Journal of Molecular Liquids 409 (2024) 125436

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Assessment of organic solvents for 2,5-furandicarboxylic acid (FDCA) and distribution in water/cyclohexanone biphasic system

Fernando Pardo [a], Hanne Oorts [a], Ane Urtiaga [a], Jesús Esteban [b,*], Gabriel Zarca [a,*]

[a] Department of Chemical and Biomolecular Engineering, Universidad de Cantabria, Av. Los Castros 46, 39005 Santander, Spain
[b] Department of Chemical Engineering, School of Engineering, The University of Manchester, Manchester M13 9PL, United Kingdom

ARTICLE INFO

Keywords:
FDCA
Polar aprotic solvents
Biphasic systems
Distribution
Solubility

ABSTRACT

2,5-furandicarboxylic acid (FDCA) is one of the most promising sugar-derived building blocks aimed to produce greener polymers, such as the 100 % recyclable bioplastic polyethylene furanoate (PEF). One incipient field of research is the development of liquid–liquid biphasic systems for FDCA production from 5-hydroxymethylfurfural (HMF) to increase selectivity and minimize undesirable by-product formation. In this work, we first performed an assessment of potential organic green solvents to form biphasic systems considering operability, along with safety, health, and environmental implications. This analysis guided the selection of eight organic solvents in which the solubility of FDCA was measured: cyclohexanone, diethyl ether, isobutyl acetate, methyl isobutyl ketone, methyl ethyl ketone, methoxycyclopentane, *tert*-butylmethyl ether, and octan-1-ol. The results revealed the superior performance of cyclohexanone as a solvent for the organic phase/water FDCA distribution owing to its higher FDCA solubility (1.364 g/L at 293.15 K). Thus, the FDCA distribution coefficient (K_{FDCA}) between water and cyclohexanone was examined at several temperatures (293.15–313.15 K) and various initial aqueous concentrations to gain deeper insight into the thermodynamics of the phase transfer process and the influence of pH on FDCA distribution between water and cyclohexanone. The resulting enthalpy and entropy of transfer were -15.3 ± 1.0 kJ mol^{-1} and -44.9 ± 4.6 J K^{-1} mol^{-1}, thus the highest value of K_{FDCA} (4.83) was obtained at 293.15 K, together with a very high separation factor (81.5) which shows the great potential of cyclohexanone to extract FDCA from aqueous solutions.

1. Introduction

The increasing demand for the production of chemicals and fuels is still dominated by the use of fossil-based feedstocks. This necessitates the substitution by renewable resources to tackle their scarcity together with the environmental impacts derived from their use, such as escalating carbon emissions and pollution. In this context, lignocellulosic biomass appears as a plentiful resource in nature, from whose fractionation lignin (15–25 %), hemicellulose (23–32 %) and cellulose (38–50 %) can be derived [1]. The latter two fractions provide opportunities to obtain hexoses, such as glucose, from whose isomerisation and subsequent dehydration, 5-hydroxymethylfurfural (HMF) can be obtained [2]. This precursor can be converted into the valuable building block 2,5-furandicarboxylic acid (FDCA), included in the US Department of Energy's top priority chemicals for the establishment of biorefineries [3], by multiple chemocatalytic routes as well as enzymatic oxidation or starting from methoxymethylfurfural [4–6]. FDCA is attracting increasing attention in recent years owing to it being a monomer for the production of polyethylene furanoate (PEF), a potential replacement for fossil-based polyethylene terephthalate. In addition to being a platform for bioplastics, it is known to be a starting material for both the production of fungicides and the production of active pharmaceutical ingredients with anaesthetic properties, and has been used as a corrosion inhibitor, among other applications [7].

The production of HMF, the main FDCA precursor, has shifted to the use of biphasic systems to mitigate the generation of undesired by-products [8,9]. Owing to this, there is a significant amount of works studying the corresponding HMF partitioning and its modelling, where the benchmark solvent for extraction is methyl isobutyl ketone (MIBK) [10–13]. From HMF as starting material, the use of multiphase systems is becoming attractive also for the production of FDCA owing to the possibility of conducting the *in situ* separation of the product from the reaction medium. One example is the FDCA synthesis using a cascade enzymatic reaction in a biphasic H_2O/ethyl acetate system, where the

---

* Corresponding authors.
E-mail addresses: jesus.estebanserrano@manchester.ac.uk (J. Esteban), zarcag@unican.es (G. Zarca).

https://doi.org/10.1016/j.molliq.2024.125436
Received 21 May 2024; Received in revised form 24 June 2024; Accepted 3 July 2024

product precipitates owing to the limited solubility in both solvents, although this will be dependent on the concentrations obtained. [14]. Another example presents the oxidation in the presence of a Ru-based catalyst in a biphasic system with *i*-octane as the initial HMF-bearing solvent [15]. In agreement with the two examples above, FDCA was obtained from HMF by precipitation from the aqueous phase in another biphasic system, which in the latter case was formed by the γ-valerolactone co-produced together with FDCA and a Na_2CO_3-saturated aqueous phase [16]. In the last example, HMF was first synthesized from fructose using a biphasic approach with methyl tetrahydrofuran as extracting agent; subsequently, this non-polar phase was fed into an electrochemical cell to conduct its oxidation to FDCA by back extraction into an aqueous solution of KOH, where the product preferentially remains [17].

Lately, there has been an increasing interest in studying the solubility of furanic compounds owing to their relevance in the development of biorefineries [18,19]. In the case of FDCA, there is a body of information on its solubility in different solvents, namely water, methanol, acetonitrile, acetic acid, ethyl acetate, MIBK, 1-butanol, and isobutanol, 1,4-dioxane, tetrahydrofuran, 2-dimethoxyethane and diethylene glycol dimethyl ether [20,21] as well as some aqueous binary mixtures based on acetic acid [20,22], dioxane [23], methanol [22], ethanol [22] and acetonitrile [20]. However, there is a knowledge gap in the information regarding its distribution in biphasic systems, not to mention the possible influence that *pH* might exert on said equilibrium considering the ionizable nature of the dicarboxylic acid. With an eye on the principles of Green Chemistry to attain more sustainable reaction and separation processes [24], it is relevant to evaluate the FDCA distribution in more solvents to make a selection among alternatives that provide advantageous distribution coefficients whilst possibly showing a favourable safety, health, and environmental (SHE) profile. For this, the CHEM21 guide provides a quick tool to assess their profile and envisage more sustainable processes [25].

Thus, it is of paramount importance to identify efficient biphasic systems for application in chemical reaction for the production of FDCA starting from different biomass substrates. For this reason, this work aims to study the solubility of this chemical in water and a selection of organic solvents as well as its distribution in the corresponding biphasic systems. An analysis of the effect of temperature, concentration and *pH* is presented here as well as insights into the phenomena associated with FDCA distribution considering the high relevance of these variables.

2. Experimental section

2.1. Materials

Deionized water (Milli-Q, *pH*: 6.5, conductivity: 1.3 μS cm^{-1}) and eight organic solvents were considered for the determination of FDCA solubility and preparation of biphasic systems. The specifications of FDCA and these organic solvents are collected in Table 1. In addition, acetonitrile (Fisher Chemicals, 99.9 wt%), ethanol, and butan-1-ol (Merck Life Science, 99.5 wt%) were used for sample preparation and analysis with HPLC, and GC-FID. All chemicals were used as received without further purification.

2.2. Solubility measurements

Solubilities were measured for FDCA in water and several organic solvents. A saturated solution was prepared by adding approximately 80 mg of FDCA and 4 mL of solvent in an Eppendorf tube. An Eppendorf Thermomixer C with a 15 mL SmartBlock was used to mix the samples under vigorous shaking (1000 rpm) with the temperature control set at 298.15 K (±0.5 K) for at least 2.5 h. Preliminary experiments demonstrated that this time was sufficient to reach the equilibrium state. Then, the samples were centrifuged at 2000 rpm for 4 min and placed in a jacketed thermostatic bath in static conditions for at least 16 h. A Julabo F25-MC circulator bath with an external Pt-100 sensor was used to ensure thermostatic conditions at the same equilibrium temperature during sample resting (temperature stability controlled by PID to ± 0.01 K). Eventually, an aliquot of the supernatant (~0.5 mL) was collected with a micropipette and transferred to a volumetric flask, weighed with a Sartorius analytical balance (BCE224i-1S, accuracy ± 0.01 mg), and diluted in acetonitrile for quantification of the FDCA content using high-performance liquid chromatography (HPLC, Agilent 1260 Infinity II). A Zorbax Extend-C18 chromatographic column (3.0 mm x 150 mm, 5 μm, Agilent) and diode array detector ($\lambda_{UV} = 265$ nm) were used. As mobile phase, a water/acetonitrile mixture (75:25 vol%, 0.7 ml min^{-1}) was found to provide optimal results for FDCA analysis. Every experiment was conducted in triplicate to ensure reproducibility, and the mean solubility value is reported with its associated standard deviation. In addition, each sample was analysed 3 times with relative deviations lower than 1 %. A set of validation experiments was performed to determine the solubility of FDCA in water, 1.72 ± 0.02 g L^{-1} at 313.15 K, which is in very good agreement (<1.0 %) with the result reported by Zhang et al. [20].

2.3. Distribution coefficients

To determine the solvent–water distribution coefficient for FDCA, first, FDCA aqueous solutions were prepared below the saturation limit at concentrations of 0.05, 0.2, 0.5, 0.7, and 0.90 g L^{-1}. Then, 4 mL of the aqueous solution and 4 mL of organic solvent were added to an Eppendorf tube, agitated, and left overnight for phase splitting, and the FDCA content was quantified following the same procedure previously described for the solubility measurements, except that the aqueous samples were collected using a glass syringe with a 12 cm long needle to avoid contamination at the aqueous-organic interface. The distribution coefficient of FDCA (K_{FDCA}) was calculated with Equation (1), as the ratio of equilibrium mass fraction concentrations of FDCA between the organic (w^{org}_{FDCA}) and aqueous (w^{aq}_{FDCA}) phases. In addition, the water partition coefficient (K_{water}) is given in Equation (2) as a function of w^{org}_{water} and $w^{aq}_{solvent}$, which correspond to the mass fraction of the organic phase in water and that of water in the organic phase, respectively. Finally, the FDCA separation factor (S_{FDCA}) was determined combining Equations (1) and (2) [26]:

Table 1
Chemicals used for distribution in biphasic systems.

Chemical name	Abbrv.	CAS No.	Source	Purity (mass)
2,5-furandicarboxylic acid	FDCA	3238-40-2	Indagoo Chemicals	0.997
cyclohexanone	ONE	108-94-1	Merck Life Science	0.990
tert-butyl methyl ether	TBME	1634-04-4	Merck Life Science	0.998
diethyl ether	DEE	60-29-7	Merck Life Science	0.990
isobutyl acetate	*i*-BuOAc	110-19-0	Merck Life Science	0.980
methyl ethyl ketone	MEK	78-93-3	Merck Life Science	0.990
methyl isobutyl ketone	MIBK	108-10-1	Thermo Scientific	0.995
methoxycyclopentane	CPME	5614-37-9	Tokyo Chemical Industry	0.995
octan-1-ol	1-OcOH	111-87-5	Thermo Scientific	0.990

$$K_{FDCA} = \frac{w_{FDCA}^{org}}{w_{FDCA}^{aq}} \quad (1)$$

$$K_{water} = \frac{w_{water}^{org}}{w_{water}^{aq}} = \frac{w_{water}^{org}}{1 - w_{solvent}^{aq}} \quad (2)$$

$$S_{FDCA} = \frac{K_{FDCA}}{K_{water}} \quad (3)$$

The mutual solvent solubility was assessed in each phase for the best-performing solvent to verify that mutual solvent saturation was achieved. The solubility of the organic solvent in the aqueous phase was determined using a gas chromatograph with a flame ionization detector (GC-FID-2010, Shimadzu) coupled to an autosampler (AOC-20S) and an auto-injector (AOC-20i) and equipped with an HP-5 column (30 m x 0.32 mm, Agilent). Ethanol was used to dilute the samples (dilution factor: 100) and butanol as the internal standard (0.4 g L^{-1}). A Karl Fischer 899 Coulometer was used to determine the water content in the organic phase using a specific reagent for water quantification in ketones (Hydranal Coulomat AK, Honeywell Fluka). A sens-ion + MM150 pH meter (accuracy ± 0.01 pH units) from Hach was used to measure the *pH* of aqueous phases.

3. Results and discussion

3.1. Rational selection of extraction solvents for the biphasic FDCA production

The identification of biphasic systems for the catalytic production of FDCA from HMF represents a considerable challenge. First, with regards to the use in reaction with *in situ* extraction, practical considerations must be considered for meaningful operation. The selected organic solvent for extraction must show (a) as little miscibility with water as possible, (b) chemical stability against oxidation, and (c) thermal stability at the reaction temperature, typically around 393–413 K [7]. Logically, the organic solvent must also show a high affinity for FDCA to enhance its separation efficiency, which is a major challenge for the design of biphasic systems for FDCA. For instance, in a similar study, a positive correlation was observed between the HMF partition and the water solubility in the organic phase within a homologous series of solvents [27]. A similar behaviour can be expected for FDCA.

To balance the FDCA extraction performance and mutual solvent and water solubilities, we mostly focused our attention on polar aprotic solvents like ethers, esters, and ketones in addition to long-chain alcohols, and evaluated their mutual solubilities. Subsequently, a group of eight organic solvents was chosen to perform the experiments, namely, TBME, DEE, CPME, *i*-BuOAc, ONE, MEK, MIBK, and 1-OcOH. The mutual solubilities of water in the organic phase (w_{water}^{org}) and the organic phase in the aqueous one ($w_{solvent}^{aq}$) are collected in Table 2, along with the water partition ratio (K_{water}). As can be seen, except for MEK, the solubility of all other selected organic solvents in water is low ($w_{solvent}^{aq} < 0.1$) and the solubility of water in the organic phase is also rather poor ($w_{water}^{org} < 0.06$). Because the amount of water in the organic phase cannot be neglected for downstream processing, *i*-BuOAc ($w_{water}^{org} = 0.014$ at 298 K) was preferred over other esters such as methyl ($w_{water}^{org} = 0.080$ at 298 K), ethyl ($w_{water}^{org} = 0.030$ at 298 K) and isopropyl esters ($w_{water}^{org} = 0.019$ at 298 K); and 1-OcOH ($w_{water}^{org} = 0.046$ at 298 K) over other shorter chain alcohols [28–30]. Moreover, MIBK was selected as a benchmark because it is usually considered an example of a green solvent that can be potentially obtained from biomass feedstock [31]. Finally, cyclohexanone was chosen among the group of solvent for further investigation because this cyclic compound was reported to provide higher HMF extraction efficiency [27,32].

In addition, the framework for the use of chemicals is becoming more and more restrictive, with regulations in place, such as the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH EC 1907/2006) and Integrated Pollution Prevention and Control (IPPC, EC 1/2008) [33,34]. For this reason, it is of paramount importance to consider the SHE profile of the organic solvents. For this purpose, the CHEM21 solvent selection guide provides a helpful and user-friendly tool to classify the SHE profile of solvents [25]. This methodology balances the solvent physicochemical properties, namely: boiling point, flash point, and autoignition temperature, and the European GHS/CLP regulation to score each SHE criterion between 1 and 10 (being 10 the highest hazard in each category), and ranks the solvent as recommended, problematic or hazardous by default. Table 2 shows the breakdown of the score of each of the SHE criteria of the eight organic solvents selected in this work and their classification as per the CHEM21 guide [25]. As a result, the use of DEE and TBME should be discouraged despite their low water affinity, yet TBME can indeed be potentially synthesised from biomass feedstock [31]. The rest of the solvents are ranked as recommended, except CPME which is classified as problematic. Other compounds such as alkylated or halogenated phenols were reported to yield high performance for HMF extraction; however, they were not considered in this work due to their poor SHE profiles mostly falling within the hazardous category (e.g. chlorophenols, *o*-propylphenol, or *o*-isopropylphenol, to mention a few) [27,35]. This highlights the need to direct the screening when considering the use of safer solvents to attain greener processes.

3.2. FDCA solubility in water and organic solvents

The experimental solubility of FDCA in water and in the eight organic solvents selected in this work at 298.15 K is plotted in Fig. 1a, with the full dataset and corresponding errors compiled in Table S1. As can be seen, the solubility was very low in *i*-BuOAc, in three of the ethers (DEE, TBME, and CPME) as well as in MIBK. In contrast, FDCA solubility was higher in MEK, 1-OcOH, and cyclohexanone, showing values of 0.814, 1.024 and 1.364 g L^{-1}, respectively. The latter was the only

Table 2
Mutual phase solubilities and water partition ratio (K_{water}) at ~293.15 K, breakdown of the score of each of the Safety, Health, and Environment (SHE) criteria and CHEM21 classification for the eight solvents selected.

Chemical	$w_{solvent}^{aq}$	w_{water}^{org}	K_{water}	Ref.	Boiling Point (°C)	Flash point (°C)	Worst H3xx[*]	H4xx[**]	S	H	E	Classification	
												By default	Revised [25]
MEK	0.276	0.112	0.155	[36]	80	−6	H319	None	5	3	3	Recommended	
MIBK	0.020	0.021	0.022	[37]	117	13	H319	None	4	2	3	Recommended	
ONE	0.097	0.054	0.059	[36]	156	43	H332	None	3	2	5	Recommended	Problematic
DEE	0.069	0.013	0.014	[38]	34	−45	H302	None	10	3	7	Hazardous	Highly hazardous
TBME	0.042	0.013	0.013	[36]	55	−28	H315	None	8	3	5	Hazardous	
CPME	0.013	0.007	0.007	[39]	118	18	H336	None	4	2	3	Recommended	
i-BuOAc	0.008	0.013	0.013	[28]	106	−1	H302	H412	7	2	5	Problematic	
1-OcOH	0.001	0.050	0.050	[40]	195	81	H319	H412	1	2	5	Recommended	

[*] H302: Harmful if swallowed, H315: Causes skin irritation, H319: Causes serious eye irritation, H332: Harmful if inhaled, H336: May cause drowsiness or dizziness.

[**] H412: Harmful to aquatic life with long lasting effects.

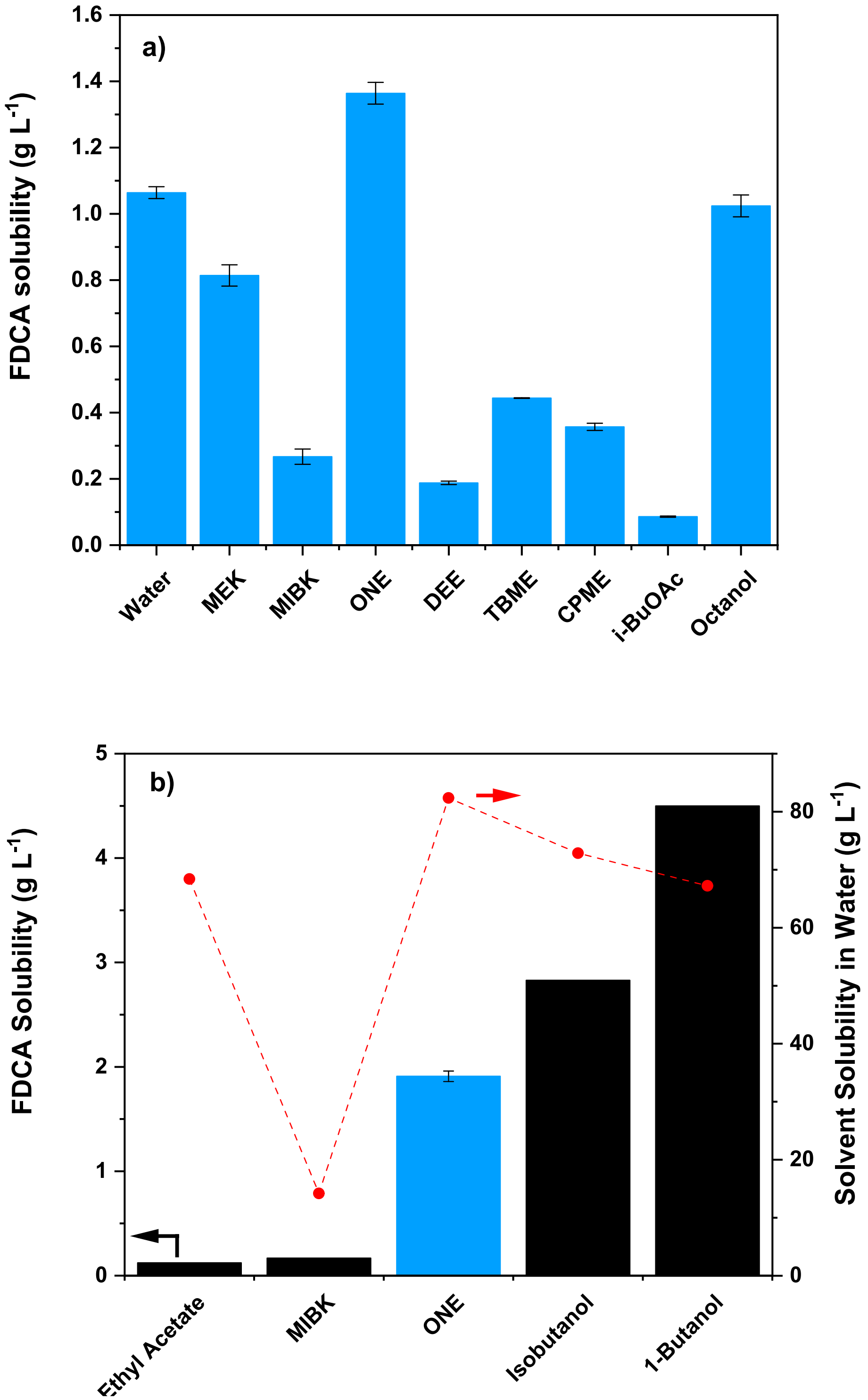

Fig. 1. a) Experimental solubility of FDCA in water and the eight organic solvents tested at 298.15 K. Error bars represent the standard deviation (STD) from triplicate measurements. b) Comparison of FDCA solubility in cyclohexanone (blue bar) and other organic solvents with limited water miscibility (black bars, [20]) at 313.15 K. Solvent solubility in water (red circles) obtained from IUPAC-NIST Solubility Data Series.

compound tested that exhibited higher FDCA solubility than water.

In addition, the FDCA solubility in cyclohexanone was also measured at 313.15 K for comparison with that reported in other organic solvents with limited water miscibility (Fig. 1b). Other available FDCA solubility data in organic solvents have been disregarded since these cannot form biphasic systems due to their full miscibility in water (namely, methanol, acetonitrile, acetic acid, 1,4-dioxane, and 1,2-dimethoxyethane [20,21]). As expected, the solubility of FDCA in cyclohexanone was lower than that in C_4 alcohols like *i*-butanol (2.83 g L^{-1} at 313.15 K) and 1-butanol (4.53 g L^{-1} at 313.15 K) [20] due to cyclohexanone being unable to form hydrogen bonds with the carboxylic groups of the FDCA molecule, but it proved higher than in other aprotic solvents, such as MIBK and ethyl acetate. With regards to the use of solvents for operability in the biphasic production of FDCA by HMF oxidation, C_4 alcohols may undergo conversion to 1-butanal [41] or other oxidation products [42]. Therefore, despite the lower ability to solubilize FDCA, cyclohexanone was selected for the assessment of more detailed distribution experiments in subsequent sections due to its inertness in liquid oxidative environments.

3.3. FDCA distribution in water/cyclohexanone biphasic systems

The distribution coefficient of FDCA between water and cyclohexanone, as per equation (1), was determined at temperatures ranging between 293.15 and 323.15 K starting from several aqueous solutions containing FDCA concentrations between 0.05 and 0.90 g L^{-1}, for experimental operability below the saturation limit in water at room temperature (1.06 g/ L^{-1} at 298.15 K). Furthermore, the mutual solubilities of cyclohexanone and MIBK (the reference solvent) with water at 298.15 K (Table S2) were successfully validated with data provided in the NIST solubility data series [37], as well as the solubility of cyclohexanone in water at different temperatures: 293.15, 303.15 and 313.15 K (Table S3).

The resulting FDCA distribution coefficients are plotted in Fig. 2 as a function of the measured equilibrium concentrations of FDCA in the aqueous phase ($C^{aq}_{FDCA,eq}$). As can be seen, there is a strong influence of the aqueous FDCA concentration on the distribution coefficient, which increased at higher concentrations. This effect is attributed to the influence of *pH* on the transfer of FDCA from the aqueous to the organic phase. At lower *pH* values, the dissociation of FDCA is hindered and its migration to cyclohexanone in molecular form is favored. In this sense, Figure S1 shows how the *pH* values decreased, as expected, with increasing equilibrium concentration of FDCA in the aqueous phase and, to a much lesser extent, at higher temperatures. It is worth noting that the experimental *pH* values obtained consistently fell within the dissociation constants of FDCA in water reported in the ECHA dossier for FDCA ($pk_{a1} = 2.3$, $pk_{a2} = 3.5$) [43].

On the other hand, Fig. 2 also shows a significant temperature influence on the FDCA distribution between water and cyclohexanone because temperature affects FDCA solubility in each phase differently. To verify this, the FDCA solubility in cyclohexanone and water were also measured at 313.15 K (1.91 ± 0.06 and 1.72 ± 0.02 g L^{-1}, respectively), hence implying a higher increase of FDCA solubility in water (61.7 %) than in cyclohexanone (40.0 %) on increasing the temperature from 298.15 to 313.15 K. This agrees well with the decreasing trend of K_{FDCA} (Equation (1) with temperature observed in Fig. 2. The FDCA distribution between water and cyclohexanone is related to the thermodynamic change of the Gibbs energy of transfer ($\Delta_{tr}G$) from the aqueous to the organic phase (Equation (4) [44].

$$\Delta_{tr}G = -RTlnK_{FDCA} \tag{4}$$

Thus, considering the relationship between the Gibbs energy and the molar enthalpy ($\Delta_{tr}H$) and entropy ($\Delta_{tr}S$) of transfer, the lnK_{FDCA} can be expressed as

$$lnK_{FDCA} = \frac{-\Delta_{tr}H}{RT} + \frac{\Delta_{tr}S}{R} \tag{5}$$

Figure S2 shows the van’t Hoff plot, which reveals a fairly constant influence of temperature on K_{FDCA} regardless of the initial FDCA concentration, as depicted by the parallel lines for each of the concentrations tested. The average values of $\Delta_{tr}H$ and $\Delta_{tr}S$ are −15.3 ± 1.0 kJ mol^{-1} and −44.9 ± 4.6 J K^{-1} mol^{-1}, respectively, which are indicative of an exothermic process. Similar values have been reported for the extraction

Table 3
Molar Gibbs energy of transfer of FDCA in biphasic systems at different temperatures and initial FDCA concentrations in the aqueous phase ($C^{aq}_{FDCA,0}$).

T (K)	$C^{aq}_{FDCA,0}$ (g L^{-1})				
	0.05	0.2	0.5	0.7	0.9
$\Delta_{tr}G$ (kJ mol^{-1})					
293.15	0.37	−1.45	−2.86	−3.22	−3.67
298.15	0.63	−1.24	−2.65	−3.00	−3.45
313.15	1.42	−0.60	−2.03	−2.35	−2.79
323.15	1.95	−0.17	−1.61	−1.91	−2.35

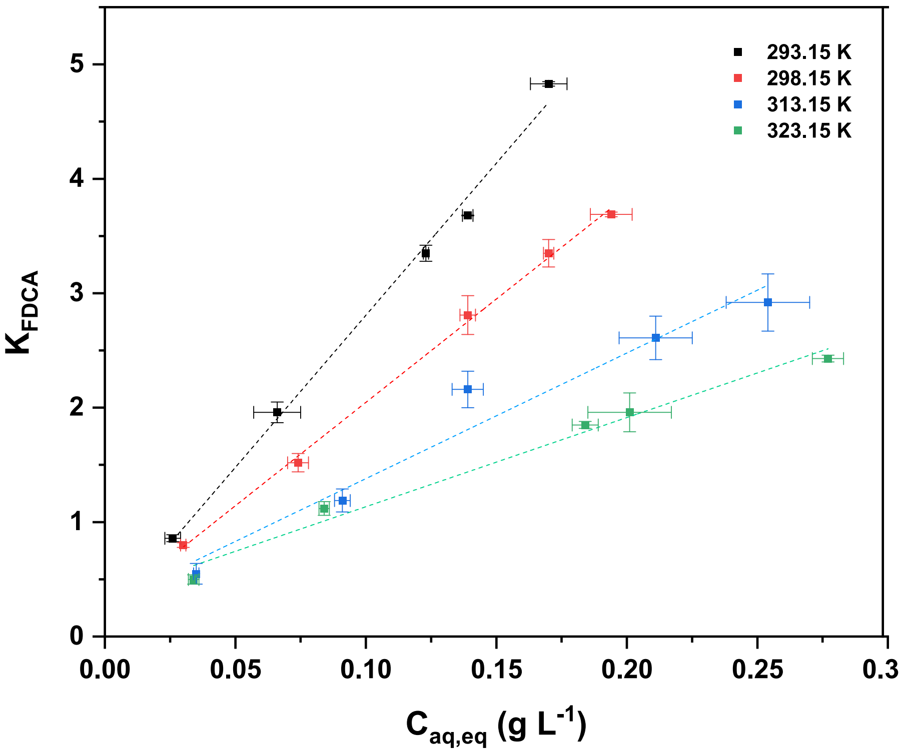

Fig. 2. Distribution coefficients of FDCA in biphasic systems with cyclohexanone as a function of equilibrium concentration in the aqueous phase and temperature. Error bars represent the standard deviation. The initial FDCA concentrations in water were, from left to right, 0.05, 0.2, 0.5, 0.7 and 0.9 g L^{-1}, respectively.

of organic compounds in 1-OcOH/water systems (e.g., vanillin, vanillic acid, and protocatechuic acid) [44,45]. The Gibbs energies of transfer of FDCA are compiled in Table 3, where the mass transfer process between the two liquid phases takes place spontaneously. The process is favoured in the highest concentration range and at low temperatures, whereas in dilute systems (0.05 g L^{-1}) the process is no longer spontaneous in accordance with the K_{FDCA} values less than unity and positive $\Delta_{tr}G$ reported in Fig. 2 and Table 3, respectively. This trend responds to a general behaviour of organic ionizable species, such as oxalic, o-phthalic, isophthalic or salicylic acid, as reported by Disdier et al. [46].

Overall, Fig. 3 shows the calculated separation factor of FDCA as a function of temperature for the most concentrated initial aqueous solutions (0.9 g L^{-1}), which ranged between 81.5 at 293.15 K, and 33.1 at 323.15 K. These separation factors are representative of the preference of cyclohexanone for FDCA with respect to water.

3.4. Outlook for the cascade production of FDCA from fructose in biphasic systems

As covered in the introduction, considerable efforts have been put into the use of biphasic systems to yield HMF from biomass-derived sugars. However, the purification of HMF and its stability proves very challenging owing to its high degradation rate by conversion to humins, which is accelerated by the high temperatures required [47]. For this reason, there is an increasing amount of work that approaches the production of furan derivatives by one-pot or cascade reactions that allow obtaining compounds with higher stability that can potentially be used as end products. One example is the production of biofuel additives dimethyl furan and dimethyl tetrahydrofuran from fructose by dehydration to HMF and subsequent hydrogenation in an ionic liquid (IL)-based biphasic system $[C_4C_1im][Cl]$/THF. Here the former reaction occurs due to the intrinsic acidity of the IL, whereas the latter is catalyzed by a Ru/C catalyst [48]. In another attempt to obtain stable furans, a biphasic system consisting of aqueous NaOH and furfural granted the aldol condensation of HMF with acetone in the former phase, followed by the hydrogenation of this product in the organic phase thanks to Pd, Pt, and Ni-based carbon nanotube catalysts [49].

Unlike in the previous two examples, only two monophasic systems have been studied for the cascade reaction from sugars to FDCA. An aqueous medium in the presence of Pd/CC and K_2CO_3 was reported starting fructose [50]. In addition, the IL $[C_4C_1im][Cl]$ was used on two occasions to provide the acidity for the fructose dehydration step (and isomerization when glucose is used as starting material), using MnO_2 [26] or Fe – Zr – O [51] as oxidation catalysts. As can be seen, the cascade production of FDCA from sugars is still in an early stage of development and there is a lack of effort using biphasic systems. The concept is presented in Fig. 4, in which the dehydration from the sugar to HMF would take place in the aqueous phase. Then, its *in situ* extraction to the organic phase would occur before its subsequent oxidation to FDCA.

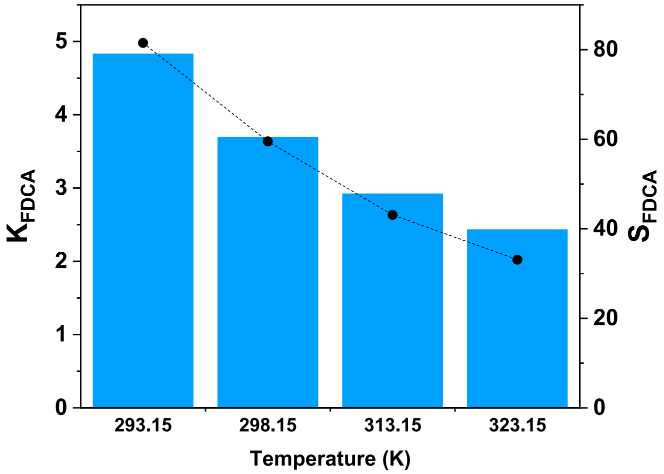

Fig. 3. Distribution coefficients K_{FDCA} (bars) and separation factor of FDCA S_{FDCA} (circles) in biphasic systems with cyclohexanone as a function of temperature. Initial equilibrium concentration in the aqueous phase is 0.9 g L^{-1}. Mutual phase solubility obtained from reference [36].

By using this approach, the advantage is that the final product can be kept in a phase separated from the one where the substrate is fed. This requires identifying an organic solvent that shows a high distribution coefficient both for HMF and FDCA, in the latter case to prevent back extraction. In previous work, Esteban et al. [32] identified cyclohexanone as a promising solvent to enable the partition of HMF in biphasic systems, reaching a value of $K_{HMF}^{ONE} = 3.66$ at 298.15 K using an initial concentration of HMF in the aqueous phase of 1 % wt. When MIBK was used as solvent, this value reached only $K_{HMF}^{MIBK} = 1.24$. The same applies to the FDCA distribution coefficient between water and MIBK, which was also measured and found to be less than unity in the present work and 5-times lower than that obtained with cyclohexanone, for instance $K_{FDCA}^{ONE} = 2.92$ and $K_{FDCA}^{MIBK} = 0.62$ at 313.15 K and $C_{FDCA,0}^{aq} = 0.9$ g L^{-1}. This translates into FDCA having a preference to remain in the aqueous phase rather than migrating to MIBK.

All in all, considering the high distribution coefficients observed in this work, together with the recommended SHE profile, cyclohexanone is a very promising solvent to perform the cascade conversion starting from sugars to FDCA through HMF as intermediate. This comparison leaves MIBK as a less attractive alternative despite it being the benchmark solvent for the reaction with *in situ* extraction to yield HMF from the same substrate [8].

4. Conclusions

This work addresses the study of FDCA distribution between organic/aqueous phases with the aim of exploring the potential of cascade biphasic reactions for its synthesis from sugars. To this end, an initial solubility study of FDCA was conducted in eight different organic solvents: cyclohexanone, diethyl ether, isobutyl acetate, methyl isobutyl ketone, methyl ethyl ketone, methoxycyclopentane, *tert*-butylmethyl ether, and octan-1-ol, which provided novel data. Cyclohexanone is identified here as a good candidate for such biphasic systems, reaching a solubility of FDCA of 1.364 g L^{-1} at 298.15 K. Cyclohexanone shows several advantages, such as being considered as a non-problematic solvent by CHEM21 in terms of its safety, health and environmental profile in addition to showing a low predisposition to oxidation, hence making it inert in the oxidative conversion of HMF to FDCA.

An in-depth study at different initial concentrations of FDCA starting from the aqueous phase and at different temperatures (0.05 – 0.9 g L^{-1}) reveals that the behavior of FDCA as an acid proton-releasing species affects the distribution between phases, favoring the migration of FDCA to the organic phase at higher FDCA initial concentrations. Regarding temperature, as an exothermic process, the distribution is favored at lower temperatures ($S_{FDCA}^{298.15\ K} = 81.5$, $S_{FDCA}^{323.15\ K} = 33.1$).

CRediT authorship contribution statement

Fernando Pardo: Writing – original draft, Supervision, Methodology, Investigation, Formal analysis. **Hanne Oorts:** Methodology, Investigation, Formal analysis. **Ane Urtiaga:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Jesús Esteban:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Gabriel Zarca:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

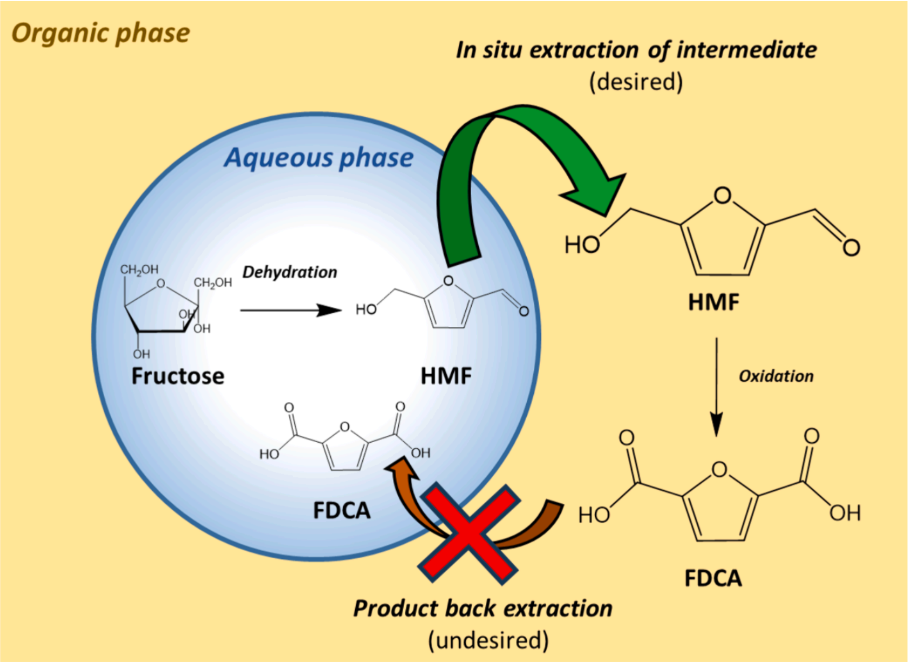

Fig. 4. Concept for the use of biphasic systems for the cascade production of FDCA starting from fructose.

Declaration of competing interest

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.

Data availability

Data will be made available on request.

Acknowledgments

This research has been performed in the framework of project P232 of the Universidad de Cantabria. F.P. acknowledges grant IJC2020-043134-I funded by MICIU/AEI/10.13039/ 501100011033 and EU NextGenerationEU/PRTR. J.E. gratefully acknowledges The University of Manchester for funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2024.125436.

References

[1] L. Dai, Y. Wang, Y. Liu, R. Ruan, C. He, Z. Yu, L. Jiang, Z. Zeng, X. Tian, Integrated process of lignocellulosic biomass torrefaction and pyrolysis for upgrading bio-oil production: A state-of-the-art review, Renew. Sustain. Energy Rev. 107 (2019) 20–36, https://doi.org/10.1016/j.rser.2019.02.015.

[2] R.J. van Putten, J.C. van der Waal, E. de Jong, C.B. Rasrendra, H.J. Heeres, J.G. de Vries, Hydroxymethylfurfural, a versatile platform chemical made from renewable resources, Chem. Rev. 113 (2013) 1499–1597, https://doi.org/10.1021/cr300182k.

[3] J.J. Bozell, G.R. Petersen, Technology development for the production of biobased products from biorefinery carbohydrates—the US Department of Energy's "Top 10" revisited, Green Chem. 12 (2010) 539–554, https://doi.org/10.1039/b922014c.

[4] J. Carro, E. Fernandez-Fueyo, C. Fernandez-Alonso, J. Canada, R. Ullrich, M. Hofrichter, M. Alcalde, P. Ferreira, A.T. Martinez, Self-sustained enzymatic cascade for the production of 2,5-furandicarboxylic acid from 5-methoxymethylfurfural, Biotechnol. Biofuels 11 (2018) 86, https://doi.org/10.1186/s13068-018-1091-2.

[5] G. Lin, W. Lin, J. Wu, Y. Zhan, F. Okejiri, M. Weng, J. Fu, Oxidation of 5–methoxymethylfurfural to 2, 5-furandicarboxylic acid over Ru/hydroxyapatite catalyst in water, Chem. Eng. Sci. 249 (2022) 117343, https://doi.org/10.1016/j.ces.2021.117343.

[6] E. de Jong, H.R.A. Visser, A.S. Dias, C. Harvey, G.M. Gruter, The Road to Bring FDCA and PEF to the Market, Polymers (basel) 14 (2022), https://doi.org/10.3390/polym14050943.

[7] M. Sajid, X. Zhao, D. Liu, Production of 2,5-furandicarboxylic acid (FDCA) from 5-hydroxymethylfurfural (HMF): recent progress focusing on the chemical-catalytic routes, Green Chem. 20 (2018) 5427–5453, https://doi.org/10.1039/c8gc02680g.

[8] J. Esteban, A.J. Vorholt, W. Leitner, An overview of the biphasic dehydration of sugars to 5-hydroxymethylfurfural and furfural: a rational selection of solvents using COSMO-RS and selection guides, Green Chem. 22 (2020) 2097–2128, https://doi.org/10.1039/c9gc04208c.

[9] S. Jha, P. Sappidi, Molecular simulations of understanding the structure and separation thermodynamics of 5-Hydroxymethylfurfural from 1-Butyl-3-Methyl imidazolium tetrafluoroborate, J. Mol. Liq. 391 (2023) 123354, https://doi.org/10.1016/j.molliq.2023.123354.

[10] D. Soukup-Carne, X. Fan, J. Esteban, An overview and analysis of the thermodynamic and kinetic models used in the production of 5-hydroxymethylfurfural and furfural, Chem. Eng. J. 442 (2022) 136313, https://doi.org/10.1016/j.cej.2022.136313.

[11] S. Mohammad, G. Grundl, R. Müller, W. Kunz, G. Sadowski, C. Held, Influence of electrolytes on liquid-liquid equilibria of water/1-butanol and on the partitioning of 5-hydroxymethylfurfural in water/1-butanol, Fluid Phase Equilib. 428 (2016) 102–111, https://doi.org/10.1016/j.fluid.2016.05.001.

[12] S. Mohammad, C. Held, E. Altuntepe, T. Köse, T. Gerlach, I. Smirnova, G. Sadowski, Salt influence on MIBK/water liquid–liquid equilibrium: Measuring and modeling with ePC-SAFT and COSMO-RS, Fluid Phase Equilib. 416 (2016) 83–93, https://doi.org/10.1016/j.fluid.2015.11.018.

[13] G. Grundl, R. Müller, W. Kunz, Salt effects on liquid-liquid equilibria in the ternary water/n-butanol/HMF system and solvent effects on HMF separation from water, J. Mol. Liq. 325 (2021) 114551, https://doi.org/10.1016/j.molliq.2020.114551.

[14] M. Milic, E. Bystrom, P. Dominguez de Maria, S. Kara, Enzymatic Cascade for the Synthesis of 2,5-Furandicarboxylic Acid in Biphasic and Microaqueous Conditions: 'Media-Agnostic' Biocatalysts for Biorefineries, ChemSusChem 15 (2022) e202102704.

[15] D. Polidoro, A. Perosa, M. Selva, Tunable Multi-Phase System for Highly Chemo-Selective Oxidation of Hydroxymethyl-Furfural, ChemSusChem 15 (2022) e202201059.

[16] L. Zhang, G. Meng, W. Zhang, X. Li, Z. Zhang, M. Yang, Y. Wu, D. Wang, Y. Li, Oriented Conversion of a LA/HMF Mixture to GVL and FDCA in a Biphasic Solvent over a Ru Single-Atom/Nanoparticle Dual-Site Catalyst, ACS Catal. 13 (2023) 2268–2276, https://doi.org/10.1021/acscatal.2c04726.

[17] T. Harhues, M. Padligur, F. Bertram, D.M. Roth, J. Linkhorst, A. Jupke, M. Wessling, R. Keller, Integrated Biphasic Electrochemical Oxidation of Hydroxymethylfurfural to 2,5-Furandicarboxylic Acid, ACS Sustain. Chem. Eng. 11 (2023) 8413–8419, https://doi.org/10.1021/acssuschemeng.3c01403.

[18] A. Borra, R.K. Kosuru, R. Bharadwaj, S. b,, Measurement and modeling of solubility of furan 2-carboxylic acid in mono and binary systems, J. Mol. Liq. 326 (2021) 115271, https://doi.org/10.1016/j.molliq.2020.115271.

[19] H.B. Rose, T. Greinert, C. Held, G. Sadowski, A.S. Bommarius, Mutual Influence of Furfural and Furancarboxylic Acids on Their Solubility in Aqueous Solutions:

Experiments and Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) Predictions, J. Chem. Eng. Data. 63 (2018) 1460–1470, https://doi.org/10.1021/acs.jced.7b01039.

[20] Y. Zhang, X. Guo, P. Tang, J. Xu, Solubility of 2,5-Furandicarboxylic Acid in Eight Pure Solvents and Two Binary Solvent Systems at 313.15–363.15 K, J. Chem. Eng. Data. 63 (2018) 1316–1324, https://doi.org/10.1021/acs.jced.7b00927.

[21] N. Zhuang, J. Wang, S. Ma, Q. Liu, W. Jia, X. Yu, Z. Li, S. Yang, Y. Sun, X. Tang, X. Zeng, L. Lin, Determination of Solubility and Thermodynamic Analysis of Solubility Behavior of 2,5-Furandicarboxylic Acid in Water and Ether Binary Solvent System, J. Chem. Eng. Data. 68 (2023) 726–743, https://doi.org/10.1021/acs.jced.2c00730.

[22] H. Ban, T. Pan, Y. Cheng, L. Wang, X. Li, Solubilities of 2,5-Furandicarboxylic Acid in Binary Acetic Acid + Water, Methanol + Water, and Ethanol + Water Solvent Mixtures, J. Chem. Eng. Data. 63 (2018) 1987–1993, https://doi.org/10.1021/acs.jced.7b01112.

[23] L. Xu, J. Fu, C. Du, Q. Xu, B. Liu, Z. Bao, Solubility of Biocompounds 2,5-Furandicarboxylic Acid and 5-Formylfuran-2-Carboxylic Acid in Binary Solvent Mixtures of Water and 1,4-Dioxane, Processes 10 (2022) 2480.

[24] P.T. Anastas, J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press, 1998.

[25] D. Prat, A. Wells, J. Hayler, H. Sneddon, C.R. McElroy, S. Abou-Shehada, P.J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, Green Chem. 18 (2016) 288–296, https://doi.org/10.1039/c5gc01008j.

[26] A. Al Ghatta, J.P. Hallett, High yield and isolation of 2,5-furandicarboxylic acid from HMF and sugars in ionic liquids, a new prospective for the establishment of a scalable and efficient catalytic route, Green Chem. 24 (2022) 3309–3313, https://doi.org/10.1039/d2gc00390b.

[27] Z. Wang, S. Bhattacharyya, D.G. Vlachos, Solvent selection for biphasic extraction of 5-hydroxymethylfurfural via multiscale modeling and experiments, Green Chem. 22 (2020) 8699–8712, https://doi.org/10.1039/d0gc03251d.

[28] M. Góral, D.G. Shaw, A. Mączyński, P. Oracz, B. Wiśniewska-Gocłowska, I. Owczarek, K. Blazej, IUPAC-NIST Solubility Data Series. 88. Esters with Water—Revised and Updated. Part 2. C5 and C6 Esters. J. Phys. Chem. Ref. Data 39 (2010), 10.1063/1.3243973.

[29] M. Góral, D.G. Shaw, A. Mączyński, B. Wiśniewska-Gocłowska, A. Jezierski, IUPAC-NIST Solubility Data Series. 88. Esters with Water—Revised and Updated. Part 1. C2 to C4 Esters. J. Phys. Chem. Ref. Data 38 (2009) 1093-1127, 10.1063/1.3243853.

[30] A. Maczynski, D.G. Shaw, M. Goral, B. Wisniewska-Goclowska, IUPAC-NIST Solubility Data Series. 82. Alcohols with Water–Revised and Updated: Part 5. C8–C17 Alcohols with Water. J. Phys. Chem. Ref. Data 36 (2007) 685-731, 10.1063/1.2391321.

[31] F.P. Byrne, S. Jin, G. Paggiola, T.H.M. Petchey, J.H. Clark, T.J. Farmer, A.J. Hunt, C. Robert McElroy, J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, Sustain. Chem. Process. 4 (2016), https://doi.org/10.1186/s40508-016-0051-z, 7.

[32] D. Soukup-Carne, P. Lopez-Porfiri, F.S. Bragagnolo, C.S. Funari, X. Fan, M. Gonzalez-Miquel, J. Esteban, Extraction of 5-Hydroxymethylfurfural and Furfural in Aqueous Biphasic Systems: A COSMO-RS Guided Approach to Greener Solvent Selection, ACS Sustain. Chem. Eng. 12 (2024) 3766–3779, https://doi.org/10.1021/acssuschemeng.3c07894.

[33] P.G. Jessop, Searching for green solvents, Green Chem. 13 (2011) 1391–1398, https://doi.org/10.1039/c0gc00797h.

[34] M. González-Miquel, J. Esteban, in: Comprehensive Biotechnology, Pergamon, Oxford, 2019, pp. 790–806.

[35] L.C. Blumenthal, C.M. Jens, J. Ulbrich, F. Schwering, V. Langrehr, T. Turek, U. Kunz, K. Leonhard, R. Palkovits, Systematic Identification of Solvents Optimal for the Extraction of 5-Hydroxymethylfurfural from Aqueous Reactive Solutions, ACS Sustain. Chem. Eng. 4 (2015) 228–235, https://doi.org/10.1021/acssuschemeng.5b01036.

[36] R.M. Stephenson, Mutual solubilities: water-ketones, water-ethers, and water-gasoline-alcohols, J. Chem. Eng. Data. 37 (2002) 80–95, https://doi.org/10.1021/je00005a024.

[37] A. Mączyński, D.G. Shaw, M. Góral, B. Wiśniewska-Gocłowska, IUPAC-NIST Solubility Data Series. 86. Ethers and Ketones with Water. Part 5. C6 Ketones with Water, J. Phys. Chem. Ref. Data 37 (2008) 1575–1609, https://doi.org/10.1063/1.2950300.

[38] A.E. Hill, The Mutual Solubility of Liquids. I. The Mutual Solubility of Ethyl Ether and Water. Ii. The Solubility of Water in Benzene. J. Am. Chem. Soc. 45 (2002) 1143-1155, 10.1021/ja01658a007.

[39] M.D. Wales, C. Huang, L.B. Joos, K.V. Probst, P.V. Vadlani, J.L. Anthony, M. E. Rezac, Liquid-Liquid Equilibria for Ternary Systems of Water + Methoxycyclopentane + Alcohol (Methanol, Ethanol, 1-Propanol, or 2-Propanol), J. Chem. Eng. Data. 61 (2016) 1479–1484, https://doi.org/10.1021/acs.jced.5b00803.

[40] P. Molyneux, Octanol/water partition coefficients Kow: A critical examination of the value of the methylene group contribution to logKow for homologous series of organic compounds, Fluid Phase Equilib. 368 (2014) 120–141, https://doi.org/10.1016/j.fluid.2014.01.014.

[41] F. Adam, I.A. Sugiarmawan, A porous ruthenium silica catalyst modified with amino benzoic acid for the oxidation of butanol with molecular oxygen, J. Porous Mater. 16 (2008) 321–329, https://doi.org/10.1007/s10934-008-9203-1.

[42] V. Fedevych, V. Zhyznevskiy, R. Tsybukh, Kinetics of the Oxidation of Tert-Butanol to Methacrolein on Calcium Ions Promoted Iron-Tellurium- Molybdenum Oxide Catalyst, React. Kinet. Catal. Lett. 73 (2001) 47–54, https://doi.org/10.1023/a:1013912502087.

[43] European Chemicals Agency (ECHA). http://echa.europa.eu/. Dissociation constants of FDCA in water. Dossier subtipe: Article 10 full. Registration date 19-Dec-2013. Full link: https://chem.echa.europa.eu/100.019.819/dossier-view/3cfcff86-a9fa-42a9-be5d-d02bf969c435/IUC5-7947e390-74a5-433c-9b44-4de87c641555_06701da2-8343-4aef-b3d0-a23433729ca1?searchText=furandicarboxylic%20acid (Last accessed May 2024). (2015).

[44] A. Noubigh, A. Mgaidi, M. Abderrabba, Temperature Effect on the Distribution of Some Phenolic Compounds: An Experimental Measurement of 1-Octanol/Water Partition Coefficients, J. Chem. Eng. Data. 55 (2009) 488–491, https://doi.org/10.1021/je900271h.

[45] T. Fujii, S.-I. Kawasaki, Effects of process parameters on vanillin partition coefficient in water-supercritical CO2 extraction, Fluid Phase Equilib. 485 (2019) 153–157, https://doi.org/10.1016/j.fluid.2018.12.030.

[46] Z. Disdier, S. Savoye, R.V.H. Dagnelie, Effect of solutes structure and pH on the n-octanol/water partition coefficient of ionizable organic compounds, Chemosphere 304 (2022) 135155, https://doi.org/10.1016/j.chemosphere.2022.135155.

[47] A. Al Ghatta, X. Zhou, G. Casarano, J.D.E.T. Wilton-Ely, J.P. Hallett, Characterization and Valorization of Humins Produced by HMF Degradation in Ionic Liquids: A Valuable Carbonaceous Material for Antimony Removal. ACS Sustain, Chem. Eng. 9 (2021) 2212–2223, https://doi.org/10.1021/acssuschemeng.0c07963.

[48] C. Li, H. Cai, B. Zhang, W. Li, G. Pei, T. Dai, A. Wang, T. Zhang, Tailored one-pot production of furan-based fuels from fructose in an ionic liquid biphasic solvent system, Chin. J. Catal. 36 (2015) 1638–1646, https://doi.org/10.1016/s1872-2067(15)60927-5.

[49] P.A. Zapata, J. Faria, M. Pilar Ruiz, D.E. Resasco, Condensation/Hydrogenation of Biomass-Derived Oxygenates in Water/Oil Emulsions Stabilized by Nanohybrid Catalysts, Top. Catal. 55 (2012) 38–52, https://doi.org/10.1007/s11244-012-9768-4.

[50] P.V. Rathod, V.H. Jadhav, Efficient Method for Synthesis of 2,5-Furandicarboxylic Acid from 5-Hydroxymethylfurfural and Fructose Using Pd/CC Catalyst under Aqueous Conditions, ACS Sustain. Chem. Eng. 6 (2018) 5766–5771, https://doi.org/10.1021/acssuschemeng.7b03124.

[51] D. Yan, G. Wang, K. Gao, X. Lu, J. Xin, S. Zhang, One-Pot Synthesis of 2,5-Furandicarboxylic Acid from Fructose in Ionic Liquids, Ind. Eng. Chem. Res. 57 (2018) 1851–1858, https://doi.org/10.1021/acs.iecr.7b04947.