



Design of an ionic liquid as a solvent for the extraction of a pharmaceutical intermediate



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ABSTRACT

Ionic liquids (ILs) have generated considerable interest as potential alternatives to traditional organic solvents in the liquid–liquid extraction process. Performing experiments with various ILs to determine the suitability of these molecules for specific tasks is expensive and time consuming. Thus, computer aided molecular design (CAMD) methodology has been employed to design an IL as a solvent for extraction in three different case studies, where the design of a single side chain attachment, an additional attachment and double attachments to an IL have been considered. Further, a CAMD problem is formulated for the extraction of a pharmaceutical intermediate, R-phenylacetylcarbinol from an aqueous phase, with bounds on properties including distribution coefficient (m), solvent loss (SL), selectivity (β), solvent power (SP), octanol–water partition coefficient, thermal decomposition temperature and melting point. These properties have been estimated using the UNIFAC-IL model and the group contribution method. The exhaustive direct search method has been employed to design potential ILs which are superior in performance to toluene, the solvent employed in current industrial practice. Further, the associations between the properties m , SL , β and SP have been determined using graphical and statistical analyses. We have identified m and SL as the independent solvent performance indicators. The potential solvents obtained from each case study are, therefore, arranged either in descending order of m or in ascending order of SL and reported here.

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1. Introduction

R-phenylacetylcarbinol (R-PAC) is an intermediate in the manufacture of pharmaceuticals such as pseudoephedrine and ephedrine which find extensive use in cold and influenza medication. Industrially, R-PAC [1] is produced using the whole cell bio-catalysis of glucose and benzaldehyde [2]. The product (R-PAC) is formed in the aqueous phase [3] and is extracted into the organic phase. Current industrial practice employs toluene as the solvent to extract R-PAC. Recently, experiments have been performed where an ionic liquid (IL), [BMIM][PF₆], has been employed to extract R-PAC from an aqueous broth successfully [4]. This is the motivation for the work reported in this article, where we aim to develop a computational approach for shortlisting potential ILs which may replace toluene in the extraction of R-PAC.

ILs are salts (composed of an organic cation and an organic or inorganic anion) that have low melting points, high thermal stability, negligible vapour pressure, non-flammability and high

solvation ability towards organic and inorganic solutes. In addition, some ILs are also considered “green solvents” as their use minimizes the impact on the environment [5]. Apart from the various desirable properties of ILs mentioned above, these molecules can also be tailored to be task specific by combining different cations and anions; and, also, by varying the alkyl chain length or by the addition of a functional group on the cation. Owing to these characteristics, ILs have emerged as solvents that can potentially replace the organic solvents, which are generally volatile though widely used in industry for separations such as extraction, azeotropic distillation, extractive distillation and absorption.

Numerous experimental studies have been reported by various researchers on the use of ILs in separations [6–9]. Zhao et al. reviewed the use of ILs in the extraction of a variety of substances including organic compounds and bio-molecules by reporting various case studies on the separation of hydrocarbons, carbohydrates and partitioning of short chain alcohols, where ILs have replaced organic solvents [6]. Han and Armstrong presented a review on the use of ILs in separations, focussing on applications in extraction and gas chromatography [7]. Further, Marciniak reviewed the effects of temperature, cation structure and anion structure of

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Nomenclature

CAMD	computer aided molecular design	UNIQUAC	universal quasi chemical
GC	group contribution	VLE	vapour liquid equilibria
IL	ionic liquid	K_{OW}	octanol water partition coefficient
LLE	liquid–liquid equilibrium	T_m	melting point
MW	molecular weight	T_d	thermal decomposition temperature
PAC	phenylacetylcarbinol	m	distribution coefficient at infinite dilution
SL	solvent loss at infinite dilution	β	selectivity at infinite dilution
SP	solvent power at infinite dilution	γ_i^∞	infinite dilution activity coefficient
UNIFAC	universal quasichemical functional-group activity coefficients		

different ILs on the separation of aliphatic and aromatic hydrocarbon mixtures, and also the mixture of n-hexane and hex-1-ene; based on selectivity and capacity, which are functions of the experimentally determined values of the infinite dilution activity coefficients (γ_i^∞) [8]. Marciniak concluded that an IL with a proper selection of a cation and an anion can be used to replace conventional organic solvents in many separation processes. In addition, Poole and Poole have addressed general issues pertaining to ILs such as cost and purification; and reviewed the use of ILs in the extraction of organic compounds for applications in extractive distillation, aqueous biphasic systems, liquid–liquid extraction, liquid phase micro-extraction and supported liquid membranes [9].

The extraction of aromatic compounds from a C₆–C₁₀ hydrocarbon mixture using ILs as an alternative to conventional organic solvents (sulfolane and N,N-dimethylformamide) have been reviewed by Hossain et al. [10]. The influence of cation type, anion type, alkyl chain length and the properties such as thermal stability, colour and solvent loss in the extraction of aromatics have also been discussed in the review. Further, Hossain et al. have focussed on the purification of the extracted aromatics and the recovery of aromatics from ILs [10]. The distribution of organic compounds, which are water contaminants, such as hexanoic acid, 1-nonanol, toluene, acetic acid and cyclohexanone into imidazolium, pyrrolidinium and phosphonium based hydrophobic ILs have been studied by McFarlane et al. [11]. High partition coefficients of organic compounds (except acetic acid) have been observed in the ILs considered in their study.

ILs are also employed as solvents in the whole cell bio-catalysis process, for *in situ* removal of products from the aqueous phase by extractive fermentation technology. Quijano and co-workers [12] have reviewed the experimental studies carried out on ILs (mostly imidazolium based) in bioreactor technology, and reported the key properties that are to be considered for selecting an IL, including viscosity, density, surface tension, solubility in water, thermal stability and toxicity towards micro-organisms. Also, these authors concluded that tuning of ILs, by varying the cation, anion and alkyl chain length, is necessary to optimize and expand the list of potential ILs that can be employed in the bioreactor technology. Further, Quijano et al. [13] performed experiments to study the compatibility of four different ILs (3 imidazolium and 1 ammonium based) in the whole-cell biotechnological process by measuring IL toxicity towards micro-organisms and biodegradability. Their study yielded [BMIM][PF₆] and [BMIM][Tf₂N] as compatible solvents.

As numerous combinations of ILs exist ($\sim 10^{18}$) [14], performing experiments to find ILs suitable for specific applications require time and are, also, expensive. Thus, a computer-aided molecular design (CAMD) based approach is employed here to design an IL as a solvent for extraction. CAMD has been widely used in literature to design organic solvents for various applications such as distillation [15], extraction [16] and crystallization [17]. With the

development of property prediction models for ILs, CAMD has also been employed in designing task specific ILs in the recently published literature [18–22]. Table 1 summarizes various case studies which employ CAMD of ILs, with a focus on the properties of interest, the property estimation models and the solution methodology employed in the literature. The computational scheme described in Scheme 1 has been employed to design an IL for the efficient extraction of R-PAC from an aqueous phase.

The organization of this article is such that first we define the problem, followed by a description of the problem formulation and the exhaustive direct search (EDS) approach. The results obtained are then analysed to determine if associations exist among the solvent performance indicators and to identify the independent objective functions. Ten potential solvents have been shortlisted on the basis of the identified objective functions (highest m values or lowest SL values) in each case study (details are given in Section 2) and are reported in Section 5. Finally, the conclusions of this study are summarized in Section 6.

2. Problem statement

The design of an IL, in this article, is basically a design of the side chain attachment (where a chain is designed utilizing the ‘side chain attachment’ groups reported in Table 2). This design has been performed to form either a single chain attachment, an additional attachment or double chain attachments. Scheme 2(a), (b) and (c) shows the probable representation of a single attachment, an additional attachment and double attachments for [PY][Tf₂N], [N-C₃OH₂][Tf₂N] and [PY][Tf₂N], respectively. Since, we employ the GC method in our study; the position of the attachment to the cation of the IL is not accounted for.

We have employed the proposed computational scheme (shown in Scheme 1 and described in the next section) to design the potential ILs for three case studies which are described below. In case study 1, the groups reported in set 1 of Table 2 are employed to design ILs with single attachment, where the attachment replaces the hydrogen bonded to the nitrogen of the cation (structure of ILs are given in Table S.4 of the Supporting information for reference), except for [–OCH₂IM][Tf₂N] (where the attachment is to the –OCH₂– group). Further, in case study 2, the ILs listed under set 2 of Table 2, which contain an existing –C₃OH attachment have been considered. Here, we have designed an additional side chain, where the attachment replaces the hydrogen bonded to the carbon atom of the cation. Finally, in case study 3, the ILs that are listed in set 1 and set 3 have been considered for the design of ILs with two side chain attachments; and here, the attachments replace two hydrogen atoms of the cation in the ILs present in set 1 and none for the IL, [(–OCH₂)₂IM][Tf₂N] of set 3 (the attachments are to the two –OCH₂– groups). The structures

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