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Effect of Novel Deep Eutectic Solvents on the Endo/Exo Ratio of Diels–Alder Reactions at Room Temperature

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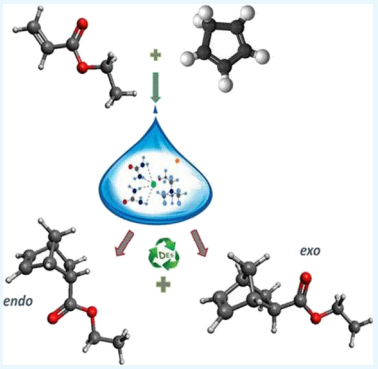
ABSTRACT: The Diels–Alder reaction is a prototypical example of a thermally allowed [4 + 2] cycloaddition with good control over the regio- and stereochemical outcomes. Therefore, Diels–Alder reactions in which adjacent stereocenters are generated at the two ends of the newly formed single bonds imply two different possible stereochemical outcomes. In cases where the dienophile has a single electron-withdrawing substituent, the outcome can often be predicted by applying the known "endo rule". Furthermore, the use of chiral eutectic solvents in asymmetric synthesis has become a novel tool to maintain sustainability in organic synthesis. In the present work, a set of recyclable and sustainable bio-based deep eutectic solvents (DESs) was designed using hydrogen bond acceptors (HBAs) with a chiral center. These compounds were used in their racemic and enantiomerically enriched forms to prepare DESs with lactic acid (LA), glycerol (Gly), and ethylene glycol, which act as hydrogen bond donors (HBDs) in the corresponding eutectic mixture. These DESs were used as solvents to study the reaction between cyclopentadiene and ethyl acrylate or butyl acrylate in typical [4 + 2] cycloadditions. The best yields and endo-selectivity were achieved using LA as the HBD in the eutectic mixtures. The results and adduct ratios obtained show that these DESs were able to improve both reaction yields and selectivity when compared to those observed in organic solvents or ionic liquids. Moreover, the reaction products (adducts) were easily recovered with diethyl ether from the reaction mixture, where they appeared as an upper layer.



1. INTRODUCTION

Alternative solvents as deep eutectic solvents (DESs) have emerged as an environmentally friendly option in different chemical processes.[1] The term DES was introduced by Abbott et al. in 2003,[2] in a report on the synthesis and study of the viscosity, conductivity, and freezing points of various eutectic mixtures formed with urea [$(NH_2)_2CO$] and different quaternary ammonium salts, such as choline chloride ($CH_2OH\ CH_2NC_3H_9Cl$) in a 2:1 ratio. In this study, it was concluded that in the formation of eutectic mixtures, the temperature-dependent increase in conductivity and the melting point depression occur because of the interaction between the urea molecules and choline chloride.

Subsequently, several DESs were prepared using a quaternary amine salt together with polyols, amides, and carboxylic acids.[3] Nowadays, the preparation of eutectic solvents is performed with a wide range of compounds used to tailor the physical and chemical properties of the DESs according to the required characteristics. Moreover, numerous studies have been conducted using a wide variety of eutectic mixtures known as natural DESs (NADESs), obtained solely from bio-based components.[4] A good example of a hydrogen bond donor compound commonly used in NADESs is glycerol, which is a versatile molecule with many potential applications.[5] Among them, *N*-(2,3-dihydroxyprop-1-yl)-*N*,*N*,*N*-triethylammonium chloride [$C_9H_{22}N^+O_2$]Cl^- (DPTAC), prepared from crude glycerol, has been used to prepare several novel DESs used as extraction solvents in lignocellulose fractionation.[6]

The use of DESs in synthetic organic chemistry is also increasing as a substitute for VOCs from an environmental point of view.[3] In organic synthesis, they can be used exclusively as a solvent, but they can also act as catalysts. This is because DESs might contain acids or bases that act as catalysts in many reactions.[7]

The Diels–Alder reaction, which is among the most powerful and well-understood reactions in organic chemistry, has been widely used as a versatile tool for the synthesis of functional materials, natural products, and unique topological polymers.[8] This reaction forms a substituted cyclohexene derivative through a pericyclic reaction between a conjugated diene and a substituted alkene. It is the prototypical example of a thermally allowed [4 + 2] cycloaddition with good control over the regio- and stereochemical outcomes. In this way, Diels–Alder reactions in which adjacent stereocenters are generated at the two ends of the newly formed single bonds

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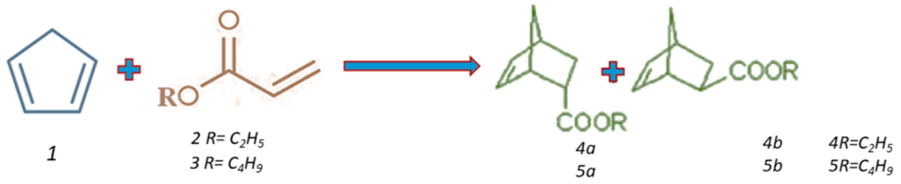

Figure 1. Diels–Alder reactions were performed in DESs to yield endo (**4a**, **5a**) and exo (**4b**, **5b**) adducts.

involve two different possible stereochemical outcomes. In cases where the dienophile has a single electron-withdrawing substituent, the outcome can often be predicted by applying the well-known "endo rule". This rule states that the transition state in which the electron withdrawal on the dienophile is oriented toward the π system of the diene is the typically preferred transition state, despite often being more sterically congested. The most widely accepted explanation for the origin of this effect is a favorable interaction between the π systems of the dienophile and the diene, an interaction described as a secondary orbital effect in which the solvent can sometimes make a substantial difference in selectivity.[9] For instance, unusual anti-1,4-adducts of anthracene derivatives have been obtained by an $AlCl_3$-assisted Diels–Alder reaction using chloroform as the solvent.[10]

Breslow et al. carried out pioneering studies in aqueous solutions instead of non-polar solvents.[11] Jaeger and Tucker presented the first study on solvent effects on Diels–Alder reactions using an ionic liquid (IL).[12] Later, Earle et al.[13] reported the use of 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([bmim][OTf]), hexafluorfosfate ([bmim][PF_6]), tetrafluroborate ([bmim][BF_4]), and lactate [bmim][lactate] as alternative solvents in Diels–Alder reactions. Currently, there are a large number of studies on Diels–Alder reactions in imidazolium ILs.[14,15] The wide range of studies using IL cover issues such as reaction kinetics,[16] shifting exo-selectivity to endo-selectivity,[17] the mechanism of asymmetry,[18] and the effects of hydrophobic solvents.[19] One such report describes the effect of a dicationic IL as a catalyst in Diels–Alder reactions to yield chiral precursors of many natural products and pharmaceuticals.[20] The use of DESs in Diels–Alder cycloaddition reactions shows a wide variety of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) in various ratios. Choline chloride as a HBA with different HBDs is one of the most commonly used compounds in the preparation of DESs. Thus, the eutectic mixture of water–choline chloride–glycerol (H_2O–ChCl–Gly) as a reaction medium in hetero-Diels–Alder reactions was used to improve the efficiency and sustainability of the synthesis of bis(indolyl)methanes. These heterocycles are widely distributed in nature and show rather diverse and interesting biological activities.[21,22] The effects of physical properties such as the viscosity of eutectic solvents on Diels–Alder reactions have also been studied;[23,24] remarkable studies have been performed using a series of low-melting sugar–urea–salt mixtures as solvents for Diels–Alder reactions in different stoichiometric ratios to achieve endo/exo proportions ranging from 2.5:1 to 5:1.[25] In one of the most recent studies, Diels–Alder reactions between *N*-ethylmaleimide as a dienophile with several dienes of different nature were performed using choline chloride and ethylene glycol (EG)-based DESs.[26] In this study, the Diels–Alder reactions were carried out under conventional heating and ultrasonic activation using less solvent, lower temperatures, and shorter reaction times. As a result, higher yields were obtained than those obtained in conventional solvents, and the data show that the activating effect of the DES can be attributed to a combined action of polarity, viscosity, and the structure of the solvent used.[27]

This study aimed to prepare a set of DESs based on *N*-(2,3-dihydroxyprop-1-yl)-*N*,*N*,*N*-triethylammonium chloride (DPTAC), $[C_9H_{22}N^+O_2]Cl^-$, which was obtained from crude glycerol. The use of renewable biomass resources for the production of DESs based on quaternary ammonium salts is not a new concept. However, most of the studies related to the preparation of such DESs use choline as the HBA, which is synthesized from ethylene oxide. DPTAC has a similar structure to choline, can be prepared from glycerol recovered from fat and vegetable oils, and also has an asymmetric carbon, which allows the preparation of chiral DESs. The DESs prepared in this study were applied to study the endo-selectivity of a model Diels–Alder reaction (Figure 1). Specifically, the reaction between cyclopentadiene (**1**) and ethyl acrylate (**2**) or butyl acrylate (**3**) was carried out at room temperature. Optical resolution studies of the acetylated structures of DPTAC were also carried out (see the Supporting Information).

2. RESULTS AND DISCUSSION

Some of the DESs described in this work have previously been used in biomass extractions.[6] Studies on the influence of these and novel DESs on the stereoselectivity of Diels–Alder reactions are now presented (Figure 2).

Eutectic mixtures (generally in a 1:2 ratio) were prepared by mixing different HBAs based on DPTAC (**7**) and HBDs such as lactic acid (LA), glycerol (Gly), and EG. The pure *R*-isomer

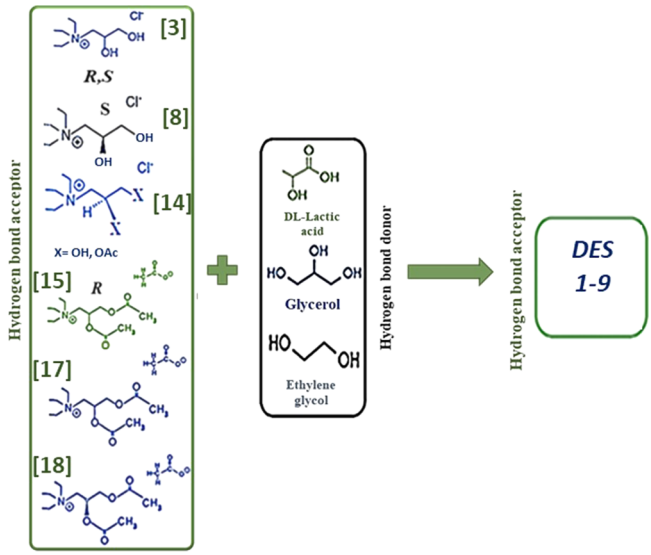

Figure 2. General scheme of bio-based DESs prepared by mixing HBAs (compounds **7** to **12**) with HBDs [(LA), (Gly), and (EG)].

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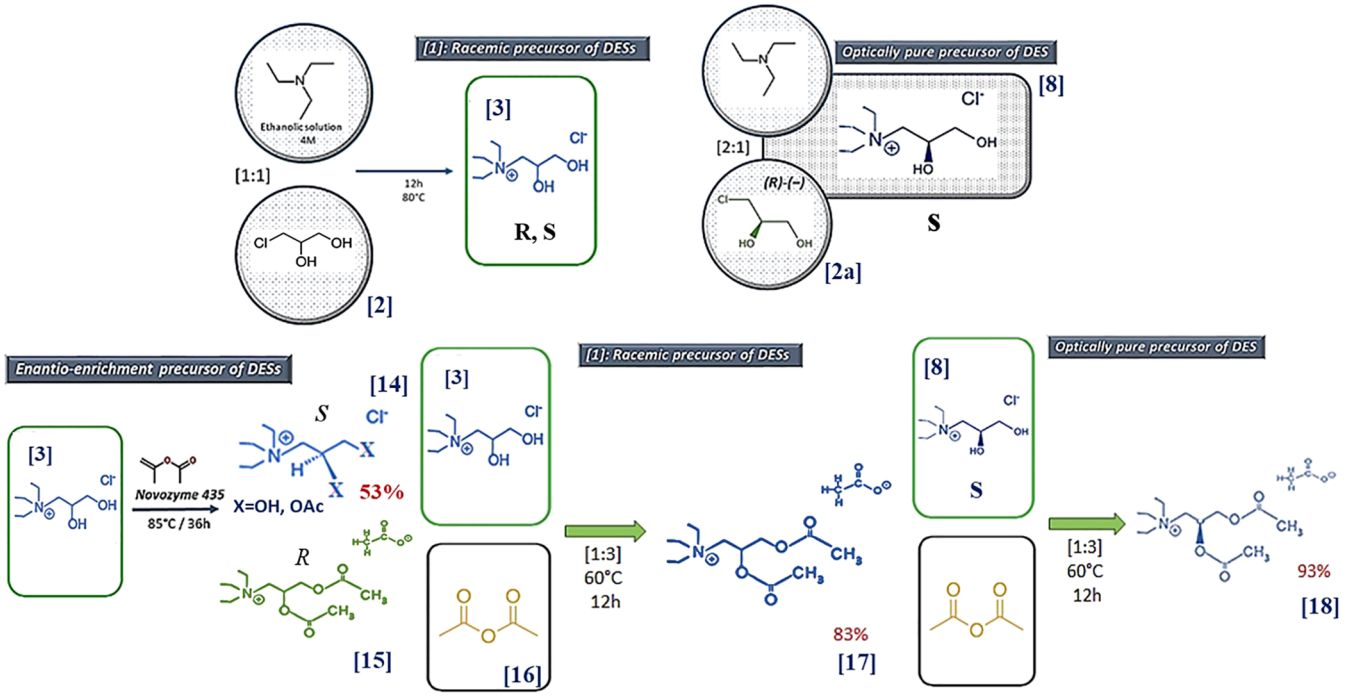

Figure 3. Synthesis of the racemic and optically enriched HBAs **7**−**12** used to prepare the DESs applied to study the Diels−Alder reactions; X = OH, OAc in compound **9**.

of DPTAC, compound **8**, was synthesized from the corresponding commercial *S*-isomer. HBAs **9**−**10** were obtained by an enzymatic acetylation process using *iso*-propylene acetate and "Novozyme 435" as a biocatalyst (which had been widely used as a biocatalyst in ILs and DESs).[28] The enzymatic acetylation of **7** was studied at 12, 24, and 36 h using FT-IR and NMR techniques (see the Supporting Information). The FT-IR studies allowed observing the progress of the esterification of the −OH groups with the acetyl groups. The specific rotatory power of these two compounds (see Supporting Information) showed that compound **10** is more enantiomerically enriched compared to compound **9** (Figure 3). Similarly, enzymatic acetylation was also scaled up using 10 g of **7**. The yields of **9** and **10** on the gram scale were like those on the mg scale (50 and 19% yields, respectively). Finally, the fully acetylated compounds **11** and **12** were synthesized from **7** and **8**, respectively, by a conventional chemical approach (see Supporting Information).

Accordingly, Table 1 shows the HBAs and HBDs used and the corresponding DESs involved in the Diels−Alder reactions.

Initially, the eutectic mixture formed by $[C_9H_{22}N^+O_2]Cl^-$ (DPTAC) [**7**] and LA (DES 1) at different molar ratios was used as a solvent to study the reaction between diene **1** and dienophiles **2**−**3** at room temperature (Table 2). The ratios of the **4a:4b** and **5a:5b** adducts obtained were analyzed by GC-FID (see Supporting Information). Although these analyses were carried out at two different injection temperatures (230 and 270 °C), better selectivity was observed at 230 °C (see Supporting Information), confirming that the injection temperature can slightly isomerize the endo adducts (**4a** and **5a**) to a more thermodynamically stable exo adducts (**4b** and **5b**).

The best yield was achieved using a 1:2 molar ratio; for this reason, the endo/exo ratios were only determined for this 1:2 ratio. These preliminary results are in agreement with those described by other authors using different DESs and reagents[14,15]

In the same way, the results presented in Table 3 show that the endo/exo values are similar for the three DESs studied using DPTAC as the HBA and different HBDs. DES 1 ([DPTAC][LA]^{rac}) allowed a higher yield than DES 7 ([DPTAC][Gly]^{rac}) and DES 8 ([DPTAC][EG]^{rac}) using

Table 1. HBAs and HBDs Used to Prepare DESs 1−8 and the Acronym of Each DES Is Indicated

[a]DES	HBA	HBD	DES acronym
[d]**1**	7	LA	[b][DPTAC][LA]^{rac}
2	8	LA	(*s*)-(−)[DPTAC][LA]
3	9	LA	[c][DPTAC][LA]$^{ee:31\%}$
4	10	LA	[c][DPTAC][LA]$^{ee:48\%}$
[d]**5**	11	LA	[b][DNTPAOAc][LA]^{rac}
6	12	LA	(*s*)-(−)[DNTPAOAc][LA]
7	7	Gly	[b][DPTAC][Gly]^{rac}
8	7	EG	[b][DPTAC][EG]^{rac}

[a]All these DESs were prepared using a 1:2 HBA/HBD stoichiometric ratio. [b]rac: DESs prepared with the racemic form of the corresponding HBA. [c]ee: enantiomeric excess percentage corresponding to the HBA used to prepare the corresponding DES. [d]These DESs were also prepared with two different stoichiometric ratios (1:1 and 1:3 HBA/HBD).

Table 2. Effect of the Molar Ratio of DES 1 in the Diels−Alder Yield Using Cyclopentadiene and Esters 2 and 3

starting ester	1:1 (%)	1:2 (%)	endo/exo ratio[a,b]	1:3
2[a]	56	78	2.8:1	69
3[a]	60	89	2.6:1	80

[a]Reactions were performed at 25 °C for 72 h using DES 1. [b]The endo/exo ratio was only determined for DES 1 at a 1:2 molar ratio. The ratios between the adducts were determined by GC-FID with an injection temperature of 230 °C.

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Table 3. Yields and Selectivity Obtained for Endo/Exo Adducts from the Reaction between Cyclopentadiene with Ester 2 Using DES 1, 7, and 8 and for Ester 3 Using DES 1

DES (1:2)	4a:4b ratio[b]	yield %	retention time (min)	5a:5b ratio[b]	yield %	retention time (min)
1	**2.7:1**	**89**	15.01:14.91	2.6:1	78	13.50:12.91
[a]**7**	2.8:1	64	15.26:15.16			
[a]**8**	2.8:1	68	15.26:15.15			

[a]Diels–Alder reactions using ester **3** were not carried out on DESs 7 and 8 based on the results achieved with ester **2**. [b]The ratios between the adducts were determined by GC-FID with an injection temperature of 230 °C. Reactions were performed at 25 °C for 72 h.

ester **2**. Considering this yield and the selectivity obtained, the Diels–Alder reactions with ester **3** were not carried out using DES 7 and 8. The better yield achieved with DES 1 might be explained by the hydrogen bond formed within the HBD and HBA. LA has a high degree of hydrogen bonding interactions because the −OH groups can exhibit the double effect: "donor–acceptor".[13,29] Moreover, the eutectic mixture formed between **7** and LA presents a coupling between a weak HBA and a strong HBD (LA), tending to be slightly more donor than acceptor of hydrogen bonds, providing a reaction medium that improves the reaction yield.[30] The Lewis acidity of the hydrogen bond within DESs could contribute to the selectivity of the Diels–Alder reaction,[31] that is, the exo adduct decreases when the acidity of the medium increases.[17] This behavior had already been observed when structures acting as Lewis acids were used as co-catalysts to enhance the selectivity in Diels–Alder reactions.[30] The results are in agreement with those reported by Deepa et al. using ILs and co-catalysts at different pH in Diels–Alder reactions.[20]

The achieved stereoselectivity can also be explained from the point of view of the solvent effect by taking into account variables such as water content, polarity (E_T), and polarizability (π^*) values; solvent–solvent and solvent–solute interactions; and preferential solvation and synergistic effects for binary solvents.[32] In a DES, self-association between components can increase the polarity and the hydrogen bond strength as discussed above. Therefore, any change in the HBD nature could lead to changes in both the polarity and hydrogen bond strength.[33] Basically, changes in the polarity of the solvent affect the way the solvent surrounds the solute and, therefore, the way they might interact. Some effects in the prepared eutectic mixtures may also be the result of hydrogen bonding between the HBD and the chloride anion, which is stabilized by a complementary bonding between the quaternary ammonium salt and the HBD.[34] According to Aryafard et al.,[35] a synergistic effect is observed in most of the eutectic mixtures containing glycerol and EG, which provides a better environment and ideal conditions for carrying out Diels–Alder reactions. The results presented in Table 3 are in concordance with those presented by Marullo et al.,[26] who measured the polarizability and polarity of different eutectic mixtures containing glycerol and EG that were used as solvents in Diels–Alder reactions. Nevertheless, a higher endo effect of the solvent was observed for the Diels–Alder reactions performed on the eutectic mixtures containing LA. These results might be because the OH groups in the HBD can also increase the solute–solvent interaction.[36,37] This phenomenon allows the formation of more dipolar species in solution, resulting in an enhanced dipolarity of the region around the reactants.[38] Finally, it should be noted that most of the DESs used have the same ratio (1:2), and therefore, this variable was not taken into account in the discussion of the results.[33]

Table 4 shows the endo/exo ratio of the Diels–Alder reactions obtained using DESs 1–4 prepared with the HBA

Table 4. Endo/Exo-Selectivity of Different HBAs Using Lactic Acid as the HBD

DES [1:2]	4a:4b ratio	retention time (min)	5a:5b ratio	retention time (min)
1	2.7:1	13.03:12.91	2.6:1	15.01:14.91
2	3.1:1	12.81:12.71	2.9:1	14.78:14.69
3[a]	3.2:1	13.27:13.16	3.4:1	15.25:15.15
4[b]	**4.8:1**	**13.27:13.15**	**4.9:1**	15.25:15.15

[a]Eutectic mixtures prepared with compound **9** (enantiomerically enriched). [b]Eutectic mixtures prepared with compound **10** (highly acetylated compound), resulting from the bio-catalyzed reaction. The ratios between the adducts were determined by GC-FID; the samples were injected at 230 °C. Reactions were performed at 25 °C for 72 h.

derivatives of **7**. The endo-selectivity decreased in the following order: DES 4 > DES 3 > DES 2 > DES 1. These results might be explained considering the studies of López-Porfiri et al.[29] focused on studying the charge delocalization through hydrogen bonding in a mixture composed of an HBA salt type **8** or **9** with an acidic HBD. The hydroxyl groups present in the HBA could interact with the lone electron pairs of the chlorine atom by hydrogen bonding as indicated above. However, the esterification of these OH would lead to the loss of this interaction. These changes in hydrogen bonding interactions could increase the selectivity of the reaction medium, which might explain the higher selectivity of DES 4 containing the more acetylated HBA. These results are also consistent with Nobuoka et al.[14] that show a clear influence on the endo adduct regarding the functional groups present in the solvents used. Furthermore, these improvements in selectivity could also be related to the change in the counterion of compound 10 in DES 4, which might change the interactions of the reaction medium.[30]

Based on the results observed for the endo-selectivity of DES 3 and DES 4 in the different Diels–Alder reactions carried out, two full acetylated HBAs: *N*-(2,3-diacetoxypropan-1-yl)-*N*,*N*,*N*-triethylamino acetate (**11**) and (*S*)-(−)-*N*-(2,3-diacetoxypropan-1-yl)-*N*,*N*,*N*-triethylamino acetate (**12**), were synthesized from **7** and **8**, respectively. These salts were used to prepare **DES 5** and **DES 6** ([DNTPAOAc][LA]^{rac} and (*s*)-(−)[DNTPAOAc][LA], respectively).[39] These two new eutectic mixtures containing fully acetylated salts were used to further study the effect of acetylation on endo adduct formation. Table 5 confirms that better endo-selectivity was achieved when acetyl groups are present instead of OH groups

Table 5. Endo/Exo-Selectivity of Adducts in Diels–Alder Reactions Using DES 5 at Different Stoichiometric Ratios and DES 6

DES 5	4a:4b ratio	5a:5b ratio
1:2	8.6:1	3.9:1
1:1	4.0:1	
1:3	5.1:1	
DES 6	**4a:4b ratio**	**5a:5b ratio**
1:2	5.3:1	3.8:1

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Table 6. Reaction of Diene 1 with Different Dienophiles in Various Solvents[a]

entry	DES/IL	dienophile	reaction conditions	yield %	endo/exo ratio	refs
1	water	ethyl acrylate	1 h, 25 °C	30	3.5:1	15
2	MeOH	methyl acrylate	30 °C, np	Np	5.2:1	44
3	diethyl ether	methyl acrylate	72 °C, 25 °C	Np	2.9:1	30
4	[EAN] (0.20 M)	methyl acrylate	72 h, 25 °C	98	2.9:1	12
5	[$AlCl_3$:BPC] (1.04:1)	methyl acrylate	72 h, 25 °C	95	5.2:1	17
6	[$AlCl_3$:BPC] (1.5:1)	methyl acrylate	1.5 h, 25 °C	80	3:1	17
7	[$GlcO(CH_2)_2N_{111}$][Tf_2N] (1:1)	methyl methacrylate	1 h, 25 °C	92	1.9:1	42
8	[bmim][CS] (1:1)	ethyl acrylate	20 h, −10 °C	66	6.1:1	14
9	[bmim][PF_6] (1:1)	methyl acrylate	1 h, 20 °C	36	8.0:1	13
10	[emim][BF_4] (1:1)	methyl acrylate	2 h, np	50	5.7:1	31
11	[$EtNH_3$][NO_3] (1:1)	methyl acrylate	72 h, 25 °C	Np	6.7:1	31
12	[fructose/DMU] (2.3:1)	methyl acrylate	8 h, 71 °C	79	2.9:1	25
13	**[DNTPAOAc][LA]^{rac} (1:2)**	**ethyl acrylate**	72 h, **25 °C**	**82**	**8.6:1**	

[a]Reaction time and temperature, yield, and endo/exo ratios are indicated. n.p: not provided, [$GlcO(CH_2)_2N_{111}$][Tf_2N]: *N*-[2-(D-glucopyranosyl)ethyl]-*N*,*N*,*N*-trimethylammonium bistriflimide. EAN: Ethylammonium-Nitrate; BPC: *N*-*l*-butylpyridinium chloride; bmim: 3-buty-*l*-methylimidazolium; emim: 1-ethyl-3-methylimidazolium; DMU: *N*,*N*′-dimethylurea. [LA]: lactic acid; and [DNTPAOAc]: 2,3-diacetoxy-*N*,*N*,*N*-triethylpropan-1-amino acetate.

in the HBA structure. Interestingly, the reaction with ester **2** produced better endo-selectivity with DES 5 containing the racemic compound **11** (ratio 1:8.6 exo/endo) than DES 6, prepared with the optically pure compound **12** (ratio 1:5.7 exo/endo). These results using ester **2** were opposite to those obtained with DES 1, containing the racemic compound **7** (ratio 1:2.7 exo/endo), and DES 2 containing the optically pure compound **8** (ratio 1:3.1 exo/endo).The differences between the higher endo-selectivity achieved in DES 6 compared to the endo-selectivity presented in DES 4 might be explained by the fact that **10** and **12** are the two enantiomers of *N*-(2,3-diacetoxypropan-1-yl)-*N*,*N*,*N*-triethylamino acetate (see the Supporting Information). A positive alpha value ([+α]) corresponds to HBA **10**, while **12** showed a negative value, which could indicate that endo-selectivity is further favored by the presence of an *S*-type structure in the DES. The same effects, although with smaller differences, appears using ester **3**, which could indicate that the steric effect of the butyl group partially counteracts the effects of acetylation. Finally, DES 5 was prepared in two different stoichiometric ratios HBA/HBD (1:1 and 1:3) to evaluate the effect of the molar ratio on the selectivity in the presence of the acetyl groups. In all cases, the most suitable ratio was 1:2, which is in agreement with the results for DES 1 shown in Table 2. Therefore, this study confirms that the yields and endo/exo-selectivity in Diels−Alder reactions are highly dependent on the DES structure.[39,40] Some of the parameters that seem to affect the behavior of DESs are the HBA/HBD molar ratios and the ability of the HBA and HBD to interact via hydrogen bonds.[29,41] Furthermore, the results confirm that the yields and endo/exo ratios also depend on the dienophile[42] and, for the first time, show the effect of the chirality present in the DES. Consequently, predicting the behavior of DESs is difficult if only one variable is considered.[43]

Ratios between the adducts were determined by GC-FID with an injection temperature of 230 °C. Reactions were performed at 25 °C for 72 h.

Despite the few studies on Diels−Alder reactions carried out in DESs, it is possible to find several reactions between diene 1 and various dienophiles under different reaction conditions and using conventional solvents and ionic solvents (Table 6).[44] For instance, the reaction between **1** and **2** in water at room temperature for 1 h shows a yield of 30% and an endo/exo ratio of 3.5:1, whereas the reaction in ethanol at 30 °C of 1 with methyl acrylate shows an endo/exo ratio of 5.2:1. Remarkably, better selectivity was achieved when conventional solvents were replaced by DESs or ILs, which provide the reaction with a hydrogen bond-rich medium. Moreover, it is possible to see the influence of the anion in the solvents.[15] Bulky anions (such as CS^- > BF_4^- > Tf_2N^-) are often used to influence and address endo-selectivity in Diels−Alder reactions.[14] Among ILs, the selectivity was higher when solvents with bulky anions based on imidazolium (entry 8−9) were used. In the case of NADESs (entry 12), the endo-selectivity might be the result of heating the reaction mixture at 71 °C, which will be in agreement with the kinetic control over the formation of the endo adduct. On the other hand, a better endo-selectivity reached for one of the DESs prepared in this work (entry 13) seems to be also possible due to the acid character of its HBD component (as was explained above). This DES exhibited a better endo-selectivity and a higher or comparable yield than similar reactions already described using conventional or other ionic solvents.

3. CONCLUSIONS

DESs were prepared using crude glycerol as the starting material to synthesize the HBAs used in this work. The chemical structure of the salts used as HBAs was tailored by synthesizing various chiral and acetylated compounds. Moderate to high yields were obtained in these Diels−Alder reactions using the described DESs. In addition, the introduction of acetyl groups in the HBA component provided an insight into the role of the hydrogen-bonding interactions in the DESs' behavior. Thereby, in this study, the selectivity of Diels−Alder reactions in eutectic mixtures seems to depend on the hydrogen-bond donating capacity of the DESs and the synergic effect between the DES components, among others. In this way, the partial or total substitution of OH groups by OAc groups enhanced the endo-selectivity compared to ILs and common organic solvents. To our knowledge, the influence of the chirality on the carbon containing the −OH group of the HBA has been studied for the first time for these types of reactions. However, the chiral environment of the

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solvent does not necessarily improve the selectivity of the reaction.

4. EXPERIMENTAL SECTION

All experiments and measurements were performed at least in duplicate.

4.1. Materials and Reagents. Acetone (99%), deuterated solvents for NMR analysis (chloroform-*d* 99.8 atom % D, dimethylsulfoxide (DMSO)-d_6 99.9 atom % D, methanol-d_4 99.8 atom % D, and acetone-d_6 99.9 atom % D), dicyclopentadiene, acetic anhydride (95%), isopropenyl acetate (99%), ethyl acrylate, and butyl acrylate were purchased from Sigma-Aldrich (St. Louis, USA). DL-LA (90%), EG (technical grade), and triethylamine (99%) were purchased from Acros (Thermo Fischer Scientific; Waltham, USA). Ethanol (96%) and diethyl ether (96%) were purchased from Scharlau (Barcelona, Spain). Hydrochloric acid (38%) was purchased from Baker (Phillipsburg, USA). Glacial acetic acid (≥99.5%) was purchased from Labkem (Dublin, Ireland). Novozyme 435 was kindly donated by Novozymes company (Madrid, Spain). Animal fat was kindly donated by "Subproductos Cárnicos Echevarria y Asociados S.L" (Cervera, Spain).

4.2. Synthesis of *N*-(2,3-Dihydroxyprop-1-yl)-*N*,*N*,*N*-triethylammonium chloride (See Figure S1 in Supporting information). *4.2.1. Synthesis of 3-Chloro-1,2-propanediol.*[6] Ethanol (1000 mL) was added to a jacketed glass reactor (5 L) containing 1000 g of animal fat at 80 °C. The mixture was mechanically stirred at 300 rpm until a homogeneous solution was obtained. Afterward, 2000 mL of 14.2% NaOH solution was added drop-wise at 60 °C (30 min in total) and the reaction mixture was refluxed for 30 min. The pH of the reaction mixture was adjusted to pH = 2 by adding drop-wise 250 mL of 98% H_2SO_4 (30 min in total). Finally, the aqueous layer was recovered and 10% NaOH solution was added at pH 7. The salts formed were allowed to precipitate at low temperature and separated by filtration. The solution was dried under vacuum and the final residue was filtered to yield the crude glycerol (80% yield).

A mixture of crude glycerol $C_3H_8O_3$ (820 mmol), glacial acetic acid (49.8 mmol), and hydrochloric acid (120 mL, 32 M) was heated under magnetic stirring at 135 °C overnight. The resulting liquid phase was recovered and distilled at 140 °C and in a temperature range from 115 to 170 °C under reduced pressure (11 mm Hg). 3-Chloro-1,2-propanediol was recovered between 115 and 118 °C under vacuum (69% yield).

4.2.2. Synthesis of $[C_9H_{22}N^+O_2]Cl^-$ 7. Compound 7 was prepared according to Beckett et al.[22] A 4.2 M solution of ethanolic triethylamine (100 mmol) was cooled in an ice bath, and then, 3-chloro-1,2-propanediol (100 mmol) prepared as above was slowly added. Finally, 60 mL of methanol was added. The mixture was heated under reflux overnight, and the solution was dried under vacuum to yield a crude yellow oil. Small portions of the oil were washed with a large excess of acetone to afford a white hygroscopic powder. Melting point (mp): 96 °C (103−106 °C)[3] (56% yield). Compound 7 was characterized by NMR, FT-IR, and MS techniques (see Supporting Information). **Compound [8]** was synthesized following the same steps described for 7.

4.3. General Procedure for Enzymatic Acetylation. Compound 7 (2.83 mmol) and a molar excess of isopropenyl acetate (5 mL) were shaken in a Lab-net 211DS incubator at 80 °C and 250 rpm in the presence of Novozyme 435 (10:1 w/w). Reactions were performed at different times. The enzyme was separated from the reaction mixture by filtration at the end of the reaction, recovering a heterogeneous liquid mixture. Layers were separated using a separating funnel and the excess of *iso*-propylene acetate was eliminated under vacuum in both fractions to yield a viscous orange liquid (53%) and a yellow solid 9 (21%).

4.4. General Procedure for Direct Acetylation. Direct acetylation of compounds 7 and **8** to obtain compounds **11** and **12** were adapted from the procedure reported by Dai et al.[4] In a 25 mL round bottom flask was placed 7 or **8** with acetic anhydride in a 1:1.5 stoichiometric ratio. The reaction mixture was stirred for 12 h at 60 °C. Then, the mixture was diluted with chloroform and the organic phase was recovered using a separating funnel and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated under vacuum to yield yellow viscous liquids in all cases.

4.5. General Preparation of DES 1−8. The novel DES preparation was based on the procedures reported by Abbott et al.[22] The HBA component was stirred at 80 °C with the corresponding HBD component in a 1:2 stoichiometric ratio until a homogeneous colorless liquid was formed. In the same way, DESs 1−6 were prepared to mix each HBA compound (7−**12**) with LA. Compound 7 also was used to prepared DES 7−**8** with glycerol (Gly) and EG, respectively. Furthermore, DES 1 and DES 5 were prepared in different stoichiometric ratios (1:1 and 1:3) under the same conditions.

4.6. Diels−Alder Reaction in DES. These reactions were performed with any catalyst according to Nobuoka et al.[14] Freshly distilled cyclopentadiene (84 μL) from dicyclopentadiene was dissolved in 5 mL of each DES in a 5 mL flask. Ethyl acrylate (108 μL) or butyl acrylate (144 μL) were added to the flask. The reaction mixture was stirred at room temperature for 72 h. Compounds were extracted using diethyl ether and the solvent removed under vacuum to yield mixtures of the endo/exo adducts. DESs were washed using hexane/ether and reused twice in the same reaction with equivalent yields and endo-selectivity. Yields of adducts obtained ranged from 56 to 89% depending on the DES and dienophile used. The endo/exo proportions were determined by GC-FID analysis.

4.7. Optical Measurements. These measurements were performed at 23 °C using an SH450 Shibuya digital polarimeter provided with a 6 V−20 W halogen lamp and a sodium filter monochromatic light on a polarization scale of +180 to −179° at 589.3 nm.

To see the complete physical, optical, spectroscopic, spectrometric, and chromatographic characterization refer to Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c00980.

^{1}H and ^{13}C NMR, FT-IR, GC-FID, and [α] of the chemicals and DESs prepared in this work (PDF)

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Author Contributions

The article was written through the contributions of all authors.

Notes

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