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Computer aided framework for designing bio-based commodity molecules with enhanced properties

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HIGHLIGHTS

- We propose a decision-making framework for designing sustainable molecules.
- The process involves managers, business experts, chemists and chemical engineers.
- We use computer aided molecular design to design bio-sourced molecules.
- We combine computer aided organic synthesis and computer aided molecular design.
- We enhance properties of existing molecules by finding suitable radicals.

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ABSTRACT

We investigate the use of computer aided molecular design (CAMD) approach for enhancing the properties of existing molecules by modifying their chemical structure to match target property values. The activity of tailoring molecules requires to aggregate knowledge disseminated across the whole chemical enterprise hierarchy, from the manager level to the chemists and chemical engineers, with different backgrounds and perception of what the ideal molecule should be. So, we propose a framework that allows the search to be successful in matching all requirements while capitalizing this knowledge spread among actors with different backgrounds with the help of SBVR (Semantics of Business Vocabulary and Rules) and OCL (Object Constraint Language). In the context of using biomass as the feedstock, we discuss the coupling of CAMD tools with computer aided organic synthesis tools so as to propose enhanced bio-sourced molecules which could be synthesized with eco-friendly pathways. Finally, we evaluate the sustainability of the molecules and of the whole decision-process as well. Specific applications that concern the use of bio-sourced molecules are presented: a case of typical derivatives of chemical platform molecules issued from the itaconic acid to substitute N-methyl-2-pyrrolidone NMP or dimethylformamide DMF solvents and a case of derivatives of lipids to be used a biolubricants.

1. Introduction

Since its emergence in the 80's, Computer Aided Molecular Design has become a standard tool for finding molecules targeting desired properties (Gani and Brignole, 1983). As exemplified in the 2003 compilation book "Computer Aided Molecular Design: Theory and Practice" under the supervision of Achenie, Gani and Venkatasubramanian (Achenie et al., 2003), successes were achieved in many application fields, particularly in solvent design, zero-CFC refrigerant design and polymer design. The CAPD (computer aided product design) extension aiming at designing mixtures was proposed as some synergy effects may appear between mixture components to match more closely with property requirements. Specific solving strategies of CAPD problems have been devised to find then both the molecules and the mixture composition: sequential (Gani, 2004; Karunanithi et al., 2005; Conte and Gani, 2011; Conte et al., 2011; Papadopoulos et al., 2013; Samudra and Sahinidis, 2013; Mattei et al.,

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2014a), global (Vaidyanathan and El-Halwagi, 1996) and evolutionary search strategies (Heintz et al., 2014a, Herring and Eden, 2015).

Then, stricter environmental, health and safety (EHS) regulations rose in the 90's and they set new pressure on chemical industry actors for finding cleaner, healthier, safer and yet performant molecules. Those molecules could well be the results of a CAMD search. Regarding the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) regulation launched in 2006 in EU (REACH, 2006), chemicals to be registered concerned in the pre-registration period that ended in Dec. 2010 those who were produced over 1000 tons/year in the EU for any substance and 1 ton/year for CMR (Carcinogenic, mutagenic and reprotoxic) substances. It has led to 143,000 pre-registrations. Since 2013, the limit has now dropped for all substances to a minimum volume of 1 ton/year in the EU. These chemicals are spread in all kind of processes concerning almost all the industrial domains. In 2012, the cost of registering chemicals to comply with REACH was estimated to exceed € 2.1 billion, based on about 30,000 substances (ECHA, 2012).

An interesting concomitant coincidence was the popularization in the late 90's of the 12 green chemistry (Anastas and Warner, 1998) and 12 green engineering principles (Anastas and Zimmerman, 2003) which has encouraged the use of biomass as raw material. This translates into R&D activities and some economists have argued that a doubly green chemistry perspective prevails among the chemical companies engaged in green activities: one perspective concerns the reduction of their impacts on environment and the other concerns the use of renewable raw materials (Nieddu et al. 2012). The first perspective is a direct transcript of the definition of sustainable growth presented by the Bruntland report (1987). The second is the seventh principle of green chemistry (Anastas and Warner, 1998) and would induce sustainable issues like toxicity (principle 4), degradability (principle 10) or safety (principle 12) to be met more easily. We have recently proposed to bias CAMD approach towards the search of molecules that may bear bio-sourced fragments selected by the user (Heintz et al. 2014a).

A drawback of CAMD approaches is that no safeguard ensures the viability of the generated structures. Therefore, the best structures proposed might be virtually excellent but practically infeasible on an industrial scale. Furthermore, one would like to use eco-friendly chemical synthesis pathways (Bandres et al., 2011) to produce new solvents. Indeed, Anastas and Warner's green chemistry principles number 2 (maximize raw product utilization), 3 (minimize toxic molecule use and release), 6 (keep energy consumption low by using ambient T and P), 8 (use direct synthesis pathways), and 9 (use catalysts) concern chemical synthesis. The usual answer to that challenge in CAMD, and more generally when scheduling the development of a new molecule, is to check after the CAMD step whether the molecules can be produced with an eco-friendly synthesis step (Bergez-Lacoste et al., 2014). An alternative approach to secure an eco-friendly synthesis was proposed by Moity et al. (2014). They have screened hundreds of chemical reactions and extracted a short list of 53 reactions that ranked high in terms of an aggregated DEF criterion (Durability, Easiness and industrial Frequency of use). A Computer-Aided Organic Synthesis (CAOS) tool named GRASS was developed. But thousands of molecules are generated by CAOS and it is difficult to screen out the least promising with respect to desired properties (Moity et al., 2014). This can be done with the help of a performance function (Moity et al., 2016) like those used in CAMD.

With CAMD generating a lot of non-viable structures and CAOS leading to a combinatorial explosion, we imagine in the present paper to solve that issue by generating with CAOS viable structures to be modified by CAMD (Moity et al., 2016). Therefore one could trace CAMD candidate molecule to renewable raw materials through the CAOS most performant candidate produce in an eco-friendly manner.

But running this sequence requires a framework broader than that of CAMD or CAOS to be successful. First, in practice, the chemical product development process involves chemical engineers (CAMD users) and chemists (CAOS users) but also many stakeholders across the strategic and tactical layers of the chemical enterprise. Properties related to product requirements are usually classified as essential, desirable and EHS properties (Harper and Gani, 2000) or similarly as product, process-related or usage-related (Costa et al., 2006). Typical EHS attributes are often decided at the strategic and tactical levels of the enterprise by managers, business process experts, product portfolio leaders, marketing office and legal department. They take the opportunity to develop their business in green chemistry either in response to a client demand or to changes in rules and regulations or any other stimuli from the outside of the company.

Second, considering the growing complexity of designing a new product that qualifies as sustainable, Hung et al. (2008) stressed the importance of information and knowledge management between people that are coming from different cultures and the importance of bringing them to consider all the sustainability issues together. This sets additional challenges. An evident solution is to wrap the chemical product design and development process into a decision-making process (Harper and Gani, 2000), following Simon's intelligence, design and choice phases (Simon, 1960) and to allow all stakeholders to be involved through a hierarchical procedure matching the enterprise organization levels such as proposed by Ng (2004) or Heintz et al. (2014b). Similar decision making approaches for integrating sustainability into process design have been proposed in the literature (Azapagic et al., 2006). But stakeholders from different culture would state requirements differently. Corporate managers will use words to express real needs (e.g. solubilizing) that should be translated for CAMD tools inputs in terms of computable property target values (e.g. solubility from SLE calculation, solubility from Hansen solubility parameters). Engineers will use mathematics, physics, chemistry and numbers to express them. In CAMD approach this translation can be achieved through problem templates (Mattei et al., 2014a, 2014b) or property relations based on user-defined attributes (Solvason et al., 2009). To harmonize the expression of requirements and their understanding by all stakeholders, Heintz and coworkers have proposed to use unambiguous semantic languages like Object Constraint Language (OCL) (OMG, 2006) for hard science statements and Semantics of Business Vocabulary and Rules (SBVR) (OMG, 2008) for literal statements (Heintz et al., 2014b).

In this paper we refine the framework of Heintz et al. (2014b) that describes the chemical enterprise wide process for finding new commodity chemicals with a CAMD approach combined with CAOS to ensure that new molecules are traceable to renewable raw materials through eco-friendly synthesis pathways. It could help chemicals manufacturers and resellers who oversee the production of a limited set of chemicals to imagine derivatives as substitute candidates. Section 2 describes the semantic languages SBVR and OCL, computer aided tools for molecular design and chemical synthesis and tools for assessing the sustainability of the whole design process. Section 3 describes the framework and exemplifies it through the solving of CAMD problems that concern the finding of bio-sourced molecules, typically derivatives of lipids and derivatives of chemical platform molecules issued from the itaconic acid feedstock as substitute solvents.

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