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Epoxy Vitriimer Materials by Lipase-Catalyzed Network Formation and Exchange Reactions

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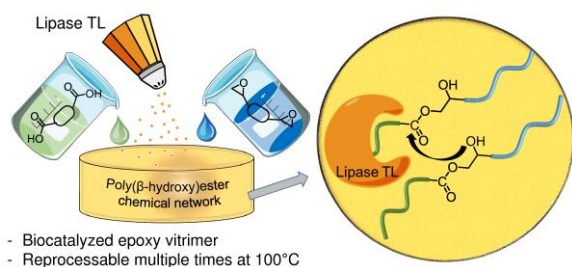
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For table of contents use only

Abstract.

The preparation and reprocessing of an epoxy vitrimer material is performed in a fully biocatalyzed process wherein network formation and exchange reactions are promoted by a lipase enzyme. Binary phase diagrams are introduced to select suitable di-acid/di-epoxide monomer compositions overcoming the limitations (phase separation/sedimentation) imposed by curing temperature inferior than 100°C, to protect the enzyme. The ability of lipase TL, embedded in the chemical network, to catalyze efficiently exchange reactions (transesterification) is demonstrated by combining multiple stress relaxation experiments at 70-100°C and complete recovery of mechanical strength after several reprocessing assays (up to 3 times). Complete stress relaxation ability disappears after heating at 150°C, due to enzyme denaturation. Transesterification vitrimers thus designed are complementary to those involving classical catalysis (e.g. using the organocatalyst TBD) for which complete stress relaxation is possible only at high temperature.

Early studies on transesterification,¹ involving ¹⁸O labelling and gas chromatography demonstrated that the alkaline alcoholysis of esters proceeds through an associative mechanism: an alcoholate attacks the C=O bond, giving rise to a tetrahedral intermediate, that then dissociates into either the starting materials or products wherein alkyl groups are swapped.²

Economically, the reaction is relevant in processes such as production of biofuels from fats^{3,4,5} or the synthesis of polyesters.^{6,7,8,9} where it is mainly for kinetic aspects that the mechanism of reaction matters.^{10,11}

Recently, the invention of vitrimers¹² prompted new interest in reaction mechanisms and the concept of *exchange reaction*,^{13,14,15,16} well exemplified by transesterification. In the first vitrimers described,^{12,17} the atoms of a poly-hydroxy-ester network are chemically bound to each other but keep ability to change partners without decreasing the total number of links. The consequence is that vitrimers are insoluble (they swell in a good solvent but do not dissolve) and yet flowable at high temperature,¹² thus combining two properties normally exclusive of each other.¹⁸

In above systems, transesterification must be catalyzed to be effective.¹⁹ In vitrimers, the first option has been to rely on Zn(II) catalysts.^{17,20} Sn(II)^{21,22}, amines,^{23,24} phosphines, guanidines²⁵ were also explored, as well as the "internal catalysis" variant in which the catalytic site is attached to the network.^{23,26}

A general difficulty is to obtain activation at low temperatures. In high-T_g vitrimers, the reprocessing window located between the T_g and the degradation temperature ensures that transesterification takes place at a temperature high enough for the catalysis to be active.^{27,22}

However, there are applications where the lowest possible T_g is sought. Soft robotics is an example where self-healing ability of vitrimer-like elastomers would be an asset to extend the lifetime of body parts;²⁸ a low healing temperature range is then required to avoid damaging

circuitry.

Two candidates as transesterification catalyst stand over the others for their ability to promote exchange reactions under mild conditions: *N*-heterocyclic carbenes^{29,30} (NHCs) and enzymes (e.g. lipase).³¹

Implementation of NHCs into epoxy networks is limited due to their air/moisture sensitivity, high cost and low selectivity towards transesterification (NHCs are powerful ring-opening catalysts for epoxide homopolymerisation).³²

Lipases are protein-type biocatalysts, able to recognize specific substrates. Their activity, low cost and stability have attracted considerable interest.³³ Our group recently showed³⁴ that lipase TL (from *Pseudomonas stutzeri*)³⁵ is able to promote epoxy-acid addition and transesterification up to 100°C, enabling the synthesis of poly(hydroxyester) chemical networks. Combining NMR analysis and enzymatic assays demonstrated that lipase side groups promote the chain-growth process (epoxy-acid addition) while the enzyme active site is involved in the process of gelation insofar branching required transesterification to take place (Figure 1). It was also demonstrated that lipase TL remains active towards transesterification, even after polymerization at 100°C.³⁴



Figure 1. a-b) Mechanism and catalyst functions involved in lipase-catalyzed synthesis of epoxy-acid chemical networks. **c)** Chemical structure of monomers (FatA: R = C₃₄ - C₅₁ alicyclic fragment, average n ≈ 2.7).

The problem is that networks thus prepared are not homogeneous. A starting mixture containing the diglycidyl ether of resorcinol (DGER) and sebacic acid (SebA) is shown in Figure 1a (left). The medium is opaque because DGER and SebA are not miscible. To make the object shown in Figure 1b (right), the mixture first heated above the melting point of SebA (130°C) was cooled down to 100°C. Then, lipase TL was added and the mixture carefully stirred during the first hours of curing until the medium becomes transparent (Figure S1). This situation is common with two-component epoxy glues that remain cloudy until reaching enough conversion, whereupon the medium becomes (at least visually) homogeneous.

When preparing 3-4 mm thick plates for rheology, we experienced that the samples lacked homogeneity: the upper and lower faces showed different Shore A hardness and appearance when stretched. (Figure S5). This gradient of composition was attributed to the sedimentation of phase separated monomers at early stage of polymerization.

Despite their inhomogeneity, those samples showed promising properties. The chemical network finely ground and reprocessed by compression molding (100°C for 24h) exhibited improved mechanical properties: increase of the elastic modulus and tensile strength, attributable to cure completion after remixing phase-separated reactive groups (Figure S6). After the first reprocessing (RP1), all reprocessed events resulted in almost identical stress-strain curves at room temperature with a initial Young's modulus of 240±50 MPa and strength of about 10±1 MPa, thus revealing ability to be reprocessed multiple times.

Based on these results, our investigations strived to achieve homogenous networks. Model study using small molecules (Figures S2-S4) gave the basis in terms of reaction conditions and stoichiometry. Of note, this study showed that the quantity of transesterification products is greater in the absence of water, probably due to faster denaturation in hot-wet environment.³⁴ Monomers hereby used are shown in Figure 1c. Phenolic epoxy resins were selected for their ability to dissolve lipase TL as well as increasing its activity.³⁴ Results with the most common diglycidyl ether of bisphenol A (DGEBA) are hereafter presented. Other resins showed ability to dissolve PimA at 100°C (Table S1 and Figure S7) but thermomechanical analysis revealed uneven curing of the network (Figure S9).

Polymerization temperature is limited to $T \leq 100^\circ\text{C}$ to preserve lipase TL activity, essential for both gelation and exchange reactions. This moderate polymerization temperature imposes a narrow selection of suitable dicarboxylic acids as most of them possess high melting points. Two alternatives to SebA were considered: pimelic acid (PimA), with a melting point of 103°C, and Pripol[®] 1040 (FatA), a liquid composition of polycarboxylic fatty acids. All these monomers (except FatA), are bifunctional and gelation would not occur in absence of exchange reaction. Since transesterification is taking place, each diepoxide monomer can form up to 4 ester links and according to the Flory theory,¹⁸ gelation is expected for such a system (see ESI). Formulations studied are reported in Table S1. In the case of FatA, a homogeneous mixture with DGEBA was obtained at 125°C, as already reported,³⁶ but cooling below 100°C to introduce the lipase led to phase separation of the two liquids. The situation was better understood with the construction of phase diagrams, where curing conditions (temperature, stoichiometry) appear as a point (Figure 2). The lack of solubility encountered with SebA is due to the high melting temperature of the diacid; albeit the situation improves with increasing the weight fraction of DGEBA, the curing point is inside the biphasic domain (Figure 2a). With FatA, the components are partially immiscible in the liquid

state (Figure 2b), the curing point stands right on the demixtion line which makes cure practically impossible, as any temperature gradient would result in either enzyme denaturation or phase separation. Eventually, the case of PimA is more favorable (Figure 2c): the melting temperature of the pure diacid is slightly above 100°C but adding the required weight fraction of DGEBA induces enough depression to remain inside the homogeneous region throughout the curing process.

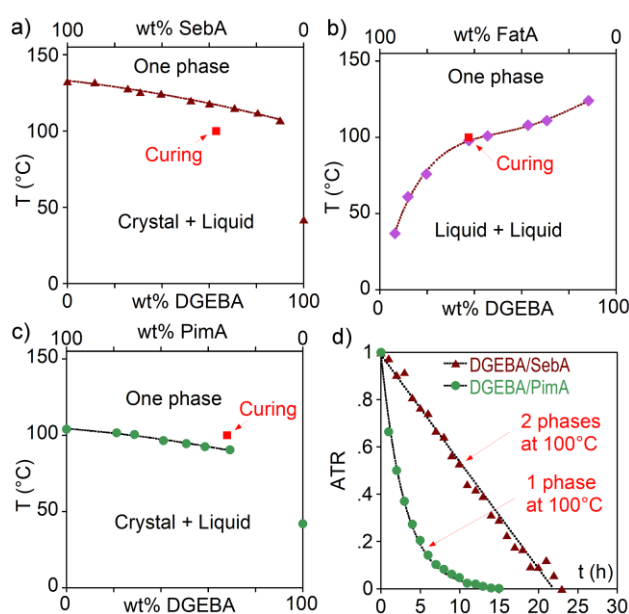


Figure 2. Position of the envisaged curing conditions (100°C at 1:1 stoichiometry) on the phase diagrams of **a)** DGEBA-SebA, **b)** DGEBA-FatA and **c)** DGEBA-PimA. Panel **d)** shows the kinetics of curing (disappearance of the epoxide signal δ_{C-O} at 917 cm^{-1}) at 100°C in the heterogeneous (SebA) and homogeneous (PimA) cases; the fits (continuous lines) are zeroth and first order reaction models, respectively.

Effects of phase homogeneity may be clearly seen on the reaction kinetics. Chain growth via polyaddition was monitored over 72h at 100°C through disappearance of the epoxide signal δ_{C-O} at 917 cm^{-1} (Figure 2d) and rise of the $\nu_{C=O}$ ester one at 1735 cm^{-1} . For DGEBA-PimA,

the carboxyl-epoxy addition appears as first order, as already reported,³⁷ with a rate constant of $5.6 \cdot 10^{-3} \text{ min}^{-1}$. With DGEBA-SebA, the reaction order drops to zero and conversion is overall much slower, revealing the effect of phase separation. The curing was also monitored by rheology to detect the involvement of transesterification through occurrence of the gel point. The result is presented in Figure S8, where onset of the storage modulus up to a value of $G' \approx 1 \text{ MPa}$ is seen. Besides, formation of a chemical network was demonstrated by the detection of an insoluble fraction (Table S1).

Stress relaxation (SR) properties of DGEBA-PimA (3 wt% lipase) were analyzed in torsion rheometry (strain $\gamma_0 = 3\%$). We first focused on relaxation properties at $T = 100^\circ\text{C}$, the upper limit to maintain enzyme viability. Successive relaxations highlight the ability of lipase to promote exchanges albeit an increase of relaxation time $\tau^*(1/e)$ from 4h to 18h was recorded after 5 days at 100°C (Figure 3a and 3b). In line with these results, the material was found to be reprocessable multiple times. Up to three reprocessing assays by grinding and compression molding at 100°C have been performed; pristine and reprocessed specimens showed nearly identical storage modulus at the rubbery plateau (E' around 1 MPa in DMA) and a stable tensile strength around 20 MPa (Figure S10).

The SR results were compared to those of a vitrimer formulation prepared with triazabicyclodecene (TBD, 3 wt%, i.e. 6 mol % vs epoxy functions). Despite a molar amount 200 times higher for TBD, the lipase-based network exhibits faster decay at 100°C . Both networks show a slightly increased relaxation modulus after each experiment. The TBD-based vitrimer demonstrated a stable characteristic relaxation time $\tau^*(1/e)$ of about 18h, even after multiple experiments at 100°C (Figure 3c and 3d), whereas the relaxation time steadily increased in the lipase-containing network. This suggests a loss of activity of the enzyme, due to its partial denaturation at 100°C , probably responsible for slowing down of the relaxation.

As for the increase in storage modulus, it is worth noticing that even after consumption of the epoxide, the transesterification reaction in Figure 1b can lead to topological maturation of the network over time. Swelling experiments (ESI table S2) performed over the same postcure time demonstrate that the insoluble fraction remains practically constant whereas the swelling ratio decreases during the first two days and then stabilizes, in qualitative agreement with a ripening effect. Dehydration of the networks, leading to ether crosslinks is another hypothesis. The reaction was observed, but at 200°C.²⁷ Yet, it could still play a part over a long time. Surface analysis of torsion bars revealed an increase in IR absorption at 1150 cm⁻¹ after 7 days at 100°C, compatible with this interpretation. Meanwhile, the observed modulus variations are of the same magnitude as the effect of geometrical corrections associated to reshaping of the specimen over repeated experiments at 100°C. At this stage, it seems difficult to disentangle the topological, geometrical and chemical effects.

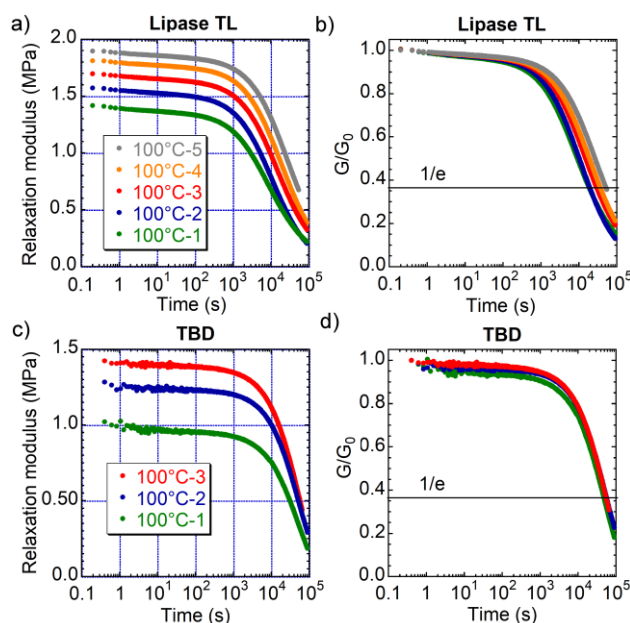


Figure 3. Non-normalized (left) and normalized (right) stress relaxation analysis (torsion mode). Networks prepared from **a-b)** DGEBA-PimA, 3wt% lipase. **c-d)** DGEBA-PimA, 3 wt% TBD. Curves 1 to 5 (resp 1 to 3) were recorded successively on the same sample.

SR results at temperatures ranging from 100 to 70°C are presented in Figure 4a and 4b. The lipase-based network is able to relax stress at temperature as low as 70°C. Two relaxations are distinguishable: the first and rapid relaxation (few seconds), with an amplitude increasing when approaching the glass transition (around 40°C, DSC) could be related to the cooperative segmental mobility.³⁸ The second relaxation, on a longer time scale (few hours), was attributed to the exchange of covalent bonds by transesterification.

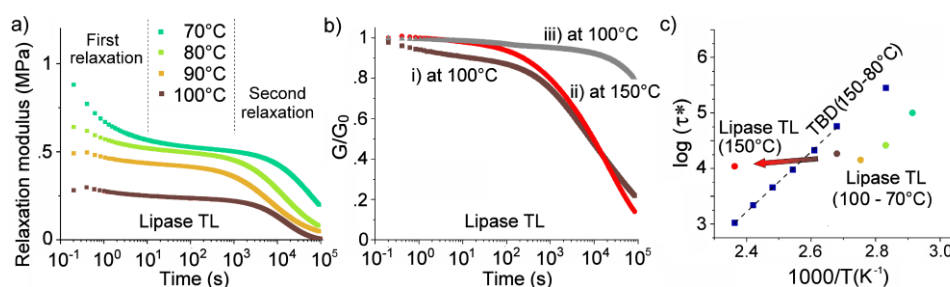


Figure 4. **a)** Non-normalized stress relaxation experiments on a single DGEBA/PimA/lipase TL specimen, from higher (100°C) to lower (70°C) temperature (torsion geometry, strain = 0.5%). **b)** Consecutive stress relaxation (normalized) data at i) 100°C, ii) 150°C, iii) 100°C on the same sample showing the effect of denaturation. **c)** Log plot of characteristic relaxation times (in s) as a function of 1000/T for lipase and TBD catalysed networks. The arrow shows the effect of enzyme denaturation.

Unlike usual catalysts, enzymes show a maximum activity peak, corresponding to a compromise between thermal activation and denaturation.^{39,40} As seen in Figure 4d, the TBD-based network exhibits a linear dependence of $\log(\tau^*)$ on $1/T$ (i.e. Arrhenius-type), with an activation energy of $E_A = 100 \text{ kJ.mol}^{-1}$ as already reported.^{25,41} In the lipase-based network, the linear dependence is limited to temperatures below 90°C, but above, the relaxation time re-increases. Such results could be explained by two competing effects:

increasing the temperature fosters molecular mobility but has deleterious consequences on the biocatalyst stability.

To confirm that relaxation is related to an enzyme catalyzed exchange, as already proved with control experiments on model molecules,³⁴ we deliberately denatured the lipase by running a SR experiment at 150°C for > 12h followed by another experiment at 100°C (Figure 4c). At 150°C, the network still relaxes but slower than the TBD-catalyzed one, and not faster than the first experiment at 100°C. Eventually, in the last experiment at 100°C, the network hardly relaxes thus demonstrating the effect of protein denaturation on the exchange reaction.

Several interrogations arise from those experiments, concerning the nature of interactions between biocatalyst and network. Epoxide functions are employed to immobilize enzymes on solid substrates to enhance their thermal stability.⁴² Enzyme side groups (thiols, amines, carboxylic acids, etc.) are able to ring-open epoxides and potentially bind to the network. Occurrence of such reactions may be the mechanism preventing polymerization induced phase separation, as already observed in epoxy/reactive toughener systems.^{43,44} Curing through addition and transesterification below 100°C also raises particular aspects like the ripening of the network over long period of time, that would require further studies.

Based on the use of phase diagrams, suitable formulation from easily accessible monomers and polymerization conditions were identified to synthesize a biocatalyzed vitrimer material. The distance between glass transition T_g around 40°C and denaturation of lipase TL above 100°C affords a workable processing window, albeit with relatively long relaxation time. The material is reprocessable multiple times. This work demonstrates the potential of a fully biocatalyzed approach for the synthesis of transesterification-based vitrimers with recycling and reprocessing properties in a mild temperature range, complementary to existing organo-metallic or organic catalysts.

Supporting Information: Materials and methods, prevision of gelation and optimization of curing conditions, reprocessing assays, formulation of homogeneous reactive mixtures, thermomechanical analyses (PDF).

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