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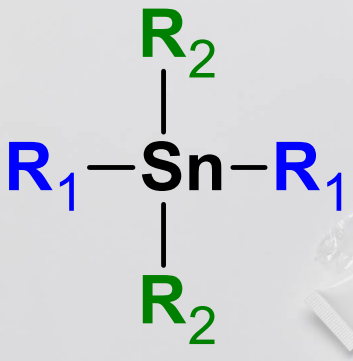

NMR based investigation of the hydrolysis of DOTE and DBTM

Federal Ministry
Republic of Austria
Sustainability and Tourism

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CONVERSION OF ORGANOTIN COMPOUNDS IN THE GASTRIC ENVIRONMENT

NMR based investigation of the hydrolysis of DOTE and DBTM

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Federal Ministry
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CONTENT

SUMMARY

Organotin compounds used in PVC production as heat stabilisers are registered in the high tonnage bands under Regulation (EC) No 1907/2006 (REACH). Not for all of them are sufficient toxicological data, especially higher tier studies, available. Nevertheless, under REACH registration, using the read-across approach is the key to avoiding unnecessary animal testing. It has been assumed previously that dioctyltin bis(2-ethylhexyl mercaptoacetate) (DOTE) and dibutyltin maleate (DBTM) form corresponding dichloride compounds under simulated gastric conditions (dioctyltin dichloride (DOTC) or dibutyltin dichloride (DBTC), respectively) and thus it was hypothesised that their toxicological behaviour is similar to the chloride forms. DOTC and DBTC are known reproductive toxicants.

The aim of the present investigations is to further characterise the metabolites of DOTE and DBTM formed in a gastric environment in order to substantiate or challenge the application of a read-across approach to DOTC and DBTC as proposed under REACH.

NMR based investigations of DOTE

Nuclear magnetic resonance (NMR) based investigations of DOTE have shown that DOTC is not formed in a simulated gastric environment (0.1 mol/L of aqueous HCl, 72 h, 40 °C). Instead, DOTE was partially converted to dioctyltin (2-ethylhexyl mercaptoacetate) monochloride (DOTECl). ^{119}Sn-NMR of the starting material revealed that the starting material contains 30% of monooctyltin tris(2-ethylhexyl mercaptoacetate) (MOTE) besides DOTE. Thus, the corresponding monochloride (MOTECl) was detected by NMR as well. The conversion of MOTE to MOTECl is significantly slower than the conversion of DOTE to DOTECl: only 36% of MOTE was converted whereas 79% of DOTE was converted to the corresponding monochloride during the reaction.

Three experiments with different extraction solvents (hexane, dichloromethane) or deuterated NMR solvents (dichloromethane-D_2, toluene-D_8) were conducted in order to investigate the influence of the organic extracts on the composition of the formed reaction products depending on their different extracting properties. Similar composition ratios of DOTE/MOTE/DOTECl/MOTECl were detected in all three experiments. Consequently, the influence of the organic extract on the composition of the formed reaction products when using different extraction solvents for NMR analysis is negligible.

The present study substantiates previous findings of a recent publication, namely that DOTE forms the corresponding monochloride (DOTECl) under simulated gastric conditions (0.1 mol/L of aqueous HCl, 72 h, 40 °C) [COSTLOW ET AL. 2017]. DOTC as a potential reaction product was not detected by NMR in any experiment. However, there are still uncertainties regarding a read-across approach applied to DOTC, since the testing conditions do not reflect the further metabolism under in vivo conditions.

NMR based investigations of DBTM

NMR based investigations of DBTM have shown that DBTM was quantitatively converted to bis(dibutylchlorotin) oxide dimer (DBDTC dimer) in a simulated gastric environment (0.1 mol/L of aqueous HCl, 72 h, 40 °C) using dichloromethane-D_2 as extraction solvent. Other potential metabolites such as DBTC or dibutyltin oxide (DBTO) were not detected. Thus, the [SCHILT ET AL. 2004] study, stating that DBTM was fully converted to DBTC and the corresponding ligand maleic acid (MA) after a 30-minute reaction time, could not be confirmed under the investigated conditions.

It has been demonstrated previously that upon hydrolysis of category members such as DBTC and DBTO, DBDTC distannoxane dimer is formed under similar conditions [P. MUNSCHI ET AL. 2010 and Y. PATEL ET AL. 2009].

Thus, it can be speculated via which intermediates (DBTO, DBTC to name only two possible pathways) the DBDTC dimer is formed during the hydrolysis of DBTM. Additional hydrolysis experiments of DBTM, DBTC and DBTO in a time-resolved fashion could help to reveal this information but are beyond the scope of this study.

In order to ensure that smaller amounts of DBTC are detectable, a spiking experiment of the DBDTC dimer with DBTC was performed which revealed that the limit of detection (LOD) of the ^{119}Sn-NMR analysis can be estimated at 3 mol%.

The present study demonstrates that DBTM forms hydrolysis products which are identical to DBTC or DBTO and therefore gives important information on the hydrolysis behaviour of DBTM.

Furthermore, it was demonstrated that DBTM, which belongs to the class of dialkyltin compounds carrying carboxyl ligands, does not form metabolites which are similar to dialkytin compounds carrying thiol ligands such as MOTE or DOTE under simulated gastric conditions.

ZUSAMMENFASSUNG

Organozinnverbindungen, die bei der PVC-Herstellung als Hitzestabilisatoren verwendet werden, sind in hochtonnagigen Mengenbereichen gemäß der Verordnung (EG) Nr. 1907/2006 (REACH) registriert. Nicht für alle von ihnen liegen ausreichende toxikologische Daten vor, insbesondere mehrstufige Studien fehlen. Ein Schlüsselansatz bei der REACH-Registrierung ist jedoch die Anwendung des „read-across“ (Analogiekonzepts), um unnötige Tierversuche zu vermeiden. Bisher wurde angenommen, dass DOTE und DBTM unter gastrischen Bedingungen die dementsprechenden Dichloridverbindungen (DOTC bzw. DBTC) bilden, und somit das toxikologische Verhalten der Chloridspezies ähnlich ist. DOTC und DBTC sind bekannte reproduktionstoxische Substanzen.

Ziel der vorliegenden Studie ist es, die unter gastrischen Bedingungen gebildeten Metaboliten von DOTE und DBTM weiter zu charakterisieren, um die vorgeschlagenen „read across“ zu DOTC und DBTC unter REACH zu belegen oder in Frage zu stellen.

NMR-basierte Untersuchungen von DOTE

Kernspinresonanz (NMR) basierte Untersuchungen von Dioctylzinn bis(2-ethylhexylmercaptoacetat) (DOTE) haben gezeigt, dass Dioctylzinn dichlorid (DOTC) unter simulierten gastrischen Bedingungen (0,1 mol/L wässrige HCl, 72 h, 40 h) nicht gebildet wird. Stattdessen wurde DOTE teilweise in Octylzinn (2-ethylhexylmercaptoacetat) monochlorid (DOTECl) umgewandelt. Die Messung des Edukts mittels ^{119}Sn-NMR ergab, dass das Ausgangsmaterial neben DOTE auch 30 % monooctylzinn tris(2-ethylhexylmercaptoacetat) (MOTE) enthielt. Somit wurde das entsprechende Monochlorid Reaktionsprodukt (MOTECl) auch durch NMR nachgewiesen. Die Reaktion von MOTE zu MOTECl verläuft wesentlich langsamer als die Umwandlung von DOTE zu DOTECl: Nur 36 % von MOTE wurden umgewandelt, während 79 % von DOTE in der Reaktion in das entsprechende Monochlorid konvertiert wurden.

Drei Versuche mit unterschiedlichen Extraktionslösungsmitteln (Hexan, Dichlormethan) oder deuterierten NMR-Lösungsmitteln (Dichlormethan-D2, Toluol-D8) wurden durchgeführt, um den Einfluss auf die Zusammensetzung der organischen Extrakte aufgrund ihrer unterschiedlichen Extraktionseigenschaften zu untersuchen. Ähnliche Zusammensetzungsverhältnisse von DOTE/MOTE/DOTECl/MOTECl wurden in allen drei Experimenten beobachtet. Folglich ist der Einfluss auf die Zusammensetzung des organischen Extrakts durch Verwendung verschiedener Lösungsmittel zur Extraktion für die NMR-Analytik vernachlässigbar.

Die vorliegende Studie untermauert frühere Ergebnisse einer kürzlich erschienenen Veröffentlichung, wonach DOTE unter gastrischen Bedingungen (0,1 mol/L wässrige HCl, 72 h, 40 °C) das entsprechende Monochlorid (DOTECl) bildet [COSTLOW ET AL. 2017]. DOTC als potentielles Reaktionsprodukt wurde in keinem der Experimente mittels NMR nachgewiesen. Es bestehen jedoch immer noch Unsicherheiten hinsichtlich eines „read across“ auf DOTC, da die Testbedingungen keinen weiteren Metabolismus unter in-vivo-Bedingungen widerspiegeln.

NMR-basierte Untersuchungen von DBTM

NMR-basierte Untersuchungen von Dibutylzinnmaleat (DBTM) haben gezeigt, dass DBTM unter simulierten gastrischen Bedingungen (0,1 mol/L wässrige HCl, 72 h, 40 °C) unter Verwendung von Dichlormethan-D2 als Extraktionslösungsmittel quantitativ in Bis(dibutylchlorzinn)oxid-Dimer (DBDTC-Dimer) umgewandelt wurde. Andere potenzielle Metaboliten wie Dibutylzinndichlorid (DBTC) oder Dibutylzinnoxid (DBTO) wurden nicht detektiert. Die [SCHILT ET AL. 2004] Studie, die besagt, dass DBTM nach 30 Minuten Reaktionszeit vollständig in DBTC und den entsprechenden Liganden Maleinsäure (MA) konvertiert, konnte unter den vorherrschenden Reaktionsbedingungen nicht bestätigt werden.

Es ist literaturbekannt, dass bei der Hydrolyse von Kategoriemitgliedern, (z. B. DBTC- und DBTO), das DBDTC-Distannoxandimer unter ähnlichen Bedingungen gebildet wird [P. MUNSCHI ET AL. 2010 und Y. PATEL ET AL. 2009].

Somit kann spekuliert werden, über welche Zwischenprodukte (DBTO, DBTC, um nur zwei potentielle Reaktionsintermediate zu nennen) das DBDTC-Dimer während der Hydrolyse von DBTM gebildet wird. Zusätzliche, zeitaufgelöste Hydrolyseexperimente von DBTM, DBTC und DBTO könnten helfen, den Reaktionsweg aufzuklären, jedoch würden diese zusätzlichen Experimente über den Rahmen dieser Studie hinausgehen.

Um sicherzustellen, dass auch niedrige Konzentrationen an DBTC nachweisbar sind, ergab ein Dotierungsexperiment des DBDTC-Dimers mit DBTC, dass die Nachweisgrenze (LOD) der ^{119}Sn-NMR-Analytik auf 3 mol% geschätzt werden kann.

Die vorliegende Studie zeigt, dass DBTM identische Hydrolyseprodukte wie DBTC oder DBTO bildet und liefert daher wichtige Informationen zum Hydrolyseverhalten von DBTM.

Weiters konnte gezeigt werden, dass DBTM, das zur Gruppe der Carboxylliganden tragenden Dialkylzinnverbindungen gehört, keine ähnlichen Metaboliten unter simulierten gastrischen Bedingungen bildet wie Dialkylzinnverbindungen, die Thiolliganden wie MOTE oder DOTE tragen.

1 INTRODUCTION

1.1 Application and function of organotin compounds

various uses of organotin compounds

Over the past eight decades, organotins have been used in a wide range of applications, mainly as pesticides and biocidal products, as a catalyst for the production of polyurethane foams, as a crosslinking agent for silicone rubbers, and as a light and heat stabiliser in the production of PVC (Figure 1).

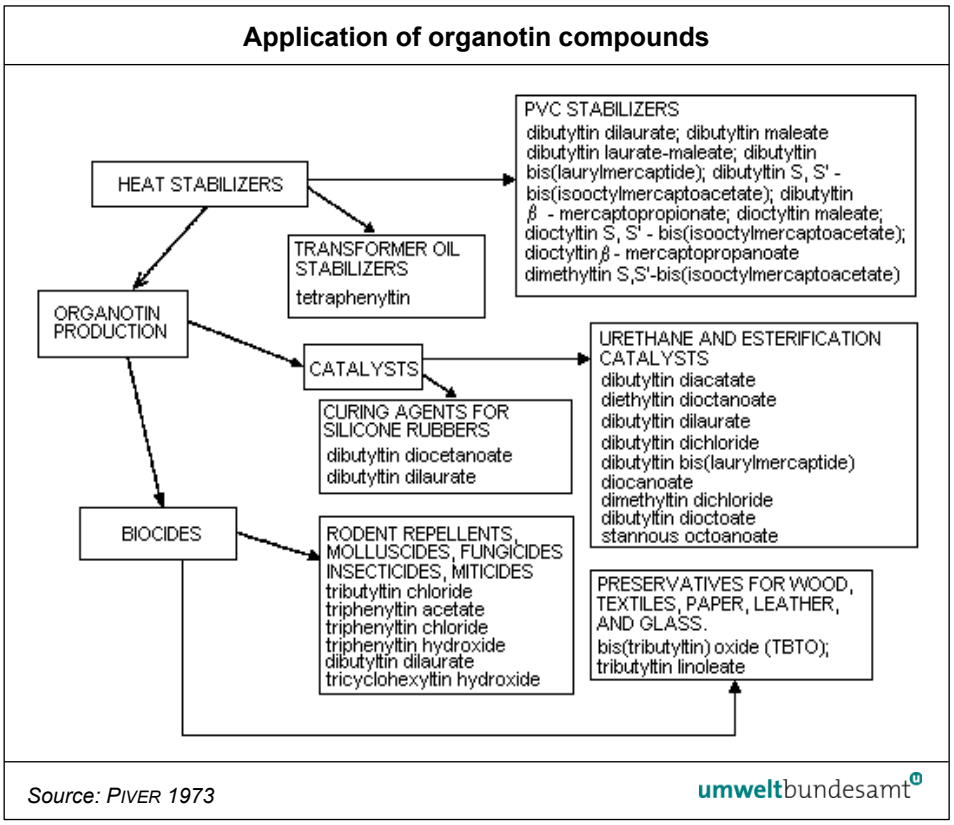


Figure 1: Application of organotin compounds

problematic effects have lead to restrictions

Due to the detrimental effects of many organotin compounds, several uses, especially those for which there is a high potential for human and environmental exposure were already restricted in the EU several years ago. This especially refers to biocidal uses, antifouling agents, treatment of industrial waters and certain articles with concentrations of tri-substituted organotin compounds, dibutyltin compound and dioctyltin compounds exceeding 0.1% (w/w) [ANNEX XVII, GROUP 21 OF REGULATION (EC) NO 1907/2006 (REACH)]. Several substances of the organotin group are still being assessed for their hazardous properties.

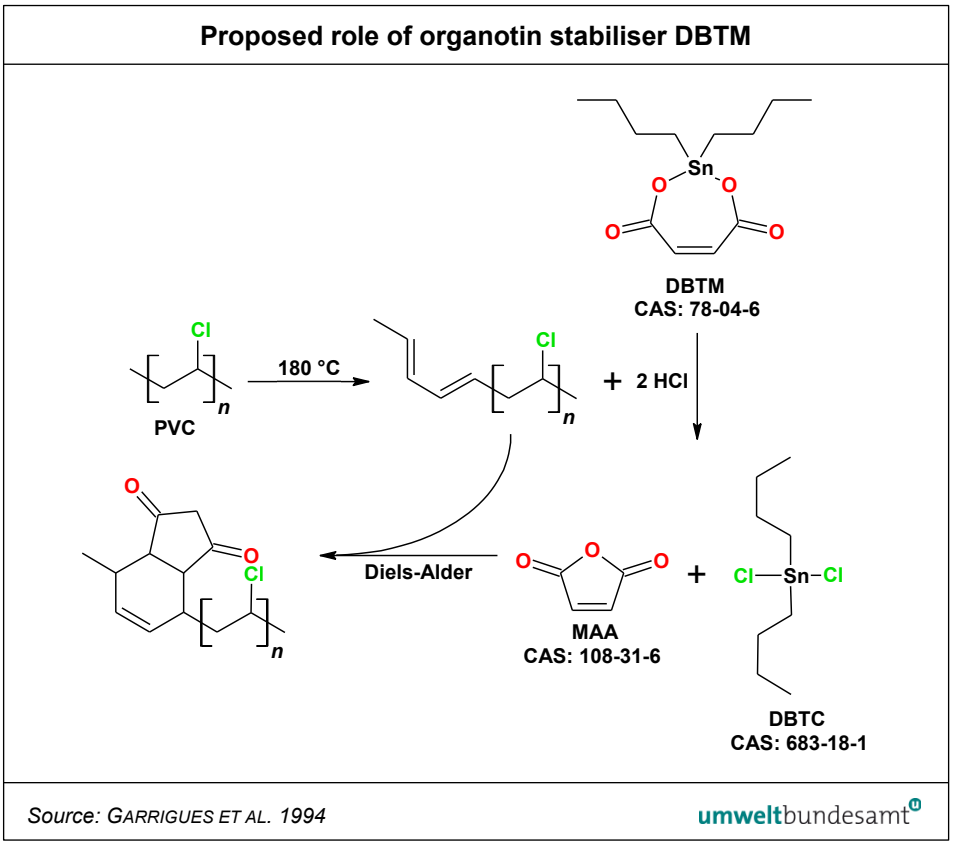
uses of PVC

Polyvinyl chloride (PVC) is a versatile thermoplastic material and is used in numerous consumer products to which humans are exposed in everyday life (e.g., bags, bottles, toys, electric articles, textiles, flooring, art, sports equipment). It is known that hydrogen chloride (HCl) is formed during the heat stabilisation process for PVC, since PVC is thermally unstable [BRAUN 1978].

function of heat stabilisers

Through HCl binding by the organotin stabiliser, an autocatalytic acceleration of an additional elimination of hydrogen chloride is suppressed, and on the other hand labile sites in the polymer are inactivated. It is proposed that the reaction of the organotin stabilisers with HCl results in the formation of organotin mono-chlorides (in the case of ligands bound via a tin-sulphur bond) and the formation of organotin dichlorides (in the case of ligands bound via a tin-oxygen bond). In the special case of DBTM, the ligand also contributes to the stabilisation of PVC, as it reacts with the polymer backbone to form a Diels-Alder adduct [GARRIGUES ET AL. 1994, Figure 2].

Figure 2: Proposed formation of the organotin dichloride DBTC and Diels-Alder adduct during the heat stabilisation process



evaluation criteria of heat stabilisers

Heat stabilisers are rated according to several criteria: The criteria are based on: efficiency as heat stabilisers, such as versatility (use with mass, suspension, and emulsion PVC), effect on the melt rheology of PVC, lubricant action, migration, plate-out, compatibility with other additives and pigments, effect on transparency, light fastness, electrical insulation, and fogging (especially for automotive interior parts). Furthermore, the approval as indirect food additives, easy handling and costs are also factors which have an impact on the choice of the most suitable heat stabiliser [WOLF & KAUL 2012].

1.2 Types of organotin stabilisers

There are two main types of tin stabilisers which are used in the production of PVC and which have a very good stabilising performance:

a. Thioacid half esters such as thio-glycolates (known as thio-tins or mer-captides (tin-sulphur bond))
b. Carboxylic half esters, often referred to as maleates or carboxylates (tin-oxygen bond)

Today, alkyltin (especially butyltin and octyltin) stabilisers are often mixtures containing both mono- and dialkyltin species and mixtures of mercaptides, es-pecially for high-volume monoalkyltin stabilisers. In stabilisers, the content of the dialkyltin component typcially ranges between 20 and 95%, and specific examples have been patented [CHO ET AL. 2013 and DENOUX ET AL. 2014].

1.3 Gastric environment studies

analytical techniques for organotin substances

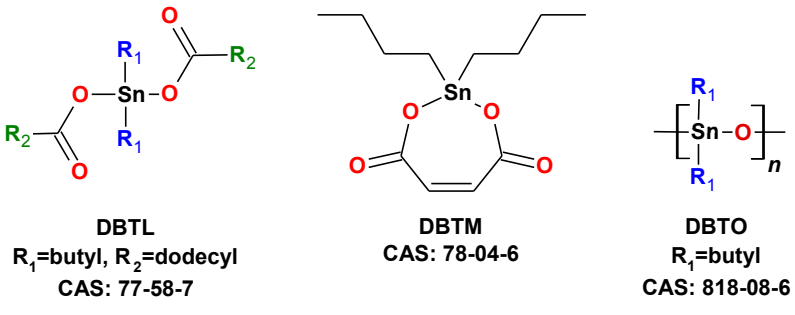
Most of the analytical techniques developed for the speciation of organotin compounds, in particular organotin cations, are based on gas chromatography (GC). GC analysis techniques show generally a good performance and accuracy of the overall analytical procedure; however, sample preparation can be demanding in comparison to other analytical techniques such as high performance liquid chromatography (HPLC) or nuclear magnetic resonance (NMR).

SCHILT ET AL. test substances

[SCHILT ET AL. 2004] reported having performed three separate experiments using GC in combination with a flame photometric detector (FPD), mass selective detector (MSD) or HPLC-UV (for the detection of maleic acid).

Each of the test substances dibutyl tin laurate (DBTL), dibutyl tin maleate (DBTM), and dibutyl tin oxide (DBTO) were individually tested under acidic conditions (pH~1-2, 0,07 mol/l HCl) at 37 °C in order to simulate the hydrolytic ac-tion (Figure 3).

Test substances according to SCHILT ET AL.



DBTL
R_1=butyl, R_2=dodecyl
CAS: 77-58-7

DBTM
CAS: 78-04-6

DBTO
R_1=butyl
CAS: 818-08-6

Source: SCHILT ET AL. 2004

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Figure 3: Test substances according to [SCHILT ET AL. 2004]

The degree of hydrolysis for the test substances was studied by determining dibutyl tin dichloride (DBTC) after different reaction times (0.5, 1.0, 2.0 and 4.0 hours). Liberation of the free corresponding ligand (laurate, maleate, ox-ide) was also analysed whenever possible. The authors of this study found that in all cases, the starting material had been hydrolysed to DBTC and the corresponding ligand. The half-lives of DBTL and DBTM were below 0.5 hours, and for DBTO 3.5 hours respectively.

For thio-glycolates organotin type compounds such as DOTE, the hydrolysis behaviour differs in comparison to carboxylic half ester-type organotin compounds:

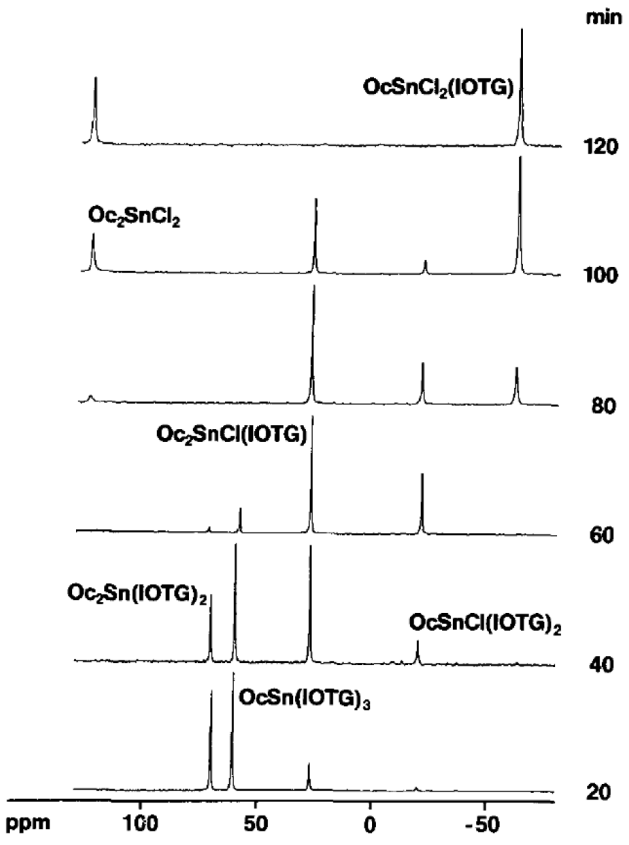
COSTLOW ET AL. test substances

In a recent publication, it is demonstrated (using ^{119}Sn-NMR) that dioctyltin bis(2-ethylhexyl thioglycolate) (DOTE) hydrolyses to dioctyltin chloro-(2-ethylhexyl thioglycolate) (DOTECl) under simulated gastric conditions, without forming DOTC [COSTLOW ET AL. 2017].

^{119}Sn-NMR is a valuable tool for the identification and quantification of all organotin species formed during PVC processing and thermal degradation [MÜLLER 1989]. References relating to ^{119}Sn-NMR spectra of DOTE ($Oc_2Sn(IOTG)_2$), MOTE ($OcSn(IOTG)_3$), and their metabolites DOTECl ($Oc_2SnCl(IOTG)$), MOTECl ($OcSnCl(IOTG)_2$), MOTEC ($OcSnCl_2(IOTG)$) and DOTC ($Oc_2Sn(IOTG)_2$) are provided in the literature (Figure 4):

Figure 4: ^{119}Sn-NMR spectra recorded in $CDCl_3$ of DOTE ($Oc_2Sn(IOTG)_2$) and MOTE ($OcSn(IOTG)_3$) transformation products in PVC at 180 °C

119Sn-NMR spectra of DOTE/MOTE transformation products after thermal degradation of PVC



Source: MÜLLER 1989

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1.4 Overview of data collected on representatives of both types of organotin stabilisers

DBTM forms part of the category of the dibutyltin (Bu_2Sn) group [CLH REPORT 2016]. The basis for the hypothesis for this category is that, following oral administration, all substances within the category behave in a predictable manner (*Table 1*). The hypothesis that category members have similar toxicological patterns has been confirmed in a comparative reproductive toxicity study [NODA ET AL. 1992].

Table 1: Data matrix for DBTO, DBTC, DBTM according to [CLH REPORT 2016] and DOTE according to [CLH REPORT 2011 and 2017]

Substance	DBTO	DBTC	DBTM	DOTE
CAS No	818-08-6	683-18-1	78-04-6	15571-58-1
Water solubility	2.55 mg/L [REACH REGISTRATION DOSSIER (ECHA, 2016D)]	Study technically not feasible. Hydrolysis upon contact with water. [REACH REGISTRATION DOSSIER (ECHA, 2016D)]	Insoluble [REACH REGISTRATION DOSSIER (ECHA, 2015G)]	The test substance rapidly decomposes in contact with water forming a range of breakdown products. The test substance can only be analysed after derivatisation, a distinction between intact test substance and breakdown products can no longer be made. It is not possible to specifically analyse the intact test substance with any technique at low levels which is required due to the expected low water solubility of the test substance [BALTUSSEN, 2016]
Hydrolysis, low pH (GC-FPD detection)	Formation of DBTC in gastric simulation studies: 43% in 0.5h, 65% in 1h, 90% in 2h, 87% in 4h [SCHILT & ZONDERVAN-VAN DEN BEUKEN, 2004]	Not relevant	Formation of DBTC in gastric simulation studies: 100% in 0.5h, 97% in 1h, 98% in 2h, 95% in 4h [SCHILT & ZONDERVAN-VAN DEN BEUKEN, 2004]	No data available
Hydrolysis, low pH (^{119}Sn-NMR detection)	No data available	Formation of $ClBu_2SnOSnBu_2Cl$ (DBDTC)[1] in gastric simulation studies: ~70% in 30s, ~85% in 1h, ~90% in 4h	Data is generated within this study	Data is generated within this study The study showed that DOTE at pH 9, 7 and 4 can be considered hydrolytically stable. After 5 days at 50 °C less than 10% DOTE was hydrolysed (t 0.5 25°C > 1 year). Under the simulated gastric conditions (0.1 M HCl/pH 1.2/37 °C, 5 days) DOTE was hydrolysed to DOTECl, its monochloride ester [CLH REPORT, 2017].

[1] ^{119}Sn-NMR revealed that DBDTC is represented by a dimeric ladder structure, a DBDTC dimer (see Figure 7)

2 AIM OF THIS STUDY

identification of reaction products

The aim of this study is to identify potential reaction products that are formed during the hydrolysis of DBTM and DOTE in a simulated gastric environment by performing (^{1}H, ^{13}C, ^{119}Sn) NMR based investigations.

In particular, this study should contribute answers to the following questions (Figure 5 and Figure 6):

- Is DOTC or DOTECl formed as a major metabolite during the hydrolysis of DOTE under simulated gastric conditions?
- Is DBTC or the oxy-bridged tin species DBDTC formed as a major metabolite during the hydrolysis of DBTM under simulated gastric conditions?

Figure 5: DOTECl and DOTC as questionable metabolites of DOTE

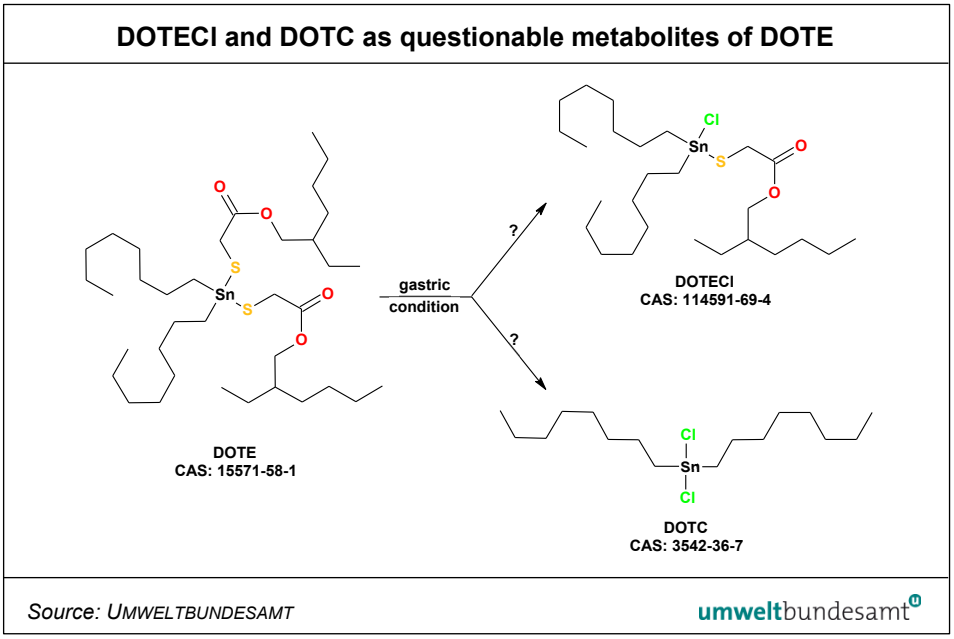
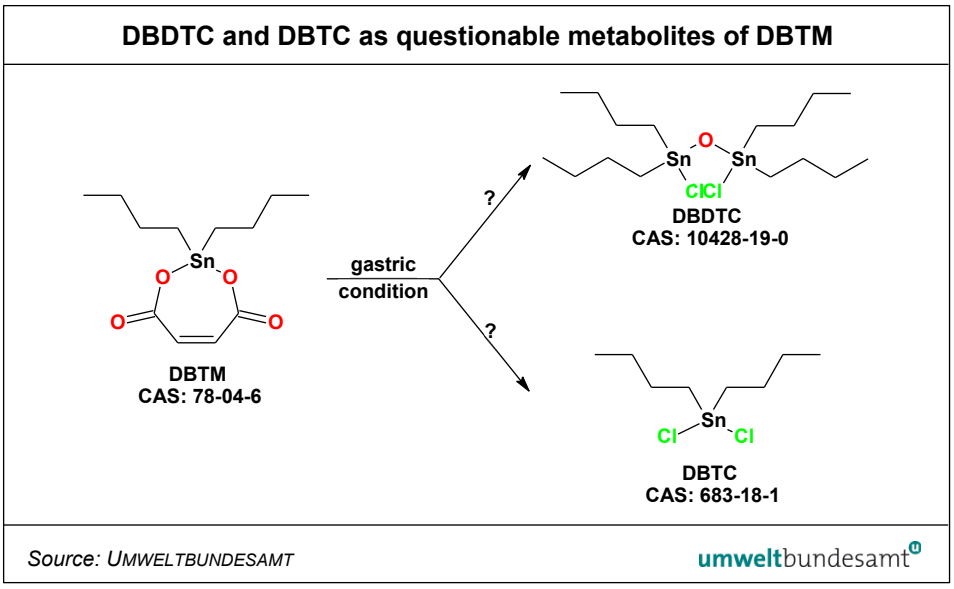


Figure 6: DBDTC and DBTC as questionable metabolites of DBTM



investigation of extraction solvents

Moreover, it is investigated whether different extraction solvents (e.g. hexane, dichloromethane) or NMR solvents (e.g. dichloromethane-D_2, toluene-D_8) have an influence on the composition of the organic extracts depending on their different extraction properties.

Based on these results, the outcome of the hydrolysis experiments with DBTM should be compared with the results generated when DOTE is used as starting material instead of DBTM.

3 EXPERIMENTAL DESIGN

3.1 Analytical instrument

^{1}H, ^{13}C and ^{119}Sn NMR analysis was performed on a Bruker Avance IIIHD 600 MHz spectrometer equipped with a Prodigy BBO cryo probe at the Vienna University of Technology (TU Wien).

3.2 Starting and reference materials

3.2.1 Starting material used for DOTE conversion

Table 2: Data provided according to the certificate of analysis

Product Name	CAS	Purity [%]	Supplier
Plastic Additive 23	15571-58-1	"Reference standard"	BOC Sciences

starting material is a mixture of DOTE and MOTE

According to the certificate of analysis provided by BOC Sciences, the purity of DOTE has not been disclosed. ^{1}H, ^{13}C, ^{119}Sn and 2D NMR spectra of the starting material in toluene-D_8 reveal that the DOTE standard is a mixture of two species, DOTE and MOTE (Table 3):

Table 3: Composition of the starting material

Purity	Plastic additive 23	
	DOTE	MOTE
Mol [%]	70	30
w/w [%]	68	32

This finding has been confirmed by information provided by other suppliers of DOTE standards such as Campro Scientific who claim to offer mixtures of DOTE:MOTE = 73:27.

To exclude inhomogeneity due to the decomposition of otherwise pure DOTE, a new batch of standards was ordered and re-measured. There was no significant difference to the initially analysed DOTE standard batch and also all earlier measured NMRs DOTE – solutions showed consistent compositions after several weeks in the solvent and upon evaporation and re-dissolution. The NMR spectra of the analysed starting material can be found in the Annex.

3.2.2 Starting and reference materials used for DBTM conversion

Compound Abbreviation	CAS	Purity [%]	Supplier	NMR solvent
DBTM	78-04-6	95	Sigma Aldrich	DCM-D_2
DBTC	683-18-1	96	Dr. Ehrensdorfer	DCM-D_2
DBTO	818-08-6	98	Sigma Aldrich	DCM-d_2 + 5% TFA
DBDTC	10428-19-0	98	Sigma Aldrich	DCM-D_2
MA	110-16-7	≥99	Sigma Aldrich	DCM-D_2

Table 4: Data provided according to a MSDS or a certificate of analysis

reference NMR spectra of educts

Initially, the starting material DBTM and potential reaction products such as DBTC, DBDTC, DBTO as well as MA (the expected byproduct in the formation of DBTC or DBTO) were measured by ^{1}H, ^{13}C and ^{119}Sn NMR where appropriate, to allow the unambiguous identification of any of these potential metabolites in the DBTM hydrolysis experiment. To achieve sufficient solubility in DCM-D2 for DBTO, a small amount of trifluoroacetic acid (TFA, ~5%) had to be added, which gave good signals in all NMR spectra. Due to the very low solubility of MA in DCM-D_2, signals were observed only in ^{1}H-NMR, whereas the ^{13}C-NMR did not reveal any detectable signal. It was decided to wait and see whether MA would become a relevant species before trying to find alternative ways of identifying MA in ^{13}C-NMR (other NMR solvents would have to be used, *ergo* also for all other species). All recorded spectra of starting and reference materials were in line with their structures except for DBDTC (CAS: 10428-19-0) which gave two sets of signals (most obvious in ^{119}Sn-NMR) at a ratio of 1:1, which is not consistent with the suggested structure. However, a literature study has revealed that the structure for the measured reference material most likely does not correspond to the structure of DBDTC (CAS: 10428-19-0), but to that of the dimeric DBDTC structure (CAS: 33194-92-2, Figure 7), [TIERNEY ET AL. 2001].

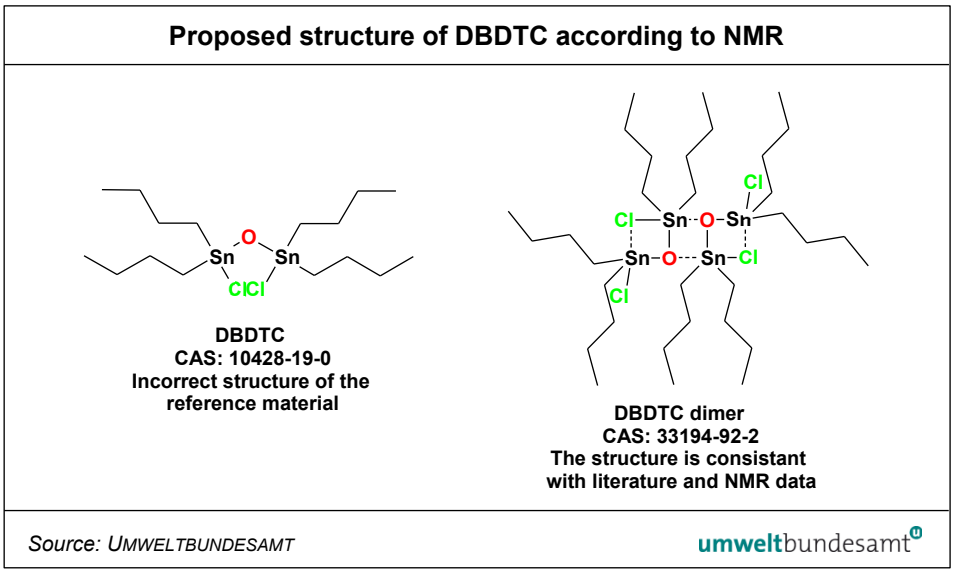


Figure 7: Proposed real structure of DBDTC as in CAS: 33194-92-2

DBDTC dimer structure

The structure of the DBDTC dimer contains two different types of Sn atoms (two of each), which is now consistent with the two signals in ^{119}Sn-NMR as well as the slightly different types of the butyl groups which were also observed in ^{1}H and ^{13}C-NMR. In addition, the observed shifts as well as the reported Sn-Sn coupling are consistent with the ones reported in the literature (observed (DCM-D_2, [ppm]: -90.34, -139.19), literature ($CDCl_3$, [ppm]: -92.0, -140.6) [TIERNEY ET AL. 2001].

3.3 Reagents

Table 5: NMR solvents and solvents used for extraction

Reagent	CAS	Purity [%]	Supplier
n-Hexane	110-54-3	95	VWR
Dichloromethane	75-09-2	Techn.	Donauchemie
Toluene-D_8	2037-26-5	99.6 (atom%)	Sigma-Aldrich
Dichloromethane-D_2	1665-00-5	99.9 (atom%)	Euroisotop

3.4 Description of the procedure

3.4.1 Procedure for the conversion of DOTE

three DOTE experiments

Three experiments using identical reaction conditions for the conversion of DOTE were performed. In each of the experiments DOTE starting material (20 mg for the first two experiments, 10 mg for the third experiment) was added to a 0.1 mol/L aqueous HCl (2 mL for the first two experiments, 1 mL for the third experiment) and the reaction mixture was stirred at 40 °C for 72 hours in a closed vessel. Workup of the reaction mixture was carried out after allowing the solution to cool down to RT and extracted under different conditions, stated below (Figure 8):

- *Experiment 1:* The reaction mixture was diluted with water (9 mL in total) and extracted with n-hexane (4 mL, three times). The combined organic layer was washed once with fresh water, filtered over cotton, split into two equal parts and evaporated. Each of the residues was re-dissolved in 1 mL NMR solvent (dichloromethane-D_2, toluene-D_8) and analysed by ^{1}H, and ^{119}Sn-NMR.
- *Experiment 2:* The reaction mixture was diluted with water (9 mL in total) and extracted with dichloromethane (4 mL, three times). The combined organic layer was washed once with fresh water, filtered over cotton, split into two equal parts and evaporated. Each of the residues was re-dissolved in 1 mL of NMR solvent (dichloromethane-D_2, toluene-D_8) and analysed by ^{1}H and ^{119}Sn-NMR.
- *Experiment 3:* The reaction mixture was diluted with water (9 mL in total) and extracted with dichloromethane-D_2. The analysis was performed using ^{1}H, ^{13}C (1D and 2D) and ^{119}Sn-NMR directly without evaporation.

three different workup procedures

Three different workup procedures were carried out in order to investigate whether different extraction solvents (hexane, dichloromethane) or NMR solvents (dichloromethane-D_2, toluene-D_8) have an influence on the composition of the organic extracts depending on their different in extraction properties.

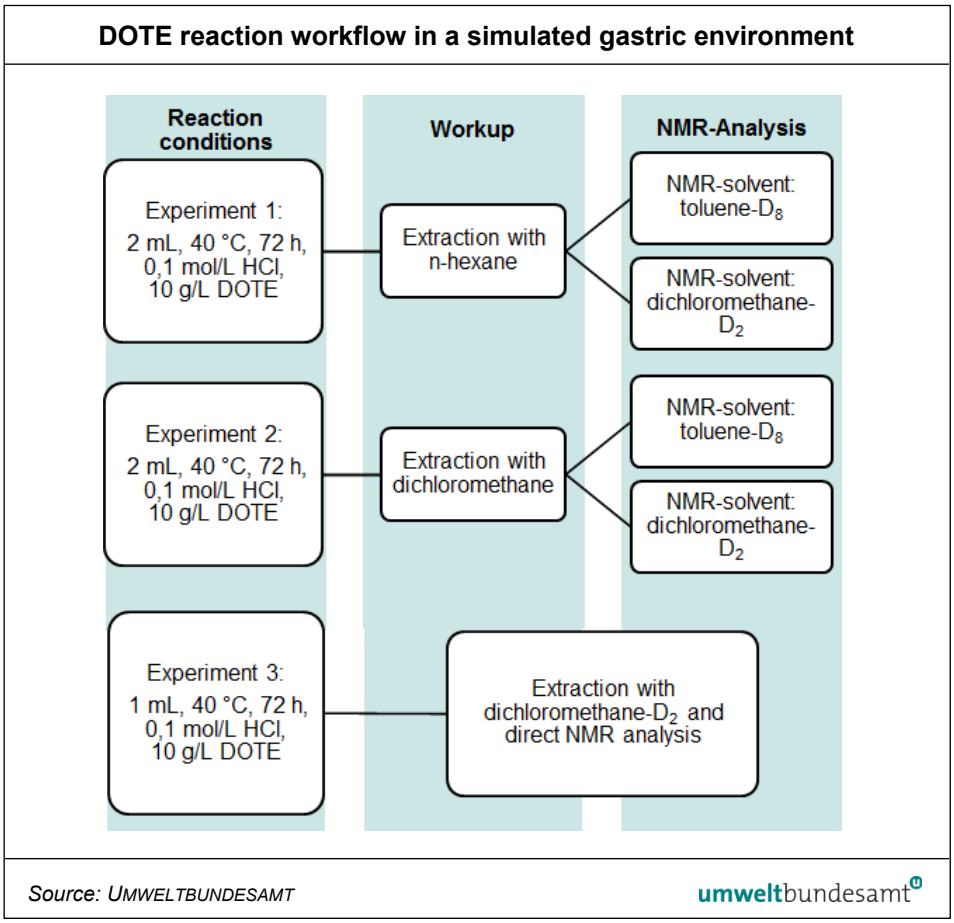


Figure 8: General workflow of DOTE reactions in a simulated gastric environment

3.4.2 Procedure for the conversion of DBTM

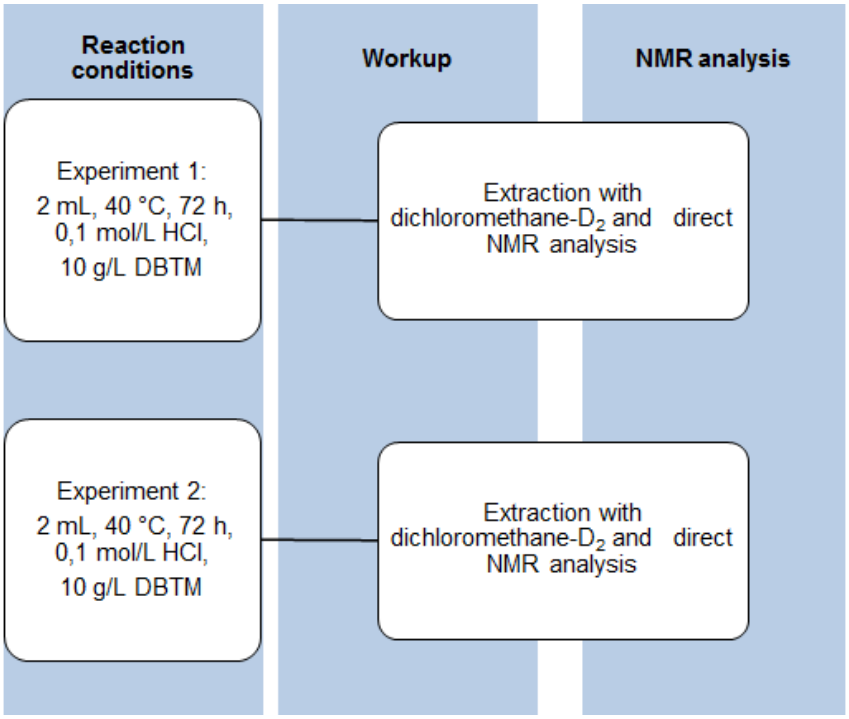
two DBTM experiments

DBTM (20 mg) was added to 0.1 mol/L of aqueous hydrochloric acid (2 mL) and the mixture was stirred at 40 °C for 72 h in a closed vessel with one shake every 24 h as the mixture remained clearly heterogeneous. Workup of the reaction mixture was carried out after allowing the solution to cool down to room temperature. The reaction mixture was separated between the aqueous layer and DCM-D_2 (2 mL). The aqueous layer was extracted with fresh DCM-D_2 two more times (0.5 mL each time) and the combined organic layers were treated with fresh H_2O, filtered over cotton and subjected to NMR analysis.

For quality control reasons (repeatability and reproducibility), the experiment was repeated in exactly the same way (Figure 9).

Figure 9: General workflow of DBTM reactions in a simulated gastric environment

DBTM reaction workflow in a simulated gastric environment



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4 DATA EVALUATION AND RESULTS

4.1 Results of the NMR based investigations of the DOTE conversion

DOTC was not observed

Based on the chemical shifts reported, as well as on the chemical shift (Table 6, entry 5: 123,7 ppm in toluene-D_8) recorded for the DOTC reference standard, no DOTC was observed by NMR in any of the organic extracts analysed under the performed experiments. The main metabolites detected after the reaction in a simulated gastric environment are DOTECl and MOTECl respectively (Figure 10).

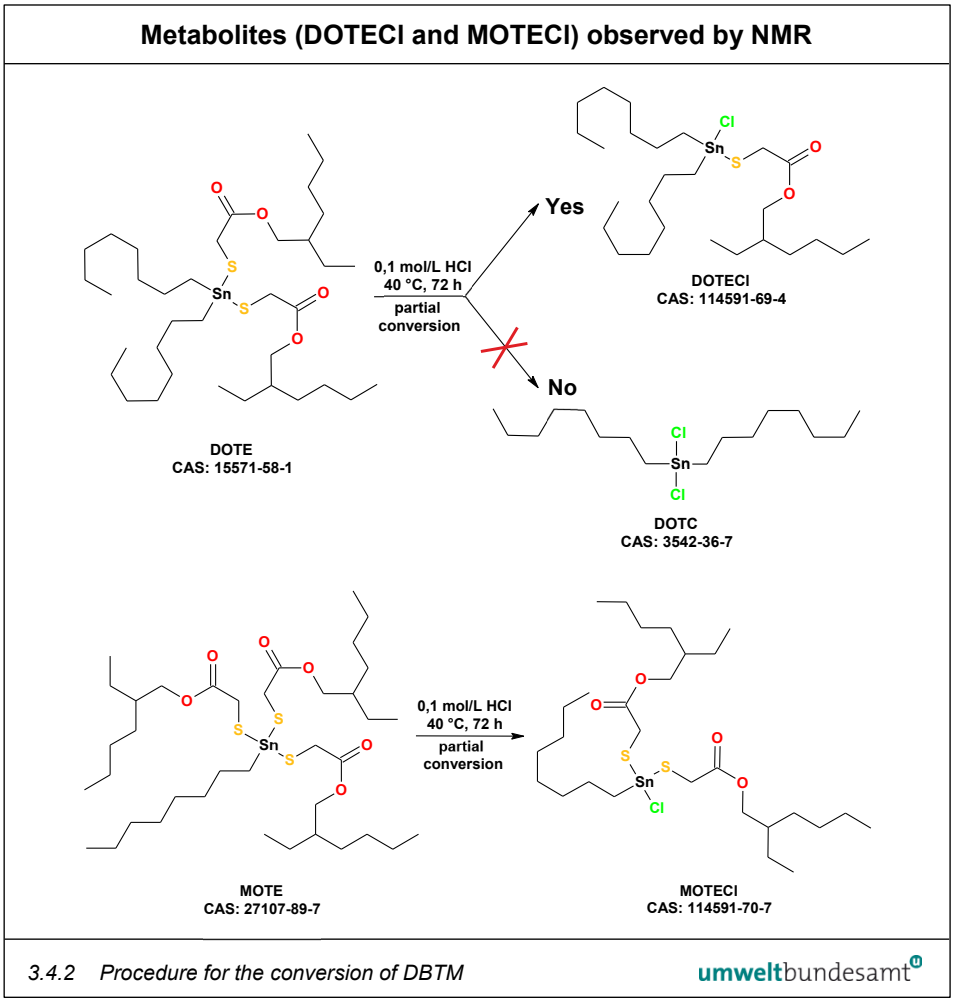


Figure 10: Metabolites (DOTECl and MOTECl) observed using ^{119}Sn-NMR

Entry	Compound	Toluene-D_8 [ppm]	Dichloromethane-D_2 [ppm]
1	DOTE	74,66	65,91
2	MOTE	66,70	55,22
3	DOTECl	34,94	22,04
4	MOTECl	-13,37	-27,26
5	DOTC	123,73	125,85

Table 6: Measured ^{119}Sn-NMR chemical shifts of reference compounds (DOTE, DOTC and generated metabolites)

Shift values for the ^{119}Sn spectra were referenced via an indirect method suggested by the IUPAC, referencing ^{1}H-NMR spectra on residual deuterated solvent signals [FULMER ET AL. 2010] and translating the reference via the ratios of magnetogyric constants to the ^{119}Sn-NMR nucleus [HARRIS ET AL. 2002].

observed metabolites of DOTE

The suggested DOTECl and MOTECl structures were also supported by the relative ratios based on ^{1}H-NMR recorded in dichloromethane-D_2, where diagnostic signals can be obtained for all relevant species in the form of SCH_2CO signals.

influence of solvents used for extraction

All five analysed NMR samples show similar compositions, in semi-quantitative terms, of the organic extracts after HCl treatment. In particular for the minor compounds, the signal-to-noise does not permit full quantification. Thus, experiment three was re-measured with more scans to guarantee enhanced signal/noise ratios for all peaks in ^{1}H-NMR and ^{119}Sn NMR while still affording similar ratios (compare Table 7, entry 5 and 6). Consequently, the influence on the composition of the organic extract when using different solvents for extraction or for NMR analysis is negligible.

Table 7: Relative ratios according to ^{119}Sn-NMR

Relative ratios according to ^{119}Sn-NMR spectra (1000 scans)					
Entry	**Experiment**	**DOTE mol [%]**	**MOTE mol [%]**	**DOTECl mol [%]**	**MOTECl mol [%]**
1	Experiment 1: (hexane → toluene-D_8)	23,0	23,6	48,2	5,1
2	Experiment 1: (hexane → CD_2Cl_2)	23,8	19,5	52,7	4,0
3	Experiment 2: (CH_2Cl_2 → toluene-D_8)	27,4	22,6	44,6	5,4
4	Experiment 2: (CH_2Cl_2 → CD_2Cl_2)	23,4	27,5	44,6	4,6
5	Experiment 3: (CD_2Cl_2)	15,2	25,8	55,7	5,7
6	Experiment 3: (CD_2Cl_2) – **15.000 scans**	**15,5**	**19,2**	**57,6**	**7,8**

reaction rate

According to the relative ratios of DOTE and MOTE observed at the end of the reaction time and compared to the DOTE/MOTE composition of the starting material, it can be assumed that the conversion of MOTE to MOTECl is comparatively slower than the conversion of DOTE to DOTECl: after a reaction time of 72 hours, 79% of DOTE has been converted, compared to only 36% of MOTE converted to the corresponding organotin monochloride.

DOTE summary

The present study substantiates previous findings of a recent publication, namely that DOTE forms the corresponding monochloride (DOTECl) under simulated gastric conditions (0.1 mol/L aqueous HCl, 72 h, 40 °C) [COSTLOW ET AL. 2017]. DOTC as a potential reaction product was not detected by NMR in any experiment. However, there are still uncertainties regarding a read-across approach for DOTC, since the testing conditions do not reflect the further metabolism under *in vivo* conditions.

4.2 Results of the NMR based investigations of the DBTM conversion

DBDTC dimer formation

All ^{1}H, ^{13}C and ^{119}Sn-NMR spectra clearly indicated a clean formation of the DBDTC dimer (CAS: 33194-92-2) identical to the reference material provided in a simulated gastric environment (0.1 mol/L of aqueous HCl, 72 h, 40 °C, Figure 11). Other potential metabolites such as DBTC (CAS: 683-18-1) or DBTO (CAS: 818-08-6) were not detected.

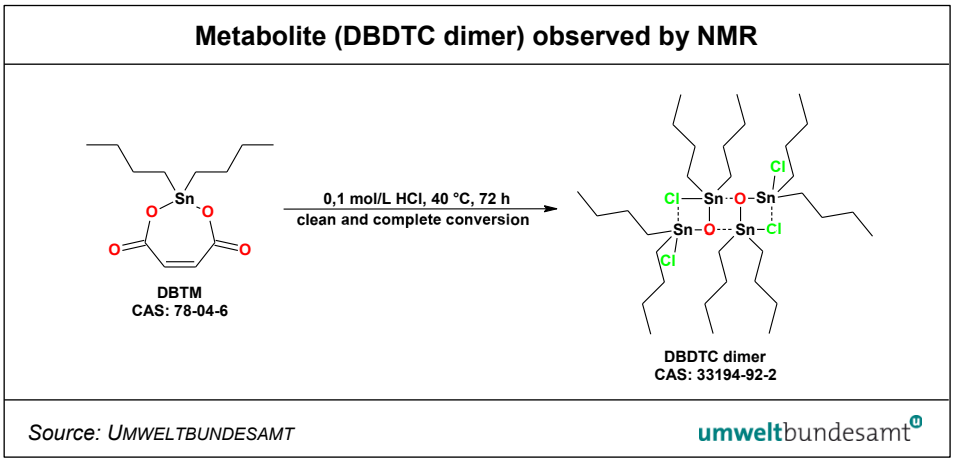


Figure 11: Metabolite (DBDTC dimer) observed using ^{1}H, ^{13}C and ^{119}Sn-NMR

DBTM summary

For DBTM the study demonstrates that it forms hydrolysis products (DBDTC dimer) that are identical to DBTC. The hypothesis that a read-across approach for DBTM and DBTC is justified is therefore substantiated.

4.3 Quality control/quality assurance

repeatability

Puzzled by the high purity of the extract, and due to the complete lack of any (even a trace of) maleic acid-related signal in ^{1}H-NMR, it was decided to repeat the experiment for quality control reasons.

The experiment was repeated in exactly the same way: again, the full conversion of DBTM to the DBDTC dimer was observed using NMR measurements. The lack of maleic acid was attributed to its low solubility in DCM and its good solubility in water (>400 g/L). A comparison (by overlaying spectra) of ^{1}H-NMR, ^{13}C-NMR and ^{119}Sn-NMR between the starting material DBTM and the observed hydrolysis product DBDTC dimer is shown in the Annex.

unambiguous identification

Chemical shift values for the ^{119}Sn spectra were referenced via the indirect method suggested by IUPAC, referencing ^{1}H-NMR spectra on residual deuterated solvent signals [FULMER ET AL. 2010] and translating the reference via the ratios of magnetogyric constants to the ^{119}Sn NMR nucleus [HARRIS ET AL. 2002].

Table 8: Measured ^{119}Sn-NMR chemical shifts of reference compounds and hydrolysis experiments

Entry	Compound	Dichloromethane-D_2 [ppm]
1	DBTM	-128,1
2	DBDTC dimer	-93,3/-139,2
3	DBTO[2]	-80,7
4	DBTC	+126,8
5	Experiment 1	-93,3/-139,2
6	Experiment 2	-93,3/-139,1

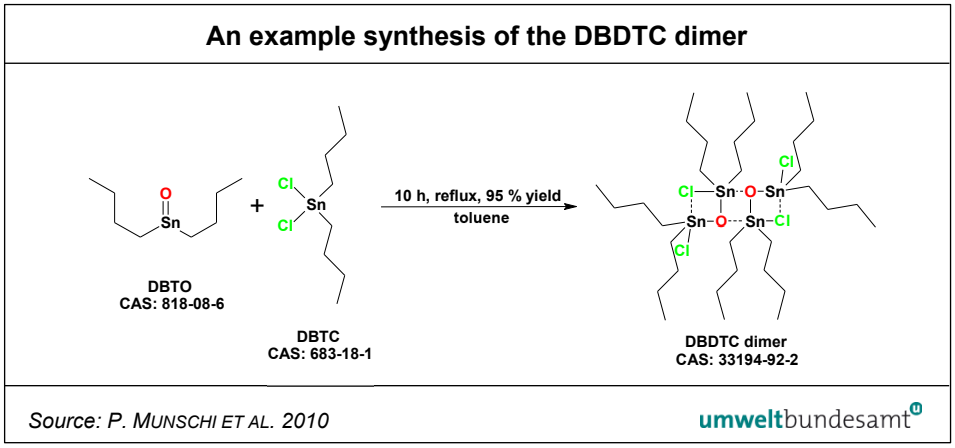
quantification

In order to estimate the amount of DBTC detectable under the NMR settings applied for the hydrolysis experiments, a spiking experiment with DBTC was conducted. Hence, a solution of 1 mg/mL of DBTC in DCM-D_2 was prepared and 100 µL were pipetted into the NMR tube which was re-measured under identical conditions (4.000 scans, 1.5 h) and the ^{119}Sn-NMR before and after the standard additions were compared. It can clearly be seen that upon addition of ~0.1 mg of DBTC to ~3-4 mg of DBDTC from the hydrolysis experiment a clear signal of DBTC can be observed in the ^{119}Sn-NMR that could not be observed prior to the addition (see Annex, Section 7.5. In a semi-quantitative fashion, an LOD for DBTC in hydrolysis extracts of ~3% can be deduced.

reference data

It is noteworthy that according to the literature, the observed distannoxane structures (e.g. DBDTC dimer) can be obtained by partial hydrolysis from the corresponding dichlorides and tin oxides [P. MUNSCHI ET AL. 2010 and Y. PATEL ET AL. 2009, Figure 12].

Figure 12: Synthesis of DBDTC dimer from DBTO and DBTC



Other references report similar conditions for the synthesis of the DBDTC dimer, such as DBTO, NH_4Cl, dioxane/water as solvents, 48 h under reflux [J. BECKMAN ET AL. 2002] or DBTC, in the presence of water and DCM as solvent [TIERNEY ET AL. 2001].

[2] Dissolved in DCM-d_2 with ~5% TFA: gives a broad signal

reaction pathway

Based on the reaction conditions applied and the results generated within this study, no conclusion can be drawn as to whether or not this would be the synthetic pathway through which the DBDTC dimer is formed. It can only be speculated through which intermediates (DBTO, DBTC to name only two possible pathways) the DBDTC dimer is formed during a hydrolysis experiment.

outlook

Additional hydrolysis experiments with DBTM, DBTC and DBTO in a time-resolved fashion could help to reveal this information but are beyond the scope of this study. However, in order to exclude the possibility that smaller amounts of DBTC are not detectable in the hydrolysis experiments when using the methods applied, a standard addition of ~3% of DBTC to the NMR solutions used in the hydrolysis experiments was made, showing that such an amount can clearly be detected.

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6 GLOSSARY

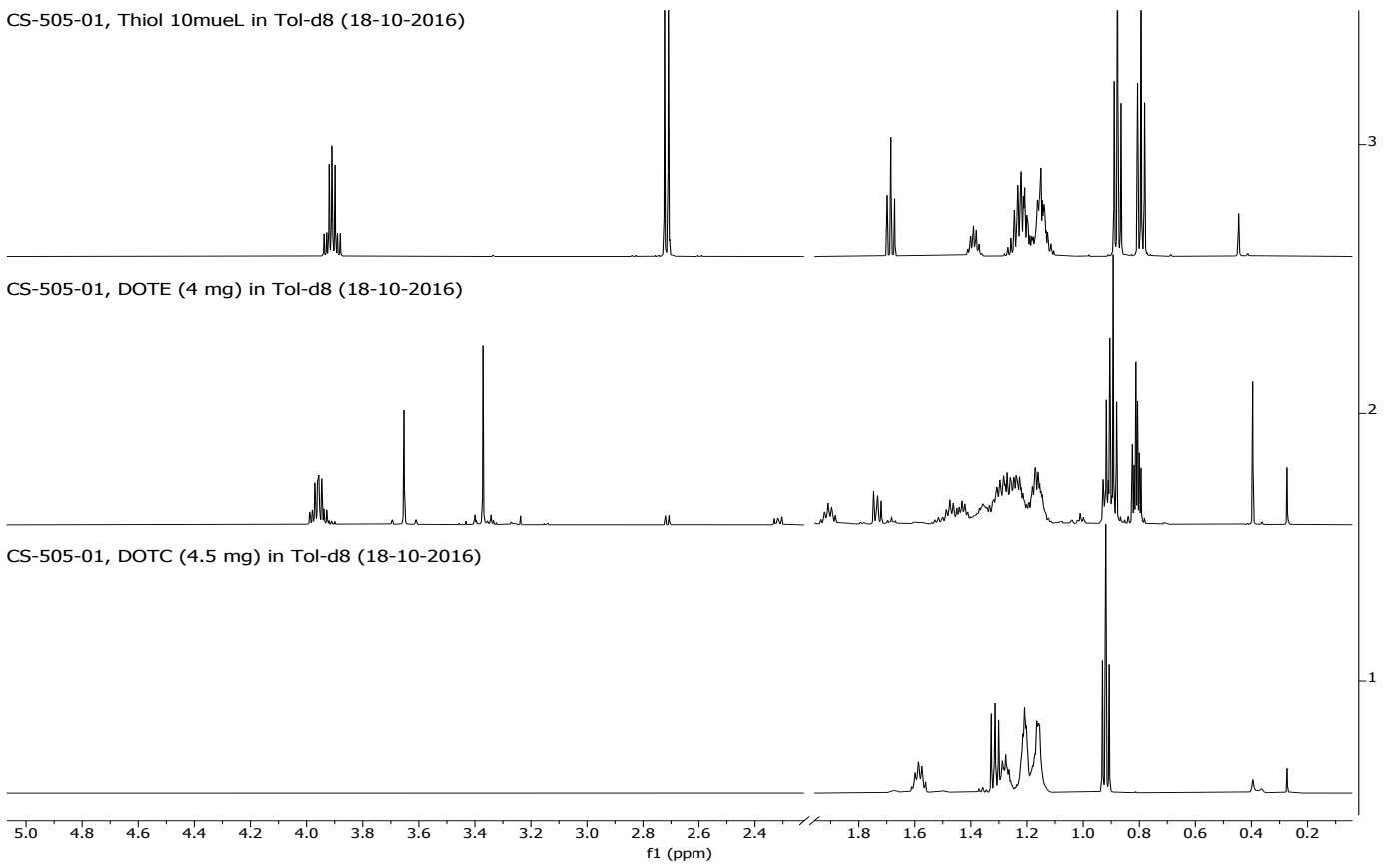
AED ..... Atom Emission Detection
APT ..... Attached Proton Test
CLH ..... Harmonized Classification and Labelling
COSY ..... Correlated Spectroscopy
DBDTC ..... 1,1,3,3-tetrabutyl-1,3-dichloro distannane (CAS: 10428-19-0)
DBDTC dimer ..... Bis(dibutylchlorotin) oxide dimer (CAS: 33194-92-2)
DBPT ..... Dibutylbis(pentane-2,4-dionato-O,O')tin (CAS: 22673-19-4)
DBTE ..... Dibutyltin bis(2-ethylhexyl mercaptoacetate) CAS: 10584-98-2)
DBTL ..... Dibutyltin dilaureate (CAS: 77-58-7)
DBTM ..... Dibutyltin maleate (CAS: 78-04-6)
DBTC ..... Dibutyltin dichloride (CAS: 683-18-1)
DBTO ..... Dibutyltin oxide (CAS: 818-08-6)
DCTODT ..... 1,3-Dichloro-1,1,3,3-tetraoctyl distannoxane (CAS: 58357-63-4)
DOTC ..... Dioctyltin dichloride (CAS: 3542-36-7)
DOTE ..... Dioctyltin bis(2-ethylhexyl mercaptoacetate) (CAS: 15571-58-1)
DOTECl ..... Dioctyltin (2-ethylhexyl mercaptoacetate) monochloride (CAS: 114591-69-4)
DOTI ..... Dioctyltin bis(isooctyl thioglycolate) (CAS 26401-97-8)
DOTO ..... Dioctyltin oxide (CAS: 870-08-6)
EHMA ..... 2-Ethylhexyl thioglycolate (CAS: 7659-86-1)
FPD ..... Flame Photometric Detector
GC ..... Gas Chromatography
HPLC ..... High Performance Liquid Chromatography
HSQC ..... Heteronuclear Single Quantum Correlation
MA ..... Maleic acid (CAS: 110-16-7)
MAA ..... Maleic acid anhydride (CAS: 108-31-6)
MOTE ..... Monooctyltin tris(2-ethylhexyl mercaptoacetate) (CAS: 27107-89-7)
MOTECl ..... Monooctyltin bis(2-ethylhexyl mercaptoacetate) monochloride (CAS: 114591-70-7)
MOTEC2 ..... Monooctyltin (2-ethylhexyl mercaptoacetate) dichloride (CAS: 114591-71-8)
MSD ..... Mass Selective Detection
MSDS ..... Material Safety Data Sheet
NMR ..... Nuclear Magnetic Resonance
PVC ..... Polyvinyl chloride
RAC ..... Risk Assessment Committee
RT ..... Room Temperature
SCH_2CO ..... Sulphurmethylene carbonyl group
TFA ..... Trifluoro acetic acid

7 ANNEX

7.1 Reference NMR spectra

7.1.1 ^{1}H-NMR overlay of DOTE, DOTC and EHMA

^{1}H-NMR overlay of DOTE, DOTC and EHMA



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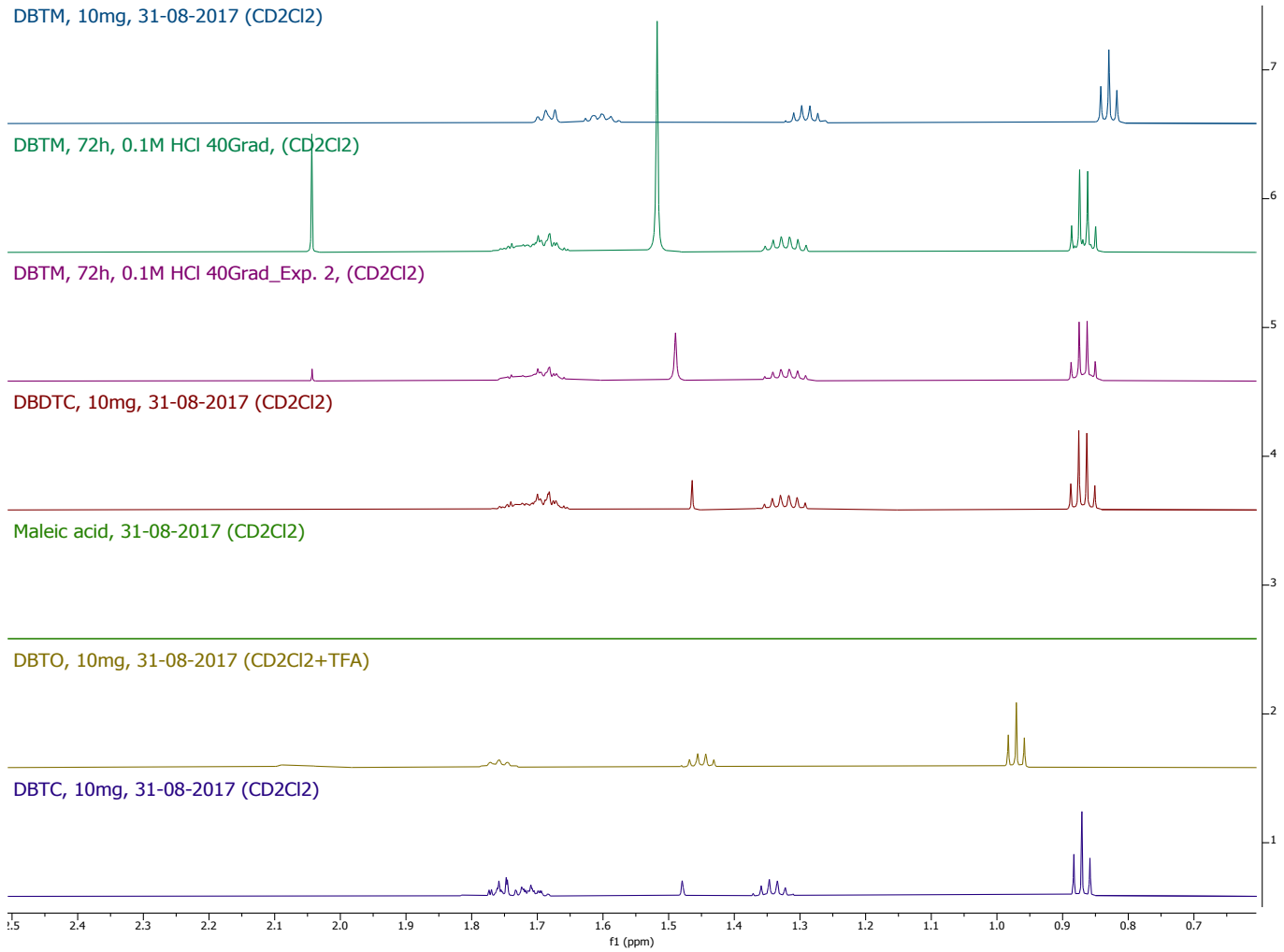
7.1.2 ^{1}H-NMR overlay of DBTM, MA, DBTDC, DBTO and DBTC

^{1}H-NMR overlay of DBTM, MA, DBTDC, DBTO and DBTC



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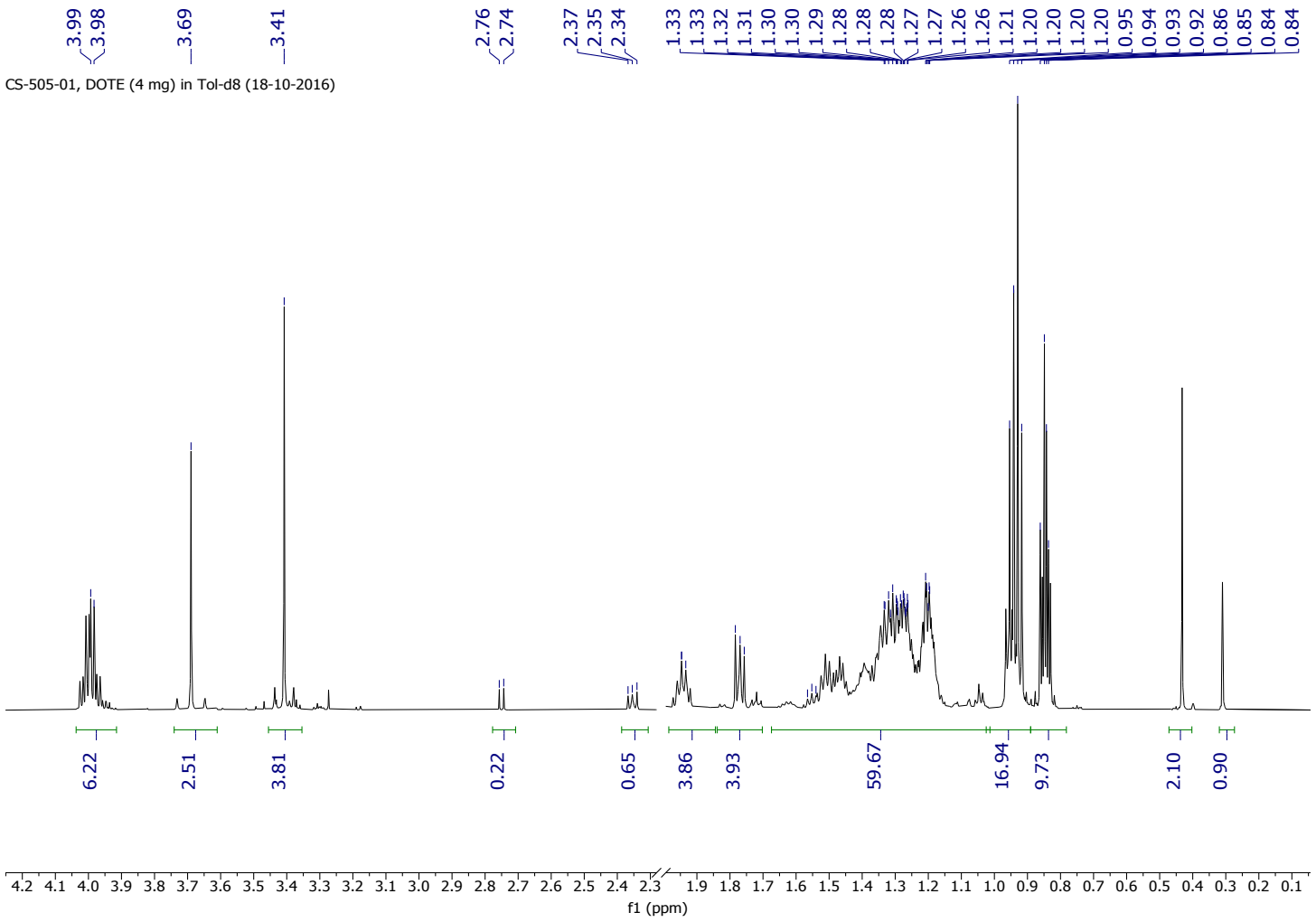
7.1.3 ^{1}H-NMR of DOTE/MOTE

^{1}H-NMR of DOTE/MOTE



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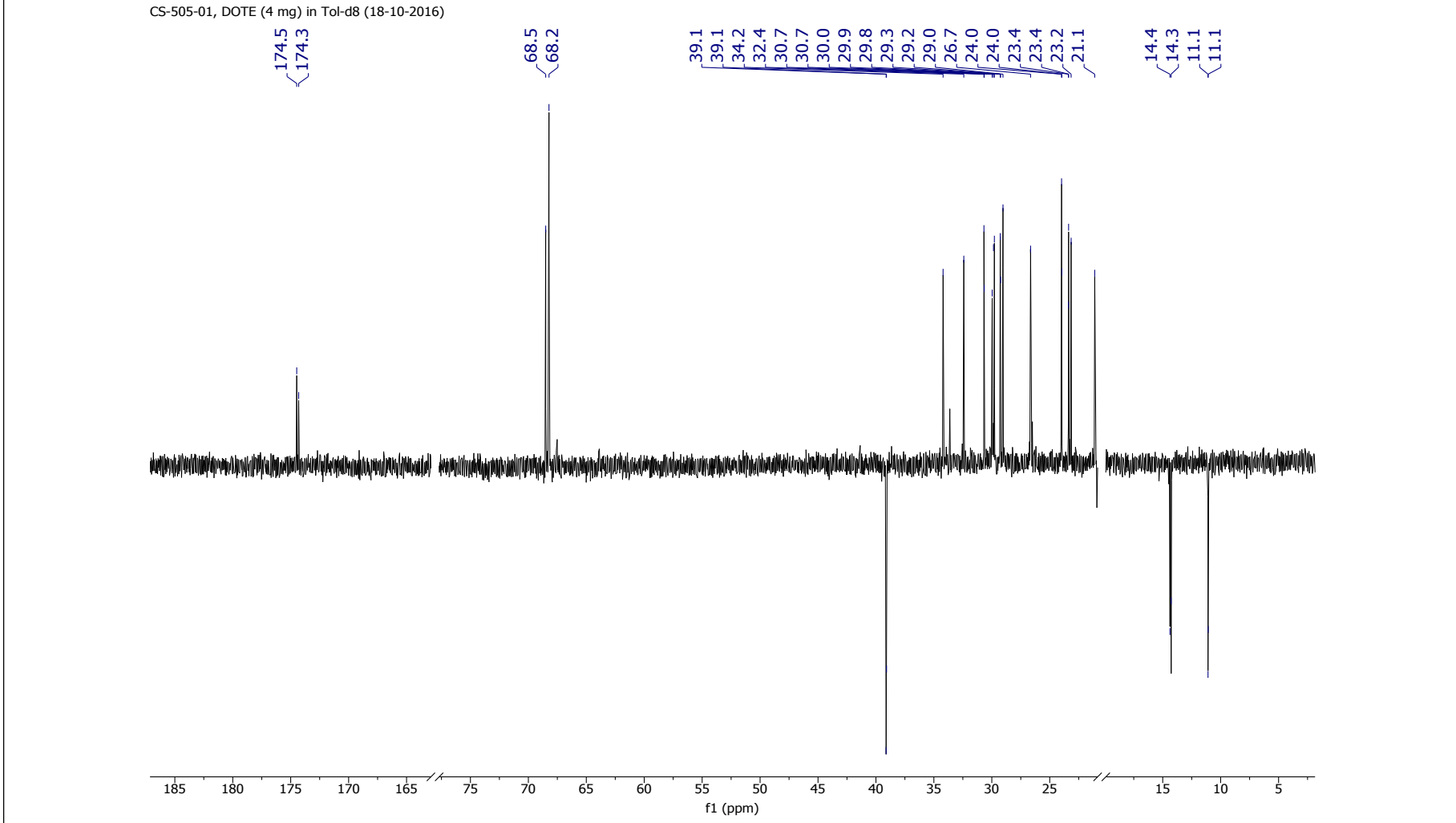
7.1.4 ^{13}C-APT-NMR of DOTE/MOTE

^{13}C-APT-NMR of DOTE/MOTE



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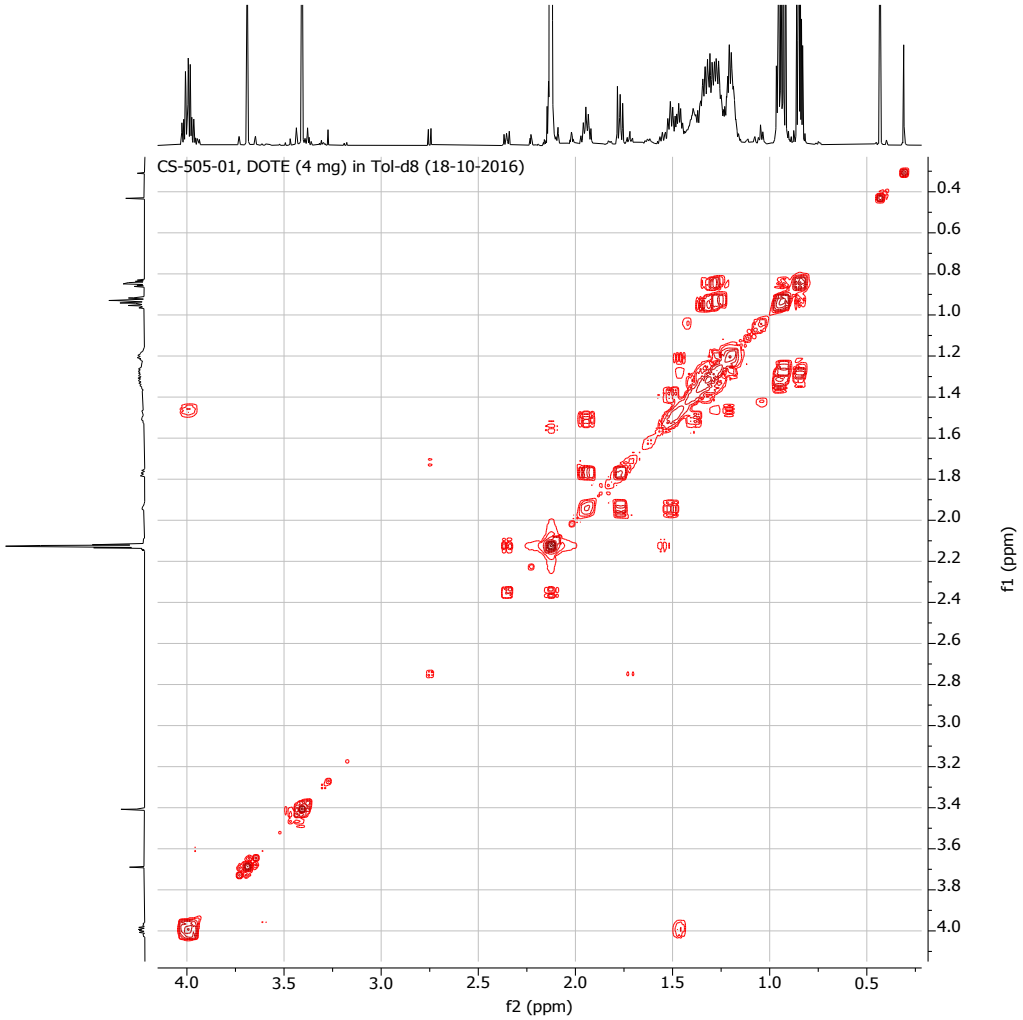
7.1.5 ^{1}H, ^{1}H-COSY 2D-NMR of DOTE/MOTE

^{1}H, ^{1}H-COSY 2D-NMR of DOTE/MOTE



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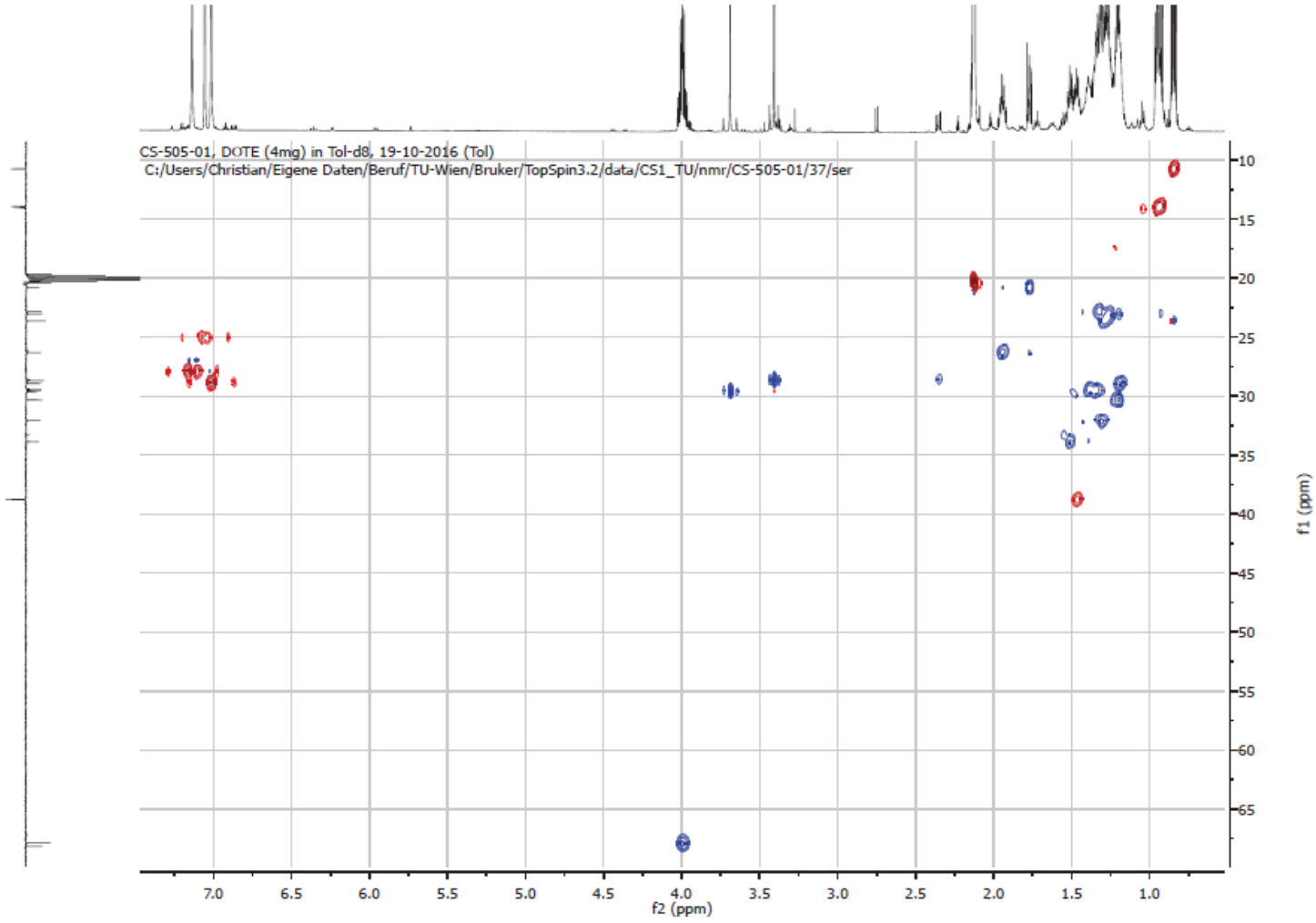
7.1.6 $^{1}H,^{13}C$-COSY 2D-NMR (HSQC) of DOTE/MOTE

$^{1}H,^{13}C$-COSY 2D-NMR (HSQC) of DOTE/MOTE



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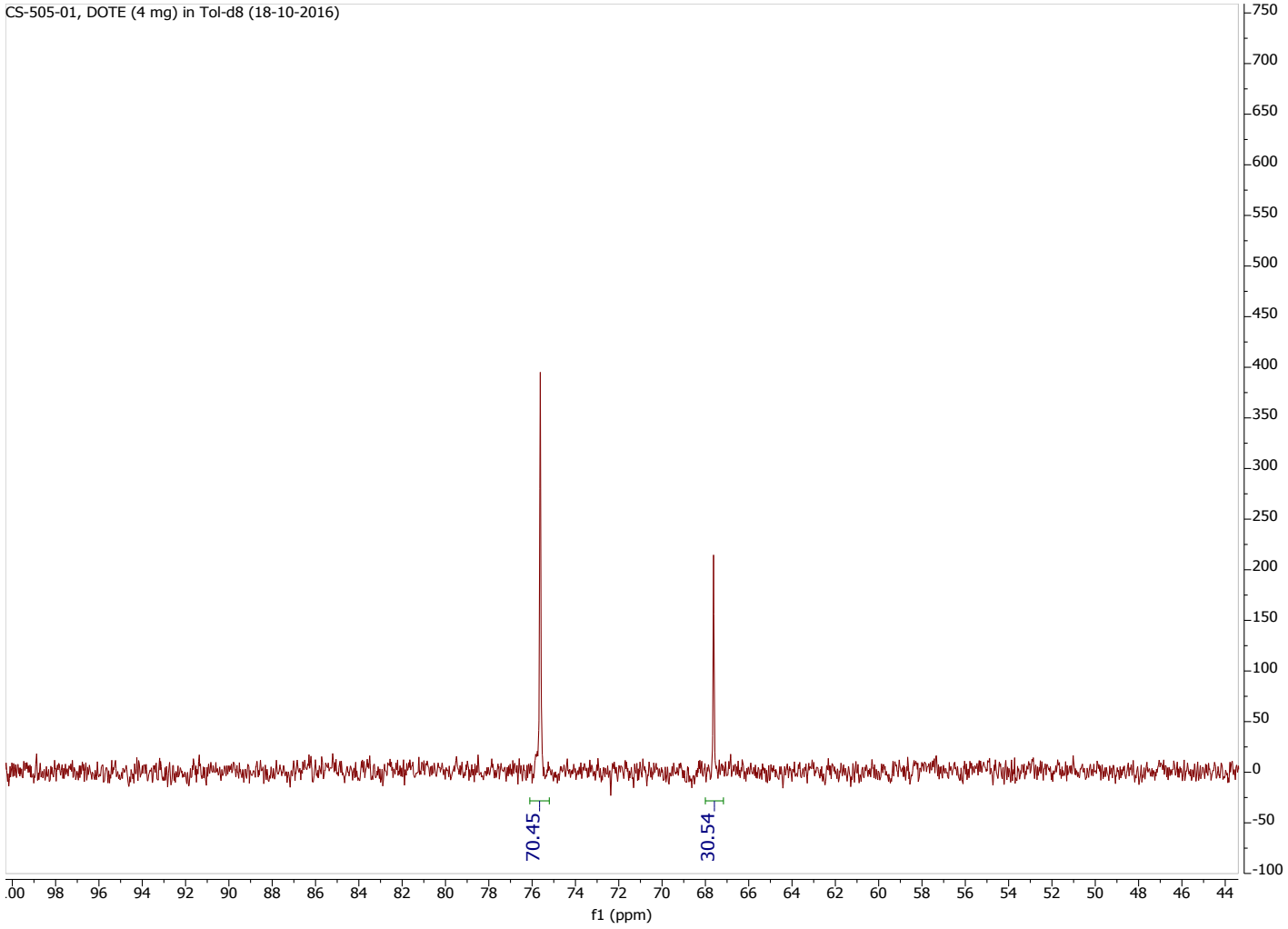
7.1.7 ^{119}Sn-NMR of DOTE/MOTE

^{119}Sn-NMR of DOTE/MOTE



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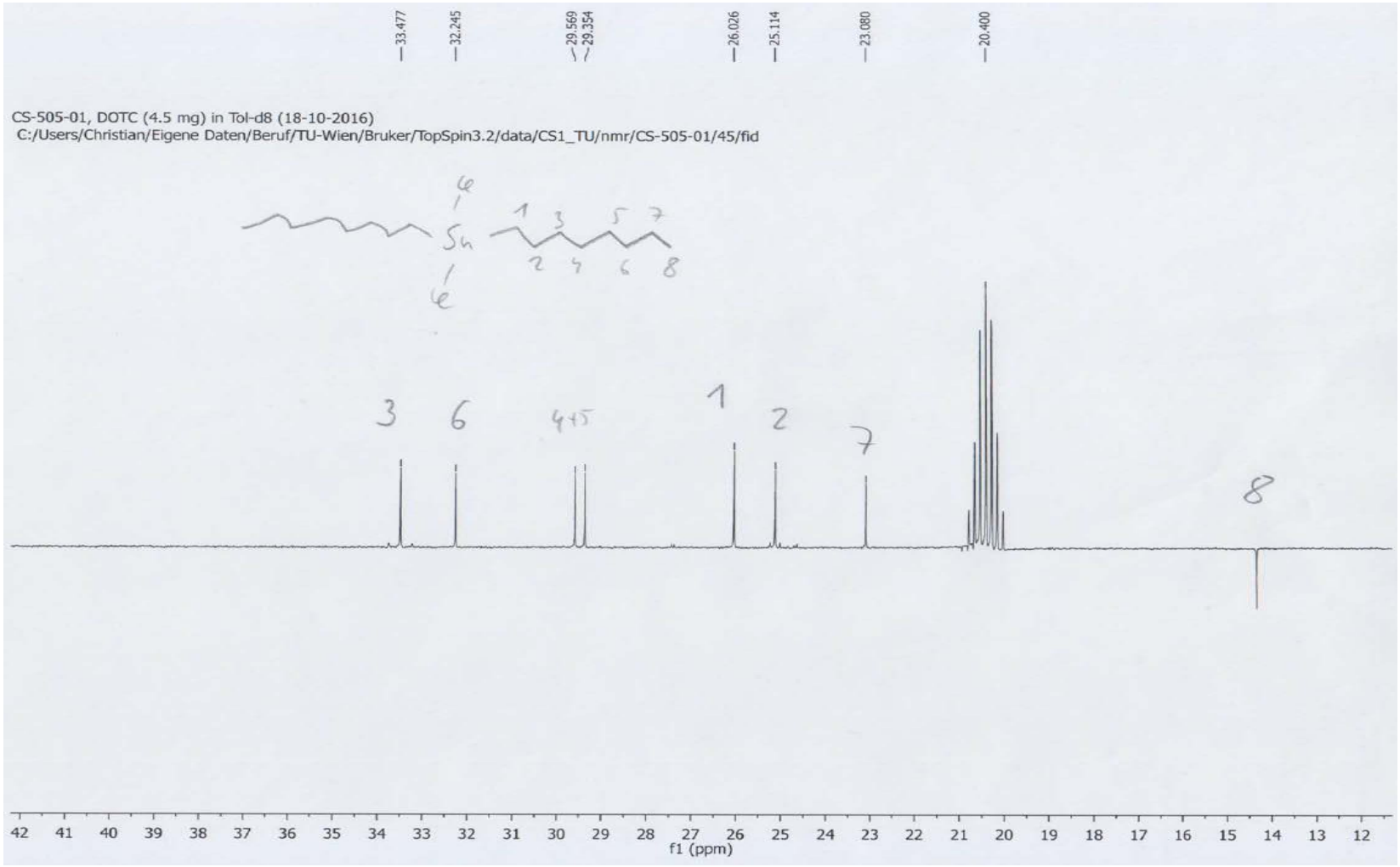
7.1.8 ^{13}C-APT-NMR of DOTC

^{13}C-APT-NMR of DOTC



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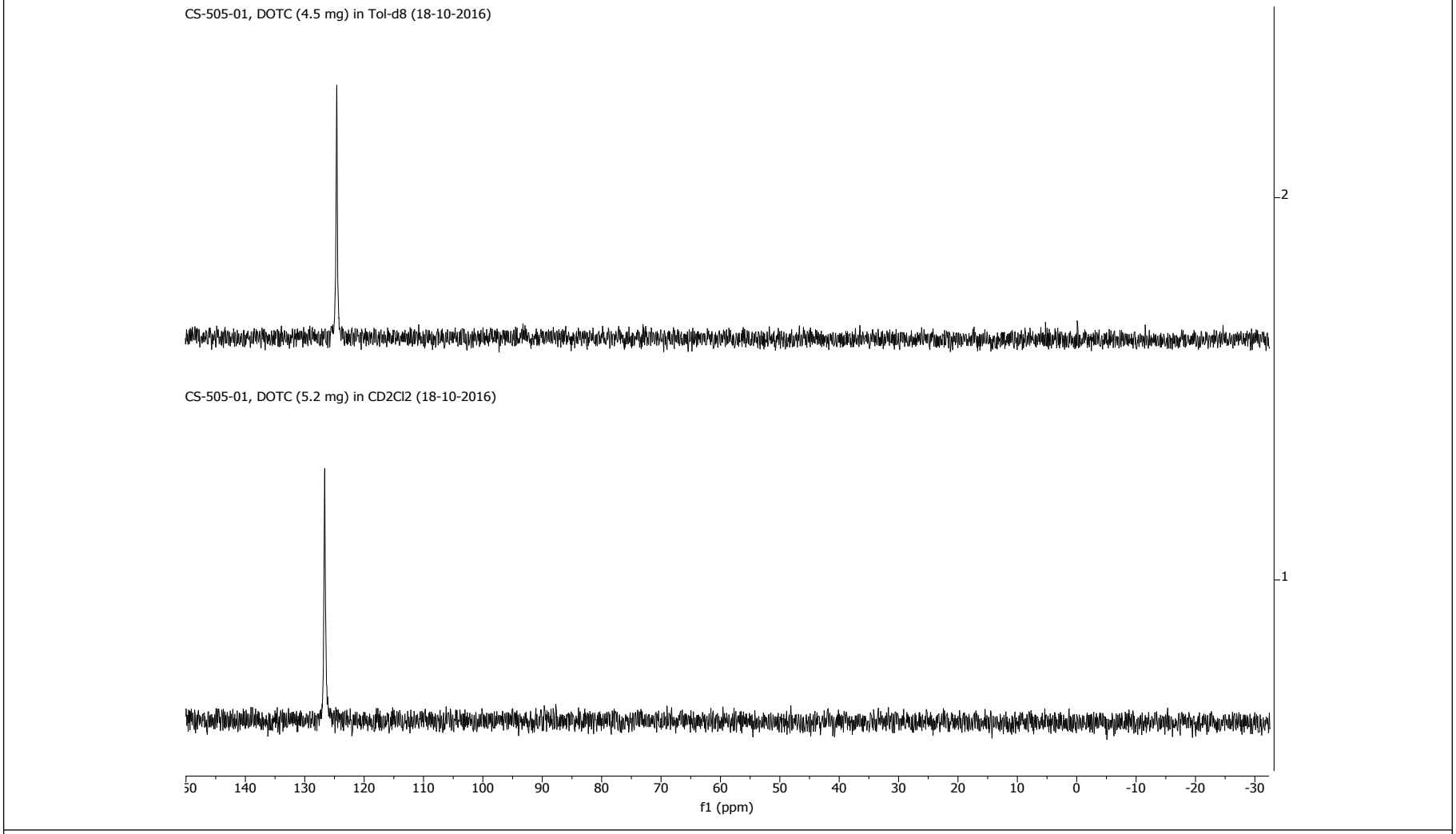
7.1.9 ^{119}Sn-NMR of DOTC (in tolene-D_8 and dichloromethane-D_2)

^{119}Sn-NMR of DOTC (in tolene-D_8 and dichloromethane-D_2)



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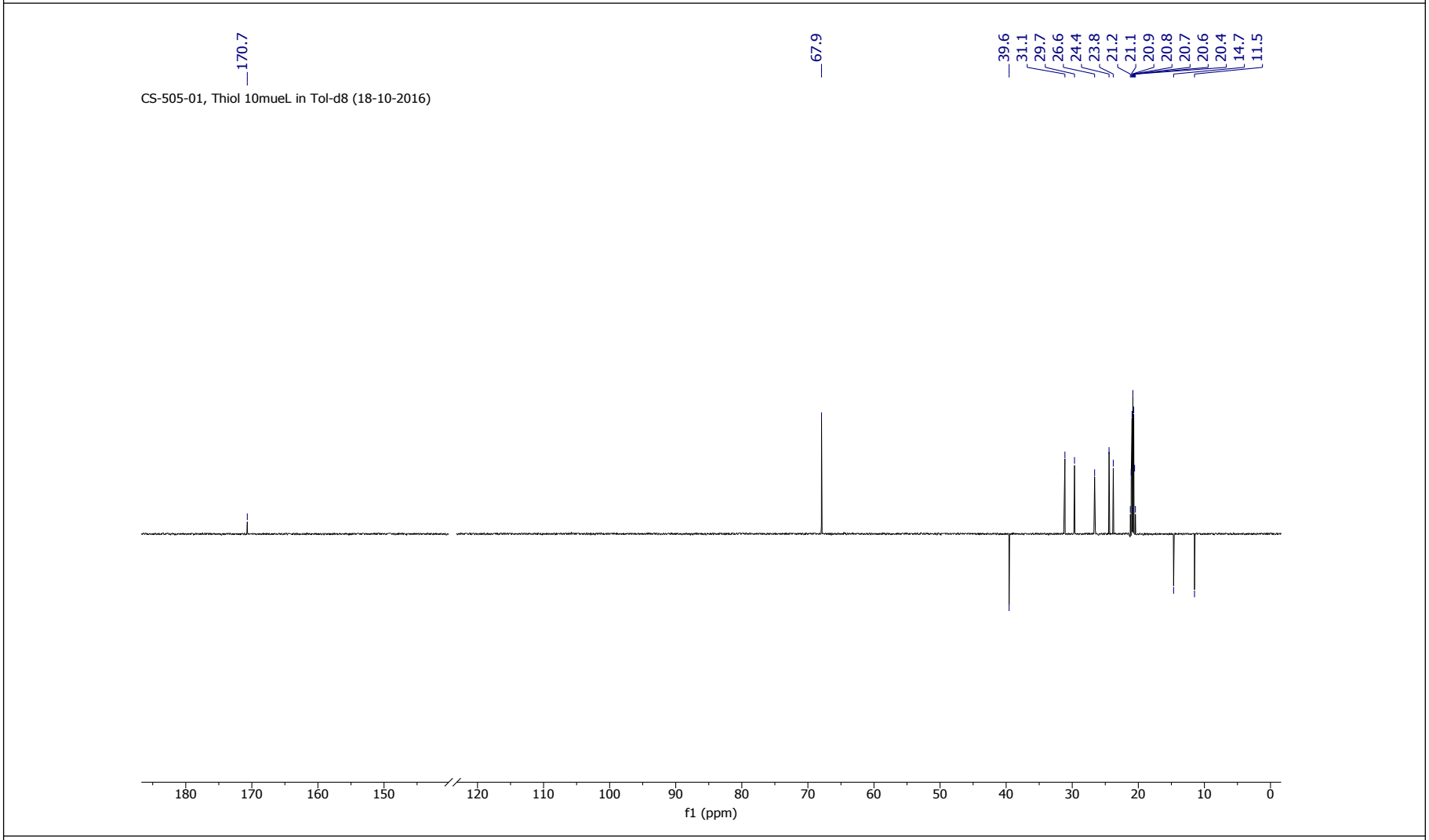
7.1.10 ^{13}C-APT-NMR of EHMA

^{13}C-APT-NMR of EHMA



Source: TU-Wien

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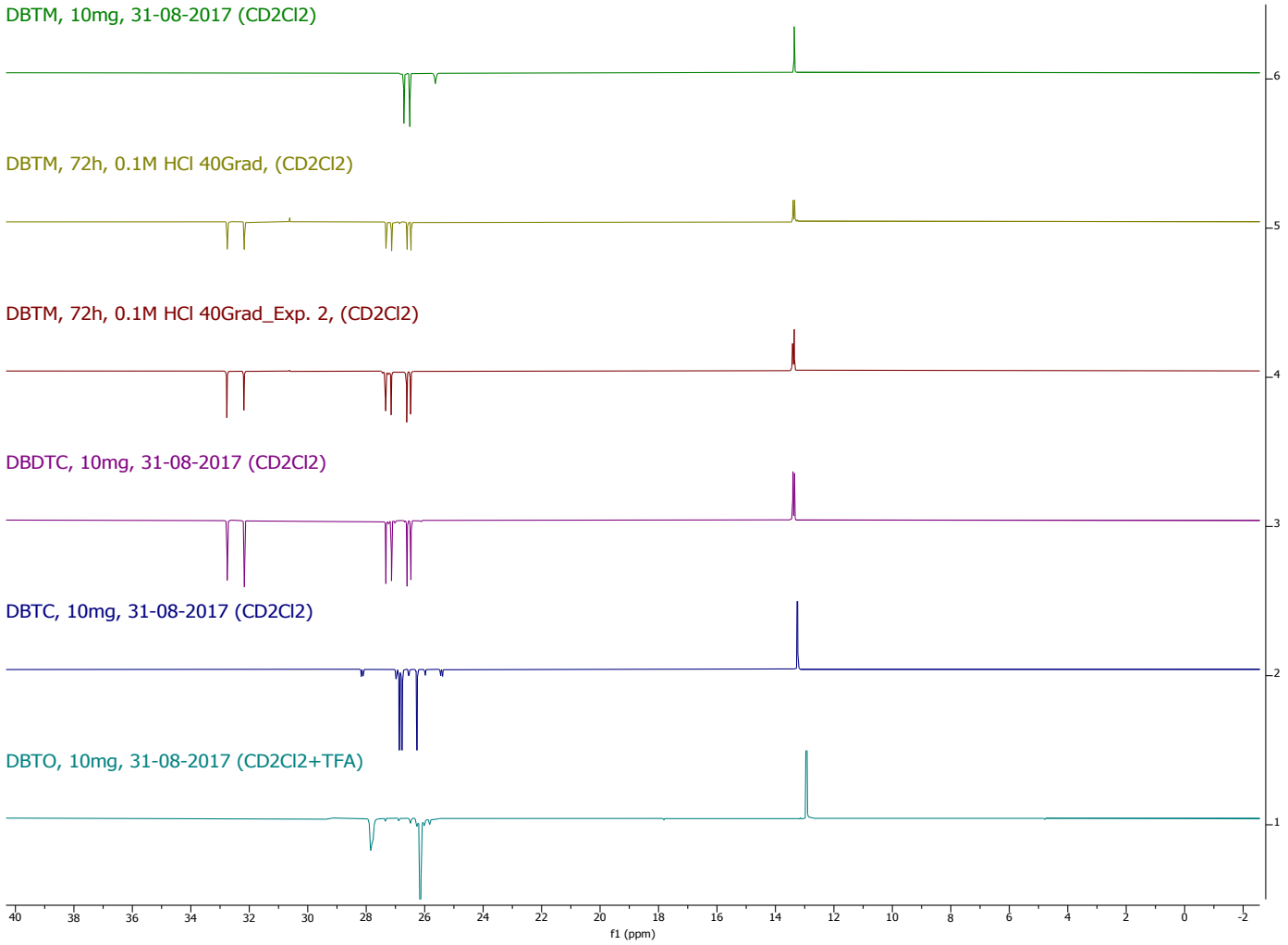
7.1.11 ^{13}C-APT NMR of DBTM, DBTDC, DBTO and DBTC

^{13}C-APT NMR of DBTM, DBTDC, DBTO and DBTC

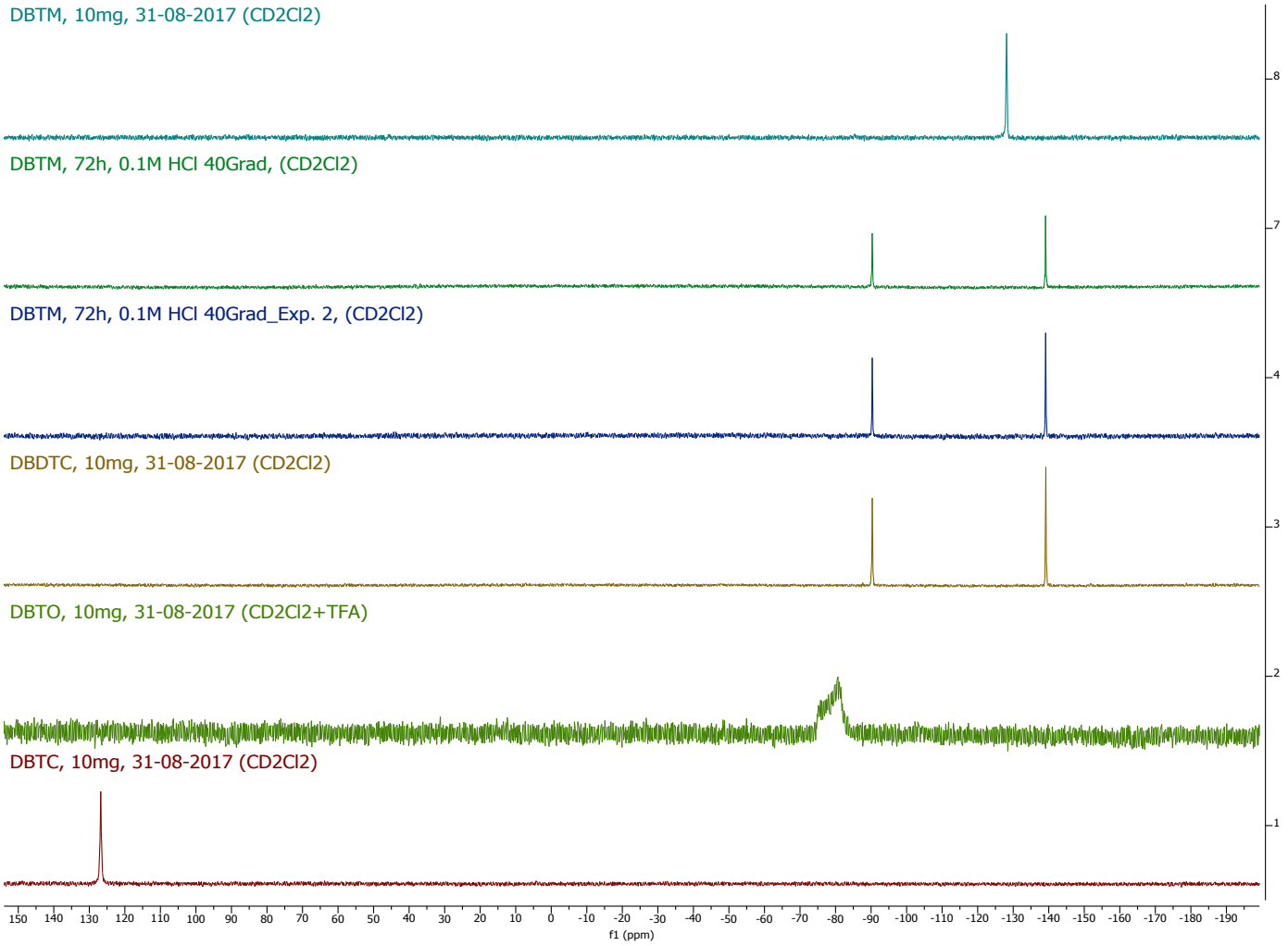


Source: TU-Wien

umweltbundesamt

7.1.12 ^{119}Sn-NMR overlay of DBTM, DBTDC, DBTO and DBTC

^{119}Sn-NMR overlay of DBTM, DBTDC, DBTO and DBTC

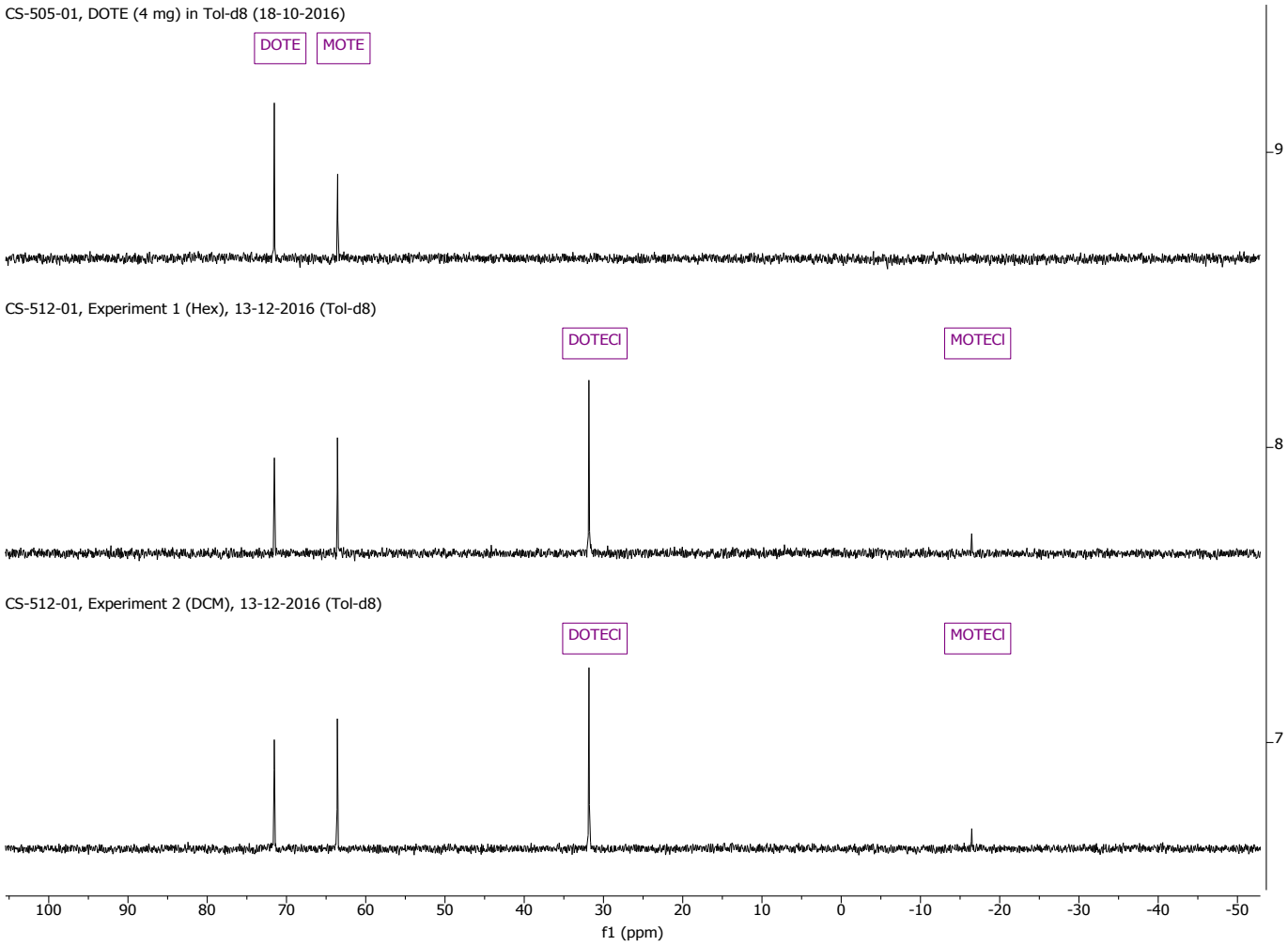


Source: TU-Wien

umweltbundesamt

7.2 ^{119}Sn-NMR overlay of DOTE experiments 1 to 3 in toluene-D_8 (1.000 scans)

^{119}Sn-NMR overlay of DOTE experiments 1 to 3 in toluene-D_8 (1.000 scans)



Source: TU-Wien

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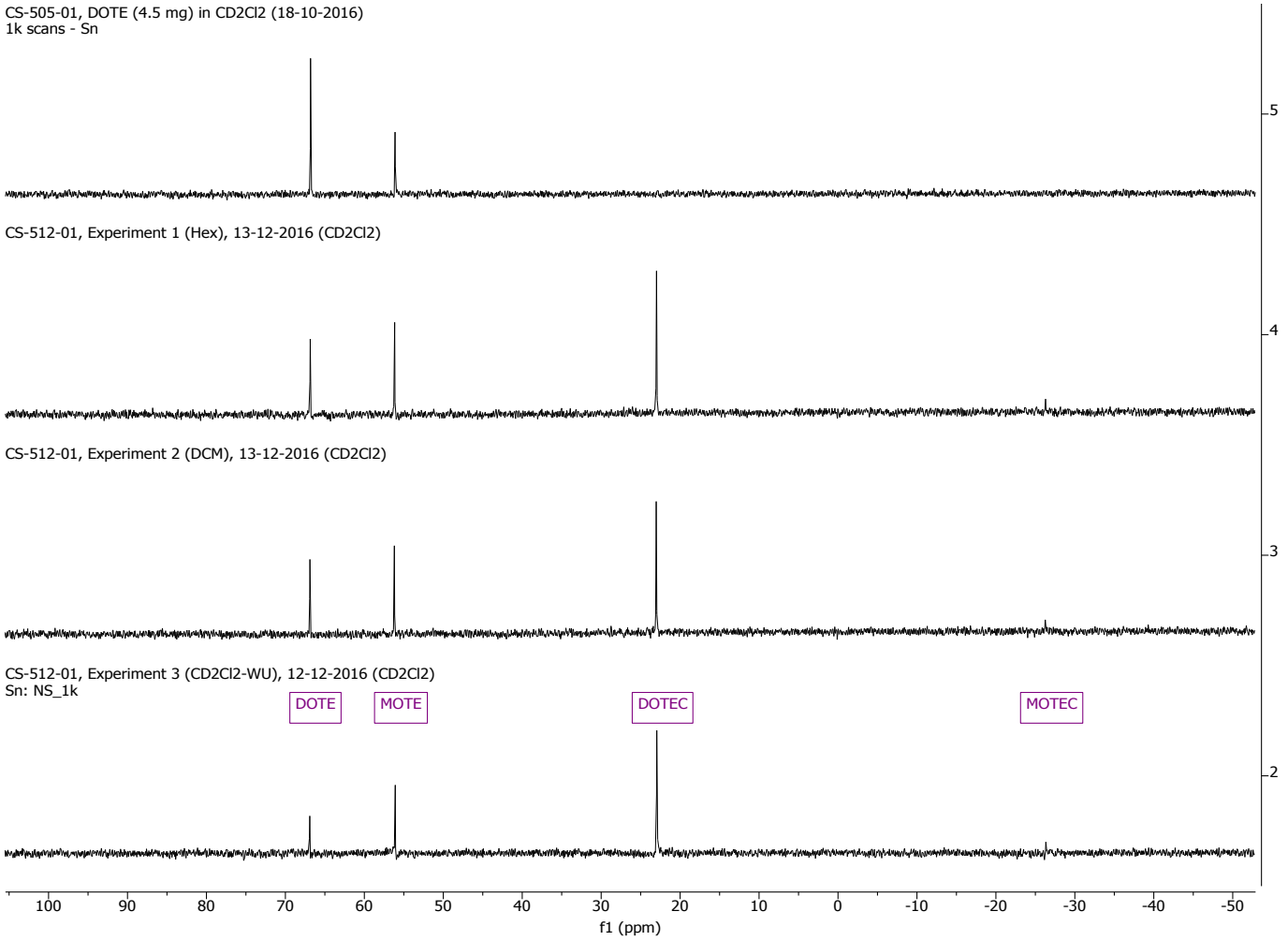
7.3 ^{119}Sn-NMR overlay of DOTE experiments 1 to 3 in dichloromethane-D_2 (1.000 scans)

^{119}Sn-NMR overlay of DOTE experiments 1 to 3 in dichloromethane-D_2 (1.000 scans)



Source: TU-Wien

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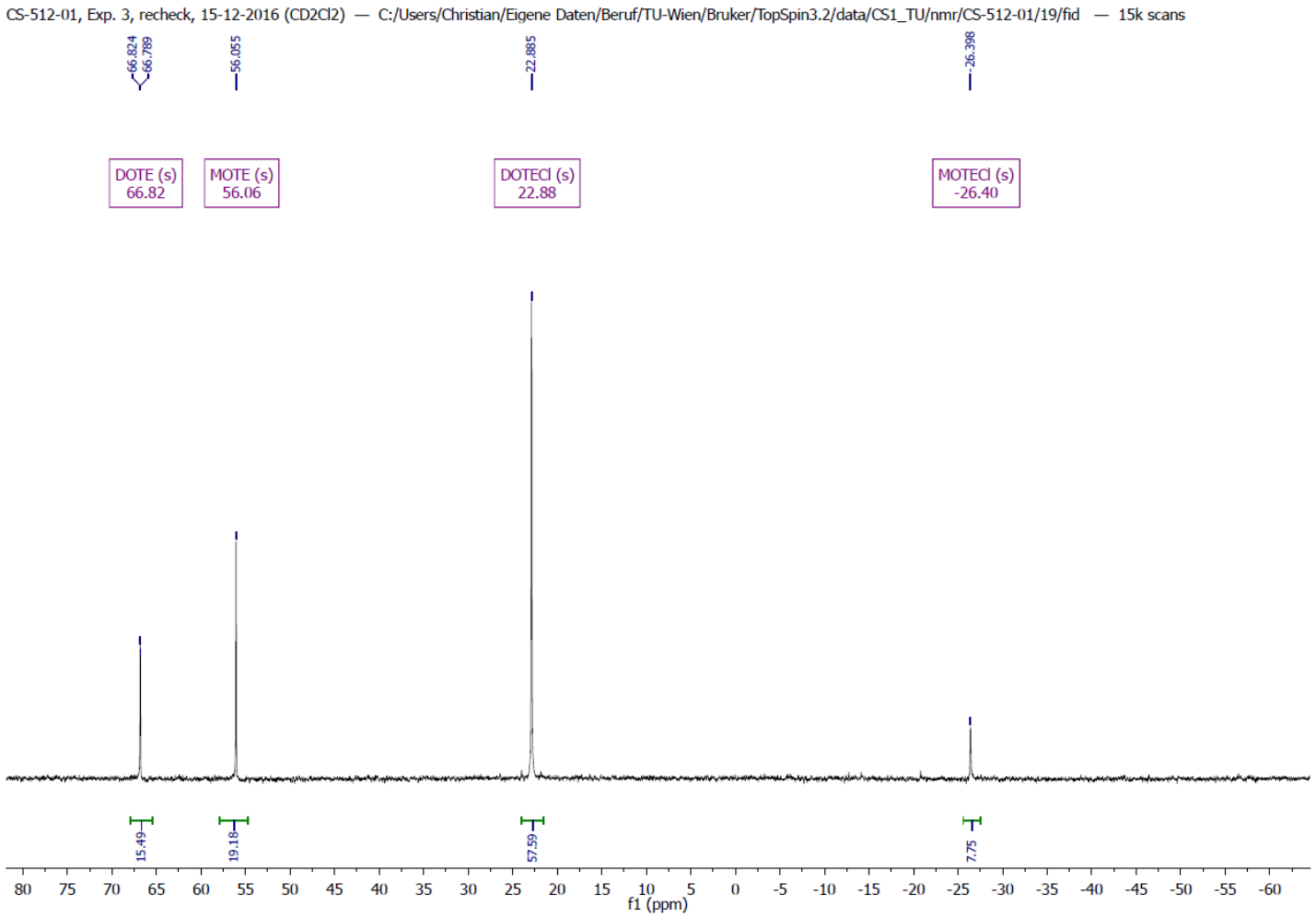
7.4 ^{119}Sn-NMR of DOTE experiment 3 with high resolution (15.000 scans) used for quantification

^{119}Sn-NMR of DOTE experiment 3 with high resolution (15.000 scans) used for quantification



Source: TU-Wien

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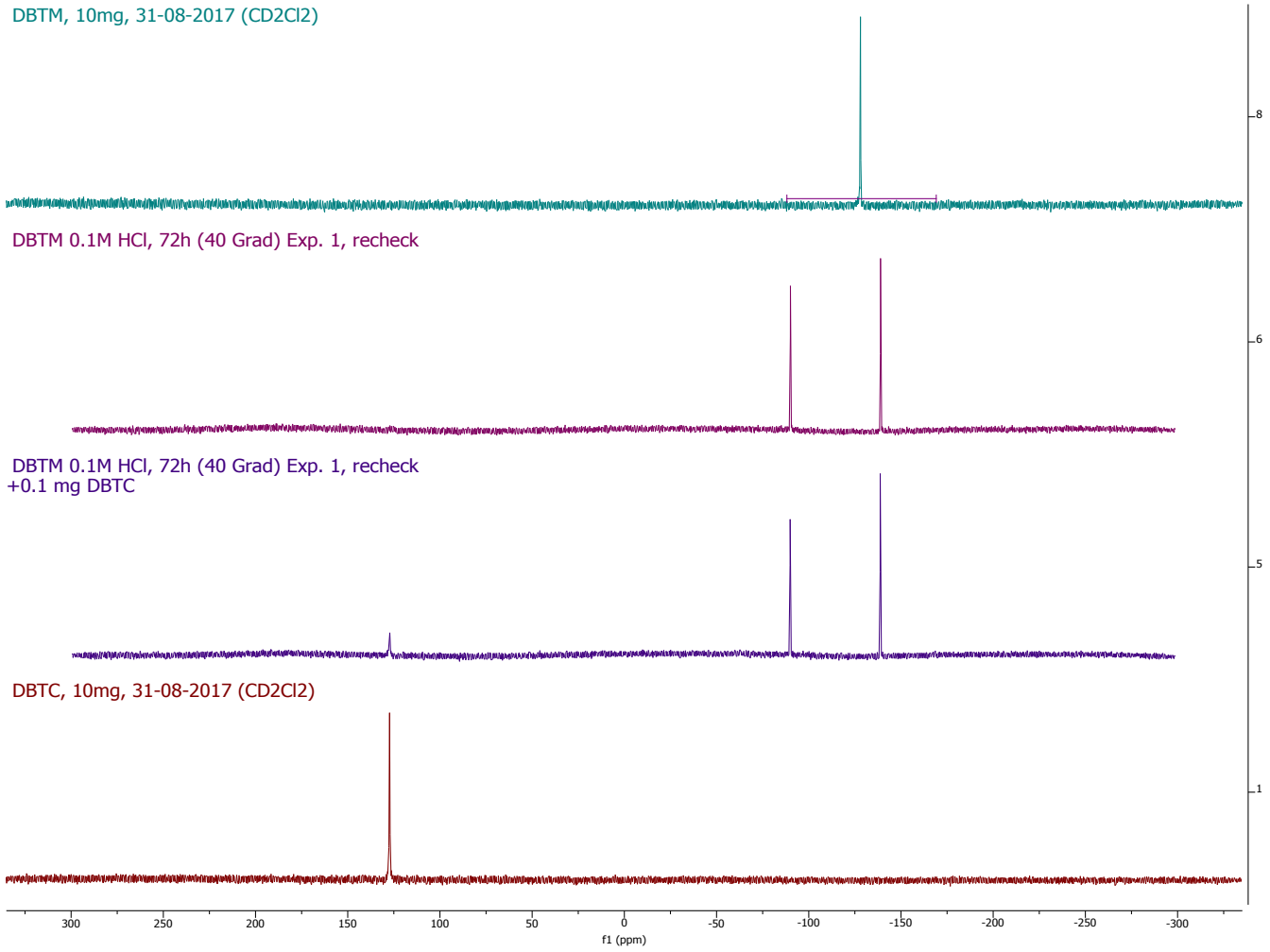
7.5 ^{119}Sn-NMR spiking experiment of DBTM with DBTC

^{119}Sn-NMR spiking experiment of DBTM with DBTC



Source: TU-Wien

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Organotin compounds used in PVC production as heat stabilisers are registered in the high tonnage bands under Regulation (EC) No 1907/2006 (REACH). Not for all of them are sufficient toxicological data available. It has been assumed previously that dioctyltin bis(2-ethylhexyl mercaptoacetate) (DOTE) and dibutyltin maleate (DBTM) form corresponding dichloride compounds under simulated gastric conditions (dioctyltin dichloride (DOTC) or dibutyltin dichloride (DBTC), respectively) and thus it was hypothesised that their toxicological behaviour is similar to the dichloride forms.
The aim of the present investigations is to further characterise the metabolites of DOTE and DBTM formed in a simulated gastric environment in order to substantiate or challenge the application of a read-across approach to DOTC and DBTC as proposed under REACH.

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