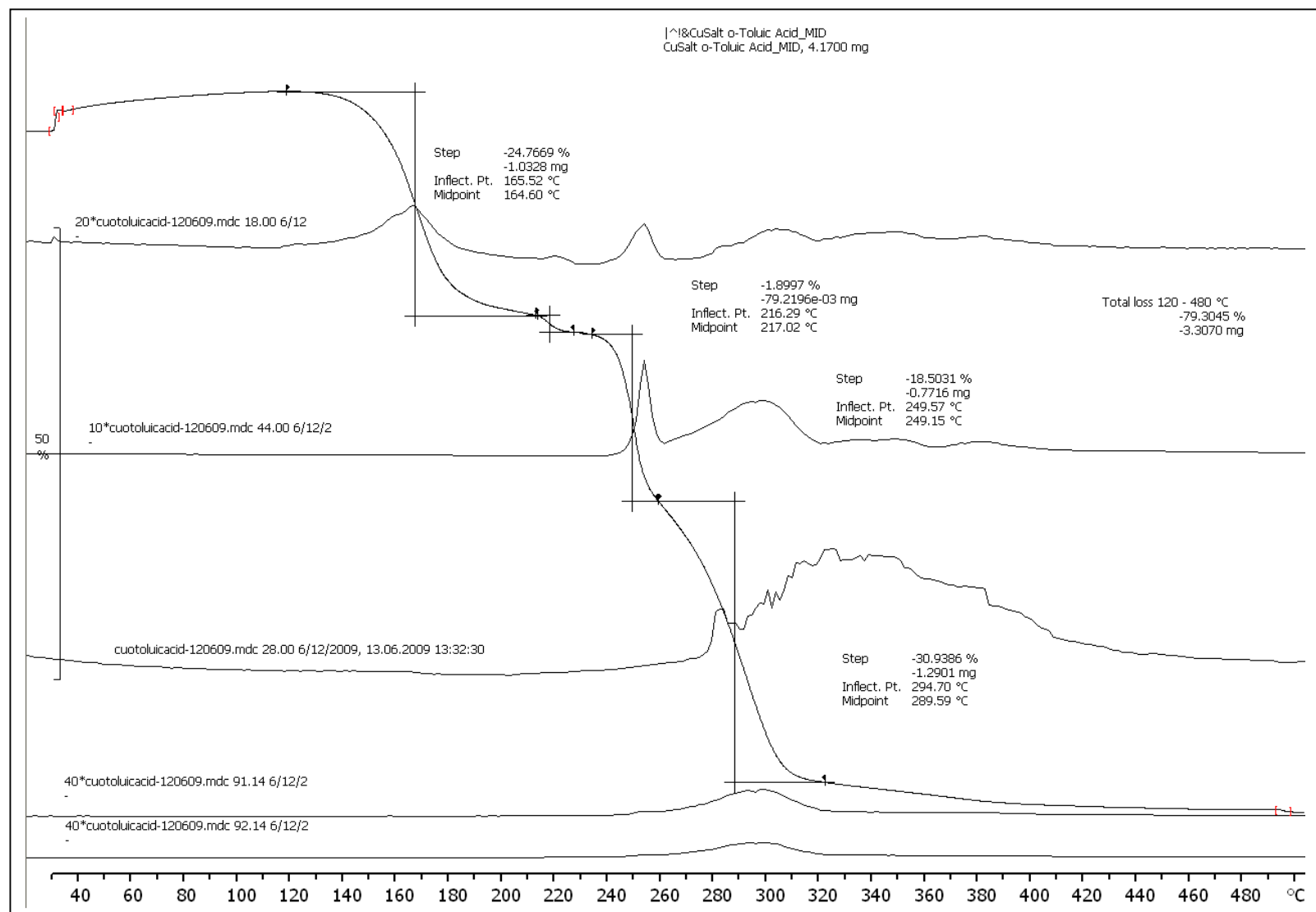
Figure 11: TGA scan of *tetrakis(μ₂-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)* (**90**).

Figure 12: TGA scan of *o*-toluic acid (**78**).

Figure 13: TGA scan of *tetrakis(μ₂-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II)* (**91**).

Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold	Shoulder
2964.647	0.676	0.345	294.002	40.544075	0
2919.042	0.719	0.040	321.924	2.933222	0
1680.792	0.217	0.804	175.781	94.734344	0
1611.262	0.220	0.330	16.295	33.609470	0
1563.093	0.442	0.225	200.207	18.712431	0
1513.497	0.632	0.117	93.350	5.300601	0
1412.616	0.182	0.850	63.804	99.486808	0
1321.292	0.519	0.243	188.538	11.893547	0
1285.526	0.289	0.725	61.799	84.264168	0
1180.952	0.455	0.574	16.425	66.266738	0
1116.604	0.621	0.395	43.717	46.025070	0
1020.564	0.703	0.210	9.981	21.270481	0
961.346	0.723	0.280	46.681	32.612774	0
840.041	0.716	0.292	26.837	33.999763	0
756.432	0.376	0.650	26.648	76.306892	0
607.152	0.664	0.342	11.169	39.973808	0
541.337	0.584	0.435	23.331	50.163605	0
468.638	0.632	0.374	26.443	43.313004	0

IR (**Plate 2**) of *tetrakis(μ₂-4-methylbenzoato)bis(4-methylbenzoic acid)copper(II)* (**91**).

Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold <	Shoulder
1588.406	0.521	0.491	20.041	69.937088	0
1490.335	0.674	0.337	65.412	47.788792	0
1461.723	0.723	0.108	17.086	12.943250	0
1277.468	0.662	0.090	4.170	3.784267	0
1264.662	0.614	0.397	65.488	55.145485	0
1244.892	0.659	0.077	48.316	5.459229	0
1151.980	0.379	0.641	22.553	90.557817	0
925.639	0.479	0.536	12.886	75.798706	0
771.634	0.330	0.699	20.638	98.746834	0
732.222	0.731	0.242	8.804	31.147562	0
686.298	0.363	0.656	12.278	91.344083	0

IR (**Plate 3**) of *m*-cresol (**10**).

Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold <	Shoulder
1731.277	0.318	0.693	22.763	80.683792	0
1268.895	0.399	0.291	16.659	32.101635	0
1232.399	0.167	0.851	25.421	98.332634	0
1176.522	0.418	0.544	9.968	56.313515	0
1142.351	0.248	0.765	19.869	89.034775	0
1068.706	0.237	0.778	26.808	90.167130	0
1018.877	0.543	0.336	7.879	38.497032	0
766.879	0.547	0.312	11.849	32.049126	0
745.601	0.269	0.750	16.705	86.226303	0
684.991	0.349	0.674	11.337	76.229301	0

IR (**Plate 4**) of 3-methylphenyl 4-methylbenzoate (**87**).

Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold <	Shoulder
1734.269	0.406	0.609	28.859	70.331688	0
1224.731	0.181	0.853	33.283	97.943663	0
1141.394	0.257	0.755	21.498	87.725357	0
1043.158	0.239	0.776	31.070	90.849040	0
767.943	0.577	0.435	14.533	50.476101	0
732.597	0.269	0.742	18.120	86.234398	0
685.806	0.434	0.573	12.082	66.813728	0
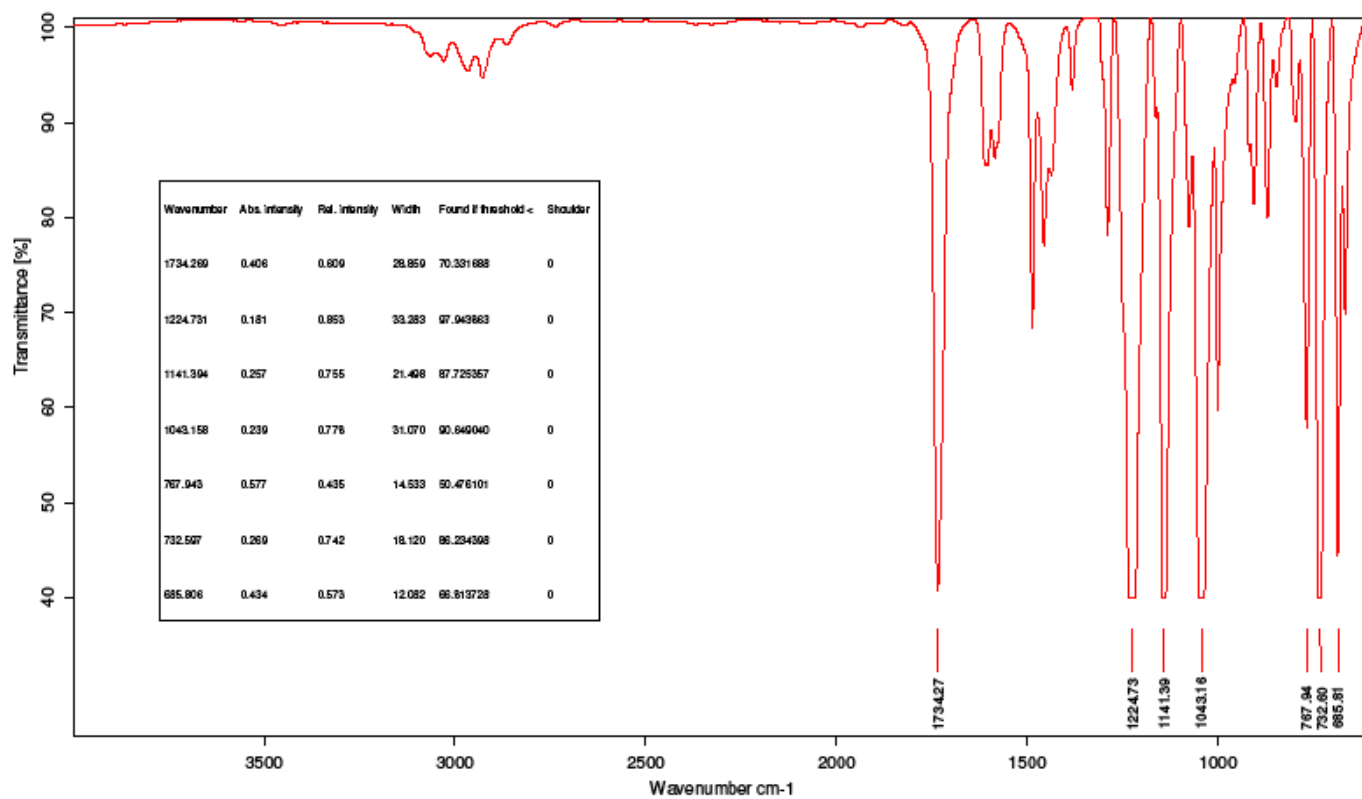
IR (**Plate 5**) of 3-methylphenyl 2-methylbenzoate (**85**).

Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold <	Shoulder
1734.269	0.406	0.609	28.859	70.331688	0
1224.731	0.181	0.853	33.283	97.943663	0
1141.394	0.257	0.755	21.498	87.725357	0
1043.158	0.239	0.778	31.070	90.649040	0
767.943	0.577	0.435	14.533	50.476101	0
732.597	0.269	0.742	18.120	86.234398	0
685.806	0.434	0.573	12.082	66.813726	0

IR (**Plate 6**) of *tetrakis(μ₂-2 methylbenzoato)bis(2-methylbenzoic acid)copper (II)* (**90**) after DSC analysis.

Plate nr. 10d HMQC

Plate nr. 10b ^{13}C
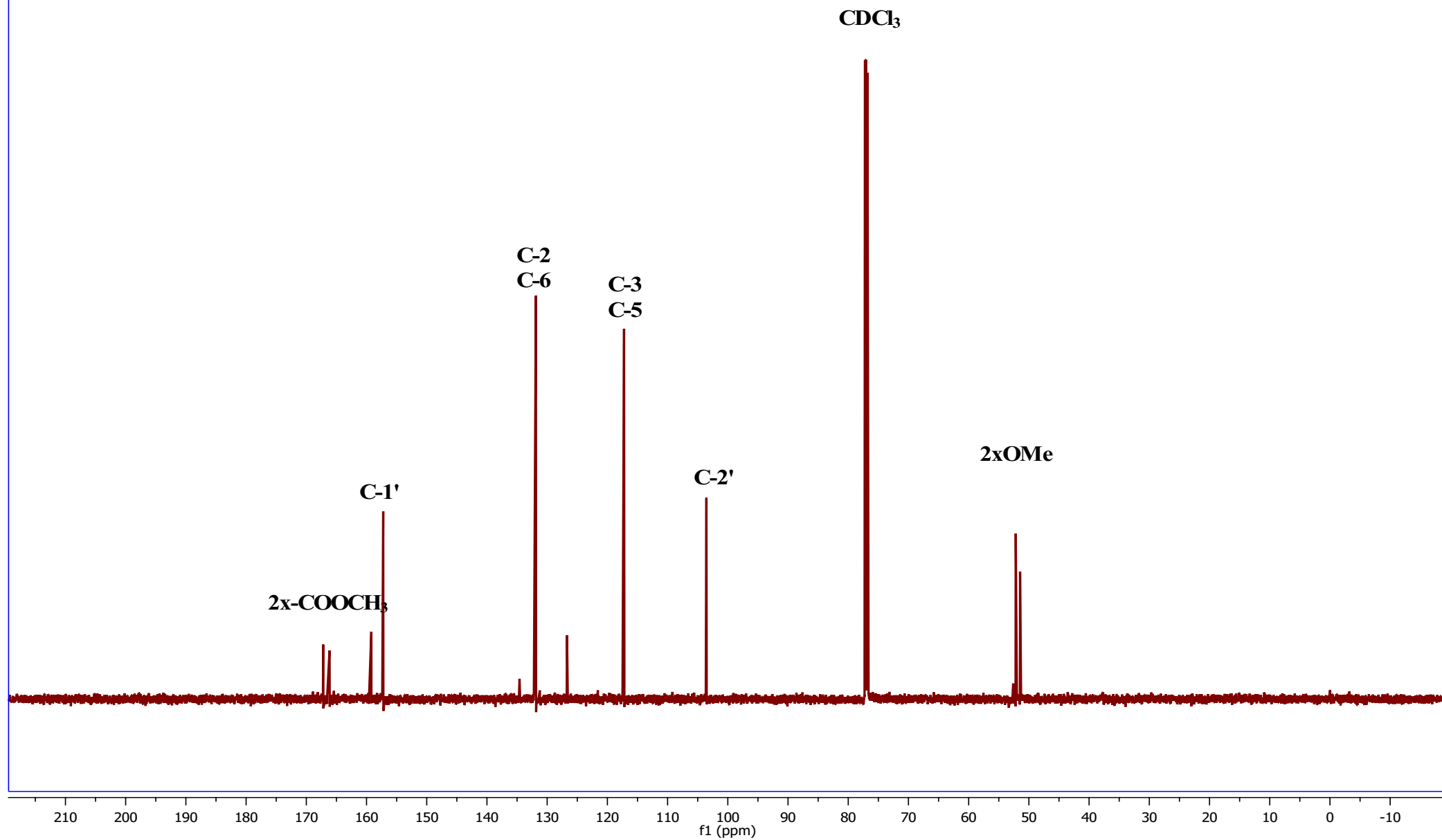
Plate nr. 11a ^{1}H NMR of methyl 4-hydroxy benzoate

(600MHz, Acetone-d$_6$) 7.96 (1H, s, OH); 6.72 (2H, d, J 8.8 Hz, H-2, H-6); 5.75 (2H, d, J 8.8 Hz, H-3, H-5); 2.65 (3H, s, OMe).

119
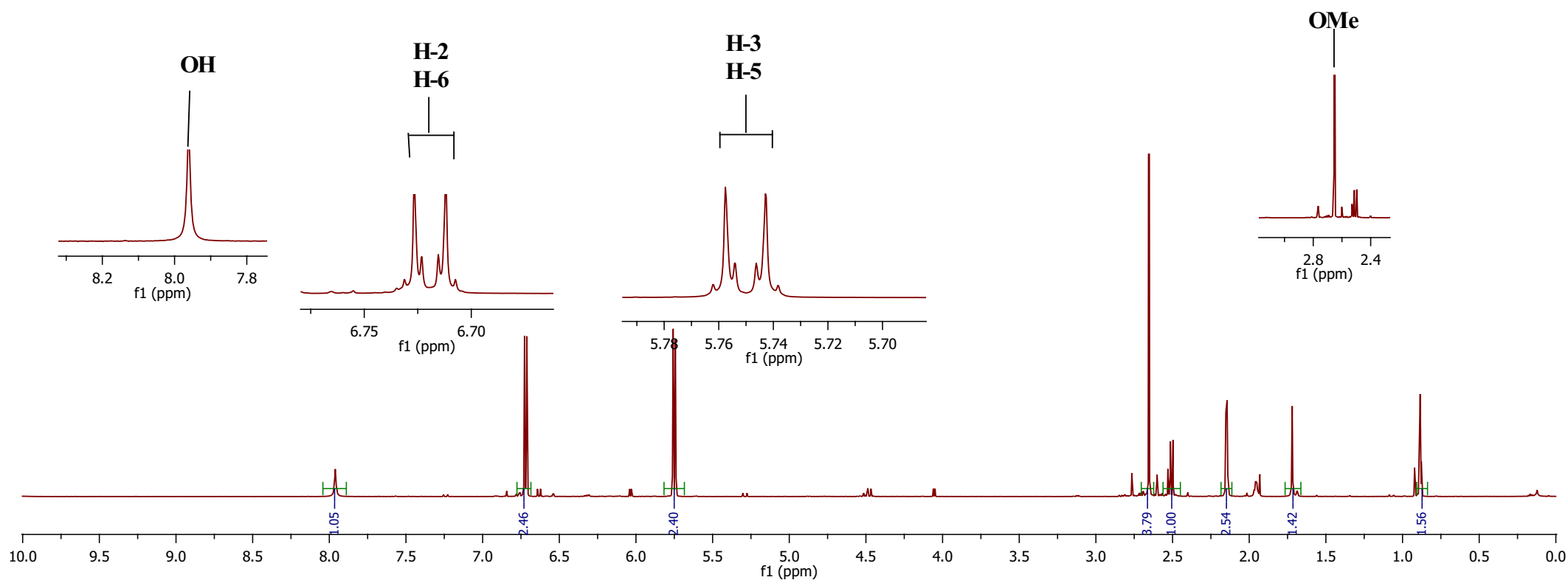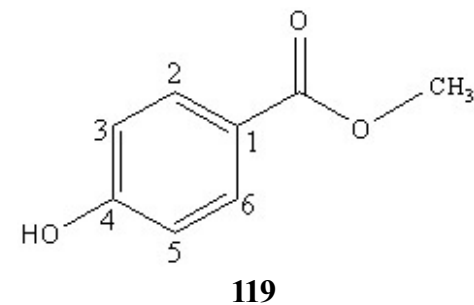
Plate nr. 9a ^{1}H NMR of (*trans*)-4-acetyl-3-methoxycyclohexanone

(600 MHz, CDCl$_3$) 3.80-3.73 (1H, m, H-3); 3.29 (3H, s, OMe); 2.97-2.91 (1H, m, H-4); 2.84 (1H, ddd, J 1.32 Hz, 4.47 Hz, 14.18 Hz, H-2); 2.41-2.38 (1H, m, H-2'); 2.36-2.34 (1H, m, H-6); 2.33-2.30 (1H, m, H-6'); 2.27 (3H, s, CH$_3$); 2.11-2.02 (1H, m, H-5) and 1.84-1.70 (1H, m, H-5')
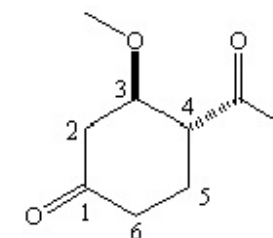
117b
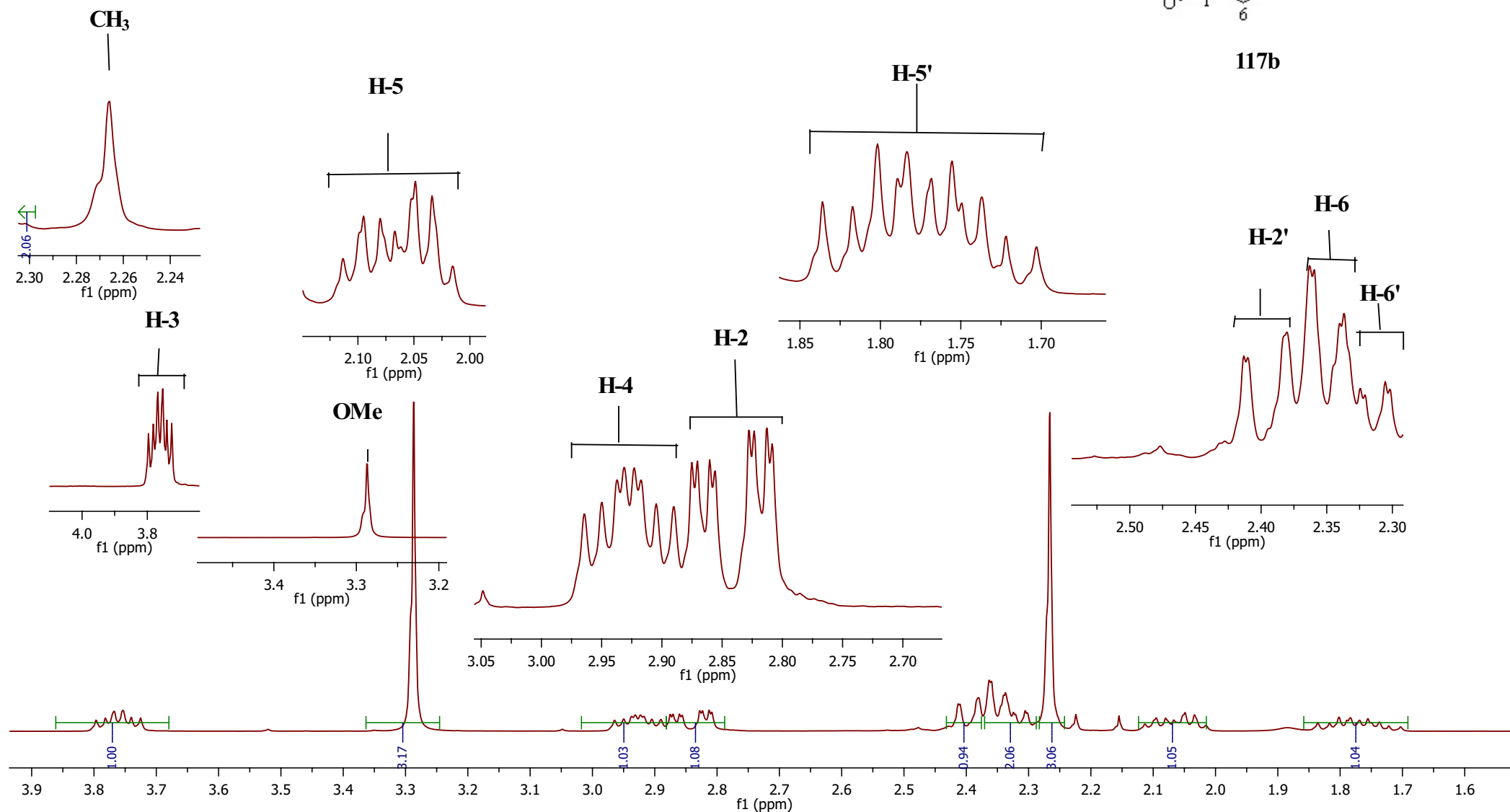
Plate nr. 8a ^{1}H NMR of (*cis*)-4-acetyl-3-methoxycyclohexanone

(600 MHz, CDCl$_3$) 4.22 (1H, br. s, H-3); 3.31 (3H, s, OMe); 2.83 (1H, dd, J 1.87 Hz, 14.98 Hz, H-2); 2.80-2.79 (1H, m, H-4); 2.53-2.51 (1H, m, H-6); 2.48-2.45 (1H, m, H-2'); 2.35-2.32 (1H, m, H-6'); 2.32-2.28 (1H, m, H-5); 2.24 (3H, s, CH$_3$) and 2.11-2.09 (1H, m, H-5')
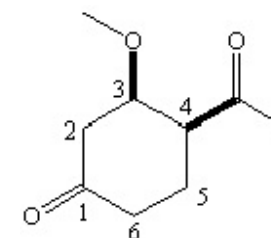
117a
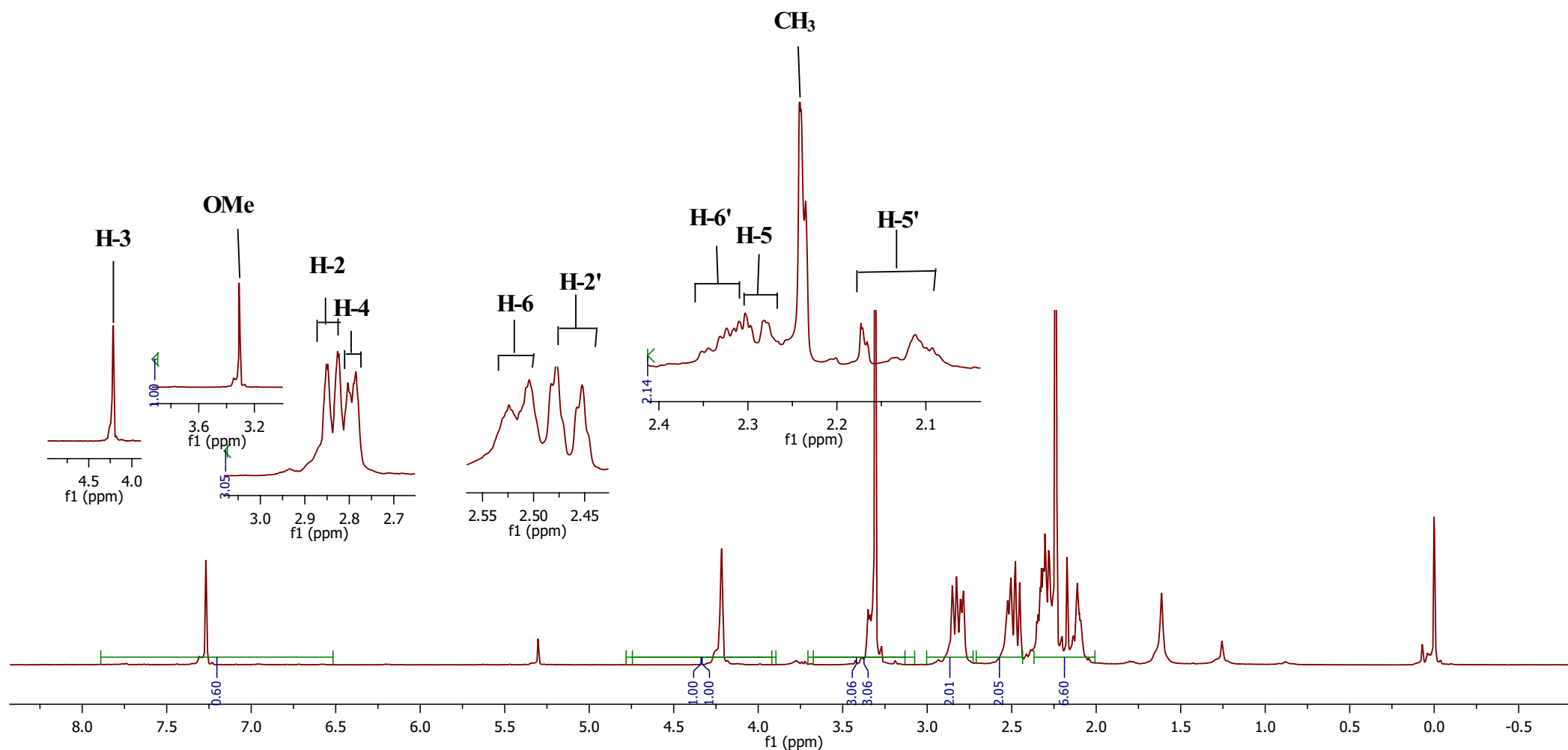
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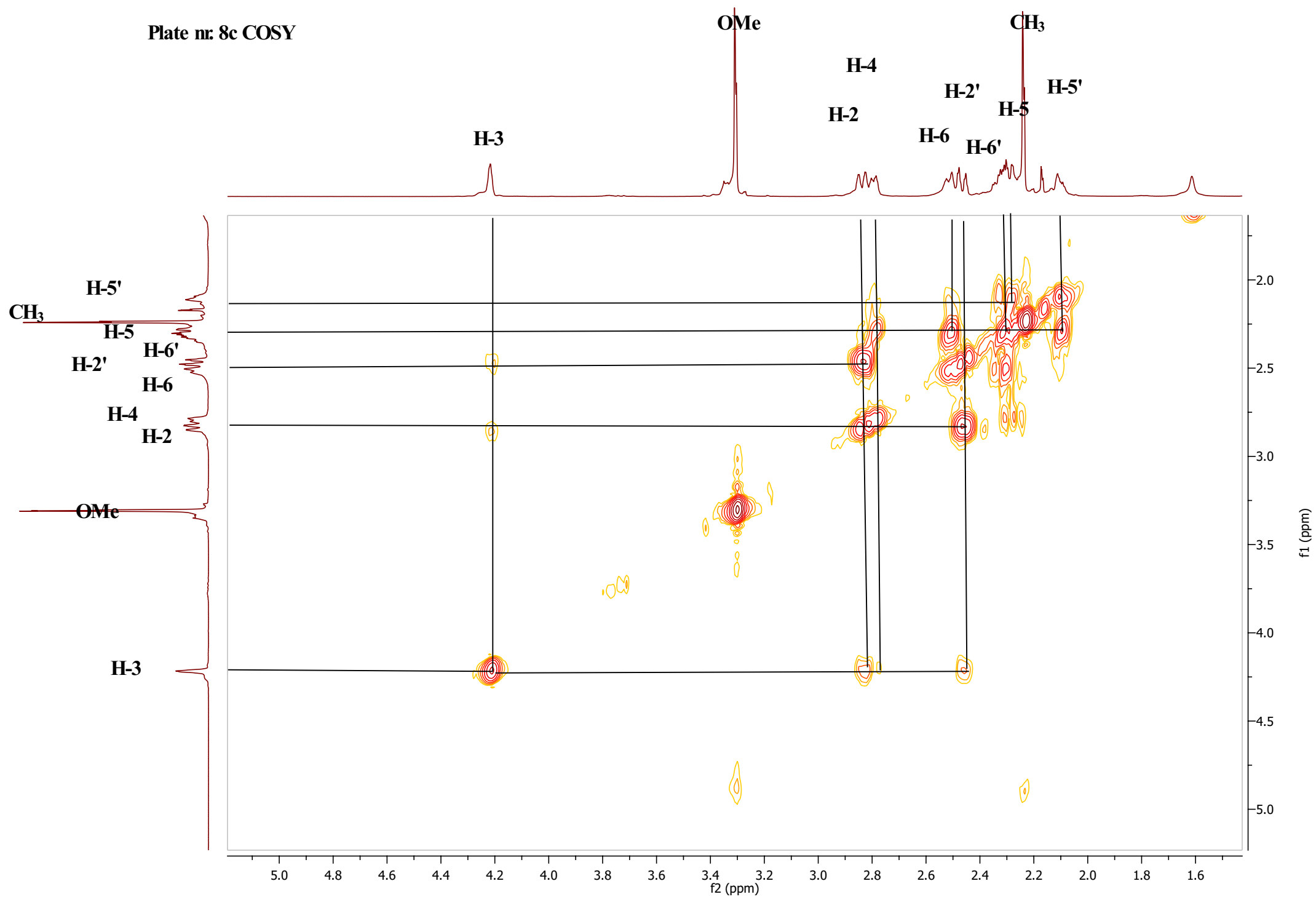
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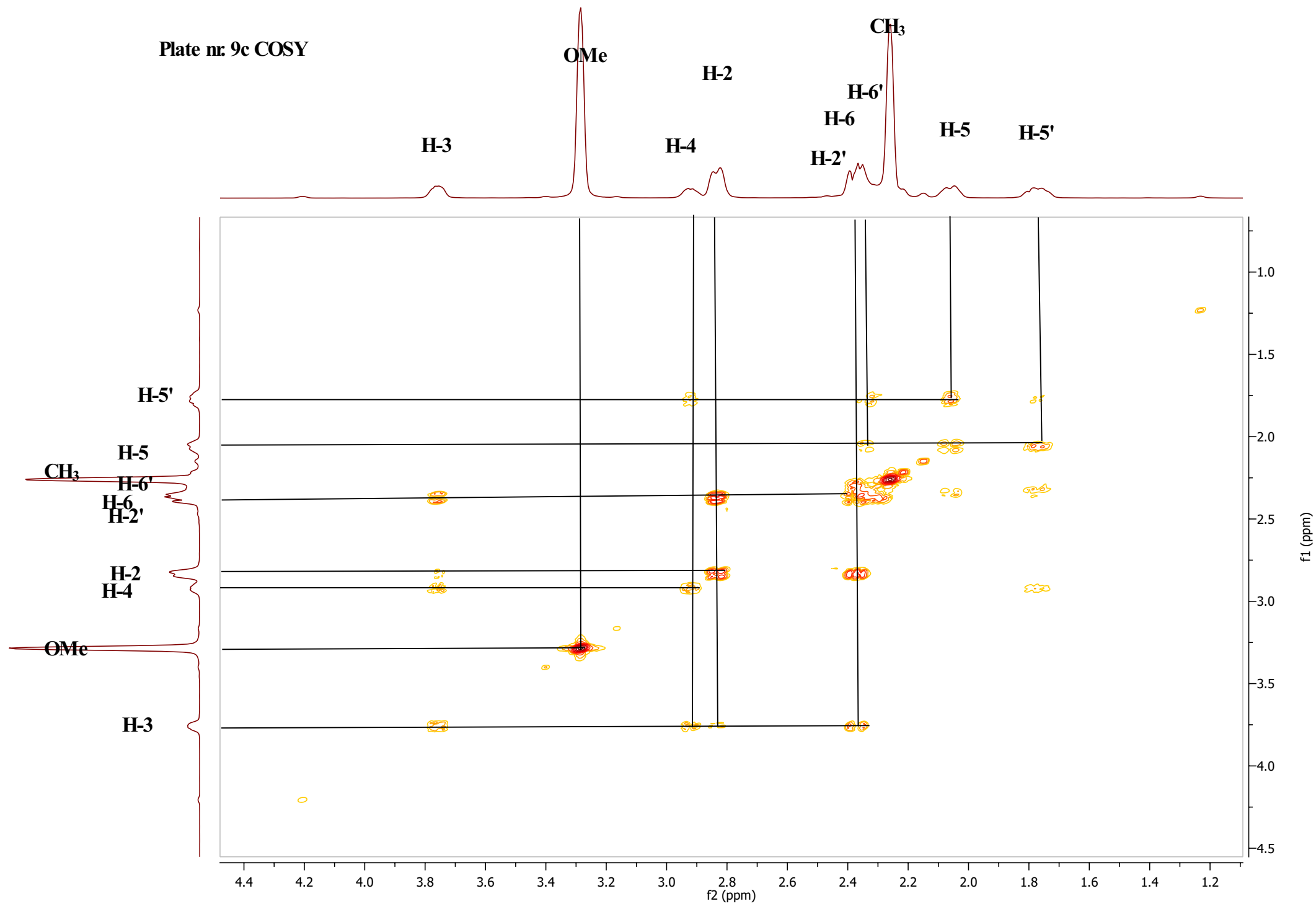
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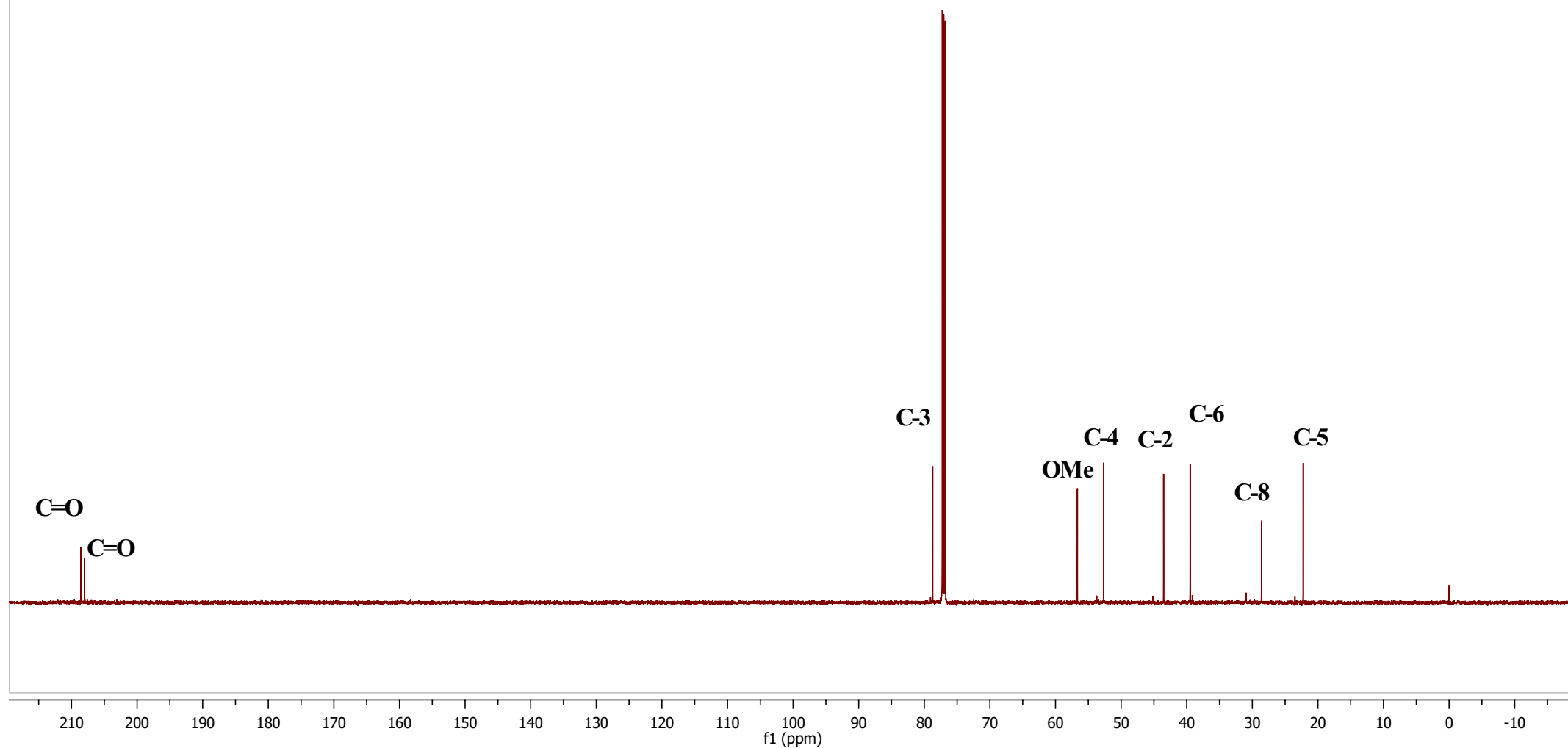
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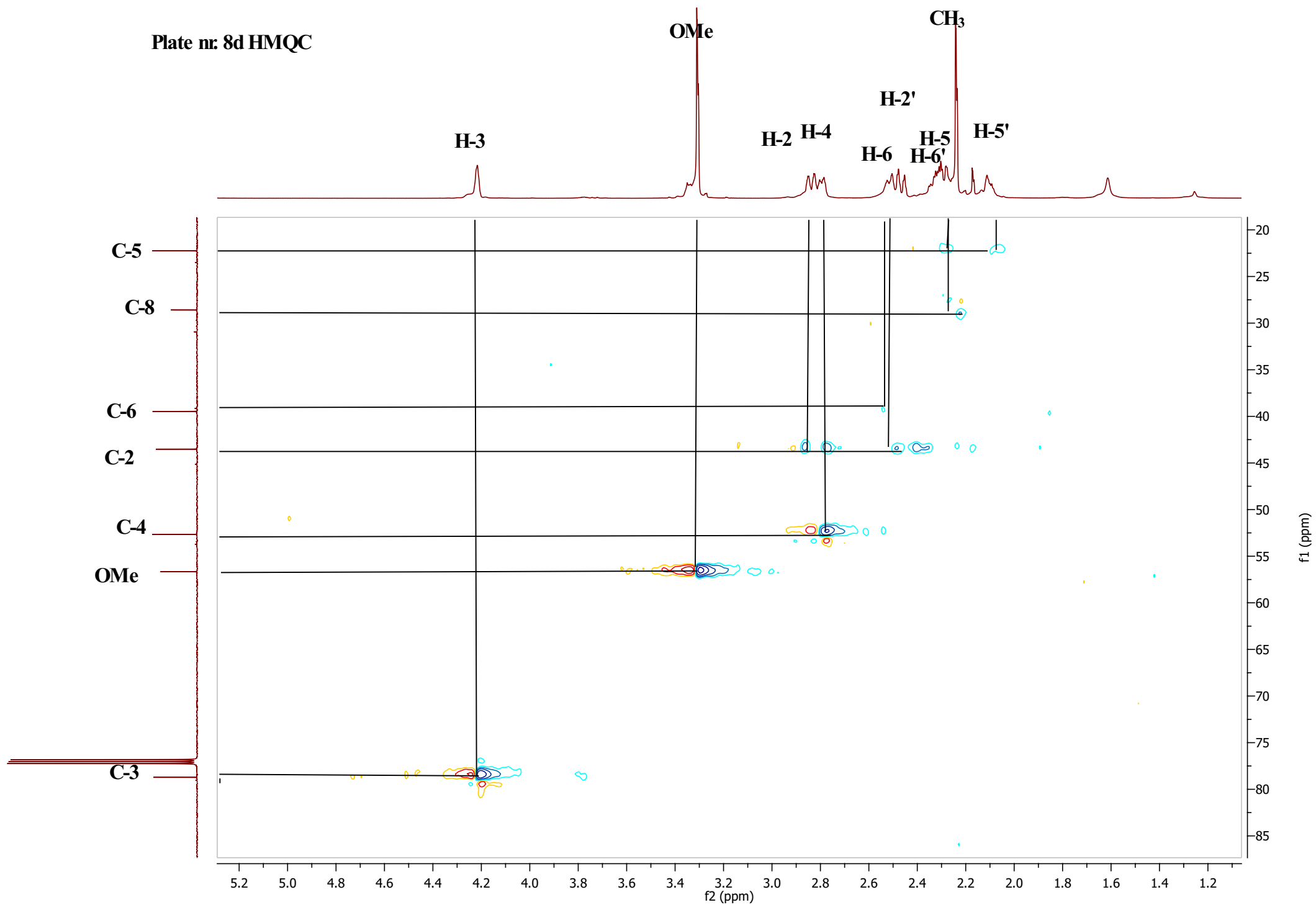
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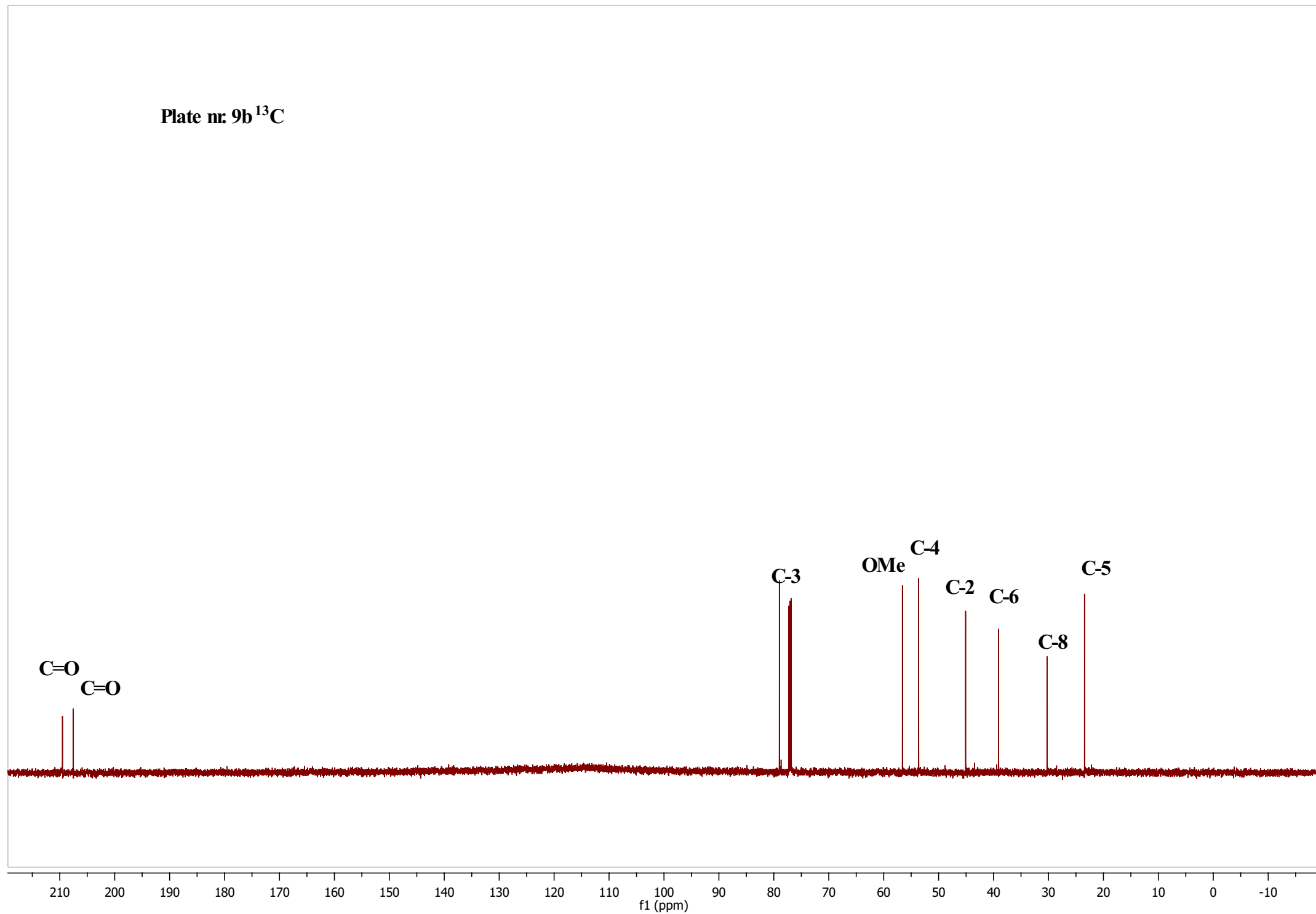
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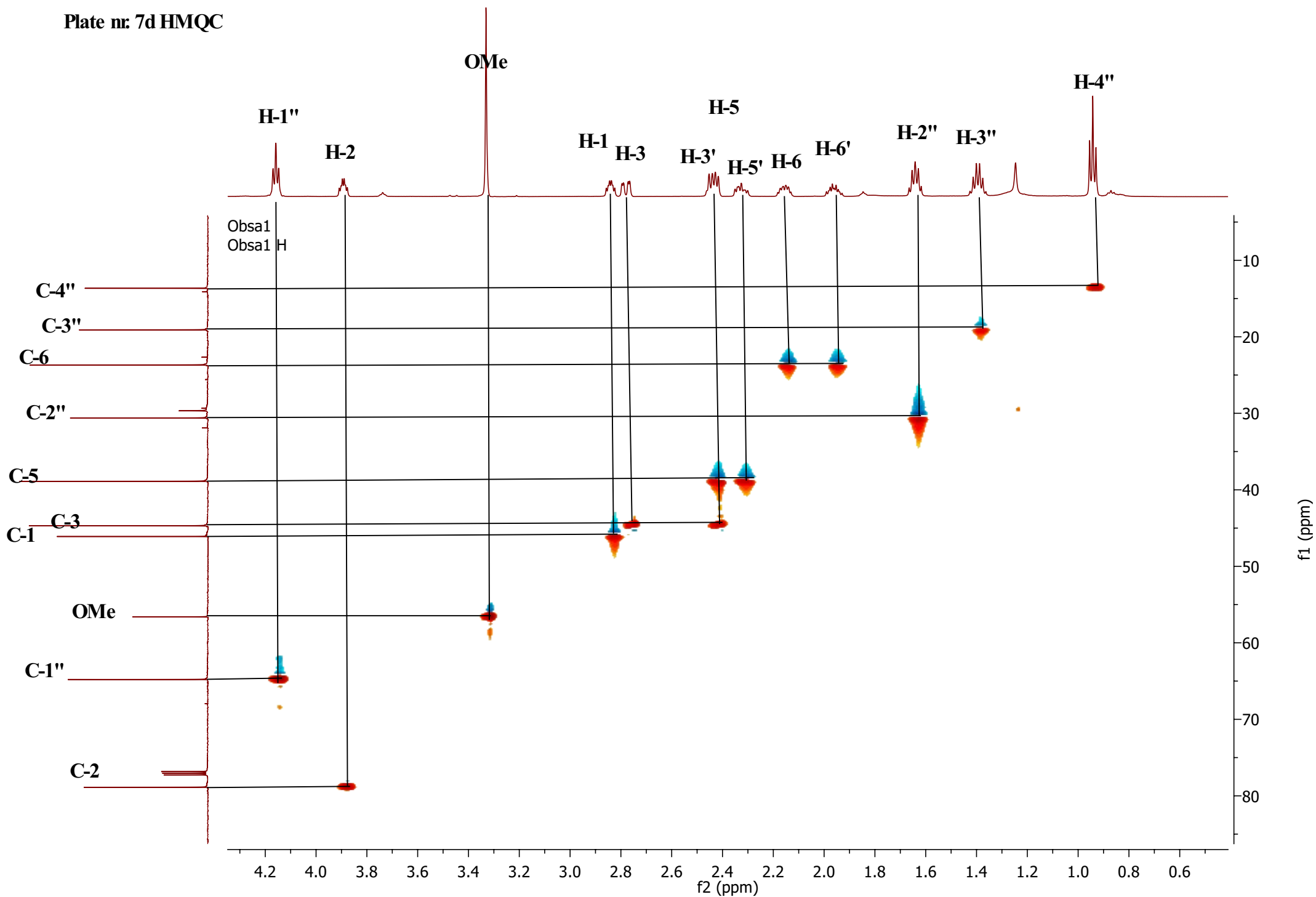
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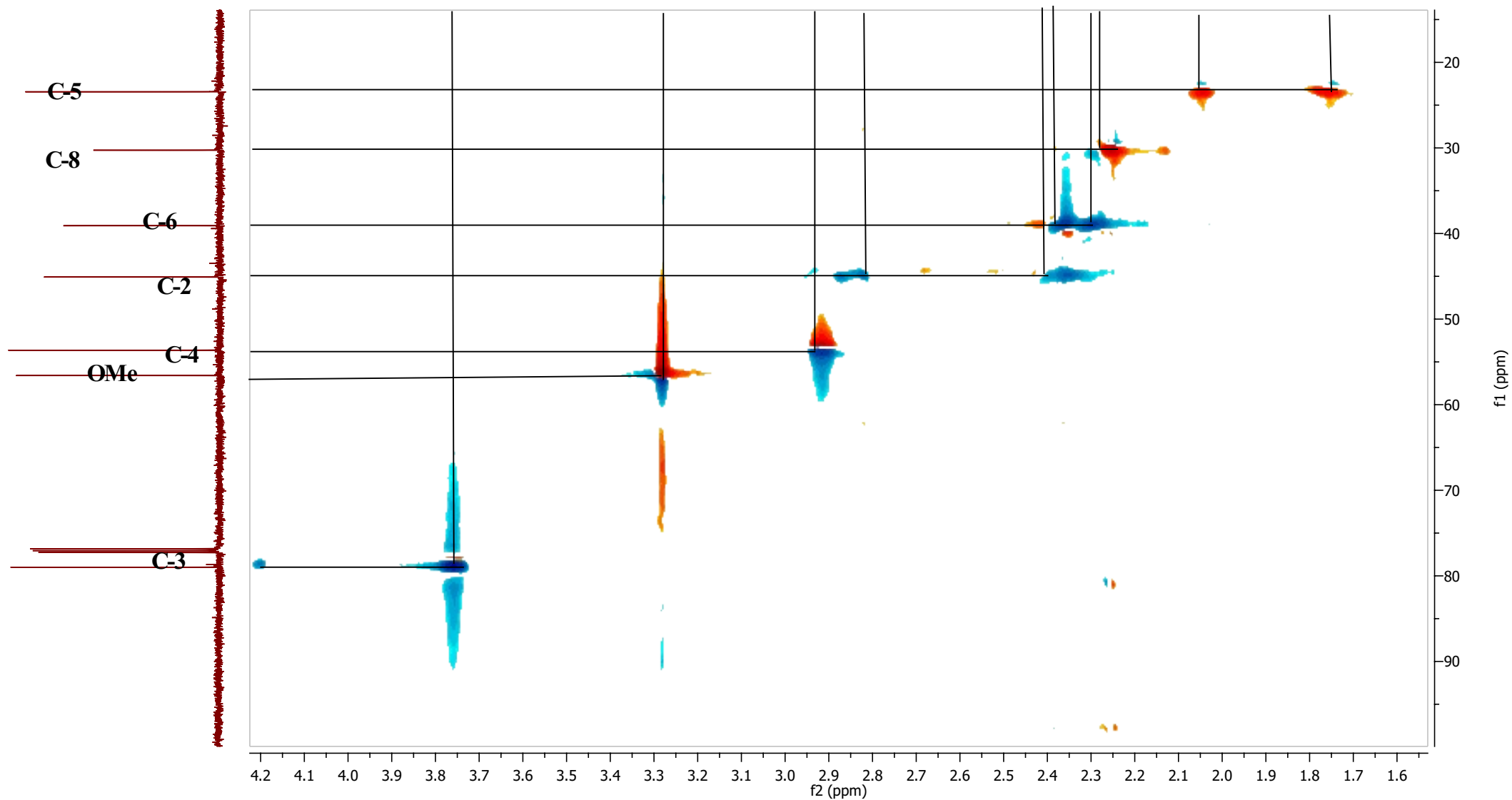
Plate nr: 5a ^{1}**H NMR of Copper salt of** *o*-**toluic acid after DSC**
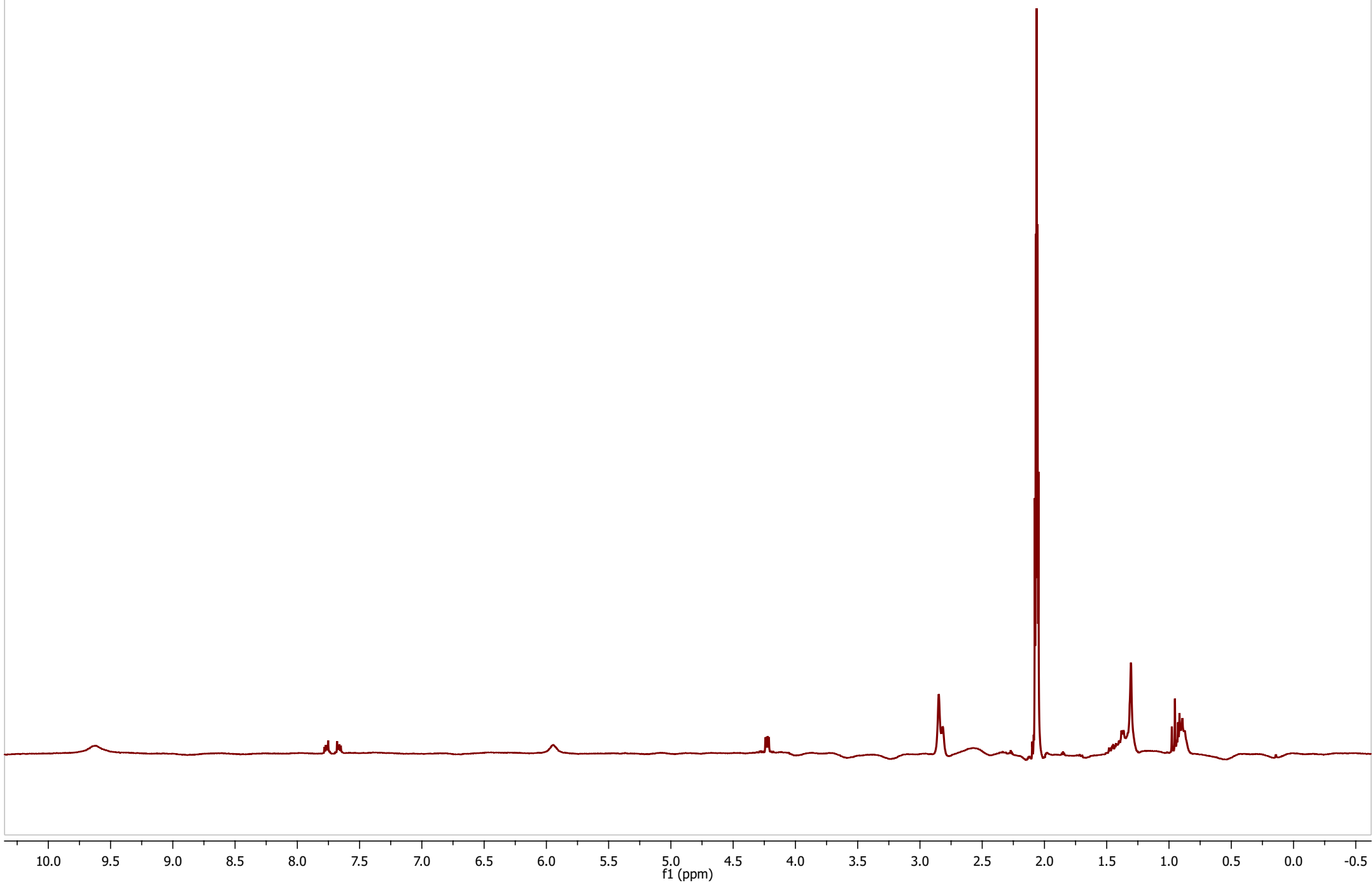
Plate nr. 2a ^{1}H NMR of *m*-cresol
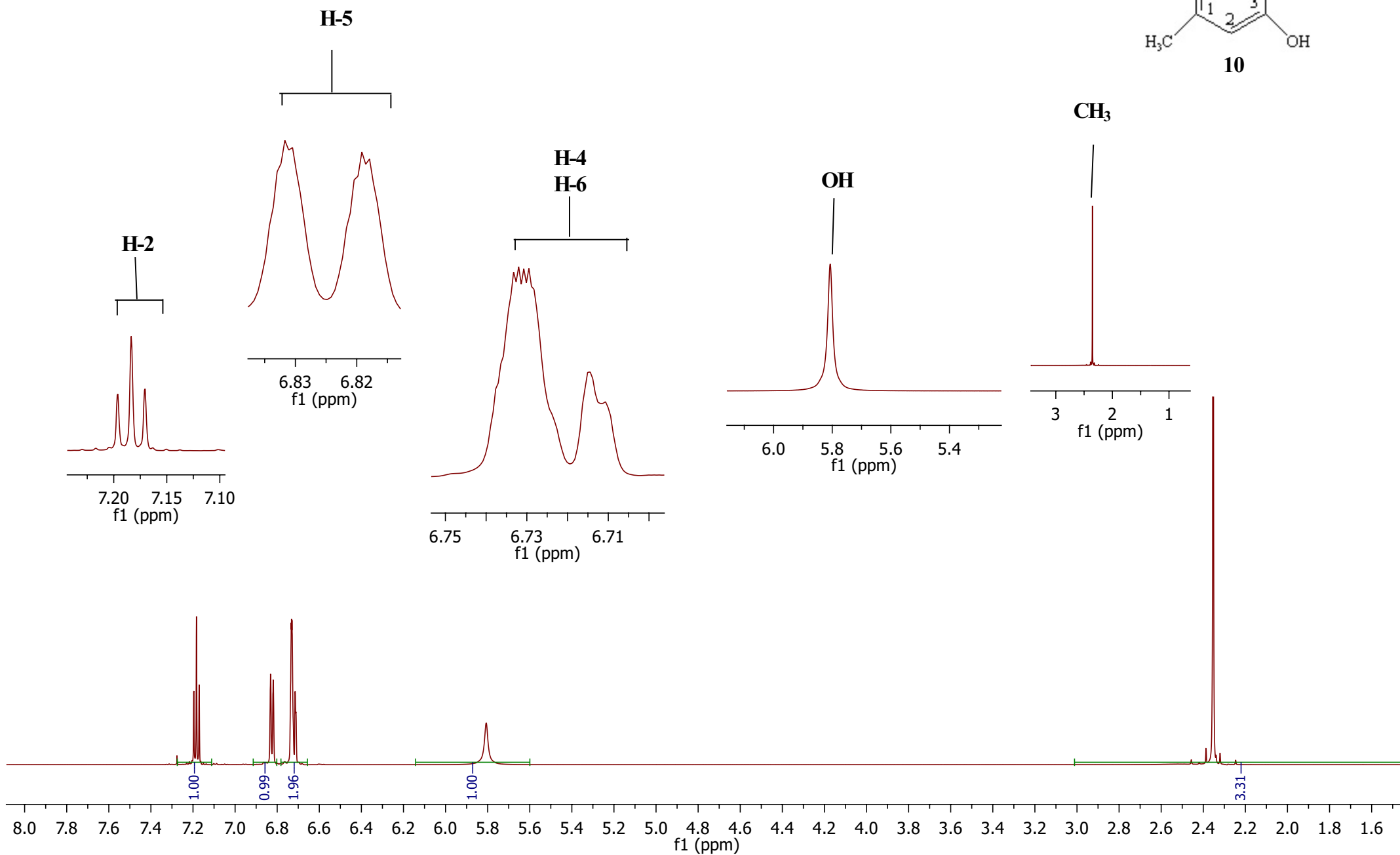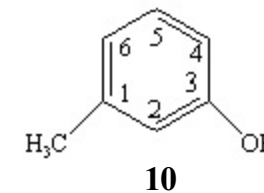
(300MHz, CDCl$_3$) 7.18 (1H, t, J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71
(2H, m, H-4, H-6); 5.81 (1H, s, OH); 2.35 (3H, s, CH$_3$)

Plate nr. 2a ^{1}H NMR of *m*-cresol

(300MHz, CDCl$_3$) 7.18 (1H, t, J 7.71 Hz, H-2); 6.84-6.81 (1H, m, H-5); 6.74-6.71
(2H, m, H-4, H-6); 5.81 (1H, s, OH); 2.35 (3H, s, CH$_3$)

H-5

H-4
H-6

OH

CH$_3$

H-2

6.83   6.82
f1 (ppm)

7.20   7.15   7.10
f1 (ppm)

6.75   6.73   6.71
f1 (ppm)

6.0   5.8   5.6   5.4
f1 (ppm)

3   2   1
f1 (ppm)

10

1.00   0.99 1.96   1.00   3.31

8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)
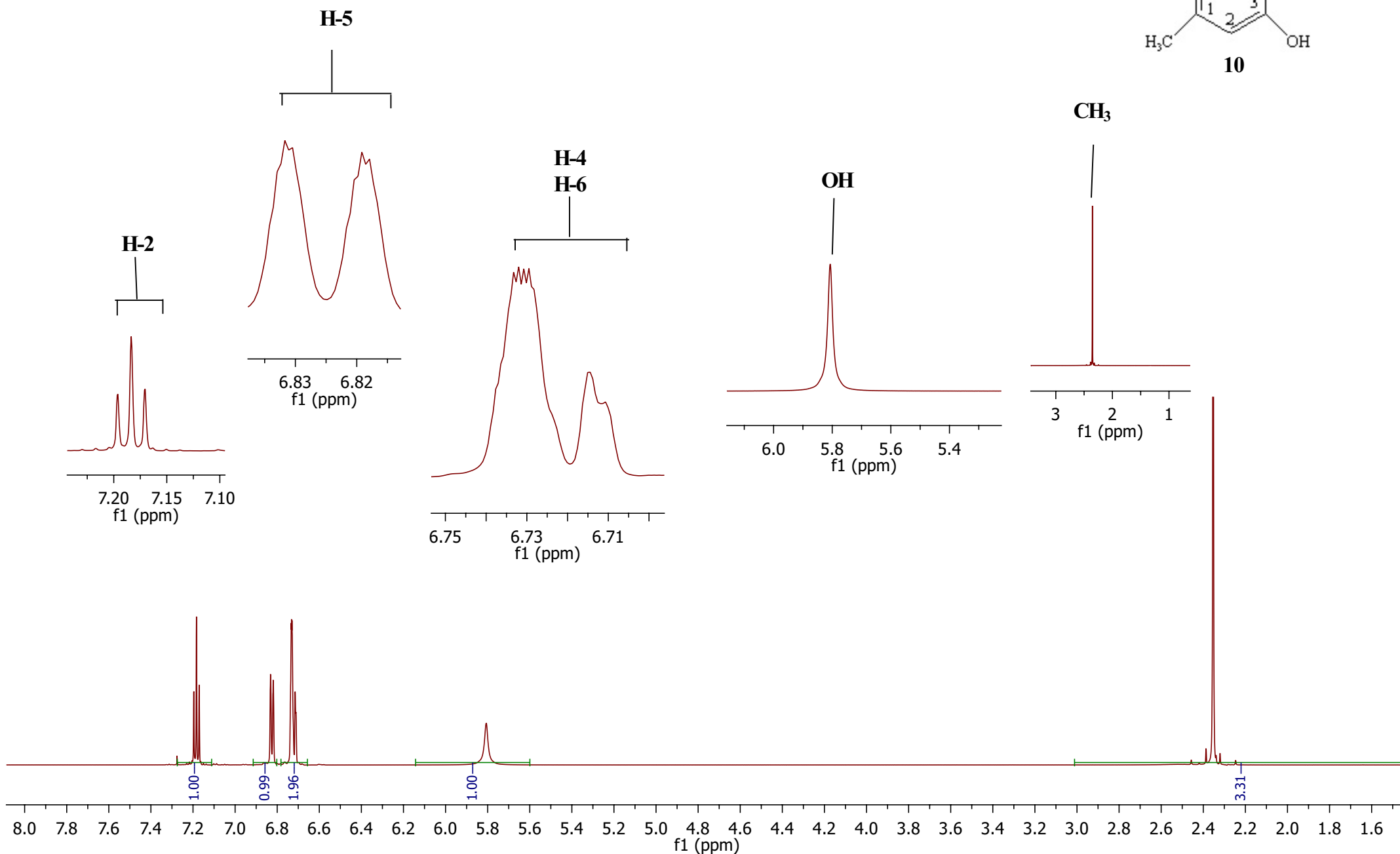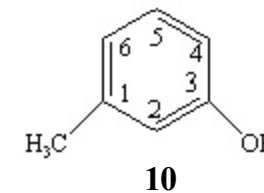
Plate nr. 1a ^{1}H NMR of Tetrakis(μ_2-2-methylbenzoato)bis[(2-methylbenzoic acid)copper(II)
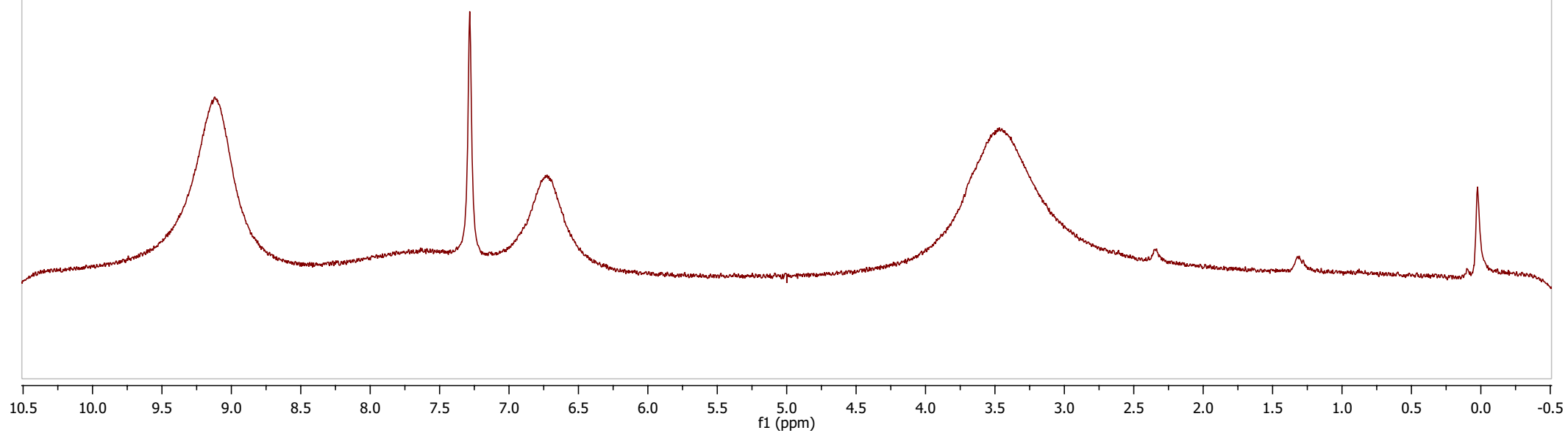
Plate nr. 10a ¹H NMR of
methyl 4-{[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]oxy}benzoate

(300MHz, CDCl₃) 8.07 (2H, d, J 8.9 Hz, H-2, H-6); 7.83 (1H, d, J 12.14 Hz, H-1');
7.12 (2H, d, J 8.9 Hz, H-3, H-5); 5.69 (1H, d, J 12.14 Hz, H-2'); 3.92 (3H, s,
OMe); 3.75 (3H, s, OMe)
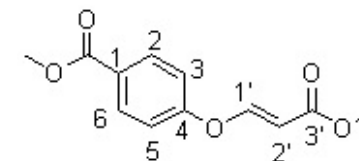
120
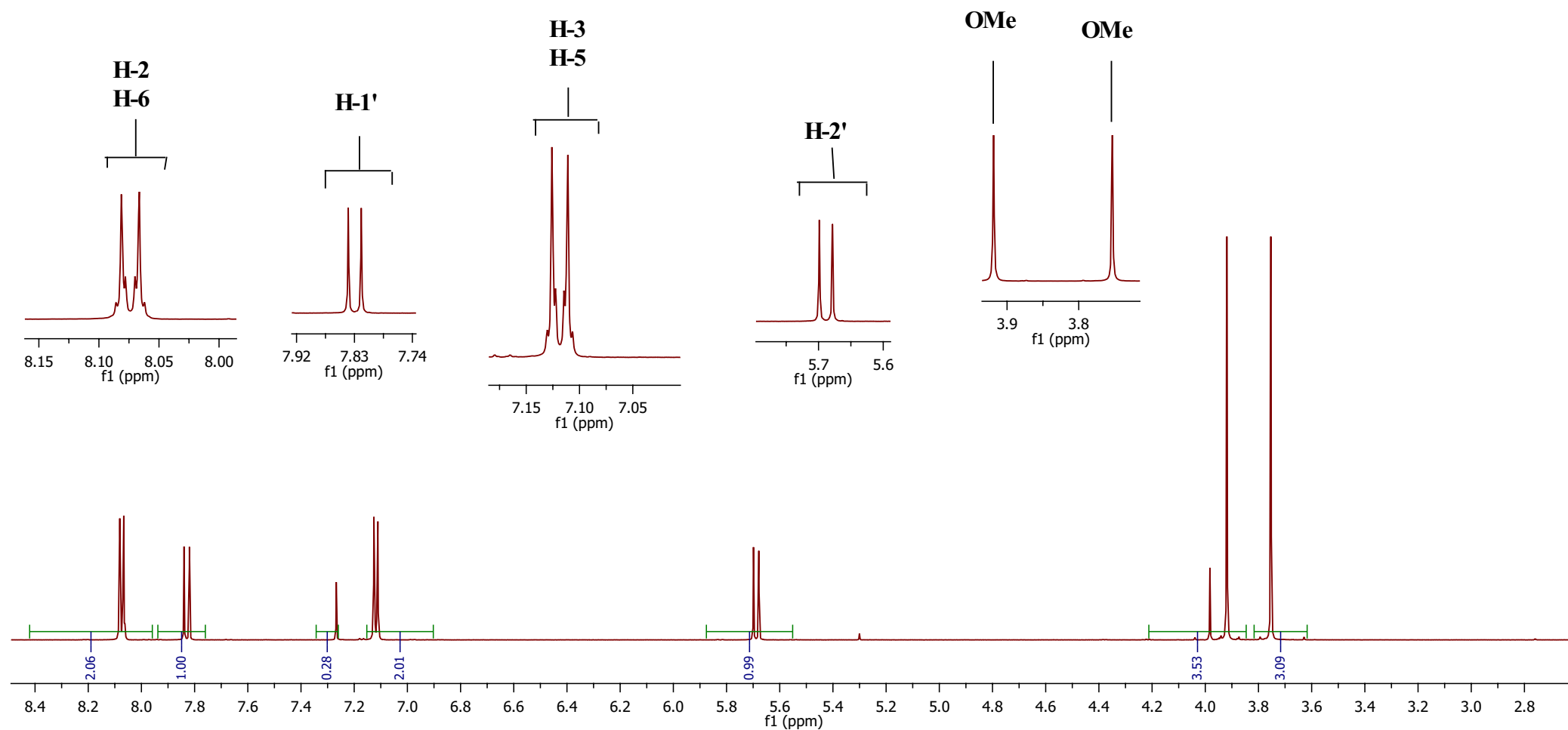
Plate nr. 4b ^{13}C
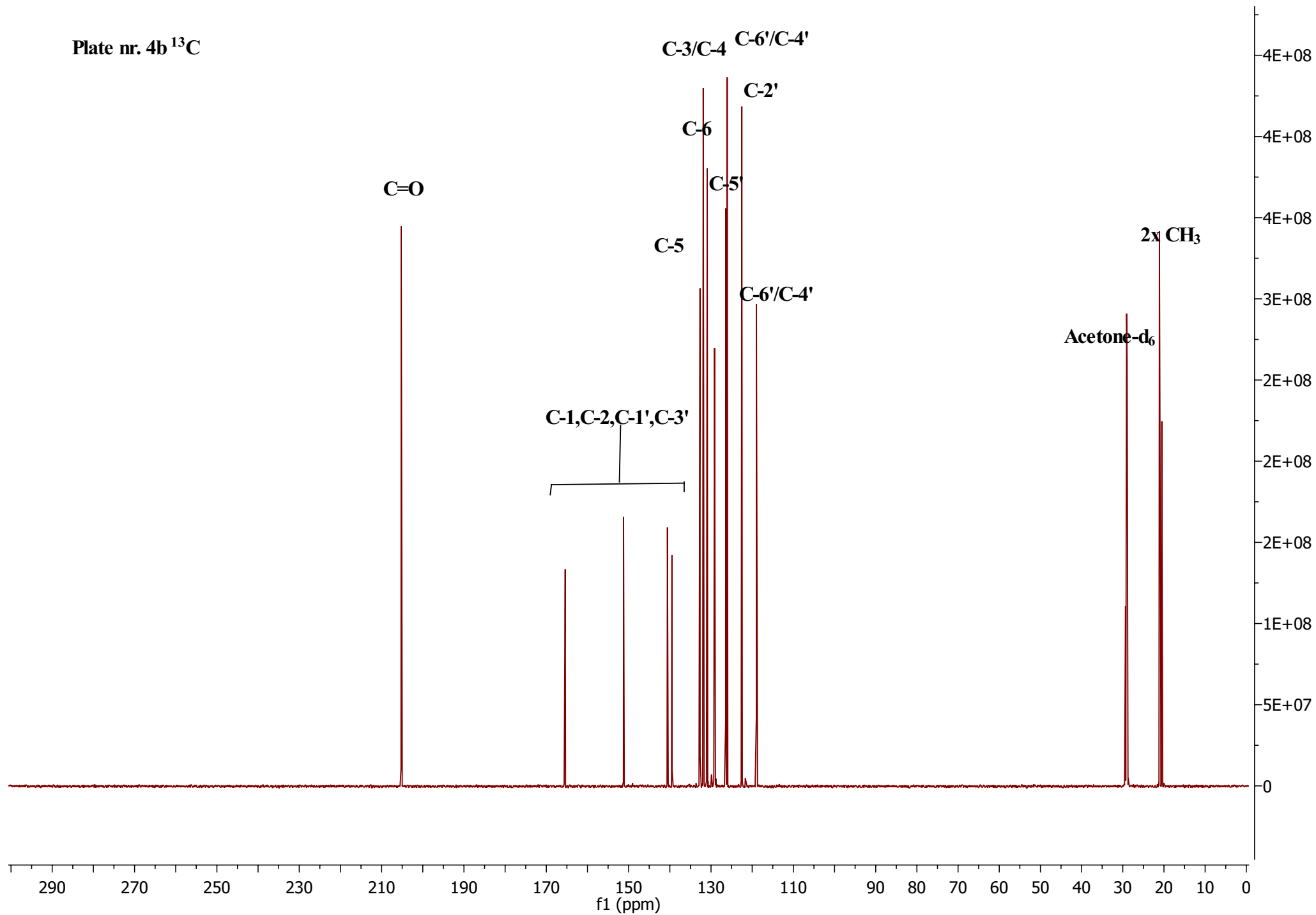
Plate nr. 3a ^{1}H NMR of 3-methylphenyl 4-methylbenzoate

(300MHz, Acetone-d6) 8.07 (2H, d, J 8.13 Hz, H-2, H-6); 7.42 (2H, d, J 8.13 Hz, H-3, H-5); 7.35 (1H, t, J 7.35 Hz, H-5'); 7.14-7.06 (3H, m, H-2', H-4', H-6'); 2.46 (3H, s, CH3); 2.39 (3H, s, CH3)
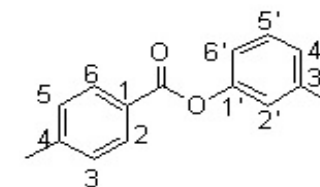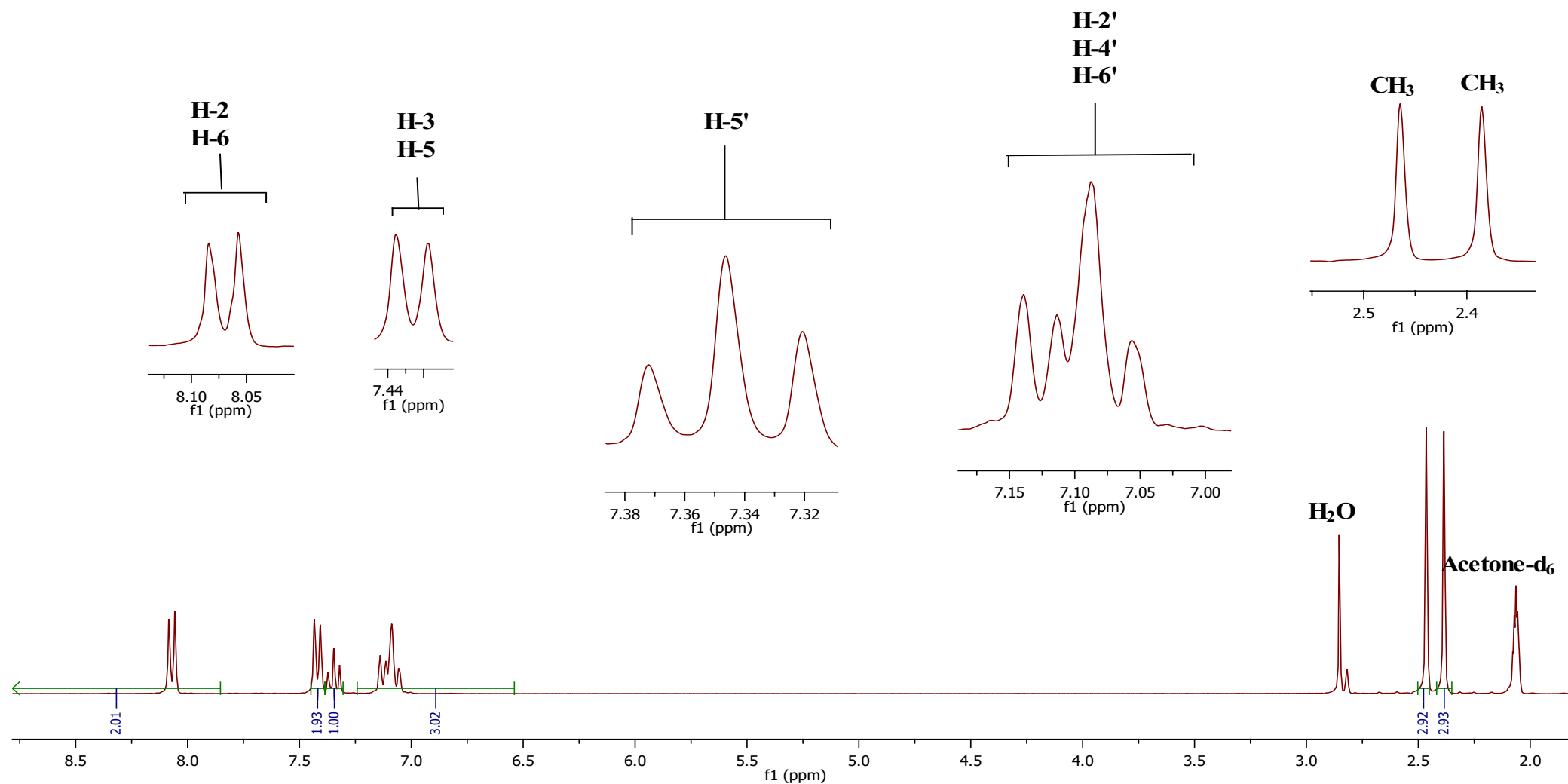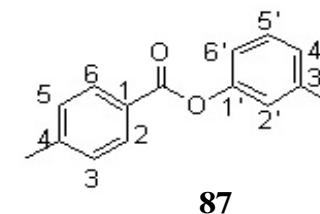

87
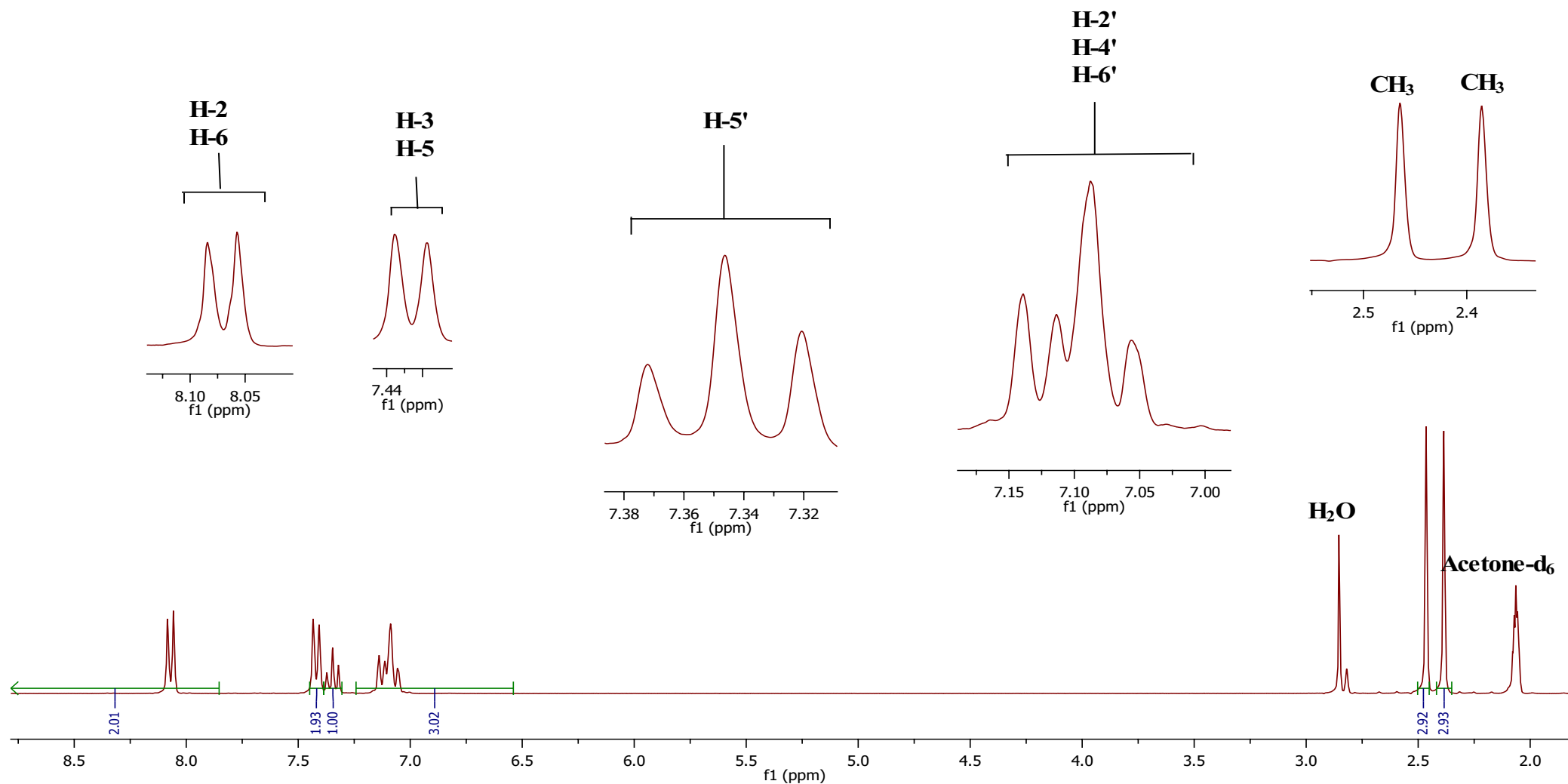
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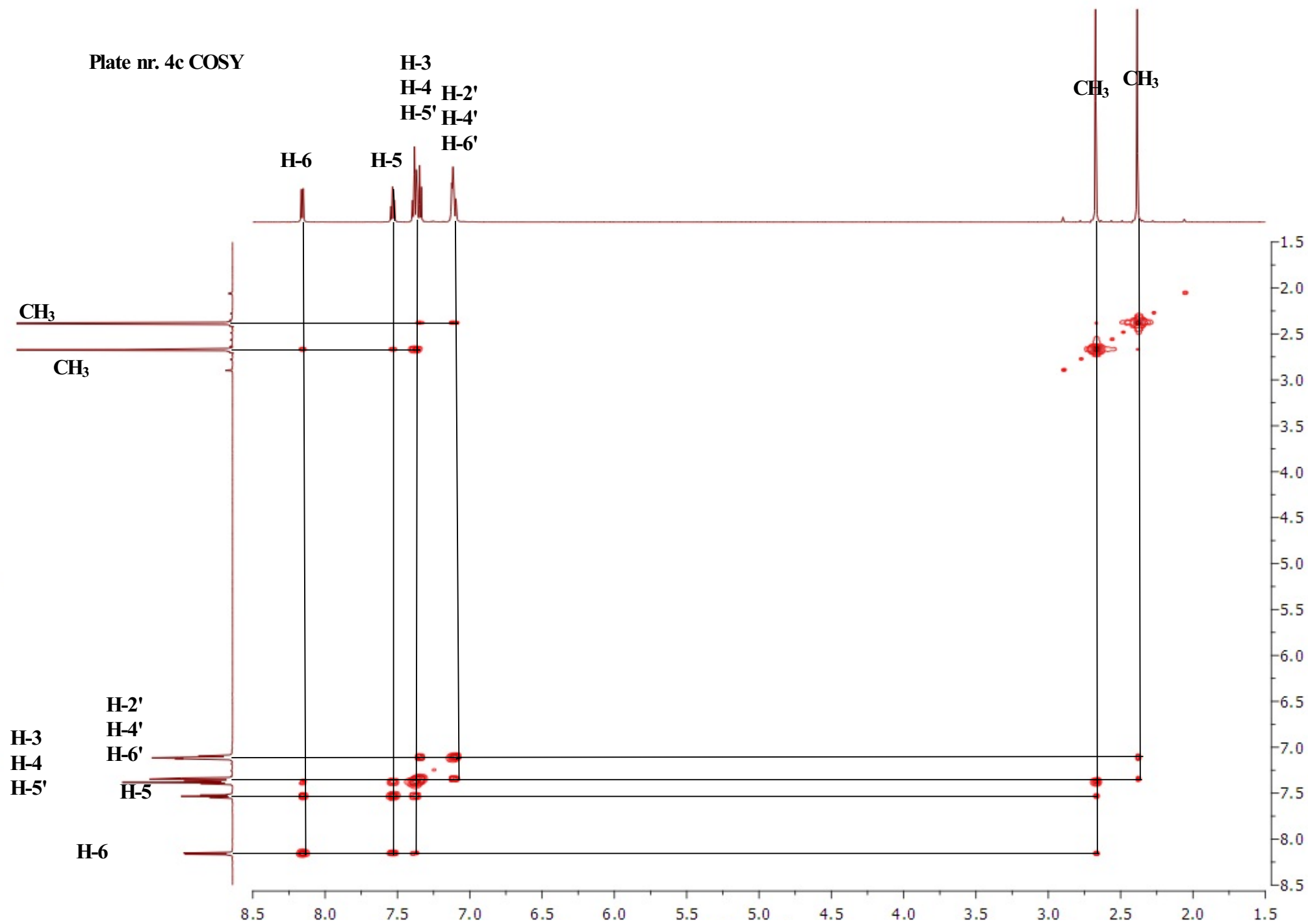
Plate nr. 4d HMQC
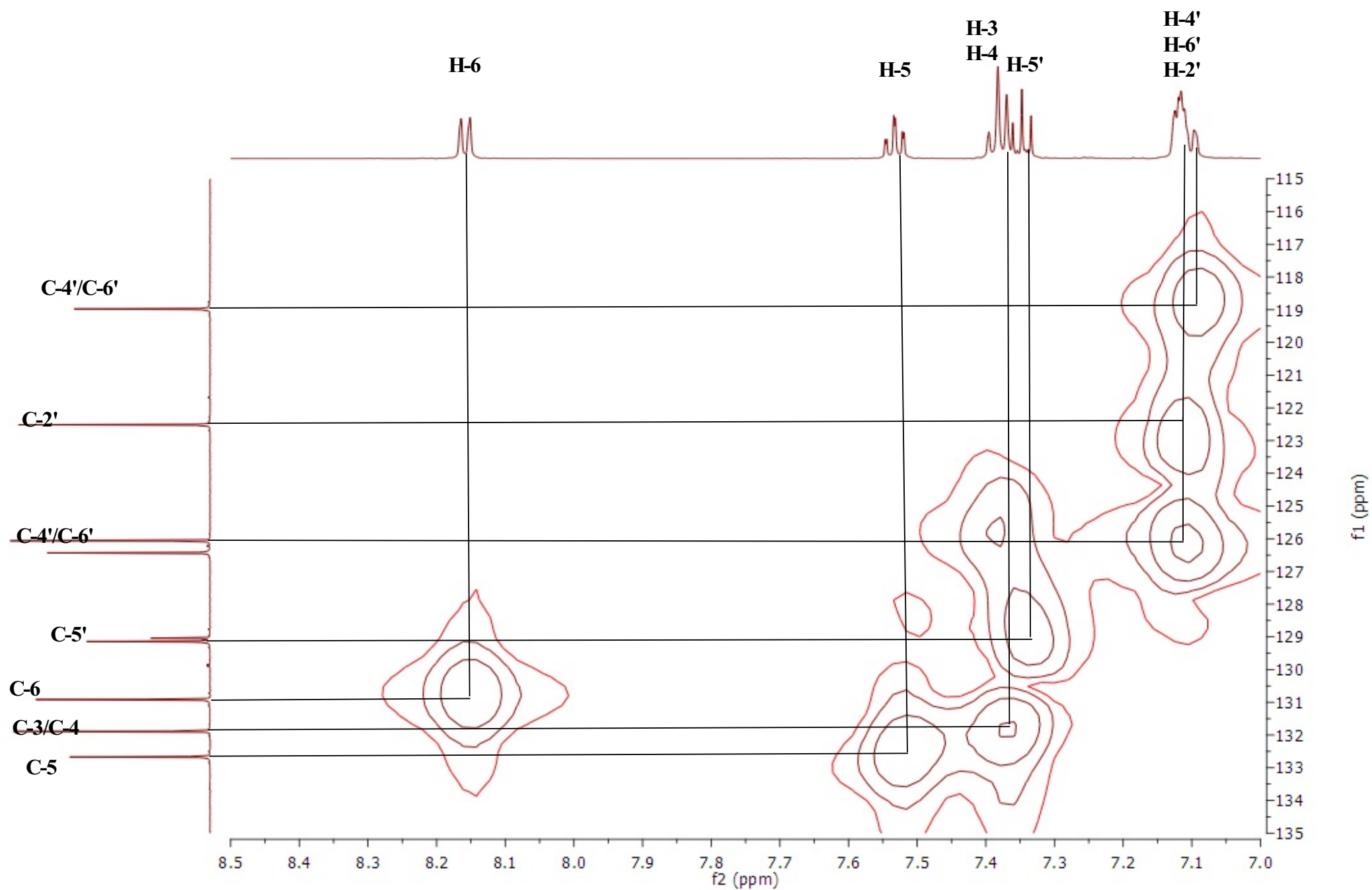
Plate nr. 4a ^{1}H NMR of 3-Methylphenyl 2-methylbenzoate

(600 MHz, Acetone-d$_6$) 8.13 (1H, dd, J 1.24 Hz, J 8.52 Hz, H-6); 7.56 (1H, dt, J 1.24 Hz, 8.52 Hz, H-5); 7.42-7.40 (2H, m, H-3, H-4); 7.35 (1H, t, J 7.4 Hz, H-5') 7.14-7.07 (3H, m, H-2', H-4', H-6'); 2.65 (3H, s, CH$_3$); 2.39 (3H, s, CH$_3$)
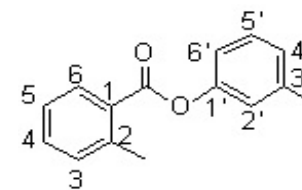
85
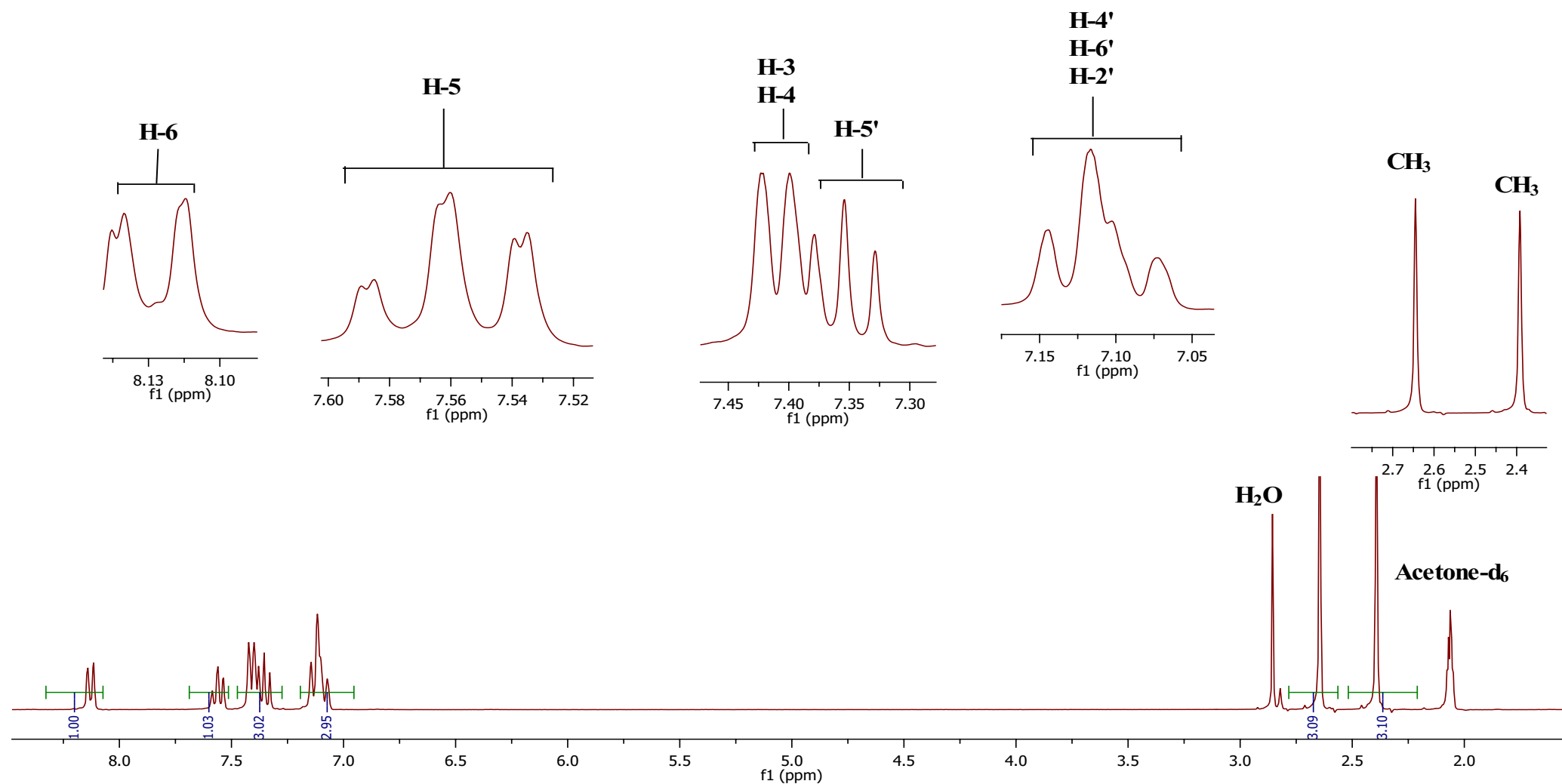
Plate nr. 3a ^{1}H NMR of 3-Methylphenyl 4-methylbenzoate

(600MHz, CDCl$_3$) 8.07 (2H, d, J 8.13 Hz, H-2, H-6); 7.42 (2H, d, J 8.13 Hz, H-3, H-5); 7.35 (1H, t, J 7.35 Hz, H-5'); 7.14-7.06 (3H, m, H-2', H-4', H-6'); 2.46 (3H, s, CH$_3$); 2.39 (3H, s, CH$_3$)
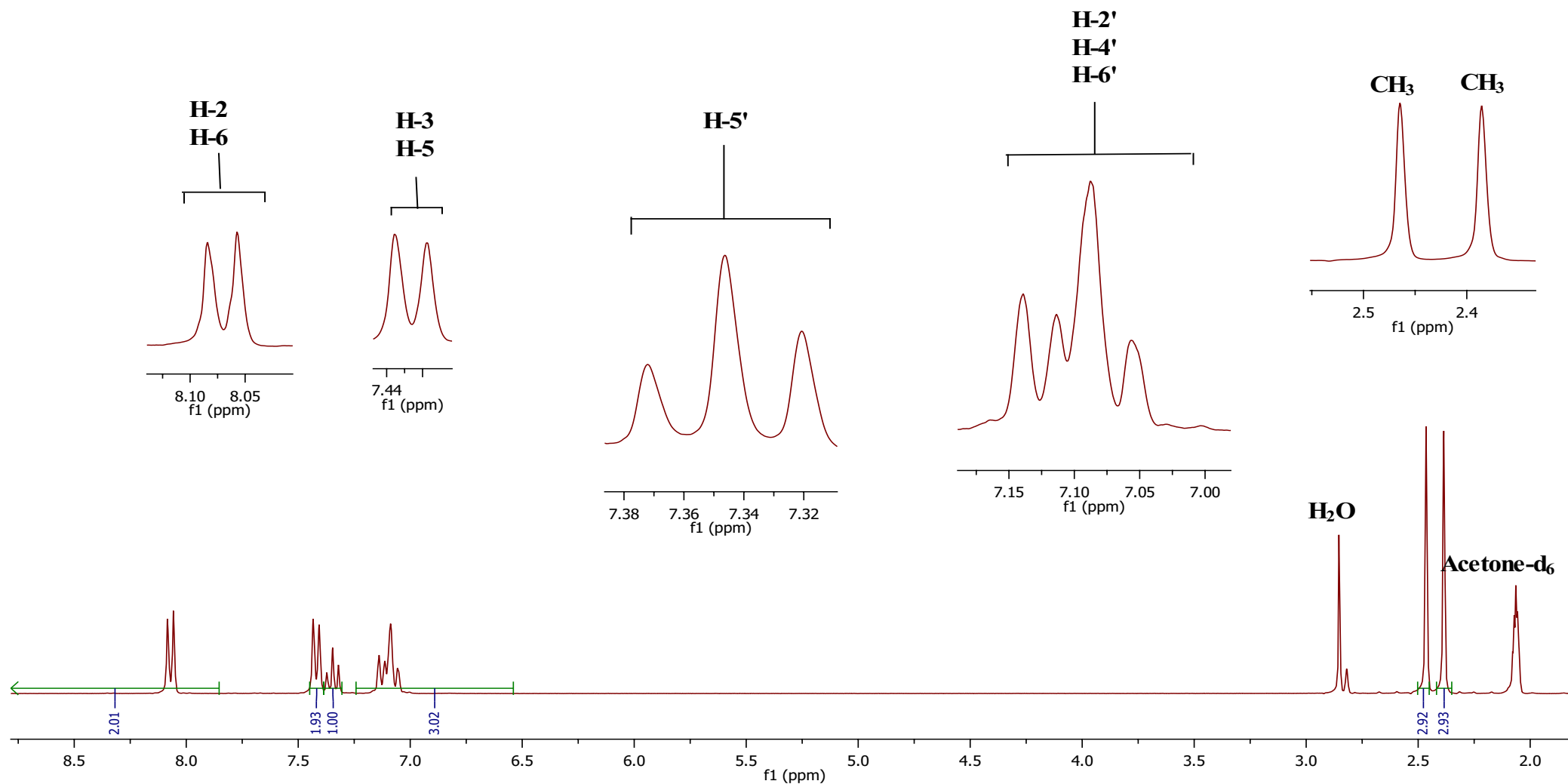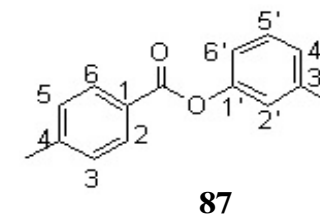
87

Plate nr. 3a ^{1}H NMR of 3-Methylphenyl 4-methylbenzoate

(600MHz, Acetone-d$_6$) 8.07 (2H, d, J 8.13 Hz, H-2, H-6); 7.42 (2H, d, J 8.13 Hz, H-3, H-5); 7.35 (1H, t, J 7.35 Hz, H-5'); 7.14-7.06 (3H, m, H-2', H-4', H-6'); 2.46 (3H, s, CH$_3$); 2.39 (3H, s, CH$_3$)

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Plate nr. 7a ¹H NMR of (*trans*)-butyl 2-methoxy-4-oxocyclohexanecarboxylate

(300 MHz, CDCl₃) 4.17 (2H, t, J 4.16 Hz, H-1''); 3.94-3.87 (1H, m, H-2); 3.34 (3H, s, OMe); 2.88-2.81 (1H, m, H-1); 2.76 (1H, dd, J 13 Hz, J 4.19 Hz, H-3); 2.48-2.45 (1H, m, H-3'); 2.43-2.41 (1H, m, H-5); 2.38-2.29 (1H, m, H-5'); 2.22-2.12 (1H, m, H-6); 2.03-1.91 (1H, m, H-6'); 1.70-1.61 (2H, m, H-2''); 1.47-1.34 (2H, m, H-3'') and 0.95 (3H, t, J 7.34 Hz, H-4'')
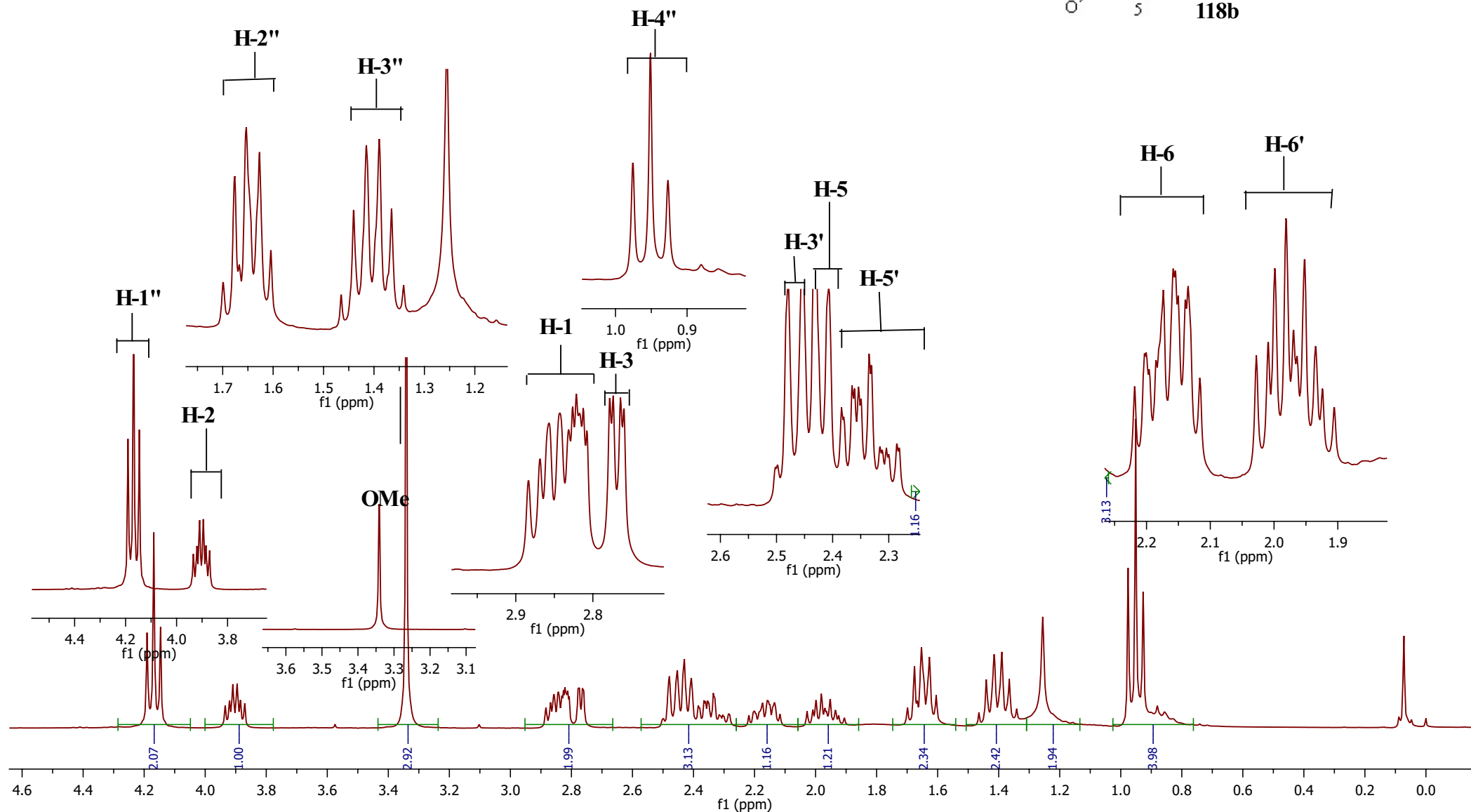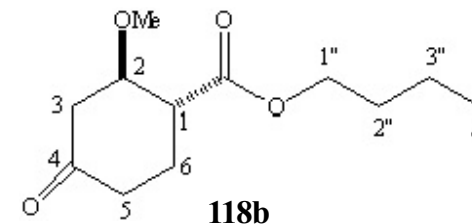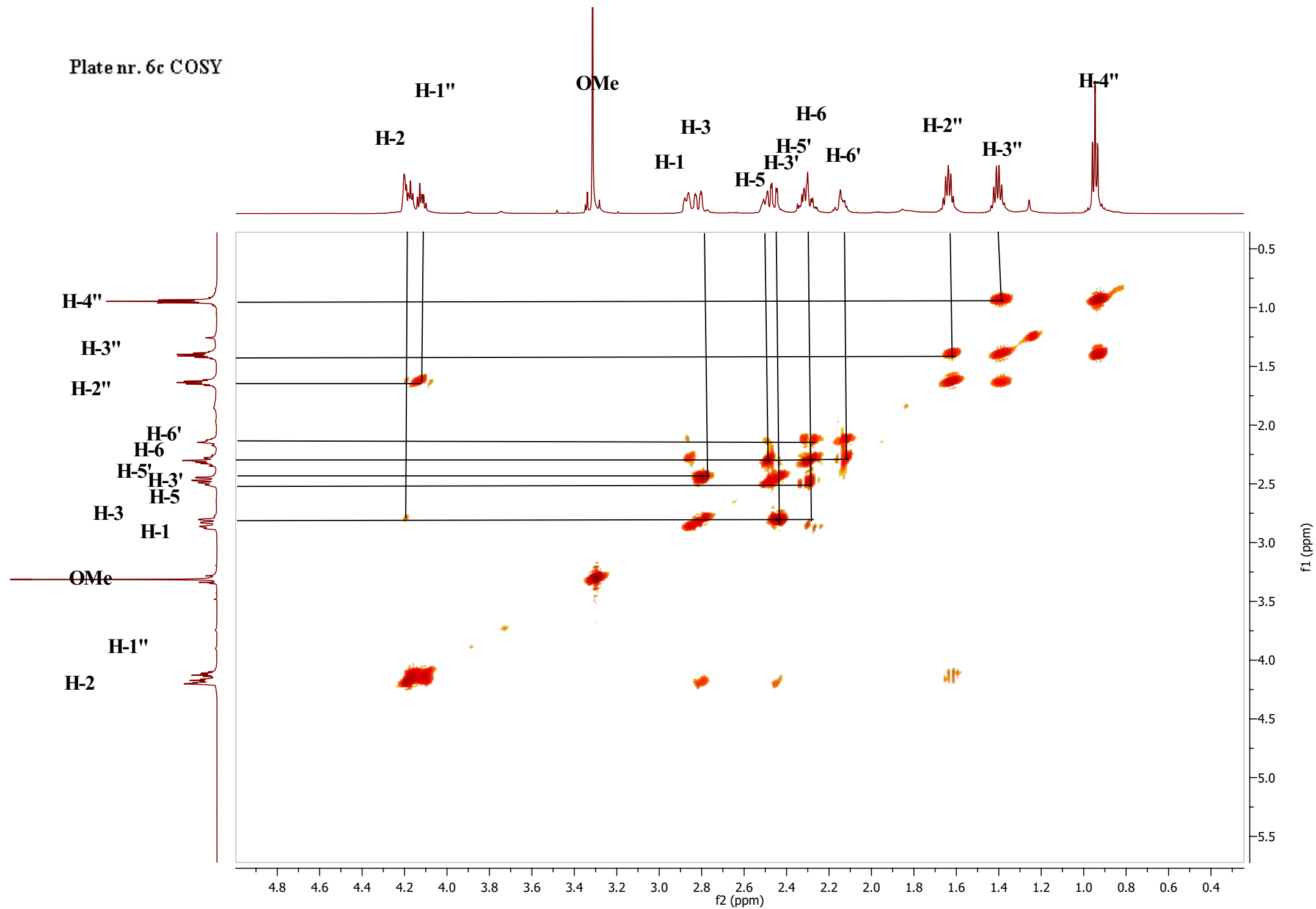
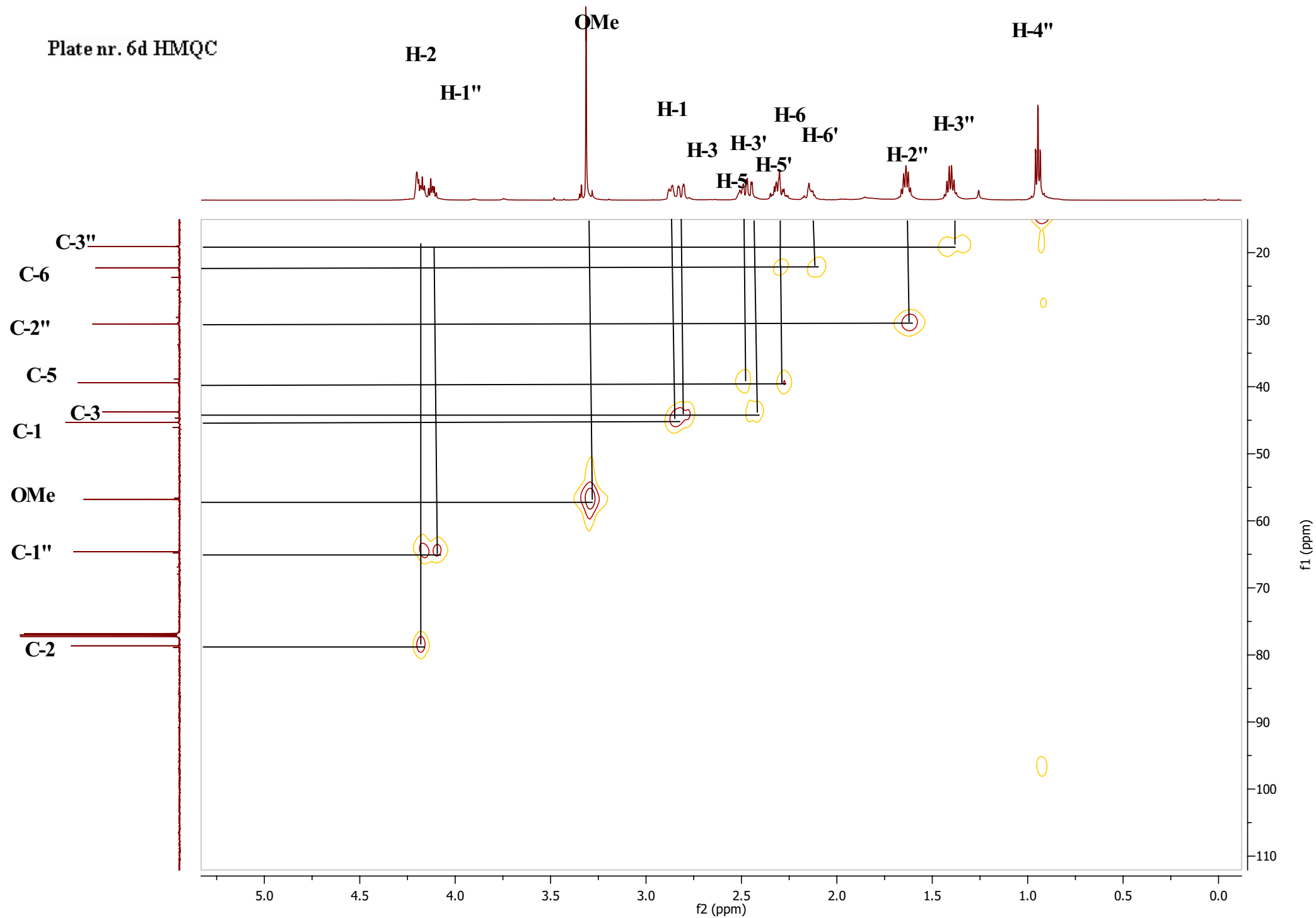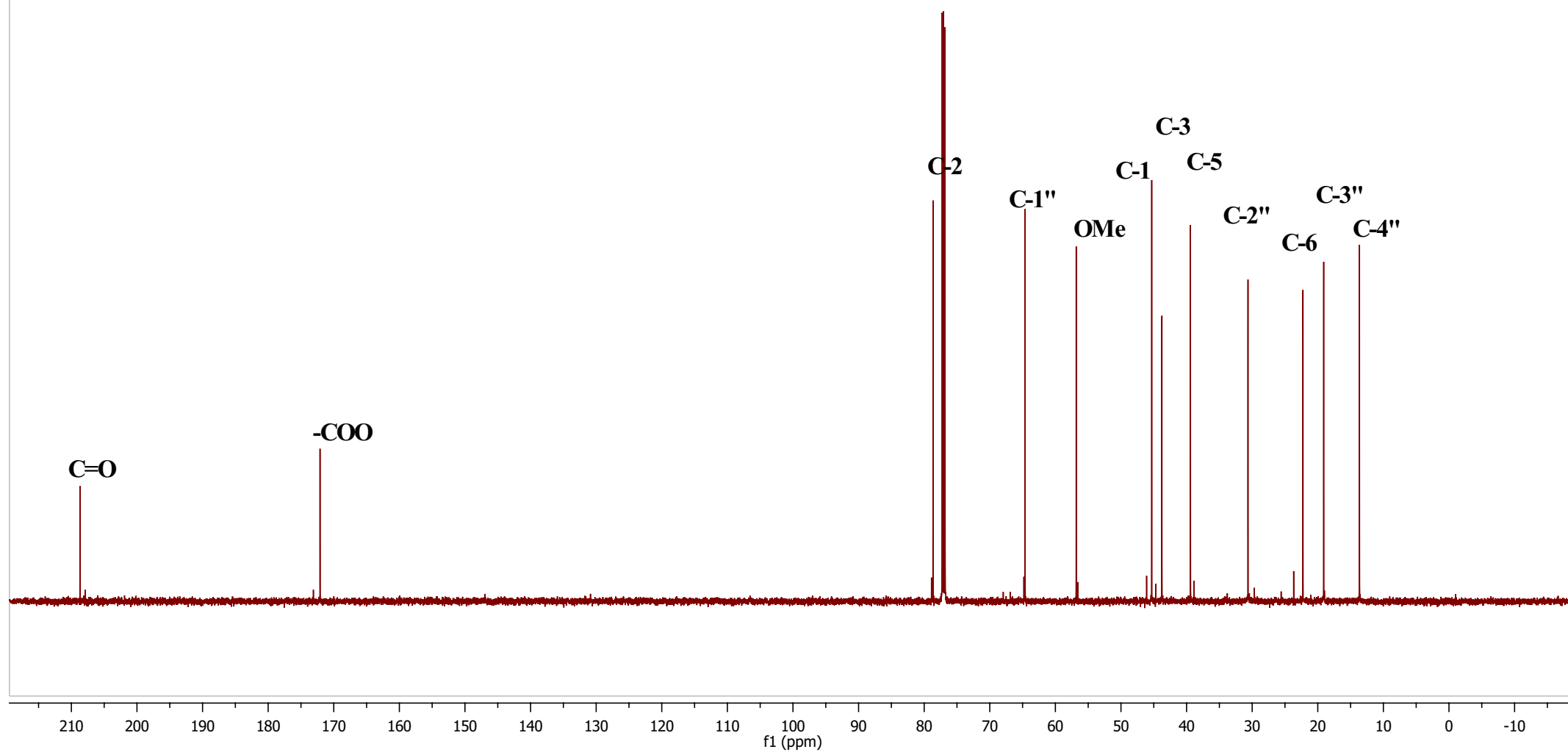Plate nr. 6c COSY

Plate nr. 6d HMQC

Plate nr: 6b ^{13}C

Plate nr. 6a ¹H NMR of (*cis*)-butyl 2-methoxy-4-oxocyclohexanecarboxylate

(600 MHz, CDCl₃) 4.23-4.18 (1H, m, H-2); 4.17-4.08 (2H, m, H-1''); 3.32 (3H, s, OMe); 2.90-2.84 (1H, m, H-1); 2.80 (1H, dd, J 2.1 Hz, J 4.08 Hz, H-3); 2.49 (1H, br.d, J 2.50 Hz, H-3'); 2.47-2.44 (1H, m, H-5); 2.34-2.26 (1H, m, H-5'); 2.24-2.19 (1H, m, H-6); 2.17-2.10 (1H, m, H-6'); 1.69-1.59 (2H, m, H-2''); 1.47-1.33 (2H, m, H-3'') and 0.95 (3H, t, J 7.3 Hz H-4'')

118a

Plate nr. 6a ¹H NMR of (*cis*)-butyl 2-methoxy-4-oxocyclohexanecarboxylate

(600 MHz, CDCl₃) 4.23-4.18 (1H, m, H-2); 4.17-4.08 (2H, m, H-1''); 3.32 (3H, s, OMe); 2.90-2.84 (1H, m, H-1); 2.80 (1H, dd, J 2.1 Hz, 4.08 Hz, H-3); 2.49 (1H, br.d, J 2.50 Hz, H-3'); 2.47-2.44 (1H, m, H-5); 2.34-2.26 (1H, m, H-5'); 2.24-2.19 (1H, m, H-6); 2.17-2.10 (1H, m, H-6'); 1.69-1.59 (2H, m, H-2''); 1.47-1.33 (2H, m, H-3'') and 0.95 (3H, t, J 7.3 Hz H-4'')
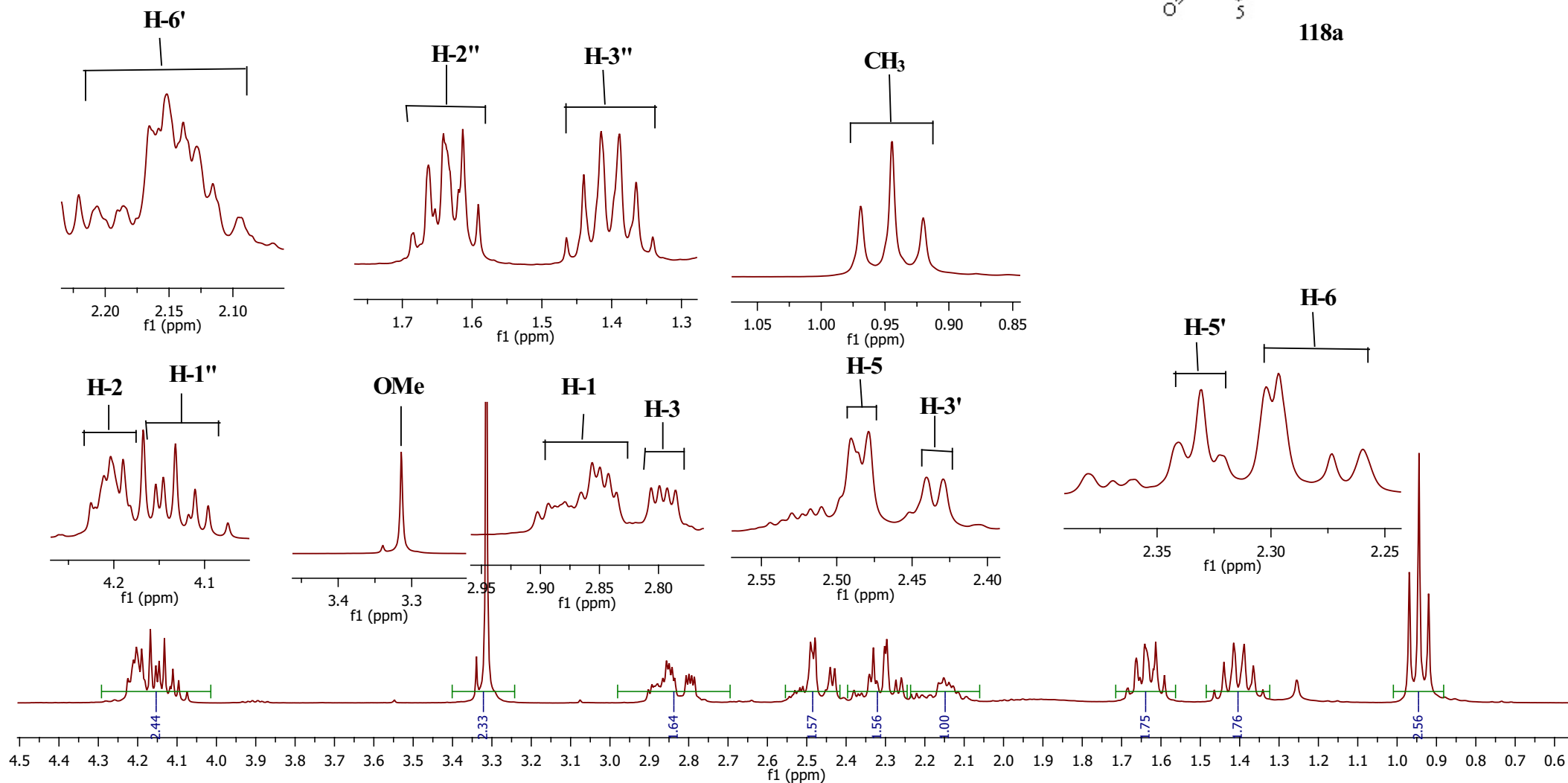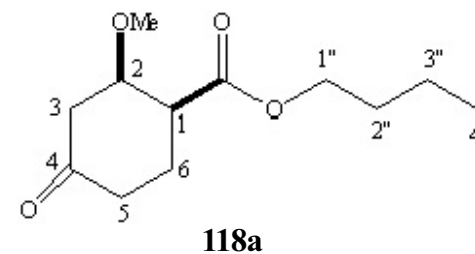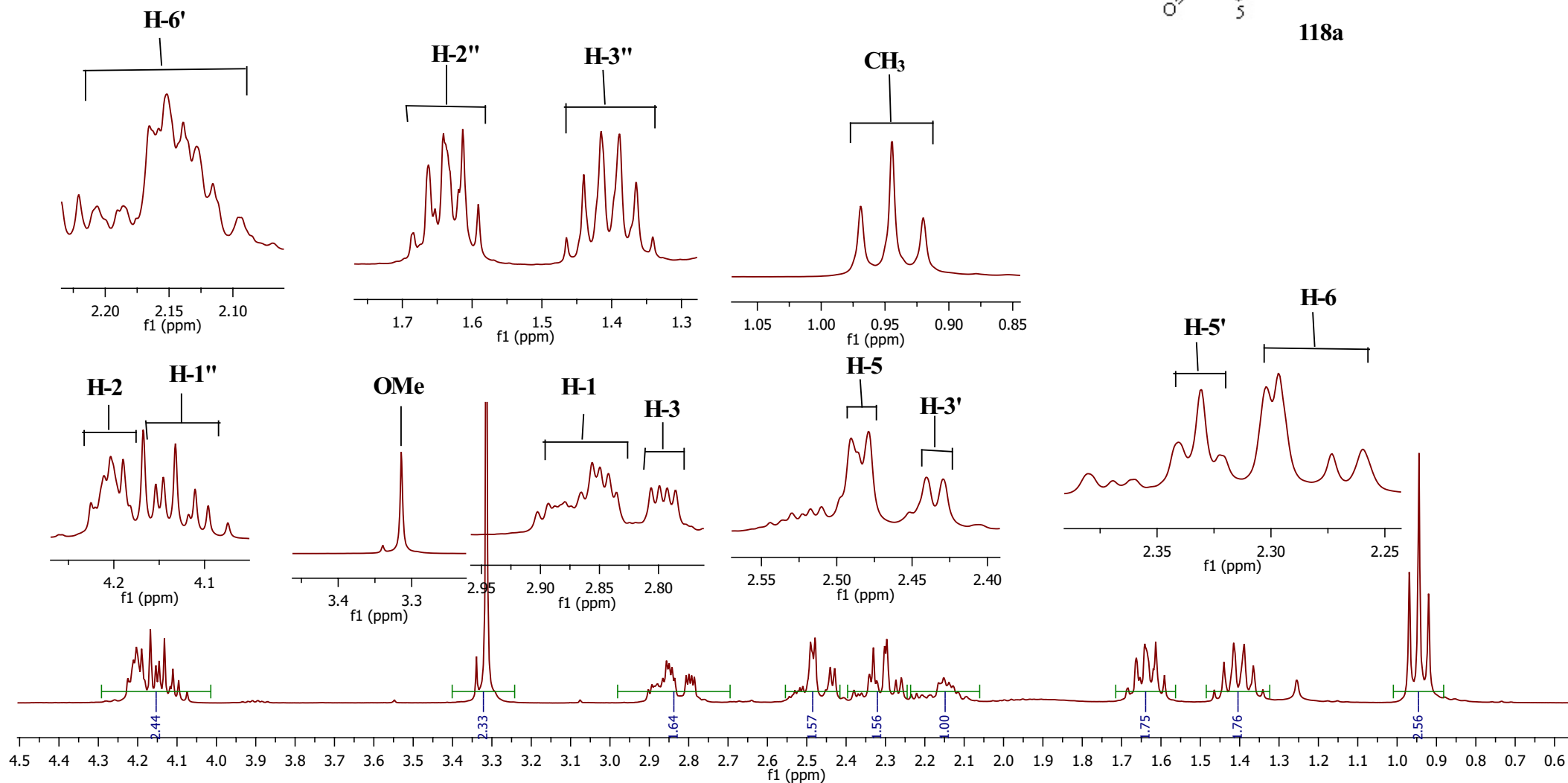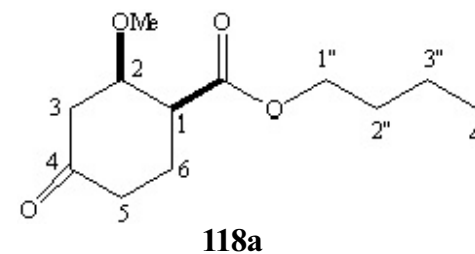

118a

Plate nr. 6c COSY

Plate nr. 7a ^{1}H NMR of (*trans*)-butyl 2-methoxy-4-oxocyclohexanecarboxylate

(300 MHz, CDCl$_3$) 4.17 (2H, t, J 4.16 Hz, H-1''); 3.94-3.87 (1H, m, H-2); 3.34 (3H, s, OMe); 2.88-2.81 (1H, m, H-1); 2.76 (1H, dd, J 1.3 Hz, 4.19 Hz, H-3); 2.48-2.45 (1H, m, H-3'); 2.43-2.41 (1H, m, H-5); 2.38-2.29 (1H, m, H-5'); 2.22-2.12 (1H, m, H-6); 2.03-1.91 (1H, m, H-6'); 1.70-1.61 (2H, m, H-2''); 1.47-1.34 (2H, m, H-3'') and 0.95 (3H, t, J 7.34 Hz H-4'')
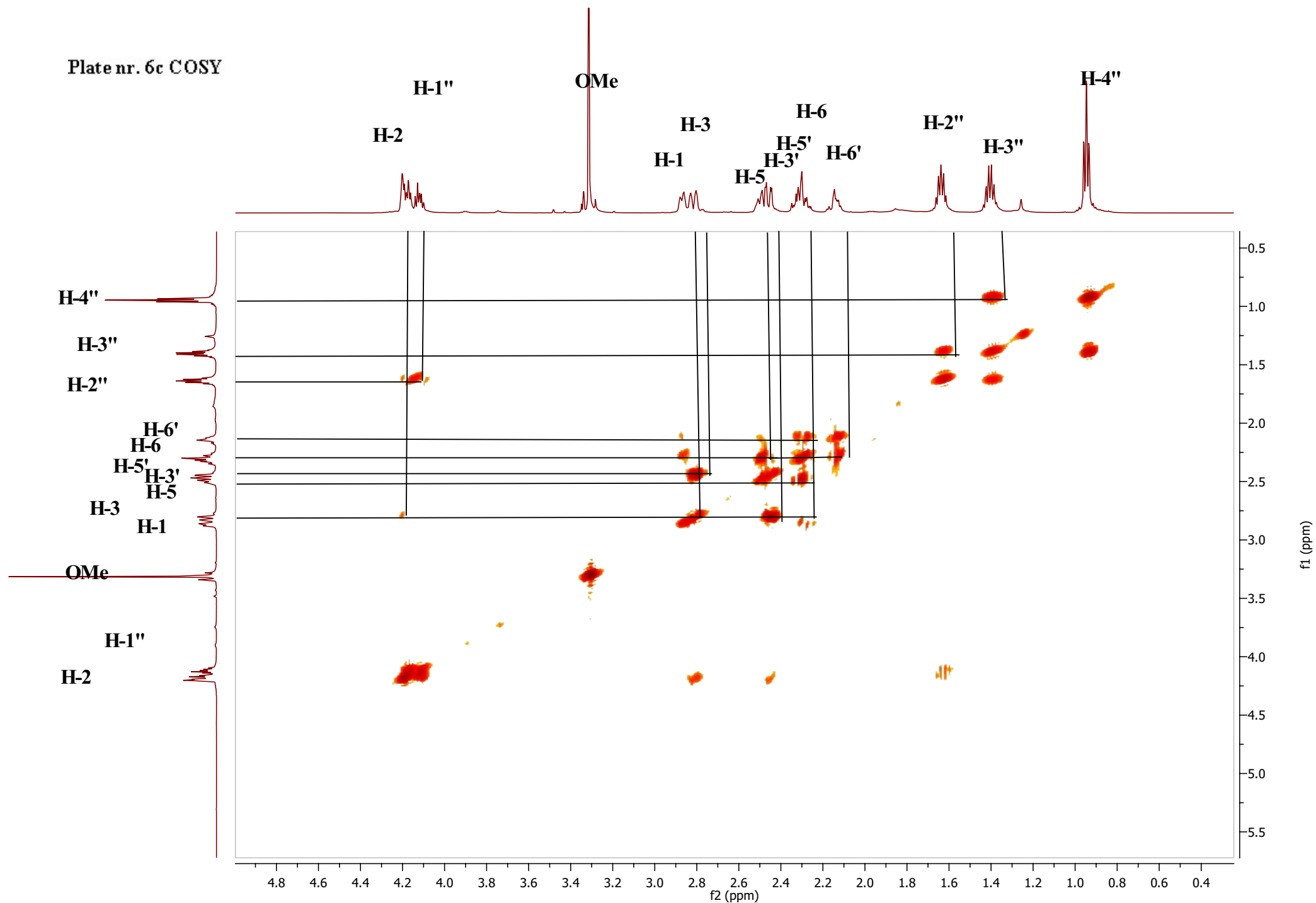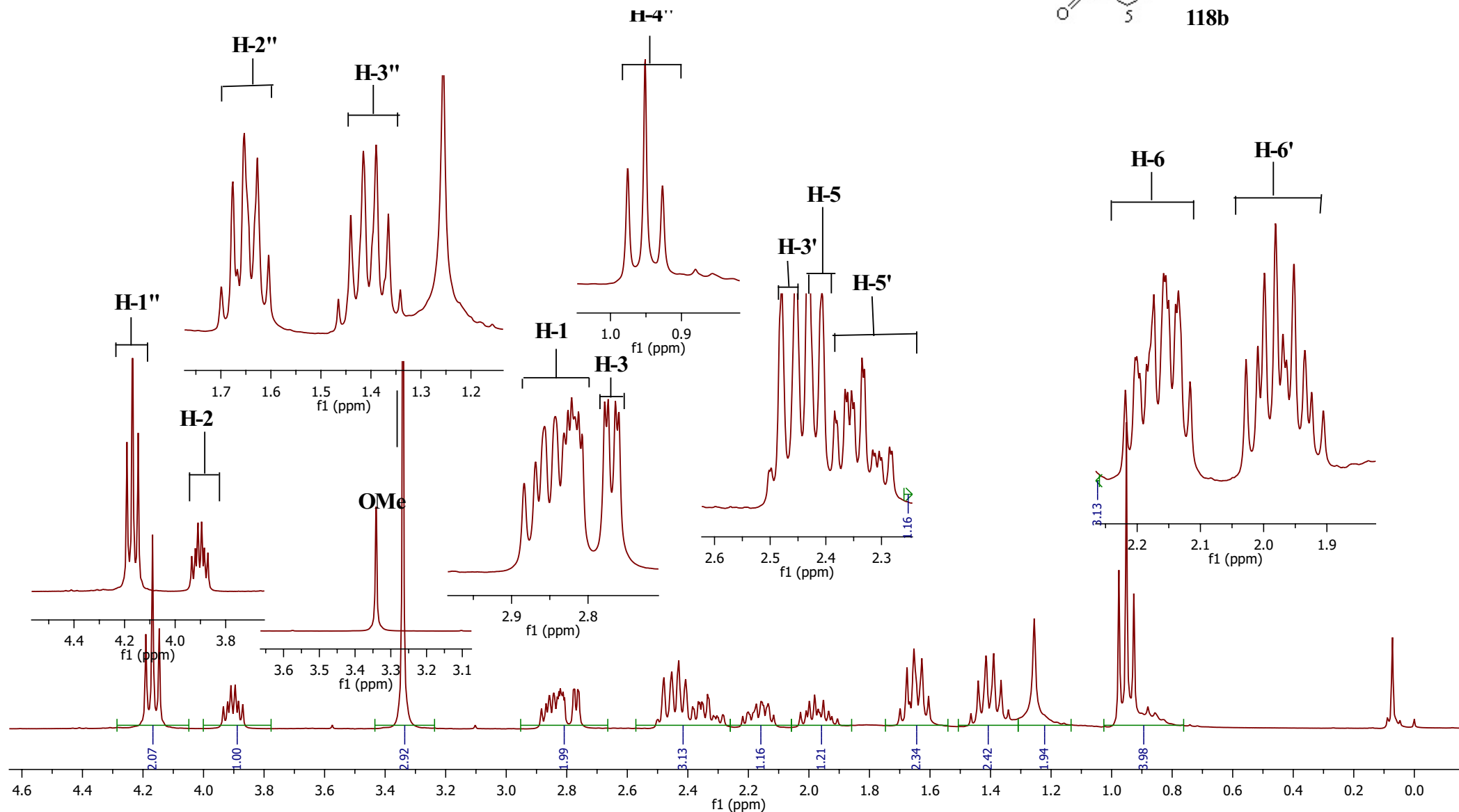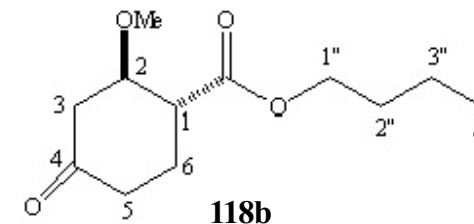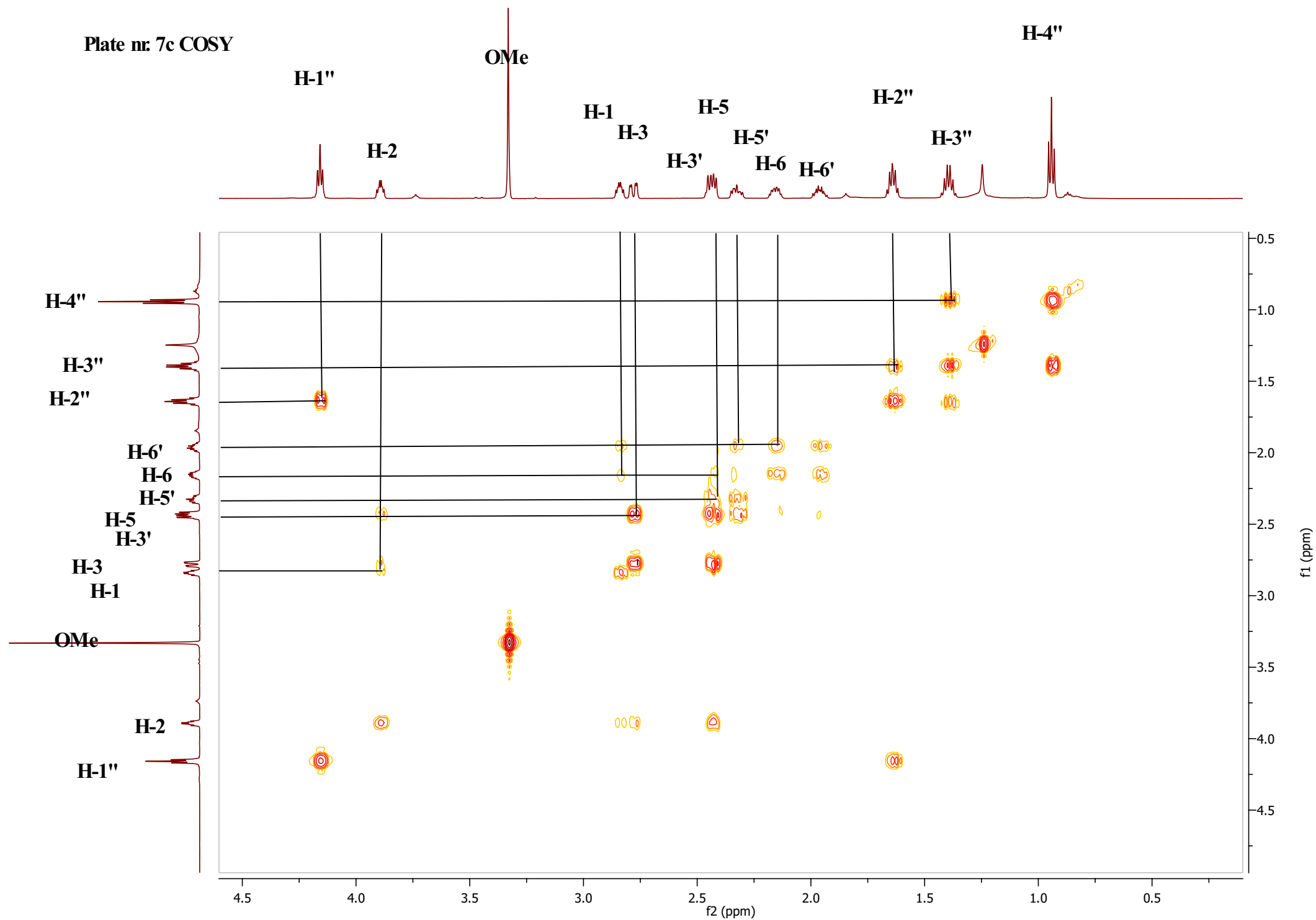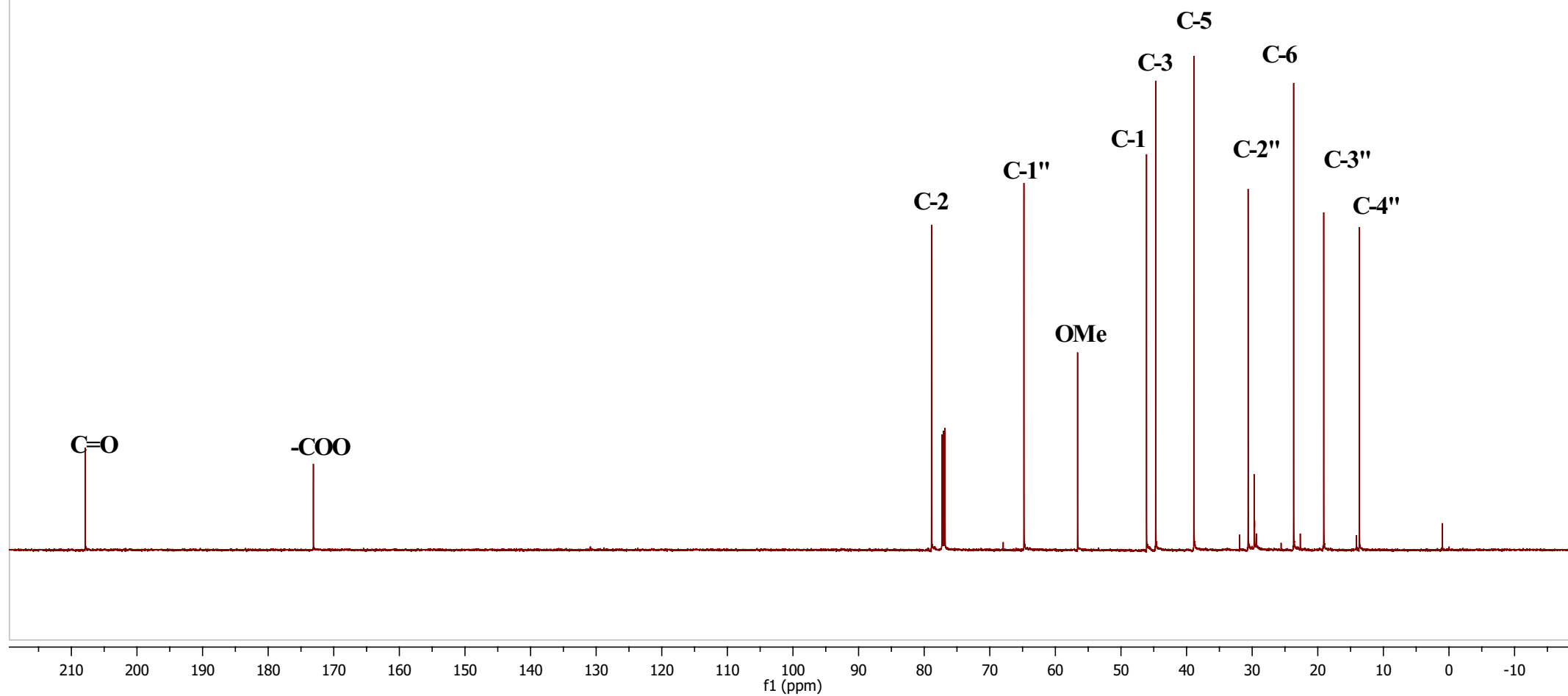

118b

Plate nr. 7c COSY
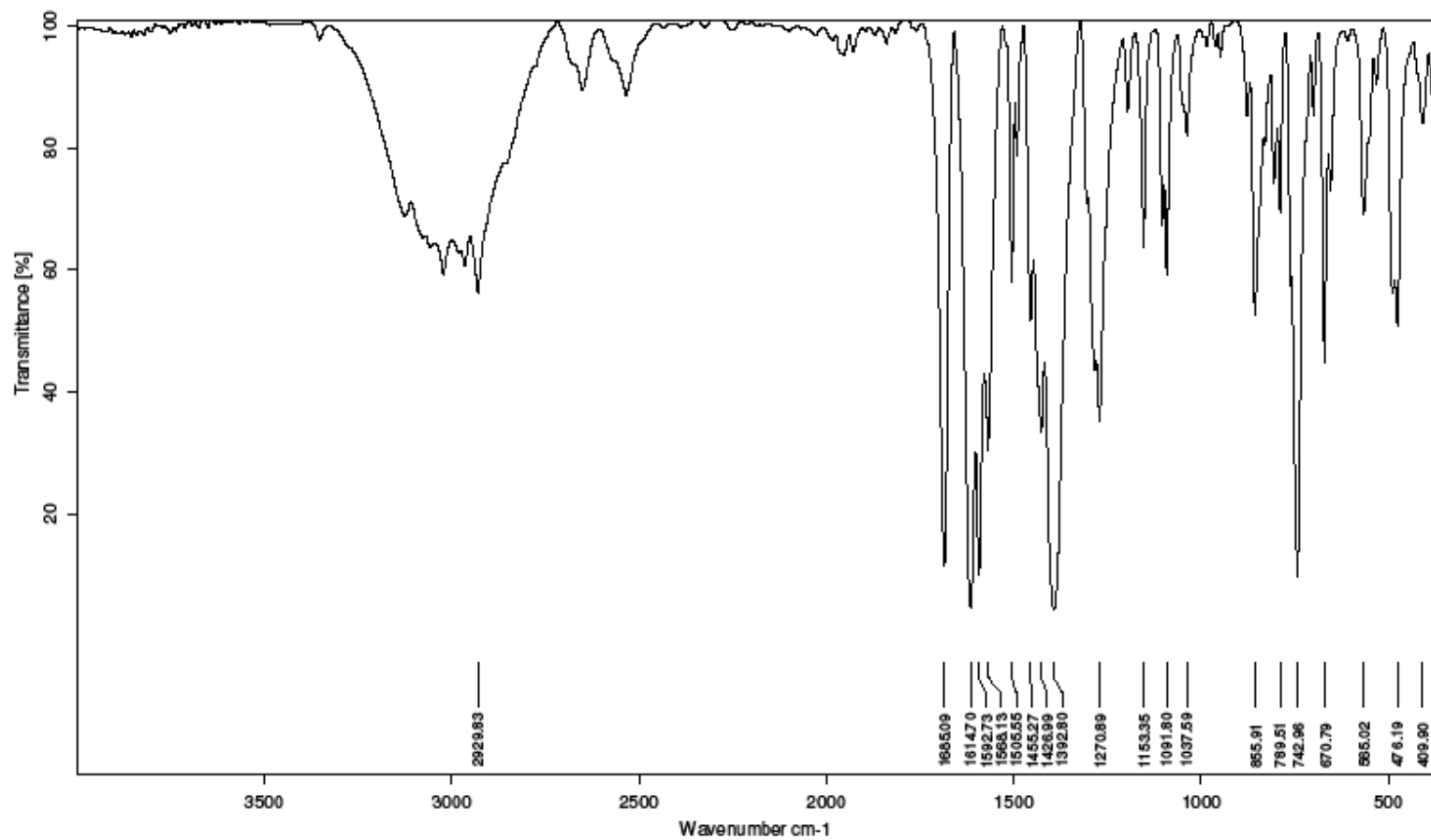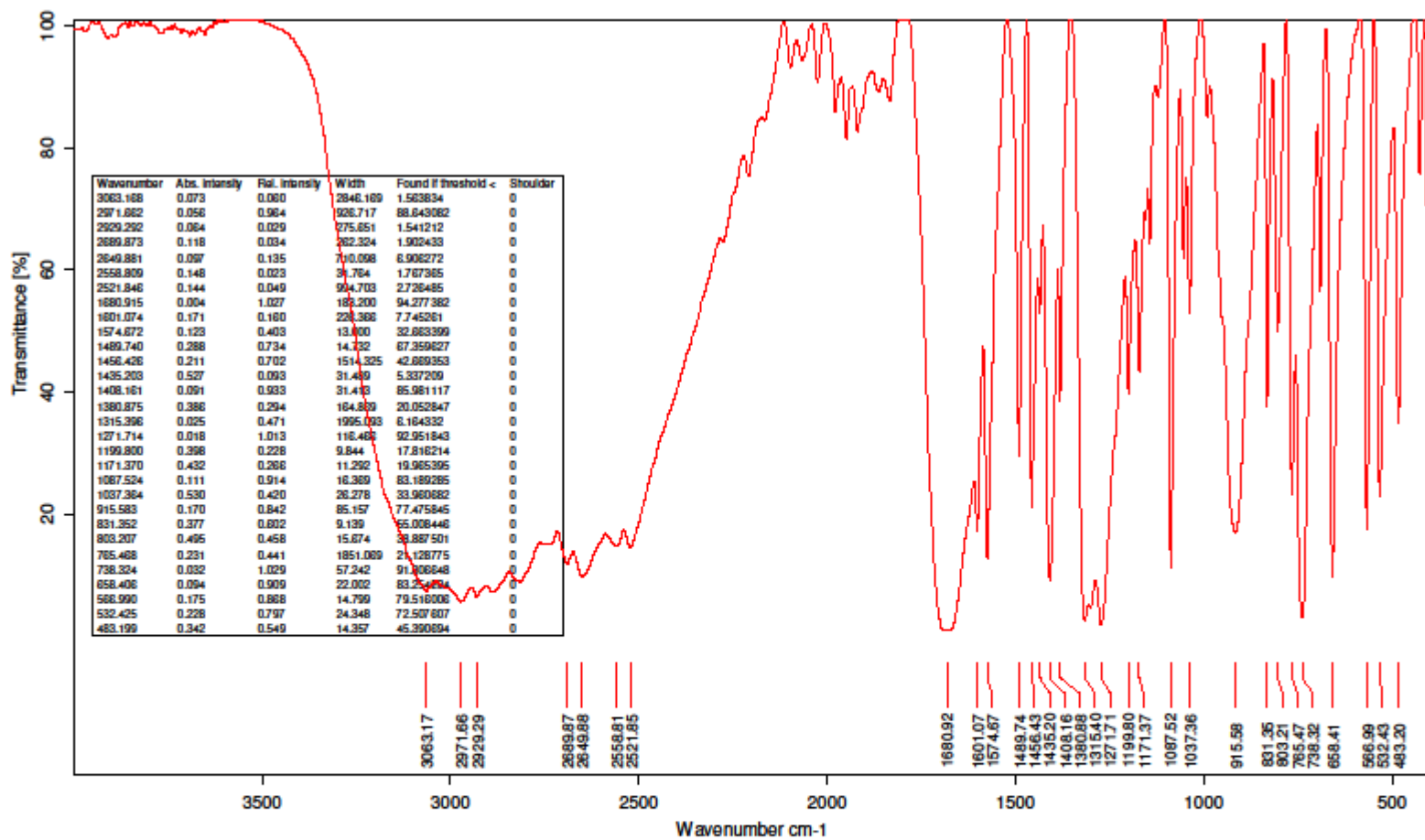
Plate nr: 7b ^{13}C

IR (**Plate 1**) of *tetrakis(μ₂-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)* (**90**).

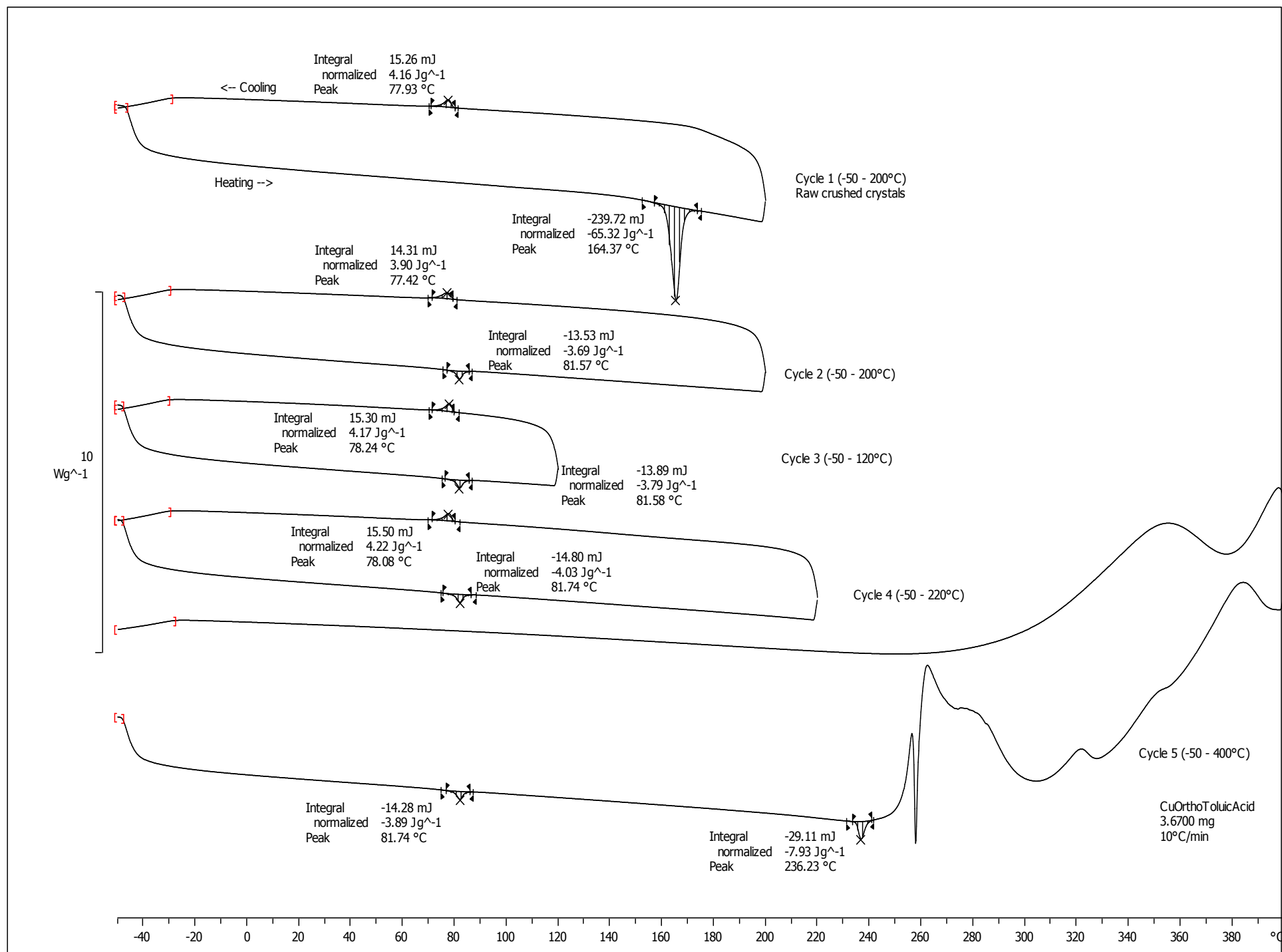| Wavenumber	Abs. Intensity	Rel. Intensity	Width	Found if threshold <	Shoulder
3063.168	0.073	0.060	2846.169	1.563834	0
2971.662	0.056	0.964	926.717	88.643082	0
2929.292	0.064	0.029	275.851	1.541212	0
2689.873	0.118	0.034	262.324	1.902433	0
2649.881	0.097	0.135	700.098	6.906272	0
2558.809	0.148	0.023	31.764	1.767365	0
2521.846	0.144	0.049	904.703	2.726485	0
1680.915	0.004	1.027	189.200	94.277382	0
1601.074	0.171	0.160	228.388	7.745261	0
1574.672	0.123	0.403	13.000	32.683399	0
1489.740	0.288	0.734	14.732	67.359627	0
1456.426	0.211	0.702	1514.325	42.689353	0
1435.203	0.527	0.093	31.459	5.337209	0
1408.161	0.091	0.933	31.413	85.981117	0
1380.875	0.386	0.294	164.869	20.052847	0
1315.398	0.025	0.471	1995.093	6.164332	0
1271.714	0.018	1.013	118.462	92.951843	0
1199.800	0.398	0.228	9.844	17.816214	0
1171.370	0.432	0.268	11.292	19.965395	0
1087.524	0.111	0.914	16.369	83.189285	0
1037.364	0.530	0.420	26.278	33.960882	0
915.583	0.170	0.842	85.157	77.475845	0
831.352	0.377	0.602	9.139	65.008446	0
803.207	0.495	0.458	15.674	38.887501	0
765.468	0.231	0.441	1851.089	21.128775	0
738.324	0.032	1.029	57.242	91.906848	0
658.408	0.094	0.909	22.002	83.253794	0
568.990	0.175	0.868	14.799	79.518008	0
532.425	0.228	0.797	24.348	72.507807	0
483.199	0.342	0.549	14.357	45.390894	0

IR (**Plate 7**) of *o*-toluic acid (**78**).

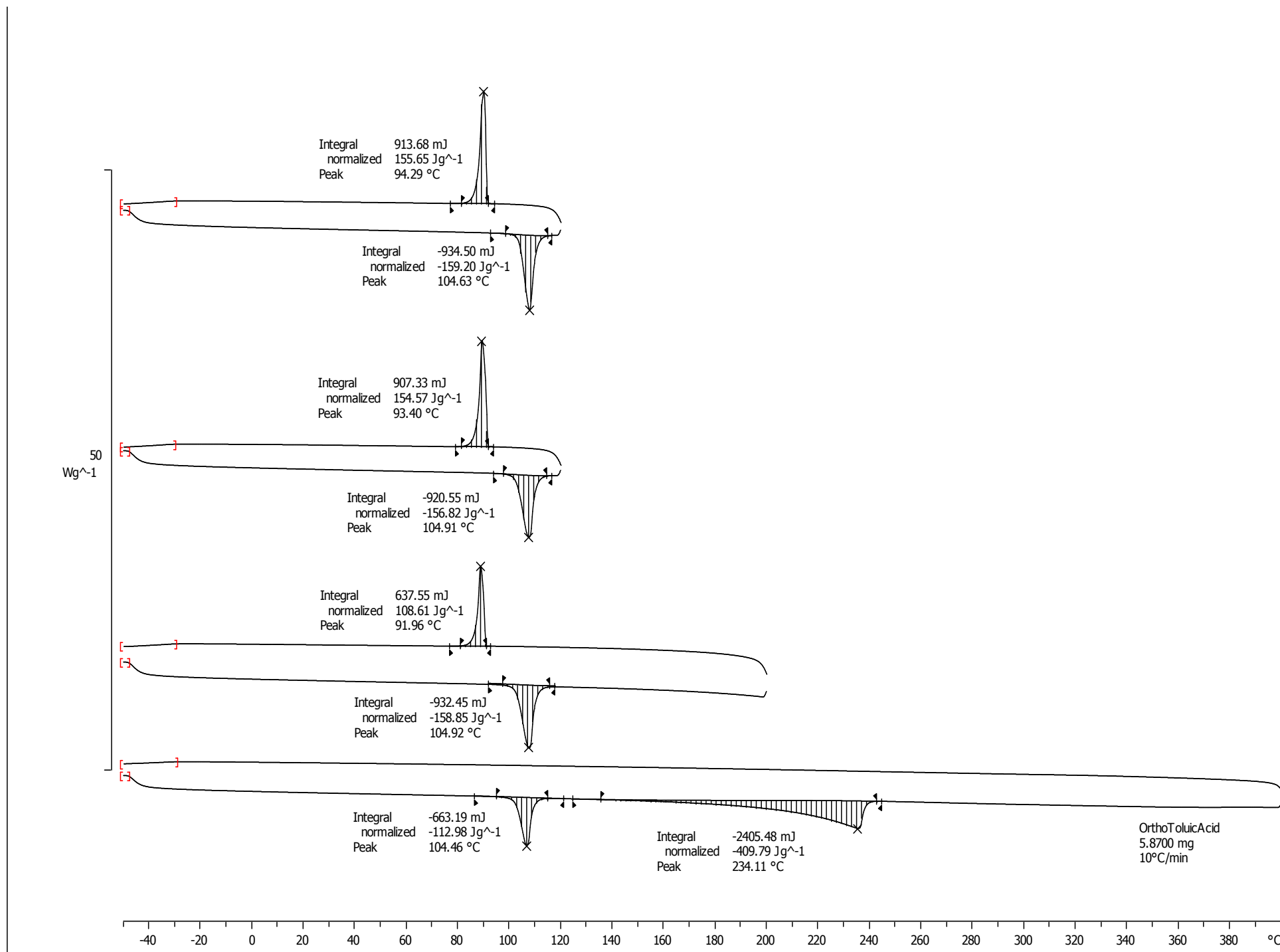**Figure 5:** DSC scan of *tetrakis(µ₂-2-methylbenzoato)bis(2-methylbenzoic acid)copper(II)* (**90**).

Figure 4: DSC scan of *o*-toluic acid (**78**).