1	Viscometric study of <i>myo</i> -inositol in aqueous Deep Eutectic Solvent
2	solutions
3	
4	Montserrat Nuez, Fernando Bergua, Carlos Lafuente, José Muñoz-Embid, Manuela
5	Artal*
6 7	Departamento de Química Física. Facultad de Ciencias. Universidad de Zaragoza. 50009. Zaragoza. Spain
8	*Corresponding autor. Tel: +34876553765. e-mail: martal@unizar.es
9	
10	Abstract
11	A viscometric study of myo-inositol in pure water and in Deep Eutectic Solvent (DES)
12	aqueous solutions is presented. Two DES based on choline chloride as acceptor group
13	and urea or glycerol as donor group are used. Experimental measurements of viscosities
14	at $p = 99.0$ kPa and at six temperatures from 293.15 to 318.15 K were performed. In
15	addition, the viscometric properties such as the <i>B</i> -coefficient, the hydration number, and
16	the activation parameters of viscous flow were calculated. From these properties, the
17	intermolecular interactions were evaluated. The results show that the studied sweetener
18	is a structure-maker compound in all solvents of this work. The solute co-solute
19	interactions are strongest in the system containing glycerol.
20	
21	Keywords: <i>Myo</i> -inositol; DES; Viscosity; Hydration number; Activation parameters of

22 viscous flow.

23 **1. Introduction**

Myo-inositol (cis-1,2,3,5-trans-4,6-cyclohexanehexol), MI, is the most abundant 24 inositol stereoisomer. It is essential in the osmotic balance between the cell tissue and its 25 26 surroundings so that its vital role as a precursor of the essential components of the cell 27 signalling and membrane trafficking has been proved [1,2]. Different MI applications are [3-13]: (i) to overcame the abiotic stress in plants; (ii) as a biomarker in diseases such 28 as Alzheimer, diabetes, encephalopathies, lupus, migraines, sclerosis, and cancer; (iii) as 29 30 drug in the treatment of leishmaniosis, polycystic ovary syndrome, depression and other metabolic and endocrine disorders. Recently, myo-inositol has been proposed as a 31 32 nutraceutical supplement for infant and adults [14,15].

According to the concept of Green Chemistry established by Anastas and Warner 33 34 [16] find out innocuous solvents is an industry goal, since their elimination in the processes is not feasible. They are necessary, among others, in the reagents dissolution, 35 as a mass and heat transfer medium. The so-called Deep Eutectic Solvents [17] are being 36 postulated as the best alternative to both traditional organic solvents and ionic liquids [18-37 22]. They are mixtures of two or more substances which form a eutectic with a melting 38 39 point lower than the corresponding of each individual component. The hydrogen bonds 40 network between the species involved induces a sharp melting temperature decrease. The 41 choline chloride, which belongs to the B-complex group of water soluble vitamins, is 42 frequently used as hydrogen bond acceptor (HBA). As hydrogen bond donors (HBD), urea, polyols, organic acids, or amino acids can be used. NMR techniques (NOESY and 43 44 DOSY experiments) have verified the existence of a supramolecular structure in the DES 45 [23-25]. So that, the final compound properties are different from those of their constituent molecules. Sometimes, modifying the solvent physicochemical properties to 46 adapt to a specific industrial process is suitable. For this, the water [21,26] is added as 47

modifier since allows to modulate the solvent thermophysical behavior. The great advantages of DESs include high solvent capacity, biodegradability and biocompatibility, as well as their low price and null reactivity with water [27]. Therefore, these compounds are especially suitable for applications related to consumption in living beings. In pharmacology, DESs are capable of increasing both the solubility of poorly water-soluble drugs and their permeability through the membranes. In the agri-food industry, they increase the extraction and separation processes efficiency [28-34].

Fluids viscosity data are very important in the industrial processes above cited. This property is a direct consequence of the molecular internal friction. Therefore, its study allows to establish the type of intermolecular interactions within the system. Taking account both the DESs and their aqueous mixtures are the new green solvents, as we have already indicated, the measure of the viscosity is required.

This paper is a continuation of our research line on the thermophysical 60 characterization of deep eutectic solvents, and the water effect on them [35,36]. Herein, 61 we study about the viscometric properties of the myo-inositol both in pure water and in 62 aqueous solutions containing a DES as co-solute, at atmospheric pressure and at T=63 64 (293.15-318.15) K. The studied DESs are composed by choline chloride ([Ch]Cl) and urea (U) or glycerol (Gly), in 1:2 mole relation. We have measured the kinematic 65 viscosity, v, and using our previously published volumetric data [35] corresponding to 66 67 the same samples, we have calculated the dynamic viscosity, η . Moreover, different properties such as the viscosity B-coefficient, the hydration number, $n_{\rm h}$, and the 68 activation parameters of viscous flow (the free energy of activation per mole of solvent, 69 $\Delta \mu_1^{\neq}$, the free energy of activation per mole of solute, $\Delta \mu_2^{\neq}$, the enthalpy of 70 activation, ΔH_2^{\neq} , and the entropy of activation, $T\Delta S_2^{\neq}$) are evaluated. 71

72 **2.** Materials and methods

73 2.1. Materials

Table 1 summarizes the information about the compounds, including the 74 75 abbreviations used in this work, and Fig. S1 (supplementary material) shows their chemical structures. Myo-inositol (>99 %) was supplied from Sigma Aldrich, and the 76 DESs were acquired already synthesized from Scionix Ltd. DESs were subjected to 77 vacuum for several hours before the solutions preparation. The water content, $m_w=253$ 78 ppm for [Ch]Cl:U and m_w =275 ppm for [Ch]Cl:Gly, was determined by the Karl Fischer 79 method (automatic titrator Crison KF 1S-2B). These values were accounted for the 80 solution preparation. For each molality, the mixtures were obtained by adding myo-81 82 inositol to a suitable amount of solvent. The latter was prepared by mixing the commercial DES with Milli Pore MilliQ water of resistivity $< 18.2 \ \mu \text{S} \cdot \text{cm}^{-1}$. A Sartorius Semimicro 83 balance (CP225-D), with an uncertainty of 0.01 mg, was used in the mass determination. 84

- 85 Table 1
- 86 Sample table

Source	Purification	Mass	Water	Molar	CAS
	method	fraction	content /	mass /	No
		purity ^a	ppm^{b}	g·mol ⁻¹	
Sigma-	Non	>0.99		180.16	87-89-8
Aldrich					
Scionix Ltd.	Vacuum	>0.98	253	86.58	
	treatment				
Scionix Ltd.	Vacuum	>0.98	275	107.95	
	treatment				
	Source Sigma- Aldrich Scionix Ltd. Scionix Ltd.	Source Purification method Sigma- Non Aldrich Scionix Ltd. Vacuum treatment Scionix Ltd. Vacuum	SourcePurificationMassmethodfractionpurityaSigma-NonAldrichScionix Ltd.VacuumScionix Ltd.ScionixScionix Ltd.Scionix<	SourcePurificationMassWatermethodfractioncontent /purityappmbSigma-Non>0.99AldrichVacuum>0.98253treatmenttreatment275Scionix Ltd.Vacuum>0.98275treatmenttreatment50.98275	SourcePurification methodMassWater fraction purityaMolar mass / ppmbSigma-Non>0.99180.16AldrichVacuum>0.9825386.58Scionix Ltd.Vacuum>0.98275107.95Scionix Ltd.Vacuum>0.98275107.95

88 ^bKarl-Fischer method

87

89 2.2. Apparatus and procedure

91 Schott-Geräte AVS-440 was used to determine the kinematic viscosity, ν , of the mixtures. The temperature was kept constant within ± 0.01 K by means of a Schott-Geräte CT52 92 93 thermostat. The calibration was carried out with ultra-pure water (SH calibration service GmbH) and the kinematic viscosity uncertainty was $U_c(\nu) = 1$ %. Apparatus was checked 94 using benzene as a reference fluid [37] and the mean relative deviation between the 95 96 literature and experimental data, equation S.1 (supplementary material), was $MRD(\nu) =$ 97 0.28%.

- 3. Results and discussion 98
- 3.1. Viscosity 99

In this section, we present experimental data for kinematic viscosity, v, of *myo*-100 101 inositol in pure water, and in [Ch]Cl:U and [Ch]Cl:Gly aqueous solutions. The values are 102 reported in the supplementary material (Table S1). The composition ranges of the solute (myo-inositol) and co-solutes (DES) were $m_{\rm B} = 0$ to 0.15 mol·kg⁻¹ and $m_{\rm A} = 0$ to 0.5 103 mol·kg⁻¹, respectively. The measurements were performed at p = 99.0 kPa and at six 104 105 temperatures from 293.15 to 318.15 K. From our ν (this work) and ρ (previously published [35]) data, we have calculated the dynamic viscosities, $\eta = \rho \cdot \nu$. The estimated 106 combined expanded uncertainty ($k \approx 2$) was $U_c(\eta) = 1\%$ and the values are also listed in 107 Table S1. 108

We have found literature viscosity data for the aqueous solutions of MI [38,39], 109 [Ch]Cl:U [40-42], and [Ch]Cl:Gly [43]. It can be seen (Fig. 1) that our results for the 110 sweetener are very similar to published by Zhang et al. [39] and slightly higher than those 111 112 from Romero et al [38]. These latter were measured at p = 75 kPa. In the published data for both DESs, our experimental data are not directly comparable since composition do 113

not match but a qualitative comparison can be carried out. For [Ch]Cl:U mixtures (Fig. 114 2a), this work is agreed with Xie et al. [41] data whereas the other values are slightly 115 inferior to both. The discrepancies may be due to a different water content, m_w , in the 116 [Ch]Cl:U because the viscosity values depend very much on the water content. [Ch]Cl:U 117 with m_w =5000 ppm was used by Shekaari et al. [42]. The paper of Yadav et al. [40] does 118 not include the m_w values or drying procedure of the compounds. Fig. 2b shows a good 119 120 agreement between the experimental data (this work) and those from literature [43] for [Ch]Cl:Gly in pure water. 121



122

123 Fig. 1. Dynamic viscosity, η , for *myo*-inositol in pure water against its molality, m_B , at

several temperatures, T. \blacksquare , this work; \bullet , Ref. [39.]; \triangle , Ref. [38.].





126 Fig. 2. Dynamic viscosity, η, for DESs aqueous solutions ((a), [Ch]Cl:U; (b), 127 [Ch]Cl:Gly) against its molality, at several temperatures, T. ■, this work; ●, Ref. [40]; 128 ▲, Ref. [41]; ▼, Ref. [42]; ★, Ref. [43]. Black, T = 293.15 K; red, T = 298.15 K; blue, 129 T = 303.15 K; cyan, T = 308.15 K; green, T = 313.15 K; magenta, T = 318.15 K.

The measured viscosity for the ChCl:U aqueous solutions was similar to those for 131 the ChCl or U in pure water [44,45] mixtures. On the other hand, the ChCl:Gly η is higher 132 than for the ChCl+water and Gly+water systems [38,44]. For the mixtures with myo-133 inositol, the viscosity is higher in the systems containing co-solute and the change is more 134 significant for the [Ch]Cl:Gly mixtures (Fig. 3 and 4). Glycerol is able to establish a 135 greater H-bonds number than urea, so the [Ch]Cl:Gly hinders the molecules movement 136 more than the [Ch]Cl:U. Moreover, η increases with increasing m_A and decreases when 137 *T* increases because the fluidity is lower in these conditions. 138



Fig. 3. Dynamic viscosity, η , for *myo*-inositol in aqueous [Ch]Cl:U solutions against its molarity, c_B , at p = 99.0 kPa, and at several temperatures: \blacksquare , T = 293.15 K; \bullet , T = 298.15K; \blacktriangle , T = 303.15 K; \checkmark , T = 308.15 K; \diamondsuit , T = 313.15 K; \triangleleft , T = 318.15 K.





146 Fig. 4. Dynamic viscosity, η , for *myo*-inositol in aqueous [Ch]Cl:Gly solutions against its 147 molarity, c_B , at p = 99.0 kPa, and at several temperatures: \blacksquare , T = 293.15 K; \bullet , T = 298.15148 K; \blacktriangle , T = 303.15 K; \checkmark , T = 308.15 K; \diamondsuit , T = 313.15 K; \triangleleft , T = 318.15 K.

150 *3.2. Hydration behaviour*

Solute-solvent interactions can also be analysed via viscosity *B*-coefficient with the Jones-Dole equation [46] that expresses the relative viscosity, η_r , as a function of the solution molarity, $c_{\rm B}$. This equation for dilute solutions of non-electrolyte solutes is the following:

$$\eta_r = \eta/\eta_0 = 1 + B \cdot c_B \tag{1}$$

155 where η and η_0 are the viscosities of the solution and solvent (water or DES+water), respectively; and B is a coefficient related to solute-solvent interactions. Normally, a B 156 positive value means that the solute is strongly hydrated, and therefore behaves as a 157 structure-making or kosmotrope agent. However, some large solutes as the 158 tetramethylammonium cation have positive coefficients but they are structure-breaking 159 160 or chaotropics substances [47]. Therefore, other parameter is preferred to check the 161 system interactions. According to the Eyring's theory of viscosity [48], if dB/dT < 0 the viscous flow activation energy for the solution is greater than for the solvent; i.e., the 162 solute is a kosmotrope. On the other hand, when dB/dT > 0, the solute is a chaotrope. 163 The sign of dB/dT shows the net balance between the structure stabilization carried out 164 165 by the hydrophobic groups and the disruption caused by hydrophilic groups.

For all the studied systems, *B*-coefficient (Table 2) was positive and decreased with *T* increasing (dB/dT < 0). So that, we can conclude, that the *myo*-inositol in pure water, and in [Ch]Cl:U and [Ch]Cl:Gly aqueous solutions behaves like a kosmotropic compound. No clear trends with composition were found, which points out to the complexity of our systems. These conclusions are in agreement with those obtained from the volumetric study [35].

The hydration number, $n_{\rm h}$, is a parameter related to the solvent molecules distribution around the solute. It can be calculated from the experimental measurements carried out in this work. The *B*-coefficient is divided into two contributions with the Einstein equation [49]:

$$B = B_{\text{size}} + B_{\text{structure}} = 2.5 V_2^0 + B_{\text{structure}}$$
(2)

$$n_{\rm h} = B_{\rm structure}/2.5 \, V_1 \tag{3}$$

where V_2^0 is the standard partial molar volume of the solute and V_1 is the solvent (water 177 178 or DES+water) molar volume. These values were taken from our previously published paper [35]. B_{size} indicates the effect of the solute size on the viscosity, and $B_{structure}$ 179 suggests the effect of the solute on the solvent structure. Therefore, the $B_{\text{structure}}$ sign can 180 be a viable criterion to determine the solute hydration behaviour. A positive value is 181 related to structure-maker solutes whereas a negative sign indicates structure-breaker 182 183 solutes. Fig. 5 shows this effect for several substances [38,44,45,50] including those studied in this work. It is observed that different sugars in aqueous solutions are 184 kosmotropes whereas the components forming the [Ch]Cl:U and [Ch]Cl:Gly (choline 185 chloride, urea, and glycerol) are chaotrope solutes. 186

187 Table 2

Calculated properties for *myo*-inositol in pure water and DES ([Ch]Cl:U or [Ch]Cl:Gly) aqueous solutions at p = 99.0 kPa, at several temperatures, *T*, and at DES molality, m_A . The viscosity *B*-coefficients are from equation 1, the corresponding standard deviations (equation S.2, supplementary material), $\sigma(\eta_r)$, and the temperature coefficients, (dB/dT). The hydration numbers, n_h , are from equation 3.

<i>T /</i> K	m_A / mol·kg ⁻¹	$B \cdot 10^3$ / m ³ ·mol ⁻¹	$\sigma(\eta_r) = \frac{\left(\frac{dB}{dT}\right) \cdot 10^3 /}{\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{K}^{-1}} \qquad n_h$	
--------------	------------------------------	--	--	--

Myo-inositol in aqueous solution

293.15	0	0.4879	(±0.0019)	0.0002	-0.0024	5.18
298.15		0.4707	(±0.0021)	0.0003	(±0.0002)	4.76
303.15		0.4598	(±0.0026)	0.0003		4.48
308.15		0.4464	(±0.0018)	0.0002		4.14
313.15		0.4410	(±0.0017)	0.0002		3.98
318.15		0.4244	(±0.0037)	0.0005		3.57
	My	o-inositol in	n aqueous [C	h]Cl:U solu	tions	
293.15	0.1109	0.5149	(±0.0050)	0.0007	-0.0027	5.72
298.15		0.4963	(±0.0052)	0.0007	(± 0.0002)	5.29
303.15		0.4788	(±0.0045)	0.0006		4.86
308.15		0.4668	(±0.0042)	0.0005		4.57
313.15		0.4585	(±0.0072)	0.0009		4.34
318.15		0.4436	(±0.0070)	0.0009		3.97
293.15	0.2219	0.5108	(±0.0036)	0.0005	-0.0032	5.60
298.15		0.4916	(±0.0031)	0.0004	(±0.0003)	5.15
303.15		0.4742	(±0.0064)	0.0008		4.74
308.15		0.4504	(±0.0021)	0.0003		4.18
313.15		0.4493	(±0.0069)	0.0009		4.12
318.15		0.4284	(±0.0045)	0.0006		3.62
293.15	0.3833	0.5023	(±0.0023)	0.0003	-0.0027	5.36
298.15		0.4918	(±0.0048)	0.0006	(± 0.0002)	5.10
303.15		0.4719	(±0.0040)	0.0005		4.64
308.15		0.4599	(±0.0061)	0.0008		4.35
313.15		0.4530	(±0.0070)	0.0009		4.15
318.15		0.4316	(±0.0054)	0.0007		3.64
	Муо	-inositol in	aqueous [Cł	1]Cl:Gly sol	utions	
293.15	0.5081	0.4952	(±0.0018)	0.0002	-0.0022	5.18
298.15		0.4821	(±0.0028)	0.0004	(±0.0001)	4.86
303.15		0.4693	(±0.0025)	0.0003		4.55

308.15		0.4635	(±0.0015)	0.0002		4.39
313.15		0.4451	(±0.0038)	0.0005		3.96
318.15		0.4403	(±0.0044)	0.0006		3.81
293.15	0.1252	0.4809	(±0.0020)	0.0003	-0.0024	5.01
298.15		0.4682	(±0.0020)	0.0003	(± 0.0002)	4.69
303.15		0.4509	(±0.0029)	0.0004		4.28
308.15		0.4395	(±0.0032)	0.0004		3.99
313.15		0.4280	(±0.0035)	0.0005		3.70
318.15		0.4226	(±0.0036)	0.0005		3.53
293.15	0.2538	0.4839	(±0.0028)	0.0004	-0.0027	5.01
298.15		0.4685	(±0.0023)	0.0003	(± 0.0002)	4.63
303.15		0.4500	(±0.0021)	0.0003		4.19
308.15		0.4351	(±0.0032)	0.0004		3.82
313.15		0.4246	(±0.0033)	0.0004		3.53
318.15		0.4177	(±0.0035)	0.0005		3.32
293.15	0.3742	0.4877	(±0.0023)	0.0003	-0.0027	5.05
298.15		0.4682	(±0.0020)	0.0003	(± 0.0002)	4.57
303.15		0.4538	(±0.0019)	0.0003		4.21
308.15		0.4385	(±0.0031)	0.0004		3.81
313.15		0.4277	(±0.0030)	0.0004		3.51
318.15		0.4191	(±0.0039)	0.0005		3.24
293.15	0.4986	0.4860	(±0.0014)	0.0002	-0.0027	4.98
298.15		0.4714	(±0.0029)	0.0004	(± 0.0002)	4.59
303.15		0.4581	(±0.0021)	0.0003		4.23
308.15		0.4399	(±0.0027)	0.0003		3.76
313.15		0.4262	(±0.0034)	0.0004		3.39
318.15		0.4212	(±0.0036)	0.0005		3.18

193 Standard uncertainties, *u*, are: $u(m_A)=0.0001 \text{ mol·kg}^{-1}$; u(T)=0.01 K; u(p)=0.5 kPa.





Fig. 5. Viscosity *B*-coefficients, *B*, against the standard partial molar volumes of the solute, V_2^0 , at *T*=298.15 K. Solid symbols, several compounds in aqueous solutions [38,44,45,50]; \triangle , *myo*-inositol in aqueous [Ch]Cl:U solutions; \triangle , *myo*-inositol in aqueous [Ch]Cl:Gly solutions; line, *B*_{size}.

The hydration numbers (Table 2) were lower than those estimated from 199 volumetric data [35] using the Pasynski method. This result is usual due to the hydrate 200 201 compressibility is despised in this method [51,52]. The highest values are found for the 202 mixtures with [Ch]Cl:U, which suggests that, in this system, the number of solvent 203 molecules disturbed by the solute is greater. In relation to the effect of the DES concentration on this parameter, n_h decreases slightly when m_A increases for [Ch]Cl:U 204 solutions and remains practically constant in those containing [Ch]Cl:Gly. We have 205 206 calculated the hydration number average values, $\overline{n_h}$, in our working composition range. The $\overline{n_h}$ values decrease with T increasing (Fig. S2) following a type-Arrhenius equation: 207

$$\overline{n_h} = A \exp(E_a/RT) \tag{4}$$

where A and E_a are the fitting parameters (Table 3), R is the gas constant, and T is the 208 temperature. The A pre-exponential factor indicates the hydration number only due to the 209 geometric factor since the interactions become negligible when $T \rightarrow \infty$. The highest 210 energetic barrier to overcome for the hydration process of the myo-inositol, E_a , is 211 obtained when the solvent contains [Ch]Cl:Gly. The other two systems show similar 212 energies. The higher the E_a value the stronger intermolecular interactions. Again, results 213 suggest that the [Ch]Cl:U presence favours the hydration structure more than [Ch]Cl:Gly, 214 and the mixtures containing this latter DES have the greatest solute co-solute interactions. 215 216 Anyway, the calculated values were small, indicating stable hydration structures in all 217 cases.

218 **Table 3**

Arrhenius fitting parameters (equation 4) for *myo*-inositol in pure water and DES
([Ch]Cl:U or [Ch]Cl:Gly) aqueous solutions.

Solvent	Α	E_a / kJ·mol ⁻¹	R^2
Pure water	0.0566	11.008	0.990
[Ch]Cl:U + water	0.0519	11.365	0.995
[Ch]Cl:Gly + water	0.0229	13.144	0.998

221

222 3.3. Activation parameters of viscous flow

Thermodynamic parameters of the viscous flow can be obtained from the viscosity B-coefficients [53]: the Gibbs free energy of activation for viscous flow per mole of solvent, $\Delta \mu_1^{0\neq}$; the Gibbs free energy of activation per mole of solute, $\Delta \mu_2^{0\neq}$; the standard partial molar entropy of activation for viscous flow, $\Delta S_2^{0\neq}$; and the standard partial molar enthalpy of activation for viscous flow, $\Delta H_2^{0\neq}$. These parameters are given in Table 4 and the equations used are the following:

$$\Delta \mu_1^{\neq} = RT \ln \left(\eta_1 V_1 / h N_A \right) \tag{5}$$

$$\Delta \mu_2^{\neq} = \Delta \mu_1^{\neq} + \frac{RT}{V_1} (B + V_2^0 - V_1) \tag{6}$$

$$\Delta S_2^{\neq} = -d(\Delta \mu_2^{\neq})/dT \tag{7}$$

$$\Delta H_2^{\neq} = \Delta \mu_2^{\neq} + T \Delta S_2^{\neq} \tag{8}$$

where η_1 is the solvent (water or DES+water) viscosity; V_2^0 and V_1 are the standard partial molar volume of the solute and the solvent molar volume [35], respectively; *h* is the Planck constant; N_A is the Avogadro number; *R* is the gas constant; and *T* is the temperature.

 $\Delta \mu_1^{\neq}$ and $\Delta \mu_2^{\neq}$ calculated data are positive and decrease with increasing 233 temperature. Regarding the effect of the DES concentration, $\Delta \mu_1^{\neq}$ increases slightly and 234 $\Delta \mu_2^{\neq}$ decreases when m_A increases. According to the transition state theory of relative 235 viscosity [53], $(\Delta \mu_2^{\neq} - \Delta \mu_1^{\neq})$ values indicate the change in the activation energy when one 236 mole of solvent is replaced by on mole of solute at infinity dilution. Then, if $\Delta \mu_2^{\neq} > \Delta \mu_1^{\neq}$, 237 as this work, the ground state is the favoured status from the free energy point of view; 238 i.e. solute-solvent interactions are stronger than in the transition state. Furthermore, the 239 higher $\Delta \mu_2^{\neq}$ value the higher structure-making tendency of the solute. Again, our results 240 241 indicate that the myo-inositol in ([Ch]Cl:U+water) solvent is the best structure-making. 242 Finally, it is observed that the formation of the transition state is a process that involves a bond breaking and increased disorder as indicated by the positives values of ΔS_2^{\neq} and 243 ΔH_2^{\neq} . These parameters are higher in the mixtures with [Ch]Cl:U. 244

245 Table 4

Activation parameters of viscous flow (free energy of activation per mole of solvent, $\Delta \mu_1^{\pm}$, free energy of activation per mole of solute, $\Delta \mu_2^{\pm}$, enthalpy of activation, ΔH_2^{\pm} , and entropy of activation, $T\Delta S_2^{\pm}$) for *myo*-inositol in pure water or DES ([Ch]Cl:U or [Ch]Cl:Gly) aqueous solutions at p = 99.0 kPa, at several temperatures, *T*, and DES molality, m_A .

TT / 17	<i>m</i> _A /	$\Delta \mu_1^{0 eq} /$	$\Delta \mu_2^{ eq}/$	$\Delta H_2^{\neq}/$	$T\Delta S_2^{\neq}/$				
I / K	mol·kg ⁻¹	kJ·mol ⁻¹	kJ·mol ⁻¹	kJ∙mol ⁻¹	kJ∙mol ⁻¹				
	Myo-inositol in aqueous solution								
293.15	0	9.29	86.46	120.73	34.27				
298.15		9.16	85.29	120.14	34.85				
303.15		9.04	84.90	120.34	35.44				
308.15		8.94	84.13	120.15	36.02				
313.15		8.84	84.42	121.03	36.61				
318.15		8.75	83.05	120.24	37.19				
	Myo-	inositol in aque	ous [Ch]Cl:U so	lutions					
293.15	0.1109	9.32	89.75	136.51	46.76				
298.15		9.20	88.44	136.00	47.55				
303.15		9.09	87.21	135.56	48.35				
308.15		8.98	86.63	135.78	49.15				
313.15		8.87	86.53	136.48	49.95				
318.15		8.80	85.43	136.17	50.74				
293.15	0.2219	9.36	88.76	155.39	66.63				
298.15		9.24	87.38	155.15	67.77				
303.15		9.13	86.14	155.05	68.91				
308.15		9.02	83.93	153.97	70.04				
313.15		8.92	84.79	155.97	71.18				
318.15		8.84	82.80	155.12	72.32				
293.15	0.3833	9.41	87.02	134.33	47.31				
298.15		9.30	86.82	134.94	48.12				
303.15		9.18	85.26	134.18	48.93				
308.15		9.07	84.66	134.39	49.74				
313.15		8.98	84.76	135.30	50.54				
318.15		8.91	82.73	134.08	51.35				

293.15	0.5081	9.45	85.63	112.63	27.00
298.15		9.34	85.06	112.52	27.46
303.15		9.23	84.46	112.38	27.92
308.15		9.12	84.74	113.12	28.38
313.15		9.03	83.20	112.04	28.84
318.15		8.95	83.50	112.80	29.30
	Myo-inosi	tol in aqueous [Ch]Cl:Gly solut	tions	
293.15	0.1252	9.38	84.89	120.88	36.00
298.15		9.26	84.35	120.97	36.61
303.15		9.14	83.08	120.31	37.23
308.15		9.03	82.53	120.37	37.84
313.15		8.93	81.92	120.38	38.45
318.15		8.85	82.16	121.22	39.07
293.15	0.2538	9.46	84.74	131.47	46.73
298.15		9.35	83.85	131.37	47.53
303.15		9.23	82.44	130.76	48.32
308.15		9.12	81.43	130.55	49.12
313.15		9.02	81.02	130.94	49.92
318.15		8.94	81.05	131.77	50.71
293.15	0.3742	9.54	84.68	129.24	44.56
298.15		9.42	83.32	128.64	45.32
303.15		9.31	82.50	128.58	46.08
308.15		9.19	81.51	128.35	46.84
313.15		9.09	81.06	128.66	47.60
318.15		9.02	80.91	129.27	48.36
293.15	0.4986	9.62	83.88	125.04	41.16
298.15		9.50	83.22	125.08	41.86
303.15		9.39	82.62	125.18	42.56
308.15		9.27	81.28	124.54	43.26
313.15		9.17	80.47	124.44	43.97
318.15		9.10	80.88	125.55	44.67
318.15		9.10	80.88	125.55	

251 Standard uncertainties, *u*, are: $u(m_A)=0.0001 \text{ mol}\cdot\text{kg}^{-1}$; u(T)=0.01 K; u(p)=0.5 kPa.

4. Conclusions

The viscosity is an important property for the industrial processes design. In this paper, viscosity data of *myo*-inositol in pure water, and in [Ch]Cl:U and [Ch]Cl:Gly aqueous solutions are presented. The measurements were performed at p = 99.0 kPa and at six temperatures from 293.15 to 318.15 K. From experimental data, other properties were calculated and the interactions were evaluated.

The *B*-coefficient values and its variation with the temperature indicates that the *myo*inositol is a structure-maker in all the mixtures studied. The greatest solute hydration numbers are found in the system containing [Ch]Cl:U. The mixtures with [Ch]Cl:Gly exhibits the strongest interactions. From activation parameters of viscous flow, we obtain that the ground state is the favoured status.

266 Acknowledgments

This research was supported by Gobierno de Aragón (Grant E-54), Fondo Social Europeo
"Construyendo Europa desde Aragón". The authors would like to thank their financial
assistance.

270 Appendix A. Supplementary data

Supplementary data related to this paper can be found in version online. Kinematic viscosities, ν , and dynamic viscosities, η . Compounds chemical structures. Arrhenius plot for the hydration number.

274 References

- [1] M. Mueckler, B. Thorens, The SLC2 (GLUT) family of membrane transporters, Mol.
- 276 Aspects Med. 34 (2012) 121-138.
- [2] S. Schneider, Inositol transport proteins, FEBS Lett. 589 (2015) 1049-1058.
- [3] R. Valluru, W. Van den Ende, *Myo*-inositol and beyond Emerging networks under
 stress, Plant Sci. 181 (2011) 387-400.
- [4] A. Saiardi, Has inositol played any role in the origin of life? Life 7 (2017) 24.
- [5] T. Taji, S. Takahashi, K. Shinozaki, Inositol and their metabolites in abiotic and
 biotic stress responses, in Biology of Inositols and Phosphoinositides, Springer,
 Berlin, 2006, pp. 239-264.
- [6] J. Sarris, J. Murphy, D. Mischoulon, G.I. Papakostas, M. Fava, M. Berk, C.H. Ng,
 Adjunctive nutraceuticals for depression: a systematic review and meta-analyses,
 Am. J. Psychiatry 173 (2016) 575-587.
- [7] A.D. Frej, G.P. Otto, R.S.B. Williams, Tipping the scales: lessons from simple model
 systems on inositol imbalance in neurological disorders, Eur. J. Cell. Biol. 96 (2017)
 154-163.
- [8] S. Benvenga, A. Antonelli, Inositol(s) in thyroid function, growth and autoimmunity,
 Rev. Endocr. Metab. Disord. 17 (2016) 471-484.
- [9] J. Pundir, D. Psaroudakis, P. Savnur, L. Sabatini, H. Teede, A. Coomarasamy, S.
 Thangaratinam, Inositol treatment of anovulation in women with polycystic ovary
 syndrome: a meta-analysis of randomised trials, BJOG 125 (2018) 299-308.
- [10] B. K. Sarkar, C. Chakraborty, A. R. Sharma, K.J. Bae, G. Sharma, G. P. Doss, D.
- Dutta, S. Ding, B. Ganbold, J. S. Nam, S. S. Lee, Novel biomarker for prostate cancer
 diagnosis by MRS, Front. Biosci (Landmark, Ed.) 19 (2014) 1186-1201.
- 298 [11] E.M. Wright, B.A. Hirayama, D.F. Loo, Active sugar transport in health and disease,
- 299 J. Int. Med. 261 (2007) 32-43.

- [12] C.C. Barron, P. J. Bilan, T. Tsakiridis, E. Tsiani, Facilitative glucose transporters:
 Implications for cancer detection, prognosis and treatment, Metab. Clin. Exp. 65
 (2015) 124-139.
- [13] M. Castillo, J.K. Smith, L. Kwock, Correlation of *myo*-inositol levels and grading of
 cerebral astrocytomas, AJNR, 21 (2000) 1645-1649.
- [14]B.D. Gill, H.E. Indyk, D.C. Woollard, Current methods for the analysis of selected
 novel nutrients in infant formulas and adult nutritionals, J. AOAC Int. 99 (2016) 3041.
- 308 [15] Commission Regulation N°609/2013; <u>http://data.europa.eu/eli/reg/2013/609/oj</u>,
 309 2013 (accessed 12 June 2013).
- 310 [16] P. Anastas, J. C. Warner, Green chemistry: theory and practice, Oxford University
 311 Press, Oxford, 2000.
- [17]Y.H. Choi, J.Van Spronse, Y.Dai, M.Verbene, F.Holllmann, I.W.C.E. Arends, G.J
 Witkamp, R. Verpoote, Are Natural Deep Eutectic Solvents the Missing Link in
 Understanding Cellular Metabolism and Physiology? Plant Physiol. 156 (2011)
 1701-1705.
- [18] A.P. Abbott, G. Capper, D.L. Davies, R.K. Rasheed, V. Tambyrajah, Novel solvent
 properties of choline chloride/urea mixtures, Chem. Commun. (2003) 70-71.
- 318 [19] A.P. Abbott, D. Boothby, G. Capper, D.L. Davies, R.K. Rasheed, Deep eutectic
 319 solvents formed between choline chloride and carboxylic acids: versatile alternatives
- to ionic liquids, J. Am. Chem. Soc. 126 (2004) 9142-9147.
- [20] A. Paiva, R. Craveiro, I. Aroso, R.L. Reis, A.R. Duarte, Natural deep eutectic
 solvents Solvents for the 21st century, ACS Sustain. Chem. Eng. 2 (2014) 10631071.

- [21] F. Pena-Pereira, A. Kloskowski, J. Namiesnik, Perspectives on the replacement of
 harmful organic solvents in analytical methodologies: a framework toward the
 implementation of a generation of eco-friendly alternatives, Green Chem. 17 (2015)
 3687-3705.
- [22] E. Durand, J. Lecomte, P. Villeneuve, From green chemistry to nature: the versatile
 role of low transition temperature mixtures, Biochimie 120 (2016) 119-123.
- [23] Y. Dai, J. van Spronsen, G.J. Witkamp, R. Verpoorte, Y.H. Choi, Natural deep
 eutectic solvents as new potential media for green technology, Anal. Chim. Acta 766
 (2013) 61-68.
- [24]C. D'Agostino, L.F. Gladden, M.D. Mantle, A.P. Abbott, E.I. Ahmed, A.Y.M. AlMurshedi, R.C. Harris, Molecular and ionic diffusion in aqueous-deep eutectic
 solvent mixtures: probing inter-mlecular interactions using PFG NMR, Phys. Chem.
 Chem. Phys. 17 (2015) 15297-15304.
- 337 [25] M.K. Hadj-Kali, K.E. Al-Khidir, I. Wazeer, L. El-Blidi, S. Mulyono, I.M. AlNashef,
- Application of deep eutectic solvents and their individual constituents as surfactants
 for enhanced oil recovery, Colloids Suf. A 487 (2015) 221-231.
- 340 [26] Y. Dai, G.J. Witkamp, R. Verpoorte, Y.H. Choi, Tailoring properties of natural deep
- eutectic solvents with water to facilite their applications, Food Chem. 187 (2015) 1419.
- 343 [27]Q. Zhang, K. de Oliveira Vigier, S. Royer, F. Jérôme, Deep eutectic solvents:
- 344 syntheses, properties and applications, Chem. Soc. Rev. 41 (2012) 7108-7146.
- [28] M. Espino, M.A. Fernández, F.J.V. Gomez, M.F. Silva, Natural designer solvents for
 greening analytical chemistry, Trends Analyt. Chem. 76 (2016) 126-136.
- 347 [29] H. Lores, V. Romero, I. Costas, C. Bendicho, I. Lavilla, Natural Deep eutectic
- 348 solvents in combination with ultrasonic energy as a Green approach for solubilisation

- of proteins: application to glute determination by immunoassay, Talanta 162 (2017)
 453-459.
- 351 [30] E. Rozema, A.D. van Dam, H.C.M. Sips, R. Verpoorte, O.C. Meijer, S. Kooijman,
- Y.H. Choi, Extending pharmacological dose-response curves for salsalate with
 natural deep eutectic solvents, RSC Adv. 5 (2015) 61398-61401.
- [31]Z. Li, P.I. Lee, Investigation on drug solubility enhancement using deep eutectic
 solvents and their derivatives, Int. J. Pharm. 505 (2016) 283-288.
- [32] A.R. Duarte, A.S.D. Ferreira, S. Barreiros, E. Cabrita, R.L. Reis, A. Paiva, A
 comparison between pure active pharmaceutical ingredients and therapeutic deep
 eutectic solvents: Solubility and permeability studies, Eur. J. Pharm. Biopharm. 114
 (2017) 296-304.
- [33] M.H. Zainal-Abidin, M. Hayyan, A. Hayyan, N.S. Jayakumar, New horizonts in the
 extraction of bioactive compounds using deep eutectic solvents: A review, Anal.
 Chim. Acta 979 (2017) 1-23.
- 363 [34]C. Guízar-González, N.R. Mustafa, E.G. Wilson, R. Verpoorte, Y.H. Choi,
 364 Application of natural deep eutectic solvents for the "green" extraction of vanillin
 365 from vanilla pods, Flavour Fragr. J. 33 (2018) 91-96.
- 366 [35]F. Bergua, M. Nuez, J. Muñoz-Embid, C. Lafuente, M. Artal, Volumetric and
 acoustic behaviour of *myo*-inositol in aqueous natural deep eutectic solvent solutions,
 J. Mol. Liq. 258 (2018) 106-113.
- 369 [36] D. Lapeña, L. Lomba, M. Artal, C. Lafuente, B. Giner, The NADES glyceline as a
- 370 potential green solvent: a comprehensive study of its physicochemical properties and
- affect of water content, J. Chem. Thermodyn.(submitted).

[37] V. Antón, H. Artigas, J. Muñoz-Embid, M. Artal, C. Lafuente, Thermophysical study
 of 2-acetylthiophene: experimental and modelled results, Fluid Phase Equilib. 433

374 (2017) 126–134.

- [38] C. M. Romero, M. S. Páez, M. J. Puchana, Effect of temperature on the volumetric
 and viscometric properties of polyols in aqueous solutions, J. Mol. Liq. 223 (2016)
 1192-1196.
- [39] J. Zhang, T. Fu, C. Zhu, Y. Ma, Volumetric and viscometric properties of amino
 acids in aqueous *myo* -inositol solution at T = (293.15 to 323.15) K and p = 0.101
 MPa, J. Mol. Liq. 242 (2017) 190-203.
- [40] A. Yadav, S. Pandey, Densities and viscosities of (choline chloride+urea) deep
 eutectic solvent and its aqueous mixtures in the temperature range 293.15 K to 363.15
 K, J. Chem. Eng. Data 59 (2014) 2221-2229.
- [41] Y. Xie, H. Dong, S. Zhang, X. Lu, X. Ji, Effect of water on the density, viscosity and
 CO2 solubility in choline chloride/urea, J. Chem. Eng. Data 59 (2014) 3344-3352.
- 386[42]H.Shekaari, M.T.Zafarani-Moattar, B.Mohammadi, Thermophysical387characterization of aqueous deep eutectic solvent (choline chloride/urea) solutions in388full ranges of concentration at T = (293.15-323.15) K, J. Mol. Liq. 243 (2017) 451-389461.
- [43] A. Yadav, S. Trivedi, R. Rai, S. Pandey, Densities and dynamic viscosities of
 (choline chloride+glycerol) deep eutectic solvent and its aqueous mixtures in the
 temperature range 293.15 K to 363.15 K, Fluid Phase Equilib. 367 (2014) 135-142.
- 393 [44] S. Shaukat, R. Buchner, Densities, Viscosities [from (278.15 to 318.15) K], and
- 394Electrical Conductivities (at 298.15 K) of Aqueous Solutions of Choline Chloride
- and Chloro-Choline Chloride, J. Chem. Eng. Data 56 (2011), 4944-4949.

- [45] T.T. Herskovits, T.M. Kelly, Viscosity studies of aqueous solutions of alcohols, ureas
 and amides, J. Phys. Chem. 77 (1973) 381-388.
- [46]G. Jones, M. Dole. The viscosity of aqueous solutions of strong electrolytes with
 special reference to barium chloride, J. Am. Chem. Soc. 51 (1929) 2950–2964.
- 400 [47] H. Zhao, Viscosity B-coefficients and standard partial molar volumes of amino acids,
- and their roles in interpreting the protein (enzyme) stabilization, Biophys. Chem. 122
 (2006) 157-183.
- 403 [48] S. Glasstone, K. Laidler, E. Eyring, The theory of rate processes. New York: Mc-404 Graw-Hill, 1941.
- [49] A. Einstein, A new determination of molecular dimensions, Ann. Phys. (Berl) 324
 (1906) 289-306.
- 407 [50] Y. Sato, O. Miyawaki, Analysis of hydration parameter for sugars determined from
 408 viscosity and its relationship with solution parameters, Food Chem. 190 (2016) 594409 598.
- [51] Y. Marcus, Concentration dependence of ionic hydration numbers, J. Phys. Chem. B
 118 (2014) 10471-10476.
- 412 [52] A.Burakowski, J.Glinski, Hydration numbers of nonelectrolytes from acoustic
 413 methods, Chem. Rev. 112 (2012) 2059-2081.
- [53] D. Feakins, D.J. Freemantle, K.G. Lawrence, Transition state treatment of the
 relative viscosity of electrolytic solutions, J. Chem. Soc. Faraday Trans. 70 (1974)
 795-806.