Journal Pre-proofs

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Please cite this article as: A. Antenucci, M. Bonomo, G. Ghigo, L. Gontrani, C. Barolo, S. Dughera, How do arenediazonium salts behave in Deep Eutectic Solvents? A combined experimental and computational approach, *Journal of Molecular Liquids* (2021), doi: https://doi.org/10.1016/j.molliq.2021.116743

H... computational approach

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How do arenediazonium salts behave in Deep Eutectic Solvents? A combined experimental and computational approach

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ABSTRACT

Despite the growing use of deep eutectic solvents as green reaction media in a number of organic syntheses, no significant reactions of diazonium salts in these solvents are known in the literature. In this paper, we present the behavior of arenediazonium tetrafluoroborates in new polyol-based DESs, the nature of which is investigated by means of a combined computational and experimental approach. A relatively fast (strictly depending on the electronic effects of the substituents bound to the aromatic ring) reduction reaction occurs initiated by the formation of a glycerolate-like species as proved by a thorough computational study aiming at elucidating the involved mechanism.

KEYWORDS

Deep eutectic solvents, diazonium salts, DFT, reaction mechanism, physico-chemical characterization

In recent years, deep eutectic solvents (DESs) attracted intensive attentions as cheap, synthetically accessible, nontoxic and biodegradable at room temperature solvents.[1–5] DESs[6] are considered to be an environmentally benign and sustainable alternative to the conventional organic solvents.[7] They do not only possess the advantages of ionic liquids,[5,8] such as designability, chemical stability, and negligible vapor pressure, but they also pose many other advantages, such as tunability, low-cost and easily sourced raw materials, as well as green and simple synthesis without using other organic solvents.[9].

Since firstly reported by Abbott and coworkers,[4] DESs were widely used in diverse fields of research including material preparation,[10] metal extraction and processing,[11,12] electrochemistry,[13–16] gas adsorption,[17–19] conversion of biomass and renewable resources into valuable chemicals[20–22] and biodiesel manufacturing .[23] For what concerns organic reactions, depending on their peculiar features, DESs may act as simple reaction media, as well as non-innocent solvents, which means that they play an active role in the reaction as catalysts or reagents.[24–27]In the light of this, it can certainly be said that DESs have every chance of becoming "the reaction media of the century".[26]

Despite the increasing use of DESs in organic synthesis has already brought to their employment within the framework of important processes (*e.g.* aldol condensation,[28] Diels-Alder cycloaddition,[29] electrocyclization reactions,[30] nucleophilic acyl substitution[31] among others), they have never been used as solvents in the reactions of diazonium salts, excluding two very recent examples. The first describes one-pot diazotization/coupling reactions in choline chloride/tartaric acid DES;[32] the second describes the electro-grafting of arenediazonium salts on carbon surfaces in the presence of ethaline.[33]

Indeed, diazonium salts are a very important class of compounds of major use in organic chemistry, as they are synthons for the preparation of a wide range of functionalized compounds.[34]

Herein, we present an experimental and theoretical approach to the hydrodediazoniation reaction of arenediazonium tetrafluoroborates in DESs. Apart from being a transition metal-free and green strategy to remove amino groups from aromatic rings, this protocol is a preliminary exploration of the behaviour of arenediazonium compounds in such media. This accounts for their background reactivity when they undergo more complex transformations, currently under investigation in our group. Moreover, the employed DESs are accurately characterized, in order to enhance the importance of the establishment of DES or DES-like interactions in the performances of the model reaction.

RESULTS AND DISCUSSION

Background of the synthetic design.

Following a previous research, which was directed towards developing the synthetic potential of arenediazonium salts in Cu catalyzed reactions,[35] we decided to test arenediazonium tetrafluoroborates

in ⬚⬚⬚⬚ on media. Incidentally, these reactions do not occur using traditional organic solvents.

, We resolved to behaviour of 4-nitrobenzenediazonium tetrafluoroborate (**1a;** Figure 1) As a model substrate and to DES formed by choline chloride/glycerol (ChCl-Gly) as solvent;[1] the latter is a combination of materials already reported in literature.[37–41]

1a
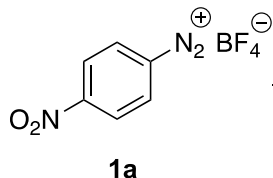
Figure 1. 4-Nitrobenzenediazonium tetrafluoroborate

Once **1a** is dissolved, at rT, in ChCl-Gly it was stable, until the addition of Cu powder. Following this addition, an almost immediate reaction occurred, as proved by (nitrogen) bubbling in the vial; however, instead of desired homocoupling product (4,4'-dinitrobiphenyl), we obtained the Sandmeyer adduct (1-chloro-4-nitrobenzene; Table 2; entry 1).[34] This is probably due to the fact that the dissolution of the ChCl in the glycerol matrix and the following DES formation lead to an halide anion that is partially negatively charged. In order to prevent Sandmeyer reaction, we changed the DES typology, exploiting the ones in which the hydrogen bond acceptor (HBA) is a salt (i.e. K_2CO_3 or Cs_2CO_3)[42] lacking halide anions. Unfortunately, no reaction occurred due to the low solubility of the salt in these mixtures (Table 2; entries 2 and 3).

In the light of these results, we tested the same approach by using alkali fluorides as HBAs. In fact, it is well known that it is impossible to obtain aryl fluorides with Sandmeyer reaction.[34] It must be stressed that DESs with choline fluoride as HBA[1] or unconventional mixtures obtained by aqueous potassium fluoride tetrahydrate are known in the literature.[43] We dissolved, in various ratio, KF or CsF as HBA in glycerol or ethylene glycol, behaving as hydrogen bond donors (HBD), heating at 80 °C, as reported in Table 1 (entries 1, 2, 3, 4, 7, 8, 9). On the other hand, NaF was found to be insoluble both in glycerol and ethylene glycol[44] (Table 1; entries 5, 6, 10). Quite surprisingly, as soon as the diazonium salt was dissolved into the Glycerol/CsF (or KF) mixture (and even before the addition of any copper source), a quick decomposition of the salt occurred as proved by the mixture bubbling. Furthermore, we decided to use, as an alternative to fluorides, other alkali metal halides (e.g. KBr, KCl), dissolving them in glycerol (Table 1; entries 11, 12) to further clarify the role of the halide anion within framework of the selected reaction. It is important to point out that these last two salts did not dissolve in ethylene glycol.

Table 1. Preparation of DESs, DES-like (DL) and salt in solvent mixtures (SiS) solvent media.

1	Gly	KF	3:1	DL
2	Gly	KF	6:1	DES
3	Gly	KF	10:1	DL
4	Gly	CsF	6:1	DES
5	Gly	NaF	6:1	SiS
6	Gly	NaF	10:1	SiS
7	EG	KF	3:1	DL
8	EG	KF	6:1	DES
9	EG	KF	10:1	DL
10	EG	NaF	6:1	SiS
11	Gly	KBr	6:1	SiS
12	Gly	KCl	6:1	SiS

[a] 0.1 mol of metal halides were heated for 2h at 80°C with respectively 0.2, 0.3, 0.6 or 1 mol of Gly. HBD = Hydrogen Bond Donor; HBA = Hydrogen Bond Acceptor; Gly = glycerol; EG = ethylene glycol.

Clarification of proposed mixtures chemical nature

Before going further with the reaction scope, it is of pivotal importance to shed more light on the chemical nature of the proposed mixture. Indeed, while the DES based on glycerol (as HBD) and choline chloride (as HBA) is well documented in literature, the ones based on KF and CsF are here proposed for the first time. The formation of a DES (and its discrimination from a "simple" salt in solvent solution) is not trivial being based on a complex interplay between hydrogen bond, electrostatic and Van Der Waals interactions. The actual formation of a DES could be proved by the sum of different experimental and computational approaches. Among these, one of the most accessible technique is the analysis of the electrochemical properties of the resulting mixture. Indeed, the type and the number of interactions that allow the solubilization of the HBA (i.e. the halide anion in the present case).in the HBD will sizably impact on the conductivity of the whole system.

As a starting point, three different mixtures, varying for the relative Gly/KF amount (namely 3:1, 6:1and 10:1), were tested. Conductivity measurements (Figure 2a) showed a nonlinear trend with respect to the concentration of the salt; the conductivity of the samples increases in the order 10:1 (0.14 mS/cm) < 1:3 (0.39 mS/cm) < 6:1 (0.71 mS/cm). On one hand, the higher (especially with respect to the 3:1 counterpart) conductivity of the 1:6 is hardly explainable without considering the establishment of intermolecular interactions; on the other, the value of 10:1 could be ascribable to the lower concentration of the salt in this mixture. To rule out the impact of [KF], we resolved to molar conductivity, Λ, (i.e. the experimental

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co[...]y [...] ([...]e)
for a selected solute/solvent couple if the obtained solution behaves ideally. In the present case, comparable Λ have been calculated for 3:1 (14 S m^2 mol^{-1}) and 10:1(16 S m^2 mol^{-1}), the half of the 6:1 ones (31 S m^2 mol^{-1}). It should be pointed out that molar conductivity also depends on the viscosity of the system but, in the present case, one could fairly assume that the variation of solution viscosity (as a consequence of the addition of different KF amount) is negligible. Thus, electrochemical data clearly point toward the peculiarity of the 6:1 mixture, that could be considered as a real Deep Eutectic Solvent.

Moreover, ^{1}H-NMR spectrum of this mixture was recorded and compared with spectrum of pure glycerol. Both were acquired in neat conditions and with D$_2$O as an internal standard. As can be seen (Supporting Information pages 10,11) from the stacking of the two spectra, glycerol (red signals) showed two peaks relating to the hydroxyl groups which, upon the formation of the DES (blue signals), coalesced. Furthermore, they are deshielded due to the formation of the hydrogen bond network.

To undoubtedly demonstrate the formation of a DES further investigations are required (that will be specifically tackled in a forthcoming paper); yet, in the present case we are mostly interested in its (active) role in the reactivity of diazonium salts. Albeit the other two mixtures cannot (at least at this stage) be classified as DESs, the presence of DES-like interactions[5] could make them suitable as solvents in the selected reaction.

Then, once the HBD/HBA ratio was fixed at 6:1, we further extended the electrochemical characterization to different mixtures varying for the nature of the cation or the anion of the HBA (*i.e.* NaF or CsF and KBr or KCl, respectively) or the choice of the HBD, by testing other aliphatic alcohols. NaF is partially unsoluble in Gly and the desired 6:1 ratio could not be reached. On the other hand, CsF has practically the same behaviour of KF, pointing out that albeit the choice of the cation is of paramount importance in the DES formation, it only plays a limited role in determining the properties of the eutectic.
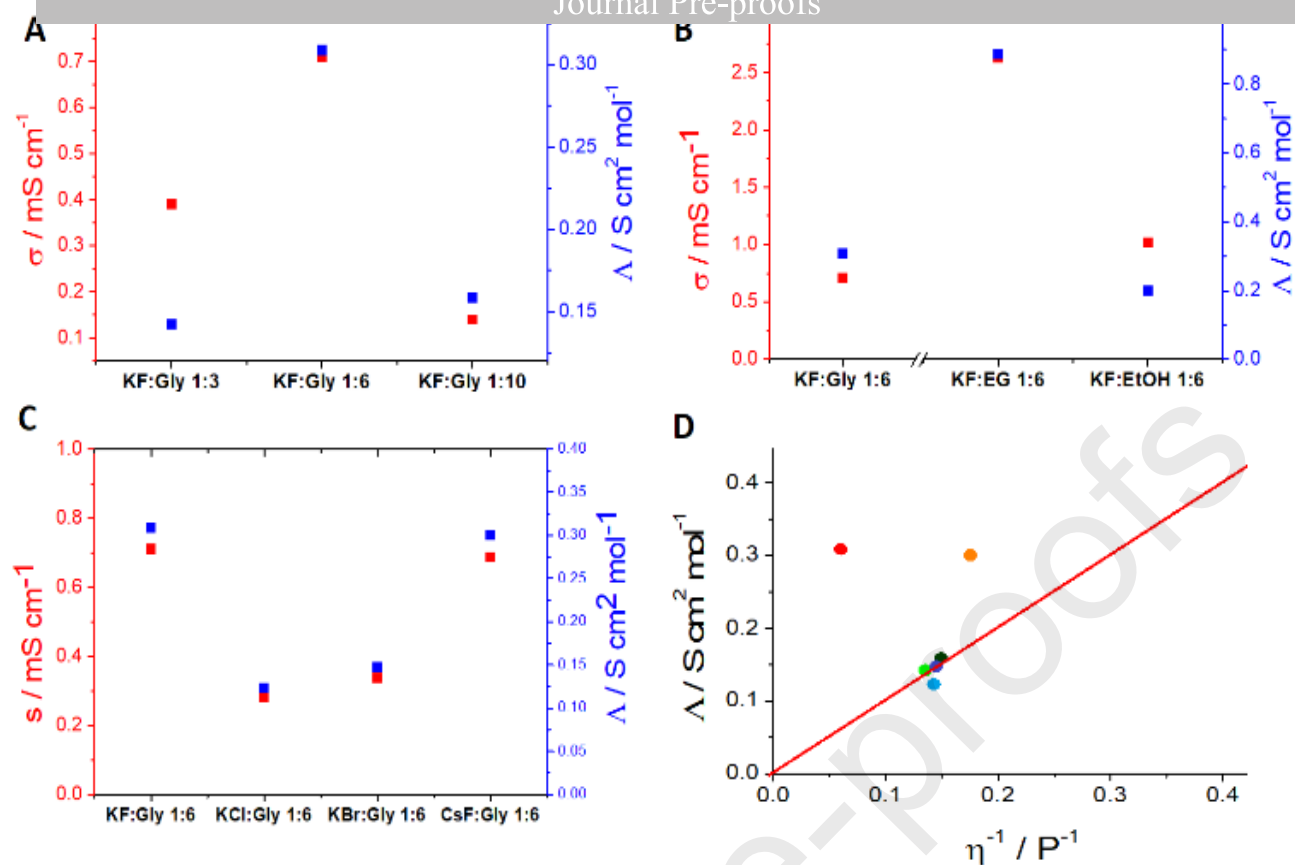
Figure 2. Conductivity (right axes, red squares) and Molar Conductivity (left axes, blue squares) of different mixtures analyzed in this work. Mixtures differ for Gly/KF ratio (a); nature of HBD (b) and nature of anion or cation in the HBA (c). (d) Walden's plot of different mixtures: Gly/KF 3:1 (light green), Gly/KF 6:1 (red); Gly/KF 10:1 (blue); Gly/CsF 6:1 (orange); Gly/KCl 6:1 (dark green) and Gly/KBr 6:1 (light blue).

The replacement of F with another halogen (both Br and Cl), instead, influences the electrochemical properties of the resulting mixture dramatically. They experience relatively low conductivity values that could be ascribed to a not optimal solvation of the halogen by the HBD, that prevents us to consider both Gly/KBr 6:1 and Gly/KCl 6:1 as Deep Eutectic Solvents.[5] A valuable tool to investigate the (non)-ideality of a mixture is the so-called Walden's plot, in which the molar conductivity of the species is represented as a function of the inverse of the viscosity of the system. In the Walden plot the bisector passing through the origin of the plot represents the behaviour of a 1 M aqueous KCl solution. As a rule of thumb mixtures placed close to this line could be considered as conventional mixtures; on the other hand, positive (negative) displacement from the bisector is a sign of the presence of intermolecular interactions that lead to an increase (decrease) of the mixture conductivity. In the present case (figure 2d), it is clear that only Gly/KF 6:1 and Gly/CsF 6:1 present a positive displacement from the bisector, further sustaining their DES-nature.

Th[...]G) similar intermolecular interactions are expected due to their structural similarity. Indeed, EG/KF 6:1 showed higher molar conductivity (0.88 S m^2 mol^{-1}) that could be explained with the lower viscosity of EG (0.16 Poise) with respect to Gly (14.12 Poise). For sake of comparison, we also analysed a EtOH/KF 6:1 mixture but a relatively low molar conductivity value was found (0.20 S m^2 mol^{-1}), despite of the much lower viscosity of ethanol (9.8*10^{-3} Poise). Among the classical solvent EtOH was chosen because it is the lower limit of the homologous series EtOH/EG/Gly, embodying 1, 2 and 3 H$_2$(CHOH)$_x$ moieties. If placed in a Walden plot EG/KF 6:1 and more clearly EtOH/KF 6:1 show a negative displacement from the bisector (not shown), probably due to the lowest amount of hydroxyl moieties that are not able to completely disrupt the ion pairs formed.[45]

In the light of these outcomes, we selected DES Gly/KF 6:1 as a model system and we added 4-nitrobenzenediazonium tetrafluoroborate (**1a**) to it. Surprisingly, almost instantaneous decomposition (in about 5 minutes; brisk boiling due to nitrogen loss) of **1a** occurred and nitrobenzene (**2a**) was formed as the only product (Table 2; entry 6). It must be stressed that this kind of decomposition occurred when **1a** is dissolved only in some of the mixtures reported on Table 1 (Table 2; entries 4, 5, 7 and 8) and even in one prepared by mixing up ethylene glycol and betaine[46] (Table 2; entry 9).

Interestingly, no decomposition was observed by dissolving the diazonium salt in bare glycerol (Table 2; entry 10), ethylene glycol (Table 2; entry 11) or other organic solvents such as EtOH (Table 2; entry 12) or DMSO (Table 2; entry 13). Moreover, even dissolving **1a** in glycerol and adding 1 or 2 equivalents of KF (for 1 equivalent of **1a**) no decomposition occurred (Table 2, entry 14). Finally, by preparing a suspension of KF in both EtOH and DMSO (1 or 2 equivalent) and adding **1a** (1 equivalent) to them, in the case of DMSO (Table 2; entry 16) a violent decomposition of **1a** occurred, with the formation of tarries. On the other hand, in the case of EtOH (Table 2, entry 15), after 2 h unreacted **1a** was still present in the reaction environment. The latter tests are crucial evidences that controlled decomposition reaction of diazonium salt could take place only if DES (or DES-like) interactions are established between the salt and the HBD. Interestingly, the behavior of salt **1a** in Gly/KBr or Gly/KCl (6:1; Table 1; entries 17, 18) was completely different than that observed in Gly/KF 6:1. In fact, **1a** did not undergo instant decomposition and after 24 hours beside **2a** a fair amount of 1-bromo-4-nitrobenzene or 1-chloro-4-nitrobenzene was recovered. Intrigued by these results, a number of other diazonium salts **1**, bearing either electron withdrawing or electron donating groups, were treated in DES Gly/KF 6:1. The results are show in Table 3.

Table 2. Behavior of **1a** in various DESs or solvents.

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$$\underset{\textbf{1a}}{O_2N-\!\!\!\!\bigcirc\!\!\!\!-N_2\ BF_4} \longrightarrow \underset{\textbf{2a}}{O_2N-\!\!\!\!\bigcirc}$$
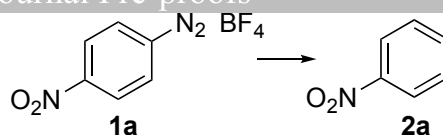
Entry	DES, mixture or solvent	Time (min)	Yield of **2a**[a] (%)
1	Gly/CC[b] 4:1	5	-[c]
2	Gly/K$_2$CO$_3$ 4:1	120	-[d]
3	Gly/Cs$_2$CO$_3$ 4:1	120	-[d]
4	Gly/KF 10:1	5	**2a**; 84
5	Gly/KF 3:1	5	**2a**; 72
6	Gly/KF 6:1	5	**2a**; 86
7	Gly/CsF 6:1	5	**2a**; 72
8	EG/KF 6:1	5	**2a**; 70
9	EG/B[e] 6:1	5	**2a**; 74
10	Gly	120	-[d]
11	EG	120	-[d]
12	EtOH	120	-[d]
13	DMSO	120	-[d]
14	KF in Gly[f]	120	-[d]
15	KF in EtOH[f]	120	-[d]
16	KF in DMSO[f]	5	-[g]
17	Gly/KBr	24h	[h]
18	Gly/KCl	24h	[i]

[a] Yields refer to pure and isolate product **2a** after a filtration on a short chromatography column (SiO$_2$; eluent: petroleum ether). [b] CC: Choline chloride. [c] The main product formed was 1-chloro-4-nitrobenzene (72%) beside **2a** (25%).[d] Positive azo coupling with 2-naphthol confirmed the presence of unreacted **1a**. [e] B: betaine. [f] The reactions were performed with 1 mmol of **1a**, 1 mmol or 2 mmol of KF and 5 mL of solvent.[g] Only tarries formed. [h]1-bromo-4-nitrobenzene was formed beside **2a**. [i]1-chloro-4-nitrobenzene was formed beside **2a**.

Table 3. Reduction of arenediazonium salts **1** in DES

$$\underset{\textbf{1}}{ArN_2^{\oplus}\ BF_4^{\ominus}} \xrightarrow[\text{Gly/KF 6:1}]{\text{rt}} \underset{\textbf{2}}{ArH}$$

Entry	Diazonium salt **1**	Time (min)	Arene **2**	Yield (%)[a]	MS (EI): (m/z)

2	3-NO$_2$C$_6$H$_4$;**1b**	5	**2a**	82	
3	2-NO$_2$C$_6$H$_4$;**1c**	5	**2a**	81	
4	4-CN; **1d**	15	**2b**; CNC$_6$H$_5$	89	103 (100, M$^+$)
5	4-COCH$_3$;**1e**	15	**2c**; CH$_3$COC$_6$H$_5$	79	120 (100, M$^+$)
6	4-Br; **1f**	60	**2d**; BrC$_6$H$_5$	81	156 (100, M$^+$); 158 (100, M$^+$+2)
7	4-MeOC$_6$H$_4$; **1g**	120	**2e**; CH$_3$OC$_6$H$_5$	69	108 (100, M$^+$)
8	3-MeOC$_6$H$_4$;**1h**	90	**2e**	71	
9	2-MeOC$_6$H$_4$;**1i**	90	**2e**	72	
10	4-MeC$_6$H$_4$;**1j**	90	**2f**; MeC$_6$H$_5$	44	92 (100, M$^+$)
11	2,6-diMeC$_6$H$_3$;**1k**	90	**2g**; 1,3-Me$_2$C$_6$H$_4$	58	106 (100, M$^+$)
12	3-Me-5-NO$_2$; **1j**	30	**2h**; 1-Me-3-NO$_2$C$_6$H$_4$	88	137(100, M$^+$)

[a] Yields refer to pure and isolate products **2** after a filtration on a short chromatography column (SiO$_2$; eluent: petroleum ether).

Investigation and elucidation of the reaction mechanism.

It is clear that the diazonium salts with electron-withdrawing groups (entries 1,2,3,4,5,6) decomposed faster than those with electron-donating groups (entries 7–11). Interestingly, the DES employed in entry 1 (Table 3) was recovered and reused in another run. Despite this DES showed traces of glyceraldehyde and dihydroxyacetone (see Experimental Section), time of reaction and yields of **2a** were almost identical to that reported in entry 1 of Table 3.

This unexpected decomposition of the diazonium salt 1 in Gly/KF DES could represent a transition metal-free and green strategy of hydrodediazoniation of arenediazonium compounds, otherwise carried out in boiling ethanol[47,48] with relatively complex catalytic systems[49,50] or, in any case, in classical volatile organic solvents.[51,52] More interestingly, it represents a measure of the background reactivity of such compounds in DESs, and this prompted us to try to elucidate the involved mechanism. In particular, we focus the quantum chemical study on the mechanism of the fast reduction of the 4-nitrobenzenediazonium tetrafluoroborate (**1a**) to nitrobenzene in Gly/fluoride DES (entries 4–7 in Table 2). The preliminary calculations indicate that the dissociation of **1a** to 4- nitrobenzenediazonium (**1a'**) and tetrafluoroborate is thermodynamically slightly favored by 0.5 kcal mol^{-1} in terms of free energy, as expected by the modest ion solvation properties of glycerol.

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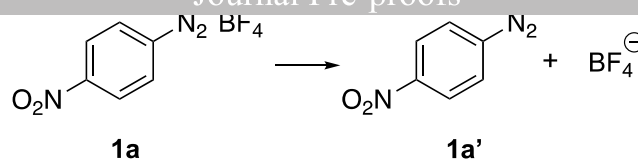
Scheme 1. Dissociation of **1a**

The experimental observation of a fast reaction suggests a radical mechanism (Scheme 2). Arenediazoniums are species with some oxidative properties depending on the substituent[53–55] and lead to the formation of arenediazenyl radicals, that can initiate a radical chain.[56,57] The calculated reduction potential of **1a'** in sulfolane ($E^{1/2}$) is 0.43 V (vs SCE)[53], in good agreement with the experimental value of 0.45 V (see Benchmarking phase in the SI). The calculated value in glycerol is identical. The high calculated $E^{1/2}$ of 2.5 V for glycerol itself excludes the possibility of this species being the reducing agent of the arenediazonium salt. This is coherent with the experimental findings that pure solvents (glycerol and structurally similar species) are not reductive (entries 10–12 in Table 2).

It should be pointed out that to make calculations faster and easier, the simulated environment was reduced to pure glycerol and **1a**; indeed, this environment and thus the mechanism is the same for some of the tested mixtures (i.e. Gly/KF -at different ratios-, Gly/KBr or Gly/KCl). Therefore, one could wonder why the reaction occurs in Gly/KF but not in the homologous mixtures based on KCl and KBr. To shed more light on this, we performed some classical molecular dynamics calculations focusing our attention on the intermolecular interaction between the halide anion and the HBD (Figure 3, top frame). Regarding Gly—OH----X interaction, we found that the fluoride anion interacts with HBD protons much more strongly than chlorine and bromine. This was hypothesized based on the H--X radial distribution function calculated on the simulation trajectory, which yields a significantly taller peak (and located at shorter distances) for H--F than the other two cases. In the first case, the peak maximum ranges from 1.55 to 1.61 Angstroms, and the integrals range from 1.78 to 2.02 depending on the hydroxyl position. When fluoride is replaced with another halide, the magnitude of this interaction is remarkably lower, and the integrals drop to 1.44-1.64 and to 1.17-1.51 for Cl- and Br- respectively and the position of the peak maximum is progressively shifted to longer distances (2.15-2.19 angstroms for H--Cl and 2.34-2.38 for H--Br); this values are also compliant with the anion dimensions. The magnitude of the H-X interaction clearly reflects also on the nature of O-H-X hydrogen bond, being the hydrogen closer to F- than to Cl- or Br-. This will lead to a negative charge accumulation on the oxygen atom and to the formation of a glycerolate-like species, that could act as a reductant toward the arenediazonium salt. MD calculations well correlates with the experimental results accounting for the reactivity of fluorine-based mixtures. Very interestingly, DES-like mixtures provide very

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go... systems.

Scheme 2. Calculated reaction mechanism for the reduction of **1a'** in Gly/KF 6:1 DES.

Looking into the mechanism, the free energies of the two possibly yielded **B** species in scheme 1 (i.e. 1-glycerolate and 2-glycerolate) differ by only 1.4 kcal mol^{-1} in favor of the former, whose calculated redox potential of 0.10 V legitimates its role of reducing agent towards the aryldiazonium, to initiate a radical chain (Scheme 1, step **i**). An estimation of the rate constant for this Electron Transfer (ET) step can be obtained through Marcus' equations.[49,58,59] The calculated value of $1.9 * 10^6$ M^{-1} sec^{-1} for k_i is consistent with our initial hypothesis on an acceptable role for 1-glycerolate.

Once the radical 4-nitrobenzendiazenyl **A** is generated, it decomposes[35,56,57] losing N$_2$ and generating the aryl radical **C** (step **1**). The monomolecular reaction rate constant k_1, calculated with the Eyring equation,[60] is $1.9 * 10^8$ sec^{-1}.

The second step, the key phase of the reduction of the arenediazonium, takes place by a Hydrogen Atom Transfer (HAT) from glycerol, the main component of the solvent system. One secondary (Figure 3) and four primary hydrogen atoms can be extracted from this molecule, the former being slightly preferred (the calculated rate constants are very close, $k_2 = 8.3 * 10^8$ sec^{-1}, k_2' $= 1.9 * 10^8$ sec^{-1}).

Si̲̲ be very fast. Its products are the nitrobenzene **2a** and the radical 2-dehydroglycerolyl **D** (or the 1-dehydroglycerolyl, not shown in Scheme 2). Both regioisomers are generated because the two carbonyl derivatives of glycerol are found as a byproducts (see Experimental section for further details). The radical **D** can proceed the radical chain by the reduction of another arenediazonium (step **3**) whose reaction rate constant k_3, estimated again by the Marcus equations, is $4.2 * 10^7$ M^{-1} sec^{-1}. This reaction is faster than the initiation step **i** because the radical **D** is a stronger reductant, possessing a calculated $E^{1/2}$ of -0.44 V (SCE). The $E^{1/2}$ calculated for 1-dehydroglycerolyl is 0.23 V, so also this species could be able to reduce the substrate. The products of step **3** are a second arenediazenenyl radical **A** that will start to a new reduction cycle and the protonated dihydroxyacetone **E** (or the protonated glyceraldehyde if step **i** generates the radical 1-dehydroglycerolyl).

Interestingly, the oxyl radical **B** yielded in the initiation step **i** can generate, through a very fast Hydrogen atom transfer (HAT) reaction, a second radical **D** (step **ii**, $k_{ii} = 4.0 * 10^9$ sec^{-1}). This species is therefore able to open a second radical chain through a reaction very similar to step **3**, which proceeds in parallel to that initiated by the deprotonated glycerolate in step **i**. All these steps are exoergonic; the absolute and relative energies are reported in ESI.

The reaction mechanism shown in Scheme 2 should be valid also for the reduction of the 4-methoxybenzendiazonium tetrafluoborate **1g** in the Gly/KF DES (entry 7, Table 3). While **1a** possess a strong electron-withdrawing group, **1g** includes a typical electron-donating group, therefore our computational study covers the two alternatives.

In this case, the dissociation of salt **1g** is thermodynamically more favored (ΔG = -2.2 kcal mol^{-1}) than that of **1a**. We explain the lower yield and the longer reaction times with the fact that **1g'** is harder to reduce; in fact, its calculated $E^{1/2}$ is -0.04 V. This leads to a considerably smaller rate constant for the initiation step, $k_i = 1.2 * 10^{-2}$ M^{-1} sec^{-1}. Such a behavior has been observed in most cases were the reaction of the arenediazonium are initiated by the reduction step.[35,57] The radical steps 1–3 also show slower reaction rate constants; k_1, k_2, and k_3 are $7.4 * 10^6$ sec^{-1}, $9.7 * 10^7$ sec^{-1}, and 1.4 M^{-1} sec^{-1}, respectively. However, despite these values, all the steps are sensibly exoergonic, therefore, irreversible. So, once the radical chain is initiated, the reaction should rapidly proceed.

A substantially identical reaction mechanism is proposed for the reduction of **1a'** in the EG/KF mixture (entries 8 and 9 in Table 2). The reaction scheme and all data are reported in the ESI. Here we only observe that the ethylene glycolate (deprotonated EG) is only slightly less reducing ($E^{1/2}$ = 0.14 V) so the ET rate constant k_i, is slightly smaller ($1.8 * 10^5$ M^{-1} sec^{-1}) but still large enough to rapidly initiate the radical chain. The radical steps 1–3 show similar or slower reaction rate constants; k_1, k_2, and k_3 are, respectively, $2.8 * 10^8$ sec^{-1}, $9.5 * 10^8$ sec^{-1}, and $9.6 * 10^4$ M^{-1} sec^{-1}. In any case, all steps are exoergonic and the rate constants

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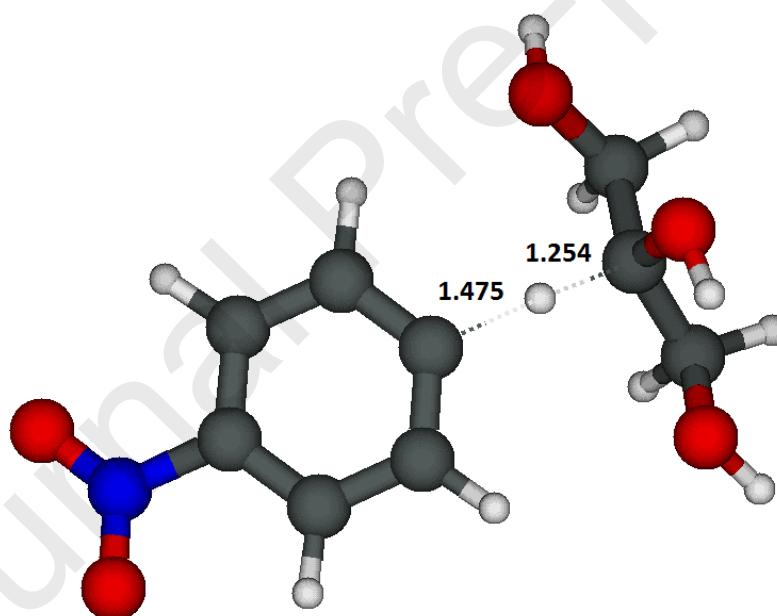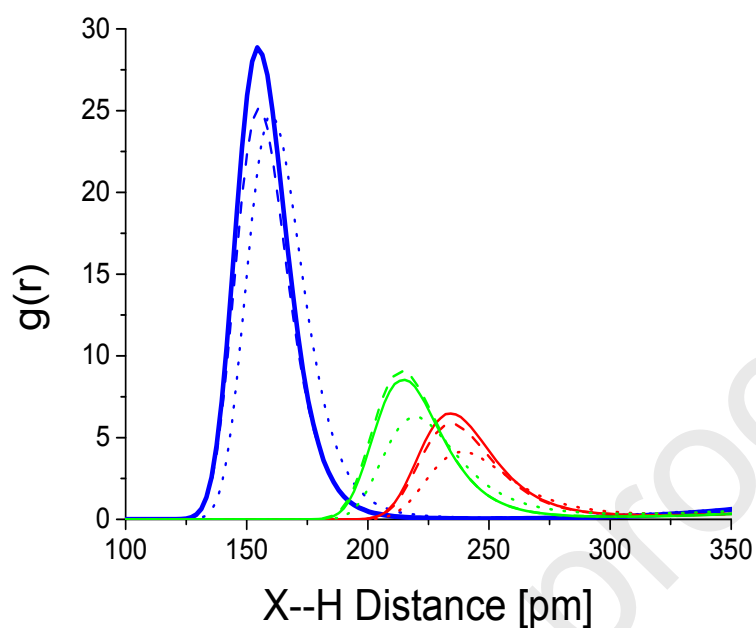
Figure 3. (top) Halogen-hydrogen radial distribution function. F: Blue; Cl: green, Br: red. Solid, dashed and dotted lines refer to different hydrogen of glycerol. (bottom) Transition structure in step 3 (Scheme 2) for the reduction of **1a'** in GL/KF 6:1 DES.

CONCLUSIONS

In this paper we proposed the synthesis and characterization of some new Deep Eutectic Solvents and DES-like systems having polyols (i.e. glycerol and ethylene glycol) as HBD and halide salts as HBA. These

seems clear that the reduction reaction takes place only in DES and (partially) DES-like system. On this ground, we proposed a plausible mechanism (corroborated by experimental evidences) in which the RDS consists in the formation of a glicerolate species able to reduce the arenediazonium salt. Albeit the mechanism calculation is based on a simplified model (i.e. glycerol plus reactant), its validity seems to be further sustained by DFT calculations and electrochemical measurements. Indeed, while the latter proves an optimal stabilization of the halide anion only for fluoride-based salts (symptoms of the DES formation), the former claims an evident delocalization of the hydrogen of the alcoholic moieties that follows the electronegativity (i.e. $F > Cl > Br$). These preliminary results can be the starting point to deepen the studies on the behavior of diazonium salts in DESs. In fact, further research aimed at studying the Ullmann reaction in Glycerol/KF DES and the Sandmeyer reaction under green conditions in Glycerol/ KBr or KCl solvent system are currently underway.

EXPERIMENTAL SECTION

General information.

All the reactions were carried out in open air glassware. Analytical grade reagents and solvents (purchased from Merck or Thermo-Fischer) were used and reactions were monitored by GC-FID, GC-MS and TLC. Column chromatography and TLC were performed on Merck silica gel 60 (70-230 mesh ASTM) and GF 254, respectively. Petroleum ether refers to the fraction boiling in the range 40–70 °C. Room temperature (rt) is 22 °C. Mass spectra were recorded on an HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column. Gas Chromatrography analyses were performed on a Perkin Elmer AutoSystem XL GC with a methyl silicone capillary column. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol ECZR spectrometer at 600 and 150 MHz respectively. Arenediazonium tetrafluoroborates were prepared as reported in the literature.[61] Structures and purity of arenes **2** were confirmed by their spectral data (NMR, MS), substantially identical to those of commercial samples. Yields of pure (GC-FID, GC-MS, TLC and NMR) and isolate **2** are collected in Table 3; their NMR spectra are reported in Supporting Informations. Conductivity measurement were carried out using a conductivity electrode (5072 from Crison, $K = 10$ cm^{-1}) with platinum plates constituting both the working and the counter electrodes. The electrode was coupled to an Autolab potentiostat/galvanostat Model PGSTAT12® from Metrohm. The potentiostat/galvanostat was remotely controlled by the computer using Nova 1.9 software. An electrochemical impedance scan was employed to measure the A.C. resistance of each solution, from which the relative conductivity was calculated. In the EIS experiments the amplitude of the potential perturbation was set to 50 mV. Impedance spectra were recorded within the frequency ranges 10^3-10^7Hz. During each measurement, temperature has been kept constant at each desired value by a water-

(stabilized for 60 sec before each run); for the measurement a lower plate with a diameter of 40 mm and an upper plate with a diameter of 20 mm were used (dg/dt = 1-100; |Slope| = 10 Pt./dec; 21 points, total time of measurement = 200 sec). Viscosity values have been averaged on three independent scans.

Computational methods.

Molecular dynamics method.

The classical molecular dynamics simulation models were performed with Gromacs suite of programs[62] using the Generalized Amber Force Field (GAFF)[63] to model the energetics of the system. The fixed point charges of glycerol atoms needed to model electrostatic interactions were calculated according to the Restrained Electrostatic Potential fit method (RESP[64]), using the B3LYP/6-31G(d) electrostatic potential calculated at the geometry-optimized structure, while the charges on cations and anions were set at +1 and -1 respectively. The cubic simulation cells contained 100 cations and anions and 600 glycerol molecules for 1:6 models, and 1000 glycerol molecules for 1:10 ones, and were prepared with the software Packmol.[65] The simulation protocol used consisted in the initial minimization followed by a 5 ns-long thermalization of the cell at 300 K in NPT ensemble with target pressure 1 atm using the Berendsen barostat. A simulated annealing cycle made up of NPT simulation at 700 K for other 5 ns and finally 5 ns at 300K was carried out to eliminate the initial bias. The edges and densities of the equilibrated cells at this stage were: GLY:KF 6:1 42.40 Å d=1.331 g cm^{-3}; GLY:CsF 6:1 42.66 Å d=1.503 g cm^{-3}; GLY:KCl 6:1 42.70 Å d=1.335 g cm^{-3}; GLY:KBr 6:1 42.91 Å d=1.411 g cm^{-3} ; GLY:KF 10:1 50 Å d=1.302 g cm^{-3}. Starting from the equilibrated system, a 5 ns trajectory in the NVT ensemble was finally produced and sampled at regular intervals (every 0.1 ps) to calculate the radial distribution functions. In every simulation, the timestep for the integration was fixed at 1 fs.

Quantum chemical method.

After a short benchmarking phase (see SI) we decided to optimize the structures of reactants, intermediate adducts and transition states using the density functional method (DFT),[66] with the functional M06[67,68] and the basis sets 6-311+G(d,p). Then, the electronic energy values where refined by single-point calculations with the basis set 6-311++G(3df,2pd).[69–71] The nature of the critical points was characterized by using vibrational analysis[72] which also furnished the Zero Point Energies (ZPE) and entropies for the calculations of the Free Energies. These have been converted from the gas phase to the 1M standard state at 1 atm and 298.15 K[73] and used to calculate the rate constant with the Eyring equation.[60] The solvent effects (glycerol, GL and ethylene glycol, EG, because at the present a method to mimic DES is not available) were introduced in all calculations using the Polarized Continuum Method

(P_____he default Gaussian values were used. The calculations were performed by the quantum package Gaussian 16-A.03.[75] The figures were obtained using the graphical program Molden.[76]

Preparation of Gly/KF 6:1 DES.

KF (5.8 g, 0.1 mol) was added at rt to glycerol (55.2 g, 0.6 mol). The suspension was stirred at 80 °C for about 2 hours. It was then cooled to rt and a clear solution was obtained, which was used without any further purification. The mp of this DES was about -45/-50 °C.

Reduction of arenediazonium salts in Gly/KF 6:1 DES; general procedure

Arenediazonium tetrafluoroborates (**1,** 5 mmol) was added at rt to Glycerol/KF (6:1, 5 mL). Immediately, a lively evolution of nitrogen was observed. The red mixture was stirred at rt for the times reported in Table 3; the completion of the reaction was confirmed by the absence of azo coupling with 2-naphthol. Then, the reaction mixture was poured into EE/H_2O (100 mL, 1:1). The aqueous layer was separated and extracted with EE (50 mL). The combined organic extracts were washed with H_2O (50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. GC-MS analyses of the crude residue showed arenes **2** as the only important products. The crude residue (tarry solid) was purified on a short column (PE) The only isolated products were arenes **2**

The aqueous layer was evaporated under reduced pressure, in order to recover the solvent system (Gly/KF 6:1). A ^{13}C NMR spectrum (D_2O, no internal standard; Supporting Information: pag. 12) was recorded. The signals are consistent with the presence, despite in small amounts, of both dihydroxyacetone **D** (Scheme 2; from intermediate **E**. Quaternary carbon at 211.97 ppm) and glyceraldehyde (quaternary carbon of the hydrated form at 89.76 ppm, primary carbon at 64.85 ppm, secondary carbon at 74.08 ppm). Primary carbon of dihydroxyacetone D is likely hidden by the signal at 62.50 ppm (primary carbon of glycerol).[77]

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NOTES

The authors declare no competing financial interest

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TOC GRAPHIC/GRAPHICAL ABSTRACT
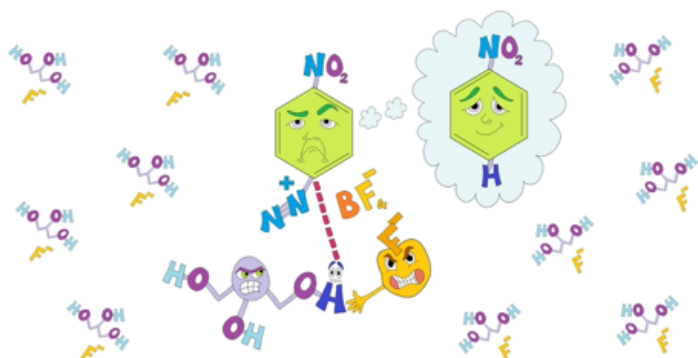
Conceptualization. M.B.; S.D.; G.G. **Methodology.** A.A.; M.B.; S.D. **Software.** G.G.; L.G. **Validation.** A.A.; M.B. **Formal analysis.** A.A.; M.B.; C.B.; S.D. **Investigation.** A.A.; M.B.; S.D. **Resources.** S.D.; G.G.; C.B.; L.G. **Data Curation**. S.D.; G.G.; L.G.; C.B. **Writing - Original Draft.** A.A.; M.B.; S.D.; G.G.; L.G. **Writing - Review & Editing.** M.B.; S.D.; C.B. **Visualization.** A.A.; M.B.; G.G.; L.G. **Supervision.** S.D.; C.B. **Project administration.** M.B.; S.D.; G.G. **Funding acquisition.** S.D.; C.B.; G.G.; L.G.

- Synthesis of new DESs and DES-like systems based on polyols as HBDs and halide salts as HBAs;
- Innovative DES design approach inspired by the necessity of rigorous classification of true DESs;
- Unveiling of reduction process of diazonium salts in a new DES formed by glycerol and potassium fluoride;
- Mechanistic study of the reduction process by DFT calculations and electrochemical measurements;
- Combined theoretical and experimental approach promotes an unprecedented and successful insight on the chemistry of DESs.

Declaration of interests

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

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