

DBS-Based Eutectogels: Organized Vessels to Perform the Michael Addition Reaction**

Carla Rizzo,^[a] Salvatore Marullo,^[a] Maurizio Benaglia,^[b] and Francesca D'Anna^{*,[a]}

Supramolecular eutectogels were obtained from the gelation of 1,3:2,4-dibenzylidene-D-sorbitol (DBS) in cholinium chloride-based deep eutectic solvents (DES), differing for the nature of the hydrogen bond donor. Ethylene glycol, diethylene glycol, triethylene glycol, glycerol and urea were tested. Soft materials were fully characterized, determining critical gelation concentration, gel-sol transition temperatures and mechanical properties. Furthermore, to have information about the organization of the gelator in the tridimensional network, resonance light scattering, circular dichroism and microscopy investigations were performed. Eutectogels were used as organized "vessels" to perform the L-proline catalyzed Michael addition reaction.

The probe reaction was carried out in gel phase and in DES solution. Data collected shed light on the effect that gel microenvironment exerts on the outcome of the reaction. In general, gel phases allowed having comparable or even better results than the ones collected in DES solution, with better results obtained in soft materials with the highest organization, as accounted for by the presence of larger aggregates and the occurrence of stronger intermolecular interactions. In turn, this accounts also for the effect of substrates structure that indicates that better yields could be obtained in the presence of more flexible nucleophile and dienones, having more extended π -surface.

Introduction

Catalysis in organized reaction media is currently a topic of great interest, thanks to the possibility of providing confined spaces that for their size, shape and electronic distribution might prove suitable to promote the outcome of a given reaction.^[1] In this context, organized reaction media offer a plethora of different systems, as they range from liquid phases to soft and hard materials.

As for liquid phases, in the last decades, a significant role has been played by ionic liquids (ILs) and deep eutectic solvents (DES). These are non-conventional solvents, frequently claimed as benign alternatives to organic solvents, thanks to their low vapor pressure and flammability.^[2] However, if analyzed from a

structural point of view, they are featured by highly organized lattices, that for ILs are held by a combination of different non-covalent interactions, like Coulomb and van der Waals interactions, as well as hydrogen bond.^[3] This latter becomes the leading interaction in the case of DES, that are obtained from the combination of an hydrogen bond donor with an hydrogen bond acceptor.^[4] In general, DES of Type III are the ones largely used, in which the hydrogen bond acceptors are represented by organic salts, whereas the hydrogen bond donors can be alcohols, carboxylic acids and so on.^[4] These eutectic mixtures exhibit physicochemical and toxicity properties completely different from pristine components and, similarly to ILs, their properties can be tuned for a specific application by simply changing the components nature.

ILs and DES have been widely used as solvents to perform classical organic reactions and, in many cases, significant improvements in terms of reaction rates, temperature, yield and selectivity have been detected.^[5]

Among hard materials, covalent organic frameworks (COF) and metal organic frameworks (MOF) have recently attracted a surge of interest.^[6] These are porous crystalline materials featured by the presence of 2D- and 3D-networks formed by strong covalent bonds (COF) or non-covalent interactions (MOF). Their main advantage, as catalysts, resides in the possibility to exert control on the nature of the catalytic center and their spatial organization.^[7]

Turning the attention to soft materials, supramolecular gels undoubtedly play a pivotal role. They are semi-solid materials obtained from self-assembly process of low molecular weight compounds or polymers and exhibit a tridimensional network, held by non-covalent interactions.^[8] This network is able to trap a large amount of solvent by the action of capillary forces. In general, the gelator represents a very low percentage in weight, frequently lower than 5%.

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[**] DBS = 1,3:2,4-dibenzylidene-D-sorbitol.

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Supramolecular gels are generally classified on the grounds of the different nature of the solvent and classically distinguished in hydro-, organo- and aerogels, when the entrapped phase is water, an organic solvent or a gas.^[9] However, in the last decade, also the possibility to obtain gel phases in non-conventional solvents, like ILs and DES, has been explored.^[10]

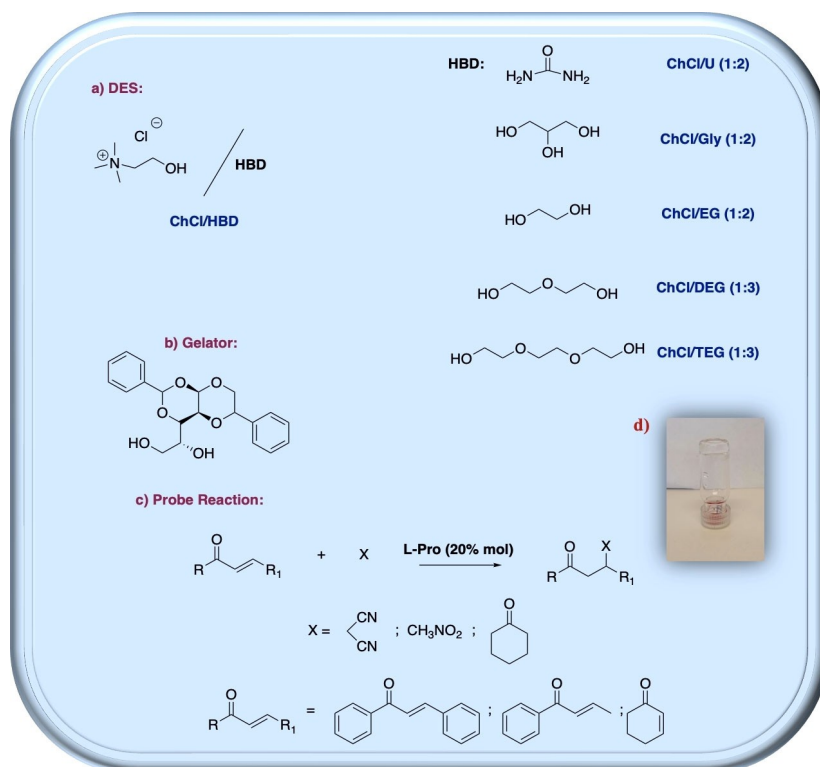
These soft materials, generally indicated as ionic liquid gels and eutectogels, allow conjugating properties of ILs and DES with the one of a semi-solid matrix, like a gel phase. Ionic liquid gels and eutectogels have been applied in different fields, like removal of contaminants,^[11] energy harvesting,^[12] anti-frosting materials,^[13] sensors^[14] and so on.

As far as applications in catalysis are concerned, supramolecular hydro- and organogels have been widely used also as reaction media, performing organocatalytic as well as bio- and photocatalytic processes.^[10c,15] Results reported so far, evidence how in many cases, large improvements in terms of yield and reaction time were obtained with respect to the ones collected in the corresponding organic solvents or water solution. This was mainly ascribed to the significant increase in the local concentration of the catalytic functions induced by gelation.^[16]

Ionic liquid gels and eutectogels have been less explored from the this point of view. However, recently, they have been used to perform asymmetric alcoholysis of the anhydrides^[17] and aldol reaction.^[10c] Data reported shed light on the ability of these reaction media to positively affect the outcome of the target reaction, with respect to the corresponding solutions. Furthermore, a certain relationship has been pinpointed

between the structural features of gel phases and their performance as reaction media.

In the light of the above considerations and in the framework of our interest in studying properties and applications of gels in non-conventional solvent media, in this work, we prepared some supramolecular gels, in DES solution, using 1,3:2,4-dibenzylidene-D-sorbitol (DBS) as gelator (Scheme 1). DBS has been widely used as gelator in water solution^[18] and recently, in IL and DES solution.^[19] As solvents, we used some cholinium chloride-based DES, differing for the nature of the hydrogen bond donor. Besides the largely used urea, glycerol and ethylene glycol, also DES based on diethylene and triethylene glycol were examined, to test the effect that the presence of ether-like bonds in the HBD of the solvent could have on the properties and performance of gel phases (Scheme 1). Properties of eutectogels obtained were analyzed, determining the critical gelation concentration (CGC) and the gel-sol transition temperature (T_{gel}). Furthermore, mechanical features of eutectogels were determined by using rheology measurements. Insights about the structural features of the eutectogels were obtained by recording resonance light scattering (RLS) spectra, to have information about the size of the aggregates featuring the soft materials. On the other hand, to have an idea of the possible tridimensional entanglement, Scanning Electron Microscopy (SEM) investigation was performed. Taking in consideration the chiral and chromophoric nature of DBS backbone, also circular dichroism analysis on both DBS solutions in DES and corresponding gel phases was



Scheme 1. Representation of a) DES, b) gelator, c) probe reaction and picture of gel phase and d) representative picture of eutectogel.

carried out, to understand how gelation process affected the organization of the gelator.

Eutectogels were tested as reaction media to perform the L-proline catalyzed Michael addition of malononitrile to *trans*-chalcone (Scheme 1).

This reaction could be of a certain interest as, being a bimolecular reaction, could give insights on the different factors affecting its outcome in a confined space. Furthermore, it is of great significance as a useful synthetic strategy for the obtainment of intermediate nitriles, able to be further transformed in 4-oxobutamides, frequently featuring many natural and synthetic compounds displaying both pharmacological and biological activity.^[20] Michael addition has been investigated in organic solvents, both as a function of solvent and base nature. Furthermore, it has been also performed in monocationic ILs, both in the presence or without catalyst,^[21] and in the presence of task-specific dicationic ILs.^[22]

In this work, L-proline was used as chiral organocatalyst, to evaluate the effect exerted by the confined reaction media on the stereochemical pathway of the reaction. Reactions were performed in gel phases and, to have a useful comparison, also in the corresponding DES solutions. Finally, to have insights about the effect of the substrate structure, investigations were carried out changing both the nature of dienone as well as the one of the nucleophile. Results collected allow shedding light on the effect that both the features of the gel network as well as structural properties of the reagents can exert on the outcome of the reaction.

Results and Discussion

Firstly, the gelling ability of DBS was tested in different DES solution. For a typical gelation test, the suitable amount of gelator and DES were weighed in a screw capped vial. The suspension was heated for 1 h at 100 °C, under magnetic stirring. Tests were performed in the concentration range 1–6 wt%. In all cases in which a clear solution was obtained, this was left to stand at room temperature overnight. The gel phase formation was assessed by using the tube inversion test.^[23]

Results of gelation tests are reported in Table 1, together with the critical gelation concentration (CGC), *i.e.* the lowest amount of gelator needed to have gel phase formation. Furthermore, Table 1 also shows T_{gel} , *i.e.* the temperature corresponding to gel-sol transition, as determined by using the lead-ball method.^[24]

Analysis of results obtained show a different phase behavior before reaching CGC and consequently gel formation. Indeed, a gel-like precipitate was obtained in presence of ChCl/U and ChCl/DEG, while in the other cases limpid solutions were obtained (Table 1).

In all cases, at the CGC, transparent gels were obtained as can be observed in Scheme 1d. Data collected in Table 1 also evidence the role played by the nature of HBD of DES in determining CGCs. Indeed, taking in consideration hydroxylated HBD, the lowest CGC was detected in ChCl/Gly, featured by the presence of a more efficient HBD with respect to ChCl/EG. On

Table 1. Range of gelator concentration investigated, CGC and T_{gel} values for eutectogels as a function of the different nature of the DES.

DES	DBS			
	Conc. ^[a] (wt %)	Result before gel formation ^[b] (wt %)	CGC ^[b,c] (wt %)	T_{gel} ^[d] (°C)
ChCl/U (1:2)	1–6	PG (1.6)	G (2.0)	80
ChCl/Gly (1:2)	0.5–6	S (0.5)	G (0.9)	78
ChCl/EG (1:2)	1–6	S (1.5)	G (2.4)	61
ChCl/DEG (1:3)	2–7	PG (3.2)	G (4.0)	74
ChCl/TEG (1:3)	2–7	S (3.3)	G (3.8)	70

[a] concentration investigated, (g) gelator/ (g) solution wt. %; [b] result before gel formation obtained from the lowest concentration investigated up to the one reported in brackets: PG = gel-like precipitate, S = soluble, G = gel; [c] Critical gelation concentration; [d] T_{gel} determined with the lead-ball method at CGC values.^[24] T_{gel} values were reproducible within 1 °C.

the other hand, taking in consideration glycol-based DES, namely ChCl/EG, ChCl/DEG and ChCl/TEG, data collected evidence that the presence of ether-like oxygen plays a detrimental effect in the gel formation, as accounted for by the significant increase in CGC values detected on going from EG to DEG and TEG.

Analysis of CGCs as a function of the solvent properties, like hydrogen bond donor ability and solvent viscosity, accounts for a certain role played by the above factors in determining gel phase formation. Indeed, lower CGCs were detected in ChCl/U and ChCl/Gly, featured by the presence of more efficient HBD species. On the other hand, also viscosity plays a role. Indeed, the above DES show higher viscosity values ($\eta = 0.5116$, 0.2468 Pa.s for ChCl/U and ChCl/Gly, respectively)^[25] with respect to the glycol-based DES ($\eta = 0.0591$ Pa.s for ChCl/EG and ChCl/TEG).^[25] A careful analysis of the above data highlights that gelation process is not completely driven by solvent viscosity. Indeed, a lower CGC value was determined in ChCl/Gly with respect to the one obtained in ChCl/U, notwithstanding the lower viscosity, and the same trend can be also evidenced comparing CGC and viscosity values in the case of ChCl/EG and ChCl/TEG. Probably, the above result accounts for a combined action of solvent viscosity and hydrogen bond donor ability of the solvent, with the latter factor also depending on the nature and number of hydrogen bond donor groups.

Similar considerations can be drawn analyzing the trend of T_{gel} values, even if obtained at different gel concentrations. Interestingly, eutectogels with the lowest CGCs (0.9 and 2 wt% for ChCl/Gly and ChCl/U, respectively), show the highest thermal stability. On the other hand, lower T_{gel} were measured in glycol-based DES, even if these gels have larger concentrations (from 2.4 to 4 wt%). The lowest T_{gel} was determined for the eutectogel formed in ChCl/EG at 2.4 wt%. Finally, CGCs being comparable in the case of ChCl/DEG and ChCl/TEG, T_{gel} decreased with the increase in the number of ether-like oxygen atom in the HBD.

On the other hand, solvent polarity does not significantly influence gel properties as ChCl/Gly, ChCl/U, ChCl/EG have

similar polarity values, ($E_{NR} = 209.5, 210.4, 211.9$ kcal/mol respectively),^[26] but the corresponding gels show different CGC and T_{gel} in dependence of the used solvent.

Rheological Investigation

Rheological features of eutectogels were evaluated performing strain and frequency sweep measurements. In the first case, the variation of elastic (G') and viscous moduli (G'') as function of the strain showed the intermediate behavior between solid and liquid materials, typical of gels. Indeed, at low percentages of strain G' is higher than G'' , showing the solid-like behavior, but the increase of strain induced the inversion of moduli at the crossover point (γ). The inversion of moduli is indicative of the transition to liquid-like behavior. The gel-like nature of eutectogels was further confirmed by frequency sweep measurements, in which, at a fixed strain chosen within the linear viscoelastic region (LVR), G' is higher than G'' without any dependence from the frequency. In Figure 1, strain and frequency sweep measurements carried out in the case of DBS/ChCl/U eutectogel are displayed. Plots corresponding to all the other eutectogels are reported in Figure S1.

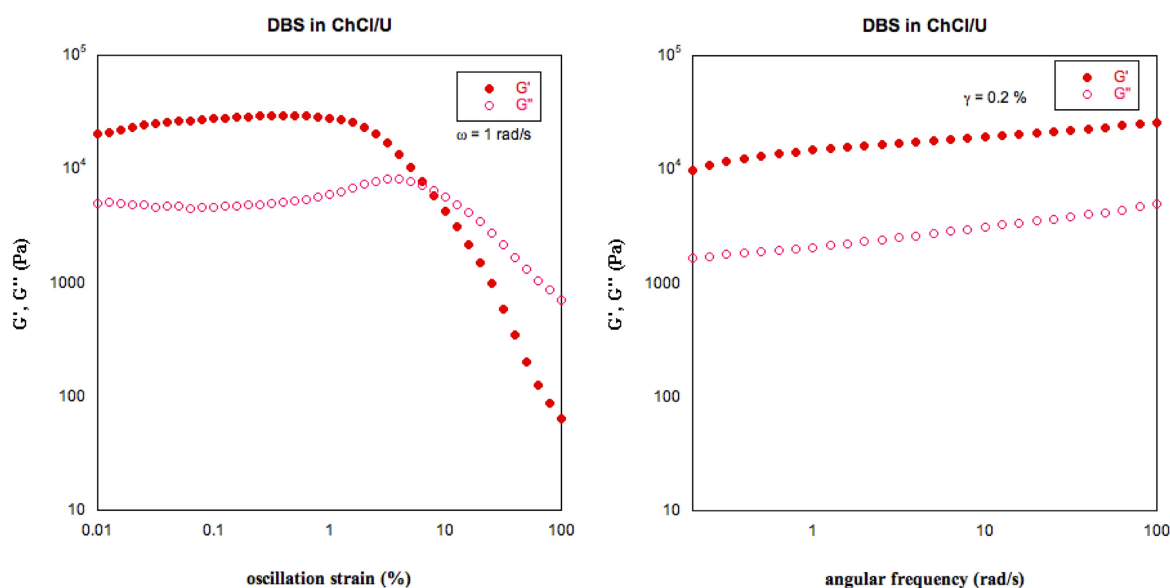


Figure 1. On the left strain sweep of DBS in ChCl/U and frequency sweep on the right.

Table 2. G' and G'' at $\gamma = 0.2\%$, $\tan\delta = G''/G'$ and values of γ at $G'' = G'$ for gels investigated at 25 °C. Error limits are based on average of three different measurements with different aliquots.

Gel	G' (Pa)	G'' (Pa)	$\tan\delta$	Crossover point [%]
DBS in ChCl/U 3 wt %	22000 ± 9000	3400 ± 2000	0.17 ± 0.04	6.289 ± 0.003
DBS in ChCl/Gly 2 wt %	630 ± 180	150 ± 10	0.24 ± 0.03	14 ± 2
DBS in ChCl/EG 4 wt %	54000 ± 18000	11400 ± 5700	0.22 ± 0.03	3.6 ± 0.6
DBS in ChCl/DEG 4 wt %	51400 ± 5500	15000 ± 3000	0.29 ± 0.03	2.2 ± 0.4
DBS in ChCl/TEG 4 wt %	41000 ± 18400	10200 ± 4500	0.253 ± 0.009	2.8 ± 0.5

Resonance Light Scattering

Gel properties were also investigated by using resonance light scattering (RLS) measurements. This technique is used to have information about systems featured by the presence of aggregates formed by chromophores^[27] and allows to have insights on the size of aggregates. Indeed, the intensity of scattered light is related to the above parameter.^[27–28] RLS proved a valuable support in characterizing gel phases. In particular, in the case of gelation processes moderately slow, measurements performed as a function of the time, allowed to have information about gelation mechanism and time needed to have gel phase.^[29] On the other hand, if fast gelation occurred, RLS proved a useful tool to have a measure of the size of the aggregates featuring the soft materials.^[11a]

As eutectogels formed by DBS showed a quite fast gelation process, we directly recorded RLS spectra corresponding to gel phase (Figure 2) and RLS intensities measured at the maximum wavelength are reported in Table 3.

Analysis of results collected gives the following trend for I_{RLS} : ChCl/U > ChCl/Gly ~ ChCl/EG > ChCl/TEG > ChCl/DEG. The largest aggregates were detected for DBS/ChCl/U and this result accounts for both the highest gel-sol transition temperature

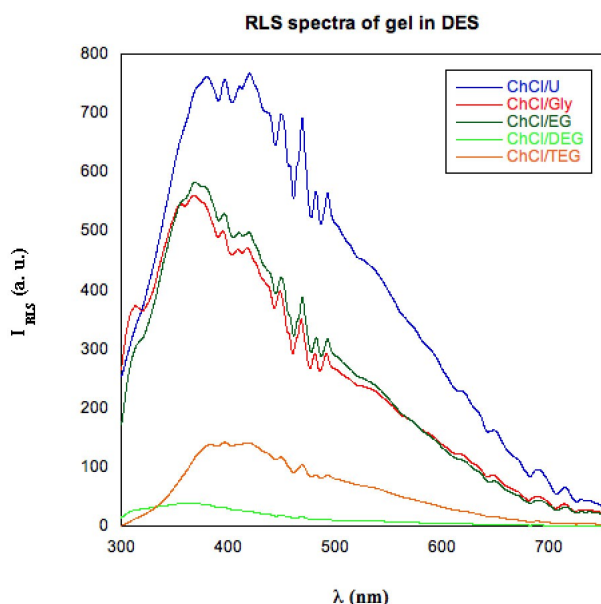


Figure 2. RLS spectra of gel phases formed by DBS as a function of the different nature of the DES.

Table 3. I_{RLS} measured at the maximum wavelength as a function of the different nature of the gel phase.

Gel	I_{RLS}
DBS in ChCl/U 3 wt %	761 a.u.
DBS in ChCl/Gly 2 wt %	558 a.u.
DBS in ChCl/EG 4 wt %	575 a.u.
DBS in ChCl/DEG 4 wt %	38 a.u.
DBS in ChCl/TEG 4 wt %	137 a.u.

detected for this gel, at the CGC, and the lower $\tan \delta$ value, that testifies the occurrence of strong intermolecular interactions in the gel network. Probably, a higher solvent viscosity and higher hydrogen bond donor ability favor the formation of more extended aggregates. Solvent viscosity has been reported to influence the self-assembly process, by impacting on the magnitude of local supersaturation during fibers growth.^[30] This also influences the packing of fibers, leading to change in thermal stability or morphology as a function of solvent viscosity.^[31] As verification, in the case of DBS/ChCl/U, according to a decrease in HBD ability and halving solvent viscosity, with respect to ChCl/U, we detected a significant decrease in I_{RLS} values. On the other hand, considering gels formed in glycol-based DESs, concentration being the same, the decrease in I_{RLS} , going from DBS/ChCl/EG to DBS/ChCl/DEG recalls the corresponding decrease in γ values. The above results probably indicate that the presence of more extended aggregates gives rise to the formation of a stronger and more interdigitated network.

Morphology of eutectogels

To have further insights on the structure of eutectogels, their morphology was investigated by Scanning Electron Microscopy (SEM). SEM images are shown in Figure 3.

Analysis of the above images shows that gels in ChCl/U, ChCl/Gly and ChCl/EG (Figure 3a–d) exhibit showed more extended aggregates than ChCl/DEG and ChCl/TEG (Figure 3e–f). In particular, gels in ChCl/Gly and ChCl/EG were characterized by a fibrous network (Figure 3b–d), while smaller and tangled aggregates with irregular geometry can be observed in the case of gels in ChCl/DEG and ChCl/TEG (Figure 3e–f, S6).

Interestingly, the above differences in morphological features can be related to the size of the aggregates. Indeed, according to I_{RLS} values previously discussed, gel phases featured by the presence of a fibrous network (ChCl/U, ChCl/Gly and ChCl/EG) showed more extended aggregates (I_{RLS} = 771, 558, 575 a.u.; Table 3) with respect to the ones based on spherulitic structural motifs (ChCl/DEG and ChCl/TEG; I_{RLS} = 38, 137 a.u.; Table 3). Furthermore, according to data collected by rheological investigation, these latter soft materials also exhibited the highest $\tan \delta$ and lowest γ values (Table 2), accounting for the occurrence of feebler intermolecular interactions in the tridimensional network.

Circular dichroism

Being formed by a chiral building block, bearing a chromophoric residue, DBS gelator gave polarimetric and UV-vis response. In particular, a 0.36 M solution of DBS in MeOH gave an adsorption band at 250 nm and an optical rotation, at 28.5 °C, equal to $\alpha = 34.7 \pm 0.3$ deg.

On the grounds of the above information, we recorded CD spectra of DBS solution (0.005 M) in MeOH and ChCl/U (Figure 4).

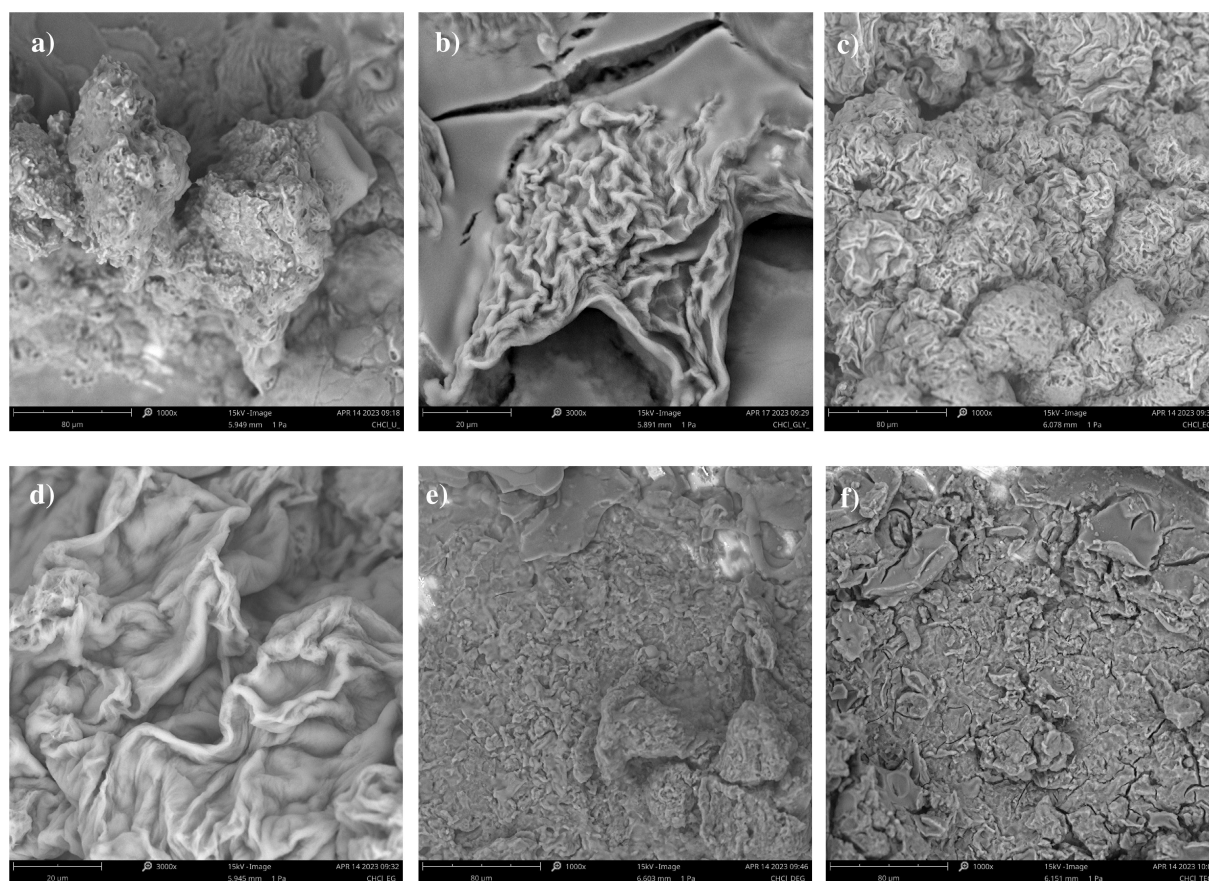


Figure 3. SEM images obtained for: a) DBS/ChCl/U (scale bar: 80 μm); b) DBS/ChCl/Gly (scale bar: 20 μm); c–d) DBS/ChCl/EG (scale bar: 80 and 20 μm); e) DBS/ChCl/DEG (scale bar: 80 μm); f) DBS/ChCl/TEG (scale bar: 80 μm).

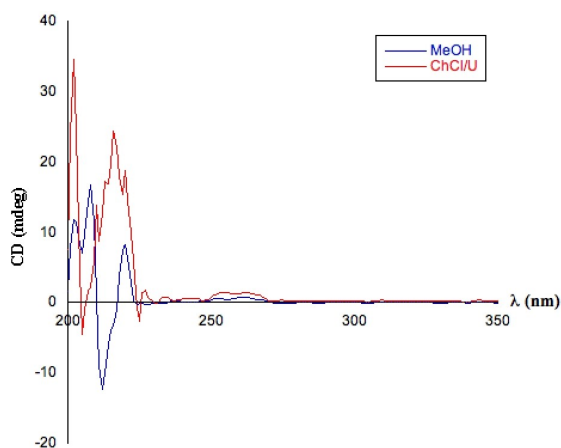


Figure 4. Circular dichroism spectra of DBS in MeOH and ChCl/U at 5×10^{-3} M.

Analysis of the above spectra sheds light on the effect of the solvent nature on the gelator ability to interact with circular polarized light. Indeed, going from MeOH to ChCl/U, a significant change in both position and intensity of CD bands was observed. In general, in DES solution more intense and red-shifted bands were detected.

The entrapment of the gelator in the gel network changed CD spectra, as shown by the comparison between DBS spectra in ChCl/U solution and gel phases (Figure 5).

In the gelatinous network, intense positive CD bands, at 253 and 259 nm, were observed, evidencing the presence of chiral aggregates. The above results perfectly agree with data previously reported in literature about the red shift of circular dichroism bands and increase in ellipticity observed as a consequence of the self-assembly occurring during gelation processes induced by pH or temperature changes.^[9,17]

On the other hand, the different nature of DES also affected CD spectra, as accounted for by the comparison among spectra recorded for all gel phases, as a function of the solvent, at the CGC (Figure S2).

Catalysis of the Michael reaction

The obtained gel phases were tested as organized reaction media to perform the base catalyzed Michael addition of malononitrile to *trans*-chalcone (Scheme 1c). To this aim, 1 eq. of *trans*-chalcone was added to the gel phase together with 2 eq. of malononitrile and 20 mol% of L-Pro. The system was stirred for 15 minutes. Then, it was kept in a minishaker, at 400 rpm, for 24 h at room temperature. At the end of the

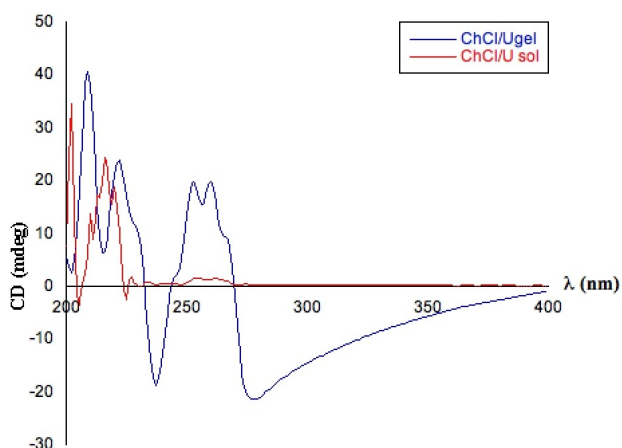


Figure 5. Comparison between circular dichroism spectra of DBS in ChCl/U solution (0.005 M) and DBS/ChCl/U gel (2.0% wt).

reaction time, the reaction mixture was extracted with ethyl acetate, after the addition of a small amount of water. It is noteworthy the fact that the gel phase kept its semi-solid appearance during the reaction and also, after the product extraction (Figure 6).

For a useful comparison, the reactions were also carried out in DES solution, to have insights about the effect that the entrapment of DES in the gel network has on the outcome of the reaction. Conversion and yield values are reported in Table 4.

In all cases, we did not observe stereoselectivity as previously found for other Michael type reactions performed in ILs or eutectogels.^[10c,22] While good enantioselectivity was obtained in DES solutions when chinchona based catalysts in presence of co-catalyst have been used.^[32]

Analysis of results collected evidences the good performance of the catalyst both in DES solution and eutectogels. Indeed, with the only exception of ChCl/Gly and DBS/ChCl/Gly, conversions ranged from 70 up to 100%, whereas yields changed in the range 52–99%. Furthermore, with the only exception (DBS/ChCl/DEG; please see entries 7–8), gel phases exhibit comparable performance to DES solution. However, surprisingly, in two cases (DBS/ChCl/U and DBS/ChCl/EG; see

Table 4. Conversion and yield values collected, for the Michael addition of malononitrile to *trans*-chalcone, both in DES solution and eutectogels at 25 °C and for 24 h.

Entry	Reaction media	Catalyst	Conversion [%] ^[a]	Yield [%] ^[a]	Yield by-product ^[a]
1	ChCl/U (1:2)	L-Pro	71	52	18%
2	gel: DBS/ChCl/U	L-Pro	100	99	–
3	ChCl/gly (1:2)	L-Pro	32	31	–
4	gel: DBS/ChCl/Gly (1:2)	L-Pro	31	29	–
5	ChCl/EG (1:2)	L-Pro	81	81	–
6	gel: DBS/ChCl/EG	L-Pro	94	91	–
7	ChCl/DEG (1:3)	L-Pro	80	80	–
8	gel: DBS/ChCl/DEG	L-Pro	73	70	–
9	ChCl/TEG (1:3)	L-Pro	73	73	–
10	gel: DBS/ChCl/TEG	L-Pro	70	62	–

[a] Conversions and isolated yields were determined after flash chromatography and they were reproducible within 4%, after triplicate runs.

entries 1–2 and 5–6), conversion and yield obtained in gel phases were significantly higher than the ones collected in the corresponding DES solutions. On the other hand, with the only exceptions of ChCl/U and DBS/ChCl/TEG, no significant differences were detected between yield and conversion, accounting for the lack of by-products formation.

In the case of ChCl/U, we observed the formation of a secondary product that, according to previous reports,^[18b] was equal to a monocyanide product deriving from dicyanide through anaerobic oxidation and subsequent base catalyzed elimination reaction. The formation of this product was generally favored by the increase in the basicity of the reaction medium.^[11b] Then, in this case, the obtainment of monocyanide could be ascribed to the higher basicity of ChCl/U with respect to other DES.

In DES solution, yields change along the following trend: ChCl/Gly < ChCl/U < ChCl/TEG < ChCl/DEG ~ ChCl/EG. To explain the above trend, we took in consideration different solvent features, like viscosity, basicity and hydrogen bond donor ability.

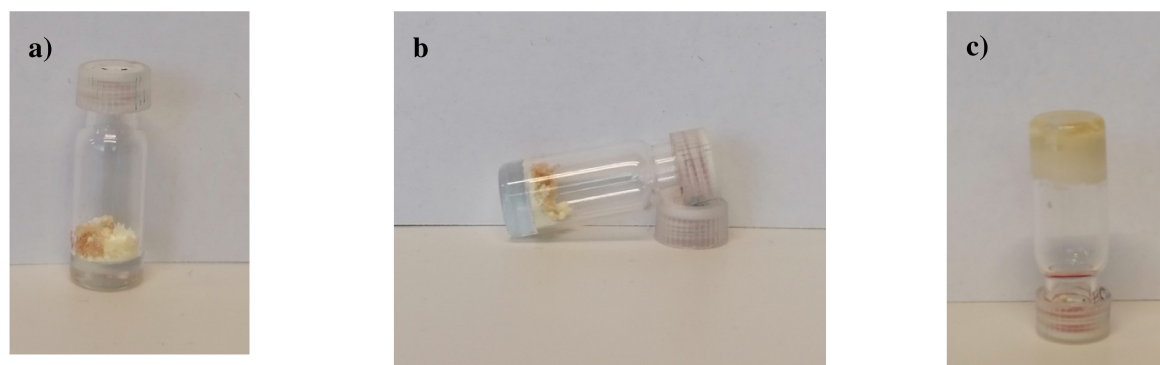


Figure 6. Picture of the gel phase at the beginning of the reaction (a–b) and after 24 h (c).

As for viscosity, the comparison between viscosity and yield trend does not allow to identify a direct relationship. In general, the outcome of the reaction should be disfavored in more viscous solvents, like ChCl/U and ChCl/Gly. However, while the lowest yield was collected in ChCl/Gly, the highest one was obtained in ChCl/U that also exhibited the highest viscosity ($\eta = 0.5116$ and 0.2468 , for ChCl/U and ChCl/Gly, respectively).^[25]

To have insights about DES basicity, we took in consideration the dissociation process of an acidic probe in DES solution. To this aim, we recorded UV-vis spectra of *p*-nitrophenol in DES solution (Figure S3). Comparison among absorption bands evidences the high basicity of ChCl/U solvent system, as indicated by the presence of a band centered 412 nm and corresponding to the adsorption band of *p*-nitrophenate. In all the other cases, the detection of UV-vis band centered at 320 nm accounts for the predominance of *p*-nitrophenol. The above result clearly indicates that despite the target reaction feels the effect of base catalysis, the outcome of the process is mainly driven by the action of the organocatalyst, as accounted for by higher yield values collected in ChCl/TEG, ChCl/EG and ChCl/DEG notwithstanding the significantly lower basicity of the above DES with respect to ChCl/U.

Organocatalytic activity can be influenced also by interactions of organocatalyst and DES,^[33] and data previously discussed about circular dichroism investigation infer for a strong interaction between DES and L-Pro (see above, Figure 5). On the other hand, data previously reported in literature about chiral L-Pro-based DES, demonstrate that the strength of the interaction between L-Pro and HBD counterpart significantly affects the organocatalytic activity of the solvent.^[34] Similarly, in our case, hydrogen bond donor ability of DES might play a significant role. Indeed, a strong solvent-catalyst interaction might reduce the catalyst availability, negatively affecting both yield and conversion values. The above hypothesis perfectly accounts for data collected, as yields significantly increased going from ChCl/U and ChCl/Gly to ChCl/EG, ChCl/DEG and ChCl/TEG, according to the decrease in the number of hydrogen bond donor sites in the HBD component of DES.

In gel phase, yields increase along the trend: ChCl/Gly < ChCl/TEG < ChCl/DEG < ChCl/EG < ChCl/U.

The best catalytic activity was detected in DBS/ChCl/U eutectogel and the obtained result cannot be ascribed to a higher basicity of L-Pro in gel phase. Indeed, as recently reported by some of us, this parameter does not significantly change on going from an L-Pro solution in ChCl/U to L-Pro-based eutectogel in ChCl/U.^[10c]

In the attempt to correlate catalytic performance of eutectogels to their structural features, we observed that this gel showed the highest T_{gel} and the lowest γ values, that accounts for a more thermally stable and rigid network featured by the occurrence of stronger intermolecular interactions. Furthermore, the above eutectogel was the one featured by the presence of larger aggregates, as accounted for by I_{RLS} values (Table 3). Consequently, in gel phase, the target reaction seems to be favored by a rigidification and a more extended organization of the tridimensional network. This result is different from the one we previously obtained by studying the

organocatalyzed alcoholysis of anhydrides in the presence of cinchona alkaloid derivative, in ionic liquid gels.^[17] Indeed, in the above case, the outcome of the reaction was favored by a less rigid network. Differently, the result now obtained is in line with the one recently obtained by some of us, studying the catalytic performance of L-Pro-based eutectogels in the aldol reaction. Indeed, also in that case, a significant increase in the enantiomeric excess was detected in parallel with the increase in structural organization of the tridimensional network.^[10c]

Furthermore, the comparison with data collected in DES solution, and for ChCl/U-base systems, sheds light on the higher yield and conversion values collected in gel phase, indicating that the entrapment of the solvent in the tridimensional network of the gel makes it a weaker HBD, so increasing the availability and, consequently the catalytic ability of L-Pro. In addition, the above effect can be also ascribed to the increase in the local concentration of the catalyst, occurring in the gelatinous network and favoring the outcome of the reaction. To have a further support to the above hypothesis, we recorded FTIR spectra of both DES and gel alone and in the presence of L-Pro (Figures S4–S5). Unfortunately, the very low concentration of the organocatalyst, with respect to the solvent, did not allow detecting significant differences because the signals of L-Pro were completely covered by the one of the DES.

As above stated, in the present case, we did not detect stereoselectivity. To verify if the above lack could be ascribed to a kinetic factor, we performed the process at significantly lower temperatures (4 and -5°C). As in the above experimental conditions the process could not be carried out in the mini shaker, we also performed the reaction, at room temperature in static conditions, to have a meaningful comparison. To this aim, we chose the best performing systems at room temperature, *i.e.* DBS/ChCl/U and DBS/ChCl/EG. Results collected are reported in Table 5.

Analysis of data collected evidences how, in the case of ChCl/U, performing the reaction in static conditions, at room temperature, induces a significant improvement in selectivity (see entry 1 in Table 4 and entry 1 in Table 5). Indeed, in this latter case, the formation of monocyanide derivative of the product was not observed. On the other hand, a significant increase in both yield and conversion was observed ($C=71$ and 84% ; $Y=52$ and 84% in dynamic and static conditions, respectively).

As far as data in DBS/ChCl/U at room temperature are concerned, performing the process in static conditions causes only a minor decrease in both yield and conversion values ($C=100$ and 93% ; $Y=99$ and 90% in dynamic and static conditions, respectively), probably due to a lower diffusion rate of the reagents in the semi-solid matrix, in the absence of stirring.

The above hypothesis was also confirmed by data collected in ChCl/EG-based systems as also in this case the lack of stirring proved more detrimental in gel than in DES solution ($C=81$ and 79% ; $Y=81$ and 77% in dynamic and static conditions in DES solution. $C=94$ and 58% ; $Y=91$ and 58% in dynamic and static conditions in DBS/ChCl/EG).

In the light of the latter result, bearing in mind that, at 4°C , the reaction must be performed in static conditions, we

Table 5. Conversions and yields corresponding to the Michael addition of malononitrile to *trans*-chalcone in DES and eutectogel, in at different temperatures and at 24 h.

Entry	Reaction media	catalyst	T	Conditions	Conversion ^[a]	Yield ^[a]
1	DES: ChCl/U (1:2)	L-Pro	25 °C	static	84	84
2	gel: DBS/ChCl/U	L-Pro	25 °C	static	93	90
3	DES: ChCl/EG (1:2)	L-Pro	25 °C	static	79	77
4	gel: DBS/ChCl/EG	L-Pro	25 °C	static	58	58
5	DES: ChCl/U (1:2)	L-Pro	4 °C	static	33	33
6	gel: DBS/ChCl/U	L-Pro	4 °C	static	78	75
7	gel: DBS/ChCl/U	L-Pro	−5 °C	dynamic	67 ^[b]	64 ^[b]

[a] Conversion and isolated yields were determined after flash chromatography and they were reproducible within 4%, after triplicate runs. [b] Reaction time: 48 h.

evaluated the temperature effect only using ChCl/U-based systems. Interestingly, a decrease in temperature from 25 down to 4 °C, has a major negative effect on the reaction performed in DES solution rather than the one carried out in the gel network. Indeed, while in DES solution the yield decreases from 84 down to 33 %, in gel phase a change from 90 down to 75 % was detected, indicating that the rigidification and the slower mass transport caused by the decrease in temperature exerts a more significant role in solution than on the three-dimensional network of the eutectogel. Unfortunately, also in this case, no *ee* was observed, as well as for the process carried out at −5 °C.

To have more insight about the outcome of the Michael addition in eutectogels, we also investigated the effect of DBS concentration in gels and the different nature of reagents. To this aim, we chose the best performing system, *i.e.* DBU/ChCl/U eutectogel, and, once chosen the best DBS concentration (Table 6), both the nature of the dienone and nucleophile were changed.

Analysis of data demonstrates that the reaction outcome was influenced by gelator concentration in gel, as at CGC concentration (2 wt%) the lowest yield was collected. The increase of DBS concentration caused a concomitant increase in reaction yield as previously observed for some L-Pro based gels,^[10c] that further decreased when the reaction was performed in gel at 4 wt%. This anomalous trend can be explained considering that DBS solubility in ChCl/U is quite limited and the gel at 4 wt% was not as homogeneous as gels at 2 and 3 wt%. Consequently, for these systems it is difficult to

Table 6. Conversions and yields corresponding to the Michael addition of malonitrile to *trans*-chalcone in DES and eutectogel, at 25 °C, for 24 h and at 400 rpm.

Entry	Reaction media	DBS (wt %)	Conversion [%] ^[a]	Yield [%] ^[a]
1	gel: DBS/ChCl/U	2	57	54
2	gel: DBS/ChCl/U	3	100	99
3	gel: DBS/ChCl/U	4	68	66

[a] Conversion and isolated yields were determined after flash chromatography and they were reproducible within 4%, after triplicate runs.

assert the correlation between gelator concentration and reaction yield.

Based on the above results, processes aimed at evaluating the effect due to the nature of reagents were carried out by using a 3 wt% gel phase, in the presence of 20 mol% of L-proline, at 25 °C for 24 h. Results collected are shown in Table 7.

Analysis of data collected clearly shows that performance of the reaction heavily depends on the nature of both reagents. In general, changing the nature of the nucleophile has a more pronounced effect on both yield and conversion value, as accounted for by the significant decrease in both the above parameters going from **2a** to **2c**. In all cases, by products formation was not observed and data collected seem to indicate that performance of the reaction is disfavored by using a more rigid and organized nucleophile, like cyclohexanone. Probably, the above results can be related to the difficulty with which a more rigid and sterically hindered nucleophile can reorganize, in a rigid gelatinous network, to better interact with the substrate.

On the other hand, nucleophile being the same, yields significantly change with the nature of the dienone structure (**1a** > **1e** > **1d**). The selectivity decreases along the following trend: **1a**~**1d** ≫ **1e**. Above data clearly indicate that yield and selectivity of the reaction are positively affected by the extension of the π -surface area of the substrate. Probably, this factor induces a more significant transition state stabilization deriving from the establishment of π - π interactions with gelator molecules. The above hypothesis is confirmed by results collected in the presence of **1d**, that feels less the above stabilizing effect. On the other hand, in the case of **1e**, that lack of this structural feature gave rise to the formation of a significant amount of by-products that we were not able to characterize.

Conclusions

Supramolecular eutectogels were prepared from self-assembly processes of DBS in cholinium chloride-based DES differing for the nature of hydrogen bond donor. Soft materials obtained were fully characterized and data collected allowed to identify

Table 7. Yield and conversion values for the Michael addition carried out in DBS/ChCl/U eutectogel, at 25 °C and for 24 h, as a function of the nature of dienone and nucleophile.

Product	Conversion [%] ^[a]	Yield [%] ^[a]
	100	99
	37	35
	17 ^[b]	16 ^[b]
Product	Conversion [%]	Yield [%]
	100	99
	54	53
	100	68

[a] Conversions and yields were determined after flash chromatography and they were reproducible within 4% after triplicate runs. [b] Reaction time: 5 days; conversion and yield determined by ¹H-NMR.

the relationship working among gel-sol transition temperature, mechanical properties and size of aggregates featuring gel

phases. Formation of gel phase at lower concentrations, with higher thermal stability, featured by the presence of more extended aggregates and having higher stiffness, was favored in DES with higher viscosity and hydrogen bond donor ability.

The above structural features played a pivotal role in determining the effect that gel phases exert on the outcome of a classical organic reaction, like the L-proline catalyzed Michael addition of malononitrile to *trans*-chalcone. Better results, with respect to the corresponding DES solutions, were collected in DBS/ChCl/U gel that was the one exhibiting the highest structural organization, as accounted for by its highest stiffness and the presence of more extended aggregates. Unfortunately, notwithstanding the use of a good organocatalyst, in no case we observed enantiomeric excess.

Analysis of results collected as a function of dienone or nucleophile structure, evidences that the progress of the reaction in these confined and organized reaction media, is favored by the presence of more structurally flexible nucleophiles that, within the rigid gel network, more easily reorganize, to interact with dienone. On the other hand, as far as dienone structure is concerned, our findings shed light on the positive role played by a more extended π -surface on the substrate, that better promote the establishment of π - π interactions with gelator molecules, stabilizing the transition state and favoring the outcome of the reaction.

Experimental section

Materials: L-proline, cholinium chloride, urea, glycerol, ethylene glycol, diethylene glycol, triethylene glycol, malononitrile, *t*-chalcone, nitromethane, 2-cyclohexen-1-one, cyclohexanone, benzalacetone, *p*-nitrophenol, trifluoroacetic acid, ethyl acetate and methanol were purchased from commercial sources and used as received.

DBS was synthesized as previously reported.^[35]

Methods: DES preparation

HBD and HBA, in ratio 1:2 or 1:3, were mixed at 80 °C for 30 min. After the complete dissolution, DES were dried under vacuum for 1 h and, then, stored under Ar atmosphere in a dessicator.

Gelation tests and T_{gel} determination

The proper amount of DBS and DES were weighed in a screw-capped vial of 1 cm of diameter to reach a total amount of 250 mg. The mixture was irradiated in ultrasonic bath for 2 min before heating at 80 °C for 1 h under magnetic stirring. The resulting hot solution was left to stand at room temperature overnight and gel formation was assured through the tube inversion test,^[36] when turning the vial upside down no flow of the solution occurred. Gelator concentration varied, starting from 1 wt% upon reaching the minimal amount of gelation concentration (CGC).

T_{gel} was determined by the lead-ball method.^[37] A lead-ball (weighing 46.2 mg and 2 mm of diameter) was placed on the top of the gel and the vial was put into a water bath. The bath temperature was gradually increased (2 °C min⁻¹) until the gel melted and the lead ball reached the bottom of the vial (T_{gel}). The T_{gel} values were reproducible within 1 °C.

Rheological measurements

Rheological measurements of eutectogels were performed on ARES G2 (TA Instruments) strain-controlled rheometer using an oscillatory mode and a plate-plate geometry tool (PP 25-2).

Strain and frequency sweeps were recorded three times on three different aliquots of gels at gelator concentration used for catalytic tests. Measurements were carried out after determining the linear viscoelastic region (LVR) of gels. Strain sweeps were recorded at a fixed angular frequency of 1 rad s^{-1} and frequency sweeps at a fixed strain of 0.2%. All measurements were performed at 25°C .

SEM measurements

Scanning Electron Microscopy (SEM) images were recorded on a PRO X PHENOM electronic scanning microscope, operating at 5 kV. Gels were placed on the stubs, and the DES was removed with acetone or MeOH to form a xerogel.

FTIR measurements

IR spectra of DES and eutectogels pure and in presence of 20 mol% of L-Pro were recorded using an IR Agilent Technologies Cary 630 FTIR instrument.

RLS Measurements

RLS measurements were carried out at 25°C on a spectrofluorometer (JASCO FP-777W) using a synchronous scanning mode in which the emission and excitation monochromators were preset to identical wavelengths. The RLS spectrum was recorded from 300 to 600 nm with both the excitation and emission slit widths set at 1.5 nm. Samples for a typical measurement were prepared injecting in a quartz cuvette (light path 0.2 cm) the limpid hot solution of gelator. The solution was left to stand at room temperature for one night to allow gel formation. The gel phase obtained at the end of the measurement was stable after the tube inversion test.

Polarimetric and circular dichroism measurements

Optical rotation of DBS solution in MeOH at $5 \cdot 10^{-3} \text{ M}$ was measured by using a glass polarimetric cell (light path 1 dm) at 25°C and it was obtained as the average value over 50 readings.

Circular dichroism (CD) spectra were recorded with a Jasco J715 spectropolarimeter, under nitrogen flow at 25°C . CD spectra were recorded for DBS solutions at a concentration of $5 \cdot 10^{-3} \text{ M}$ in MeOH or DES. While spectra of gels, previously formed in quartz cuvette of 0.2 cm, were recorded at CGC concentration of DBS in DES. CD spectra of each DES were recorded as well and were subtracted to CD spectra of the corresponding eutectogels.

DES basicity measurements

p-Nitrophenol at 0.0002 M was dissolved in the corresponding DES. The solution was spectrophotometrically analyzed using quartz cuvette with light path of 0.2 cm.

General procedure for the addition of trans-chalcone to malononitrile

1 eq. of *trans*-chalcone reacted with 2 eq. of malononitrile using 20% mol of L-proline, the reaction was carried out both in DES and

in eutectogels at 25°C . At lower temperatures, the reaction temperature was ensured using a Thermo Haake EK45 immersion cooler with an open-bath circulator, equipped with a water/ethylene glycol mixture bath.

All reaction components were stirred for 15 min, then, the reaction mixture was performed in a mini shaker at 400 rpm for 24 h. Then, the reaction mixture was extracted with ethyl acetate after addition of a small amount of water (50 μL). Typically, 250 mg of gel or DES were used with 25 mg of *t*-chalcone. The reaction product was obtained after flash chromatography with petroleum ether and acetate 5:1.

Reactions, with different substrates or nucleophiles, were carried out in the best performing gel, *i.e.* DBS in CHCl_3/U (1:2) at 3 wt%, at 400 rpm and 25°C for 24 h, using 20% mol of L-proline.

After dissolution in isopropanol (1 mL), the enantiomeric composition of the product was determined by HPLC analysis (210 nm, Chiralpak AS-H, flow of 0.5 mL/min, eluent formed by *n*-hexane/isopropanol = 70:30): $t_{\text{minor}} = 21 \text{ min}$; $t_{\text{major}} = 24 \text{ min}$.

All reaction products were in agreement with what previously reported.^[38]

2-(3-oxo-1,3-diphenylpropyl)malononitrile (3a), $^1\text{H NMR}$, CDCl_3 δ (ppm): 3.68 (dd, $J_1 = 18 \text{ Hz}$, $J_2 = 12 \text{ Hz}$, 2H), 3.96 (m, 1H), 4.66 (d, $J = 6 \text{ Hz}$, 1H), 7.47 (m, 7H), 7.63 (t, $J = 9 \text{ Hz}$, 1H), 7.98 (d, $J = 9 \text{ Hz}$, 2H). $^{13}\text{C NMR}$, CDCl_3 δ (ppm): 28.8, 40.1, 41.2, 111.7, 111.8, 128.0, 128.1, 128.9, 129.2, 129.4, 134.2, 135.8, 136.5, 196.7.

4-nitro-1,3-diphenylbutan-1-one (3b), $^1\text{H NMR}$, CDCl_3 δ (ppm): 3.46 (dd, $J_1 = 6 \text{ Hz}$, $J_2 = 3 \text{ Hz}$, 2H), 4.23 (q, $J = 9 \text{ Hz}$, 1H), 4.70 (dd, $J_1 = 12 \text{ Hz}$, $J_2 = 9 \text{ Hz}$, 1H), 4.84 (dd, $J_1 = 12 \text{ Hz}$, $J_2 = 6 \text{ Hz}$, 1H), 7.34 (m, 5H), 7.46 (t, $J = 6 \text{ Hz}$, 2H), 7.58 (t, $J = 6 \text{ Hz}$, 1H), 7.92 (d, $J = 6 \text{ Hz}$, 2H). $^{13}\text{C NMR}$, CDCl_3 δ (ppm): 39.3, 41.5, 79.7, 127.5, 127.9, 128.0, 128.7, 129.1, 133.5, 136.3, 138.9, 196.9.

2-(3-oxo-1,3-diphenylpropyl)cyclohexan-1-one (3c), $^1\text{H NMR}$, CDCl_3 δ (ppm): 1.25 (m, 1H), 1.64 (m, 3H), 1.77 (m, 1H), 1.99 (m, 1H), 2.41 (m, 1H), 2.52 (m, 2H), 2.72 (m, 1H), 3.22 (m, 1H), 3.45 (m, 1H), 3.72 (m, 1H), 7.24 (m, 5H), 7.45 (m, 3H), 7.91 (m, 2H). $^{13}\text{C NMR}$, CDCl_3 δ (ppm): 24.2, 28.4, 32.4, 41.3, 42.5, 44.3, 55.9, 126.4, 126.7, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 132.8, 137.1, 142.2, 142.7.

2-(3-oxo-1-phenylbutyl)malononitrile (3d), $^1\text{H NMR}$, CDCl_3 δ (ppm): 2.22 (s, 3H), 2.77 (m, 1H), 3.13 (m, 1H), 3.75 (m, 1H), 4.64 (m, 1H), 7.44 (m, 5H). $^{13}\text{C NMR}$, CDCl_3 δ (ppm): 24.2, 39.1, 40.9, 44.7, 127.0, 127.6, 127.9, 129.0, 129.2, 129.4, 136.1, 162.5.

2-(3-oxocyclohexyl)malononitrile (3e), $^1\text{H NMR}$, CDCl_3 δ (ppm): 1.67 (m, 2H), 2.31 (m, 6H), 3.17 (m, 1H), 3.88 (d, $J = 3 \text{ Hz}$, 1H). $^{13}\text{C NMR}$, CDCl_3 δ (ppm): 25.1, 27.9, 28.5, 33.4, 36.7, 39.8, 110.4, 110.8, 177.8.

Associated Content: Supporting Information. Plots of strain and frequency sweep measurements for gel in different DES. CD spectra of DBS gels in different DES at the CGC. UV-vis spectra of *p*-nitrophenol (0.0002 M) in different DES solutions. FT-IR spectra of DES and eutectogels pure and in presence of 20 mol% of L-Pro, SEM images. NMR spectra of catalysis products.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: catalysis · deep eutectic solvents · 1,3:2,4-dibenzylidene-D-sorbitol · eutectogels · Michael addition reaction · supramolecular chemistry

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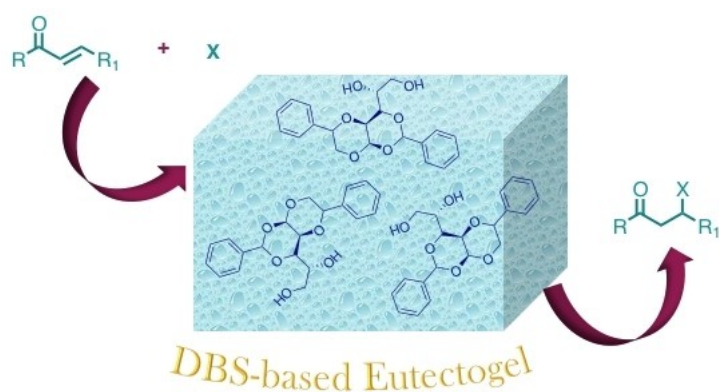
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Supramolecular eutectogels were used as reaction “vessel” to perform the Michael addition reaction. Data

collected allowed to identify the relationship between structural features of soft materials and catalytic activity.

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DBS-Based Eutectogels: Organized Vessels to Perform the Michael Addition Reaction

