

Tuning Deep Eutectic Solvents for Greener Oxidations: The Role of Solvent Properties in Aldehyde-to-Acid Transformations

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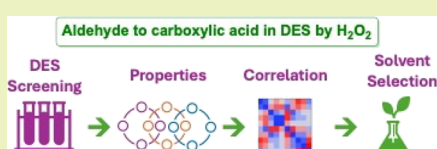
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ABSTRACT: Deep eutectic solvents (DESs) are emerging sustainable alternatives to traditional organic solvents, yet their influence on chemical reactivity remains underexplored. Here, we investigate the oxidation of aldehydes to carboxylic acids using diluted hydrogen peroxide in a diverse set of 20 DESs. We identify a strong correlation between DES pH and reaction efficiency, with optimal yields observed in mildly basic DESs. Surprisingly, even in the presence of excess KOH, DES pH significantly influenced product distribution, highlighting the importance of solvent-intrinsic properties. Urea-based DESs consistently outperformed others, while acidic systems, particularly those based on chlorocholine chloride, favored side reactions. Comprehensive analysis of DES physical properties, including density, viscosity, and polarity, revealed interdependencies that impact reactivity. These findings highlight the need to consider both composition and physicochemical characteristics when selecting DESs for green oxidation processes, offering valuable insights for the rational design of sustainable reaction media.

KEYWORDS: deep eutectic solvents, aldehyde oxidation, design of experiments, physical properties, sustainable reaction media



INTRODUCTION

Solvents are essential in organic synthesis. They improve reactivity (and sometimes selectivity), facilitate temperature and kinetic control, and enable standard purification techniques. While most of the organic chemistry found in textbooks was developed in volatile organic solvents (VOCs) such as toluene, THF, or DCM, growing awareness of their environmental and health hazards, along with increasing regulatory pressure, continues to drive interest in alternative reaction media. Common replacements for VOCs include water, supercritical CO₂ or ionic liquids.^{1–4}

Over the past two decades, Deep Eutectic Solvents (DESs) have gained increasing prominence as versatile designer solvents. These mixtures of hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs) exhibit a pronounced depression in melting point relative to their individual components, often resulting in a liquid form at room temperature.^{5,6} DESs have found important applications across extraction and sorption technologies, biomass processing, and metal electrodeposition.^{7,8} In synthesis and catalysis, they have primarily been employed to improve the ‘green credentials’ of organic reactions.^{9–11} However, a growing body of evidence highlights their instrumental role in enhancing yield, selectivity and even feasibility for a range of transformations when compared to conventional VOCs. For example, cinnamic acid derivatives can be prepared *via* a Perkin condensation in choline chloride/urea (ChCl/U) at mild temperature without the need for additional reagents or catalysts (Scheme 1a).¹² Also, a series of DES were specifically designed to mediate the Friedel-Crafts alkylation of

phenol with *tert*-butanol, with a combination of choline bisulfate and *p*-TsOH displaying the best catalytic activity and selectivity at just 30 °C (Scheme 1b).

As part of our interest on the sustainable preparation of heterocycles, we reported the preparation of 1,2,3-triazolines *via* azide-alkene dipolar cycloaddition reactions in ChCl/U (Scheme 1c).^{13,14} The enhanced thermal stability of both starting azides and resulting triazolines enabled multi-gram scale access to these compounds overnight, whereas traditional azide-alkene cycloadditions are typically limited to highly activated substrates and/or require reaction times spanning weeks or even months.^{15,16} Furthermore, we uncovered an unprecedented activation pathway for the formation of pyrazolines from azides and electron deficient alkenes in the same DES.¹⁷

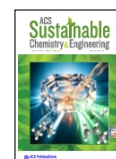
These intriguing results warrant a closer examination of the nature and characteristics of DESs since a deeper understanding of the properties of these designer solvents that influence their suitability for various applications is both timely and important. The significance of factors such as polarity and hydrogen-bonding capacity is well established for conventional organic solvents.¹⁸ However, DES encompass a vast chemical space,

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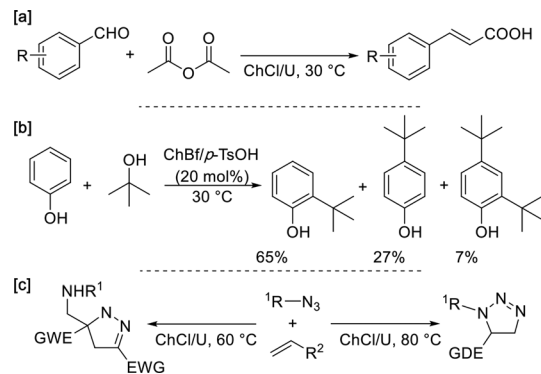
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Scheme 1. Selected DES Applications in Organic Synthesis: [a] Perkin condensation, [b] Friedel-Crafts alkylation, [c] Dipolar cycloadditions



even when considering only components derived from naturally occurring substances (i.e. NADES)¹⁹ which are prime candidates for greener and more sustainable reaction media. In the literature, a growing volume of experimental²⁰ and computational²¹ data on the physical properties of DES is available. This has paved the way for predictive modelling of such properties in new combinations.²² Nevertheless, our understanding on how these physical attributes, along with the bulk microstructure of DES,²³ affect chemical reactivity remains very limited. This gap is arguably delaying their broader adoption as solvents of choice for organic solvents.

Oxidation reactions are key transformations in both academia and industry that often suffer from poor atom economy and the generation of superstoichiometric amounts of toxic waste. Consequently, sustained efforts have been directed toward developing greener oxidation strategies in organic synthesis.²⁴ In this context, hydrogen peroxide is regarded as an environmentally friendly and safe oxidant since water is the only produced by product.²⁵ Oxidation chemistry is an area in which DES have proven particularly useful, offering a greener approach and sometimes improving chemical reactivity.^{26–30} Herein we report the oxidation of aldehydes to the corresponding carboxylic acids in a range of different Deep Eutectic Solvents with a focus on the physical properties of the designer solvents that influence chemical reactivity.

RESULTS AND DISCUSSION

Model Reaction and Optimization Studies

Nagarkar and co-workers reported the efficient oxidation of aldehydes to carboxylic acids in ChCl/U (1:2) without the need for additional reagents.^{31,32} This transformation was an ideal starting point for our studies, given that ChCl/U not only outperformed conventional standard solvents (e.g. MeCN, MeOH, toluene), but also alternative DES systems such as ChCl/glycerol (Gly) or ZnCl₂/U. Unfortunately, attempts to replicate these findings using *p*-anisaldehyde consistently failed, and only trace amounts of the corresponding acid were observed by ¹H NMR spectroscopy under the reported conditions. Modifications such as increasing reaction temperature from 50 °C to 70 °C or oxidant loadings (3 or 6 equivalents compared to the reported 1.5) did not improve conversion to the acid. Similarly, poor results were obtained when using MeCN as

solvent, and with *p*-chlorobenzaldehyde or cyclohexanecarbaldehyde as substrates.³³ Under these conditions, bisamides were the only identified reaction products.³⁴

Hydrogen peroxide is a relatively weak oxidant due to the poor leaving group nature of the hydroxide ion. To overcome this limitation, it is typically combined with metal catalysts or other activators to enhance the oxidation efficiency.³⁵ We selected a base as activator since the resulting HO₂[−] perhydroxyl anion is a potent nucleophile that has been used in this reaction in organic solvents.³⁶ With *p*-anisaldehyde as the model substrate, oxidation in ChCl/U (1:2) with excess of H₂O₂ and KOH afforded the desired carboxylic acid **2a** in 55% NMR yield alongside amide **3a**, and *N*-carbamoyl-4-methoxybenzamide **4a** as minor by-products (Table 1, entry 1). The formation of **4a** is attributed to the reaction between the aldehyde and urea under oxidative conditions. This reaction has been reported with aldehydes and amines.^{37,38} A similar transformation with urea is expected to be sluggish due to its reduced nucleophilicity. Also, the reaction of **4a** with KOH in DES led to the formation of both acid **2a** and amide **3a**, confirming the role of carbamoyl **4a** as precursor in the formation of amide **3a**.

As anticipated, the presence of both base and oxidant was essential for appreciable acid formation (Table 1, entries 2 and 3). Comparable results were obtained when urea-hydrogen peroxide was employed as the oxidant, whereas sodium percarbonate resulted in extensive decomposition of the reaction mixture (Table 1, entries 4 and 5). Increasing the H₂O₂ loading significantly improved the yield of acid **2a** (Table 1, entries 1, 6 and 7). Notably, with 12 equivalents of H₂O₂ (a 30% aqueous solution) a marked decrease in system viscosity was observed. To determine whether improved performance was attributable to oxidant excess or viscosity reduction, we conducted a control reaction using the initial 6 equivalents of H₂O₂ and added 26 equivalents of water to match the total solvent volume. No precipitate was observed in any of these reactions regardless of the peroxide loading, and therefore, the amount of water in the reaction mixture. Hence, the obtained yields support viscosity as a key factor for the increased reaction performance (Table 1, entries 6 and 8).

Initially, the hydrogen peroxide solution was added in four aliquots over a 20-minute period to mitigate undesired exotherms and decomposition (Table 1, entry 8). Extending the oxidant addition period to 40 minutes resulted in a modest improvement in product yield, whereas similar conversions were recorded with shorter dosing timings (Table 1, entries 10 and 11). Regardless of the addition rate, prolonged stirring beyond 10 minutes following the final H₂O₂ aliquot consistently failed to produce further conversion, suggesting rapid peroxide degradation under the reaction conditions. Gratifyingly, the reaction proceeded efficiently with a reduced base loading of 2 equivalents (Table 1, entry 12). However, alternative bases only led to lower yields of acid **2a** (Table 1, entries 13–17). This included reactions with NaOH as well as NaHCO₃, an additive known to form peroxydicarbonate ions (HCO₄[−]) as the active oxidising species.³⁹

With these preliminary results in hand, we next conducted a full factorial Design of Experiments (DoE) study, followed by an augmented design to a response surface methodology (RSM) framework, to gain some insight into the reaction variables with the largest statistical significance and how they are interconnected. JMP Pro 18 software was used to create

Table 1. Initial Optimization Studies^a

entry	oxidant (equiv)	base (equiv)	addition (min)	H ₂ O (equiv)	1a (%) ^b	2a (%) ^b	3a (%) ^b	4a (%) ^b
1	H ₂ O ₂ (6)	KOH (4)	20	–	13	55	16	<5
2	–	KOH (4)	20	–	83	<5	–	–
3	H ₂ O ₂ (6)	–	20	–	72	9	–	–
4	UHP (6)	KOH (4)	0	–	17	53	12	<5
5	2Na ₂ CO ₃ ·3H ₂ O ₂ (6)	KOH (4)	20	–	19	ND	ND	9
6	H ₂ O ₂ (12)	KOH (4)	20	–	13	72	<5	–
7	H ₂ O ₂ (3)	KOH (4)	20	–	27	26	11	<5
8	H ₂ O ₂ (6)	KOH (4)	20	26	<5	73	<5	<5
9	H ₂ O ₂ (6)	KOH (4)	0	26	25	63	<5	<5
10	H ₂ O ₂ (6)	KOH (4)	10	26	23	70	–	<5
11	H ₂ O ₂ (6)	KOH (4)	40	26	<5	82	6	–
12	H ₂ O ₂ (6)	KOH (2)	10	26	18	77	–	<5
13	H ₂ O ₂ (6)	NaOH (2)	10	26	27	57	–	–
14	H ₂ O ₂ (6)	TMG (2)	10	26	23	28	<5	–
15	H ₂ O ₂ (6)	DBU (2)	10	26	23	28	<5	<5
16	H ₂ O ₂ (6)	NaHCO ₃ (2)	10	26	44	12	–	–
17	UHP (6)	KOH (2)	10	52	20	68	–	–

^aReaction conditions: **1a** (1 mmol), CHCl₃/U (1:2, 2 mL). ^{b1}H NMR yields/recoveries are the average of at least two independent experiments with respect to 1,3,5-trimethoxybenzene as internal standard. ND = Not determined. UHP = Urea-hydrogen peroxide. TMG = 1,1,3,3-Tetramethylguanidine. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

experimental designs, statistical modelling, and data analysis. Based on the results compiled in Table 1, we defined reaction temperature and equivalents of H₂O₂, KOH, and water as the key factors to investigate, while concentration and reaction times were set to fixed values. Acid **2a** was the major reaction product in all experiments, and the carboxylic acid ‘actual by predicted’ plot showed a very good fit with the model, despite the presence of a few outliers. The model fit remains robust and provided valuable guidance to identify the optimal conditions for the reaction. It notably showed that 75 °C was the optimal temperature and that the addition of water was beneficial, but this effect is intrinsically intertwined with other factors such as the stoichiometry of the reaction.³³

The software generates a prediction profiler that models the predicted yield as a function of selected factor values. These relationships are best visualized as 3-dimensional response surfaces showing predicted yields against any two of the explored factors. The response surface illustrating the relationship between predicted yield, oxidant and base equivalents displays a clear maximum at high equivalents of both reagents (Figure 1). The modelled ideal conditions were 4 equivalents of KOH, 9 equivalents of hydrogen peroxide, and 59 total equivalents of water at 75 °C.

The predicted yield of 78 ± 9% was validated experimentally with an obtained yield for **2a** of 80% (±5% since the yield was determined by ¹H NMR spectroscopy). However, this value remains comparable to the yield obtained under our preferred reaction conditions (Table 1, entry 12: 2 equivalents of KOH, 6 equivalents of hydrogen peroxide, 26 equivalents of water at 75 °C), which employed lower excesses of all chemicals. These conditions are also better in terms of safety. It is worth mentioning that the predicted carboxylic acid yield under the chosen conditions was 65 ± 9%, which is very close to the experimental value of 77%.

According to the model, lower temperatures favor the formation of *N*-carbamoyl **4a**. Experimentally, this compound was obtained in 12% yield at 60 °C. In contrast, amide **3a** was experimentally observed in yields of up to 25% when reactions were conducted at 90 °C, consistent with the model’s prediction of increased formation at higher temperatures. Amides are versatile intermediates and essential in industrial applications including pharmaceuticals or polymer production.⁴⁰ While no optimization towards the production of **3a** was carried out as part of this work, these preliminary results open the possibility of converting aldehydes into amides without requiring large excess of strong acids, or precious metals as catalyst.⁴¹

Before moving on to explore the effect of using different DES components in this oxidation reaction, a selection of aldehydes were subjected to our optimized conditions to make sure they are compatible with differently functionalized aldehydes (Table 2).⁴² In these reactions, pure carboxylic acids **2** were obtained after an aqueous workup with no additional purification steps required. The reaction is sensitive to steric hindrance and yields considerably dropped with mesitylaldehyde as 71% of the starting aldehyde was recovered unreacted (Table 2, entry 3). A high acid yield was obtained with 4-trifluorobenzaldehyde (Table 2, entry 6), despite the formation of a small amount of the corresponding benzylic alcohol, issue of a Cannizzaro disproportionation.⁴³ This is expected for a relatively electron poor aldehyde in the presence of excess KOH.

We tested several heteroaromatic aldehydes such as furfural and picolinaldehyde. However, the high water solubility of the starting materials and their corresponding acids prevented the efficient recovery of organic compounds from the aqueous phase. Gratifyingly, thiophene-2-carboxylic acid **2g** could be isolated in a fair yield (Table 2, entry 7). The use of KOH also led to chemoselectivity issues and unsurprisingly it reacted with esters or nitrile substituents on the aromatic ring.³³ Also, while

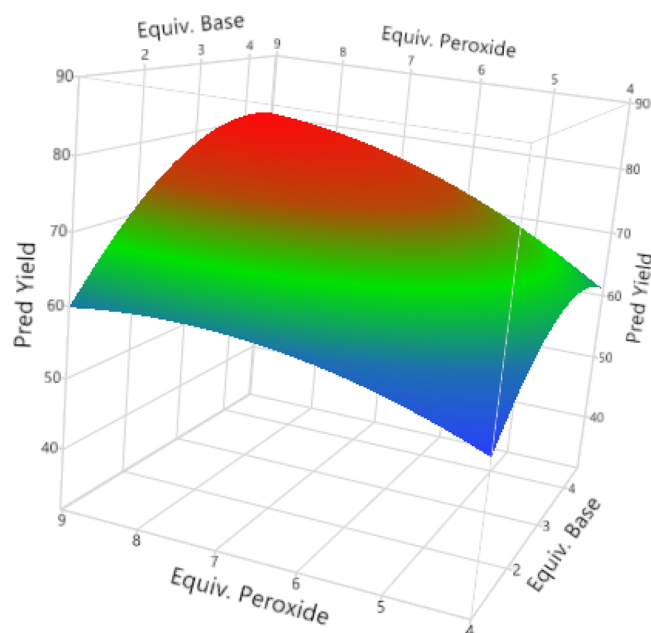


Figure 1. Plot of predicted yield of **2a** against peroxide and base equivalents (temperature set to 75 °C, water added set to 59 equivalents).

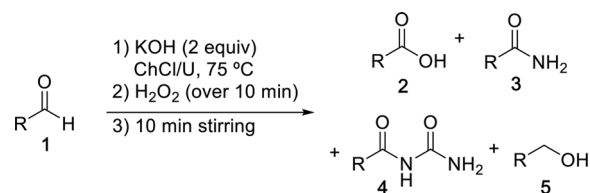
the reaction of cinnamaldehyde led to the formation of a complex mixture of compounds, an aliphatic carboxylic acid could be successfully isolated under these reaction conditions (Table 2, entry 8). Furthermore, the lower yields observed in several cases can be traced back to the instability of the starting aldehydes. Indeed, when benzaldehyde was subjected to the reaction condition in the absence of hydrogen peroxide, only 47% was recovered after 20 minutes of stirring.

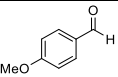
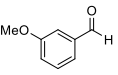
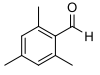
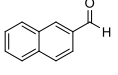
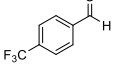
Gratifyingly, the formation of acid **2a** was successfully scaled up to 20 mmol scale.³³ The calculated E-factor and process mass intensity (PMI) for this reaction (187 and 188, respectively) are comparable to those estimated for a related system reported in methanol (169 and 170, respectively).^{33,36} Both E-factor and PMI are dominated by solvent contributions and therefore the slightly higher PMI and E-factor observed for the DES process is due to the higher molecular weight and density of ChCl/U relative to methanol (1.22 vs 0.79). This hydrogen peroxide oxidation avoids the use of transition metals, and ensures a high atom economy for the process (89%). The present conditions require a lower excess of strong base (2 instead of 4 equivalents of KOH) than the reported counterpart. Moreover, methanol (associated with significant health and safety concerns)⁴⁴ is here replaced by a DES with well documented biodegradability and low toxicity.⁴⁵ This is reflected in a high EcoScale⁴⁶ score of 84/100 for the DES-based system.

Effect of DES Composition in the Reaction Outcome

With a reliable set of reaction conditions in hand, we then investigated the effect of changing the DES on the oxidation of *p*-anisaldehyde. We selected twenty different DESs with varying HBAs and HBDs that are liquid at near room temperature or 75 °C. In this selection, we excluded components incompatible with the reaction conditions, such as carboxylic acids (e.g. lactic or oxalic acids). Similarly, phosphonium-based DESs were deemed unsuitable due to the undesired oxidation of the phosphonium salt.

Table 2. Aldehyde Oxidation in ChCl/U^a



Entry	Aldehyde	1 (%) ^b	2 (%) ^b	3 (%) ^b	4 (%) ^b	5 (%) ^b
1	 1a	18	77 (78)	--	<5	--
2	 1b	6	58 (51)	--	--	<5
3	 1c	71	18 (14)	--	--	--
4	 1d	19	56 (50)	--	--	--
5	 1e	7	60 (51)	--	--	--
6	 1f	<5	82 (83)	--	--	9
7	 1g	<5	57 (56)	11	6	--
8	 1h	<5	39 (33)	--	--	--

^aReaction conditions: **1** (1 mmol), KOH (2 equiv), water (26 equiv), ChCl/U (2 mL), then H₂O₂ (6 equiv). ^b¹H NMR yields/recoveries are the average of at least two independent experiments with respect to 1,3,5-trimethoxybenzene as internal standard. Isolated yields are shown in brackets.

We first screened a series of choline-based DESs with different hydrogen bond donors (Table 3). Using choline chloride as the HBA, all HBDs tested led to clean reactions, however, higher recoveries of the starting aldehyde negatively impacted the yields of acid **2a** (Table 3, entries 1–4). A similar trend was observed with choline bromide as the HBA (Table 3, entries 5–7). The only by-products detected in these reactions were trace amounts of acetals resulting from the reaction of glycerol or ethylene glycol. In contrast, DESs based on chlorocholine chloride, where the hydroxy group of the HBA cation is replaced by a chloro substituent, resulted in very low yields of acid and the formation of various unexpected by-products in the presence of glycerol or ethylene glycol (Table 3, entries 8–10). In these reactions, 4-methoxyphenol was the major product and small amounts of benzoquinone were also observed. This suggests a significant solvent effect that promotes a competing oxidation pathway related to the Dakin reaction.^{47,48}

Table 3. Oxidation of Aldehydes in Different Choline-Based DES^a

entry	HBA	HBD	1a (%) ^b	2a (%) ^b	observations
1	ChCl	U	18	77	traces of <i>N</i> -carbamoyl 4a
2		Gly	43	47	traces of acetals
3		EG	38	44	traces of acetals
4		Ace	23	62	–
5	ChBr	U	20	70	–
6		Gly	42	49	traces of acetals
7		EG	39	49	–
8	ClChCl	U	57	16	traces of 3a
9		Gly	44	10	4-methoxyphenol (16%), <i>p</i> -benzoquinone (7%) and traces of acetals
10		EG	48	11	4-methoxyphenol (13%) and traces of <i>p</i> -benzoquinone and acetals

^aReaction conditions: 1a (1 mmol), KOH (2 equiv), water (26 equiv), DES (2 mL), then H₂O₂ (6 equiv). ^b¹H NMR yields/recoveries are the average of at least two independent experiments with respect to 1,3,5-trimethoxybenzene as internal standard.

Table 4. Oxidation of Aldehydes in Other DES^a

entry	HBA	HBD	ratio	1a (%) ^b	2a (%) ^b	observations
1	TMAC	U	1:2	<5	77	traces of 3a, 4a and 5a
2		Gly	1:2	41	40	–
3		EG	1:2	28	50	traces of 5a
4	TBAC	Gly	1:3	41	37	–
5		EG	1:3	28	55	–
6	Bet	U	1:4	12	75	traces of 4a
7		Gly	1:4	54	31	traces of acetals
8		EG	1:4	29	56	traces of acetals
9	U	Ace	1:2	7	57	unknown by-product(s) (~10%)
10	Gly	U	5:2	17	72	traces of acetals

^aReaction conditions: 1a (1 mmol), KOH (2 equiv), water (26 equiv), DES (2 mL), then H₂O₂ (6 equiv). ^b¹H NMR yields/recoveries are the average of at least two independent experiments with respect to 1,3,5-trimethoxybenzene as internal standard.

The results with ClChCl-containing DESs could indicate a key role of the hydroxyl group in choline chloride for the success of the oxidation reaction. However, when we tested other ammonium salts as HBAs, it became clear that it is not necessarily the case (Table 4). Comparable or slightly lower yields were obtained with choline chloride, tetramethylammonium chloride or tetrabutylammonium chloride as HBAs. It should be noted that both TBAC and betaine are partially extracted during the workup, which prevents the direct isolation of pure acids from the reaction mixture by simple aqueous extraction.

Interestingly, the best results were systematically obtained in DESs with urea as the HBD. Very similar results were obtained with either ChCl or TMAC-based DESs, with the only difference being that the formation of trace amounts of *p*-methoxybenzyl alcohol 5a was observed in TMAC/U and TMAC/EG systems.

These results highlight the critical influence of DES composition on the outcome of the oxidation reaction. Subtle changes in the HBA structure can dramatically alter the reaction pathway. The consistent performance of urea-based DESs across different HBAs might suggest that the nature of the HBD plays

a more decisive role in promoting the desired oxidation to carboxylic acids.

Effect of DES Physical Properties on the Reaction Outcome

The DES screening revealed that multiple combinations of HBAs and HBDs can be suitable for a given reaction. However, selecting a specific DES for a particular reaction remains a challenge. To address this, we measured key physicochemical properties for each DES such as density, viscosity, pH and polarity, aiming to explore potential synergistic effects between discrete variables (e.g. DES composition), and continuous variables (e.g. measured properties).

For consistency, all measurements were conducted with a water content equivalent to that present at the start of the reaction (ca. 30%). Since no precautions were taken during the preparation and storage of the DESs to prevent water uptake (and given that DES composition and component ratio influence water absorption),⁴⁹ we determined the exact water content in each sample using a Karl-Fischer titrator. Still, the overall water content showed no major deviations, with all measured values ranging between 29.2% and 31.7%. We successfully

measured the selected properties for all DESs screened in this study, and the obtained values are included in Table 5.

Density and viscosity are critical physical properties in process chemistry, as they directly influence mixing efficiency, mass transfer rates, and overall reaction performance. Understanding these parameters is essential for accurate scale-up and reliable process control. Densities were measured at 25 °C and 50 °C, and values then extrapolated to 75 °C based on their well-established linear dependence on temperature.^{33,50–52} The measured densities fall within a relatively narrow range between 1.204 g/mL for ChBr/U (1:2) and 0.973 g/mL for TBAC/EG (1:3), the latter being the only DES with a density lower than 1 (Table 5, entry 15). When grouped by HBD, the density trend appears to be: U $\approx$ Gly > EG. For HBAs, among DESs that share HBA/HBD ratios, the density follows the order: ChBr > ClChCl > ChCl > TMAC. This range of DES densities is broadly comparable to water and DMSO, and slightly lower than most ionic liquids, which often exceed 1.2 g/mL. This suggests that these DESs can offer similar handling and mixing characteristics to standard solvents, while retaining some of the tunable properties of ionic liquids.

Viscosity shows greater variation among the different DESs, with values ranging from 34.35 cP for the most viscous aqueous DES, TBAC/Gly (1:3), to 4.29 cP for U/Ace (1:2) at room temperature (Table 5). The strong hydrogen bond network in DESs typically results in significantly higher viscosity values, frequently exceeding 100 cP and in some cases reaching tens of thousands of cP, especially for hydrophilic DESs like those studied here. However, the presence of water and elevated temperatures can substantially disrupt these interactions, leading to dramatic reduction in viscosity. Indeed, previous studies on ChCl/U (1:2) with water content comparable to ours reported a viscosity of 1.80 cP at 70 °C,^{53,54} which is lower than that of DMSO at room temperature ($\sim$ 1.99 cP). Slightly higher values (i.e. 3.79 and 2.17) were reported for wet ChBr/Gly (1:2) and

ChBr/EG (1:2) at 50 °C.⁵⁵ Overall, these moderate viscosity values are consistent with the literature and even lower values are expected at the actual oxidation temperature.

We next employed solvatochromic probes to determine Reichardt's E_T -N solvent polarity, along with Kamlet–Taft parameters: α (hydrogen bond donating ability/acidity), β (hydrogen bond accepting ability/basicity), and π^* (polarizability/dipolarity).⁵⁶ E_T -N and α values could not be obtained for certain solvent systems (namely ClChCl/Gly, ClChCl/EG and TBAC/EG) due to the absence of a visible absorbance maximum with the probe, Reichardt's dye 33. This may be attributed to the protonation of the dye under measurement conditions, which would suppress the characteristic band. All measured E_T -N values fall within a narrow range of 0.85–0.91, with two notable outliers: U/Ace (1:2) at 0.83, and TBAC/Gly (1:3) at 0.77. For comparison, common organic solvents such as DMSO and acetone have E_T -N values of approximately 0.44 and 0.35, respectively, while more polar solvents like ethanol and water reach 0.65 and 1.00, respectively.

The α parameter shows a broader spread, ranging from 1.51 for TMAC/EG (1:2) to 1.24 for TBAC/Gly (1:3). These values are higher than those of solvents like methanol or water (0.98 and 1.17, respectively) and are comparable to or exceed those for common ionic liquids, confirming strong hydrogen bond ability. Similarly, parameter β values range widely, with TBAC/Gly (1:3) showing the highest basicity (β = 0.57), and Bet/U (1:4) the lowest (β = 0.28). These values are similar to or lower than standard polar solvents such as DMSO (0.76), acetonitrile (0.40), and water (0.47). Finally, the π^* parameter varies from 1.36 for Gly/U (5:2) and Bet/U (1:4) to 1.22 for TBAC/Gly (1:3) and Bet/EG (1:4), indicating moderate to high dipolarity. These values are similar to those of highly polar solvents such as DMSO (π^* = 1.00) and ionic liquids like [BMIM][BF₄] (π^* $\approx$ 1.20–1.40). It is important to note that while the presence of water tends to increase the

Table 5. Physical Properties of Studied DESs

entry	HBA	HBD	ratio	water content (%)	density (g/mL) ^a	viscosity (cP)	E_T -N	α	β	π^*	pH ^b	2a (%) ^c
1	ChCl	U	1:2	29.8	1.108	6.23	0.89	1.44	0.33	1.31	7.92	77
2		Gly	1:2	30.2	1.107	13.29	0.90	1.45	0.31	1.30	4.01	47
3		EG	1:2	30.1	1.059	7.96	0.88	1.45	0.39	1.25	6.95	44
4		Ace	1:2	30.7	1.040	7.51	0.86	1.42	0.42	1.24	6.03	62
5	ChBr	U	1:2	29.2	1.204	4.54	0.90	1.43	0.30	1.34	8.00	70
6		Gly	1:2	30.0	1.185	9.76	0.91	1.49	0.33	1.31	3.91	49
7		EG	1:2	30.2	1.153	5.96	0.89	1.48	0.36	1.26	6.10	49
8	ClChCl	U	1:2	29.9	1.136	6.40	0.85	1.37	0.40	1.30	6.67	16
9		Gly	1:2	30.4	1.128	15.64	ND	ND	0.36	1.25	2.99	10
10		EG	1:2	30.2	1.086	9.20	ND	ND	0.42	1.29	3.05	11
11	TMAC	U	1:2	31.5	1.076	6.44	0.86	1.36	0.33	1.30	7.83	77
12		Gly	1:2	30.4	1.081	15.62	0.89	1.46	0.38	1.28	4.05	40
13		EG	1:2	31.0	1.027	8.49	0.90	1.51	0.44	1.25	5.85	50
14	TBAC	Gly	1:3	31.6	1.025	34.35	0.77	1.24	0.57	1.22	4.10	37
15		EG	1:3	31.7	0.973	17.35	ND	ND	0.53	1.25	4.64	55
16	Bet	U	1:4	29.8	1.143	6.71	0.85	1.33	0.28	1.36	7.81	75
17		Gly	1:4	30.2	1.134	17.90	0.89	1.47	0.40	1.26	6.05	31
18		EG	1:4	30.3	1.065	7.70	0.86	1.45	0.45	1.22	7.43	56
19	U	Ace	1:2	30.5	1.054	4.29	0.83	1.34	0.39	1.27	6.23	57
20	Gly	U	5:2	30.3	1.151	13.10	0.89	1.40	0.31	1.36	8.32	72

^aExtrapolated values at 75 °C. ^bMeasured at 75 °C. ^c¹H NMR yields are the average of at least two independent experiments with respect to 1,3,5-trimethoxybenzene as internal standard. ND = Not determined.

polarity of DESs,^{57,58} higher temperatures in ChCl-based DESs led to a linear decrease of $E_T N$ and α while β and π^* remained constant.⁵⁹

The greatest variation among the measured physical properties was observed in pH values, which were determined at 75 °C, reflecting the chemical space covered by the DES components. The values obtained are in accordance with expectations and in general, the HBD appears to exert the strongest influence on the resulting pH of each DES. Urea-based DESs are slightly basic, with pH values ranging from 7.81 to 8.32, whereas glycerol-containing DESs are generally acidic, with pH values between 6.05 and 2.99, except for Gly/U (5:2), which behaves more like a urea-based system and has a basic pH of 8.32. EG-based DESs display pH in the range of 5.85 to 7.43, with the Bet-containing DES marking the high end of the scale. Noteworthy, DESs containing ClChCl consistently show lower pH values than those with other HBAs and fall outside the ranges described above. For example, ClChCl/U is just below neutral, while both ClChCl/Gly and ClChCl/EG are very acidic (pH $\sim$ 3.0).

A correlation analysis using Pearson's correlation coefficient (r) revealed notable relationships among the physical properties of the DESs studied (Figure 2 and Table S7). The strongest positive correlation was observed between molecular weight and viscosity, consistent with the expectation that larger, more complex molecules hinder flow and increase resistance. Viscosity also showed moderate correlations with $E_T N$ polarity, and the Kamlet–Taft parameters α and β , indicating that more viscous DESs tend to exhibit stronger hydrogen bonding interactions and higher polarity. This aligns with literature reports that viscosity in DESs is influenced by the strength and extent of hydrogen bonding networks, which also affect solvatochromic behaviour.⁶⁰

Interestingly, density displayed moderate positive correlations with $E_T N$ and π^* , and a strong negative correlation with β . This suggests that denser DESs tend to be more polar and less basic, possibly due to tighter molecular packing and reduced availability of lone pairs for hydrogen bond acceptance. These trends are consistent with findings in ionic liquids, where density and polarity often co-vary due to ion pairing and structural organization.⁶¹ The $E_T N$ polarity parameter

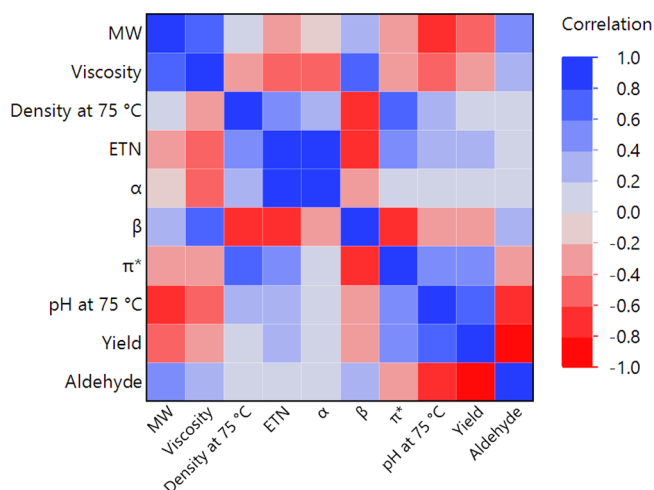


Figure 2. Color map of Pearson's correlations for physical properties, *p*-anisic acid **2a** yield, and *p*-anisaldehyde **1a** recovery.

correlated well with the Kamlet–Taft parameters, particularly π^* , which is expected given their shared dependence on dipolar interactions. However, the Kamlet–Taft parameters themselves did not show strong intercorrelations, except for a minor negative correlation between α and β , and a strong negative correlation between β and π^* . This reflects the complex interplay between hydrogen bond donating and accepting abilities in DESs, which can vary independently depending on the specific HBA/HBD combination.

Importantly, although pH is not the sole influencing factor, a clear positive correlation was observed between the pH values of the DESs and the yield of the oxidation reaction. This finding was somewhat unexpected, given that the transformation was carried out in the presence of excess KOH. To investigate this further, we closely monitored the oxidation of *p*-anisaldehyde **1a**. Reaction progress was tracked through time-point experiments, with ^1H NMR spectroscopy used to determine yields and recoveries with respect to an internal standard. Furthermore, *in situ* measurements of temperature and pH were recorded using an EasyMax reactor (Figure 3). Upon addition of the peroxide, a pronounced exotherm was observed, with the first injection resulting in a temperature increase of approximately 20 °C. Subsequent injections produced progressively smaller temperature rises, likely due to the consumption of the starting aldehyde. Each peroxide addition also led to a decrease in pH, followed by a gradual upward drift over time. By the end of the reaction, the pH had decreased by approximately two units relative to the initial value.

Each peroxide injection corresponded with an increase in carboxylic acid formation, with the first two additions producing the most significant increases. Beyond the second injection, the incremental formation of **2a** diminished, and after the fourth injection the reaction plateaued with only marginal additional

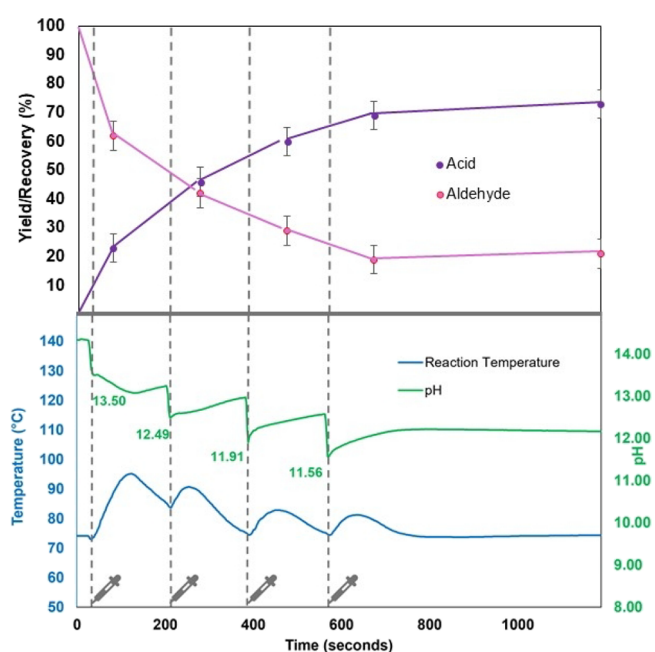


Figure 3. ^1H NMR yields and recoveries for the oxidation of **1a** over time under optimized conditions (top); EasyMax reactor *in situ* monitoring of reaction temperature (blue) and pH (green) of oxidation reaction under optimized conditions (bottom).

product formation observed during the final 10 minutes of stirring. Adding a fifth peroxide injection did not result in further aldehyde conversion under these conditions.

These results can be directly correlated with the pH-dependent speciation of hydrogen peroxide with pH. The oxidation to carboxylic acid in ChCl/U was observed to plateau once the pH dropped below 13 (Figure 3, top). The concentration of the hydroperoxide anion, the more reactive oxidising species, is maximal at $\text{pH} \geq 13$ and decreases sharply between pH 13 and 12. At lower pH, neutral H_2O_2 predominates and acts as the oxidant. This shift in speciation is particularly relevant to the atypical results obtained with ClChCl-based DESs, which led to very low yields of acid **2a** and 4-methoxyphenol as the main reaction product in ClChCl/Gly. This suggests competing transformation related to the Dakin reaction.⁶²

The ClChCl/Gly DES exhibited the lowest pH among the 20 systems studied, with a measured value of 2.99. Based on this, we hypothesized that at such low pH values, the side reaction becomes kinetically competitive with respect to the desired oxidation to the carboxylic acid. To test this, we conducted a control experiment in which the pH of the ClChCl/Gly DES was increased to 11 by the addition of KOH. Under these modified conditions, the reaction predominantly yielded unreacted *p*-anisaldehyde **1a** (75%), with only small amounts of acid **2a** (6%) and 4-methoxyphenol (<5%) detected. The final pH of the reaction mixture was measured at 4.58.

The determining role of pH was further highlighted in the solvent recycling experiments. After workup,³⁹ excess water was removed with a rotary evaporator, and the precipitated KCl was filtered off. Since the pH had been lowered to 2 to ensure complete precipitation of the desired carboxylic acid, the recovered ChCl/U was subsequently treated with amphoteric KHCO_3 , raising the pH to 5.90. ^1H NMR analysis revealed no significant differences between used and fresh batches of DES.³³ However, when the model reaction was carried out in recycled DES the yield of acid **2a** decreased to 40%, with 49% of starting *p*-anisaldehyde recovered. This is comparable to the outcome of the oxidation in TMAC/EG (Table 4, entry 3). Furthermore, when the recovered ChCl/U DES was basified directly after the workup (pH ca. 9), excess water had to be distilled off, and no KCl precipitated in this process. Despite the higher pH, the initial reactivity was not restored, and acid **2a** was obtained in only 15% yield. These results underscore that while the pH of a DES-based reaction mixture can be externally adjusted, the intrinsic properties of the DES, particularly its buffering capacity and inherent acid-base behaviour, play a decisive role in the final reaction outcome.

CONCLUSIONS

This study demonstrates that the intrinsic properties of deep eutectic solvents (DESs), particularly pH, play a decisive role in determining the outcome of hydrogen peroxide-mediated aldehyde oxidations. Despite the presence of excess base, the pH of the DES strongly influenced the speciation of hydrogen peroxide and, consequently, the efficiency and selectivity of the oxidation. Urea-based DESs consistently delivered high yields of carboxylic acids, while acidic DESs, especially those based on chlorocholine chloride, promoted competing pathways such as the formation of 4-methoxyphenol. Control experiments confirmed that simply adjusting the pH externally is

insufficient to override the inherent reactivity dictated by the DES matrix.

These findings highlight the importance of considering both the composition and physicochemical properties of DESs when designing green oxidation processes. The broad pH range accessible through DES formulation offers a unique opportunity to tailor reaction environments without the need for additional reagents. However, this same tunability introduces complexity, as subtle changes in solvent structure can lead to significant shifts in reactivity. We demonstrate that pH is not merely a tunable reaction parameter in DES, but a fundamental property that can govern oxidant speciation and reaction selectivity. This non-intuitive buffering behaviour of DES means that nominal pH adjustments do not necessarily translate into predictable changes in the reaction. The failure to achieve solvent recycling in this work despite the different conditions tested highlights a practical limitation linked to this complexity. A detailed understanding of how pH evolves and is internally regulated within a given DES is therefore essential for rational reaction design, solvent recycling, as well as scalability. A deeper understanding of DES-mediated transformations is key for broader adoption of DESs in green synthesis, where solvent choice can be leveraged not only for environmental benefits but also as a strategic tool to control chemical reactivity.

EXPERIMENTAL SECTION

General Considerations

All chemicals were obtained from commercially available sources and used without further purification. DESs were prepared following a simple mix and heat procedure.⁶³ All reactions were carried out in air, without taking any precautions to exclude moisture. NMR spectra were measured on Bruker AVANCE 400 spectrometers (^1H : 400 MHz, ^{13}C : 101 MHz, ^{19}F : 377 MHz) at 20 °C. The chemical shifts (δ) are given in ppm relative to tetramethylsilane standard or residual DMSO signal. The multiplicity is given as br, s, d, t, and m for broad, singlet, doublet, triplet and multiplet, respectively. Water content of DESs was measured using a HI933 Karl Fischer volumetric titrator. Viscosity measurements were carried out at room temperature using a microVISC-mRheosense viscometer. Density of DESs was measured at 25 °C and 50 °C using a Mettler Toledo Easy D40 densiometer. Polarity was determined using 4-(2,4,6-triphenylpyridinio)-2,6-dichlorophenolate (Reichardt's Betaine Dye 33), *N,N*-diethyl-4-nitroaniline and 4-nitroaniline solvatochromic probes using a Cary-60 spectrometer at room temperature. pH was measured using a Mettler Toledo SevenEasy S20 pH Meter at 75 °C. JMP Pro 18 software was used for the Design of Experiments (DoE) study.

General Procedure for the Oxidation of Aldehydes in DES

In a 14 mL scintillation vial equipped with a magnetic stirrer bar, aldehyde (1.0 equiv) was stirred at 250 RPM in ChCl/U (1:2) (2 mL, 0.5 M) and heated to 75 °C. Water (26 equiv) and KOH (50% w/w in water, 162 μL , 2 equiv) were added, followed by H_2O_2 (30% w/w in water, 618 μL , 6 equiv) in four equal portions over 10 minutes. The reaction mixture was stirred for a further 10 minutes, and then cooled to room temperature, diluted with water (5 mL) and extracted with EtOAc (3×5 mL) to remove unreacted starting materials as well as any organic impurities. The aqueous layer was then acidified with aqueous HCl (2 M); the pH was checked using indicator paper to ensure that the reaction mixture was acidic (pH $\sim$ 2). The mixture was then extracted with EtOAc (3×5 mL). The combined organic layers were washed with water and brine (15 mL each), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The

desired carboxylic acids **2** were obtained analytically pure without any further purification steps.

p-Anisic acid (**2a**)

Following the general procedure from *p*-anisaldehyde (122 μ L, 1 mmol), the title product was obtained as a white solid (119 mg, 78%). Spectroscopic data are in accordance with the literature.⁶⁴

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.69 (br s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.5, 163.3, 131.8, 123.4, 114.2, 55.8.

■ ASSOCIATED CONTENT

Data Availability Statement

FAIR data containing primary NMR FID files can be accessed at Imperial College Research Services Data Repository, DOI: 10.14469/hpc/15582

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.6c02551>.

Experimental procedures, design of experiment details, compound characterization, and density and polarity data (PDF)

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Notes

The authors declare no competing financial interest.

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■ GLOSSARY – DES COMPONENTS

Ace	acetamide
Bet	betaine
ChBf	choline bisulfate
ChBr	choline bromide
ChCl	choline chloride
ClChCl	chlorocholine chloride
EG	ethylene glycol
Gly	glycerol
GuH	guanidine hydrochloride
TBAC	tetrabutylammonium chloride
TMAC	tetramethylammonium chloride
U	urea

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