Inline analytical supported process development towards alternative bio-based plasticizers

Category 1 - Sustainability: How to improve a sustainable use plasticisers and/or flexible vinyl

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Polymers like polyvinyl chloride (PVC) are indispensable in our today's society. PVC can be used in various applications like for example flooring, tubing, packaging films, child toys or medical single use equipment. The annual worldwide demand of PVC is still growing and was exceeding 41.3 million tons in the year 2016 [1]. Depending on the application, more rigid or soft polymers are needed. By addition of plasticizers flexible products can be obtained. Here, phthalate based plasticizers are often used since the 30s of the last century [2], with diethylhexyl phthalate (DEHP) as the most common example applied [3].

During the last decades, the use of DEHP and other phthalates has been restricted [4]. In several studies, an endocrine disrupting effect in mammals has been demonstrated. An anti-androgenic effect of metabolites of the plasticizer DEHP has been shown in rats [5] and also an effect on the reproductive systems was noticed [6]. Therefore, the application of DEHP and other phthalate based plasticizers have been in the EU and US in the last years.

There are various alternatives available on the market, either fossil-based or based on renewable resources. As an example for the latter, vegetable oils like soybean or linseed oil can be used [7,8]. The contained double bonds can be epoxidized [9], the resulting oxirane group acts as scavenger and entraps the hydrogen chloride released by the polymer, thus leading to a stabilization [8]. Also cardanol, a byproduct obtained in cashew production, can be processed to bio-based plasticizers, which are not in direct competition with the food market [10]. Further examples are citric acid or glycerol based esters which are easily biodegradable and its precursors can be produced by fermentation [11].

Following the 12 Principles of Green Chemistry (PGC), raw materials should be preferred over fossil feedstock when technically applicable and also economically feasible [12]. Recently, the United Nations (UN) published the 17 Sustainable Development Goals (SDG), which includes the approach of PGC [13]. Substitution of fossil-based plasticizers can decrease the carbon footprint of plasticized PVC to a high extent and can support transferring the PVC industry into a circular economy, recycling the polymer and applying plasticizers based on renewable resources [14].

Since the bio-based starting materials are derived from plants processed in a biorefinery, these can lack of a constant quality [15], which is problematic in view of the process design of the following reactions. A process with fixed parameters will not be able to compensate these deviations, leading to a lower yield or selectivity of single reaction steps resulting in a lower efficiency of the overall process. Here inline analytics in combination with flexible process models can help to achieve a consistent product quality using raw materials with varying composition [16].

In contrast to offline analytics, like for example gas or liquid chromatography of representative samples, the inline measurement is carried out within the reactor vessel [17]. Often tools like infrared or Raman spectroscopy are applied inline. Beside the velocity of the measurement, also the high data density is supporting the process development. Probes working after the principle of attenuated total reflection (ATR) are often applied. The measurement is not affecting the composition of the reactor (non-destructive) and no sampling or workup are required [18].

Besides enhancing the process development, according to the 12 PGC, inline analytics are an enabler for achieving a Greener Chemistry: "*Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances"* [19]. The inline analytical process control can increase the efficiency of chemical reactions and at the same time help to prevent side reactions, by this means also the SDG 12 : responsible consumption and production is addressed [13].

A variety of different plasticizer substituents is available, differing in their content of renewable resources and also showing large alterations in their chemical structure in respect to the class of *ortho*-phthalates. Aim of the project "*Bio-Weichmacher*" (Bio-plasticizers), is the synthesis of fully bio-based plasticizers along with conserving the structure of cyclic di-esters with ester groups in 1,2-position. The general workflow of the described process is depicted in Figure 1. As starting materials so-called platform chemicals derived from biomass in a bio refinery concept are used. From platform chemicals, different building blocks are synthesized, which are further esterified with fatty alcohols by application of a biocatalyst. Already in the early stage of process development, inline analytics are used for a detailed process characterization. Therefore, the time needed for sampling and the subsequent (offline) analysis can be reduced significantly. The newly developed plasticizers have to be analyzed in terms of applicability and furthermore on their ecotoxicity and on possible adverse effects on mammals.

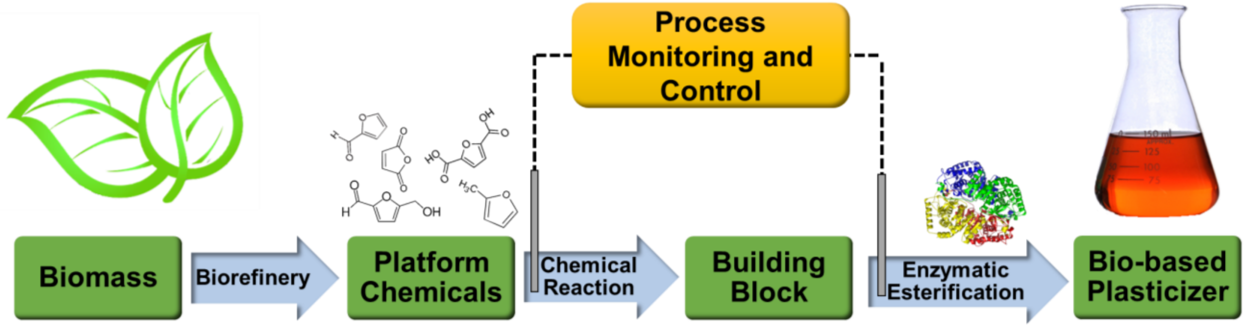

Figure 1: Workflow of the Project "Bio-Weichmacher" (Bio-plasticizers). From platform chemicals obtained in a bio refinery building blocks are synthesized, which are esterified with fatty alcohols using a lipase. All steps of the chemo-enzymatic synthesis are monitored inline in real-time by infrared spectroscopy.

Biomass is a resource, which is available in high amounts of 10^{11} tons/year worldwide [20].The main components of biomass are biopolymers like cellulose, hemicellulose and lignin [21]. Platform chemicals, like for example 5-hydroxymethylfurfural (5-HMF), furfural, sugar alcohols and different acids like succinic or maleic acid can be produced on the basis of lignocellulose in a bio-refinery [22]. From the various platform chemicals derived from a biorefinery concept, different building blocks are synthesized, which are esterified with fatty alcohols leading to a fully bio-based plasticizer. Here, either acid catalyzed or enzymatic esterification can be applied. Biocatalytic esterification can be done by lipases or other enzymes originating from the enzyme class of hydrolases (EC 3). Advantage of this enzymatic approach is the significant reduction of the reaction temperature. Waste can be reduced, since no organic or mineral acids are used as catalyst, which are needed to be neutralized afterwards [23].

Only a limited number of literature is available describing the enzymatic esterification of di-acids in 1,2-position. Martín *et al.* [24] were investigating the esterification of phthalic acid with ethanol catalyzed by a lipase from the thermophilic organism *Geobacillus thermocatenulatus*. In an ionic liquid, 1-butyl-3-methyl imidazolium hexafluorophosphate ([BMIM] [PF_6]), they reported a yield of 100% after 6 hours at 120 °C with a ratio of 67% monoester and 33% diester. However, in the case of plasticizers, a full conversion of both acid groups is required. Therefore, a screening for biocatalysts showing a low selectivity is needed. Beside commercially available enzyme preparations, also wild type enzyme libraries are screened for activity towards cyclic substrates containing two acid groups in 1,2-position. Enzymes can be immobilized on suitable carriers, which enables an efficient separation after the reaction is finished. The stability of the enzymes can be increased significantly, enabling a reuse of the enzyme preparation [25]. A large variety of different carrier materials and immobilization protocols is available [26].

Due to the reversibility of esterification reactions, an enzyme catalyzing the esterification can *vice versa* be able to hydrolyze the ester bond in a (micro) aqueous environment. Here, the identified enzymes, which are applied in the described reaction sequence, are be tested on the degradation of the plasticizers contained in the PVC polymer matrix. So far, an enzyme is identified, the application within the reaction sequence is investigated.

To analyze the single reactions of the chemo-enzymatic sequence by means of inline analytics, attenuated total reflection Fourier transform infrared spectroscopy (ATR FTIR) is used. Since it is a relative measurement technology, chemometric models based on reference measurements are needed. For developing these models allowing a real-time prediction of the actual concentration within the reactor, pure component infrared spectra are needed. Therefore, the final product and all intermediates were synthesized and purified. From these reference spectra, pure component models are designed, which are combined into a resulting Indirect Hard Model [27] describing the single reaction step. After calibration with respective offline data and a successful validation with an independent data set, the model can be applied for a detailed thermodynamic and kinetic process characterization. Based on inline data, kinetic models describing the chemo-enzymatic reaction sequence are set up. The kinetic models can be applied during the scale-up from lab to pilot or even production scale [28]. Additionally, the developed inline analytics are the basis for an efficient process monitoring enabling a real-time process control, which allows to detect and correct deviations in an early stage. ATR FTIR can also be applied to the preparation of plasticized PVC.[29] The formulation is controlled precisely and the duration of the formulation process can be optimized. Consequently, here energy can be saved, reducing the carbon footprint of the plasticized PVC, which is also addressed by the SDG number 7 [13].

Summarizing, a chemo-enzymatic process for the synthesis of alternative plasticizers for application in PVC is developed. The process development is done according to the PGC: Based on renewable platform chemicals derived from biorefinery, different possible building blocks are synthesized. These building blocks are esterified with fatty alcohols. A possible application of biocatalysts can increase the overall process sustainability. ATR FTIR is used for detailed characterization of the whole reaction sequence. The single reaction steps are investigated and respective chemometric models for an inline analytical measurement are designed. Based on the inline data measured, kinetic models describing the single reaction steps are obtained.

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