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Metal-Free Functionalization of Linear Polyurethanes by Thiol-Maleimide Coupling Reactions

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Abstract. A new approach for the metal-free functionalization of aliphatic polyurethanes has been explored by the combination of polyaddition step-growth polymerization and thiol-maleimide coupling reactions. A maleimide containing diol has been incorporated in different ratios into an aliphatic PU backbone. The incorporated amount of a masked maleimide containing diol could be calculated from ^{1}H NMR analysis and TGA analysis. Subsequently, the PU's were coupled with several thiols containing hydroxyl, acid and chloride groups via the thiol-maleimide coupling reaction. ^{1}H and 2D DOSY NMR techniques demonstrated that the thiols were indeed covalently bond onto the polyurethanes. Although DMSO is the best solubilizing solvent for the PU's, the efficiency of the thiol-maleimide reaction is lowered as a result of thiol-based impurities. Conversions higher than 90% were obtained in NMP as solvent. This approach resulted in a new metal-free functionalization platform for polyurethanes, which could be further applied to PU-materials including elastomers and foams.

Keywords: Polyurethanes, Thiol-maleimide coupling, Metal-free functionalization

Communication to the editor

Polyurethanes (PU's) are a versatile class of polymers used in today's high-performance applications. The urethane linkage imparts most of the important physical properties, leading to the suitable use of PU's in construction, automotive, flooring and sports.[1] The basic feeds in the synthesis of polyurethanes are diisocyanates, diols or polyols and a catalyst. Due to the wide availability of these monomers, a wide range of materials can be synthesized with unique and on-demand properties.[2] Recently, much attention is paid to the development of functional polymers, including polyurethanes, as these materials would lead to new applications that can broaden the classical market. Preferably, these functionalization strategies are straightforward with high yields and with little or no by-products.[3] Lately, the highly efficient, regiospecific and orthogonal copper(I) catalyzed alkyne-azide cycloaddition reaction has been used with great effect for this purpose.[4,5] This is the most popular reaction of the chemical concept 'click' chemistry and has led to a significant contribution in both organic and polymer chemistry.[6-9] The combination of 'click' chemistry and polyurethanes has yet been explored by Fournier et al.[10,11] A small alkyne containing diol was incorporated in linear PU chains, as well as in films and foams and these materials were subsequently reacted with a range of azide-containing molecules. Despite the excellent yields and the universal character of this azide-alkyne cycloaddition reaction, this method has still some remaining drawbacks. Firstly, the remaining copper catalyst, often difficult to remove completely, can cause undesired coloring and secondly, there are safety concerns with low molecular weight azides.

Recently, efforts have been made to the application of suitable metal-free click reactions, including the reaction of azides with substituted cyclooctynes,[12] the 1,3-dipolar cycloaddition of nitrile oxides and alkynes[13] and the thermal click reaction of alkynes to azide-containing siloxanes.[14] Another highly clean, fast and efficient metal-free reaction is the reaction between thiols and maleimides.[15] Maleimides are an important class of substrates for biological, pharmacological and chemical applications. They are very susceptible to Michael additions across the double bond and are commonly applied in the field of bioconjugation in combination with thiols. The thiol-maleimide coupling reaction is indeed often proposed as another example of ‘click’ chemistry as it is a fast, relatively easy reaction with a single isomer product, offering high yields and having low sensitivity to oxygen and water. In the past, a wide variety of catalysts have been used to initiate this reaction,[16] although in recent reports mostly a tertiary amine is used. This thiol-maleimide reaction started gaining an increasing attention in polymer chemistry during the last years. For example, Dove and co-workers[17] synthesized maleimide-terminated poly(lactic acid) and coupled them with several functionalized thiols. The latest research trends show for instance that thiol modified aptamers have been conjugated with maleimide-containing PEGs,[18] maleimide-containing hydrogels have been synthesized *via* a Diels-Alder strategy[19] and RAFT polymers have been modified with enes and maleimides.[20,21]

Maleimide functionalized copoly(urethane-urea)s have been prepared by Gaina and co-workers.[22] Dibenzyldiisocyanate and 5-maleimidoisophthalic diisocyanate were reacted with a macrodiol, diethylene glycol and trimethylol propane. Networks were synthesized by thermal polymerization of the maleimide functions, leading to an increase of the mechanical properties.[22] The UV-promoted thiol-ene chemistry has recently successfully been applied on PU’s. UV-curable coatings based on blending multifunctional thiol- and multifunctional ene-terminated PU aqueous dispersion mixtures were prepared by Yang and co-workers.[23] The films prepared by this method were found to exhibit good physical properties. Jung and co-workers reported the grafting of poly(ethylene glycol) methacrylate (PEGMA) on a thiolated PU surface using UV mediated thiol-ene chemistry.[24] An allylated PU surface was reacted with tetra-thiols in order to increase the functionalities on the surface. Then, PEGMA was grafted onto the thiolated PU surface by irradiating with UV light, changing the surface properties of conventional PU’s.[24]

In this contribution, we targeted the design of functionalized linear PU’s by thiol-maleimide reactions without the use of a toxic catalyst or UV light, but only mediated by a tertiary amine. This functionalization approach is demonstrated herewith for PU’s synthesized by the classical tin-catalyzed polyaddition reaction of polyol and polyisocyanate. However, the strategy can generally be combined with other PU synthesis procedures using non-metallic catalysts,[25,26] leading to a completely metal-free pathway for fabrication of functionalized PU materials. For this purpose, a furan-protected maleimide-containing diol monomer (FMD, Scheme 1) has been synthesized, as previously reported.[27-28] A predetermined mixture of 1,4-butanediol (BDO) and FMD was added to an equimolar amount of hexamethylenediisocyanate (HDI). The synthesis was performed in EtOAc at 50 °C with approximately 20 – 30 µL of dibutyltin dilaurate (DBTDL) as catalyst and the reaction was allowed to stir under inert atmosphere for 2 h. During its formation, the linear PU (PU-FMD-m, with m the amount of incorporated FMD in the feedstock) precipitated in the medium, and the obtained polymer was subsequently filtered off and extensively washed with EtOAc and acetone to remove all unreacted compounds. The PU's were dried under vacuum overnight prior to further characterizations. The overall reaction sequence is shown in Scheme 1 and the molecular weights of the PU's are given in Table 1.

Scheme 1

Table 1

^{1}H NMR analysis of the synthesized polymers (see Figure 1, lower spectrum), with the exception of PU-FMD-5 that was not able to be analyzed as a consequence of its insolubility in DMSO-*d6*, revealed that FMD was successfully incorporated in the PU backbone. The specific signals coming from the furan-maleimide adduct moiety are clearly visible at δ = 5.11 and 6.54 ppm, although fewer of these groups were present than theoretically estimated from the original feedstock (see Table 1). This can be ascribed to a combination of early precipitation of the PU in EtOAc during its formation and the higher sterical constraints of FMD compared to the small BDO molecule.

A final step was the retro-Diels-Alder deprotection of the maleimide group by heating the PU's overnight at 100 °C under vacuum, yielding aliphatic PU's with pendant maleimide functions. This deprotection has been confirmed both by ^{1}H NMR (Figure 1) and TGA (see the Supporting Information). The furan-protected maleimide signals completely disappear and the new signal of the double bond in the maleimide structure appears at δ = 7.01 ppm, partially covered by the urethane signal between δ = 7.02 and 7.14 ppm. The TGA of the furan-protected PU's clearly shows a decrease in mass at an early stage, which is ascribed to the loss of the furan group. As an example, the TGA curve of PU-FMD-50 is considered. This curve displays a first decrease in weight starting at 125 °C, which is not observed in the TGA of the deprotected material PU-MD-50 (shown in Supporting Information). This decrease of 7.5 wt % corresponds to the loss of the maleimide protecting furan groups, from which the fraction of FMD units in the PU can be calculated (39.3 mol% in this example). These values for all polymers obtained by TGA are listed in Table 1 and are in good agreement with the values obtained by ^{1}H NMR. Besides, there is residual char left when the PU's are heated up to 1100 °C, which is ascribed to the abovementioned thermal crosslinking of the maleimide groups.[22]

Figure 1

Following maleimide deprotection of the PU's, the reaction of maleimide groups with several thiols, such as 1-thioglycerol, benzylmercaptan, 4-chlorobenzylmercaptan and 1-dodecanethiol, thiosalicylic acid was studied (see Scheme 1 and Supporting Information). For these functionalization reactions, two equivalents of the thiols, according to the MD units, have been applied in DMSO as solvent, in combination with 1 equivalent of NEt_3 at room temperature or slightly elevated temperatures. After stirring overnight, the PU's were precipitated in EtOH or acetone and dried under vacuum. Analysis by ^{1}H NMR (see SI) reveals the appearance of new signals and a concurrent decrease in the signal at δ = 7.01 ppm, which is a combination of the maleimide signals and the urethane signals. In order to further demonstrate that the thiols are covalently attached to the PU's, 2D DOSY NMR (Diffusion Ordered Spectroscopy) was applied to the reaction mixture before precipitation. In DOSY NMR, the signals of the different compounds are separated as a function of their diffusion coefficient, i.e. small molecules have a larger diffusion coefficient than a macromolecule and will appear at the bottom of the DOSY spectrum.[29] In the particular example shown in Figure 2, PU-MD-50 has been grafted with 4-chlorobenzylmercaptan under the abovementioned conditions at room temperature, yielding PU-MD-50-CB. From DOSY analysis it can be concluded that there is remaining unreacted 4-chlorobenzylmercaptan visible at δ = 7.31, 7.38 and 3.79 ppm. Nevertheless, these benzylic signals at δ

= 7.31 and 7.38 ppm also appear in PU-MD-50-CB, proving 4-chlorobenzylmercaptan has been covalently bound on the PU by the thiol-maleimide coupling reaction.

Figure 2

The efficiency of the thiol-maleimide reaction has been confirmed by integration of the signals in the ^{1}H NMR spectrum of PU-MD-25-TG, which consists of PU-MD-25 coupled with 1-thioglycerol (TG). In this spectrum, one of the TG signals is clearly separated from all the others and can be integrated without interference. At room temperature, the efficiency of this reaction is 75%, which is not as high as the nearly 100% conversion of the copper catalyzed azide-alkyne cycloaddition reaction on linear PU-chains.[10] One of the possible reasons is the low solubility of these PU materials. Also, although DMSO was found as one of the best solvents to perform the coupling reactions at room temperature, side reactions can occur with thiol-based impurities in DMSO.[17] On the other hand, there is no loss of product due to removal of a toxic catalyst.

In order to eliminate the side reactions in DMSO, PU-functionalization in *N,N*-dimethylacetamide (DMA), *N,N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) has been examined. Nevertheless, the PU's were only soluble in NMP at elevated temperatures (> 50 °C). Again, two equivalents of TG, according to the MD units of PU-MD-25, have been used in combination with 1 equivalent of NEt_3 at 50 °C. After heating overnight, the modified PU-MD-25 was precipitated in EtOH and dried under vacuum prior to ^{1}H NMR analysis. This showed (see ^{1}H NMR spectrum in SI) that the coupling efficiency increased up to 92 %, which is in better agreement with the term 'click' chemistry.

The efficiency of the PU-functionalization has further been assessed, under the optimized conditions with NMP as solvent and at 50 ^{o}C, by examining the coupling reactions of PU-MD-25 also with 1 and 5 equivalents of TG relative to the MD units. With equimolar ratio of thiol to maleimide, a coupling efficiency of only 65% was obtained. Thus, a thiol to maleimide molar ratio larger than unity was necessary for achieving high functionalization efficiency. This was likely due to disulfide bond formation, which is a primary side reaction in thiol Michael addition reactions.[30] On the other hand, using 5 equivalents of TG did not further improve the reaction efficiency. Hence, 2 equivalents of the thiol used were sufficient to obtain a maximum conversion of more than 90%.

In conclusion, a new approach for the metal-free functionalization of aliphatic polyurethanes has been explored by the combination of polyaddition and thiol-maleimide coupling. A maleimide containing diol has been incorporated in different ratios into the PU backbone and subsequently coupled with several thiols containing hydroxyl groups, acid groups and chlorides, via the efficient thiol-maleimide coupling reaction. Analysis of functionalized polymers by ^{1}H and 2D DOSY NMR techniques, demonstrated that the thiols were indeed coupled onto the polyurethanes. Although DMSO is the best solubilizing solvent for the PU's, higher conversions were obtained in combination with NMP as solvent. This approach resulted in a new functionalization platform for polyurethanes, which could be further applied to PU-materials including elastomers and foams.

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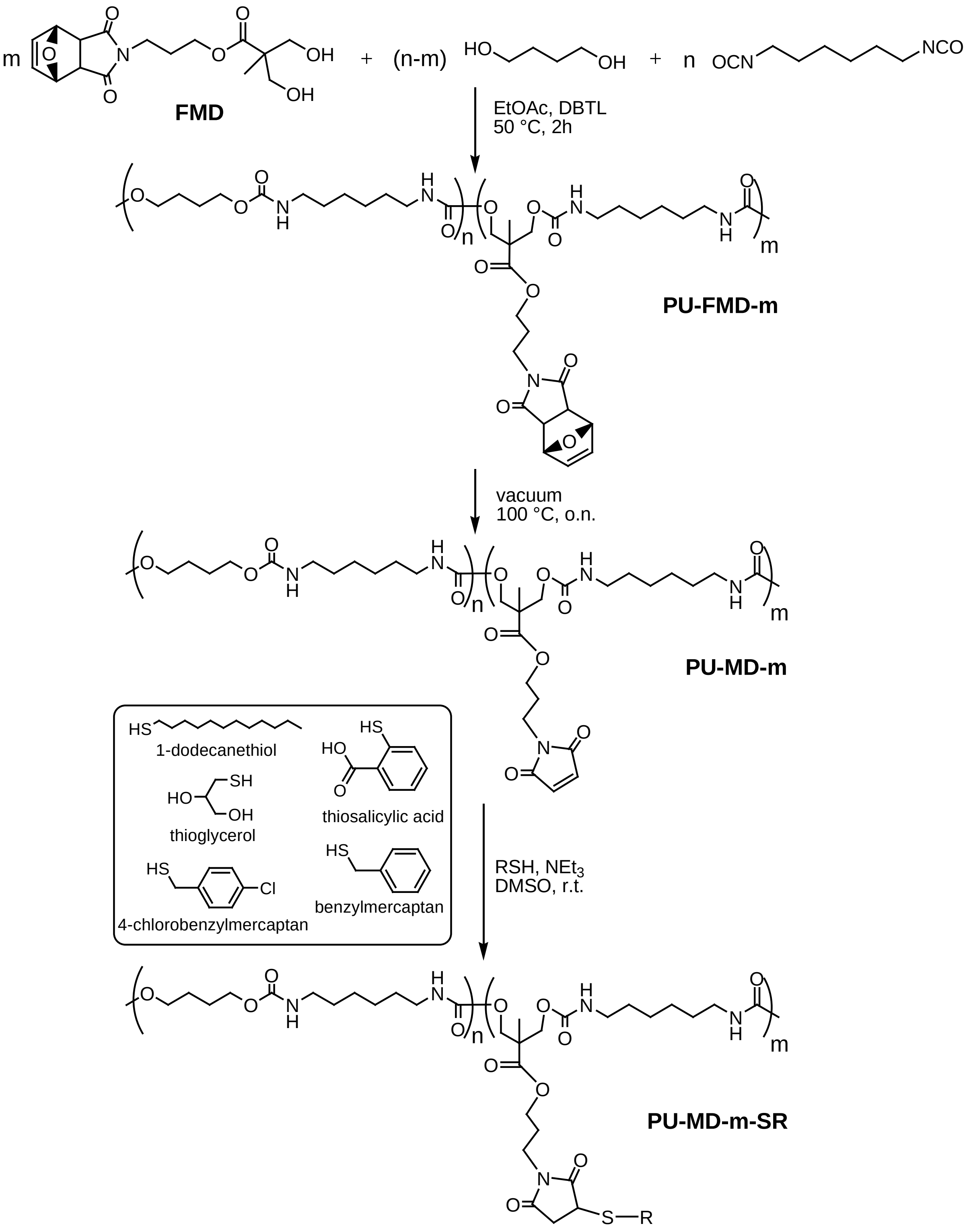
Supporting Information Available: Experimental details, TGA-spectra and the ^{1}H NMR spectra of PU-FMD-50, PU-MD-50 and PU-MD-25-TG in DMSO and NMP. This material is available free of charge via the Internet at http://pubs.acs.org.



Scheme 1. Overall reaction sequence for the synthesis of thiol functionalized linear PU.

Table 1. Characteristics of the aliphatic polyurethanes prepared from HDI, BDO and FMD.

Entry [a]	M_w [b]	mol% FMD[c]	mol% FMD[e]

	(g/mol)	(^{1}H NMR)	(TGA)
PU-FMD-5	11900	- [d]	5.4
PU-FMD-10	8500	8.1	8.8
PU-FMD-25	11600	18.8	16.8
PU-FMD-50	10600	35.0	39.3

[a] Indicated value in the reference names relates to the amount of incorporated MFD (mol %) in the feed composition.

[b] Determined by GPC (solvent: DMA), calibrated with PMMA standards.

[c] Composition determined by ^{1}H NMR in DMSO-*d6*.

[d] Not soluble in DSMO-*d6*.

[e] Heating ramp: 10 °C/min under air from 25 to 1100 °C.

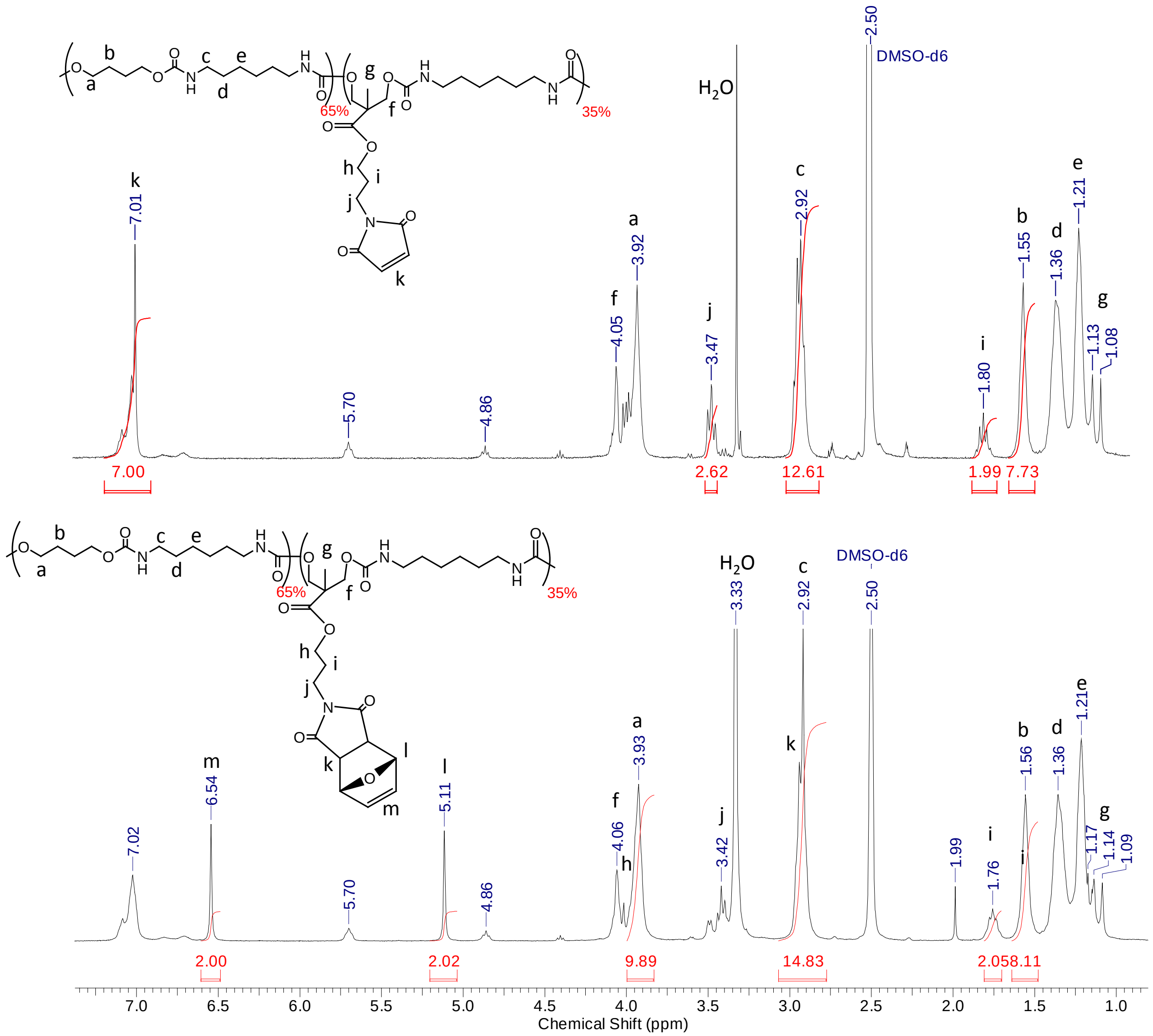


Figure 1. ^{1}H NMR spectra (300 MHz, DMSO-d_6) of the furan-protected maleimide containing PU-FMD-50 (lower spectrum) and the maleimide functionalized PU-MD-50 after retro-Diels-Alder deprotection of the maleimide groups (upper spectrum).

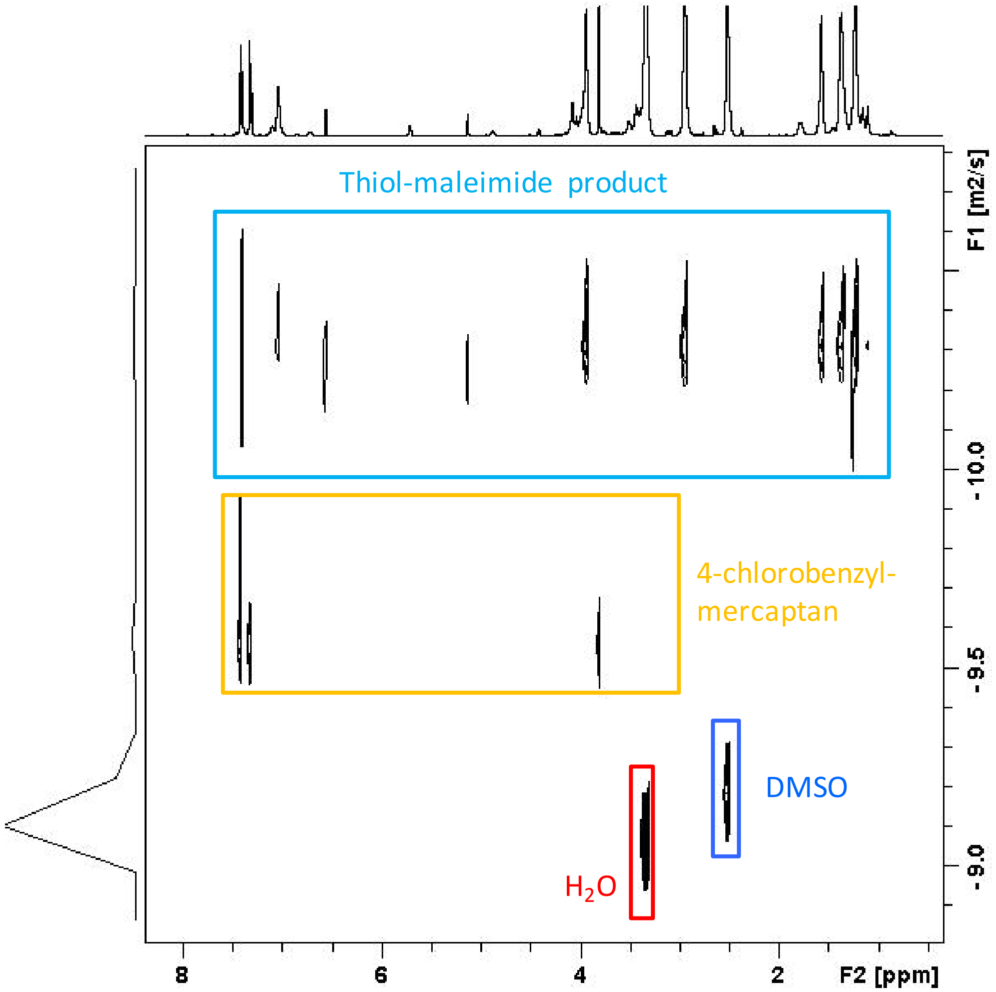


Figure 2. 2D DOSY NMR spectrum of PU-MD-50-CB.

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