ADVANTAGES AND DRAWBACKS OF THIOL-ENE BASED RESINS FOR 3D-PRINTING

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ABSTRACT

The technology of 3D printing is conquering the world and awakens the interest of many users in the most varying of applications. New formulation approaches for photo-sensitive thiol-ene resins in combination with various printing technologies, like stereolithography (SLA), projection based printing/digital light processing (DLP) or two-photon polymerization (TPP) are presented. Thiol-ene polymerizations are known for its fast and quantitative reaction and to form highly homogeneous polymer networks. As the resins are locally and temporally photo-curable the polymerization type is very promising for 3D-printing. By using suitable wavelengths, photoinitiator-free fabrication is feasible for single- and two photon induced polymerization. In this paper divinyl ethers of polyethylene glycols in combination with star-shaped tetrathiols were used to design a simple test-system for photo-curable thiol-ene resins. In order to control and improve curing depth and lateral resolution in 3D-polymerization processes, either additives in chemical formulation or process parameters can be changed. The achieved curing depth and resolution limits depend on the applied fabrication method. While two-/multiphoton induced lithography offers the possibility of micron- to sub-micron resolution it lacks in built-up speed. Hence single-photon polymerization is a fast alternative with optimization potential in sub-10-micron resolution. Absorber- and initiator free compositions were developed in order to avoid aging, yellowing and toxicity of resulting products. They can be cured with UV-laser radiation below 300 nm. The development at Fraunhofer ILT is focusing on new applications in the field of medical products and implants, technical products with respect to mechanical properties or optical properties of 3D-printed objects. Recent process results with model system (polyethylene glycol divinylether/ Pentaerithrytol tetrakis (3-mercaptopropionat), Raman measurements of polymer conversion and surface modifications using bifunctional crosslinkers are presented with advantages, drawbacks and a general outlook.

Keywords: Stereolithography, digital light processing, photopolymerization, thiol-ene, resin, biocompatible, initiator-free, multiphoton polymerization, light curing, surface functionalization, UV-curing, 3D printing, additive manufacturing, rapid prototyping.

1. INTRODUCTION

Since the beginning of light based rapid prototyping with first stereolithography processes in the 80s[1], many different approaches were made to formulate suitable resins for these processes. Known from adhesives and coating technologies acrylic and epoxy resins were the first obvious candidates for three-dimensional photopolymerization via free radical or ionic reaction. Although acrylates have deficits due to oxygen inhibition and brittleness of polymerization products and epoxy resins from slower curing speed, these reaction types are still state of the art compositions in stereolithography resins. Alternative approaches use combined formulations with e.g. acrylates and epoxy in interpenetrating networks[2] or dual cure systems, which combine functionalities of fast curing and stability by subsequent post-curing of the second compound.[3,4] The demand for new resins with advanced curing speed for faster processes, tailored mechanical properties for technical applications and biocompatible resins for biomedical applications[5] will require new formulations beyond acrylates and epoxides. Thiol-ene reactions are known for around 100 years now[6], but came back into interest since the 70s/80s and by now a lot of scientific groups are working with that reaction in many applications. The work of Charles E. Hoyle and Christopher N. Bowman, two of the pioneers in thiol-ene chemistry of the last decades, and especially their review article in *"Angewandte Chemie, International Edition"* [7] has demonstrated the wide range of thiol-ene reactions

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and inspired a lot of other researchers, myself included, to look into the capability of this reaction. The reaction can be initiated by light, is not inhibited by oxygen (in contrast to acrylates) and forms homogeneous networks with lower shrinkage and almost 100% conversion. Therefore thiol-ene reactions are a very powerful tool for stereolithography resins. Even if there are still some disavantages in shelf- or pot life due to an oxidative disulfide formation or an unpleasant odor, there are good prospects for new resins based on thiol-ene chemistry, alone or in combination with e.g. (meth-) acrylate, epoxy or isocyanate chemistry in interpenetrating networks or dual cure systems.

1.1 Stereolithography resins

Stereolithography resins are photocurable, viscous liquids which are curable by light. By definintion, stereolithography is a crosslinking or solidifying (curing) of a photosensitive Monomer (resin) by local light irradiation. Starting from a high number of small molecules (prepolymers/monomers) a highly crosslinked network (thermoset) is formed during the process of curing. Most of the resins contain photoinitiators, additives or inhibitors with low molecular weights for initiation of a photopolymerization reaction, control of curing depth or enhancement of resolution and shelf/pot life. Usually resins contain photoinitiators in concentrations between 0.5 and 12 % (w). A photoinitiator absorbs the incident light, forms a radical or ionic species and starts the polymerization or crosslinking of the resin by radical transfer (acrylic) or ring opening reaction (epoxy). (From: P. Bártolo, Stereolithography)[8]

Most of the commercially available resins are based on (meth-)acrylic and/or epoxy functional groups. In this paper the reactive species in prepolymers/monomers are thiols in combination with vinyl ether groups. These functional groups are able to react in a thiol-ene reaction by radical initiation. The thiol-ene reaction can be assigned to the group of click-reactions.[9]

1.2 Thiol-ene reaction

The thiol-ene reaction is a reaction between mercapto compounds (-SH/"thiol") with a C-C double bond of an (meth-) acrylate, vinyl, allyl or norbornen functional group of the "ene" compound. For photo initiated thiol-ene the reaction follows a radical addition of thiyl-radical to an electron rich or electron poor double bond (not to be confused with a catalyzed anionic michael addition). After the initiation by a photoinitiator (or thiol compound itself < 300nm) the mechanism has two main alternating reaction steps: Propagation of the thiyl radical to the ene compound and chain transfer with hydrogen abstraction [Figure 1a)][7]. In the case of di- and polyfunctional thiols and enes a polymer chain or polymer network is formed via radical step growth mechanisms.[10]

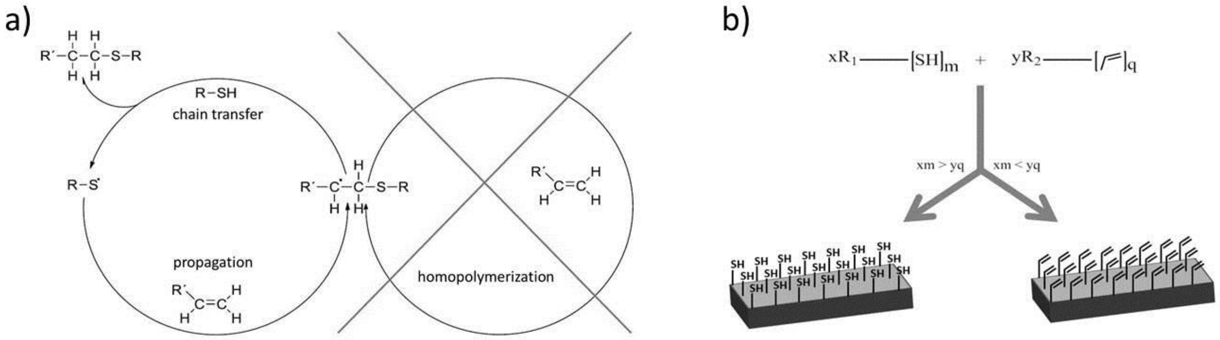

Figure 1: a) Mechanism of radical thiol-ene reaction (source Hoyle & Bowman[7]) b) off stoichiometric thiol-ene with excess of ene or thiols (source Carlborg[12])

Thiol-ene polymerizations react either initiated by a radical transfer from a photoinitiator or by direct spontaneous trigger with low wavelength UV-irradiation.[11] Another benefit of thiol-ene chemistry is the control of surface and bulk chemistry by off stoichiometric thiol-ene (OSTE)formulations.[12,13] Working with off stoichiometric formulations thiol > ene or ene > thiol directly leads to remaining species in bulk or on surface. Due to the addition mechanism of one single thiol to one single vinyl group in an equimolar ratio, without homopolymerisation of the ene-compound, functional groups remain in network or on product surface. These residues of either thiols or vinyl groups can be used for subsequent surface modification or for a second thermal curing or crosslinking reaction in bulk[14]. In our work these residues were used for a biofunctionalization of substrate surfaces by immobilizing bioactive compounds like proteins or peptide sequences (e.g. RGD). Maleimides react with thiol groups and NHS-ester with amines, hence bifunctional crosslinkers having both functionalities are suitable for these immobilization reactions.[15]

2. MATERIALS AND METHODS

2.1 Resin formulation

A simple test model consisting of a bifunctional vinyl ether compound (“ene”), Polyethylene glycol (divinylether), and a tetrafunctional thiol, Pentaerithrytol tetrakis (3-mercaptopropionat), was used to investigate the principle feasibility in three different printing techniques, SLA, DLP and TPP. All the compounds were purchased from Sigma Aldrich and were used as delivered.

Table 1: chemicals used for resin formulation and surface functionalization experiments

chemical	**function**	**CAS/Prod. No.**	**supplier**
Polyethylene glycol (divinylether) (Mn~240-250) → “ene”	prepolymer/ monomer	50856-26-3	Sigma Aldrich
Pentaerithrytol tetrakis (3-mercaptopropionat) → „thiol“	prepolymer/ monomer	7575-23-7	Sigma Aldrich
Phenylbis (2,4,6-trimethylbenzoyl) phosphine oxide	photoinitiator	162881-26-7	Sigma Aldrich
β-carotene	absorber	7235-40-7	Sigma Aldrich
Succinimidyl-[(N-maleimidopropionamido) -diethylenglycol] ester → SM(PEG)2	linker	22102	Thermo Scientific
Succinimidyl-4-(p-maleimidophenyl) butyrate → SMPB	linker	22416	Thermo Scientific
N-succinimidyl 3-(2-pyridyldithio) propionate → SPDP	linker	21857	Thermo Scientific
Bodipy FL-C3-EDA	fluorescent dye	195305-12-5	Invitrogen

The resin formulation for DLP experiments contains a photoinitiator, Phenylbis (2,4,6-trimethylbenzoyl) phosphine oxide, due to wavelengths >400 nm [Figure 2b]. The ratio thiol:ene was 1.5:1 and absorber (β-carotene, λ_{max}= 469/497 nm) was added to control curing depth of polymerization process. The selection of absorbing agent was made with respect to biocompatibility of the resulting polymer matrix. For technical applications other pigments or dyes are possible.

The resin formulation for SLA and TPP experiments contains no photoinitiator and no absorber. All the given ratios for thiol and ene´s were molar ratios of functional groups (n/thiol – n/ene).

2.2 Experimental setup

Feasibility tests for DLP were carried out with commercially available Printer S60 mini (Rapidshape Heimsheim, Germany) with customized reservoir/vat for smaller amounts of resin (min. 4ml) and suited platform 25x25mm. The modifications were made due to the development of small amounts and cost intensive resins. The process parameters for

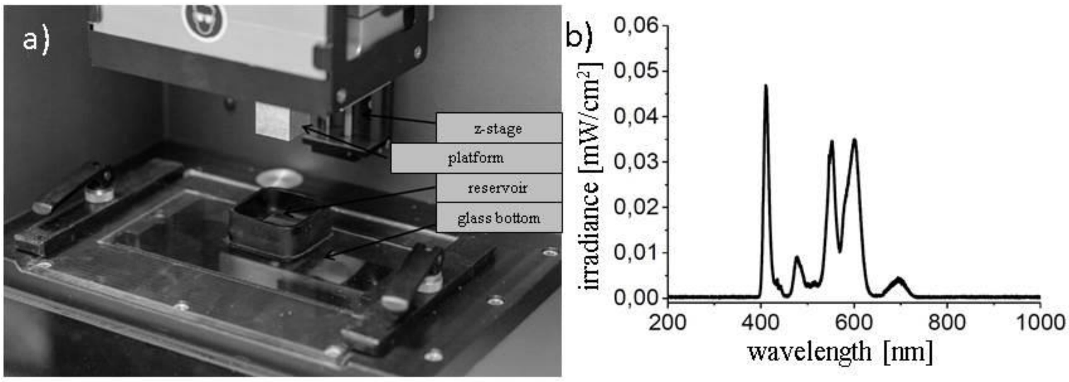

Figure 2: a) Experimental setup S60 mini (Rapidshape, Germany) with customized reservoir and smaller platform. b) Spectrum of light source, measured in reservoir.

successful print jobs were, exposure time 4s each layer, intensity 3.34 +/- 0,050 mW/cm^2 (measured), burn in factor (first 15 layers) 300%, layer thickness 100 µm, push and release force 50 mN/mm^2. Post curing of samples was done with flash light (G 171 Otoflash NK Optik GmbH, Baierbrunn, Deutschland) with 5000 flashes.

Feasibility tests for SLA in initiator free approaches were done with laboratory setup (Figure 3a). A 266 nm Nd:YAG microchip laser (HCX-V-11001 Horus Laser S.A.S, Limoges, France, 10 kHz, ns, P_{max} = 9mW at sample) was used together with a galvanometer scanner for beam guidance, a telecentric f-theta lens for focusing (f=50mm) and a z-axis in polymer vat for layer control.

For TPP experiments a laboratory setup (Figure 3b) a 532 nm Nd:YAG microchip laser (10 kHz, sub ns) was focused by microscope objective (Olympus, 40x, NA 0.6) through a plate (fused silica) into a polymer drop. The layer thickness was controlled by a µ-axis in z-direction. For characterization of TPP results the ascending voxel method[16] was used to determine the voxel size.

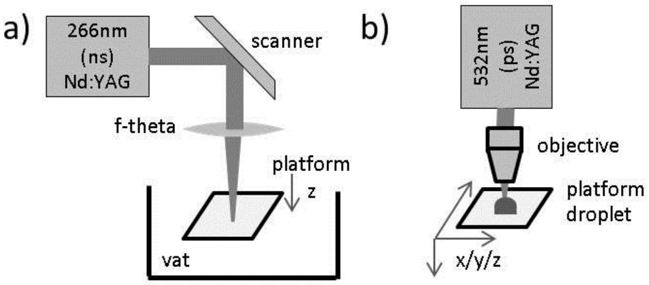

Figure 3: Experimental setup a) 266 nm stereolithography b) Two-photon polymerization

2.3 Analytics

Raman spectroscopy was used for conversion measurement of remaining thiol- or ene-groups in photopolimerized samples. All the measurements were done at Raman spectrometer RFS 100/S (Bruker Corporation, Billerica, US) with 1064nm (Nd:YAG) light source at a power of 240mW. Each sample 1000 scans were recorded.

Liquid samples of resin in the ratios 1/1, 1.2/1, 1.3/1, 1.5/1, 1.7/1 und 2/1were prepared by simple mixing (lab shaker) with 1% photoinitiator (w/w) and measured before and after curing. The sample curing was done with UV-lamp (3UV-38 UVP LLC, Upland US) with 3.1 mW/cm^2 at λ=365 nm wavelength in a duration of 15 minutes. After base line correction the peaks were integrated in the limits 1629 cm-1 und 1599 cm-1 (vinyl) and 2628,1 cm^{-1} and 2437,1 cm^{-1} (thiol).

2.4 Surface functionalization

For surface modification of cured samples (off stoichiometric) bifunctional linker SM(PEG)2, SMPB and SPDP were used as described in product instructions with Bodipy. In a first step linker were coupled to amino group of Bodipy dye via active ester reaction at pH 7.4 in aqueous solution at RT (1.5x access of linker to dye). After 1h reaction time the samples were washed with NaCl solution (1,5 M) for 48h and a second time with ethanol (70%)/ NaCl solution (1,5 M) 1:1 for further 48h. The functionalization results were measured by fluorescent analysis (Olympus MVX 10, XC50, X-Cite Series 120Q light soure and software: ImageJ, National Institute of Health, Bethesda, USA) and evaluated by comparison of grey scale values.

3. RESULTS AND DISCUSSION

3.1 Feasability of thiol-ene resins in DLP

The first feasibility tests were done with DLP technology printing for thiol-ene resin with photoinitiator and β-carotene (absorber). For formulations with β-carotene concentrations higher than 0.5% (w/w) good printing results could be achieved. The concentration of 0.5% is beyond the limit of solubility, thus β-carotene precipitates from solution and acts as a pigment in the resin formulation. In a solved state the absorbance of the absorber is insufficient for control of curing depth. For the formulation 1.5:1 thiol:ene ratio lateral resolution around 400 µm (inner diameter 3D-Siemen’s star) and 150 µm vertical resolution [Figure 4a] could be achieved. Due to the rubberlike mechanical properties, the compression of samples to glass ground plate in the printer allows no higher resolution for these materials. The free surface method of e.g. stereolithography is preferred. (DLP also can be applied to free surface method)

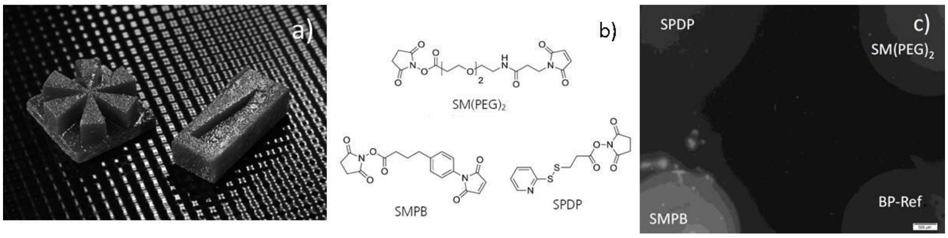

Figure 4: a) Siemens star and prism tests for resolution testings b) bifunctional crosslinker for surface functionalization c) Exemplary fluorescence measurements with Bodipy FL EDA for comparison by grey scale values.

By immobilization of bodipy® FL EDA it could be demonstrated that thiols remain on the surface of cured samples with off stoichiometric formulation. The crosslinking reagent SMPB, Succinimidyl-4-(p-maleimidophenyl) butyrate, showed strongest signal in grey scale and is suitable for immobilization of molecules to thiol-ene surfaces. Biofunctionalization experiments with RGD (peptide sequence from extracellular matrix) and growth factors (e.g. TGF-b), both for biomedical applications are content of current research.

3.2 Conversion

Different ratios of thiol and ene from 1:1 to 2:1 in resin formulation before and after curing (with photoinitiator/without absorber) could be measured by raman spectroscopy. The conversion of thiol and ene (vinyl) groups is shown in Figure 5. There is an almost full conversion for vinyl groups even in the polymer product derived from 1:1 ratio resin. The amount of remaining thiol groups after curing [Table 2] reaction fit to the theoretical number of thiols for an equimolar reaction of thiol to enes without any (or less) homopolymerization of the vinyl compound. These results meet the studies shown in literature before.[7]

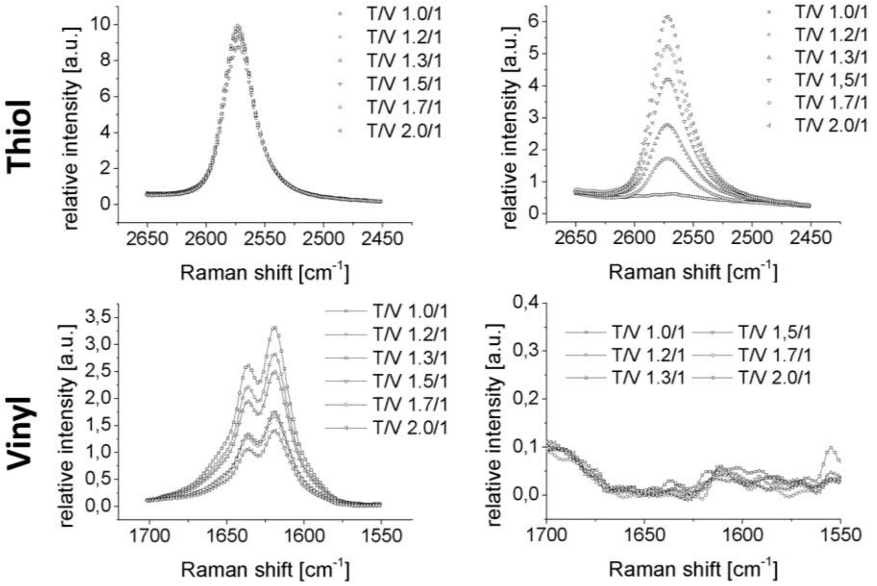

Figure 5: Raman spectra of thiol-ene resin for different ratios thiol:vinyl (T/V) before and after curing (UV-lamp 365 nm/ photoinitiator). Spectra normalized to thiol peaks.

Conversion measurements of initiator free formulation will be the next step in our research. If there´s a comparable conversion to samples with photoinitiators, the approach without is a promising way to avoid (cyto-)toxicity, yellowing and aging effects of photoinitiator in printed samples. Especially biomedical and optical application may profit from these advantages.

Table 2: Comparison of remaining thiol groups after photochemical curing, measured and theoretical quantity

t/v ratio	**peak area**	**thiol [%]**	**thiol $_{\text{(theor.)}}$ [%]**
1/1	0,18	1,93	0,00
1,2/1	1,63	17,52	16,67
1,3/1	2,28	24,50	23,08
1,5/1	3,90	41,91	33,33
1,7/1	4,18	44,92	41,18
2/1	4,82	51,80	50,00

3.3 SLA 266 nm results

In first feasibility test with initiator-free formulations in a 266 nm stereolithography process, curing depths (Voxel height) from 25-250µm could be achieved in a process window with fluences from 5 to 80 J/cm^2 with corresponding lateral resolution (voxel width) between 20-130 µm. Starting from an exposure of 12 J/cm^2 (30 pulses) the voxel show hair-like structures at top end of their shape [Figure 6a]. These structures may be caused by light scattered by polymerization nuclei at the beginning of the curing process. Usually smooth surface are wanted for printed polymer parts, but there might be applications, where rough surfaces with high surface area are wanted (e.g. cell adhesion or catalysis). In stereolithography processes the layer to layer adhesion might be improved by these structures, even if there is a remaining roughness in the surface layer.

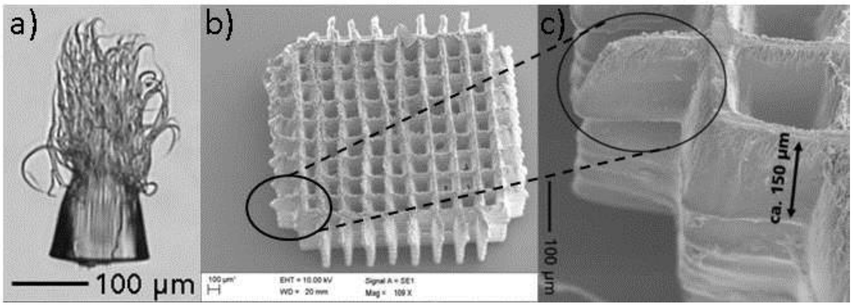

Figure 6: SEM-images (LEO 1455EP, Zeiss, Oberkochen, Deutschland), initiator free resin: a) single thiol-ene voxel with hair-like structures b) multilayer thiol-ene scaffold c) single layer with 150 µm layer thickness and fibrous surface.

First scaffolds for cell experiments had layer sizes of 150 µm and have been printed without any initiator. Cytotoxicity and proliferation extraction tests with human fibroblast cells (HFF) showed good results regarding their biocompatibility.

3.4 TPP 532 nm results

In our first trials with 532 nm (sub ns) laser source, voxel sizes from less than 1 µm to 5 µm could be achieved in a process window between $P_{\varnothing}$ 1 mW (curing threshold) and 3.5 mW (damage threshold). These results meet our expectations, that the 266 nm results can be transferred to a TPP process by doubling the wavelength. Recent results will be presented at Photonics West/SPIE 3D Printing conference in San Francisco February 2015.

4. CONCLUSION AND OUTLOOK

We have shown with a simple model system (Polyethylene glycol divinylether / Pentaerithrytol tetrakis (3-mercaptopropionat) that 3-dimensional photopolymerization is feasible for DLP, SLA and TPP/MPP. For DLP a biocompatible resin using β-carotene as absorbing agent for the control of curing depth was developed. In this case the usage of a photoinitiator is unavoidable due to low intrinsic absorbance of the resin in the wavelengths of light source emission around 400 nm. Initiator free formulations were applied for 266 nm SLA and 532 nm TPP processes. There are still some problems with product stiffness/hardness to be solved. Additionally the control of local curing for lateral resolution and curing depth have to be improved for the additive manufacturing of high resolution objects. We are continually looking for new resin formulations that may solve these current drawbacks. Further work with the model resin and some other thiol-ene formulation are under investigation and will be presented in publication(s) soon. It will contain process parameters and working curves for 266 nm stereolithography and 532 nm two-photon polymerization as well as biocompatibility, mechanical properties and resolution capabilities for initiator free approaches. Further resin formulations based on thiol-ene with dual cure mechanisms are under investigation and will be published in 2015/16. There is an enormous amount of research currently being conducted on thiol-ene chemistry and resin formulation and hopefully new resins based on thiol-ene will be de developed in the next years.

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