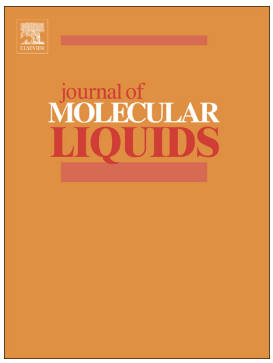

Assessment of the organocatalytic activity of chiral l-Proline-based Deep Eutectic Solvents based on their structural features

Matteo Tiecco, Diego A. Alonso, Diego Ros Ñíguez, Gianluca Ciancaleoni, Gabriela Guillena, Diego J. Ramón, Alberto Apio Bonillo, Raimondo Germani

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ASSESSMENT OF THE ORGANOCATALYTIC ACTIVITY OF CHIRAL L-PROLINE-BASED DEEP EUTECTIC SOLVENTS BASED ON THEIR STRUCTURAL FEATURES

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ABSTRACT

The impact on the environment of polluting and volatile organic solvents represents nowadays a severe problem. In order to reduce the incidence on the environment of chemical applications, Deep Eutectic Solvents (DESs) represent a step ahead in this field thanks to their green properties. These novel liquids are formed by inter- and intra-molecular weak interactions between two species and they are synthesised by simply heating and mixing them without any solvent. These solvents also show interesting catalytic capabilities, since their properties are truly tuneable.

In this paper L-Proline-based Chiral Deep Eutectic Solvents (CDESs) were prepared and used as green and organocatalytic reaction media in a probe asymmetric Michael addition; in this reaction the L-Proline acts as solvent component as well as chiral organocatalyst. The results were analysed with NMR studies taking in account the availability of the L-Proline considering the strength of the association of it with the counterpart of the liquids. With DFT studies, the geometry and energy of the adducts are showed and a qualitative rationale to the reaction stereoisomers distribution is given.

KEYWORDS

Deep Eutectic Solvents; Enantioselectivity; Green Chemistry; Asymmetric Organocatalysis; Active Solvents.

1. INTRODUCTION

Deep eutectic solvents (DESs) are a novel class of organic liquids that have increased their relevance in the green chemistry framework due to their unique properties[1–3]. DESs can be divided into different sub-classes depending on the molecules they are made of[4], however they can be simply interpreted as mixtures of a hydrogen bond donor (HBD) molecule and a hydrogen bond acceptor (HBA) molecule. These weak interactions between the two species determine a difficult lattice organization of the structures, therefore a liquid formation[5]. Recently, Ribeiro-Claro and co-workers, via inelastic neutron scattering measures, showed that the DESs can be interpreted as mixtures of intra- and inter-molecular weak interactions between the two species, leading to a better comprehension of the structures of these novel green liquids; being this of prominent importance for novel DESs preparation[6].

Born as a "side-class" of ionic liquids, DESs share with them many properties such as: low or absent vapour pressure (that can lead to "out of the hood" procedures, pointing out to economic and environmental advantages); low flammability; high recycle and re-use capabilities, and so on[7–10]. However, DESs show lower (and in some cases absent) toxicity compared to ionic liquids with lower their environmental, just thanks to their higher biodegradability and to the bioavailability of their components[11–14]. Moreover, their preparation is simple: generally, they are made only by mixing and heating the two components (often solids), leading to a liquid with a 100% of yield; no solvent or other reactant are needed for their preparation, increasing their availability compared also to other environmental friendly solvents[15].

The use of DESs presents many advantages in several research area thanks to the range of structural differences that can be obtained by just changing their components[16–18]. If the HBD and the HBA molecules have natural source, the liquids are named NADESs: Natural Deep Eutectic Solvents; these liquids have an increased green impact for their bioavailability and biocompatibility[3,19]. Some relevant examples of their uses are: the possibility of working in non-anhydrous conditions in procedures that usually need the absence of water (thanks to the structural role of water in those mixtures)[20,21]; the catalytic properties of those liquids (such as Brønsted or Lewis acids)[22–24]; their reducing properties (when formed by reducing molecules)[25]; and the excellent extraction/preconcentration capabilities[26,27]. These properties promote their use as substituents of volatile organic compounds (VOCs) in many applications[28]. In these years, when environmental and economic issues are at the forefront of human and planetary health, these liquids represent a convincing alternative to VOCs[29].

In organic synthesis, DESs are finding fruitful applications for the cleanliness, the purity of the obtained products, and the quickness of the developed synthetic procedures. In this field, the role of DESs can be defined as “active” or “innocent” if they participate as reactant or catalyst in the chemical transformation or they just act as green and environmental friendly liquids[30–33]. However, so far, the potential catalytic activity of DESs is unpredictable and only can be assessed after trial and error procedures. Therefore, it would be very desirable to find some physical-chemical measurements that could somehow anticipate the possible activity of a given mixture. Recently, we have reported the first enantioselective transformations using chiral Deep Eutectic Solvents (CDESs) as both green medium and organocatalyst[34]. The two enantiomers of camphorsulfonic acid were used as HBD in the mixtures with different HBAs, leading to room-temperature liquids. The yields and the enantiomeric excesses observed in the conjugate addition of indole to chalcone correlated with the properties of the liquids; in particular it was observed that the catalytic properties of camphorsulfonic acid relied on its “freedom” or availability, which was related to the strength of the interaction with the HBA counterpart.

In this work, the preparation of novel chiral Deep Eutectic Solvents (CDESs) based on L-Proline as HBA and their use as green media and chiral organocatalyst in the asymmetric Michael addition is shown. Starting from the knowledge acquired on the structure/activity experience in this topic[5,34–36], a correlation between the observed results with the strength of the binding of the L-proline in the DESs with the HBD counterpart and with the structural features of the liquids obtained was performed using NMR and DFT studies. Glycerol/L-Proline and *p*-toluenesulfonic acid · H_2O/L-Proline mixtures were used and analysed to compare the results obtained with the novel CDESs with the already reported liquids with L-proline as HBA[37–39].

2. EXPERIMENTAL

2.1 GENERAL

Unless otherwise noted, all commercial reagents and solvents were used without further purification. Reactions under argon atmosphere were carried out in oven-dried glassware sealed with a rubber septum using anhydrous solvents. ^{1}H NMR (300 MHz) spectra were obtained on a Bruker AC-300, using $CDCl_3$ as solvent and TMS (0.003%) as reference, unless otherwise stated. Chemical shifts (δ) are reported in ppm values relative to TMS and coupling constants (*J*) in Hz. Analytical TLC was performed on Merck aluminium sheets with silica gel 60 F254. Analytical TLC

was visualized with UV light at 254 nm Silica gel 60 (0.04-0.06 mm) was employed for flash column chromatography whereas P/UV254 silica gel with $CaSO_4$ (28-32%) supported on glass plates was employed for preparative TLC. Chiral HPLC analyses were performed on an Agilent 1100 Series (Quat Pump G1311A, DAD G1315B detector and automatic injector) equipped with chiral columns using mixtures of hexane/isopropanol as mobile phase, at 25 °C. The deep eutectic solvents were sonicated in an ultrasounds apparatus P-Selecta (360W). The well-known conjugate addition compounds were just characterized by ^{1}H NMR and chiral HPLC analyses. All referenced synthesized compounds are in accordance with the data reported in the literature.

2.2 DESs PREPARATION

Urea, choline chloride, acetamide, (1S)-(+)-10-Camphorsulfonic acid, tetramethylammonium chloride, D-(+)-glucose, $ZnCl_2$, 1,6-hexanediol, *S*-(+)-mandelic acid, picolinic acid, L-(+)-tartaric acid, citric acid, phenol, glycolic acid, diethylene glycol, 1,4-butanediol, glycerol and L-proline were purchased from Sigma-Aldrich, Merck or Alfa Aesar (purities >98%); the solid samples were used after drying under vacuum over silica gel and P_2O_5, the liquid reactants were used without further purifications.

In a 10 mL round-bottomed flask L-Proline was weighed, then specific molar ratios (from 0.5 to 1 to 8:1) of the counterpart were weighed in the same flask. After each addition, the mixture was mixed with a vortex and then put at 80°C under magnetic stirring until homogeneous and stable fluids are formed at the proper molar ratio at room temperature.

The freezing points were determined with a thermometer using an acetone/liquid nitrogen mixture for cooling the samples in a Dewar; the measures were repeated in triplicate and the values have errors from ±1 to ±3°C.

Water contents were measured with a Karl-Fischer titration with Metrohm 684 KF Coulometer: (**Thymol/L-Proline** = 1.4% w/w; **Glycolic acid/L-Proline** = 2.4% w/w; **Diethylene glycol/L-Proline** = 5.0% w/w; **1,4-butanediol/L-Proline** = 3.6% w/w; **Glycerol/L-Proline** = 8.6% w/w, ***p*TSA/L-Proline** 9.0% w/w); all the measures were replicated in triplicate and have errors ranging from 0.1% to 0.2%.

Thermogravimetric analyses were carried out on a METTLER TOLEDO TGA/DSC2 apparatus under nitrogen atmosphere at 25 °C and using a heating rate of 10 °C min^{-1} up to 400 °C.

2.3 CONJUGATE ADDITIONS. GENERAL PROCEDURE

trans-β-Nitrostyrene (0.10 mmol) was added to the corresponding CDES at 30°C and the obtained mixture was stirred for 10 minutes at the same temperature. Then, the nucleophilic ketone (0.20 mmol) was added to the reaction mixture, which was vigorously stirred for the corresponding time (3 or 5 days). Then, EtOAc (1 mL) was added to the reaction and the resulting mixture was sonicated for 1 minute. The organic phase was collected, and the mixture was extracted again two times with 1 mL of EtOAc under ultrasound irradiation. The combined organic solvents were evaporated under reduced pressure to give the crude reaction product which was analysed by ^{1}H NMR and chiral HPLC.

(3*S*,4*R*)-3-methyl-5-nitro-4-phenylpentan-2-one[40].

Colourless oil; δ_H: 0.99 (d, *J* = 7.4 Hz, 3H), 2.23 (s, 3H), 2.92-3.00 (m, 1H), 3.67 (td, *J* = 9.2, 5.4 Hz, 1H), 4.70-4.61 (m, 2H), 7.12-7.15 (m, 2H), 7.24-7.32 (m, 2H); chiral HPLC analysis: Chiracel AS column, Hexane/*i*PrOH: 90/10, flow rate = 1.0 mL/min, λ = 210 nm, retention times: *syn* 9.7 (minor enantiomer), 11.0 (major enantiomer) min, *anti* 12.2 (major enantiomer), 14.4 (minor enantiomer) min.

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl)]cyclohexanone[40].

Yellow solid; mp 122-130 °C, δ_H: 1.23-1.31 (m, 2H), 1.60-1.78 (m, 3H), 2.07-2.12 (m, 1H), 2.40-2.48 (m, 2H), 2.70-2.75 (m, 1H), 3.74-3.82 (td, *J* = 9.9, 4.6 Hz, 1H), 4.62-4.69 (dd, *J* = 12.5, 9.9 Hz, 1H), 4.89-4.99 (dd, *J* = 12.5, 4.5 Hz, 1H), 7.16-7.20 (m, 2H), 7,28-87,37 (m, 3H); chiral HPLC analysis: Chiralcel AS-H column, Hexane/iPrOH: 95/05, flow rate = 1.0 mL/min, λ = 210 nm, retention times: *syn* 13.2, 17.6 min, *anti* 16.1, 19.1 min.

2.4 NMR STUDIES OF HBD/L-PROLINE INTERACTIONS

^{1}H NMR spectra were measured at 298 K on a Bruker Avance III HD spectrometer. All the spectra were calibrated on $CDCl_3$ solvent signal and were registered with a single scan.

2.4.1 NMR Titrations

The titrations were performed recording the ^{1}H NMR spectra adding subsequent amounts of L-Proline to weighed solutions of HBDs with concentrations ranging from 0.039 M to 0.045 M in the different experiments. No internal standards were used as the integrations were calibrated on the weighed HBD. The binding constants were determined fitting the data using

http://supramolecular.org (Prof. Pall Thordarson and Sir Fraser Stoddart)[41,42] using 1:2 fitter, L-BFGS-B method with non-cooperative flavour, no dilution correction and with subtraction of initial values. Except for GA/L-Pro sample, none of the $\Delta\delta$ *vs.* [L-Pro] curves reached plateau, but the fittings were excellent with low errors (2.4% for GA/L-Pro; 3.0% for BD/L-Pro; 5.2% for GLY/L-Pro; 1.7% for DEG/L-Pro respectively).

2.4.2 ^{1}H NMR Analysis

Stock solutions of L-Proline were prepared dissolving it in $CDCl_3$/MeOD 75/25 v/v. The HBD molecules were weighed in NMR tubes and the proper amount of the stock solution of L-Proline were added with syringe in order to have the same concentration of HBD and L-Proline in each tube. The same L-Proline stock solutions were added in another tube and analysed for the spectra of the sample without HBD. All the samples were shaken vigorously for some minutes to prevent bad shimmed spectra. The concentrations of the samples were ranging from 0.039 M to 0.045 M in the different HBD experiments.

2.5 THEORETICAL CALCULATIONS

All the geometries have been optimized with ORCA 4.1.0[43,44] using the B3LYP functional in conjunction with the def2-TZVP basis set and the def2/J auxiliary basis set. The RIJCOSX approximation has been used. The contribution of dispersion has been taken into account by using the D3 correction[45] with Becke-Johnson energy damping. The polar environment has been considered using the conductor-like polarizable continuum model (C-PCM) and using the parameters of acetone (ε_r = 20.7). All the thermodynamic properties have been computed at the same level of theory. All the geometries showed no imaginary frequencies or, in some cases, vary small and unavoidable imaginary frequencies (<15 cm^{-1}) related to relative translational motions between the noncovalently bound components of the adducts. The list of coordinates of the optimized geometries of the adducts are available in the Supplementary Material section.

3. RESULTS AND DISCUSSION

3.1 PREPARATION OF NOVEL L-PROLINE-BASED DEEP EUTECTIC SOLVENTS

A large set of molecules was tested as counterpart of L-Proline (L-Pro) to prepare DESs liquids at room temperature. In this screening, molecules that formed DESs with other counterparts

reported in literature were tested, as well as other hydrogen-bond capable molecules; L-Pro was tested as HBA as well as HBD since it is known its dual role[46,47]. Urea, choline chloride, acetamide, (1*S*)-(+)-10-camphorsulfonic acid, tetramethylammonium chloride, D-(+)-glucose, $ZnCl_2$, 1,6-hexanediol, *S*-(+)-mandelic acid, picolinic acid, L-(+)-tartaric acid, citric acid and phenol were tested in the molar ratio range from 0.5:1 to 8:1 with L-Pro. However, none of these mixtures gave stable liquids at room temperature, showing higher melting points, unstable mixtures during time, non-formation of liquid phases even adding molar equivalents of water. On the contrary, 1,4-butanediol (BD), diethylene glycol (DEG) and thymol (THY) gave stable liquids at room temperature. Furthermore, three other L-Proline-based DESs were used and analysed in this work[39,46,48]: Glycolic Acid and L-Proline (**GA/L-Pro**), Glycerol and L-Proline (**GLY/L-Pro**) and *p*-toluenesulfonic acid · H_2O and L-Proline (***p*TSA/L-Pro**). The acronym of the mixtures, their molar ratio and the freezing points are reported in Table 1. In the Supplementary Material section the molar ranges for all the tested molecules are reported in Table S1, the eutectic profiles of the novel mixtures are reported in Figure S1, and the thermogravimetric analysis of the liquids are reported in Figure S2.

Table 1: Composition, acronyms, freezing points, molar ratios of L-Proline-based Deep Eutectic Solvents used in this work.

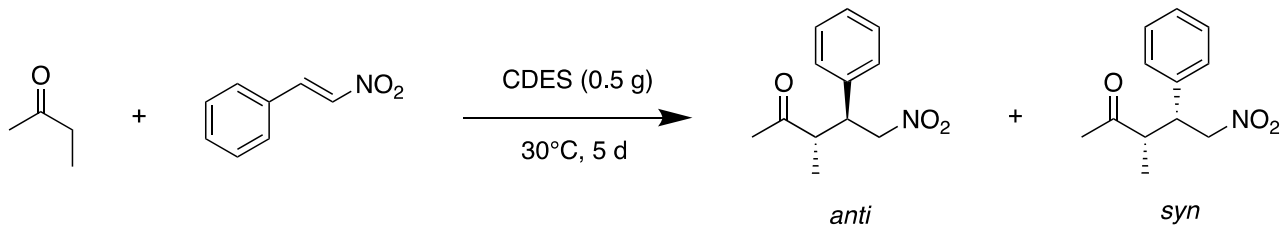
HBD	HBA	DES acronym	freezing point (°C)	molar ratio (HBD/L-Pro)
glycolic acid	L-Proline	GA/L-Pro	-9	3/1
1,4-butanediol	L-Proline	BD/L-Pro	11	3/1
diethylene glycol	L-Proline	DEG/L-Pro	-49	3/1
thymol	L-Proline	THY/L-Pro	-12	7/1
glycerol	L-Proline	GLY/L-Pro	-31	3/1
p-toluenesulfonic acid · H_2O	L-Proline	*p*TSA/L-Pro	12	2/1

All these mixtures showed freezing points lower than room temperature, with **DEG/L-Pro** mixture showing the lowest freezing point in the set (-49°C). Due to the natural presence of glycolic acid (that can be obtained and it is present in the sugar beet) and thymol (that is a molecule present in the oil of thyme, **GA/L-Pro** and **THY/L-Pro** mixtures can be considered NADESs. Regarding the role of the counterparts, in all of these mixtures L-Pro can be considered as an HBA[5,49–52].

The prepared liquids were then used as active green reaction media/organocatalysts in the Michael addition of butanone to *trans*-β-nitrostyrene, taking advantage of the enamine activation capability of L-Proline.

3.2 APPLICATION OF L-PROLINE DESs AS GREEN REACTION MEDIA/ORGANOCATALYSTS

The prepared CDESs were tested as catalysts in the Michael addition of butanone to *trans*-β-nitrostyrene (Scheme 1); this probe reaction is reported in literature in different media with reaction times from 1 to 8 days[53–57], so it was performed in 5 days. The results are reported in Table 2. As shown, when using ***p*TSA/L-Pro** as CDES (entry 1), no reaction was observed at 30°C, after 5 days. This result is probably a consequence of the highly acidic character of the CDES that can cause a detrimental effect in the conjugate addition of ketones to nitro-olefins maybe because of a catalyst protonation[40]. With **THY/L-Pro** liquid (entry 2), no reaction conversion was observed after five days. This could be due to the hydrophobicity of the liquid caused by the HBD (thymol) that is present in the hydrophobic phase as demonstrated in a previous work[50]. As depicted in Table 2, the rest of the CDES afforded the Michael addition product with low (15% for **GA/L-Pro**: 3/1, entry 3) to very high conversions (almost quantitative for all the other mixtures) and moderate *syn*/*anti* diastereoselectivities (from 60/40 to 85/15). With respect to the enantioselectivity, only the chiral eutectic solvent **GA/L-Pro** showed good asymmetric induction affording both diastereomers with high enantioselectivities (*syn*: 86% *ee*; *anti*: 95% *ee*, Table 2, entry 3). The other three mixtures (**BD/L-Pro**, **DEG/L-Pro** and **GLY/L-Pro,** entries 4-6 respectively) showed only racemates in the *anti* diastereomers, while low enantiomeric excesses were observed for the *syn* (13% with **BD/L-Pro** entry 4, 26% with **DEG/L-Pro** entry 5). Both racemates were observed with **GLY/L-Pro** mixture (entry 6).



Scheme 1: CDES-catalysed conjugate addition of butanone to *trans*-β-nitrostyrene.

Table 2: Conversion, diastereomeric and enantiomeric excesses in CDES-catalysed conjugate addition of butanone to *trans*-β-nitrostyrene.

Entry	CDES	Conversion (%)[a]	*dr* (*syn*/*anti*)[a]	*ee* (*syn*/*anti*)[b]
1	*p*TSA/L-Pro: 2/1	< 5	nd [c]	nd [c]
2	THY/L-Pro: 7/1	< 5	nd [c]	nd [c]
3	GA/L-Pro: 3/1	15	60/40	86/95
4	BD/L-Pro: 3/1	> 95	75/25	13/rac
5	DEG/L-Pro: 3/1	92	85/15	26/rac
6	GLY/L-Pro: 3/1	> 95	80/20	rac/rac

[a]Determined by ^{1}H NMR analysis in the crude reaction mixture. [b] Determined by chiral HPLC analysis. [c] No product observed.

In literature the L-Pro catalyzed conjugate addition of linear ketones, such as butanone and 2-pentanone, to *trans*-β-nitrostyrene has shown from very low to moderate enantioselectivities along with a strong solvent effect. Usually, only dipolar (protic and aprotic) solvents such as DMSO[58] (85%, 50% *de*, 10% *ee*), MeOH[59] (70%, 97% *de*, 76% *ee*), EtOH[59] (91%, 64% *de*, 12% *ee*), and H_2O[60] (no reaction) have been used in this particular transformation. Also, L-proline has failed to provide high enantioselectivities when using ionic liquids, such as [bmim][PF_6][61] (68%, 80% *de*, 45% *ee*) as reaction medium.

3.3 NMR STUDIES OF HBD/L-PROLINE INTERACTIONS IN THE NOVEL DESs

The results observed in the addition of butanone to *trans*-β-nitrostyrene in the different CDESs were analysed with structural NMR studies on the CDESs considering the strength of the interactions between L-Proline and the HBD counterparts[34]. The amino acid is present, in fact, in all the mixtures but the observed conversions and the enantiomeric excesses are largely different among the novel liquids probably due to the different interactions between L-Proline and the corresponding counterpart HBD. Therefore, the balance between the two roles of L-Pro was analyzed in a semi-quantitative approach.

The first study performed was the determination of the association constants (*K*) of the HBD with L-Pro via NMR titration[41,42,62]. **THY/L-Pro** and ***p*TSA/L-Pro** mixtures were not analyzed in this study because they did not show conversion in the reaction. The analyzed CDESs have different solubility properties, therefore, and in order to obtain a homogeneous set of data, all the experiments were conducted in the solvent mixture $CDCl_3$/MeOD: 75/25 (v/v). Chloroform is a suitable solvent for determining the H-bond interactions because it is aprotic, while methanol is a

disaggregating solvent and it can interfere with the hydrogen bonds between the species; the 25% v/v amount of MeOD is a compromise between solubility and preservation of the CDES interactions. However, these data presented valuable indications on the structures of the different CDESs. In the Supplementary Material section, the graphs of $\Delta\delta$ on [L-Pro] are reported.

Under the studied conditions, **DEG/L-Pro**, **BD/L-Pro** and **GLY/L-Pro** mixtures showed very low association constants (lower than 10^{-8}, 10^{-7} and 10^{-10} M^{-1} respectively), therefore they cannot be considered for a quantitative and comparative analysis. However, the shift of the signals of the HBD when adding L-Pro is an evidence of weak interactions occurring between the species. Interestingly, **GA/L-Pro** CDES showed an association constant of 0.73 M^{-1}, a value that is low but it is far higher than the others, indicating the presence of an interaction between glycolic acid and L-Pro which is stronger than the observed with the other HBDs. In the Michael addition of butanone to *trans*-β-nitrostyrene, **GA/L-Pro** mixture showed the lowest conversion (15%) but the highest enantiomeric excess for both diastereomers (86/95% *ee*). These data suggest that the interaction between L-Pro and GA interferes with the reaction (i.e. an interaction or steric hindrance on the nitrogen of L-Pro), but once the chiral enamine is formed, this "more structured" system leads to higher enantiomeric excesses. The possibility of protonation of L-Pro by GA can be excluded due to the similarities shown by the ^{1}H NMR spectra of the CDES and L-Pro. These data are supported by the ***p*TSA/L-Pro** liquid results that showed no conversion of the reactants even after five days. The spectrum of L-Pro, in fact, is largely different when *p*TSA is added (see Supplementary Material) so suggesting a stronger interaction that can inhibit the catalytic activity of the organocatalysts, even if this liquid is reported in literature as based on weak interactions.

The shifts of the ^{1}H NMR signals of L-Pro in the presence of the HBD molecule were then used to determine the strength of the HBA-HBD interactions. The more the HBD interacts with L-Pro, the higher shifts could be observed. In these experiments, the sum of the absolute values of the shifts for each signal ($\Sigma_{|\Delta\delta|}$) were evaluated to compare the different effects observed in the L-Pro-based CDESs. In Table 3, the values of $\Sigma_{|\Delta\delta|}$ and the association constants (*K*) are reported as well as the conversions, the diastereomeric excesses and the enantiomeric excesses obtained for the model conjugate addition reaction.

Table 3: Association constants (*K*), sum of absolute values of $\Delta\delta$ ($\Sigma_{|\Delta\delta|}$) of the CDESs, conversion, diastereomeric ratio and enantiomeric excesses, in the addition of butanone to *trans*-β-nitrostyrene catalysed by CDESs.

Entry	CDES	*K* (M^{-1})	$\Sigma_{\|\Delta\delta\|}$ (ppm)	Conversion (%)[a]	*dr* (*syn/anti*)[a]	*ee* (*syn/anti*)[b]
1	GA/L-Pro: 3/1	0.74	0.043	15	60/40	86/95
2	DEG/L-Pro: 3/1	*n.a.*[c]	0.011	92	85/15	26/rac
3	BD/L-Pro: 3/1	*n.a.*[c]	*n.a.*[d]	> 95	75/25	13/rac
4	GLY/L-Pro: 3/1	*n.a.*[c]	*n.a.*[d]	> 95	80/20	rac/rac

[a] Determined by ^{1}HNMR analysis in the crude reaction mixture. [b] Determined by chiral HPLC analysis. [c] Values lower than 10^{-8} M^{-1}. [d] Values lower than 0.01 ppm.

The CDES **GA/L-Pro** showed the highest value of $\Sigma_{|\Delta\delta|}$ in the set (0.043 ppm), **DEG/L-Pro** mixture showed a lower value (0.011 ppm), while **BD/L-Pro** and **GLY/L-Pro** mixtures showed values lower than 0.01 ppm and therefore they were not considered. These values are really low, but still the de-aggregating properties of MeOD must be considered. However, these experiments gave important indications about the structural features of the liquids. As observed, the interaction between L-Pro and the glycolic acid in the GA/L-Pro liquid was stronger than the detected between L-Pro and the other HBDs (Table 3, entry 1). In particular, the hydrogen in position 2 (H2) of the chiral organocatalyst showed the highest shift (downfield) of all the studied signals and experiments, as demonstrated in Figure 1, where the superimposed ^{1}H NMR spectra of L-Pro in the presence and in the absence of the correspondent HBD for H2 of L-Pro are shown. All the spectra are reported in Supplementary Material section.

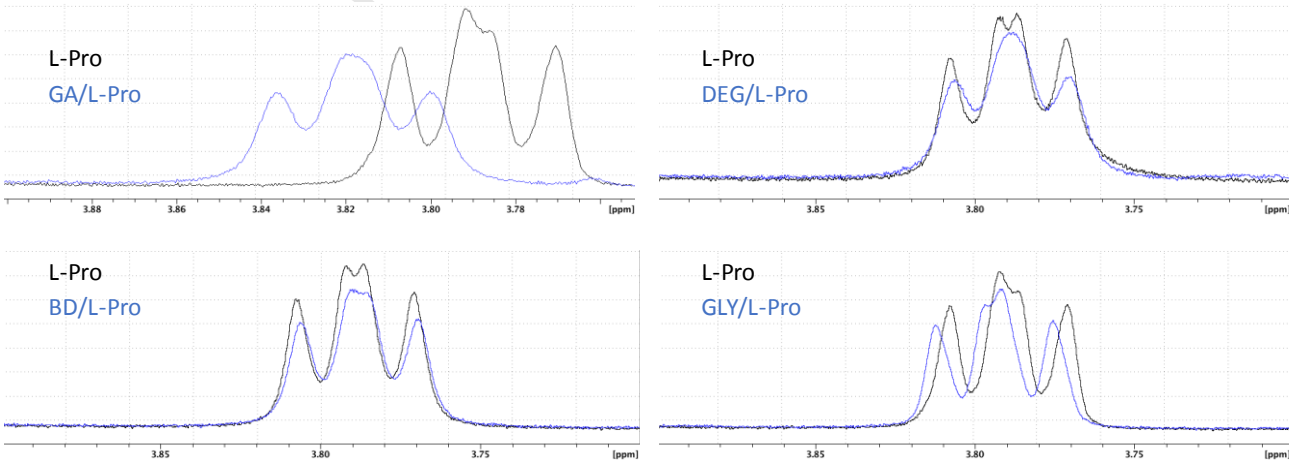


Figure 1: ^{1}H NMR (400 MHz, $CDCl_3$/MeOD: 75/25 v/v) spectra of H2 of L-Proline (black) the corresponding CDES (blue).

These NMR experiments showed results similar to those obtained from the NMR titration studies: **GA/L-Pro** showed the strongest interaction between the HBD and the L-Pro. Furthermore, analysing the data from the model asymmetric organocatalyzed reaction, it can be observed that the stronger interaction between L-Pro and the HBD is, the lower the conversion of the reaction (Table 3, entry 1). On the contrary, the enantiomeric excess is favoured by these structured systems, as corroborated with the **DEG/L-Pro** mixture, which showed a slight lower interaction, thus increasing the conversion (from 15 to 92%) but decreasing the *ee* (from 86 to 26% *ee* for the major *syn* diastereomer) (Table 3, entries 1 and 2). Finally, for those mixtures where the HBA/HBD interactions are weak (**GLY/L-Pro** and **BD/L-Pro**), the reaction conversions are quantitative but only racemic diastereomers were observed.

3.4 DFT STUDIES

The results obtained from the NMR experiments suggested to investigate the interactions occurring between L-Pro and the HBD counterpart with computational calculations. Thus, DFT calculations were performed [B3LYP-D3/def2-TZVP/c-PCM (ε_r = 20.7) level of theory] on the different adducts involved in the organocatalytic conjugate addition reaction. Considering the nature of the interactions, a polar environment was necessary to correctly assess the energy of the adducts. Unfortunately, the experimental determination of the polarity of a DES is not straightforward[62], so the polarity of acetone was used (polarity index: 5.1; dielectric constant: 20.7)[63] as an educated guess and compare all the adducts under the same computational conditions.

Figure 2 shows the optimized structure of the 1:1 adducts between L-Pro and GLY, GA, DEG and BD. As seen in the geometry of the 1:1 **GLY/L-Pro** adduct, the secondary –OH groups of glycerol points directly toward the lone pair of the nitrogen of L-Pro, whereas the carboxylic moiety of the latter interacts with one of the primary –OH groups of the HBD. A similar HBD/HBA adduct geometry is obtained using GA and BD, whereas in the case of DEG, the amino proton (and not the nitrogen lone pair) is involved in the inter-molecular interaction.

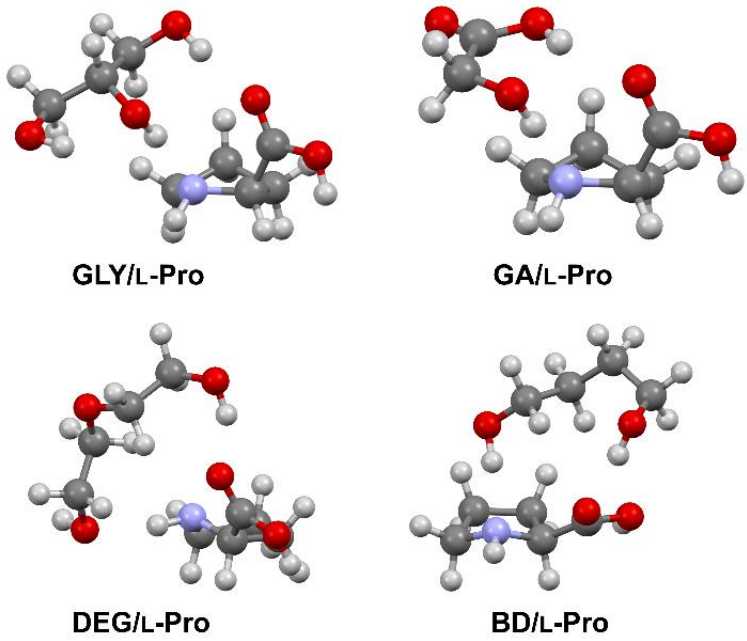
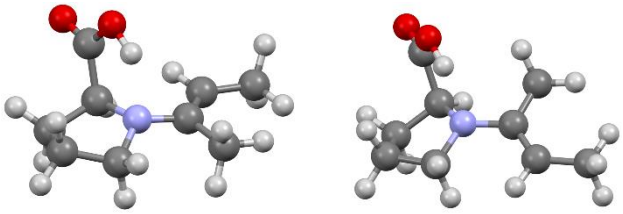


Figure 2: DFT optimized geometries of adducts formed between L-Pro and GLY, GA, DEG and BD.

The stability of the CDESs adducts, with respect to the isolated components, follows the trend (ΔE): **GA/L-Pro** (-3.8 kcal/mol) < **BD/L-Pro** (-3.0 kcal/mol) < **GLY/L-Pro** (-2.7 kcal/mol) < **DEG/L-Pro** (+2.2 kcal/mol). The Gibbs free energy is positive in all the cases (9.0 kcal/mol for **GA/L-Pro**), but it should be remembered that in the CDES many other interactions are present, contributing to lower ΔG. Notably, the most stable adduct is GA/L-Pro, coherently with its lowest reaction conversion value (Table 3, entry 1).

In order to give a rationale to the different enantioselectivities obtained in the Michael addition of butanone to β-nitrostyrene with CDESs, firstly the two most stable enamines **E1** (s-*cis* or *syn* enamine) and **E2** (s-*trans* or *anti* enamine) formed by reaction between L-Pro and butanone have been optimized (Figure 3). The former resulted to be slightly less stable than the latter (0.4 kcal/mol). Interestingly, in the isolated enamine the carboxylic acid establishes a hydrogen bond with the lone pair of the nitrogen atom (N···H distance 1.916 Å), which is not necessarily true in the DES.



E1 (0.0) **E2** (-0.4)

Figure 3: DFT optimized geometries of **E1** and **E2**. The relative Gibbs energy is given in parenthesis (kcal/mol).

In fact, it is important to underline that the amino group of L-Pro is heavily involved in the interaction with the second component of the CDES. Then, the system was modelled as follows: the enamine interacts with both the HBD and *trans*-β-nitrostyrene (NS) at the same time, giving a ternary adduct. For this, one of the enantiofaces of the enamine will be occupied by the HBD, forcing **NS** to interact with the other enantioface and, therefore, producing a specific enantiomer. In conventional solvents, a high selectivity in this test reaction is explained by a HB interaction between the carboxylic group of L-Pro and the nitro group of NS[59,64,65], but in this case also the solvent is able to establish HBs with L-Pro, making the situation more complex. Under the hypothesis that the activation barrier of the addition will likely be similar for all of the studied adducts, a high *ee* is expected in those cases where one adduct is much more stable than the others. Considering also the possibility to have the two different enamines (*anti* and *syn*), it means that 8 ternary adducts have been optimized for each HBD. To differentiate them, the following nomenclature was adopted: the suffix **–nA** indicates that the electrophile does not interact with the carboxylic group of the enamine (**-nB**, if it does). Further, the suffix **1** indicates that the **NS** interacts with the other components through its *si* face, **2** if through the *re* face. In Figure 4 are reported the optimized geometries of GA/L-Pro adducts with the relative Gibbs energies, all the adducts of the other mixtures are reported in Supplementary Material section. Table 4 summarizes the results, indicating the relative energy for each group of ternary adducts, setting the most stable as the reference, and the isomer coming from that geometry.

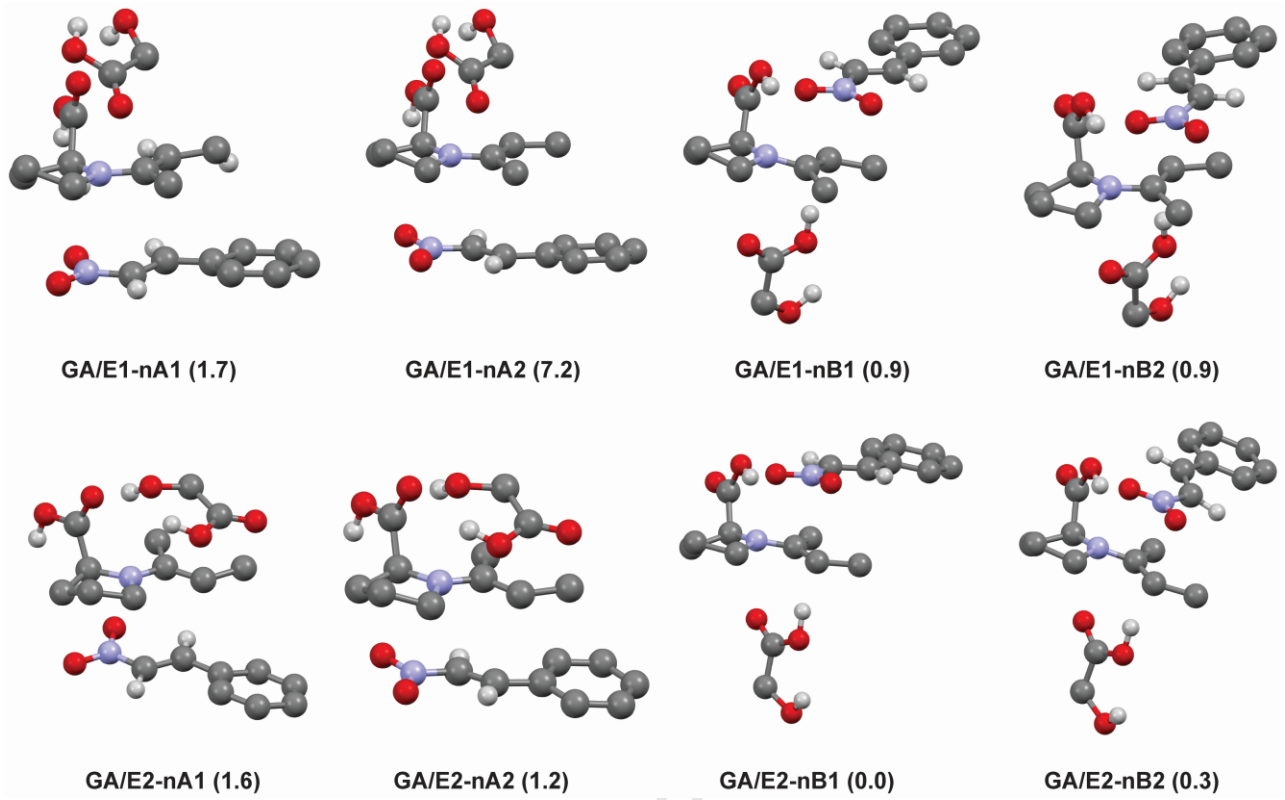


Figure 4: DFT optimized geometries of Glycolic Acid/L-Proline. Only selected hydrogen atoms are explicitly shown. Relative Gibbs energies, in kcal/mol, are given in parenthesis.

The relative energies of the ternary allow to semi-quantitatively rationalize the observed experimental results for the model Michael addition reaction. In fact, among the possible **GA/E1** and **GA/E2** adducts, **GA/E2-nB1** and **GA/E2-nB2** are quite close in energy (0.3 kcal/mol, Table 4), but the former leads to the formation of the *anti* isomer, whereas the latter to the formation of the *syn* one. This allows to justify the low diastereomeric excess experimentally found for this system (60/40). Generally speaking, the parameter Δd can be defined as the energy difference between the most stable configuration leading to the *anti* isomer and that leading to the *syn* one. As seen for **GA/E**, Δd directly relates with the *de* of the reaction.

The same strategy can be used to give a rationale for the *ee*. In fact, Δ*anti* can be defined as the energy difference between the most stable adducts leading to the isomers *anti(S,S)* and *anti(R,R)*. In the case of **GA/E**, Δ*anti* is 0.9 kcal/mol, which reflects in a 1:0.22 ratio in concentration between the two enantiomers, qualitatively coherent with a quite high *ee* (experimental = 95).

Analogously, Δ*syn* can be defined as the energy difference between the most stable adducts leading to the isomers *syn(S,R)* and *syn(R,S)* and it is related to the *ee* of the *syn* isomer. For **GA/E**, it is 0.6 kcal/mol, leading to a lower *ee* (experimental = 86).

It is useful to compare the values of Δd, Δ*anti* and Δ*syn* for all the systems. By using DEG, many adducts are close each other in energy. In this case Δd, Δ*anti* and Δ*syn* are 0.5, 0.4 and 0.3 kcal/mol, respectively, allowing to predict a moderate *de* (experimental = 85/15) and low *ee* values (experimental = rac for *anti*, 26 for *syn*).

In the case of BD, Δd, Δ*anti* and Δ*syn* are 0.5, 0.3 and 0.7 kcal/mol, respectively, allowing to predict a moderate *de* (experimental = 75/25), a low *ee* value for the *anti* isomer (experimental = rac) and a moderate *ee* for the *syn* isomer (experimental = 13). Finally, for GLY, Δd, Δ*anti* and Δ*syn* are 1.3, 0.1 and 0.4 kcal/mol, respectively, allowing to predict a high *de* (experimental = 80/20) and low *ee* values (experimental = rac for both the isomers).

This simple framework allows giving a qualitative rationale to the isomers distribution.

Table 4: Energies and energies differences (Δd, Δ*anti* and Δ*syn*) between the most stable configurations of the ternary adducts (kcal/mol). For each isomer, the most stable adduct is underlined.

Adduct	Relative energy	isomer produced	Adduct	Relative energy	Enantiomer produced
GA/E1-nA1	1.7	*anti(S,S)*	**BD/E1-nA1**	1.6	*anti(S,S)*
GA/E1-nB1	<u>0.9</u>	*syn(R,S)*	**BD/E1-nB1**	<u>0.7</u>	*syn(R,S)*
GA/E1-nA2	7.2	*syn(S,R)*	**BD/E1-nA2**	3.3	*syn(S,R)*
GA/E1-nB2	<u>0.9</u>	*anti(R,R)*	**BD/E1-nB2**	<u>0.8</u>	*anti(R,R)*
GA/E2-nA1	1.6	*syn(R,S)*	**BD/E2-nA1**	3.7	*syn(R,S)*
GA/E2-nB1	<u>0.0</u>	*anti(S,S)*	**BD/E2-nB1**	<u>0.5</u>	*anti(S,S)*
GA/E2-nA2	1.2	*anti(R,R)*	**BD/E2-nA2**	2.3	*anti(R,R)*
GA/E2-nB2	<u>0.3</u>	*syn(S,R)*	**BD/E2-nB2**	<u>0.0</u>	*syn(S,R)*
Δd	<u>0.3</u>		**Δd**	<u>0.5</u>	
Δanti	<u>0.9</u>		**Δanti**	<u>0.3</u>	
Δsyn	<u>0.6</u>		**Δsyn**	<u>0.7</u>	
DEG/E1-nA1	3.5	*anti(S,S)*	**GLY/E1-nA1**	4.0	*anti(S,S)*
DEG/E1-nB1	<u>0.3</u>	*syn(R,S)*	**GLY/E1-nB1**	<u>0.4</u>	*syn(R,S)*
DEG/E1-nA2	2.0	*syn(S,R)*	**GLY/E1-nA2**	2.1	*syn(S,R)*
DEG/E1-nB2	<u>0.5</u>	*anti(R,R)*	**GLY/E1-nB2**	<u>1.3</u>	*anti(R,R)*
DEG/E2-nA1	3.7	*syn(R,S)*	**GLY/E2-nA1**	1.6	*syn(R,S)*
DEG/E2-nB1	<u>0.9</u>	*anti(S,S)*	**GLY/E2-nB1**	<u>1.4</u>	*anti(S,S)*

DEG/E2-nA2	4.4		*anti(R,R)*	**GLY/E2-nA2**	2.6		*anti(R,R)*
DEG/E2-nB2	0.0		*syn(S,R)*	**GLY/E2-nB2**	0.0		*syn(S,R)*
Δd		0.5		**Δd**		1.3	
Δanti		0.4		**Δanti**		0.1	
Δsyn		0.3		**Δsyn**		0.4	

Finally, the Michael addition of cyclohexanone to *trans*-β-nitrostyrene was also studied using the chiral deep eutectic mixtures (Scheme 2). As depicted, **GA/L-Pro** afforded again the corresponding conjugate addition product with the lowest yield (9%). However, both diastereoselectivity and enantioselectivity were very similar for all the tested eutectic mixtures.

Surprisingly, cyclohexanone is the model nucleophile in organocatalyzed conjugated additions in organic solvents due to the high enantioselectivity it typically shows[54,55]. The fact that this is not the case in the studied CDESs, demonstrates again the strong substrate dependence that asymmetric organocatalysis usually involves.

CDES	Yield (%)	dr (*syn/anti*)	ee (*syn/anti*)
*p*TSA/l-Pro	< 5	-	-
GLY/l-Pro	94	> 20/1	20 / -
GA/l-Pro	9	> 20/1	23 / -
DEG/l-Pro	89	> 20/1	23 / -
BD/l-Pro	92	> 20/1	32 / -

Scheme 2: CDES-catalyzed conjugate addition of cyclohexanone to β-nitrostyrene.

4. CONCLUSIONS

In this paper L-Proline-based chiral Deep Eutectic Solvents (CDESs) were prepared and used as green and organocatalytic reaction media in a model Michael addition. The results were interpreted with NMR studies in terms of the strength of the bind of L-Proline with the

counterpart in the different liquids. The "freedom" of the L-Proline had a key role for its reactivity in terms of conversion of the reactants, but also conversely in the enantiomeric excesses: stronger interactions of L-Proline to the HBD (such as the case of **GA/L-Pro**) led to adducts in the DESs that lowered the conversions to 15% (because of the non-availability of the nitrogen of L-Proline) but increased the enantiomeric excesses (up to 86%/95% for the two diastereomers) thanks to the higher structuration of the adducts. On the other hand, weaker interactions of L-Proline with the counterpart (such as the case of the other mixtures **DEG/L-Pro**, **BD/L-Pro** and **GLY/L-Pro**) led to quantitative conversion values but showed lower enantiomeric excesses or also racemic products (from 26% to racemates). The interactions occurring between the CDESs species and the energies of the adducts of the Michael addition were analysed with DFT studies, that gave a rationale of the isomers' distribution.

The data coming from the use of the CDESs in another Michael addition (cyclohexanone to *trans*-β-nitrostyrene) showed results that are promising for further studies on the use of those liquids in asymmetric synthesis as the data are still coherent with the results of the structural features of these liquids, but with different entities.

Thus, this work represents an approach to the activity of the DESs in terms of the strength of the binding between the two components of the liquids. This could facilitate the interpretation of the activity of these sustainable liquids and help in the design of novel structured liquids of this class.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

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ASSESSMENT OF THE ORGANOCATALYTIC ACTIVITY OF CHIRAL L-PROLINE-BASED DEEP EUTECTIC SOLVENTS BASED ON THEIR STRUCTURAL FEATURES

AUTHORS CONTRIBUTION

Matteo Tiecco: conceptualization, methodology, investigation, resources, writing - original draft, Project administration, visualization;

Diego Alonso: methodology, validation, resources, writing - original draft, investigation;

Diego Ros Niguez: investigation;

Gianluca Ciancaleoni: methodology, software, formal analysis, investigation, writing - original draft, funding acquisition;

Gabriela Guillena: Writing - Review & Editing, funding acquisition;

Diego Ramon: Writing - Review & Editing, funding acquisition;

Alberto Apio Bonillo: investigation;

Raimondo Germani: supervision, Writing - Review & Editing.

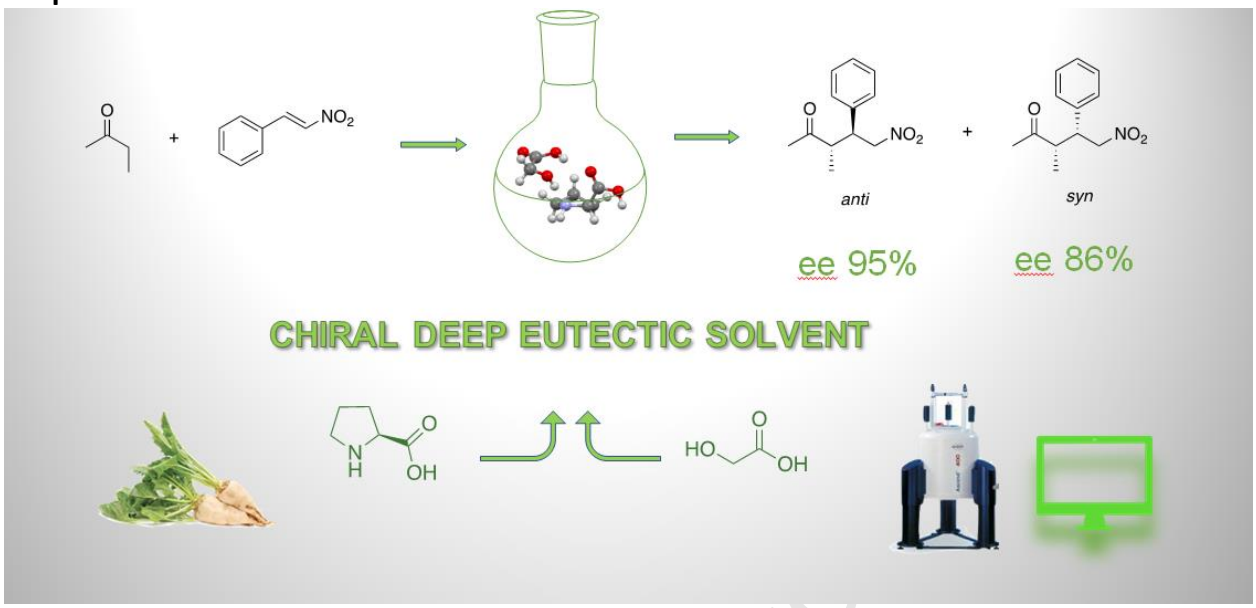
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NONE

Graphical abstract



ASSESSMENT OF THE ORGANOCATALYTIC ACTIVITY OF CHIRAL L-PROLINE-BASED DEEP EUTECTIC SOLVENTS BASED ON THEIR STRUCTURAL FEATURES

HIGHLIGHTS

- Novel L-Proline-based Chiral Deep Eutectic Solvents (CDESs) were prepared
- The CDESs were used as green and organocatalytic reaction media
- A semi-quantitative NMR approach based on the features of the liquids is proposed
- Organocatalytic activities (ee up to 95%) correlated with HBD-HBA association strength
- DFT studies gave a qualitative rationale of stereoisomers distribution