

# Computer-aided solvent selection for multiple scenarios operation of limited-known properties solute

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**Abstract.** Solvents have been applied for both production and separation of the complex chemical substance such as the pyrrolidine-2-carbonyl chloride ( $C_5H_8ClNO$ ). Since the properties of the target substance itself are largely unknown, the selection of the solvent is limited by experiment only. However, the reaction carried out in conventional solvents are either afforded low yields or obtained slow reaction rates. Moreover, the solvents are also highly toxic and environmental unfriendly. Alternative solvents are required to enhance the production and lessen the harmful effect toward both organism and environment. A costly, time-consuming, and laborious experiments are required for acquiring a better solvent suite for production and separation of these complex compounds; whereas, a limited improvement can be obtained. On the other hand, the combination of the state-of-the-art thermodynamic models can provide faster and more robust solutions to this solvent selection problem. In this work, a framework for solvents selection in complex chemical production process is presented. The framework combines a group-contribution thermodynamic model and a segment activity coefficient model for predicting chemical properties and solubilities of the target chemical in newly formulated solvents. A guideline for solvent selection is also included. The potential of the selected solvents is then analysed and verified. The improvement toward the production yield, production rate, and product separation is then discussed.

## 1. Introduction

Multiphase reacting system has broad range of application area including the manufacture of petroleum-based products, the production of chemicals, pharmaceuticals, and agro-bio products. Some important examples include: (1) phase transfer catalyst (PTC) involved systems, which has been recognized since 1940s, receiving much attention as an efficient alternative organic synthesis operation [1,2]; (2) epoxidation of unsaturated fatty acid by hydrogen peroxide to produce phthalates substitution [3,4]; (3) hydroformylation processes that produce aldehydes from olefins [5]; (4) production of pyrethroid compound insecticide [6,7]; and, (5) biodiesel production [8]. In these systems, multiple phases are created by the immiscibility between co-exist solvents such as aqueous/organic, ammonium/organic, supercritical-CO<sub>2</sub>/ionic liquid, or separated by permeable membrane. The reactants and catalysts (including also biocatalysts and enzymes) can exist in different liquid phases, allowing novel synthesis paths as well as higher selectivity, conversion, and yield. Furthermore, after the reaction, reactants, catalyst and products may end up in different liquid phases, making the separation tasks easier.



Phenomena related to this system including partitions and diffusions of each chemical species between phases, dissociation of inorganic salt in aqueous phase, reactions, and accumulation of chemical species at interface has already been described mathematically in the previous work [9,10]. Solvent selection is one of the main aspect toward the reactor design since it could help speeding up the reaction; as well as, reducing the separation effort. However, the effect of the solvents toward the production and separation were barely described. Moreover, due to the complexity of the involved chemical substances, the required properties for the calculation are largely unknown.

In this work, systematic framework for solvent selection is formulated and presented. Combining with the multiphase reacting model constructed by the previous work, it could help accelerating the reaction; as well as minimizing the separation effort to produce pyrrolidine-2-carbonyl chloride (PCC,  $C_5H_8ClNO$ ) process.

## 2. Solvent selection methodology

The methodology for selecting good solvents for the reaction is presented in figure 1. The methodology is divided into 3 parts: solute properties estimation, solvent usability estimation, and solvents collection and generations.

### 2.1. Solute properties estimation

To choose a good solvent, first the properties of solute must be estimated first. The solute properties, such as melting temperature and heat of fusion, are collected from the database; or, if not available, estimated by the well-described group-contribution method [11,12].

### 2.2. Solvent usability test

The solubilities and the partitions of the desired solute in various solvents, distinguished by solubility parameters [13], are then calculated. Due to the limit in availability of the binary interaction between groups of the group-contribution based method such as UNIFAC, these values are calculated from the simpler segment-based thermodynamic model (NRTL-SAC, [14,15]). The preferred solvent is then identified.

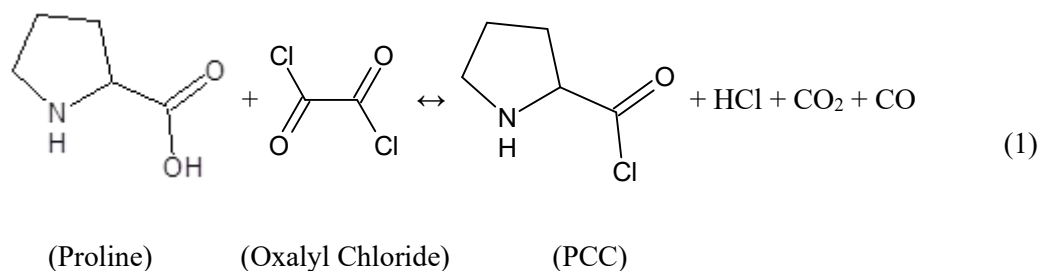
### 2.3. Novel solvents collection and generation

The solvent with similar properties are then collected and verified. By using pure compound properties as screening criteria, novel solvents can also be generated through group contribution based method.

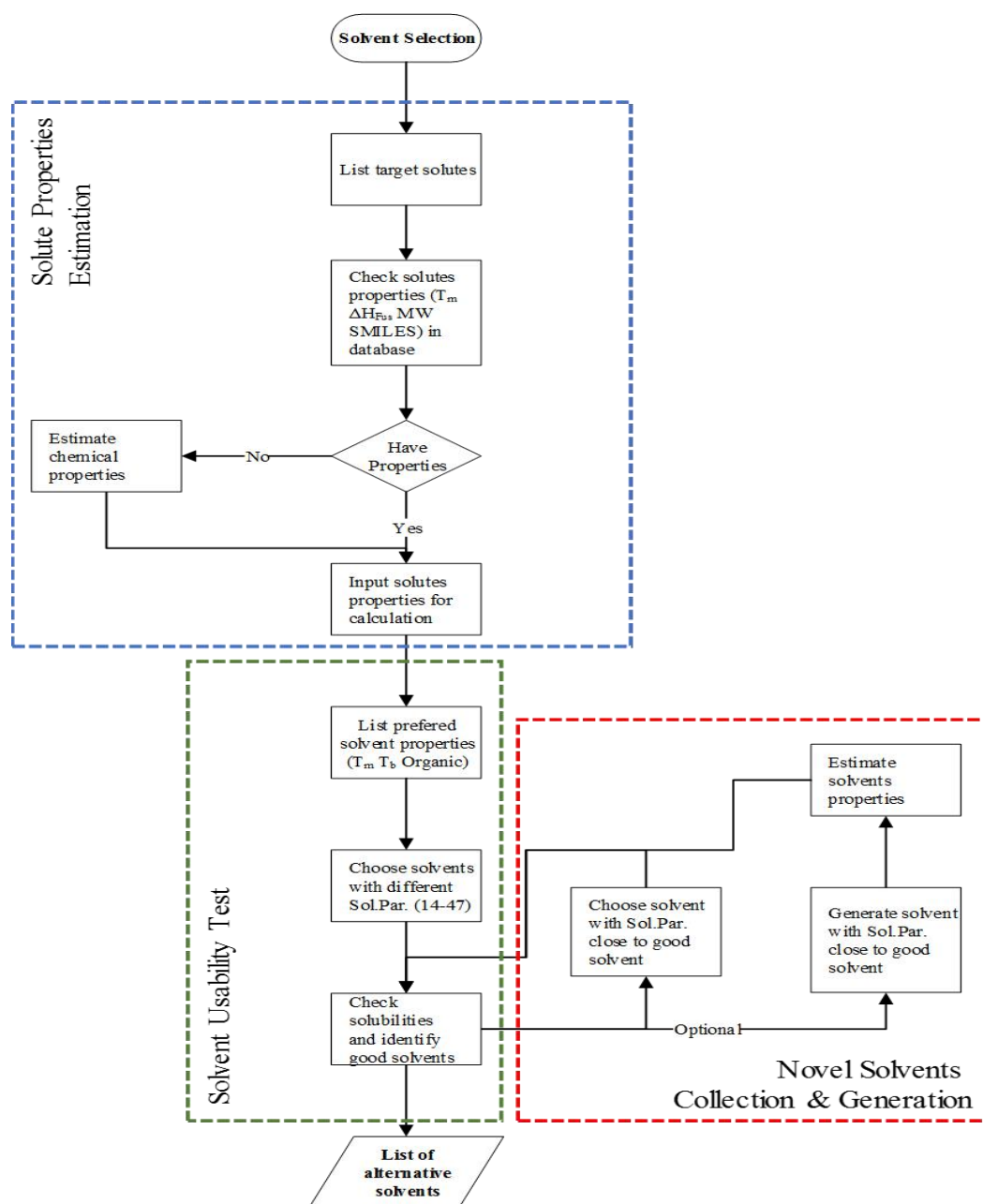
The selected solvents from this methodology are then used as substitute solvent for calculating the activity coefficients, partitions, rates, and balance in the model in the next section. In this work, the conventional solvents and novel solvents, obtained from this methodology, of the production of PCC process are employed to demonstrate the capability of this methodology.

## 3. Model of the PCC production process

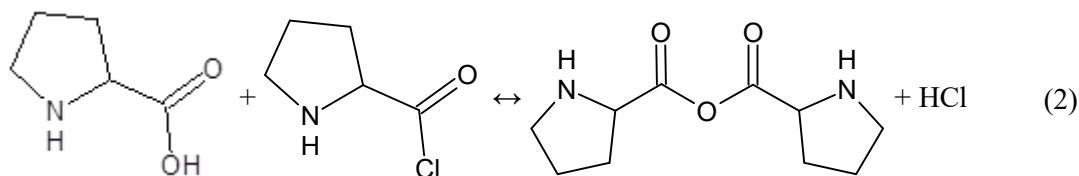
Pyrrolidine-2-carbonyl chloride (PCC) is produced from the reaction between proline and oxalyl chloride in the presence of dimethyl formamide (DMF) catalyst as shown in reaction 1.



The reaction is carried out in biphasic water-solvent systems with less than 40% conversions in the conventional solvents: dichloromethane, chloroform, chlorobenzene, and dioxane. Moreover, the PCC product and proline can also further be dimerized into unwanted amino product as shown in reaction 2.



**Figure 1.** Solvent Selection Methodology.



The mathematical model describes this reacting system is constructed with the multiphase modelling framework in my previous work [9]. PPC, proline, oxalyl chloride, and the DMF catalyst are considered to be heterogeneous species, while the other chemicals are considered to be homogeneous compound. Hence, from module 1 of the framework, the partitions of the heterogeneous compounds between the aqueous and the organic phases are described by the following equations 3-6.

$$P_p = \frac{\gamma_p^\alpha}{\gamma_p^\beta} \quad (3)$$

$$P_o = \frac{\gamma_o^\alpha}{\gamma_o^\beta} \quad (4)$$

$$P_{PC} = \frac{\gamma_{PC}^\alpha}{\gamma_{PC}^\beta} \quad (5)$$

$$P_D = \frac{\gamma_D^\alpha}{\gamma_D^\beta} \quad (6)$$

where  $P_i$  denotes the partition of the  $i$  compound,  $\gamma_i^j$  denotes the activity coefficient of the  $i$  compound in the  $j$  phase which are calculated from the designated thermodynamic model(s),  $\alpha$  and  $\beta$  denote the phase aqueous and organic, and  $P$ ,  $O$ ,  $PC$ ,  $D$  denote the compounds proline, oxalyl chloride, PCC, and DMF respectively.

The reversible reactions are only taking place in the organic phase; hence, according to the module 2 of the framework, the reaction rates are expressed as the following equations 7 and 8.

$$R_1 = k_1 \left( C_P^\beta \gamma_P^\beta C_O^\beta \gamma_O^\beta - \frac{C_{PC}^\beta \gamma_{PC}^\beta}{K_1^{Eq}} \right) \quad (7)$$

$$R_2 = k_2 \left( C_P^\beta \gamma_P^\beta C_{PC}^\beta \gamma_{PC}^\beta - \frac{C_W^\beta \gamma_W^\beta}{K_1^{Eq}} \right) \quad (8)$$

where  $C_i^j$  denotes the concentration of the species  $i$  in the phase  $j$ ,  $W$  denotes the waste species,  $R_m$  denotes the rate of reaction,  $k_m$  and  $K_m^{Eq}$  denote the rate coefficient, and the equilibrium constant of reaction  $m$  respectively.

From the module 3 of the framework, the balance equations of the reactive species are established as following equations 9-17, assuming the reactor is a continuous fed-batch reactor.

$$\frac{d\xi_1}{dt} = R_1 V^\beta \quad (9)$$

$$\frac{d\xi_2}{dt} = R_2 V^\beta \quad (10)$$

$$N_P^\alpha = N_P^0 - \xi_1 - \xi_2 + F_P^0 t - N_P^\beta \quad (11)$$

$$N_O^\alpha = N_O^0 - \xi_1 + F_O^0 t - N_O^\beta \quad (12)$$

$$N_{PC}^\alpha = N_{PC}^0 + \xi_1 - \xi_2 + N_{PC}^\beta \quad (13)$$

$$N_{HCl}^\alpha = N_{HCl}^0 + \xi_1 + \xi_2 \quad (14)$$

$$N_{CO_2}^a = N_{CO_2}^0 + \xi_1 \quad (15)$$

$$N_{CO}^a = N_{CO}^0 + \xi_1 \quad (16)$$

$$N_W^\beta = N_W^0 + \xi_2 \quad (17)$$

where  $\xi_m$  denotes the extent of the reaction  $m$ ,  $V^j$  denote the volume of the phase  $j$ ,  $N_i^0$  denotes the initial amount of the species  $i$ ,  $t$  denotes the reaction time,  $F_i^0$  denotes the inlet flow of the species  $i$ , and  $N_i^j$  denotes the amount of the species  $i$  in the phase  $j$  at any given time  $t$ .

#### 4. Application and results

For the PCC production process, the substitute solvents should be liquid at operating condition (boil at temperature more than 350 K), they should help improving the solubilities of the reactant, accelerating the reaction, and purifying the product.

First, the reactants (proline and oxalyl chloride) and product (PCC) are considered to be target solutes; their properties are estimated by group contribution method [16] and shown in table 1. Heat of fusion ( $\Delta H_{Fus}$ ) and melting temperature ( $T_m$ ) are required for solubilities calculations, Hansen and Hildebrand solubility parameters [17,18] are used for solvent screening.

**Table 1.** Estimated target properties of solutes.

Chemical	Sol Par.	$\delta_D$	$\delta_P$	$\delta_H$	$\Delta H_{Fus}$ (kJ/mol)	$T_m$ (K)	$T_b$ (K)
<b>Proline</b>	24.83	17.54	6.28	12.33	15.40	358.69	521.66
<b>Oxalyl Chloride</b>	16.54	16.34	7.69	6.99	12.53	262.99	394.05
<b>PCC</b>	19.1	24.46	12.41	20.08	18.03	315.38	471.68

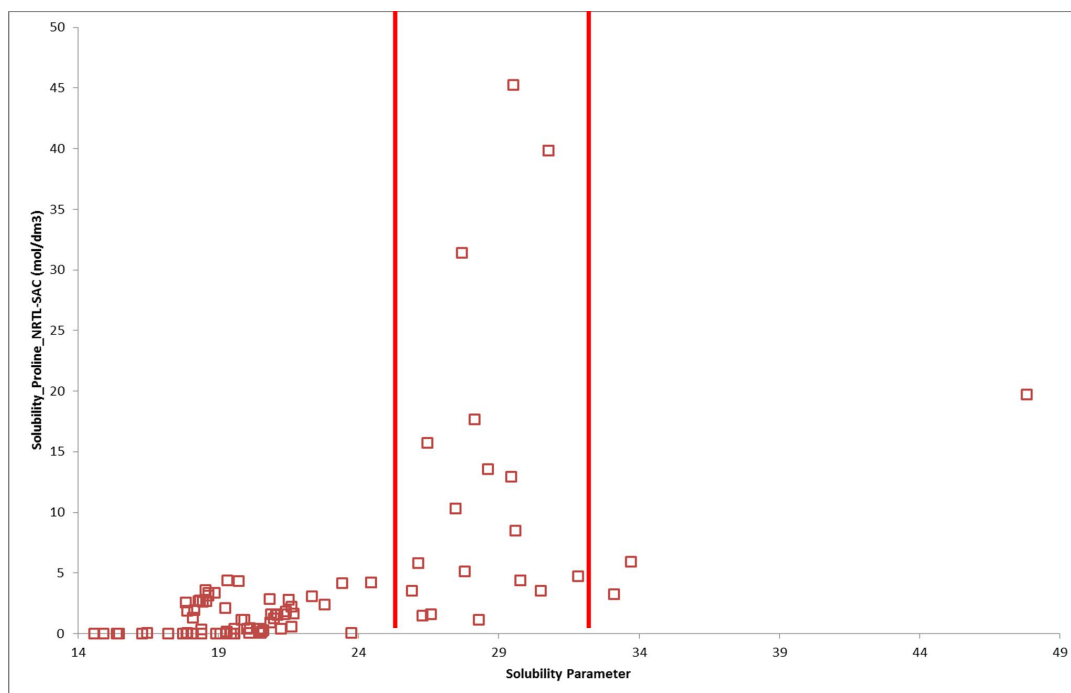
The solvents with different solubility parameters are then tested with proline and PPC for their solubilities, the results are shown in figures 2 and 3 respectively. It is appeared both proline and PCC are well-soluble in the solvents which have solubility parameters between 26-32; therefore, the solubility parameters limit are included into the criteria for solvent selection.

The solvents are then created and screened according to the criteria listed in table 2. The desired solvents should be liquid at room temperature, have boiling point match the operating condition, and shouldn't contain ethers or esters group to prevent the reaction with proline.

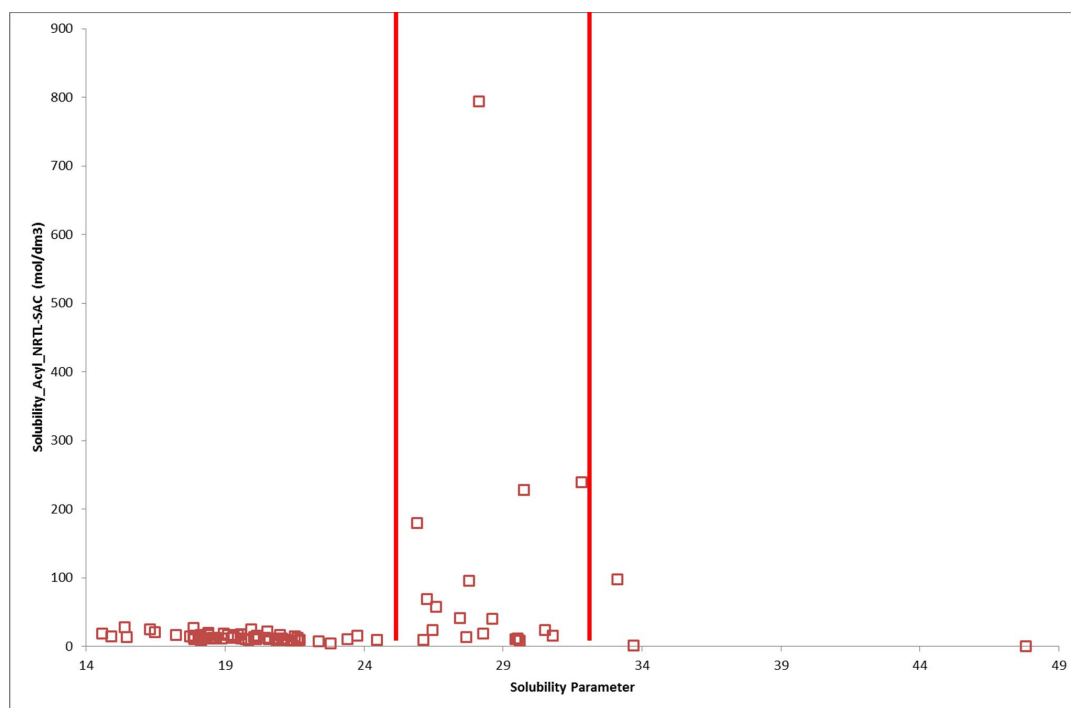
From these criteria, more than 150 thousand solvents are created; hundreds of solvents pass the criteria; and 52 solvents are the common solvents in the database. These solvents are then classified for different usage based on the operation scenarios and calculation from the model from section 3. Only solvents that provide noticeable improved results will be displayed and discussed.

**Table 2.** Solvents screening criteria.

	Constraint
<b><math>T_b</math></b>	>350
<b><math>T_m</math></b>	<293
<b>Sol Par.</b>	26-32
<b><math>\delta_D</math></b>	14-20
<b><math>\delta_P</math></b>	3-10
<b><math>\delta_H</math></b>	2-9
<b>Group</b>	No ethers and esters



**Figure 2.** Solubilities of proline in different solvent.



**Figure 3.** Solubilities of PCC in different solvent.

#### 4.1 Single solvent operation

The single solvent operation assumed using a solvent with high solubility for both proline and PCC for simplest operation, the solvent work as carrier for reactants and product; as well as, reactive phase. The solvents, their properties, and the improvement on the rates of reaction are shown in table 3.

**Table 3.** Selected solvents for single solvent operation scenario.

Solvent	Sol Par.	$T_m$	$T_b$	Solubilities (mol/dm <sup>3</sup> )		Improvement (Time)
				Proline	PPC	
<b>Methyl-diethanolamine</b>	28.14	252.2	518.0	17.69	794.37	3.78
<b>Hydracrylonitrile</b>	28.61	227.2	494.2	13.59	39.61	11.60
<b>3-amino-1-propanol</b>	29.76	284.2	460.7	4.39	227.76	1.11
<b>N-methylformamide</b>	30.50	269.4	472.7	3.53	23.79	1.81

All selected solvents improve the solubilities of both proline and PPC; however, only hydracrylonitrile gives extensive improvement on the rate of reaction (11.60 time compare to conventional solvent). Because of the reversible reaction from PPC back to proline and side reaction between proline and PPC, the solvents with high PPC solubilities provide limited improvement.

#### 4.2 Single phase, multiple solvents

In this scenario, 2 solvents are combined, the first solvent is fed together with proline-oxalyl chloride reactants, where the reaction is taking place in this solvent. The second solvent, which is completely miscible with the first solvent, is then fed into the system for dissolving PCC product. The selected solvents, their solubility parameters, and the improvements are reported in table 4.

For both 1<sup>st</sup> solvents the rates of reaction are increasing due to the increasing solubility of proline; the reaction in 1,3-propylene-glycol has a bit higher rate of reaction because of the solubility of proline is higher than in 2-methyl-1,3-propanediol; however, the 2<sup>nd</sup> solvents have similar trend of impact toward the reaction rates.

**Table 4.** Selected solvents for single phase, multiple solvents operation scenario.

Solvent 1	Sol Par.	Solvent 2	Sol Par.	Improvement (Time)
<b>2-methyl-1,3-propanediol</b>	27.68	<b>Methyl-diethanolamine</b>	28.14	18.54
		<b>Monoethanolamine</b>	31.83	17.35
		<b>3-amino-1-propanol</b>	29.76	19.21
		<b>1-amino-2-propanol</b>	25.89	22.50
		<b>Methyl-diethanolamine</b>	28.14	24.51
<b>1,3-propylene-glycol</b>	30.78	<b>Monoethanolamine</b>	31.83	21.23
		<b>3-amino-1-propanol</b>	29.76	25.51
		<b>1-amino-2-propanol</b>	25.89	30.33

#### 4.3 Multiphase, multiple solvents

The last scenario operates using 2 solvents; the first solvent is fed together with proline-oxalyl chloride reactants, where the reaction is taking place in this solvent; however, in this scenario, the second solvent is not miscible with the first solvent and its sole purpose is to extract the PCC product from the reacting phase, hence accelerating the reaction further. The selected solvents, their solubility parameters, and the improvements are reported in table 5.

In this scenario, the improvements are more extensive compare to other scenario; moreover, the final product is extracted from other impurities making it easier for separation steps. Nonetheless, the design of the reactor and the complexity reactor operation must be taken into account; the revised design-operation of the reactor is highly advised.

**Table 5.** Selected solvents for multiphase, multiple solvents operation scenario.

Solvent 1	Sol Par.	Solvent 2	Sol Par.	Improvement (Time)
Water	47.81	Beta-Propiolactone	26.58	40.23
		2-Methylnonane	15.38	55.57
		2,6-Dimethyl-4-Heptanol	17.87	57.80
		Isopropylcyclohexane	16.29	56.79
		2-methyl-1,3-propanediol	27.68	54.55
Allylamine	19.93	1,2-propylene-glycol	25.89	53.57
		1,3-propylene-glycol	30.78	55.54

## 5. Conclusion

A solvent selection methodology help systematizing the solvent selection procedure. The combination of group contribution and segment contribution method help broadening the range of application of the system. This methodology has been applied to the complex pyrrolidine-2-carbonyl chloride production process. Together with the model built from the multiphase modelling framework, improvement toward production rate can be achieved.

## References

- [1] W H C Rueggeberg, A Ginsbu'rg and R K Frantz 1946 *Ind. Eng. Chem.* **38** pp 207–11
- [2] S Shirakawa and K Maruoka 2013 *Angew. Chem. Int. Ed. Engl.* **52** pp 4312–48
- [3] E Santacesaria, G Vicente, M Di Serio and R Tesser 2012 *Catal. Today* **195** pp 2–13
- [4] L H Gan, S H Goh, K S Ooi and J Am 1992 *Oil Chem. Soc.* **69** pp 347–51
- [5] H Nowothnick, A Rost, T Hamerla, R Schomäcker, C Müller and D Vogt 2013 *Catal. Sci. Technol.* **3** pp 600–05
- [6] A A Chrisochou, K Schaber and K Stephan, 1997 *J. Chem. Eng. Data* **42** pp 551–57.
- [7] S Panke, M Held and M Wubbolts 2004 *Curr. Opin. Biotechnol.* **15** pp 272–9.
- [8] H Amiri, K Karimi and S Roodpeyma 2010 *Carbohydr. Res.* **345** pp 2133–8.
- [9] A Anantpinijwatna, S H Kim, M Sales-Cruz, J P O'Connell and R Gani 2016 *J. Chem. Eng. Data* **61** pp 4090–103
- [10] A Anantpinijwatna, M Sales-Cruz, S H Kim, J P O'Connell and R Gani 2016 *Chem. Eng. Res. Des.*
- [11] J Marrero and R Gani 2001 *Fluid Phase Equilib.* pp 183–208
- [12] A T Karunanithi, L E K Achenie and R Gani 2005 *Ind. Eng. Chem. Res.* **44** pp 4785–97
- [13] C M Hansen 1969 *Ind. Eng. Chem. Prod. Res. Dev.* **8** pp 2–11
- [14] C Chen and P Crafts 2006 *Ind. Eng. Chem. Res.* pp 4816–24
- [15] C -C Chen and Y Song 2004 *Ind. Eng. Chem. Res.* **43** pp 8354–62
- [16] H E González, J Abildskov and R Gani 2007 *Fluid Phase Equilib.* **261** pp 199–204
- [17] J B Durkee 2004 *Met. Finish.* **102** pp 42–50
- [18] C M Hansen 2007 *Hansen Solubility Parameters: A User's Handbook, Second Edition*, CRC Press