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A mild, efficient and catalyst-free thermoreversible ligation system based on dithiooxalates†

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We demonstrate a novel and ready to prepare thermoreversible hetero Diels−Alder dilinker on the basis of dithiooxalates, enabling the mild, rapid and catalyst-free linkage of diverse diene species under ambient conditions for applications in the fields of, for example, modular ligation, self-healing or recyclable materials and surface modification amongst others. The linker was studied using quantum chemical calculations, and experimentally in small molecular reactions *via* UV/Vis spectroscopy, mass spectrometry and NMR as well as in step-growth polymerizations with diene-difunctional building blocks – characterized *via* (temperature dependent) SEC and HT NMR – as an example for efficient polymer ligation.

Introduction

With the increasing demand for smart materials, more and more dynamic chemistries as for example supramolecular hydrogen bonding, ligand–metal complexation, π–π stacking and thermo- or photoreversible covalent links such as disulphide bridges, alkoxyamines, boronic esters, triazolinedione or Diels–Alder (DA) adducts are being utilized to enable the generation of self-healing and other stimuli-responsive materials.[1–11] Important attributes of such reversible ligation systems are (retro) reaction ability, formed bond strengths, reaction rate (for both the forward and backward reaction) and efficiency.[5,12] While, *e.g.*, hydrogen bonding enables dynamic bond exchange even at ambient temperature, reversibly bonded covalent systems most often require elevated temperatures for self-healing properties.[1,4,5,10,12] On the other hand, the latter allow for mechanically resilient materials and higher application temperatures due to the higher association forces.[12,13] One of the first and now most commonly employed reactions for self-healing materials – also due to convenient synthesis routes – is the DA reaction of maleimide- with furan-functional species.[14–17] While it is facile to handle, it demands relatively high retro temperatures and long forward and retro reaction times. Key developments as for example the implementation of hetero DA (HDA) pairings, hybrid networks or the harnessing of entropic effects allow for faster reaction rates, efficient self-healing and the tuning of reaction temperatures, yet the individual properties of each reaction pairing are still to be optimized.[5,18–23] For example, cyanodithioesters allow for very fast HDA reactions with a variety of dienes, yet the respective dienophile can only be handled in a trapped state with, *e.g.*, cyclopentadiene as protecting group.[13,24] Thus, these systems need to be heated *in situ* to approximately 120 °C to reactivate the functional species, leading to possible side reactions or substrate degradation. Other HDA methods as for example the RAFT HDA reaction of dithioester end-groups with dienes readily occur under ambient conditions, yet mostly rely on the addition of a catalyst to achieve fast reaction times.[18,25–29] A promising candidate for fast, mild and catalyst free reaction conditions are dithiooxalates (Scheme 1),

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†Electronic supplementary information (ESI) available: Synthetic details, characterization *via* NMR, UV/Vis, SEC, MS, TD SEC setup, computational methods and data. See DOI: 10.1039/c6py00470a
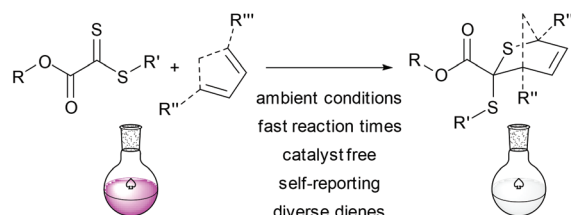
Scheme 1 General scheme of dithiooxalates in a HDA reaction with dienes.

which were previously employed in rapid and catalyst free as well as catalyzed small molecular reactions with multiple dienes under ambient conditions to yield heterocycles, while to our knowledge they were never employed either in studies of thermoreversibility or as multifunctional linker species.[30–34]

Results and discussion

While other variable molecules with higher functionalities can be realized in a facile way, a difunctional dithiooxalate was designed as a model system for multifunctional linkers (MTTA, Scheme 2). As a starting point and support for the experimental analysis of the novel HDA linker, quantum chemical *ab initio* calculations of thermodynamic reaction parameters were obtained *via* the Gaussian 09 software package.[35] For details of the employed calculation methods refer to the ESI.† The resulting temperature dependent equilibrium constants for each (retro) Diels–Alder reaction were used to determine the temperature at which the equilibrium degree of debonding equals 20%, as this is known to allow for self-healing properties as well as a good comparison of characteristics.[15,24] Initially, the reactions of a small (monofunctional) model of MTTA with a variety of common dienes (furan, cyclopentadiene (Cp), 2,3-dimethyl-1,3-butadiene (DMBD), sorbic alcohol and ethyl sorbate (Fig. 1)) in acetonitrile (MeCN) were computationally screened to allow for qualitative comparisons (Table 1). More accurate calculations, considering both ligations of the full (difunctional) MTTA linker, were then undertaken for selected dienes to allow for direct comparison with the (small molecule) experiments. Accordingly, the formation of a DA adduct of furan and dithiooxalates is predicted to be thermodynamically highly unlikely under ambient conditions due to the equilibrium being strongly shifted to the reactants, while the other pairings should allow for facile product formation. The theoretical results for the small monofunctional model of MTTA suggests the possibility to thermocycle the DA reaction for adducts of dithiooxalates with Cp, and possibly also the sorbic derivatives. However, reaction with DMBD should result in a very

Table 1 List of computationally determined temperatures for DA reaction equilibrium constants of a dithiooxalate with different diene species in MeCN corresponding to a degree of debonding of 20%[a]

Methyl 2-(methylthio)-2-thioxoacetate + …	$T_{20\% \text{ debonding, theo.}}$ [°C]
Furan	−169
Cyclopentadiene	166
Cyclopentadiene (full system)[b]	105
2,3-Dimethly-1,3-butadiene	427
Sorbic alcohol	240
Sorbic alcohol (full system)[b]	240
Ethyl sorbate	225

[a] Unless stated otherwise, all calculations were based on a single ligation equilibrium for a small (monofunctional) model of MTTA, for a concentration of reactive groups of 0.05 M. Refer to the ESI for more information. [b] Based on the 2-step ligation equilibria for the full (difunctional) MTTA.

stable adduct. When the 2-step reactions with MTTA itself are considered, the 20% debonding temperature for reaction with Cp decreases to 105 °C, placing it in good agreement with experiment (*ca.* 100 °C, *vide infra*) and making it very attractive for further study. This decrease in temperature is primarily the result of entropic factors, which increase the extent of debonding at a given temperature for heavier and longer reactants. In contrast, the 20% debonding temperature of sorbic alcohol remained unchanged because additional hydrogen bonding interactions between opposite ends of the doubly ligated product counteract the entropic effects. Of course the greater entropic effects in polymeric versions of these reactions would be expected to lead to lower debonding temperatures, but nonetheless this system is expected to be useful for applications requiring high retro temperatures.

After these promising results, experimental studies should enable a detailed exploration of the nature of dithiooxalates as HDA linkers. For the actual synthesis of a dithiooxalate dilinker, literature procedures were adopted, optimized and transferred to readily available starting materials and a difunctional core molecule, ethylene glycol, with a total yield of 60% ethane-1,2-diyl bis(2-(methylthio)-2-thioxoacetate) (MTTA, Scheme 2).[30,36] For more detailed information regarding the synthetic procedure refer to the ESI.† To gain further insight into the kinetics of the deep purple MTTA linker in HDA processes, UV/Vis spectroscopic measurements were performed on the model systems of Table 1, as the disappearance of the characteristic absorbance of the C=S double bond (Scheme 1, refer to Fig. S2† for a UV/Vis spectrum) at 500 nm allows for the facile observation of the reaction conversion with time, concomitantly giving the linker its self-reporting nature. Variable equivalents of diene to dilinker as well as ambient temperature *vs.* elevated temperature (50 °C) were assessed for a suitable overview of reaction conditions. MeCN was employed as solvent due to its solvation and UV/Vis properties at the wavelengths in question as well as its relatively high boiling point. Nevertheless, *e.g.*, dichloromethane can be used with similar reaction efficiency, allowing for a more facile solvent evaporation. As theoretically expected, the addition of furan to a
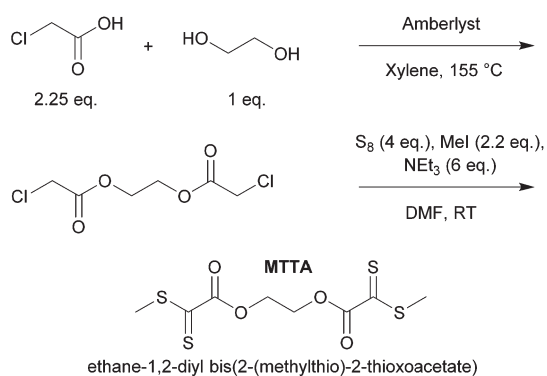
Scheme 2 Reaction scheme for the generation of a 2-(methylthio)-2-thioxoacetate difunctional HDA linker (MTTA).
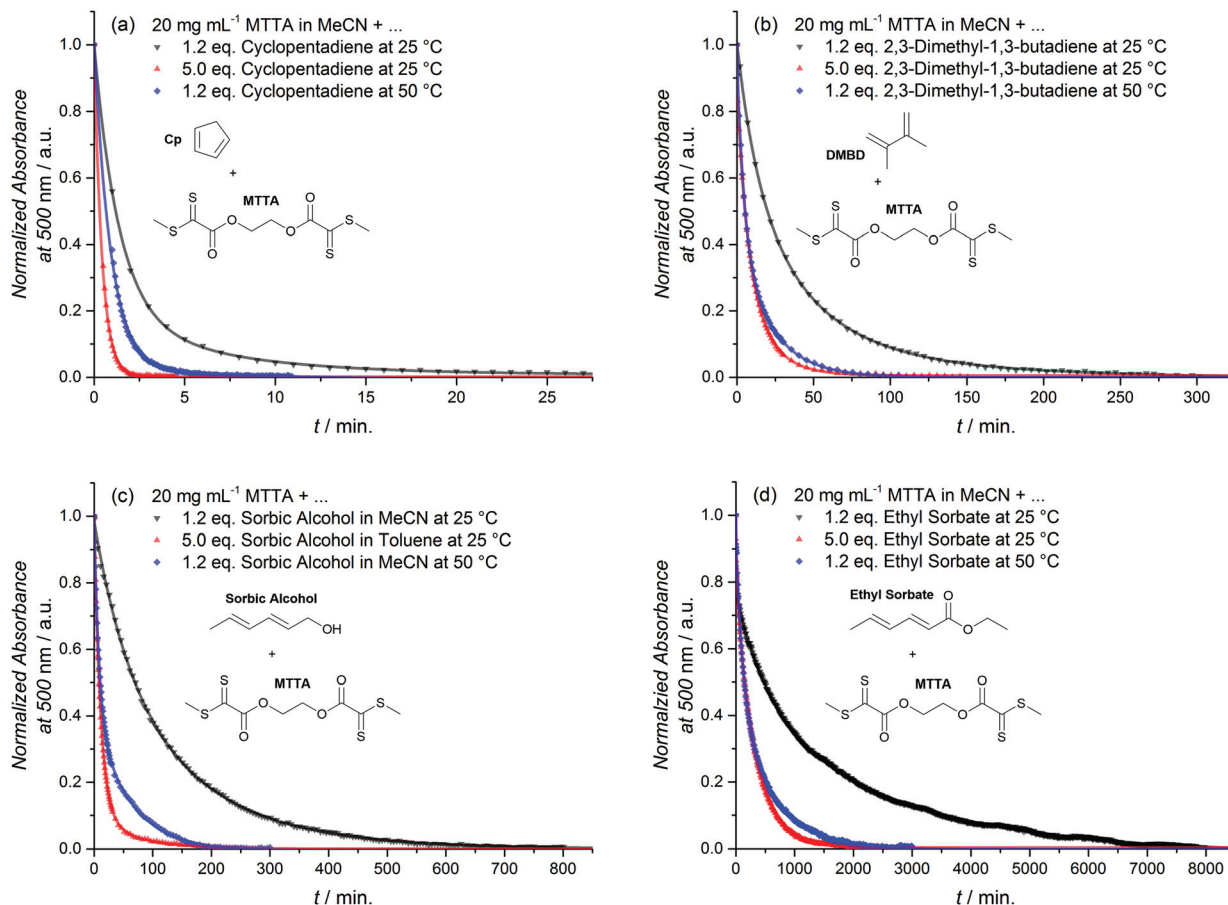
Fig. 1 Kinetic plot of the C=S double bond absorbance at 500 nm of a reaction mixture of 20 mg mL^{-1} MTTA in acetonitrile or toluene and several dienes *vs.* time with different equivalents of diene species as well as reaction temperatures.

solution of MTTA did not lead to any decoloration. Naturally, the dienes with more (Cp) or less (DMBD) forced *cis*-configuration undergo faster reaction than the open chain sorbic derivatives (Fig. 1). To guarantee full conversion and thus discoloration of the dienophiles, a minimal excess of dienes was employed. The quantitative conversions and generally rapid reaction times – in the case of Cp merely minutes – highlight the efficiency of the reaction, making it suitable for polymer conjugation without the need for complex purification steps and even step-growth or cross-linking processes.[37] Rate coefficients with a typical error of ±15% – determined by repeated measurements of the kinetics – could be calculated *via* the normalization of reactant concentrations and the assumption of 2nd order kinetics in the absence of the retro reaction, which is reasonable at the employed temperatures (Table 2, refer to ESI† for details on the calculations). The reaction rates of each diene correlate well within the error margin for different concentrations and approximately double per 10 K. Employing these reaction rate coefficients, an activation energy of on average approximately 52 kJ mol^{-1} K^{-1} was determined *via* the Arrhenius equation.[38] For further characterization of the DA adducts *via* ^{1}H NMR as well as mass spectrometry refer to the ESI (Fig. S3–6†).

Table 2 List of rate coefficients (±15%) for the DA reaction of MTTA with different equivalents of dienes in MeCN at ambient or elevated (50 °C) temperature

20 mg mL^{-1} MTTA in MeCN + …	k [L mol^{-1} s^{-1}]
1.2 eq. furan at 25 °C	—
1.2 eq. Cp at 25 °C	7.1×10^{-2}
5.0 eq. Cp at 25 °C	7.3×10^{-2}
1.2 eq. Cp at 50 °C	3.6×10^{-1}
1.0 eq. Cp$_2$P^{t}BuA	4×10^{-1}
1.2 eq. DMBD at 25 °C	3.4×10^{-3}
5.0 eq. DMBD at 25 °C	2.5×10^{-3}
1.2 eq. DMBD at 50 °C	1.8×10^{-2}
1.2 eq. sorbic alcohol at 25 °C	1.7×10^{-3}
5.0 eq. sorbic alcohol at 25 °C^a	1.9×10^{-3}
1.2 eq. sorbic alcohol at 50 °C	8.4×10^{-3}
1.0 eq. IPDI-SA	7×10^{-3}
1.2 eq. ethyl sorbate at 25 °C	1.2×10^{-4}
5.0 eq. ethyl sorbate at 25 °C	0.9×10^{-4}
1.2 eq. ethyl sorbate at 50 °C	6.4×10^{-4}

^{a} Measured in toluene due to poor solubility in MeCN.

In order to transfer the linking abilities to polymeric systems, equimolar amounts of a Cp difunctional poly(*tert*-butyl acrylate) (Cp$_2$P^{t}BuA, Fig. 2(a)) were employed in a step-growth reaction with the MTTA linker. The reaction was moni-
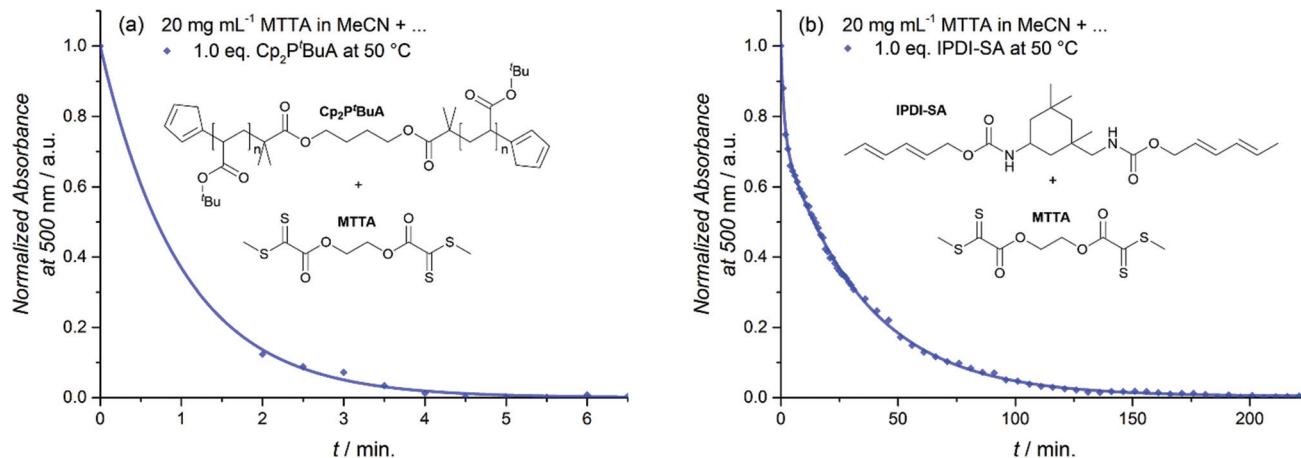
Fig. 2 Kinetic plot of the C=S double bond absorbance at 500 nm of a reaction mixture of 20 mg mL^{-1} MTTA in acetonitrile with equimolar amounts of (a) Cp difunctional poly(*tert*-butyl acrylate) (Cp$_2$P^{t}BuA) or (b) isophorone bis(sorbic carbamate) (IPDI–SA) at 50 °C.
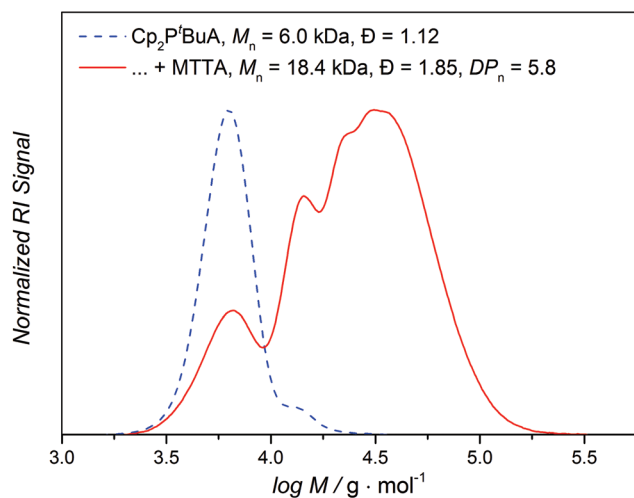

Fig. 3 SEC trace of Cp$_2$P^{t}BuA (---) and its DA step-growth adduct (—) with equimolar amounts of MTTA (20 mg mL^{-1} in MeCN), measured in THF at 35 °C.

tored by UV/Vis spectroscopy at 50 °C and again 20 mg mL^{-1} of linker substrate as these reaction conditions proved to be very efficient for near to equimolar ratios in the small molecular test reactions and allowed for full conversion in less than 5 minutes. The diene difunctional species readily react with the dienophile dilinker in a step-growth manner (Fig. 3), demonstrating its efficiency and suitability for polymer functionalization and possible cross-linking applications *via* diene multifunctional polymers or the employment of a higher functional core material during the synthesis of the linker. Although prolonged solvation durations, solution viscosity and the slight coloring of the Cp$_2$P^{t}BuA difunctional species lead to a less reliable evaluation of UV/Vis spectra and thus presumably larger error margins, the rate coefficient of approximately 0.4 L mol^{-1} s^{-1} of the step-growth reaction is in good agreement with the small molecular test reactions (Table 2). The step-growth reaction of MTTA with a small molecular open-chain diene difunctional isophorone bis(sorbic carbamate) (IPDI–SA) led to similar results (Fig. 2(b), refer to Fig. S8 in the ESI† for SEC) with its reaction rate of 7×10^{-3} L mol^{-1} s^{-1} being comparable to sorbic alcohol (Table 2), again indicating the efficiency of the linkage.

Importantly, as a linear model system for self-healing or other thermoreversibly cross-linked materials, the adduct of either Cp or Cp$_2$P^{t}BuA with the dilinker underwent high temperature (HT) ^{1}H NMR measurements (Fig. 4) to demonstrate the thermocyclability of the (retro) DA reaction. The systems with Cp functional groups were chosen for such a thermoreversibility study due to their favorable reaction rates (Table 2) as well as their quantum chemically predicted desirable retro DA temperatures (Table 1). Upon heating, signals of free Cp groups are emerging with increasing temperature and vanishing again during cooling of the sample to ambient conditions (Fig. 4). The experimental results allow for an estimation of the temperature dependent degree of bonding *via* the ratio of the integral signal values of free Cp units to bound ones in HDA adducts (Fig. 4), which is in very good accordance with the computational result for the reaction of a full linker system with Cp, although a different solvent has to be considered. While, due to overlapping signals of free Cp units and DA adducts, a quantitative calculation of the degree of debonding is difficult, for the small molecular adduct of MTTA + Cp, approximately 20% debonding at 100 °C can be assumed (for comparison: in the quantum chemical calculations, 20% debonding was achieved at 105 °C, refer to Table 1), whereas the polymeric adduct of MTTA + Cp$_2$P^{t}BuA showed up to 50% debonding at the same temperature – presumably due to the lower concentration of reactive end-groups per volume in the polymeric sample, a slight excess of diene end-groups or the occurrence of entropic effects.[22] The reversibility of the DA step-growth reaction of MTTA and Cp$_2$P^{t}BuA was additionally evidenced by temperature dependent size exclusion chromatography experiments (TD SEC, Fig. 5; for details refer to ESI†).[39]
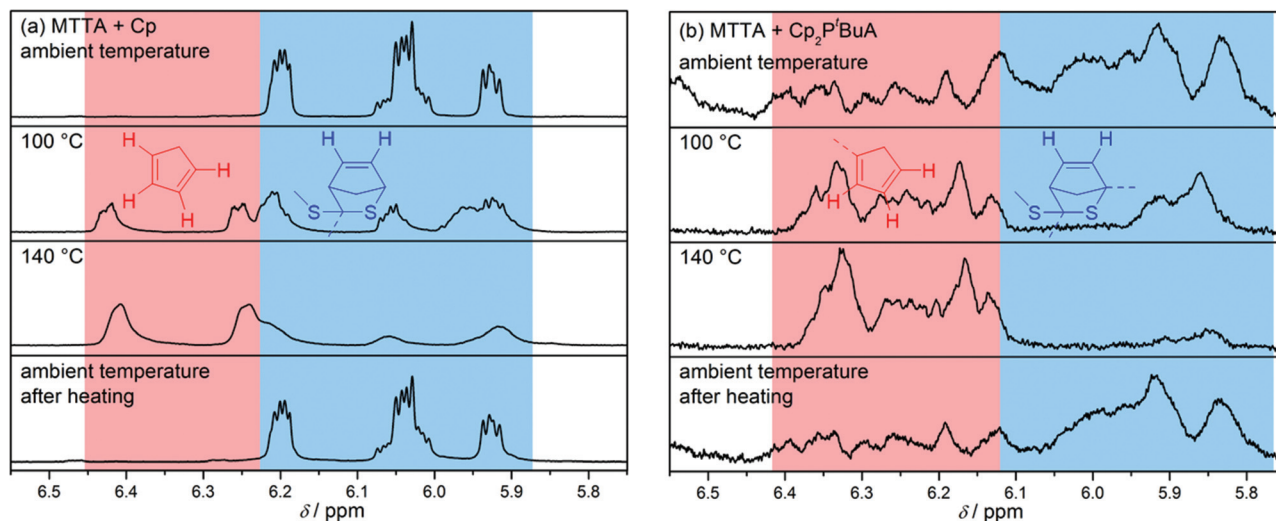
Fig. 4 Demonstration of the thermoreversibility of the DA adduct of (a) MTTA and Cp or (b) MTTA and Cp α,ω-functionalized polymers via ^{1}H HT NMR measurements in toluene-d$_8$.
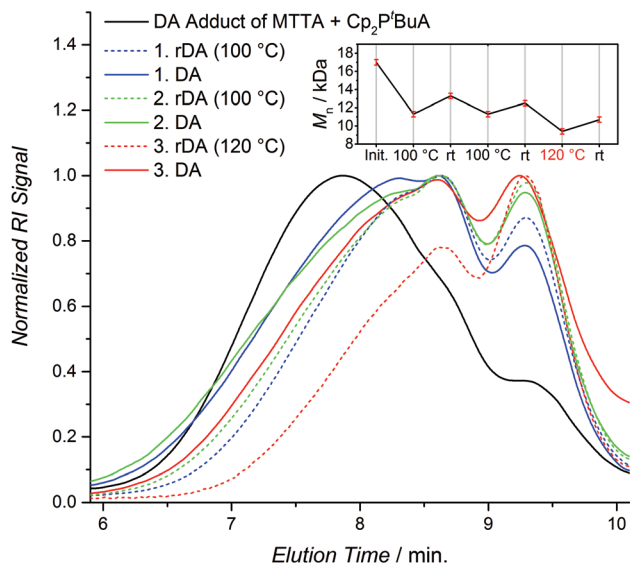

Fig. 5 SEC trace of the step-growth polymer formed from equimolar amounts of MTTA and Cp$_2$P^{t}BuA after multiple thermocycles. The rDA reactions were induced by heating the sample to 100–120 °C, the forward DA reactions were achieved upon cooling to ambient temperature. Inset: fluctuation of the molar mass of the DA step-growth adduct as a function of the bonding/debonding cycles.

As demonstrated in Fig. 5, the molar mass distribution reproducibly shifts from high to low molar mass and back again over multiple heating/cooling cycles, with lower elution times indicating higher molar masses and *vice versa* (for more details, refer to Fig. S10 in the ESI†). Evidently, the extent of rDA or DA conversion is controlled by the respective reaction temperature, as higher temperatures lead to lower degrees of polymerization *via* shifting the reaction equilibrium towards the retro reaction (compare computational % debonding

curves in the ESI† for a qualitative visualization of the characteristic temperature range of the investigated debonding process). Consequently, the thermoreversible character of the investigated Diels–Alder pairing and thus its suitability for an application in stimuli-responsive macromolecular structures could be demonstrated.

Conclusions

The generation and use of a dithiooxalate multifunctional species – ethane-1,2-diyl bis(2-(methylthio)-2-thioxoacetate) – was established as a novel and easily accessible HDA linker in a total yield of 60% from cheap and readily available starting materials. It was demonstrated *via* quantum chemical calculations in addition to various experiments that this linker enables – also in equimolar reaction mixtures – very mild, catalyst and protecting group free as well as rapid and quantitative reaction characteristics for both thermoreversible and irreversible hetero Diels–Alder linkage of different diene species. For example, an addition of cyclopentadiene groups can be established within minutes, while rapid and substantial cleavage (~20%) can be monitored from approximately 100 °C on. Alternatively, the ligation of non-functional open-chain dienes such as 2,3-dimethyl-1,3-butadiene allow for a thermally very stable linkage. In an outlook, the employment of sorbic derivatives – which also readily undergo Diels–Alder reactions with dithiooxalates within hours – may lead to the development of debonding systems with retro temperatures above 150 °C. Consequently, due to its valuable characteristics, the reported dienophile dilinker or similar systems may find application in, *e.g.*, self-healing materials, organic sheets, the generation of complex molecular architectures or fast ligation at ambient temperature of sensitive materials.

Acknowledgements

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