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# Thermo-switchable hydrophobic solvents formulated with weak acid and base for greener separation processes

Julian Castaneda Corzo<sup>1</sup>, Karine Ballerat-Busserolles<sup>1</sup>, Jean-Yves Coxam<sup>1</sup>, Arnaud Gautier<sup>1</sup>, Jean-Michel Andanson<sup>1,\*</sup>

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## Abstract

Switchable solvents are changing properties when exposed to an external stimulus. As example, for thermomorphic multiphasic system (TMS), temperature changes can induce phase separations. Aqueous systems presented here are formulated with a carboxylic acid (weak acid) and an amphiphilic tertiary amine (weak base). They show thermo-switchable hydrophobicity and after separation, the weak acid and base are mainly found in the organic phase while the aqueous phase is mostly composed of water, up to 99 wt%. The phase separation temperature (cloud point) can be tuned from 20 to 80°C depending on the choice of the carboxylic acid and on the acid : base molar ratio. A collection of saturated aliphatic carboxylic acids and benzoic acid derivatives have been investigated to evaluate the impact of different physico-chemical properties on the cloud point. The octanol/water partition coefficient (log P) and acidic constant (pKa) were identified as key physico-chemical properties to adjust the phase separation temperature. Finally, as illustration of the efficiency of these systems to remove a chemical from water, it has been shown that 99% extraction of an anionic dye, methyl orange, could be achieved with most of the tested TMS.

**Keywords:** Thermomorphic multiphasic system (TMS), deep eutectic solvent (DES), protic ionic liquid (PIL), dye extraction

## 1. Introduction

Solvents represents often 80 to 90 wt% of chemicals used in industrial processes like in the synthesis of pharmaceutical ingredients [1]. For the development of a sustainable chemistry, selection guides for greener solvents are established, based on parameters representative of safety, health and environmental impacts [2,3]. Over these requirements, the amount of energy necessary for separation of the product from the solvent is often an important parameter. Therefore, one of the main challenges identified to make a greener chemistry is to suppress highly energetic steps like distillation [4]. The aspect of sustainability of green solvents, including thermomorphic multiphasic system (TMS), ionic liquid (IL) and deep eutectic solvent (DES), was recently reviewed in details [5]. However, it is not because a solvent is a DES that it should necessarily be considered as green. Ideally, a solvent should be cheap, safe, stable, degradable, renewable, non-hazardous and atom economic in their synthesis [6]. To acquire a better knowledge of the sustainability of a solvent, a rigorous life cycle analysis could be performed [7].

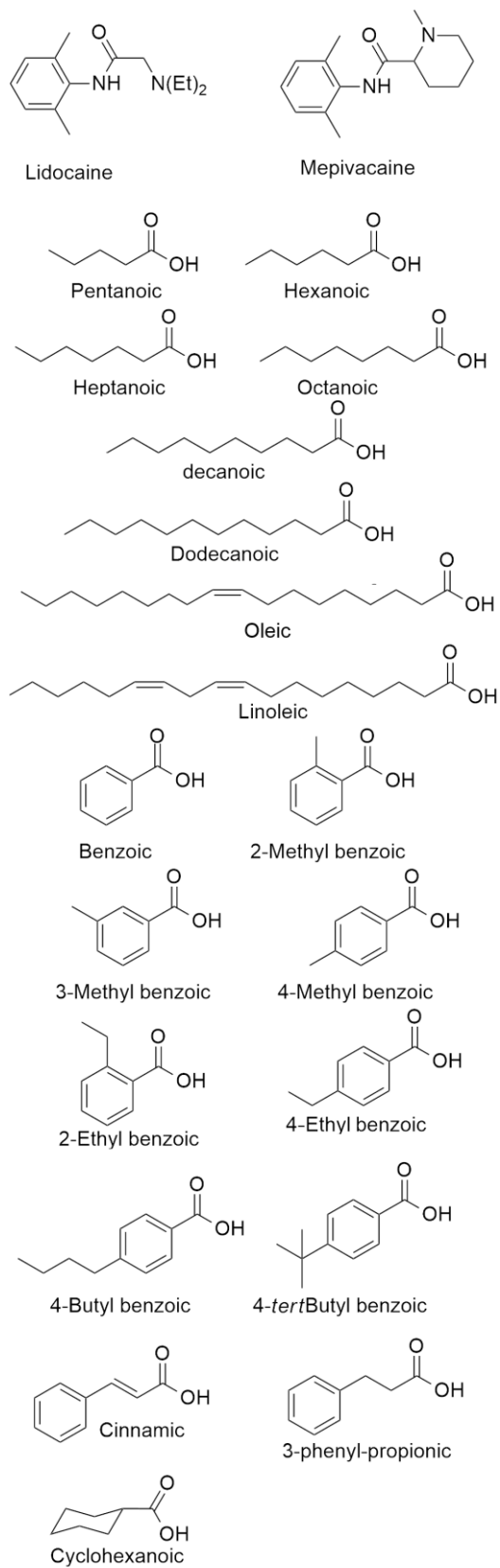
Switchable hydrophilicity solvents (SHS) are aqueous solvents capable to change from monophasic to biphasic depending on the activation of a trigger. It is therefore possible to use advantageously both homogenous and heterogenous systems depending on the step of the process. For example, bubbling CO<sub>2</sub> can induce the switch from biphasic to monophasic and then, flowing N<sub>2</sub> to desorb CO<sub>2</sub> can generate the change back to the monophasic solution [8–10]. With this type of solvent, chemical reactions can be performed in a homogenous system before recovering the hydrophilic product in water. In this way, a costly distillation step can be avoided.

Temperature can also be used as stimulus to induce a phase separation. Changing the temperature of a batch reactor is easily accessible which makes this stimulus practical in various cases. A TMS is a system that could either possess a LCST (lower critical solution temperature) or UCST (upper critical solution temperature), if the separation occurs when heating or cooling, respectively [11]. As an example, an aqueous DES made of mono-ethanol-amine and 4-chlorophenol possessed a UCST allowing efficient extraction of aromatic amino acids [12]. Some aqueous amine solutions also present an LCST and the mutual solubility data for many binary mixtures have been reviewed in details [13,14]. These systems have been evaluated for CO<sub>2</sub> capture process [15], particularly to limit energy cost of solvent regeneration after the absorption of CO<sub>2</sub> from an exhaust gas. Therefore, numerous systems have been tested, including aqueous amine solution possessing an LCST [16,17].

TMS are also of interest for metal extraction [18,19] or catalyst recovery [20]. Among the systems presenting LCSTs, mention may also be made of solutions including IL [21,22]. Because of their low volatility, aqueous IL showing LCST have been considered for extraction of metal ions [23] and

proteins [24]. DES have been proposed initially by Abbott's group as "systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species" [25]. The field of DES is growing rapidly even if the a clear definition has not been yet established [26]. In the last few years, extraction of various molecules and ions from water has been tested in a wide range of hydrophobic DES [27,28]. As solvents, the DES are of interest because of their much lower volatility than usual VOS. As example, systems made with the mixture of decanoic acid or lidocaine with menthol have a partial pressure around  $10^{-5}$  bar at 70°C [29].

A low mutual solubility of water and DES will be of key importance for extraction or separation process. As an example, the aqueous DES made of oleic acid (OA) and lidocaine (LD) at (1:1) molar ratio and with 50 wt% of water has a LCST at 25°C and show a phase separation rather abrupt; less than 1 wt% of organic molecules are present in the aqueous phase at 50°C and around 5 wt% for water in the DES phase [30]. LD is an amphiphilic tertiary amine while OA is a hydrophobic fatty acid. The dry mixture (OA:LD) has been initially presented by Bica *et al.* as the first example of liquefaction of a solid pharmaceutical in the form of a neutral acid – base complex [31]. However, the presence of the LCST in the aqueous mixture has been explained by the decrease of the quantity of ions when increasing the temperature; ions resulting from acid – base reaction between LD and OA are more soluble in water than the molecular LD and OA. This acid – base reaction is less favourable when increasing temperature as the  $pK_a$  of tertiary amines like LD are decreasing [32,33]. The decrease of the solubility of organics in water leads to the liquid – liquid phase separation [30]. The applicability of this first TMS based on an aqueous DES (OA:LD) has already been illustrated in the field of biocatalysis with an effective separation allowing the recycling of a catalytic enzyme [34]. The aim of this work is to investigate other aqueous mixtures of weak acid – base to better understand the physico-chemical properties that lead to a phase separation. The idea is to identify aqueous solutions with different phase diagrams for a wider range of utilizations. Moreover, the presence the double bond in case of the OA can restrict application such as palladium catalysis or radical based reactions. In the aqueous DES (OA:LD), the LD is the amphiphilic molecule that permit water and the fatty acid (OA) to coexist in the same liquid phase. It was then chosen to combine LD with various hydrophobic carboxylic acid and also, to test a very similar amphiphilic molecule: the mepivacaine (MEP). Both molecules possess a tertiary amine group, an amide group and a dimethylphenyl group (Scheme 1). MEP and LD are both active pharmaceutical ingredients (API) known as local anesthetics. They have comparable physico-chemical properties, in particular both hydrophobicity and  $pK_a$  are similar for LD and MEP [33]. The tested aliphatic and aromatic acids that will be combined with the weak base are also represented in Scheme 1.



Scheme 1: Structures of the weak bases (lidocaine and mepivacaine) and weak acids used in this study.

## 2. Materials and methods

### 2.1. Chemicals

Chemicals used are listed in Table 1, together with furnisher and purity. All chemicals were used without further purification. The water used in this work was systematically mono-distilled.

Table 1. Chemicals used in this study.

Acronym	IUPAC name	CAS number	Purity	Source
Lidocaine (LD)	2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide	137-58-6	>99%	TCI
Mepivacaine (MEP)	(RS)-N-(2,6-dimethylphenyl)-1-methyl-piperidine-2-carboxamide	96-88-8	95%	ABCR
Oleic acid (OA)	(Z)-Octadec-9-enoic acid	112-80-1	>98%	TCI
	Pentanoic acid	787-70-2	>98%	TCI
	Hexanoic acid	142-62-1	>98%	TCI
	Heptanoic acid	11-14-8	>98%	TCI
	Octanoic acid	127-07-2	>98%	TCI
	Decanoic acid	334-48-5	>98%	TCI
	Dodecanoic acid	143-07-7	>98%	TCI
	Linoleic acid	cis, cis-9,12-Octadecadienoic acid	60-33-3	>97%
benzoic acid		65-85-0	>99%	TCI
2-methylbenzoic acid		118-90-1	>98%	TCI
3-methylbenzoic acid		99-04-7	>98%	TCI
4-methylbenzoic acid		99-94-5	>98%	TCI
2EB acid	2-ethylbenzoic acid	612-19-1	>98%	TCI
	4-butylbenzoic acid	20651-71-2	>98%	TCI
	4-tert-butylbenzoic acid	98-73-7	>99%	TCI
3PP acid	3-phenylpropionic acid	501-52-0	>98%	TCI
cyclohexanoic acid	Cyclohexanecarboxylic acid	98-89-5	>98%	TCI
cinnamic acid	3-phenylprop-2-enoic acid	621-82-9	>98%	TCI
Methyl orange	sodium (E)-4-((4-(dimethylamino)phenyl)diazenyl) benzenesulfonate	547-58-0	85%	Sigma-Aldrich

### 2.2. Solvent preparation

The solvents are prepared by weighting method (typically 1 to 10 g). The DES are obtained by adding the weak acid to the base and heating the mixture slightly above the melting temperatures of both chemicals. All mixtures become clear transparent liquids after few minutes. The mixtures are then cooled down at room temperature and the same weight of water is added to prepare aqueous mixtures. Some DES made with derivatives of benzoic acid were solid at room temperature. In these

cases, the DES is heated up to fusion before adding water. The full list of all DES prepared for this work is given in supplementary materials.

### 2.3. Cloud point determination

Liquid – liquid phase separation of aqueous solution of DES has been observed at microscopic and macroscopic scales. With an optical microscope (Leica DM2500M), a sample (around 10-20 mg) is placed between two glass slides into a thermally controlled stage (Linkam LTS420). The thickness of liquid sample between the two glasses slides is around 10-20  $\mu\text{m}$ . The sample is heated at 1°C/min and images of the sample observed in transmission are recorded every 6 seconds. The temperature of the first image showing droplets is defined as the cloud point.

For the macroscopic observation, around 3 mL of a sample is placed into a closed glass vial together with a blue magnetic stirrer bar (Fig. 1). The vial is immersed in a thermostatic water bath with two glass windows (Julabo 18V) which is heated at 0.5°C/min. A submersible magnetic stirrer (Micro from Thermo Scientific) is placed directly below the vial allowing the sample to be continuously mixed with the blue magnetic stirrer. Images are taken every 12 seconds, the temperature of the first image with a white solution is considered as the cloud point. Both methods present a reproducibility standard deviation estimated about 0.5°C. Example of a cloud point determination for an aqueous solution of DES is presented in Fig. 1.

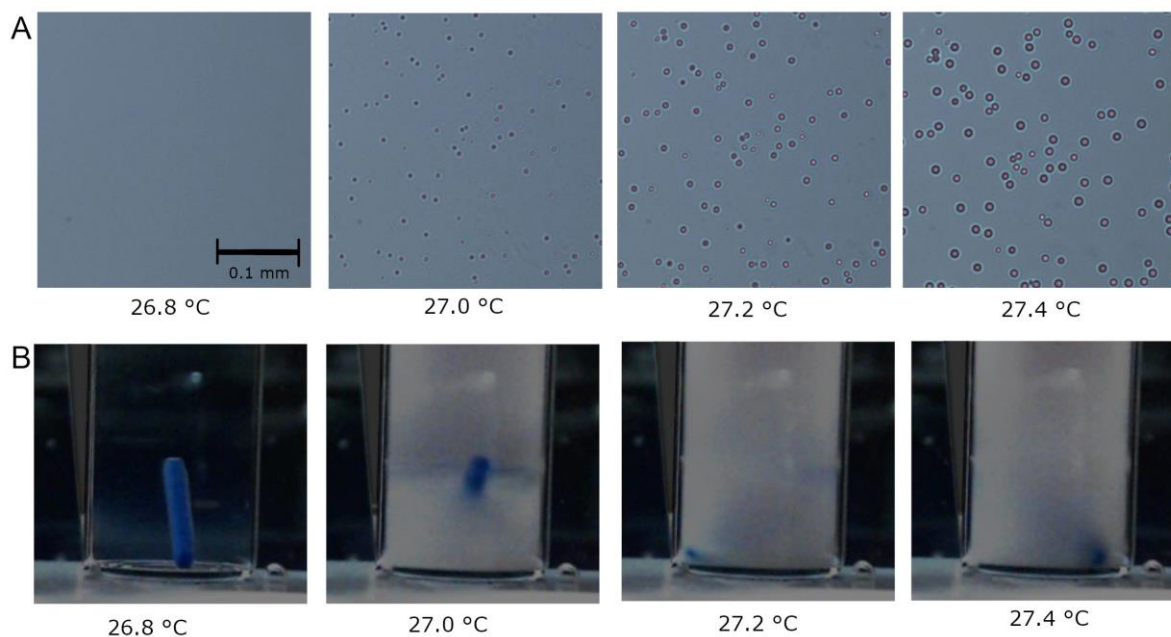


Fig. 1. Cloud point determination at 27 °C for a solution of DES (lidocaine : decanoic acid with a (1:1) molar ratio), 50 wt% in water. Images recorded for a sample with a microscope (A) and for a sample in a glass vial (B).

## 2.4. Quantification of chemicals in both phases

The amount of water in the organic phase was measured by Karl-Fischer technique using a DL32, Mettler-Toledo titrator. The concentration of organics in the aqueous phase were obtained using a mass spectrometer coupled with liquid chromatography (UHPLC-HRMS, Ultimate 3000 coupled with an orbitrap Q-Exactive from Thermo Fisher).

## 2.5. Dye extraction

The experiment consists in mixing about 1.5 g of DES with same weight of an aqueous solution of methyl orange (85 ppm). After 5 minutes at room temperature the vial containing the mixture is placed into a water bath, pre-heated at 40°C or 60°C. After 15 minutes, about 0.7 ml of the aqueous phase is taken and diluted with water and ethanol for UV-Vis spectroscopy. About 0.2 ml of each phase are also taken for chemical analysis (Karl-Fischer for the organic phase and mass spectrometry for the aqueous phase). Extraction efficiency (EE) is calculated (Eq. 1) from ratio of dye concentrations in the aqueous phase before ( $C_{\text{before}}$ ) and after ( $C_{\text{after}}$ ) the extraction.

$$EE = (C_{\text{before}} - C_{\text{after}}) / C_{\text{before}} \quad \text{Eq. 1}$$

The concentrations of dye in aqueous phase are determined from the measurements of peak intensity, using a UV-vis spectrophotometer (Jasco V650). Reported EE are obtained from two extraction experiments carried out in same conditions.

## 3. Results

### 3.1. Effect of hydrophobicity and $pK_a$ of DES constituents on the cloud point

#### 3.1.1. LD and MEP with linear aliphatic acid

The original DES investigated by our group was formulated with oleic acid (OA) and lidocaine (LD) at a (1:1) molar ratio. The 50 wt% aqueous solution of this DES displays a reversible phase separation close to room temperature [30]. The effect of weak acid hydrophobicity was analysed by replacing the OA with other weak acids. Similarly, LD has been replaced by MEP which possesses similar physico-chemical properties. The general composition of the solution is maintained at 50 wt% of water. Cloud points for DES composed of a linear aliphatic acids and LD (or MEP) are represented in Fig. 2.



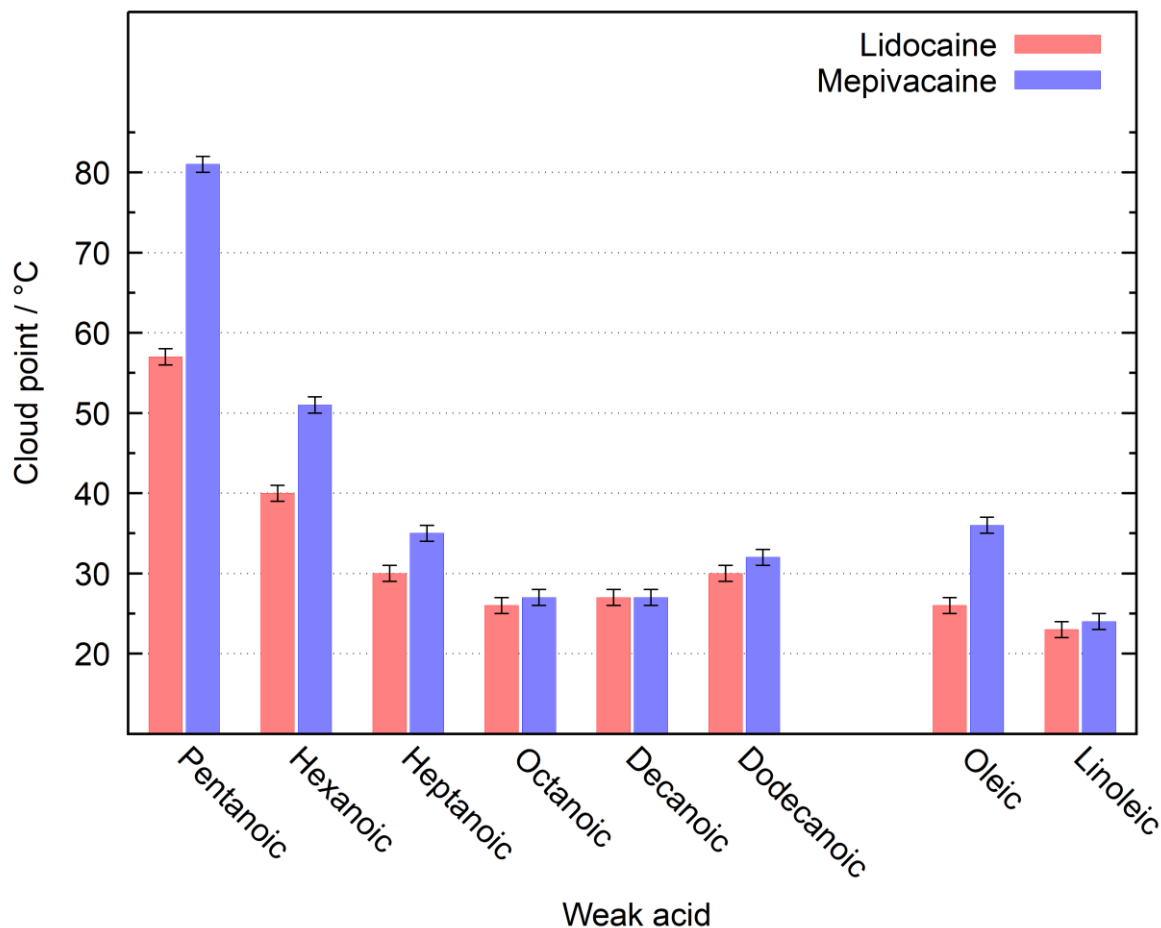


Fig. 2. Cloud point of aqueous DES solutions composed of linear aliphatic acid + lidocaine (or mepivacaine) + water. The molar ratio (acid:base) is (1:1) and the quantity of water is fixed at 50 wt%.

Primarily, all the aqueous DES solutions tested with linear aliphatic carboxylic acid possess a cloud point between 23 and 81°C. Both the length of the carboxylic acid and the choice of weak base (LD or MEP) are changing the phase separation temperature. For saturated aliphatic acids, the cloud point first quickly decreases with the length of the chain (C5 to C8), with a minimal value for octanoic and decanoic acids. The same behaviour for cloud points as function the length of the aliphatic chain (Fig. 2) is found for both bases, LD or MEP, with similar minimal cloud point values observed for octanoic and decanoic acids (26-27°C).

$\Delta pK_a$  between LD and MEP is around 0.27 at 25°C (8.19 and 7.92 for LD and MEP, respectively) [33], however, the cloud points are similar for DES with octanoic and decanoic acids (26 - 27°C). A hypothesis for having similar cloud points while having different  $pK_a$  could be the hydrophobicity of the base.  $K_{ow}$  (or  $P$ ) is the partition coefficient of unionized chemical between octanol and water

phase, and it is commonly used to evaluate the affinity of a molecule between hydrophilic and lipophilic phases. While the higher  $pK_a$  of LD induce a higher amount of ions, its hydrophobicity is also higher ( $\log P$  are 2.48 and 1.95 for LD and MEP at 25°C, respectively) [33], both properties could therefore compensate and give a similar cloud point.

For shorter acids (pentanoic to heptanoic acids), higher cloud points are observed when using MEP instead of LD. The cloud point behaviour as function of the base might be explained by a faster decrease of the  $pK_a$  with temperature for MEP than for LD : between 25 and 36°C, the  $pK_a$  of LD decreases from 8.19 to 7.77 ( $\Delta pK_a = 0.42$ ) while the  $pK_a$  of MEP decreases only from 7.92 to 7.72 ( $\Delta pK_a = 0.20$ ) [33]. While for mixtures separating close to room temperature, cloud points are similar for mixtures made with LD and MEP, for solvents possessing a higher cloud point, it is higher in the case of MEP mixtures because its  $pK_a$  is decreasing slower. This observation is coherent with the description of the phase separation in this weak acid – base mixtures: a lower  $pK_a$  of the amine induce a lower concentration of ions, and therefore, a decrease of the solubility of organic species in water, up to the phase separation between organics and aqueous phases.

The aqueous solution of stearic acid (C18 saturated acid), with either LD or MEP, is never monophasic in the limits of our experiments. Therefore, it cannot be compared to oleic acid (C18 enoic acid) and linoleic (C18 dienoic acid). Both unsaturated C18 acids are highly hydrophobic and should have comparable  $pK_a$ . These properties alone cannot explain the significant cloud point differences. With the MEP as weak base, the cloud points are 36°C with oleic and 24°C with linoleic. Therefore, other parameters should also play a role in the phase separation temperature. Parameters related to supramolecular organization of the liquid phase, such as surface tension or critical vesicular concentration could impact also impact the cloud point [35].

### 3.1.2 LD or MEP with benzoic acid derivatives

Many physico-chemical properties are changing simultaneously when changing the alkyl chain of the carboxylic acid and it is challenging to correlate them to cloud points. By replacing the saturated aliphatic chain of the carboxylic acid by benzoic acid derivatives, it is however possible to decorrelate the change of parameters like hydrophobicity and  $pK_a$ . Aqueous solutions (50 wt%) of DES (1:1 molar ratio) were prepared with benzoic acids and seven benzoic acids derivatives with one alkyl groups as substituent (methyl, ethyl, n-butyl or tert-butyl) (Fig. 3).

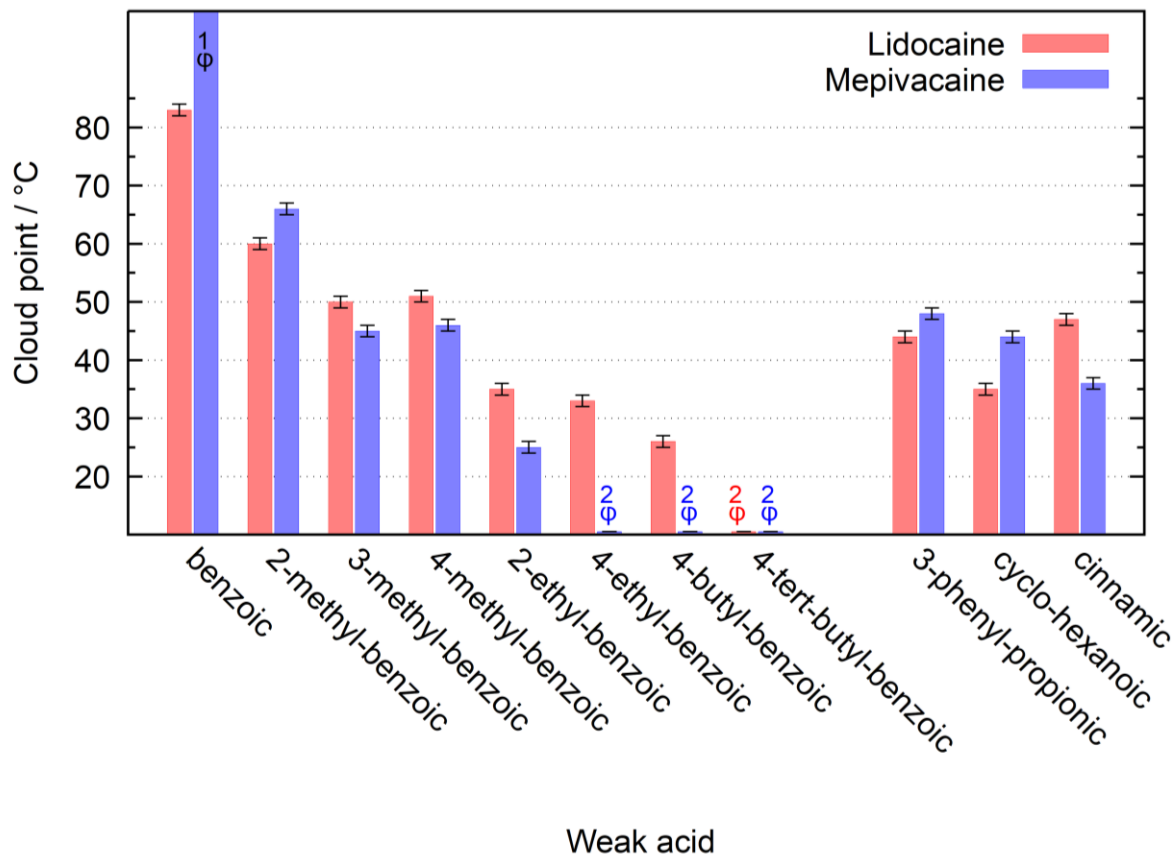


Fig. 3. Cloud point of aqueous DES solutions composed of cyclic carboxylic acid + lidocaine (or mepivacaine) + water. The molar ratio (acid:base) is (1:1) and the quantity of water is fixed at 50 wt%. (1φ): always monophasic between 20°C and 90°C. (2φ): biphasic system at room temperature.

For benzoic acid with LD, the cloud point (83°C) is higher than for the linear heptanoic acid (30°C), which could be explained by a lower  $pK_a$  for benzoic acid (4.2) than for heptanoic acid (4.9). Overall alkyl substitution on the benzene ring is systematically decreasing the phase separation temperature and the longer is the alkyl chain of the substituent the lower is the cloud point (Fig. 3).

For methyl substitutions, the position of the substituent changes the  $pK_a$  without a significant change of the hydrophobicity. The ortho substitution induces a lower  $pK_a$  (4.0) compared to benzoic acid (4.2). On the other hand, with the para or meta substitution, the  $pK_a$  increases (4.3). Cloud points of para and meta methyl-benzoic acids are similar and lower than that of the ortho. Cloud points are therefore correlated with the  $pK_a$ : lower is the  $pK_a$ , higher is the temperature.

Regarding the substitution on para position with ethyl, butyl and tert-butyl groups, the cloud point decreases due to higher hydrophobicity and no miscibility was found for the 4-tert-butyl-benzoic acid.

When separating the benzyl group from the carboxylic acid, the cloud points are decreased, 83°C (benzoic acid-LD) versus 44°C (3-phenyl-propionic acid-LD). This evolution could be correlated with  $pK_a$  4.2 for benzoic and 4.6 for 3-phenyl propionic.

In order to test the impact of the aromaticity, aqueous solutions of a aqueous DES mixture were also prepared with cyclohexanoic acid. The lower cloud point for cyclohexanoic acid (35°C with LD) than for benzoic acid (83°C with LD) could be correlated with the higher  $pK_a$  of cyclohexanoic acid (4.9 versus 4.2 for benzoic). Compare to linear aliphatic chain, the cycle will lead to cloud point increases; 30°C and 35°C for heptanoic vs 35°C and 44°C for cyclohexanoic acid, with LD and MEP, respectively. As both acids have similar  $pK_a$  (4.9), the difference could be related to a lower  $\log K_{ow}$  of cyclohexanoic acid (1.96) compare to heptanoic acid (2.42).

A correlation between cloud points,  $pK_a$  and  $\log K_{ow}$  were tested. A mediocre correlation exists between the cloud point and either the  $\log P$  or  $pK_a$ . A better correlation is found when using ( $pK_a + \log P$ ) (Fig. 4). This sum is related to the distribution coefficient ( $D$ ) of both ionized and un-ionized acid forms. When  $pK_a \ll pH$ ,  $\log D$  for the acid is close to ( $\log P + pK_a - pH$ ) [36]. In this work, the  $pH$  is systematically between 6 and 8. Moreover, mono carboxylic acids considered in this work have  $pK_a$  between 3.9 and 5 and  $\log P$  above 1.8. Therefore, the dashed line in Fig. 4 corresponds to the correlation between cloud points and distribution coefficients of ionized and neutral acid forms between lipophilic and hydrophilic phases.

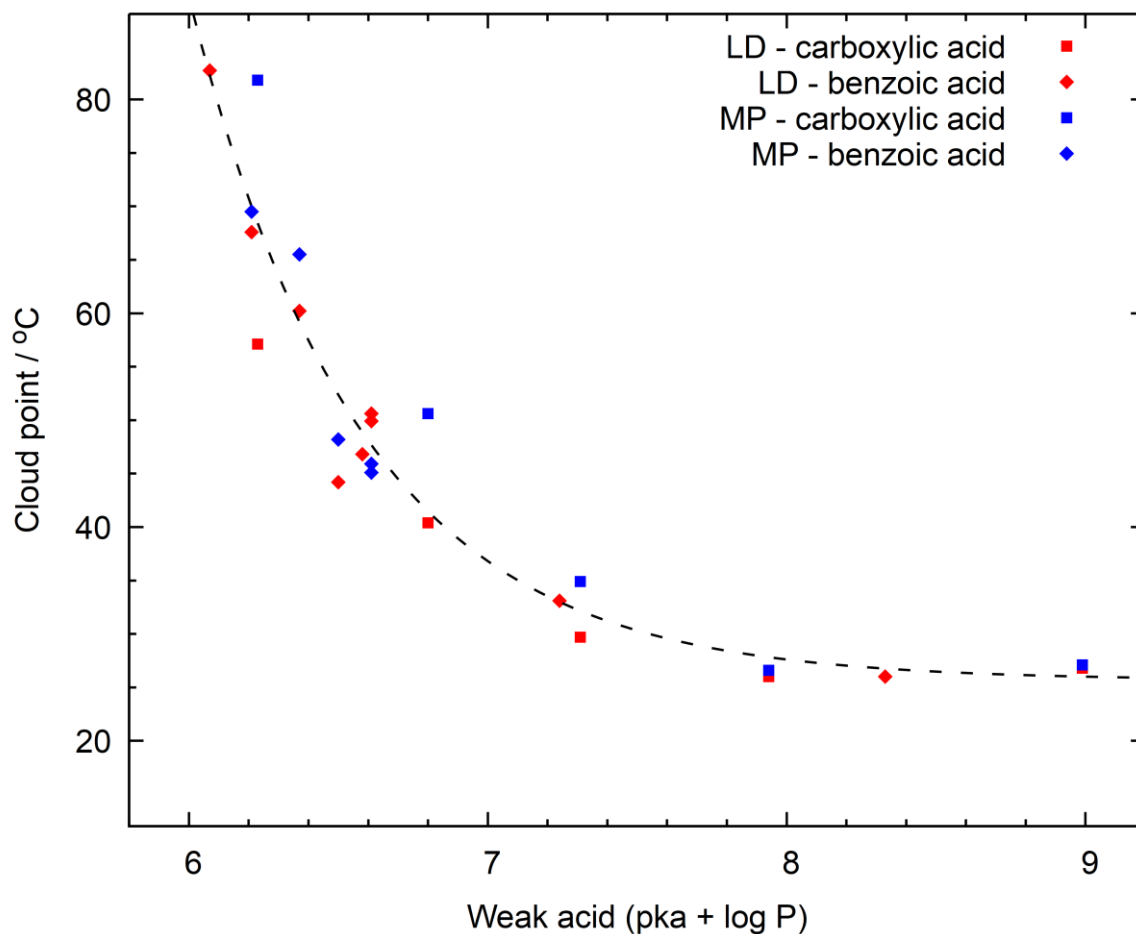


Fig. 4. Correlation between cloud points and  $(pK_a + \log P)$  for aqueous solution (50 wt%) of weak acid with lidocaine (LD) or mepivacaine (MEP) (1:1 molar ratio).

### 3.2. Impact of the ratio between the weak acid and base on the cloud point

LD – weak acid ratio were tested for three acids (benzoic, pentanoic and phenyl propionic acids). Cloud points were obtained with the optical microscope. It reaches a maximum value around the equimolar (acid : base) ratio (Fig. 5). If we considered that the increasing quantity of ions tends to increase the cloud point, it might indicate that it corresponds to a maximum ion concentration at this composition. Changing the (acid:base) ratio is therefore a practical way to decrease the cloud point for a specific application.

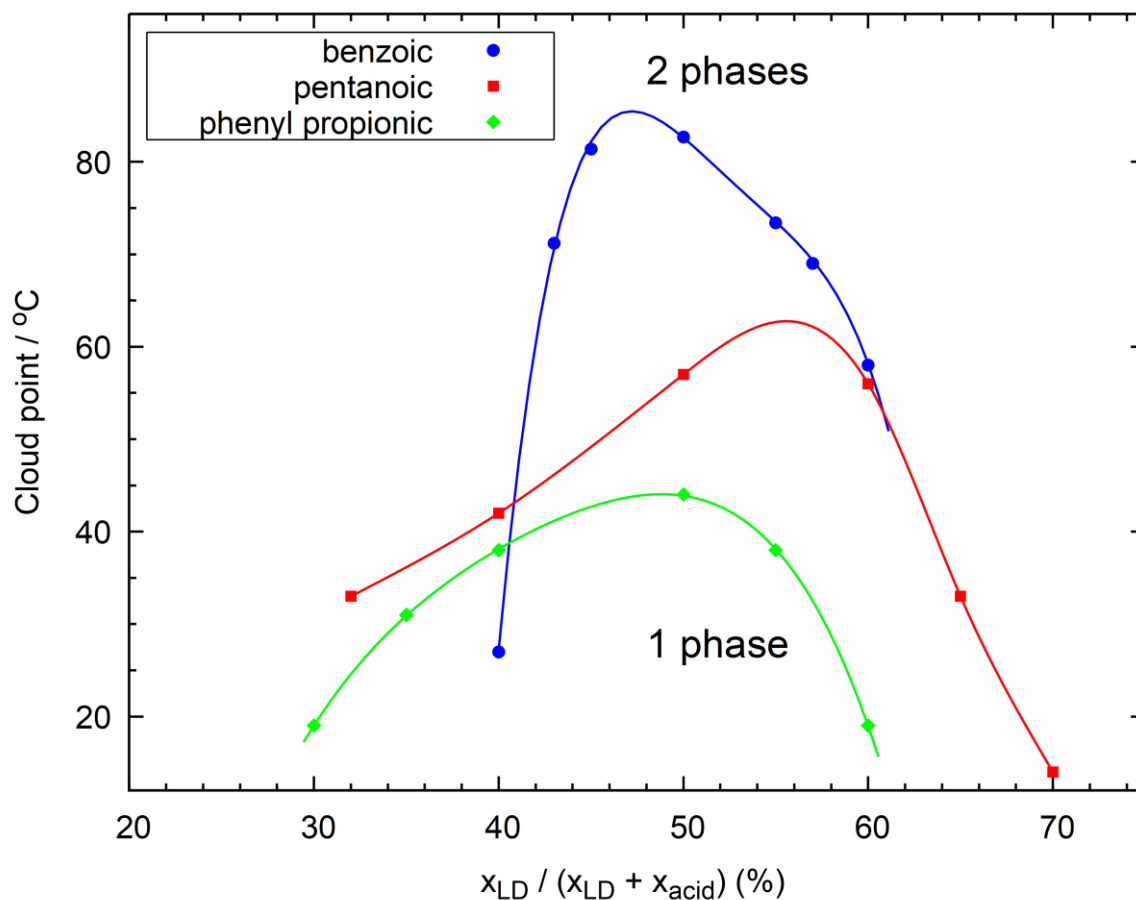


Fig. 5. Impact of LD – weak acid ratio on cloud point for DES aqueous solution 50 wt%. Lines are only drawn as a guide to the eye.

The acid:base ratio has clearly an impact on the hydrophobicity of the mixtures. While in this present work, we are using aqueous (carboxylic acid:LD) (1:1), the same system with a (2:1) molar ratio has been used by several research groups as an hydrophobic DES (decanoic acid:lidocaine) for extraction of metals [37] and organic molecules like toluene [38].

Phase separation temperature with two acids where also assessed; mixtures with LD, water and both benzoic and decanoic acids (Fig. 6). The amount of water is kept constant at 50 wt%. The molar ratio between acids and LD is fixed at (1:1), only the proportion between the two acids is modified. The evolution of the cloud point is not linear, it is not even monotonous: a minimum temperature is found for a mixture with a minor quantity of benzoic (benzoic acid: decanoic acid: LD), (39: 1: 40). Using two acids will therefore allow to simply tune the cloud point without the need of testing new chemicals.

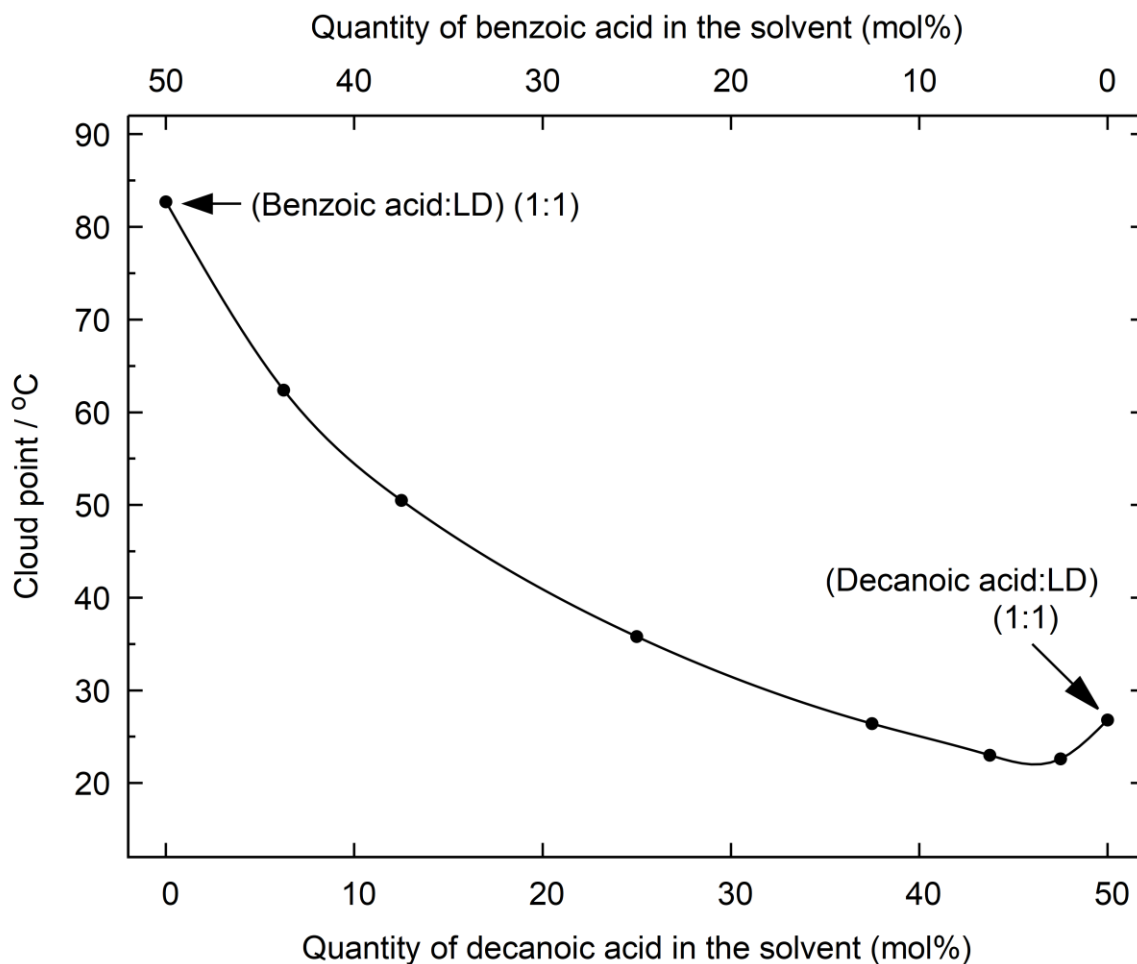


Fig. 6. Evolution of cloud point in a mixture with 2 acids (benzoic and decanoic), lidocaine and water. Quantities of acids are given in mole percent in the DES mixture (without water). The solid lines are only drawn as a guide to the eye.

### 3.3. Quality of the separation

The quality of the phase separation was investigated for 10 representative systems at 2 temperatures (

Table 2, lines 1-10). All systems were composed of LD as the weak base and one weak acid, either pentanoic, decanoic, 2-ethyl-benzoic (2EB) or 3-phenyl-propionic (3PP). The best separation was obtained with the decanoic acid at 60°C. When increasing the extraction temperature from 38 to 60°C, the amount of water in the organic phase decreases from 24 to 12 wt% but the amount of organic chemicals in the aqueous phase remains constant at 1.1 wt%. It should therefore be possible to perform extraction around 10°C above the cloud point to remove chemicals from the aqueous phase, as for dye extraction. The separation could be improved with an acid having a longer alkyl

chain. For example, using oleic acid, less than 0.5 wt% of organics remains in the aqueous phase and less than 5 wt% of water, in the organic phase [30].

Table 2. Quality of the phase separation for 50 wt% DES-water systems (1-10) and, efficiency of dye (methyl orange) extraction from water (1-12). <sup>(1)</sup> 2EB: 2-ethyl-benzoic, <sup>(2)</sup> 3PP=3-phenyl-propionic. <sup>(3)</sup> pure decanoic acid, <sup>(4)</sup> 10 wt% of LD in octanol. <sup>(5)</sup> EE: extraction efficiency.

	Solvent	(Acid:base) (mol%)	Cloud point	Extraction temperature	Water in organic phase	Acid in aqueous phase	LD in aqueous phase	EE <sup>5</sup>
1	Decanoic acid:LD	(50:50)	27°C	38°C	24 wt%	0.4 wt%	0.7 wt%	99%
2	Decanoic acid:LD	(50:50)	27°C	60°C	12 wt%	0.4 wt%	0.7 wt%	99%
3	Pentanoic acid:LD	(50:50)	57°C	60°C	34 wt%	9 wt%	17 wt%	89%
4	Pentanoic acid:LD	(68:32)	33°C	40°C	31 wt%	8 wt%	11 wt%	89%
5	Pentanoic acid:LD	(68:32)	33°C	60°C	34 wt%	5 wt%	9 wt%	90%
6	2EB <sup>1</sup> acid:LD	(50:50)	35°C	40°C	26 wt%	6 wt%	10 wt%	96%
7	2EB <sup>1</sup> acid:LD	(50:50)	35°C	60°C	12 wt%	4 wt%	6 wt%	99%
8	3PP <sup>2</sup> acid:LD	(50:50)	44°C	60°C	20 wt%	3 wt%	5 wt%	99%
9	3PP <sup>2</sup> acid:LD	(35:65)	31°C	40°C	29 wt%	4 wt%	7 wt%	97%
10	3PP <sup>2</sup> acid:LD	(35:65)	31°C	60°C	12 wt%	3 wt%	5 wt%	99%
11	Decanoic acid <sup>3</sup>	100% <sup>3</sup>	-	60°C	-	-	-	2%
12	LD in octanol <sup>4</sup>	10 wt% <sup>4</sup>	-	60°C	-	-	-	50%

The separation using pentanoic acid is not as effective: 30°C above the cloud point, 15 wt% of organics in the aqueous phase and, the quantity of water in the organic phase is still above 30 wt%. In the case of linear alkyl carboxylic acid, the more hydrophobic is the acid, the better is the separation. For acids with an aromatic ring (3-methyl-benzoic acid, phenyl-propionic acid), the quality of the phase separation seems also more limited (at least 8 wt% of organic in the aqueous phase) while the amount of water in the organic phase could be comparable to the one obtained with decanoic acid (12 wt%).

The quality of the separation of these new mixtures built on weak acid – base can be compared to the well-studied aqueous amine solution. With the larger amines like 1-ethylpiperidine (LCST at 9°C), the solubility of amine in the aqueous phase is around 2 wt%, and the solubility of water in the organic phase 7.5 wt%, at 40°C (31°C above the cloud point) [39]. The most similar amine system with an LCST to the aqueous (decanoic acid:LD) (1:1) could be with diisopropylamine which has an LCST at 28°C. At 60°C, the amount of organic in the aqueous phase is 2.9 wt% while the quantity of water in the organic phase is 8.1 wt% [40]. Therefore, compare to aqueous amine, the quality of the phase separation of the aqueous (decanoic acid:LD) (1:1) system is significantly better regarding the amount of organics in the aqueous phase around 30°C above their cloud point. The difference in phase separation is even larger closer to the cloud point: at 40°C the amount of organic in the



aqueous is 1.1 wt% with the aqueous (decanoic acid:LD) (1:1) mixture while it is 6.35 wt%[40] for aqueous diisopropylamine mixture.

### 3.4. Extraction efficiency of methyl orange from water

Extraction of methyl orange (MO) was performed with several TMS as a simple illustration of the ability to extract organic ions. Extraction of the ionic dye was evaluated in 12 solvents: 10 TMS, as well as neat decanoic acid, which is a hydrophobic solvent (melting temperature around 32°C) and LD diluted in octanol (

Table 2). Results from the TMS are always much better than decanoic acid or LD. 89-99% extraction efficiency (EE) is reached with TMS compare to 2% with decanoic acid and, 50% with LD. An EE of 50% correspond to a same concentration of MO in both phases while an EE of 99% to a dye concentration about 100 times higher in the organic phase than in the aqueous phase. The presence of ions in the TMS is therefore improving considerably the extraction of the ionic dye.

Within the TMS systems, those made with pentanoic acid are the less effectives: around 90% EE. The poorer separation between aqueous and organic phases (15 to 26 wt% of organic in aqueous phase) is most probably explaining the lower EE (

Table 2, lines 3-5). TMS based on decanoic, 2-ethyl-benzoic and 3-phenyl-propionic acids can reach 99% extraction. Surprisingly, even when the amount of organic in the aqueous phase rise to 8 wt% (

Table 2, lines 8 and 10), the EE can still reach 99%. This better dye extraction than organic separation might be explained by a cooperative effect of several hydrophobic/amphiphilic molecules/ions around the dye. There is however a correlation between the amount of organic in the aqueous phase and the EE: less than 10 wt% of organics in the aqueous phase gives a better extraction (99%).

Nevertheless, quality of the extraction is not only driven by the quality of the separation between DES and water. As example, an acid with an aromatic ring (2EB:LD,

Table 2, line 6), with 16 wt% of organic in the aqueous phase, is still performing better than the pentanoic acid, with 15 wt% of organic in the aqueous phase (

Table 2, line 5): EE of 96% vs 90%. This higher EE could be explained by a possible stronger interaction between the aromatic MO and the 2-ethyl-benzoic acid than with the aliphatic pentanoic acid. These results are illustrating that it should be possible to design TMS with particular chemical properties to target specific application.

#### 4. Conclusions

More than 30 new aqueous thermomorphic multiphasic systems (TMS) possessing a low critical solution temperature between 20 and 83°C were identified. These systems are constituted of water, a weak carboxylic acid and a weak base (either lidocaine or mepivacaine).

For the systems analysed in this work, a correlation between the log D of the acid and cloud point was revealed. Considering that the  $pK_a$  of the weak bases decrease considerably with the temperature, and the solubility of ions in water are much higher than those of the corresponding neutral molecules, the increase of the temperature is inducing a decrease of the quantity of ions in the systems up to the cloud point where the second liquid phase appears. The correlation between the log D and the phase separation temperature confirmed this description of the origin of the phase separation in these aqueous weak acid – base systems. Moreover, this description is also coherent with the fact that more extremes temperatures are obtained for mixtures made with mepivacaine as a base because compare to the lidocaine, the  $pK_a$  of mepivacaine being less sensitive to temperature. With this understanding of these mixtures, designing new TMS should be facilitated.

The quality of the separation between the aqueous and organic phase was also determined. For the TMS made with one of the most hydrophobic acid, the quality of the separation is highly effective: the amount of organic in the aqueous phase could be as low as 1.1 wt% around 10°C above the cloud point for a system that separates slightly above room temperature (27°C).

Finally, several TMS were tested to perform extraction of an ionic dye: 99% extraction could be obtained around 10°C above the cloud point while individual weak base or acid are unable to achieve an effective extraction.

#### CRedit author statement

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#### References

- [1] D.J.C. Constable, C. Jimenez-Gonzalez, R.K. Henderson, Perspective on Solvent Use in the Pharmaceutical Industry, *Org. Process Res. Dev.* 11 (2007) 133–137. <https://doi.org/10.1021/op060170h>.
- [2] D. Prat, A. Wells, J. Hayler, H. Sneddon, C.R. McElroy, S. Abou-Shehada, P.J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.* 18 (2016) 288–296. <https://doi.org/10.1039/C5GC01008J>.
- [3] D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani, P. Hosek, Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes, *Org. Process Res. Dev.* 17 (2013) 1517–1525. <https://doi.org/10.1021/op4002565>.
- [4] P.G. Jessop, Searching for green solvents, *Green Chem.* 13 (2011) 1391–1398. <https://doi.org/10.1039/C0GC00797H>.
- [5] V. Hessel, N.N. Tran, M.R. Asrami, Q.D. Tran, N. Van Duc Long, M. Escribà-Gelonch, J.O. Tejada, S. Linke, K. Sundmacher, Sustainability of green solvents – review and perspective, *Green Chem.* 24 (2022) 410–437. <https://doi.org/10.1039/D1GC03662A>.
- [6] Y. Chen, T. Mu, Revisiting greenness of ionic liquids and deep eutectic solvents, *Green Chem. Eng.* 2 (2021) 174–186. <https://doi.org/10.1016/j.gce.2021.01.004>.
- [7] Q. Zaib, M.J. Eckelman, Y. Yang, D. Kyung, Are deep eutectic solvents really green?: A life-cycle perspective, *Green Chem.* 24 (2022) 7924–7930. <https://doi.org/10.1039/D2GC01752K>.
- [8] P.G. Jessop, L. Phan, A. Carrier, S. Robinson, C.J. Dürr, J.R. Harjani, A solvent having switchable hydrophilicity, *Green Chem.* 12 (2010) 809–814. <https://doi.org/10.1039/B926885E>.
- [9] P.G. Jessop, L. Kozycz, Z.G. Rahami, D. Schoenmakers, A.R. Boyd, D. Wechsler, A.M. Holland, Tertiary amine solvents having switchable hydrophilicity, *Green Chem.* 13 (2011) 619–623. <https://doi.org/10.1039/C0GC00806K>.
- [10] J.R. Vanderveen, J. Durelle, P.G. Jessop, Design and evaluation of switchable-hydrophilicity solvents, *Green Chem.* 16 (2014) 1187–1197. <https://doi.org/10.1039/C3GC42164C>.
- [11] Y. Qiao, W. Ma, N. Theyssen, C. Chen, Z. Hou, Temperature-Responsive Ionic Liquids: Fundamental Behaviors and Catalytic Applications, *Chem. Rev.* 117 (2017) 6881–6928. <https://doi.org/10.1021/acs.chemrev.6b00652>.
- [12] D. Xiong, Q. Zhang, W. Ma, Y. Wang, W. Wan, Y. Shi, J. Wang, Temperature-switchable deep eutectic solvents for selective separation of aromatic amino acids in water, *Sep. Purif. Technol.* 265 (2021) 118479. <https://doi.org/10.1016/j.seppur.2021.118479>.
- [13] M. Góral, D.G. Shaw, A. Mączyński, B. Wiśniewska-Gocłowska, P. Oracz, IUPAC-NIST Solubility Data Series. 96. Amines with Water Part 1. C4–C6 Aliphatic Amines, *J. Phys. Chem. Ref. Data.* 41 (2012) 043106. <https://doi.org/10.1063/1.4755288>.
- [14] M. Góral, D.G. Shaw, A. Mączyński, B. Wiśniewska-Gocłowska, P. Oracz, IUPAC-NIST Solubility Data Series. 96. Amines with Water Part 2. C7–C24 Aliphatic Amines, *J. Phys. Chem. Ref. Data.* 41 (2012) 043107. <https://doi.org/10.1063/1.4755953>.
- [15] A. Gautam, M.K. Mondal, Review of recent trends and various techniques for CO<sub>2</sub> capture: Special emphasis on biphasic amine solvents, *Fuel.* 334 (2023) 126616. <https://doi.org/10.1016/j.fuel.2022.126616>.
- [16] S. Zhang, Y. Shen, L. Wang, J. Chen, Y. Lu, Phase change solvents for post-combustion CO<sub>2</sub> capture: Principle, advances, and challenges, *Appl. Energy.* 239 (2019) 876–897. <https://doi.org/10.1016/j.apenergy.2019.01.242>.
- [17] O. Longeras, A. Gautier, K. Ballerat-Busserolles, J.-M. Andanson, Tuning critical solution temperature for CO<sub>2</sub> capture by aqueous solution of amine, *J. Mol. Liq.* 343 (2021) 117628. <https://doi.org/10.1016/j.molliq.2021.117628>.
- [18] D. Dupont, K. Binnemans, Recycling of rare earths from NdFeB magnets using a combined leaching/extraction system based on the acidity and thermomorphism of the ionic liquid [Hbet][Tf<sub>2</sub>N], *Green Chem.* 17 (2015) 2150–2163. <https://doi.org/10.1039/C5GC00155B>.
- [19] S. Kono, H. Kazama, T. Mori, T. Arai, K. Takao, Significant Acceleration of PGMs Extraction with UCST-Type Thermomorphic Ionic Liquid at Elevated Temperature, *ACS Sustain. Chem. Eng.* 6 (2018) 1555–1559. <https://doi.org/10.1021/acssuschemeng.7b04447>.
- [20] J. Bianga, K.U. Künnemann, T. Gaide, A.J. Vorholt, T. Seidensticker, J.M. Dreimann, D. Vogt, Thermomorphic Multiphase Systems: Switchable Solvent Mixtures for the Recovery of Homogeneous Catalysts in Batch and Flow Processes, *Chem. – Eur. J.* 25 (2019) 11586–11608. <https://doi.org/10.1002/chem.201902154>.

- [21] J. Lachwa, J. Szydłowski, V. Najdanovic-Visak, L.P.N. Rebelo, K.R. Seddon, M. Nunes da Ponte, J.M.S.S. Esperança, H.J.R. Guedes, Evidence for Lower Critical Solution Behavior in Ionic Liquid Solutions, *J. Am. Chem. Soc.* 127 (2005) 6542–6543. <https://doi.org/10.1021/ja0510257>.
- [22] K. Fukumoto, H. Ohno, LCST-Type Phase Changes of a Mixture of Water and Ionic Liquids Derived from Amino Acids, *Angew. Chem. Int. Ed.* 46 (2007) 1852–1855. <https://doi.org/10.1002/anie.200604402>.
- [23] D. Depuydt, L. Liu, C. Glorieux, W. Dehaen, K. Binnemans, Homogeneous liquid–liquid extraction of metal ions with non-fluorinated bis(2-ethylhexyl)phosphate ionic liquids having a lower critical solution temperature in combination with water, *Chem. Commun.* 51 (2015) 14183–14186. <https://doi.org/10.1039/C5CC05649G>.
- [24] Y. Kohno, S. Saita, K. Murata, N. Nakamura, H. Ohno, Extraction of proteins with temperature sensitive and reversible phase change of ionic liquid/water mixture, *Polym. Chem.* 2 (2011) 862–867. <https://doi.org/10.1039/C0PY00364F>.
- [25] E.L. Smith, A.P. Abbott, K.S. Ryder, Deep Eutectic Solvents (DESs) and Their Applications, *Chem. Rev.* 114 (2014) 11060–11082. <https://doi.org/10.1021/cr300162p>.
- [26] B.B. Hansen, S. Spittle, B. Chen, D. Poe, Y. Zhang, J.M. Klein, A. Horton, L. Adhikari, T. Zelovich, B.W. Doherty, B. Gurkan, E.J. Maginn, A. Ragauskas, M. Dadmun, T.A. Zawodzinski, G.A. Baker, M.E. Tuckerman, R.F. Savinell, J.R. Sangoro, Deep Eutectic Solvents: A Review of Fundamentals and Applications, *Chem. Rev.* 121 (2021) 1232–1285. <https://doi.org/10.1021/acs.chemrev.0c00385>.
- [27] A.M. Ramezani, R. Ahmadi, Y. Yamini, Homogeneous liquid-liquid microextraction based on deep eutectic solvents, *TrAC Trends Anal. Chem.* 149 (2022) 116566. <https://doi.org/10.1016/j.trac.2022.116566>.
- [28] N. Schaeffer, J.H.F. Conceição, M.A.R. Martins, M.C. Neves, G. Pérez-Sánchez, J.R.B. Gomes, N. Papaiconomou, J.A.P. Coutinho, Non-ionic hydrophobic eutectics – versatile solvents for tailored metal separation and valorisation, *Green Chem.* 22 (2020) 2810–2820. <https://doi.org/10.1039/D0GC00793E>.
- [29] K. Xin, I. Roghair, F. Gallucci, M. van Sint Annaland, Total vapor pressure of hydrophobic deep eutectic solvents: Experiments and modelling, *J. Mol. Liq.* 325 (2021) 115227. <https://doi.org/10.1016/j.molliq.2020.115227>.
- [30] O. Longeras, A. Gautier, K. Ballerat-Busserolles, J.-M. Andanson, Deep Eutectic Solvent with Thermo-Switchable Hydrophobicity, *ACS Sustain. Chem. Eng.* 8 (2020) 12516–12520. <https://doi.org/10.1021/acssuschemeng.0c03478>.
- [31] K. Bica, J. Shamshina, W.L. Hough, D.R. MacFarlane, R.D. Rogers, Liquid forms of pharmaceutical co-crystals: exploring the boundaries of salt formation, *Chem. Commun.* 47 (2011) 2267–2269. <https://doi.org/10.1039/C0CC04485G>.
- [32] A.V. Rayer, K.Z. Sumon, L. Jaffari, A. Henni, Dissociation Constants (pKa) of Tertiary and Cyclic Amines: Structural and Temperature Dependences, *J. Chem. Eng. Data.* 59 (2014) 3805–3813. <https://doi.org/10.1021/je500680q>.
- [33] G.R. Strichartz, V. Sanchez, G. Richard Arthur, R. Chafetz, D. Martiny, Fundamental Properties of Local Anesthetics. II. Measured Octanol: Buffer Partition Coefficients and pK: a: Values of Clinically Used Drugs, *Anesth. Analg.* 71 (1990). [https://journals.lww.com/anesthesia-analgesia/Fulltext/1990/08000/Fundamental\\_Properties\\_of\\_Local\\_Anesthetics\\_\\_II\\_.8.aspx](https://journals.lww.com/anesthesia-analgesia/Fulltext/1990/08000/Fundamental_Properties_of_Local_Anesthetics__II_.8.aspx).
- [34] L.-E. Meyer, M.B. Andersen, S. Kara, A Deep Eutectic Solvent Thermomorphic Multiphasic System for Biocatalytic Applications, *Angew. Chem. Int. Ed.* n/a (2022). <https://doi.org/10.1002/anie.202203823>.
- [35] T. Yin, MisranMisni, L. Hin, Z. Md, Effect of Unsaturation on the Stability of C18 Polyunsaturated Fatty Acids Vesicles Suspension in Aqueous Solution, *Bull. Korean Chem. Soc.* 32 (2011) 59–64. <https://doi.org/10.5012/BKCS.2011.32.1.59>.
- [36] T.D. Bergazin, N. Tielker, Y. Zhang, J. Mao, M.R. Gunner, K. Francisco, C. Ballatore, S.M. Kast, D.L. Mobley, Evaluation of log P, pKa, and log D predictions from the SAMPL7 blind challenge, *J. Comput. Aided Mol. Des.* 35 (2021) 771–802. <https://doi.org/10.1007/s10822-021-00397-3>.
- [37] D.J.G.P. van Osch, D. Parmentier, C.H.J.T. Dietz, A. van den Bruinhorst, R. Tuinier, M.C. Kroon, Removal of alkali and transition metal ions from water with hydrophobic deep eutectic solvents, *Chem Commun.* 52 (2016) 11987–11990. <https://doi.org/10.1039/C6CC06105B>.
- [38] C.-C. Chen, Y.-H. Huang, S.-M. Hung, C. Chen, C.-W. Lin, H.-H. Yang, Hydrophobic deep eutectic solvents as attractive media for low-concentration hydrophobic VOC capture, *Chem. Eng. J.* 424 (2021) 130420. <https://doi.org/10.1016/j.cej.2021.130420>.
- [39] R.M. Stephenson, Mutual solubility of water and pyridine derivatives, *J. Chem. Eng. Data.* 38 (1993) 428–431. <https://doi.org/10.1021/je00011a026>.

- [40] R.M. Stephenson, Mutual solubility of water and aliphatic amines, *J. Chem. Eng. Data.* 38 (1993) 625–629. <https://doi.org/10.1021/je00012a039>.