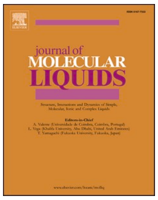
Journal of Molecular Liquids 424 (2025) 127110

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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



Double-Brønsted acidic deep eutectic solvents and their applications as solvents and catalysts in chemical transformations

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ARTICLE INFO

Keywords:
DESs
Brønsted acids
Catalysis
Theoretical melting curves
Aldol condensation
Indoles synthesis

ABSTRACT

The number of novel Deep Eutectic Solvents (DESs) liquids reported in literature is increasing in recent years thanks to the high number of H-bond capable molecules that possess the features to give stable liquids when mixed in binary systems.

In this work a predictive approach based on the theoretical melting curves crossing points was used to generate a novel class of DESs: double Brønsted-acidic DESs. These liquids were identified as DESs thanks to the comparison of the experimental melting points with the theoretical curves and with ionic conductivity measures. Considering that the catalytic properties of the DESs are correlated with the properties of the forming molecules, the novel DESs were tested as acidic reaction media in model reactions. In the Claisen-Schmidt transformation, the double-acidic DESs gave excellent results. The indole synthesis from alkynes involved for the first time to our knowledge the use of simple Brønsted-acid catalysis without any metal or any other catalyst.

1. Introduction

Deep Eutectic Solvents (DESs) are a class of organic liquids that are finding fruitful applications in many different topics as substitutes to common volatile organic compounds (VOCs) for their advantageous and environmentally friendly features [1–4]. The green features of these systems are based on: they can have low or absent vapor pressure; they can have low or absent toxicity; they can be formed by natural-source molecules (NADESs: NaturalDESs); their synthesis does not require any solvent with 100 % yields and atom economy; they can be easily recycled and re-used and so on [3,5–9]. The reduction of the impact of human beings on the environment and the development of novel strategies and industrial protocols that could possess green advantages or low impact on the environment is nowadays mandatory to face the severe matters of pollution and climate change [10–13].

Over their green properties, DESs also have interesting and peculiar structural features: they are formed via weak interactions, mainly H-bonds, between two species: a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA). The mixtures of these two molecules (also with high melting points) lead to the formation of stable liquid systems by simply mixing and heating them. The interactions occurring between the two different species (HBD-HBA) as well as the ones occurring between the same species (HBA-HBA and HBD-HBD) determine the impossibility of a regular crystal lattice formation, therefore leading to liquids [14–19]. The family of hydrophobic DESs is also interesting: H-bond-based mixtures that can separate from water and that are widely applied as extracting liquids. This is also more interesting, considering that the hydrophobicity of the HBD is the only driving force leading to hydrophobic DESs [20–24]. Also binary mixtures with water as a component can be hydrophobic/water separable if the counterpart is hydrophobic, such as in the case of thymol [25]. Many different H-bond capable molecules can form DESs, therefore many different classes and families of novel DESs are increasing in number in the literature [26–28]. Surely not all of the mixtures possess the same advantages in terms of their environmentally friendly features, so a proper choice of the proper systems, and the development of novel ones,

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https://doi.org/10.1016/j.molliq.2025.127110
Received 26 September 2024; Received in revised form 24 January 2025; Accepted 6 February 2025

is a key factor in this scientific topic [29–32].

The third interesting and notable factor of the DESs' chemistry is represented by their catalytic behavior. Because the properties of the molecules forming them correlate with the properties of the liquids, these liquid systems can show acidic, basic, reducing, and also organocatalytic asymmetric properties [33–38]; the catalysis mechanisms are driven by the association constants between the two species, therefore on the "availability" of the catalyst [35,39]. The supramolecular structure of these systems also has a role in their catalytic properties. For example, a DES formed by acid molecules can also show a basic catalysis behavior by involving an acid proton in the H-bonds network of the liquids [40].

Although a large number of liquid systems are reported in the literature, nowadays to define if a mixture is a DES, it is mandatory a comparison of the theoretical melting point curves compared to the experimental ones [41–43]. A shift, a deepening, of the melting point of the mixture at the eutectic point, is evidence of the non-ideality of the system driven by the microscopic inhomogeneity and structural features [44]. This has great relevance in case one of the components is already a liquid, otherwise it should be impossible to define the mixture as a DES rather than a simple solution or eutectic mixture (EM) [45].

This paper presents a novel class of DESs: double Brønsted-acidic DESs. These mixtures are formed by mixing two Brønsted acid molecules leading to liquid systems. Their realization was made with a predictive approach carried out with a theoretical melting curves analysis of a wide set of DES-forming molecules, followed by the verification of their DESs identity by comparison with experimental melting point measures. These mixtures were then applied as "active" reaction media in some interesting organic transformation chosen as "proof of concept", usually promoted by different catalytic systems, showing good selectivities and yields. While other Brønsted/Lewis double acids mixtures were already realized and successfully used in different topics in literature [46–48], to the best of our knowledge, this class of DESs has not been reported, characterized and used yet.

2. Experimental

2.1. Reagents and DESs preparation

Choline chloride, trimethylglycine, L-histidine, glycine, L-proline, (+)-camphorsulfonic acid, citric acid monohydrate, urea, *p*-toluensulphonic acid monohydrate, oxalic acid dihydrate, glycolic acid, phenylacetic acid, thymol, L-menthol, glycerol, acetic acid, DL-lactic acid, ethylene glycol, 1,2-propanediol were purchased from Merck, Sigma–Aldrich, Carlo Erba suppliers (purities all >99 %) and they were used without any further purification. The DESs were prepared by weighting the reactants in screw-sealed vials with low headspace, then mixing them with a vortex and heating them with a heat gun until stable and uniform liquids were observed. The mixtures were heavily shaken to avoid any inhomogeneity due to the evaporation of the components (especially water). Then the liquids were left to cool to room temperature.

2.2. Theoretical and experimental solid–liquid phase diagrams

The experimental melting points were measured via immersion of the different samples at different molar ratios in a liquid nitrogen bath in a Dewar with a thermometer. The mixtures were then left to heat at room temperature and the melting points were taken in triplicates in order to avoid any kinetic matter on the observed values. All the measures showed standard deviations of the triplicates <1 °C.

The theoretical curves were drawn in Microsoft Excel software by using Formula (1) which represents the solid–liquid equilibrium curve in a eutectic mixture [41–43]:

$$ln(\chi_i \bullet \gamma_i) = \frac{\Delta_m h_i}{R} \bullet \left(\frac{1}{T_{m,i}} - \frac{1}{T}\right) + \frac{\Delta_m Cp_i}{R} \bullet \left(\frac{T_{m,i}}{T} - ln\frac{T_{m,i}}{T} - 1\right) \quad (1)$$

where χ_i is the mole fraction of component i, γ_i is its activity coefficient in the liquid phase, $\Delta_m h_i$ and $T_{m,i}$ are its melting enthalpy and temperature, respectively, $\Delta_m Cp_i$ is its heat capacity change upon melting, R is the ideal gas constant, and T is the absolute temperature of the system. Eq. (1) can be simplified by considering the heat capacity change upon the melting of a substance as negligible; therefore Eq. (2) was used:

$$ln(\chi_i \bullet \gamma_i) = \frac{\Delta_m h_i}{R} \bullet \left(\frac{1}{T_{m,i}} - \frac{1}{T}\right) \quad (2)$$

The theoretical melting temperatures were determined from the theoretical curves by considering the activity coefficients $\gamma_{\mathrm{i}} = 1$. The eutectic points were determined as the minimum in the experimental curves and compared to the theoretical ones.

The experimental γ_{i} values were determined via Eq. (3) by using the experimentally observed melting temperatures:

$$\gamma_i = \frac{\exp\left[\frac{\Delta_m h_i}{R}\left(\frac{1}{T_{m,i}} - \frac{1}{T}\right)\right]}{\chi_i} \quad (3)$$

2.3. Ionic conductivity measures

Ionic conductivities were measured with a VioLab 60 series conductivity meter at 25.0 ± 0.1 °C using a water thermostat. The water dilutions of the samples were made by mixing the proper amount of water with the DESs and leaving the mixtures stirring at room temperature overnight for a proper homogenization of the samples.

2.4. Thermogravimetric measures

The Thermogravimetric analyses (TGA) were performed with Netzsch STA 2500 Regulus thermal analyzer, equipped with Al_2O_3 crucibles. 10 mg of samples were heated from room temperature to 450 °C, under nitrogen atmosphere with a heating rate of 5 °C/min.

2.5. Synthesis

2.5.1. General remarks

All chemicals and solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique, using silica gel (pore size 60 Å, particle size 230–400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), Silica on TLC Alu foils with a fluorescent indicator (254 nm) was employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). ^{1}H NMR analyses were performed with a 300 MHz or 400 MHz spectrometer at room temperature. The coupling constants (J) are expressed in Hertz (Hz) and the chemical shifts (δ) in ppm. The multiplicity of the proton spectra was described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), dt (double triplet), dd (double doublet), m (multiplet), br (broad). Microwave-enhanced reactions were performed with the single-mode microwave synthesizer "Biotage® Initiator Classic". Compounds **1a,c,f**, and **2a-f**, were purchased from standard chemical suppliers and directly used without further purifications. Compound **4** was prepared according to literature procedures [49]. Products **1a-e**, **3a-h**, **5**, and **6** are known compounds and were identified by comparison with spectral data reported in the cited references.

2.5.2. Claisen-Schmidt reaction

In a vial, the ketone **1a,c,f** (1 eq.) and the aldehyde **2a-f** (1.2 eq) were added to GA/+CSA/H_2O (0.5 mL). The mixture was heated at 90 °C in an oil bath and monitored via TLC. After completion, water was added and the crude was extracted with EtOAc. The organic layers were reunited, washed with $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography over silica gel to yield **3a-h**.

The detailed synthetic procedures and the NMR data are reported in Supporting Information section (**S1**).

2.5.3. Synthesis of indoles

In a vial, 4-methyl-N-(2-(phenylethynyl)phenyl)benzenesulfonamide **5** was added to the selected DES (0.5 mL). The mixture was heated (see Table 3 for heating method, time and temperature). After completion, the mixture was poured in water and extracted with EtOAc. The organic layers were reunited, washed with $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography over silica gel to yield selectively **5** and **6**.

The detailed synthetic procedures and the NMR data are reported in Supporting Information section (**S2**).

3. Results and discussion

3.1. Novel double Brønsted acidic DESs prediction and realization

In order to define if a liquid mixture is a Deep Eutectic Solvent, a comparison between the experimental melting point curves with the theoretical ones is nowadays mandatory. A deepening in the melting point values, and sometimes also a shift in the molar fraction of the eutectic point is required to identify the mixture as non-ideal with interactions occurring between the components. Therefore, the theoretical melting point curves must show a crossing point, corresponding to the theoretical eutectic, which could eventually differ from the experimental one. To obtain novel DESs liquids the first step of this work was the study of the theoretical melting point curves of a wide set of molecules already reported in literature as DESs' components and the evaluation of eventual crossing points between those curves. The drawn curves were the ones of choline chloride, trimethylglycine, L-histidine, glycine, L-proline, (+)-camphorsulfonic acid, citric acid monohydrate, urea, *p*-toluensulphonic acid monohydrate, oxalic acid dihydrate, glycolic acid, phenylacetic acid, thymol, L-menthol, glycerol, acetic acid, DL-lactic acid, ethylene glycol, 1,2-propanediol. These molecules share between them values of enthalpy of fusion and of melting points that determine curves (according to Eq. (2)) with proper slopes that determine many crossing points between them. In the Supporting Information section (Fig. S1), all the theoretical melting point curves are reported in the same graph. From this theoretical approach, we focused on a homogenous set of molecules in terms of structural characteristics, Brønsted acid molecules: (+)-camphorsulfonic acid (+CSA), citric acid monohydrate ($CA{\cdot}H_2O$), *p*-toluensulphonic acid monohydrate (*p*$TSA{\cdot}H_2O$), oxalic acid dihydrate ($OA{\cdot}2H_2O$), glycolic acid (GA), phenylacetic acid (PAA), DL-lactic acid (LA), in Fig. 1 the structures are reported.

Acid components, particularly *p*$TSA{\cdot}H_2O$, are already reported in the literature as effective DESs components mixed with differently structured HBAs such as ammonium salts, neutral molecules, or zwitterions. However, the theoretical melting curves of these mixtures show interesting cross points between themselves, and this deserves an exploration whether these binary mixtures might be liquid DESs. In Fig. 2 the theoretical melting curves of the Brønsted acids are reported.

As emerged from the melting curves, all the analyzed Brønsted acids show crossing points in the theoretical curves with all the analyzed counterparts, so in principle all those mixtures might give DESs systems. Therefore, we mixed and heated all the combinations of molecules in binary mixtures in molar ratios from 1:7 to 7:1 in order to evaluate if these systems gave liquids. From this screening, a first set of mixtures was excluded as they experimentally did not give liquid systems but solid or semi-solid adducts even at high temperatures.

Those systems that, on the contrary, gave liquids were analyzed by measuring the melting points at different molar fractions to compare the melting point with the theoretical curves, to identify the eutectic point and to compare the curves with the theoretical ones. The liquid mixtures (at different molar ratios) were: GA with the counterparts $pTSA{\cdot}H_2O$, $OA{\cdot}2H_2O$, $CA{\cdot}H_2O$, +CSA and PAA; $OA{\cdot}2H_2O$ with $pTSA{\cdot}H_2O$, $CA{\cdot}H_2O$ and +CSA; $pTSA{\cdot}H_2O$ with $CA{\cdot}H_2O$ and +CSA; $CA{\cdot}H_2O$ with +CSA.

The next step was the comparison of the theoretical melting curves with the experimental melting points at different molar fractions and the activity coefficient analysis. From these analyses, three main classes of liquids were observed: DES systems, Eutectic Mixtures (EM), and peculiar systems with molar fraction shift only from the theoretical ones. The DESs systems were: GA/$pTSA{\cdot}H_2O$, GA/$OA{\cdot}2H_2O$, GA/$CA{\cdot}H_2O$, GA/+CSA, $OA{\cdot}2H_2O$/$CA{\cdot}H_2O$, $pTSA{\cdot}H_2O$/$CA{\cdot}H_2O$, $CA{\cdot}H_2O$/+CSA in which a shift of the molar fraction and a lowering of a melting point compared to the theoretical curves was observed, with activity coefficients lower than 1. The Eutectic mixtures (EM) were: GA/PAA and $OA{\cdot}2H_2O$/$pTSA{\cdot}H_2O$, which showed an almost complete overlap of the experimental melting points with the theoretical curves with activity coefficients equal to 1. Finally, the two mixtures that gave peculiar profiles, showing a shift in the molar fraction of the experimental melting point but not a lowering of the melting point values were:

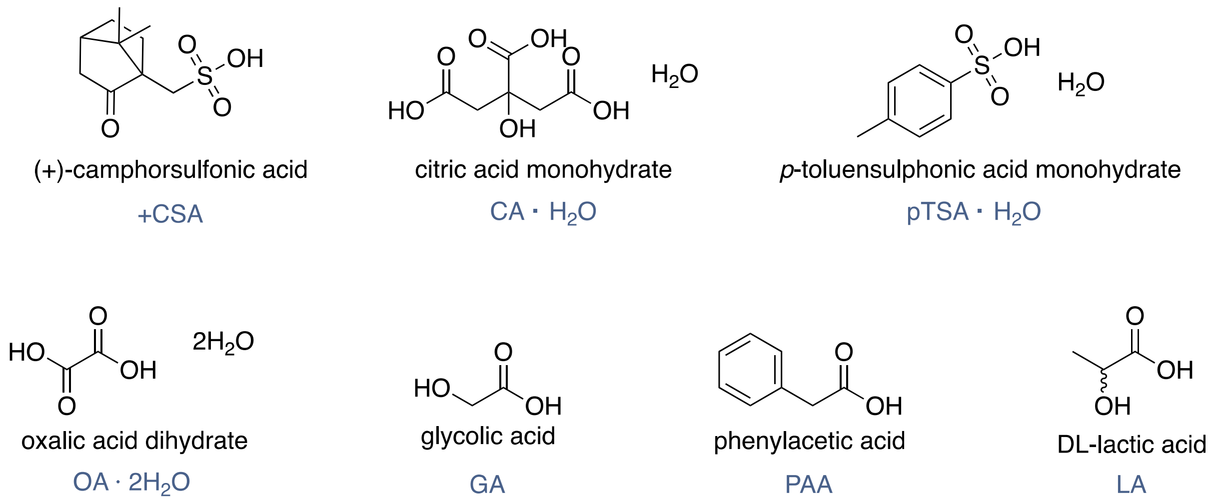


Fig. 1. Structures and acronyms of the Brønsted acids analyzed: (+)-camphorsulfonic acid (+CSA), citric acid monohydrate ($CA{\cdot}H_2O$), *p*-toluensulphonic acid monohydrate ($pTSA{\cdot}H_2O$), oxalic acid dihydrate ($OA{\cdot}2H_2O$), glycolic acid (GA), phenylacetic acid (PAA), DL-lactic acid (LA).

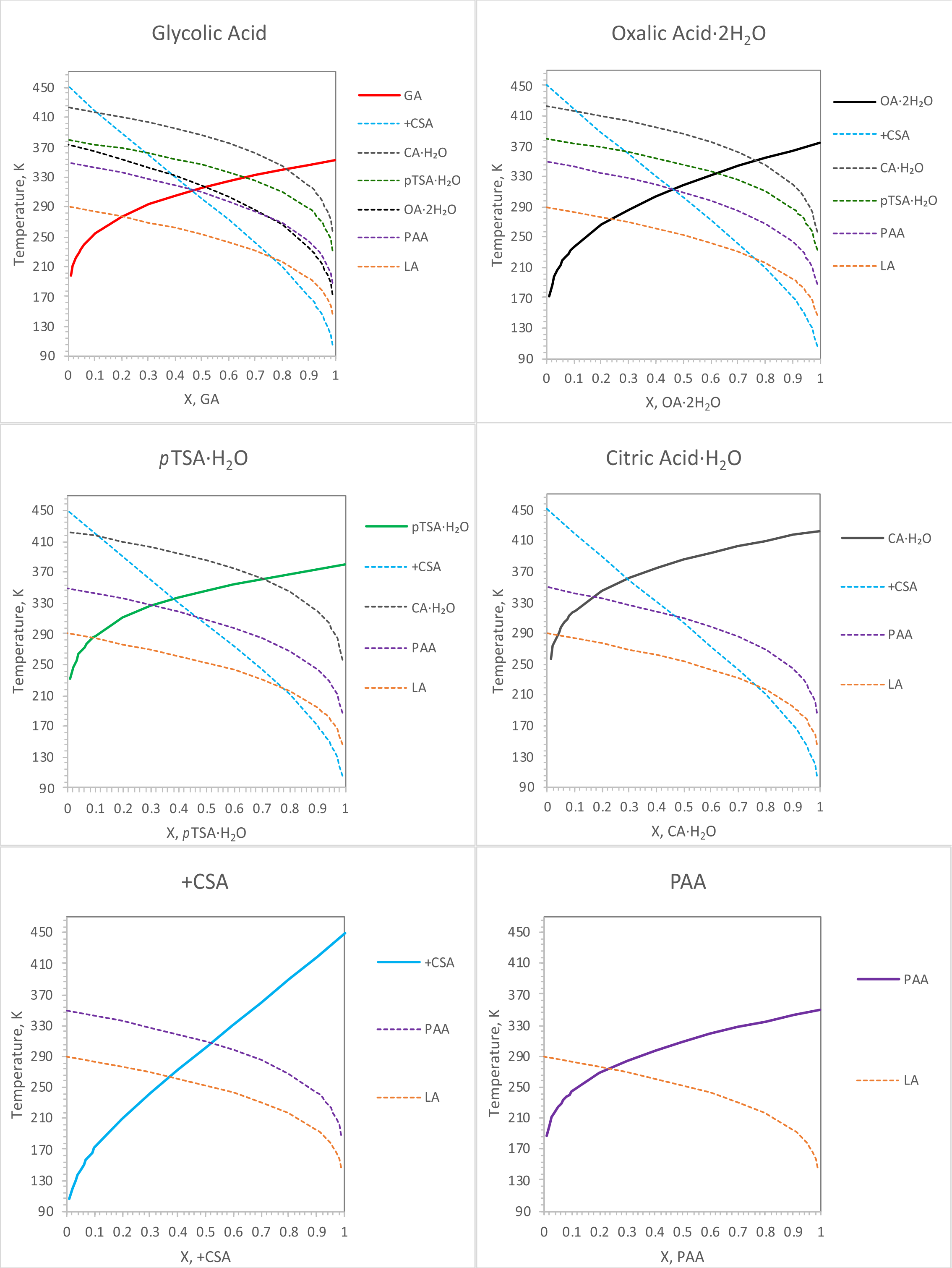


Fig. 2. Theoretical melting point curves comparisons of Brønsted acidic molecules. Top left = GA/other acids; top right = OA·H_2O/other acids; middle left = pTSA·H_2O/other acids; middle right = CA·H_2O/other acids; bottom left = +CSA/other acids; bottom right = PAA/other acids. + CSA = (+)-camphorsulfonic acid; citric CA·H_2O = acid monohydrate; pTSA·H_2O = *p*-toluensulphonic acid monohydrate; OA·$2H_2O$ = oxalic acid dihydrate; GA = glycolic acid; PAA = phenylacetic acid (PAA); LA = DL-lactic acid.

pTSA·H_2O/+CSA and OA·$2H_2O$/+CSA. In Fig. 3 three examples of these mixtures are reported: a DES (GA/pTSA·H_2O), an EM (GA/PAA), and OA·$2H_2O$/+CSA, a peculiar system showing only a shift in the molar fraction of the eutectic; all the profiles are reported in Supporting Information in Fig. S2.

Rogošić and co-workers in a recent work also observed peculiar eutectic systems in which only shifts of the eutectic points were observed [50]; as well as in this work, these mixtures were not identified as DESs because of the lack of the lowering in the melting points values.

Also in the DESs' group, some mixtures resulted unstable over time, giving solid matrixes again after some hours or days at room temperature, even if they showed low melting points. This could be due to a re-

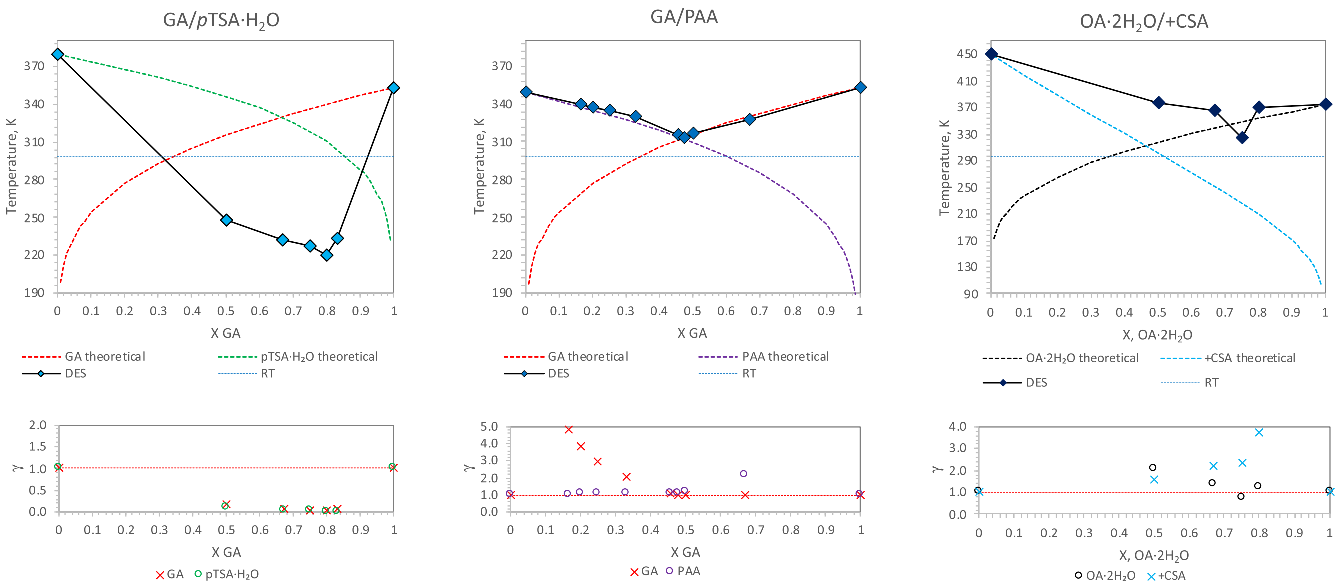


Fig. 3. Comparison of the theoretical melting curves with the experimental melting points for the des identification. left = GA/pTSA·H$_2$O DES: diamonds = experimental melting points, dashed red line = GA theoretical melting point curve, green dashed line = pTSA·H$_2$O theoretical melting point curve, blue dashed line = room temperature, red crosses = GA activity coefficients, green circles = pTSA·H$_2$O activity coefficients; CENTER = GA/PAA Eutectic Mixture (EM): diamonds = experimental melting points, dashed red line = GA theoretical melting point curve, purple dashed line = PAA theoretical melting point curve, blue dashed line = room temperature, red crosses = GA activity coefficients, purple circles = PAA activity coefficients; RIGHT = OA·2H$_2$O/+CSA system: diamonds = experimental melting points, dashed black line = OA·2H$_2$O theoretical melting point curve, light blue dashed line = +CSA theoretical melting point curve, blue dashed line = room temperature, light blue crosses = PAA activity coefficients, black circles = OA·2H$_2$O activity coefficients. + CSA = (+)-camphorsulfonic acid; pTSA·H$_2$O = p-toluensulphonic acid monohydrate; OA·2H$_2$O = oxalic acid dihydrate; GA = glycolic acid; PAA = phenylacetic acid (PAA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

organization or crystallization of the molecules inside the liquids giving again solid adducts, therefore leading to a solidification of the samples. In this set, GA/pTSA·H$_2$O and GA/+CSA DESs showed a peculiar behavior as they can remain liquid at room temperature for weeks if left still, but once stirred at room temperature they become solids. Those mixtures were heated again, also with a microwaves source, to try a better and deeper propagation of the heat inside the samples, but they solidify whenever mixed again. Considering the structural role of water inside a DES at low percentages and also considering that almost all of these mixtures are made with molecules that possess structural water (so they can be properly considered ternary mixtures), we added equivalents of water to the liquids to push forward to the liquid status of the DESs. Some of the mixtures did not properly liquify adding also three equivalents of water, while on the contrary the mixtures GA/pTSA·H$_2$O and GA/+CSA gave stable liquids at room temperature that remained liquids for months after their realization whenever water was added.

In Table 1 all the prepared mixtures and the workflow made for the realization of the novel liquids are reported.

Table 1

Novel DESs realization: Binary Combination = molecules forming the mixture; Liquid Mixture = liquid status of the mixtures at room temperature in at least one point of molar ratios spanning from 7/1 to 1/7; Liquid Identity = DES, ES or Xi shift identity via comparison of experimental melting points with theoretical curves; Stable at RT = liquid stability after days at room temperature and after stirring; Stable at T > 60 °C = liquid stability at temperatures higher than 60 °C; Stable by H$_2$O addition = stability at room temperature after addition of equivalents of water; DES Eutectic Point Molar Ratio = final composition of the stable DES at RT.

Binary combination	Liquid mixture	Liquid identity	Stable at RT	stable at T > 60 °C	Stable by H$_2$O addition	DES eutectic point molar ratio
GA/+CSA	**yes**	**DES**	*no*	*no*	**yes 2.5 eq.**	**GA/+CSA/H$_2$O – 5/1/2.5**
GA/CA·H$_2$O	**yes**	**DES**	*no*	**yes**	no	**–**
GA/pTSA·H$_2$O	**yes**	**DES**	*no*	**yes**	**yes 2 eq.**	**GA/pTSA/H$_2$O – 4/1/3**
GA/OA·2H$_2$O	**yes**	**DES**	*no*	*no*	*no*	–
GA/PAA	**yes**	EM	*no*	**yes**	*no*	–
GA/LA	*no*	–	–	–	–	–
OA·2H$_2$O/+CSA	**yes**	Xi shift	*no*	*no*	*no*	–
OA·2H$_2$O/CA·H$_2$O	**yes**	**DES**	*no*	**yes**	*no*	–
OA·2H$_2$O/pTSA·H$_2$O	**yes**	EM	*no*	*no*	*no*	–
OA·2H$_2$O/PAA	*no*	–	–	–	–	–
OA·2H$_2$O/LA	*no*	–	–	–	–	–
pTSA·H$_2$O/+CSA	**yes**	Xi shift	*no*	*no*	*no*	–
pTSA·H$_2$O/CA·H$_2$O	**yes**	**DES**	**yes**	–	–	**pTSA·H$_2$O/CA·H$_2$O – 1/2**
pTSA·H$_2$O/PAA	*no*	–	–	–	–	–
pTSA·H$_2$O/LA	*no*	–	–	–	–	–
CA·H$_2$O/+CSA	**yes**	**DES**	**yes**			**CA·H$_2$O/+CSA – 3/1**
CA·H$_2$O/PAA	*no*	–	–	–	–	–
CA·H$_2$O/LA	*no*	–	–	–	–	–
+CSA/PAA	*no*	–	–	–	–	–
+CSA/LA	*no*	–	–	–	–	–
PAA/LA	*no*	–	–	–	–	–

The water addition to a DES liquid can have peculiar effects, in particular low percentages (generally lower than about 17–20 % w/w) can have a structural role by directly participating into the H-bond network of the liquid system giving ternary systems [18,51–54]. The structural role of water can be measured by the study of ionic conductivity profiles of the water dilution of a DES. A first part with a lower slope and then an inflection point is commonly observed in this first region of the profiles, indicating the participation of the water in the DESs' structures [52]. In order to verify the role of the added water in the GA/pTSA·H_2O and GA/+CSA mixtures, a measure of the ionic conductivity of these mixtures with different water additions (from 5 % to 95 % w/w) was made. In Fig. 4 the two ionic conductivity profiles of the water dilutions of GA/pTSA·H_2O and GA/+CSA DESs are reported.

The ionic conductivity profiles of the water dilutions of the DESs GA/pTSA/H_2O and GA/+CSA/H_2O showed the typical bell-shaped profiles with the maximums corresponding to the aggregations of the systems as reported in the literature for other DESs systems. However, contrary to what observed with other DESs, the first part at low water additions showed a really lower slope. This can be attributed to an intimate participation of the water in the DESs structure. If it was not so, the protonation of water by the acidic components could have led to the presence of protons in the systems, which are really mobile and therefore an increment of the overall ionic conductivity. The low values observed, on the contrary, suggest the participation of the water in the DESs structures, leading to ternary systems acid/acid/water. This is also suggested by the amounts of water that are at integers of molar ratios with the other acid compounds and can be considered parts of the systems rather than solvents for the counterparts.

Generally, in a DES one of the molecules is considered as HBD and the other one as HBA [55]. In these novel mixtures, the pKa values of the forming molecules can suggest these roles, but the presence of water and the ternary nature of the systems made impossible to identify them. However, even if the HBD role has importance in themes such as the hydrophobicity of the resulting liquids, in these liquids it is not relevant (all the molecules of the resulting liquids are hydrophilic) and could need a deeper and out-of-focus study, surely not appropriate for this work.

3.2. Thermal stability of double Brønsted acidic DESs

The thermal stability of the novel double Brønsted acidic DESs was evaluated via thermogravimetric analyses that determined the temperature at which the liquids started thermically decomposing with the slope changes in the weight % vs. temperature curves. The TGA thermograms are reported in Fig. 5, in Supporting Information all the single curves with the derivatives are reported.

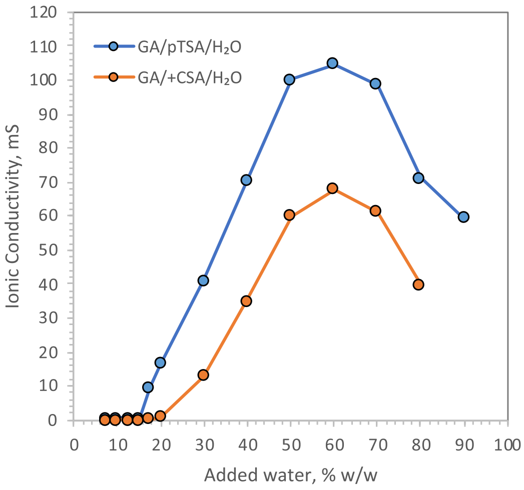


Fig. 4. Ionic Conductivity profiles of the water dilutions of the GA/pTSA/H_2O (blue dots) and GA/+CSA/H_2O (orange dots) DESs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The DESs that did not need water addition for their liquid status (CA·H_2O/+CSA and pTSA·H_2O/CA·H_2O) showed a superior thermal stability compared to the other two that needed additional water (GA/+CSA/H_2O and GA/pTSA/H_2O). CA·H_2O/+CSA DES showed the first step of degradation at about 150 °C while pTSA·H_2O/CA·H_2O liquid showed a first slight decrement in the weight just before 100 °C (maybe due to water loss) and then a steep decrease at about 120 °C. The two DESs with added water GA/+CSA/H_2O and GA/pTSA/H_2O showed a differently shaped thermal degradation. GA/+CSA/H_2O showed a monotonic decrease starting at about 75 °C where about 5 % in weight was lost, then a decrease of about 50 % of its weight by increasing by much the temperature (until about 200–250 °C). GA/pTSA/H_2O showed a starting thermal degradation at about 75 °C with a first step and then a decrease until 200–250 °C. Similar trends, with similar values of starting degradation points, were observed in TGA analyses performed with water-based DESs [45], so these profiles could be related to the water loss from the systems.

3.3. Use of double Brønsted acidic DESs in organic transformations

DESs can exibit catalytic properties when formed by catalytic molecules, with peculiar mechanisms that depend on the association constant of the forming substances [35,39]. In this study, all components of the liquids can act as catalysts, as both are Brønsted acids. Moreover, water, a constituent of these systems, can be partially protonated and act as an additional acid catalyst. In the final part of this work, we briefly explored, as a "proof of concept", the activity of our novel double-acidic DESs as "active" media for potential application in synthetic organic chemistry without delving into the catalysis mechanisms, which are beyond the scope of this study and deserve a separate investigation. In particular, we focused on the activity of the glycolic acid-based double-acidic DESs (GA/pTSA/H_2O and GA/+CSA/H_2O) as in a couple representative organic transformations. The citric acid-based novel mixtures (pTSA·H_2O/CA·H_2O and CA·H_2O/+CSA) were not tested in this work due to the well-known reducing properties of the citric acid itself, that could act in a different and peculiar way in chemical transformations [56]. Therefore, they deserve a stand-alone work about them that is currently in progress in our laboratories. We selected two model reactions that are usually performed in the presence of a Brønsted-acidic

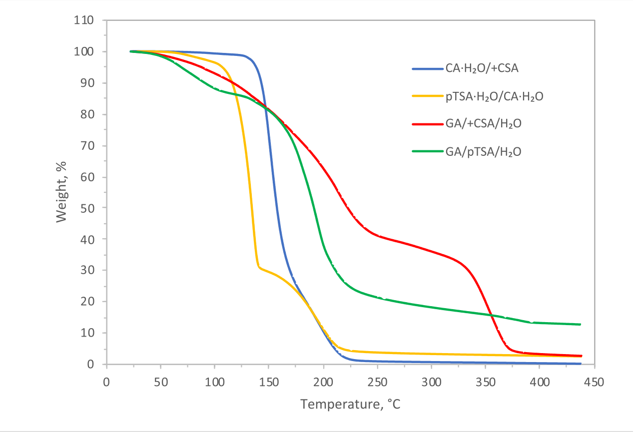


Fig. 5. Thermogravimetric analyses (TGA) of the double-Brønsted acidic DESs: CA·H_2O/+CSA (blue line); pTSA·H_2O/CA·H_2O (yellow line); GA/+CSA/H_2O (red line); GA/pTSA/H_2O (green line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

catalyst and/or a transition metal catalyst, i.e. the aldol condensation and the indole synthesis.

Thus, we tested our DESs as promoters for acidic-catalysed aldol-type condensation reactions. Aldol condensation by reaction between two carbonyl compounds is a powerful and well-known C–C bond formation strategy [57,58]. In particular, the Claisen–Schmidt [59] variant is a useful tool to obtain conjugated enones in a single step. We have already demonstrated the effectiveness of a different CSA-based DES in promoting this reaction [60]. Thus, we were interested in evaluating and comparing the activity of our new double-acidic DESs. The results are detailed in Table 2.

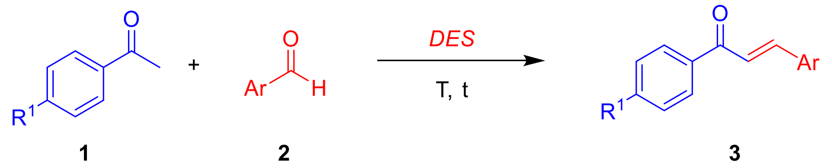
Among the two double-acidic DES tested, GA/+CSA/H_2O gave the best results. The reactions on the model substrates (benzaldehyde **2a** and 4′-methylacetophenone **1a**) at 70 °C under traditional heating gave the corresponding chalcone derivative **3a** with the same yields (68 %) in the same reaction time (6 h) (Table 2, entries 1 and 2). By increasing the temperature to 90 °C, the reactions are complete in half time (Table 2, entries, 3 and 4), but GA/pTSA/H_2O gave the desired product **3a** in lower yield in a dirtier reaction crude (Table 2, entry 3), whereas GA/+CSA/H_2O provided **3a** in excellent yields in a cleaner reaction crude (Table 2, entry 4). Consequently, the scope of the approach was investigated in GA/+CSA/H_2O at 90 °C (Table 2, entries 5–11). The substitution in every position of the phenyl ring of the benzaldehyde with different halides as inductive EWGs was well tolerated and the corresponding chalcones **3b-d** were obtained in yields ranging from very good to excellent (Table 2, entries 5–7). Heteroaromatic aldehydes were tolerated as well despite a reduction of yields was observed, and the condensation products **3e-f** were obtained in only 47 and 57 % yields, respectively (Table 2, entries 8–9). Finally, the presence of a halide in the para position of the phenyl ring of the acetophenone **1** did not hamper the reaction, and the corresponding products **3 g-h** were obtained in good yields (Table 2, entries 10–11). Also in this reaction, the double role of the DES (solvent + catalyst) is essential to the outcome of the transformation. For comparison with the other +CSA-based DES, the result of the related condensation of benzaldehyde with acetophenone, performed in the +CSA/SB3-Cy DES reported in our previous study[60], is shown in entry 12. This DES is characterized by the presence a non-protic sulfobetaine as a counterpart: SB3-Cy (3-(cyclohexyldimethylammonio)propane-1-sulfonate). In this case, at the same temperature (90 °C) longer reaction times were required (16 h) to obtain the desired product **3l** in 67 % yield.

To further explore the possible synergistic effect of the double-acidic DES system, the model reaction was also performed in two well-known acidic DESs with choline chloride as counterpart, i.e. ChCl/pTSA and ChCl/MA (ChCl = choline chloride; MA = Malonic Acid) (Table 2, entries 13 and 14). Reactions were performed under the best reaction conditions identified for each system, and compared considering the similitude of at least one acidic component. The complete failure of the reaction in ChCl/MA confirmed the need for at least one strong acidic counterpart in the DES system (Table 2, entry 14). Interestingly, the reaction in ChCl/pTSA displayed the same performance obtained with GA/pTSA/H_2O (Table 2, entry 1 vs entry 14). Nevertheless, the yields are always lower with respect to those obtained with the best double acidic system selected for this purpose (Table 2, entry 4 vs entry 14).This behaviour suggests that the right combination of DES constituents may strongly influence the reaction outcome.

As mentioned above, aldol condensation has been widely studied in the literature in a wide range of different conditions and with different catalysts [61], therefore a direct comparison of the results is quite difficult and can lead this work out of focus. Commonly the acid-catalysed Claisen-Schmidt reaction can be realized by the use of sulfuric, boric or citric acids, acidic resins, or also nature-derived catalysts such as bamboo-derived acidic catalyst [62]. Most of them, however, show longer reaction times (about 24 h) and higher temperatures (120 °C) compared to these protocols with the use of double Brønsted-acidic DESs catalysts that represent a promising reaction media/catalyst for this relevant organic transformation. Also the use of acidic Ionic Liquids was explored for this transformation. Also in these cases a direct comparison is quite difficult, but ionic liquids usually have more troublesome preparation and handling and widely known Ionic Liquids (such as imidazolium-based ones) showed longer times and higher temperatures [63].

Subsequently, we were intrigued to investigate the activity of our double acidic DESs as mimics of transition metal catalysts to prepare aromatic heterocycles by intramolecular reactions of arylalkynes bearing a proximate nucleophile. 2-Alkynylanilines are versatile substrates for the synthesis of nitrogen-containing heterocycles [64], and in connection with our interest in their synthesis starting from these

Table 2
Claisen-Schmidt reactions in double-acidic DESs.



Entry[a]	1	R^1	2	Ar	DES	T (°C)	t *(h)*	3	3 Yield %[b]
1	**a**	H	**a**	4-Me-Ph	GA/pTSA/H_2O	70	6	**a**	68
2	**a**	H	**a**	4-Me-Ph	GA/+CSA/H_2O	70	6	**a**	68
3	**a**	H	**a**	4-Me-Ph	GA/pTSA/H_2O	90	3	**a**	60[c]
4	**a**	H	**a**	4-Me-Ph	GA/+CSA/H_2O	90	3	**a**	**90**
5	**a**	H	**b**	4-F-Ph	GA/+CSA/H_2O	90	2	**b**	95
6	**a**	H	**c**	3-Cl-Ph	GA/+CSA/H_2O	90	3	**c**	76
7	**a**	H	**d**	2-Br-Ph	GA/+CSA/H_2O	90	2	**d**	100
8	**a**	H	**e**	4-Pyridinyl	GA/+CSA/H_2O	90	3	**e**	47
9	**a**	H	**f**	2-Thiophenyl	GA/+CSA/H_2O	90	2	**f**	57
10	**f**	F	**a**	4-Me-Ph	GA/+CSA/H_2O	90	3	**g**	77
11	**c**	Cl	**a**	4-Me-Ph	GA/+CSA/H_2O	90	1	**h**	100
12	**a**	H	**i**	Ph	+CSA/SB3-Cy	90	16	**l**	67[d]
13	**a**	H	**a**	4-Me-Ph	ChCl/pTSA	70	6	**a**	67
14	**a**	H	**a**	4-Me-Ph	ChCl/MA	90	3	**a**	N.R.

[a] Reaction conditions: 0.2 mmol (**1a-c**), 0.24 mmol (**2a-f**), 0.5 mL DES. [b] Yields referred to pure isolated products.

[c] Together with several unidentified by-products detected by TLC of the crude.

[d] literature data; SB3-Cy = 3-(cyclohexyldimethylammonio)propane-1-sulfonate [60].

versatile substrates [65–68], we briefly evaluate the possibility of using our double acidic DESs for the synthesis of the indole nucleus [69]. Different methodologies have been proposed for preparing N-free and N-protected indoles starting from 2-alkynylanilines [70], including base-promoted cyclizations [71–73] and many protocols involving transition metal-catalysed processes. Among them, the most investigated are Pd-, Cu-, Ag-, and Au- catalysed cyclizations [65,74–77]. Conversely, to the best of our knowledge, there are no effective protocols in the literature that involve the use of simple Brønsted-acid catalysis. We were pleased to find that our double acidic DESs demonstrated to be able to promote also this tricky transformation, albeit the product was obtained in moderate yields. The more representative results of this screening are disclosed in Table 3.

It is worth noting that the two DESs used in this transformation displayed a different behavior. When 4-methyl-N-(2-(phenylethynyl) phenyl)benzenesulfonamide **4** was heated by traditional heating at 80 °C in GA/pTSA/H_2O DES for 24 h, 2-phenyl-1H-indole **5** was isolated as main product in 44 % yield (Table 3, Entry 1). In contrast, under the same conditions in GA/+CSA/H_2O DES the corresponding *N*-protected 2-phenyl-1-tosyl-1H-indole **6** was isolated in 27 % yield (Table 3, Entry 2). Thus, GA/pTSA/H_2O seemed to be the DES of choice for a cyclization/N-deprotection domino process. A slight temperature rise only allowed a reduction of the reaction times (Table 3, Entry 3). We tried to improve the yields by moving to a more effective heating system, such as dielectric heating, but the only advantage observed was the reduction of the reaction times in the face of a small decrease in yields (Table 3, Entries 4 and 6). On the other hand, the reaction in GA/+CSA/H_2O DES under microwave heating failed (Table 3, Entry 5). Each attempt to improve the reaction yields was unsuccessful, because, as expected, the hydration of the alkyne was a competitive path, and the corresponding ketone arising from the hydration of the triple bond was always detected as the main by-product. For comparison with other DESs containing a single acidic component, the reaction was performed in ChCl/pTSA and ChCl/MA (Table 3, entries 7 and 8) under the optimal reaction conditions. The reaction in ChCl/pTSA gave the desired product in lower yield (31 % vs 41 %, cfr. Table 3, entries 7 and 6), whereas ChCl/MA was found to be unsuitable for promoting this reaction.

4. Conclusions

The predictive approach based on the comparison of the theoretical melting curves permitted to successfully obtain novel, peculiar, and also surprising DESs mixtures, that is the case of double Brønsted-acidic DESs. The same theoretical approach was already used in another recent work and permitted in that case to filter out molecules in a set to be tested for novel DESs realization [78]; in this case, this approach allowed to obtain peculiar mixtures by including molecules to be tested in a set. These novel DESs can be reasonably considered ternary systems because of the water present in the mixtures in integers of molar units; this is because of the water present in the forming molecules and/or added to the systems to give them stability. Some of the mixtures, in fact, gave liquids but unfortunately tend to re-solidify; ionic conductivity measures, however, identify the mixtures as DESs even with small amounts of added water considering its role in the structures of the DESs systems.

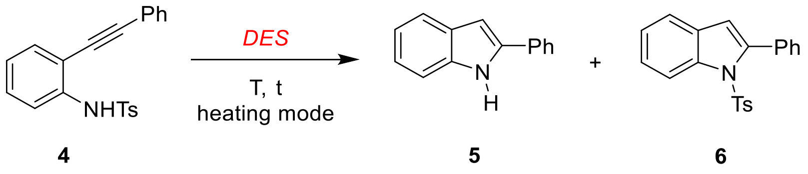
The double Brønsted-acidic DESs were then successfully used as active catalytic reaction media in the Claisen-Schmidt aldol condensation of aldehydes to ketones, showing better results than the ones obtained with acidic DESs formed by the same acidic molecules but with other HBA components. Finally, even if with not so high yields, the indoles synthesis via cyclization of alkynes was successfully made without any metal catalyst, but only exploiting the Brønsted-acidic features of the reaction media for the first time to our knowledge.

The results obtained in this work open up for novel DESs realization with the same predictive approach as well as for the use in acid-catalysed chemical transformations of this novel effective class of double Brønsted-acidic Deep Eutectic Solvents. Moreover, this innovative class of liquids could also be useful in many other topics such as for example: electrolytes, fuel-cell applications, biodiesel synthesis, electrodeposition of metals and so on [79].

CRediT authorship contribution statement

Alejandro Torregrosa-Chinillach: Methodology, Investigation, Conceptualization. **Alessandra Gritti:** Investigation. **Elisa Brambilla:** Investigation. **Dominica Del Grosso:** Investigation. **Elison Lepore:** Methodology, Investigation. **Diego A. Alonso:** Writing – review & editing, Validation, Funding acquisition. **Rafael Chinchilla:** Writing – review & editing, Validation, Funding acquisition. **Giorgio Abbiati:** Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Matteo Tiecco:** Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Funding acquisition, Formal analysis, Data curation.

Table 3
Synthesis of indole in double-acidic DESs.



Entry[a]	DES	T (°C)	Heating	t *(h)*	5 Yield %[b,c]	6 Yield %[b,c]
1	GA/pTSA/H_2O	80	Oil bath	24	44	–
2	GA/+CSA/H_2O	80	Oil bath	24	–	27
3	GA/pTSA/H_2O	90	Oil bath	4	45	–
4	GA/pTSA/H_2O	80	MW	0.25	37	–
5	GA/+CSA/H_2O	80	MW	1	–	–
6	GA/pTSA/H_2O	80	MW	2	41	–
7	ChCl/pTSA	80	MW	2	31	–
8	ChCl/MA	80	MW	2	N.R.	–

[a] Reaction conditions: 0.2 mmol (**4**), 0.5 mL DES.

[b] Yields referred to pure isolated products.

[c] Due to the presence of water in the DESs, the reaction always gave not negligible amounts (15–35 %) of the corresponding ketones arising from the hydration of the triple bond.

Declaration of competing interest

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.

Acknowledgements

This work has been funded by: NGEU – PNRR, DM 117/2023 (Elison Lepore's scholarship). Alejandro Torregrosa-Chinillach was visiting researcher at ChIP Research Center (University of Camerino, Italy) under financial support from Banco Santander and the University of Alicante (Code: 70304B0001).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2025.127110.

Data availability

Data will be made available on request.

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