The Solvent Selection framework: solvents for organic synthesis, separation processes and ionic-organic synthesis

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Published in:
Proceedings of the 22nd European Symposium on Computer Aided Process Engineering

Publication date:
2012

Ian David Lockhart Bogle and Michael Fairweather (Editors), Proceedings of the 22nd European Symposium on Computer Aided Process Engineering, 17 - 20 June 2012, London.

The Solvent Selection framework: solvents for organic synthesis, separation processes and ionic-liquids solvents

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Abstract

This paper presents a systematic integrated framework for solvent selection and solvent design. The framework is divided into several modules, which can tackle specific problems in various solvent-based applications. In particular, three modules corresponding to the following solvent selection problems are presented: 1) solvent selection and design for organic synthesis, 2) solvent screening and design of solvent mixtures for pharmaceutical applications and 3) ionic liquids selection and design as solvents. The application of the framework is highlighted successfully through case studies focusing on solvent replacement problem in organic synthesis and solvent mixture design for ibuprofen respectively.

Keywords: API, CAMD, crystallization, solvent selection framework, solubility

1. Introduction

Solvents are widely used in a myriad of applications as reaction mediums, reactants or carriers in the chemical industry in general. In the pharmaceutical industry, for instance, it is common to using anti-solvents in crystallization processes to precipitate the active ingredient, while other solvents are still required for the final formulation. In other words, solvents play an important role in both process and product design. Nevertheless, solvent selection and design represent a complex problem, which requires decision making at early stages of the design process to identify the best candidates. Decisions will be taken depending on different multi-objective criteria such as process feasibility and economics. An important aspect is also the environmental impact, a crucial factor in the disposal of huge amounts of industrial solvents, which must match the requirements of the "Green Chemistry Principles" [1].

Currently, solvent selection problems are still solved based on trial-and-error procedures. Such procedures imply getting results that may not be optimal. From a mathematical point of view, the possibilities are in thousands and, by considering solvent mixtures, the combinatorial problem grows even more. A systematic approach is then highly desirable. Although systematic model-based methods have been proposed [2, 3], they need to be extended in terms of modelling and problems they can solve. The solvent selection framework that is presented here is based on the combination of knowledge from industrial practice, computer-aided tools, and molecular design

(CAMD) principles and it is intended for solvent selection and design in product design as well as process design applications.

2. Framework

The proposed systematic approach is depicted in the framework shown in figure 1, where it can be noted that there are 7 modules to cover all possible solvent screening/design problems. In this paper, modules I, II & III are being presented.

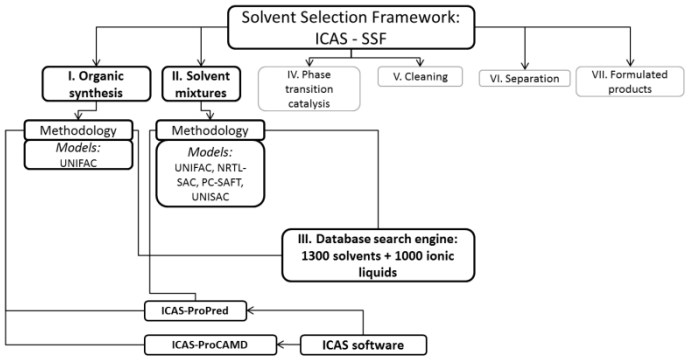

Figure 1 – Framework for solvent screening and Design. Highlighted in bold are the modules covered in this study.

2.1. Module I

This module is dedicated to solvent selection and design for organic synthesis. It uses the solvent selection methodology developed by Gani et al. [2, 3], which has been extended to allow multi-step chemical synthesis as well as solvent substitution for specific reactions. The methodology involves five steps for each reaction:

1. Problem identification: an objective for the given system is chosen by identifying the actual functions of the solvent.
2. Search criteria definition: the solvent functions that satisfy the operational needs of the process are defined in terms of a set of search criteria (R-indices), which, in turn, are defined in terms of physical and chemical properties.
3. Performing the search: the search step consists of the generation and property identification of solvent candidates and the assignment of the RS-indices [3] following the reaction–solvent properties.
4. Score table assignment: the scores are assigned to each solvent based on the calculated values of RS indices. They indicate how close the candidate solvents match the target-properties.
5. Matrix of solvents: after the scores table has been generated, a short list of feasible solvents is obtained for each reaction step and presented as a matrix with rows of solvents and columns of reactions. The best solvent should be optimal for more than one reaction.

2.2. Module II

This module is dedicated to solvent selection for separation processes in the pharmaceutical industry. One of the important tasks is often the identification of a pure solvent or anti-solvent for a specific Active Ingredient (API). Solvents, lipids and other compounds are commonly employed in product formulations as well as in API

processing. In addition, it might be needed to design solvent mixtures to improve the solubility performance. This module consists of the following steps:
1. Preliminary solvent screening by CAMD approach [4]: here the design constraints are imposed on important properties, such as, the solubility parameter, melting and boiling temperatures.
2. Secondary screening: this is achieved by ranking the candidates in decreasing order of solvent power, which is calculated through an appropriate model for activity coefficient.
3. Solubility verification: here the solubility of the API is calculated with different rigorous models (such as UNIFAC, NRTL-SAC, PC-SAFT).
4. Solvent mixture design: this step is needed to improve the solubility performance of the system. Two non-ideal mixing effects can occur, 1) a decrease or 2) an increase of solubility. In both cases a model-based procedure is used to identify the best mixture for the assigned purpose.
5. Final selection/verification: a proper experimental design can be set-up to identify the best from the remaining few candidates.

2.3. Module III

Ionic liquids (ILs) are potential solvents for liquid extraction processes. ILs are characterized as designer solvents [5] since it is possible to fine-tune their intrinsic thermo-physical properties by simply replacing the cation and/or the anion for a specific application such as extractive distillation and liquid–liquid extraction. This module includes a database of organic solvents (ca. 1300 compounds) and ionic liquids (ca. 1000 compounds) and a search engine based on chemical properties of the compounds, including their characterization in terms of UNIFAC and other group-contribution method parameters so that solubility and other needed calculations can be performed through ICAS - SFF.

3. Case studies

The solvent selection framework and the developed methods/tools have been implemented as software called SSF. It contains the database, property model libraries, links to other tools such as ICAS-ProPred for property prediction, ICAS-ProCAMD for computer aided molecular design, among others. The reported case studies are solved through SSF.

3.1. Solvent replacement for multistep organic synthesis

The objective of this case study is to find replacement solvents for each reaction step (see figure 2).

$$C1 \xrightarrow[DMF]{Stage1} C2 \;\; ; \;\; C3 \xrightarrow[DCM]{Stage2} C4$$

Figure 2 – Reaction scheme.

1. Problem definition. The objective is to find replacement for Dimethylfomamide (DMF) and Dichloromethane (DCM) that fulfills the solvent properties but are more benign with respect to environment, health and safety. Reactions are taking place in liquid phase. The reactants are in solid form, addition of solvent will decrease the concentration of the solid reactants in solution thereby increasing reaction rate and yield. The physical properties of the involved compounds are first estimated (using ICAS-ProPred) and reported in Table 1. The names of the compounds are not given for reasons of confidentiality.

Table 1. Physical properties of reactants and products predicted through ICAS-ProPred.

Species	Mw	Tm[K]	Tb[K]	SP [Mpa0.5]	HPSP [Mpa0.5]	HHSP[Mpa0.5]
C1	115.17	35.31	473.7	27.72	6.99	15.72
C2	309.36	433.16	698.1	17.53		
DMF	7306	212.7	426.1	23.95	10.06	9.88
C3	541.12	502.99	779.6			
C4	504.66	521.6	776.62			
DCM	84.93	178.1	313.2	20.37	7.6	4.07

2. Search criteria definition

Stage 1: solvents need to dissolve reactants and products (17< SP < 24); solvents must be liquid within the range 200-380 K (260 K < Tm and Tb > 380K).

Stage 2: solvents need to dissolve reactants (17< SP < 25) and need not dissolve products; solvents must be liquid within the range 180-260 K (180 K < Tm and Tb > 260 K).In both reaction steps solvents must have better environment health and safety properties.

3. Performing the search, Scoring table assignment and Final matrix of solvents. The solvents satisfying the search criteria are generated using ICAS-ProCAMD and verified through ICAS-ProPred and CAPEC-database.

Results are:

Stage 1: 3-pentanone, 2-hexanone, Cyclohexyl acetate, Cyclopentanone, 2-ethyl-1-butanol, Diacetone alcohol, 4-methyl-2-pentanol, 2-ethoxyethanol, 1-heptanol, 2-methoxyethanol, 1-hexanol.

Stage 2: 3-pentanone, Di-n-Propylamine, Methyl ethyl ketone, n-butylamine, 2-Pentanone, Ethyl acetate, Methyl isobutyl ketone, n-pentyl amine, 3, 3-dimethyl-2-butanone, diethylamine, Methyl Isopropyl Ketone, Isopropyl acetate, Pyrrolidine, n-Butylamine, Ethyl Isopropyl Ketone.

Then RS-indices are obtained using a rule-based algorithm and translated into scores according to the scoring algorithm. Eventually the final matrix of solvents is reported in table 2:

Table 2. Solvents matrix. Detailed solution of this problem as well as solutions of multi-step reaction problems can be obtained from the authors.

Name	Stage 1	Stage 2	Total score
3-pentanone	1	1	104
Pyrrolidine	1	0	70
2-methoxyethanol	0	1	70
Cyclopentanone	0	1	62

3.2. Solvent mixture design for Ibuprofen.

In this case study, a solvent mixture for ibuprofen is designed. The first step is the preliminary screening by Pro-CAMD and the determination of the activity coefficient at infinite dilution of the API, which is needed for solvent power (SP) calculation. Solvent power is calculated with an extended NRTL-SAC model, which requires parameters for the four conceptual segments. Every compound is represented by these parameters and usually experimental data has been recommended [6]. In this paper, however, these

parameters are predicted through a GC^+ model. The combination of the GC^+ model with the NRTL-SAC constitutes the UNISAC model, which has been implemented in this module to allow model-based solvent mixture design.

By ordering the solvent candidates in decreasing order of SP, the best candidates are chosen and rigorous solubility calculations are carried out to identify the best solvents needed in dissolution processes for instance and the best anti-solvents needed in crystallization processes for instance. The three best solvents were found to be N, N-dimethylacetamide, trichloroethylene and pyridine, while the three best anti-solvents were dichloromethane, n-octane and methanol.

The next step consists of fixing one solvent from the best candidates, defining the desired solubility profile for the solvent mixture and performing the mixture design. For crystallization to be carried out, a solvent mixture that causes a solubility decrease is needed. The points on figure 3 represent the desired solubility profile and the curves the fittings resulting from the design procedure. In a similar way solvent mixtures that can enhance solubility can also be found.

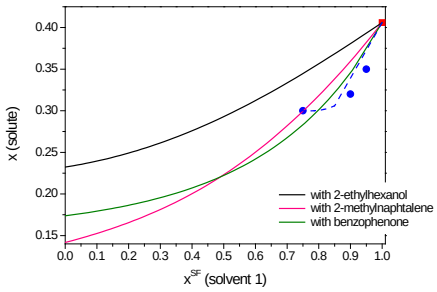

Figure 3 – Solvent mixture design graph.

4. Conclusions

An integrated computational tool for solvent selection and design has been developed and showed good performances for different common solvent-based processes. Further features will be added to the tool in order to extend the domain of application.

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