Journal of Molecular Liquids 262 (2018) 285–294

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Deep Eutectic Solvents formed by chiral components as chiral reaction media and studies of their structural properties

Tommaso Palomba [a], Gianluca Ciancaleoni [b], Tiziana Del Giacco [a], Raimondo Germani [a], Federica Ianni [c], Matteo Tiecco [a,*]

[a] Department of Chemistry, Biology and Biotechnology, University of Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy
[b] Department of Chemistry and Industrial Chemistry, University of Pisa, via Giuseppe Moruzzi 13, 56124 Pisa, Italy
[c] Department of Pharmaceutical Sciences, University of Perugia, Via del Liceo 1, 06123 Perugia, Italy

ARTICLE INFO

Article history:
Received 7 March 2018
Accepted 19 April 2018
Available online 23 April 2018

Keywords:
Chiral Deep Eutectic Solvents
Chiral quaternary ammonium salts
Camphorsulfonic acid
Enantioselective reactions
Structured liquids
NMR analysis

ABSTRACT

We present the realization, the use as reaction media/chiral organocatalysts/acid catalysts and the structural properties of novel chiral Deep Eutectic Solvents. These liquids are formed by mixtures of chiral HBD and HBA molecules that are common, relatively cheap and commercially available (the two enantiomers of camphorsulfonic acid as HBD) or easily one-step synthesized molecules from commercially available compounds ((*S*)- and (*R*)-*N*,*N*,*N*-trimethyl-(1-phenylethyl)ammonium methanesulfonate as HBA). These liquids proved to be highly-structured as showed by different yields and enantiomeric excesses observed in a probe reaction, suggesting these liquids to form diastereoisomerically different liquids by changing one of the two enantiomers. Their structural features were analyzed via ^{1}H Pulsed Field gradient Spin Echo (PGSE) NMR, NMR titration, ^{1}H NMR analyses of formation and differences in the chemical shifts of the peaks of the liquids. Density Functional Theory (DFT) optimization helped to define the structures of these liquids. The methanesulfonate counterion of HBA molecule showed to be relevant in order to obtain these highly-structured liquids as it interacts specifically with the HBD. These chiral Deep Eutectic Solvents revealed to be promising novel high-structured media for enantioselective reactions.

1. Introduction

Low melting point mixtures that possess green advantages are rapidly increasing their relevance in the recent chemistry, with the aim of reducing the environmental impact of the organic solvents [1,2]. In this field, Ionic Liquids (ILs) have been playing a significant role; in these salts the dispersion and/or the delocalization of the charges lead to poorly coordinating ions and, therefore, to low melting points of the salts (lower than 100 °C) [3]. ILs have many green properties such as: negligible volatility, high recycle capabilities, low flammability just to mention some of them. For these reasons ILs have been playing relevant roles as reaction and extraction media [4–6]. Moreover, in some chemical reactions these liquids allowed to obtain products otherwise not obtainable with the use of common organic solvents and also easy workup procedures. Unfortunately, these liquids proved to be toxic and resulted low biocompatible because of their low biodegradability [7–9]. Moreover, their synthesis requires synthetic passages involving the use of common organic solvents; therefore, even if these liquids have many advantages compared to typical organic solvents, they still have some green disadvantages.

Deep Eutectic Solvents (DESs) are a new class of organic solvents that can be classified as a sub-class of Ionic Liquids (due to the presence of salts in many of these systems), but they are differently structured and they have many further green advantages compared to ILs [10,11]. Different classifications of these liquids are reported in literature depending on their structures, but they can be simply interpreted as mixtures of a hydrogen-bond donor (HBD) molecule and a hydrogen-bond acceptor (HBA) one at the proper molar ratio [10,12]. These H-bond interactions lead to a decrease of the melting points of these mixtures of molecules, even at room temperature. The syntheses of these systems do not involve the use of any organic solvent because they are prepared by simply mixing and heating two solid compounds until a homogeneous liquid is formed; this is also favourable and "green" in terms of the atom economy of the process [13].

There are many classes of DESs reported and studied in literature, such as glycerol-based, sugar-based, zwitterion-based ones and so on, with well-defined and unique features and properties [14–16]. A relevant class of these mixtures is represented by Natural Deep Eutectic Solvents (NADES): mixtures of molecules of natural sources, therefore highly bio-compatible, bio-renewable and in many cases cheap [17–19].

* Corresponding author.
E-mail address: matteotiecco@gmail.com (M. Tiecco).

https://doi.org/10.1016/j.molliq.2018.04.096
0167-7322/

The first and most studied NADES reported in literature is a mixture of choline chloride and urea at 2:1 M ratio [20,21]. In this case the H-bond interactions occurring between the hydrogens of urea and the chloride counterion of choline lead to a decrease of the electrostatic interactions between the ammonium and the chloride itself, provoking a high decrease of the melting point of the mixture (m.p. Urea = 134 °C; m.p. Choline Chloride = 302 °C; f.p. DES (Choline Chloride/Urea) = 12 °C).

Beside the green preparation procedures of these liquids, recent studies also showed that these mixtures are non-toxic, biodegradable and biocompatible; this is also more relevant in the case of the NADES due to the natural origin of the molecules composing them [22–25]. As a significant example, Choline chloride/Glycerol mixture was recently studied as non-toxic drug carrier in living organisms [26].

For these reasons DESs are rapidly increasing their relevance in the green chemistry literature; their application is wide and concerns solvents for organic synthesis, extraction media, media for the synthesis of nanoparticles, electrochemistry, biocatalysts, and so on [27–33].

DESs represent a novel step forward in the green chemistry, and many topics about these liquids are yet to be explored. The step forward in this topic is represented by the use of smart DESs: solvents that could play an active role (such as a catalytic one) in the reaction or in the process where they are applied. Their use as reaction media/organocatalyst for enantioselective reactions and the study of the properties of chiral DESs is still lacking. Recently Ñíguez, Guillena and Alonso published a work about the dissolution of a chiral organocatalyst in a choline chloride/glycerol mixture that led to interesting results [34]; an enantioselective L-proline catalyzed inter-molecular aldol reaction was successfully performed in various DESs by Martìnez and co-workers [35]; high stereo- and enantioselective additions were performed dissolving a chiral amine in choline-based DESs [36]. However, the chirality of the DES itself, and its effect in the asymmetric synthesis topic, is yet to be explored.

This topic has already been studied and interpreted in Ionic Liquids literature; there are many works about the dissolution of chiral auxiliaries in these media and also about the functionalization of classic Ionic Liquids with chiral auxiliaries branches [37–41]. In these works, a low enantioselectivity induction is reported using liquids made of chiral molecules with non-specific interactions with the reagents [37,42]. The specific interactions of the reagents with the chiral auxiliary, or with the supported chiral auxiliary, is in fact a key-factor in order to obtain a good enantioselectivity in a chemical reaction or an effective chiral recognition [43,44].

In this work, we present the realization and the structural characterization of novel Chiral Deep Eutectic Solvents based on the combinations of both enantiomers of chiral HBD and HBA molecules. The molecules used in this work as chiral HBD were the two enantiomers of Camphorsulfonic acid ((1*R*)-(−)-10-Camphorsulfonic acid and (1*S*)-(+)-10-Camphorsulfonic acid, −CSA and +CSA); the HBA molecules were the two enantiomers of *N*,*N*,*N*-trimethyl-(1-phenylethyl) ammonium methanesulfonate (FR and FS), easily synthesized in one step from the corresponding primary amines. All these compounds are cheap and they are commonly used as chiral resolution reagents. We successfully used these novel chiral liquids as reaction media/chiral organocatalysts/acid catalysts in a Michael-type Friedel-Crafts addition probe reaction. The structural features of these liquids were studied via different NMR techniques; besides molecular modelling studies were performed to obtain a structural interpretation of the data.

The chirality of the molecules composing the liquid mixtures revealed to be necessary but not sufficient to obtain a significant enantiomeric excess in the probe reaction, so suggesting these DESs as highly-structured liquids. As confirmation of this, no enantiomeric excesses were observed with liquids with non-chiral components, and different yields and different enantiomeric excesses were observed for the mixtures with the same enantiomer of the HBD but with the two enantiomers of the HBA (+CSA/FR and +CSA/FS). All these data suggested the existence of diastereoisomerically different liquids made with different enantiomer couples. This was proved via different NMR studies. NMR diffusion data revealed a marked self-aggregation process in chloroform, leading to the existence of clusters of about four HBD/HBA couples. The observed association constants were different for the diastereoisomerical different liquids. The ^{1}H NMR analysis revealed differences in the DESs formation ($\Delta\delta_{form}$, shifts of the signals between the DES and the pure compounds, $\delta_{DES} - \delta_{pure\ compounds}$) and between the two DESs ($\Delta\delta_{DESs}$ = shifts of the signals between two different DESs mixtures) in all the combinations of the enantiomer couples, with a correlation between the differences of the yields (Δ_{yields}) in the two liquids in the studied Michael addition with the differences of the chemical shifts ($\Delta\delta_{DESs}$) of the ^{1}H NMR spectra. Finally, the geometry of the various adducts have been optimized by Density Functional Theory in order to obtain a hypothesis of the structures of these novel liquids.

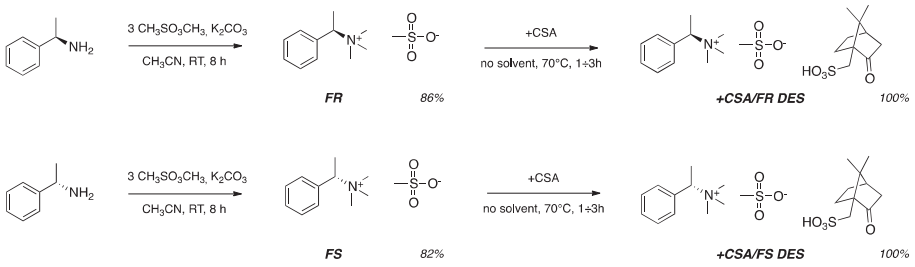
2. Results and discussion

2.1. DESs preparation and use as chiral media

2.1.1. DESs preparation

The first step of this work was the preparation of the chiral HBA molecules; the HBD (the two enantiomers of Camphorsulfonic acid, +CSA and −CSA) are in fact commercially available. Quaternary ammonium methanesulfonate HBA molecules were chosen in a set of differently structured molecules that we recently had developed in order to obtain halogen-free DESs [12,15,25,45]. (*R*)- and (*S*)-*N*,*N*,*N*-trimethyl-(1-phenylethyl)ammonium methanesulfonate (FR and FS) were synthesized in one step from the correspondent primary amines via reaction with methyl-methanesulfonate in good yields (over 80%). These solids (m.p. = 166–168 °C) were separately mixed with +CSA (m.p. = 198 °C) and heated at molar ratio 1:1 to give viscous liquids with low freezing points (20 °C) (Scheme 1).

In supporting information section (Fig. S1) the eutectic profiles of these mixtures, depending on the molar ratios, are reported. The HBD: HBA molar ratios used in this work were all 1:1, also because the melting points vary very little changing the composition of the mixtures; at these molar ratios, the freezing points of the liquids with all the combinations of the two enantiomers of CSA and of the two quaternary ammonium salts were measured (also with racemic mixtures) and they



Scheme 1. Chiral DESs realization: synthesis of (*R*)- and (*S*)-*N*,*N*,*N*-trimethyl-1-phenylethanaminium methanesulfonate (FR and FS) via methylation of the primary amines; mixtures with (1*S*)-(+)-10-Camphorsulfonic acid to give the DESs.