Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information for

Solvent Selection for Biphasic Extraction of 5-Hydroxymethylfurfural via Multiscale Modeling and Experiments

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Supporting Figures

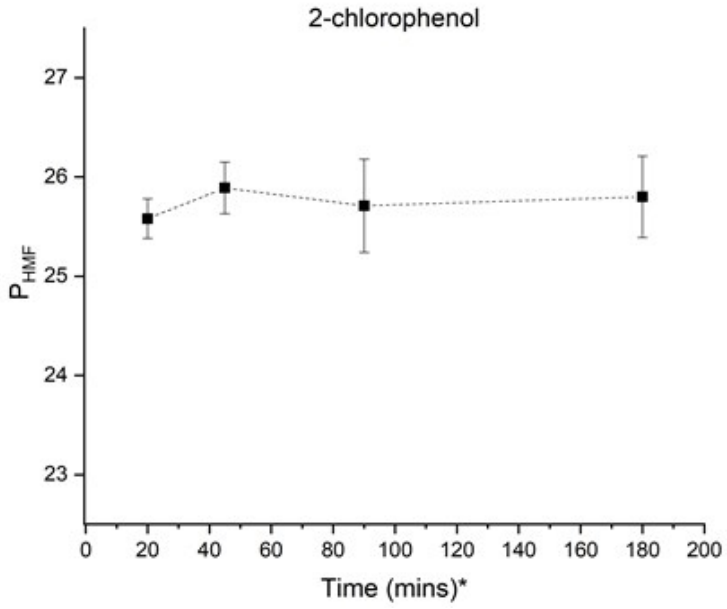

Figure S1. Variation of P_{HMF} versus mixing time for 2-chlorophenol at 298 K.

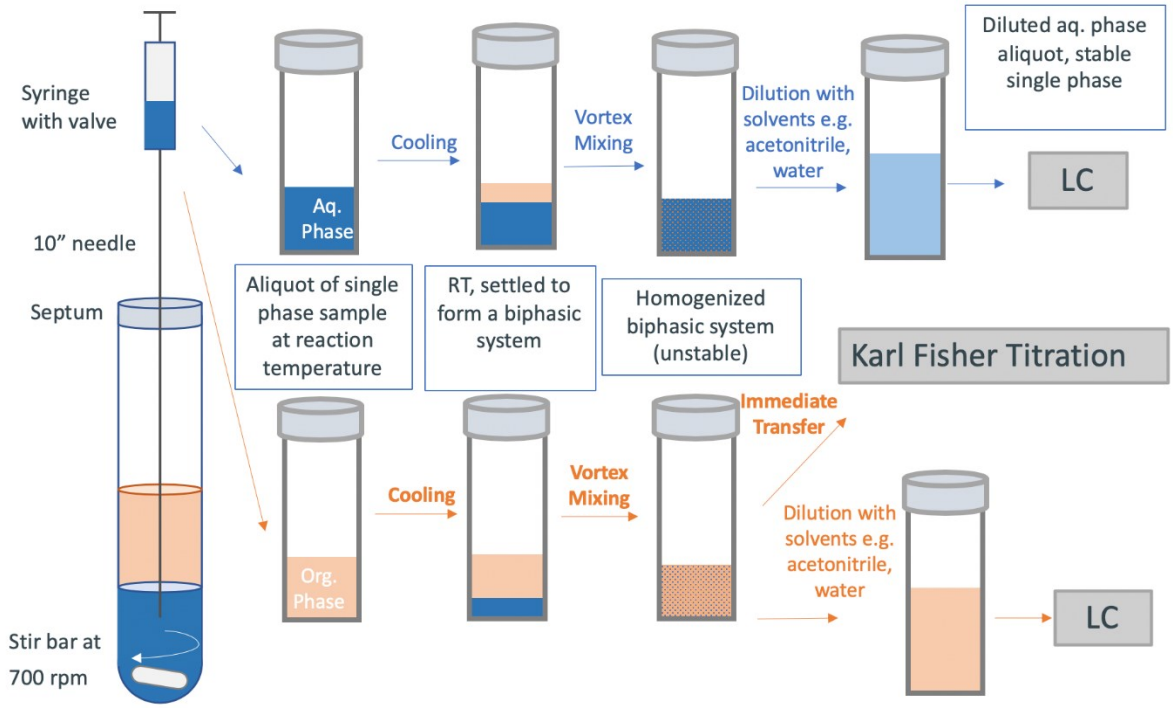

Figure S2. High temperature *in situ* sampling and sample workup procedure to preserve phase composition.

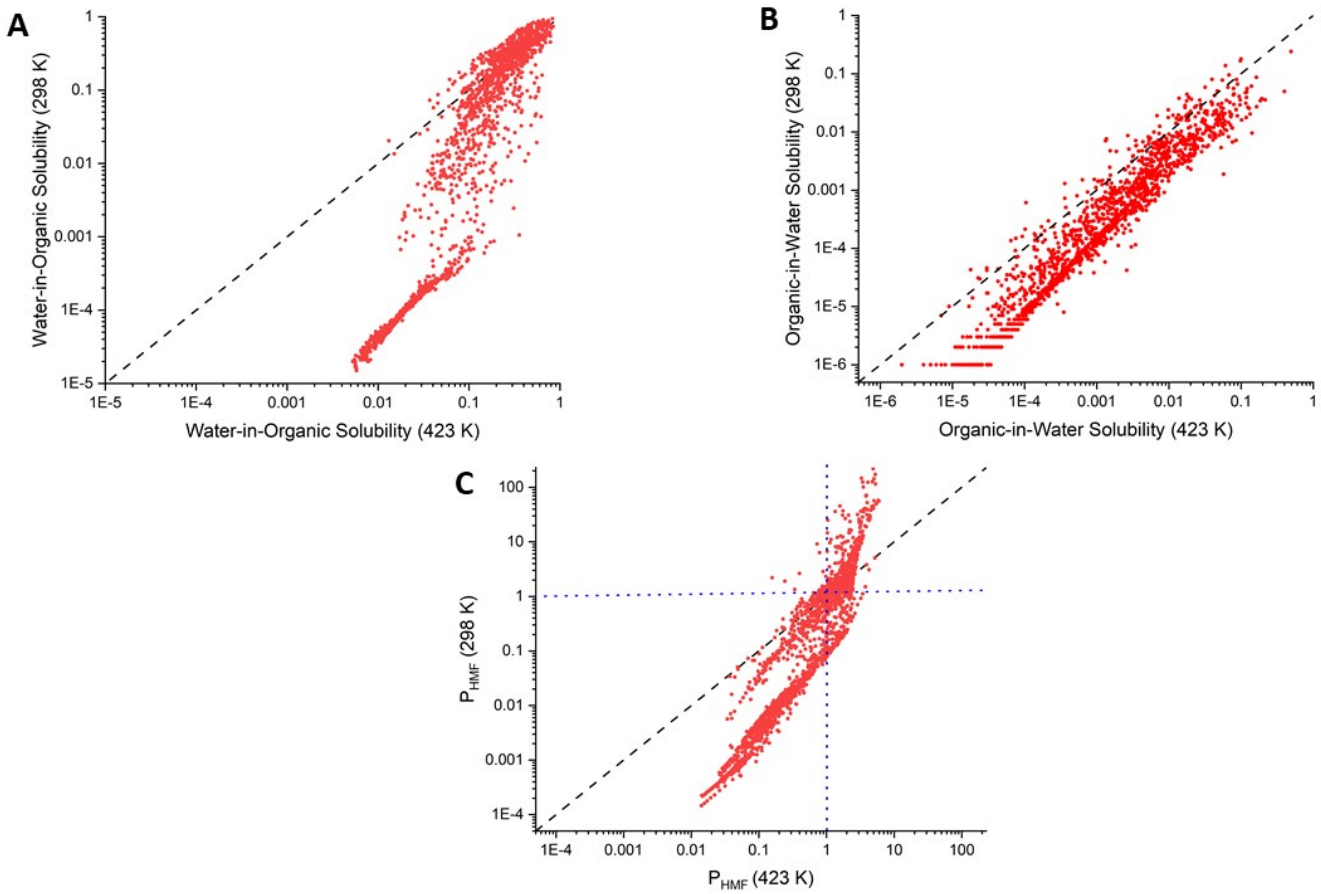

Figure S3. Mutual phase solubilities (A-B) and P_{HMF} variation (C) in different biphasic systems across the ADF COSMO-RS database at 298 K and 423 K.

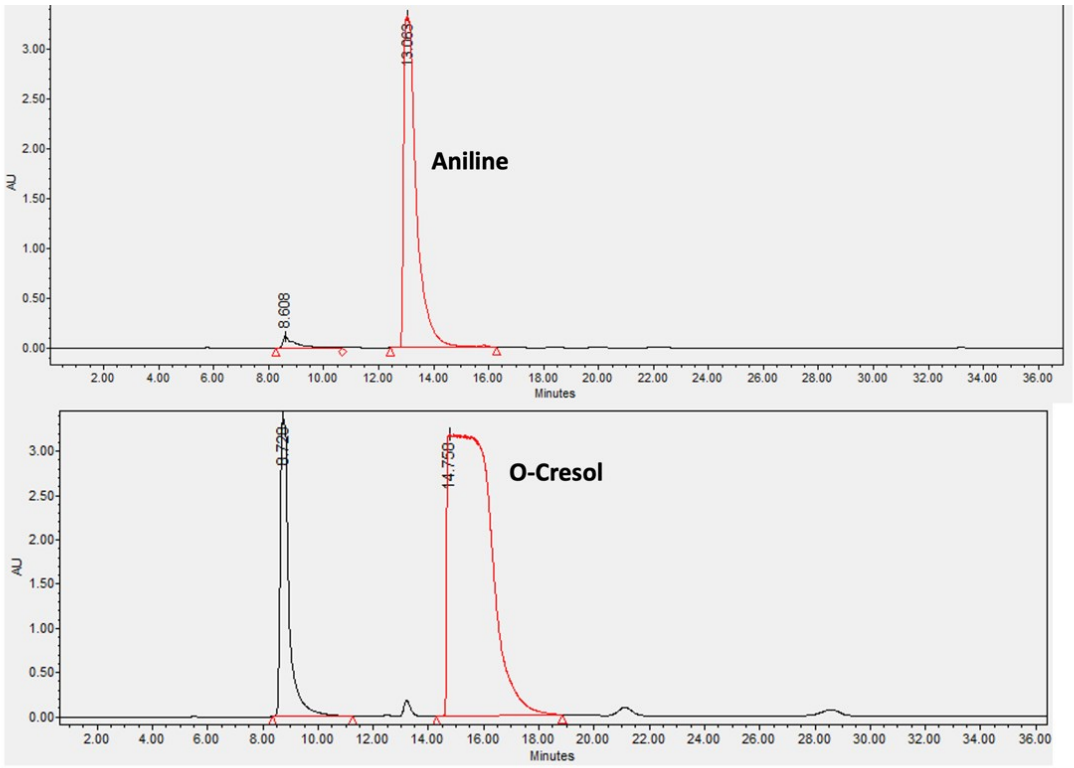

Figure S4. HPLC chromatographs for aniline and o-cresol organic phase samples of 298 K HMF partition experiments. In aniline, HMF is present in trace amounts under the same experimental conditions and similar expected P_{HMF} values, suggesting that HMF has been consumed.

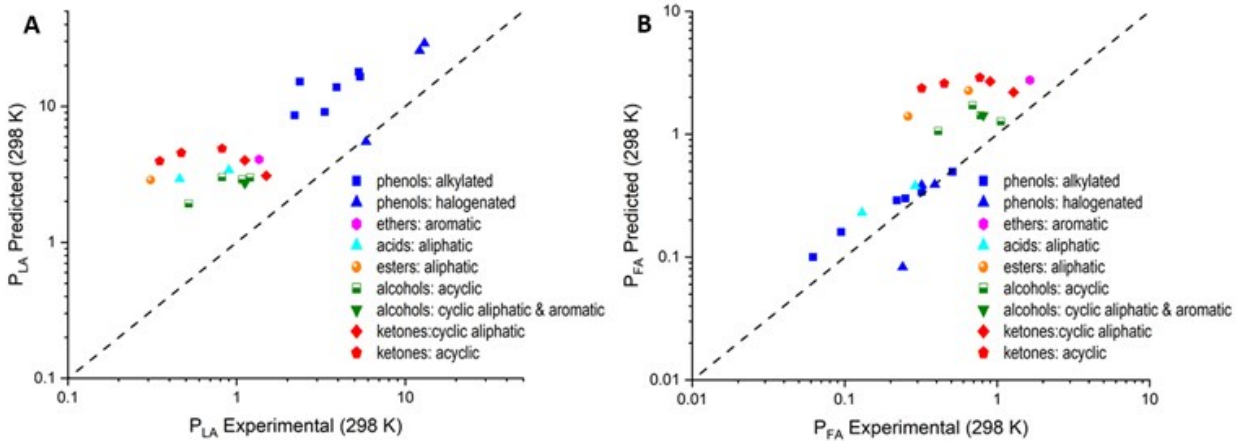

Figure S5. Parity plot comparing experimental and predicted A) P_{LA} and B) P_{FA} at 298 K.

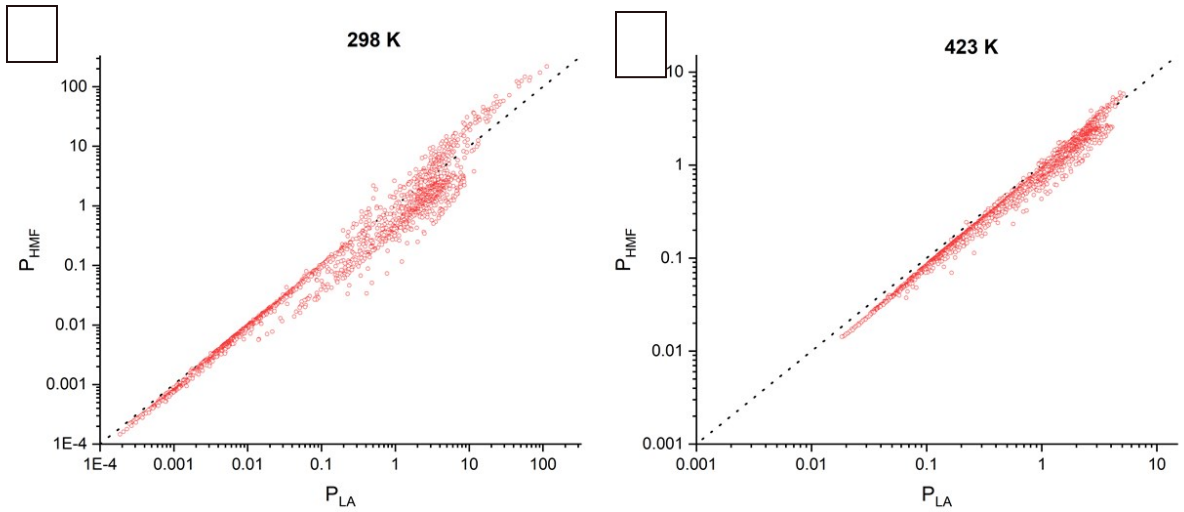

Figure S6. Parity plot showing global correlation of P_{HMF} with P_{LA} over the COSMO-RS dataset at **A)** 298 K and **B)** 423 K.

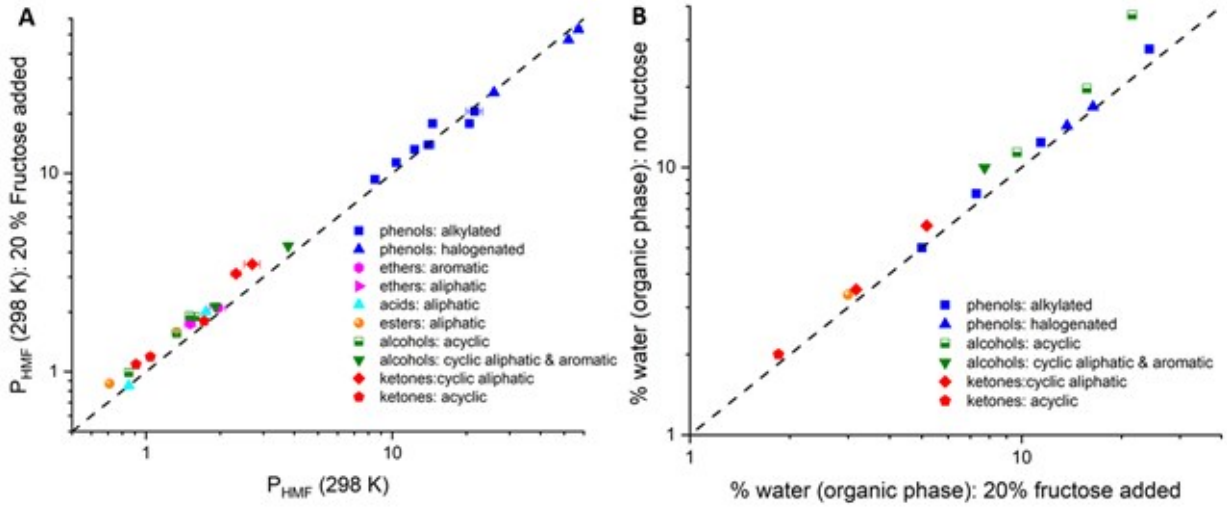

Figure S7. Parity plot showing the effect of 20 wt% fructose addition on A) P_{HMF} and B) water content in the organic-rich phase for different water-solvent biphasic systems.

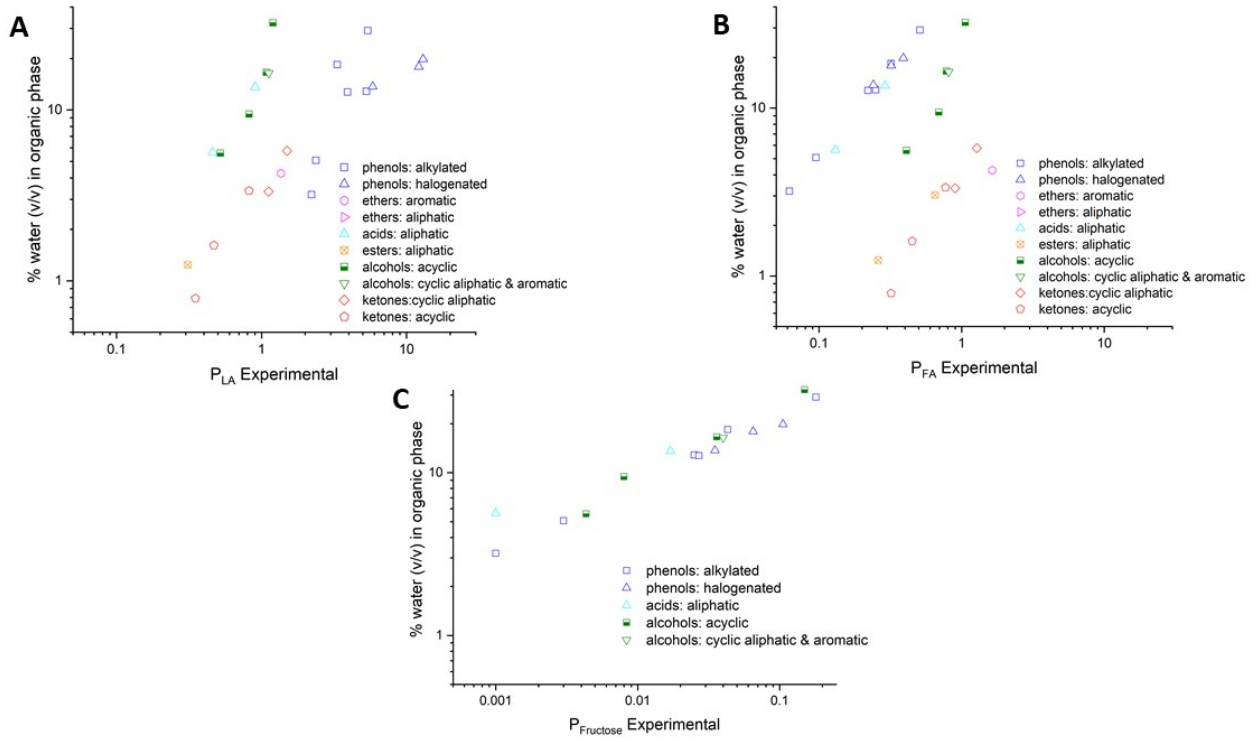

Figure S8. Experimental data of variation of water content with (A*)* P_{LA}, (B) P_{FA}, and (C) P_{Fructose} in the organic-rich phase.

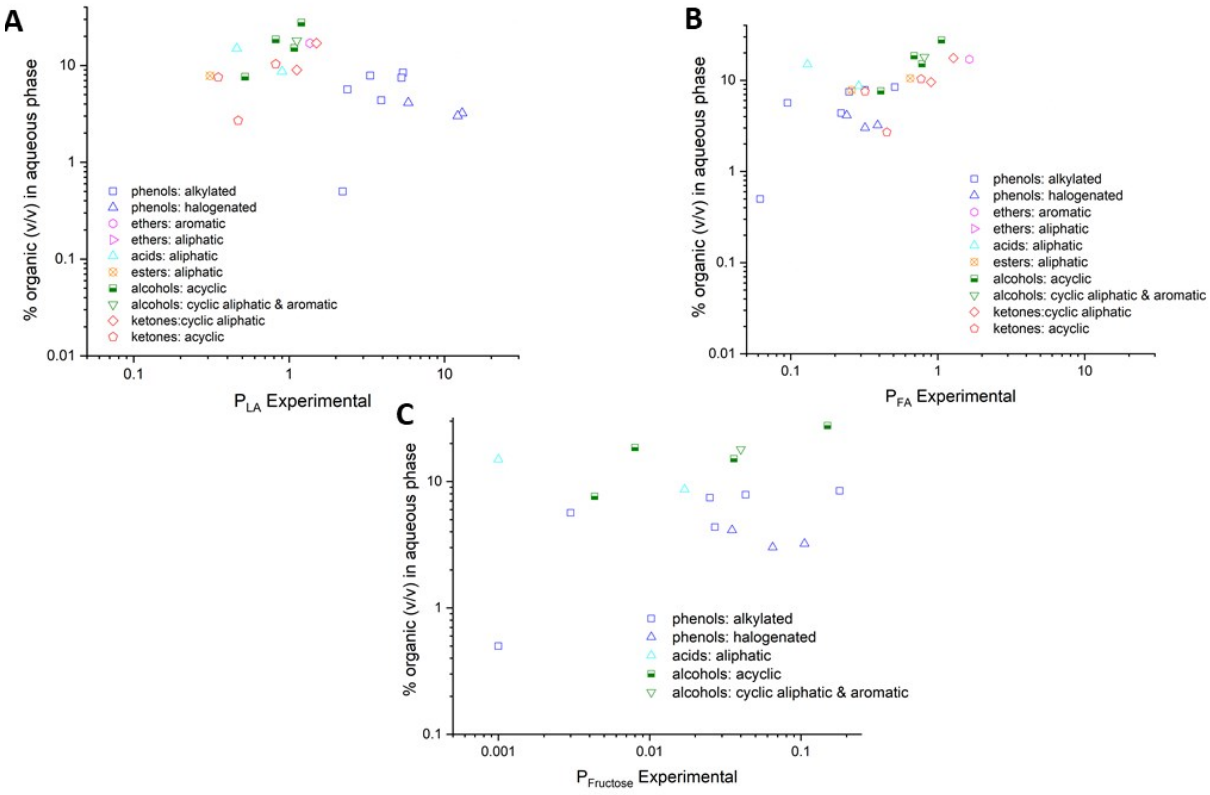

Figure S9. Experimental data of variation of organic content with (A) P_{LA}, (B) P_{FA}, and (C) $P_{Fructose}$ in the aqueous-rich phase.

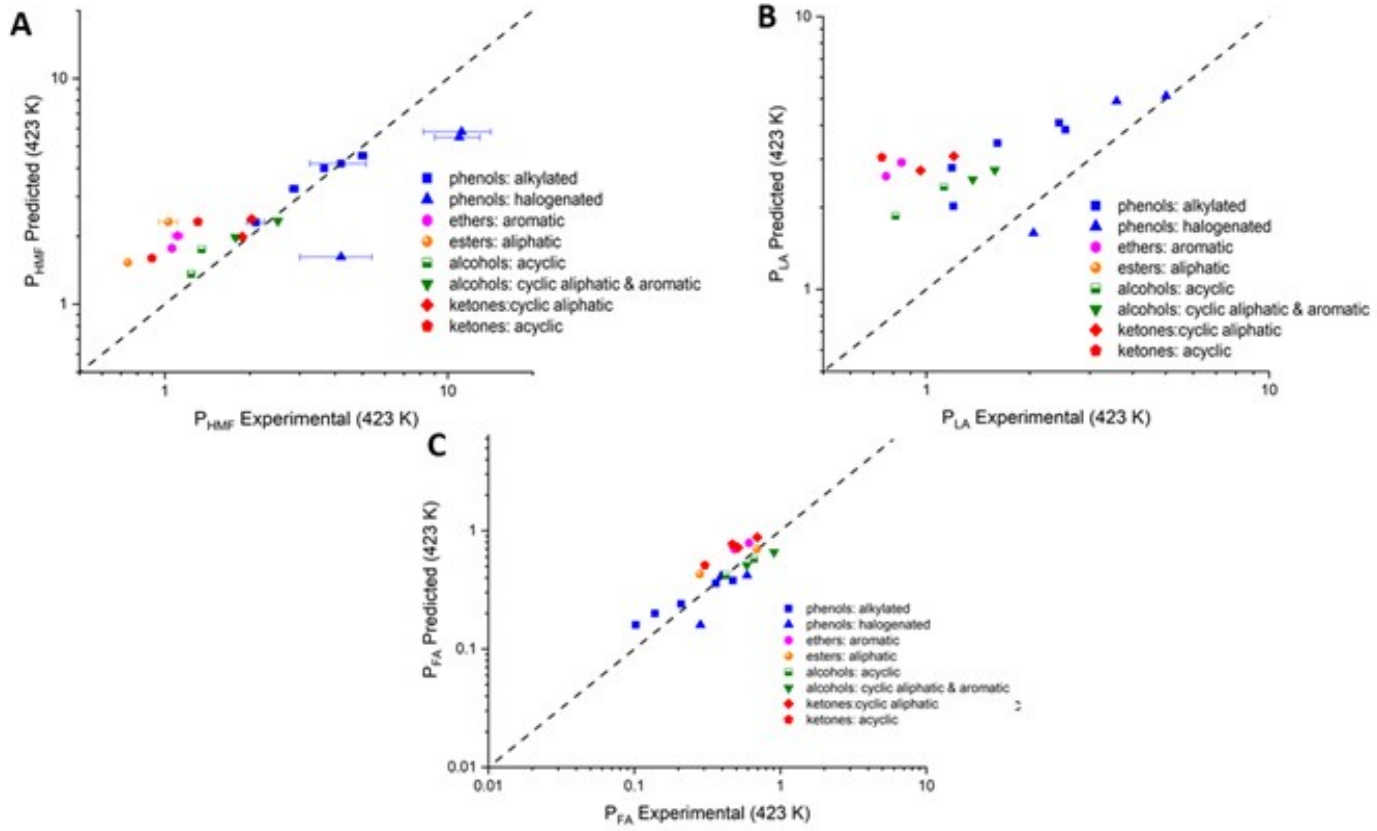

Figure S10. Parity plot comparing experimental and predicted A) P_{HMF}, B) P_{LA}, and C) P_{FA} at 423 K.

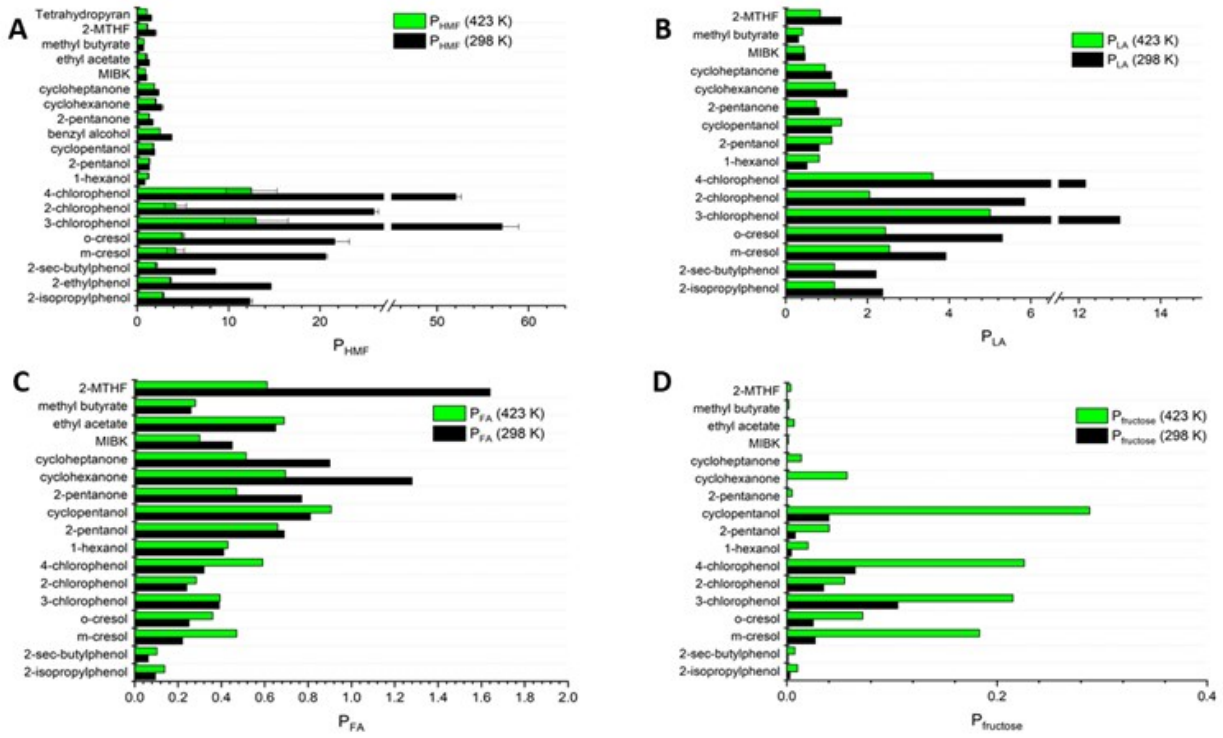

Figure S11. Bar graphs highlighting the variation of experimental A) P_{HMF}, B) P_{LA}, C) P_{FA}, and D) $P_{Fructose}$ with temperature (298 K and 423 K).

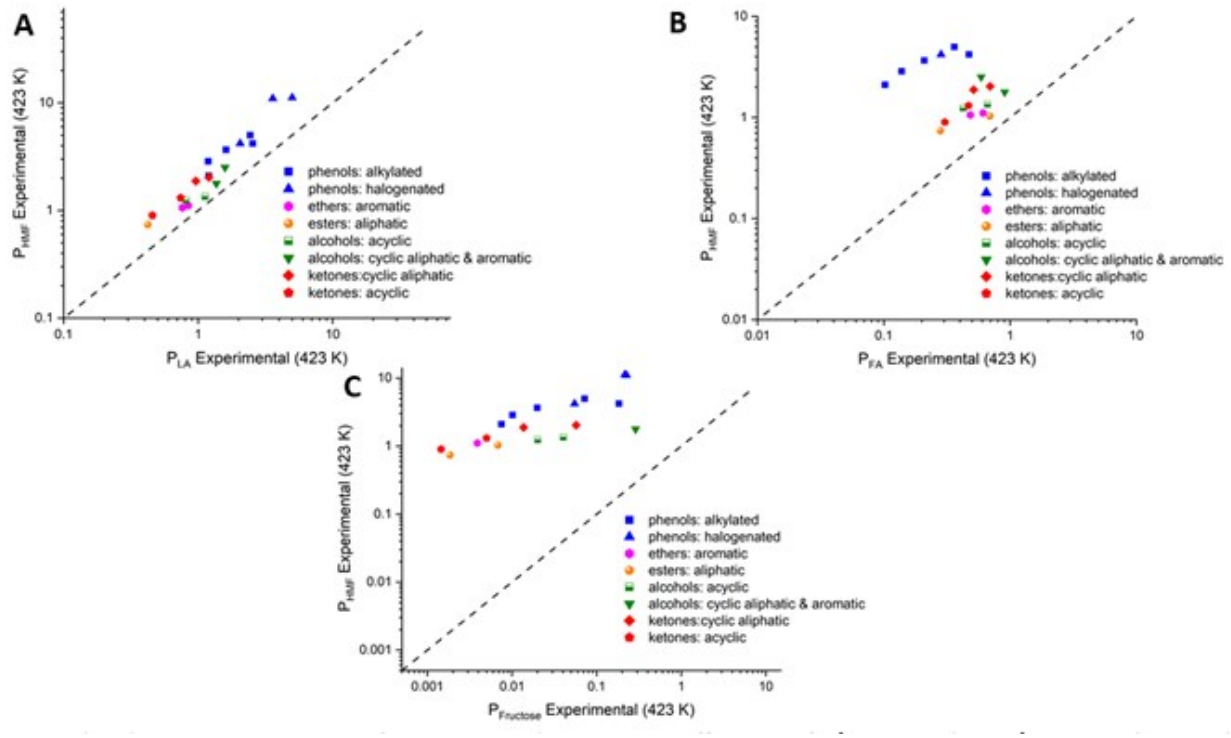

Figure S12. Parity plot comparing experimental A) P_{HMF} and P_{LA}, B) P_{HMF} and P_{FA}, and C) P_{HMF} and $P_{Fructose}$ at 423 K.

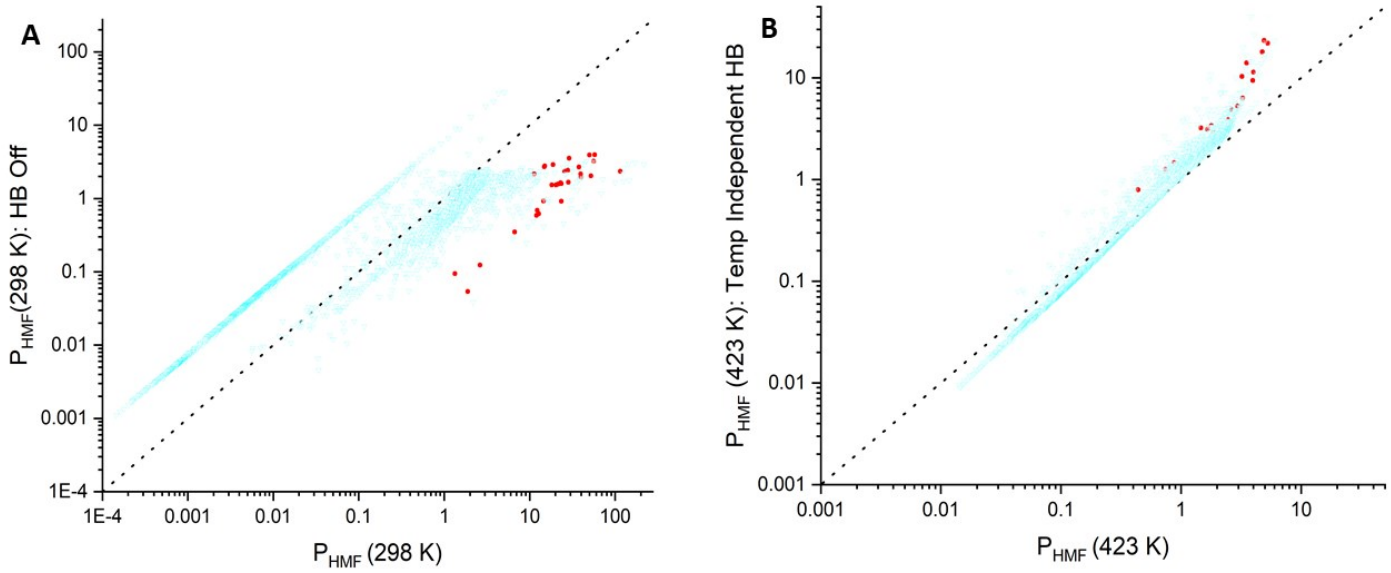

Figure S13. Parity plots showing the % change in P_{HMF} for different extraction systems at A) 298 K, when the COSMO-RS HB term for all components of the ternary solvent-water-HMF system is turned off, and B) 423 K, when the temperature dependence of the COSMO-RS HB term is turned off, *i.e.*, f_{hb} =1 (Substituted phenols marked in red).

Supporting Tables

Table S1. List of Chemicals, Vendor, Product ID, and Purity.

Solvent Name	Vendor, Product ID, and Purity
1-butanol	Sigma-Aldrich 281549, 99.5%
1-hexanol	Sigma-Aldrich H13303, ≥98.0%
1-hexene	Sigma-Aldrich 240761, ≥99%
1-nonanol	Sigma-Aldrich 74280, ≥98.0%
1-octene	Sigma-Aldrich O4806, 98%
2-butanol	Fisher Chem. 01664-1, 99.4%
2-chloroaniline	Sigma-Aldrich 23310, ≥98.0%
2-chlorophenol	Sigma-Aldrich 185779, ≥99%
2-decanone	Sigma-Aldrich 196207, 98%
2-ethylphenol	Sigma-Aldrich E44000, 99%
2-heptanone	Sigma-Aldrich 537772, ≥99.5%
2-isopropylphenol	Sigma-Aldrich 129526, 98%
2-MTHF	Sigma-Aldrich 414247, >99%
2-octanol	Sigma-Aldrich 74858, ≥99.5%
2-pentanol	Sigma-Aldrich P8017, 98.0%
2-pentanone	Sigma-Aldrich 471194, ≥99.5%
2-sec-butylphenol	Sigma-Aldrich B99006, 98%
3-chloroaniline	Sigma-Aldrich C22407, 99%

3-chlorophenol	Sigma-Aldrich C62808, 98%
3-methoxyphenol	Sigma-Aldrich 328456, 96%
4-chlorophenol	Sigma-Aldrich 185787, ≥99%
5-hydroxymethylfurfural	Sigma-Aldrich H40807, 99%
acetonitrile	Fisher Chem. A955-4 LC/MS Grade
butyl acetate	Sigma-Aldrich 287725, ≥99%
butyric acid	Sigma-Aldrich 103500, ≥99.0%
chlorobenzene	Sigma-Aldrich 284513, 99.8%
cycloheptanone	TCI C0466, >98.0%
cyclohexane	Sigma-Aldrich 227048, 99.5%
cyclohexanone	Sigma-Aldrich 39824, ≥99.0%
cyclopentanol	Sigma-Aldrich C112208, 99%
D-fructose	Sigma-Aldrich F0127, ≥99.0%
diethylether	Sigma-Aldrich 309966, 99.9%
dioxane	Sigma-Aldrich 236309, 99.8%
dipropylether	Sigma-Aldrich 111333, ≥99%
ethyl acetate	Sigma-Aldrich 270989, 99.8%
formic acid	Sigma-Aldrich 33015, ≥98%
gamma-valerolactone	Sigma-Aldrich W310301, ≥99.0%
hexanal	SA 115606, 98%
hexanoic acid	TCI H0105, >98.0%
levulinic acid	Sigma-Aldrich W262701, 99%
m-cresol	Sigma-Aldrich C85727, 99.0%
methyl butyrate	Sigma-Aldrich 246093, 99%
MIBK	Sigma-Aldrich 360511, ≥98.5%
m-toluidine	Sigma_Aldrich 511218, 99%
o-cresol	Sigma-Aldrich W348007, ≥99.0%
octanal	Sigma-Aldrich O5608, 99%
octane	Sigma-Aldrich 296988, ≥99.0%
octanoic acid	TCI O0027, >98.0%
pentafluorophenol	TCI P0919, >98.0%
pentanal	Sigma-Aldrich 110132, 97%
pentane	Sigma-Aldrich 236705, ≥99%
pentanoic acid	TCI V0003, >98.0%
phenol	Sigma-Aldrich 328111, ≥99%
tetrahydropyran	TCI T0110, >98.0%
toluene	Sigma-Aldrich 244511, 99.8%

Table S2. Water-in-Ketone Standards and Measured Water Contents for KF Method Validation.

Sample	Water wt% as Prepared	Measured Water wt%
MIBK, Pure	-	Undetected
MIBK, 1 wt%	1.000	0.99
Cyclohexanone, Pure	-	Undetected
Cyclohexanone, 2 wt%	1.998	1.96 ± 0.06
Cyclohexanone, 4 wt%	3.995	3.93 ± 0.03

Table S3. Partition coefficients of HMF, fructose, LA, and FA at 298 K and 423 K.

	Solvents	P_{HMF}		$P_{Fructose}$		P_{LA}		P_{FA}	
#		**298 K**	**423 K**	**298 K**	**423 K**	**298 K**	**423 K**	**298 K**	**423 K**
1	**pentafluorophenol**	35 ± 2							
2	**2-isopropylphenol**	12.3 ± 0.3	2.9 ± 0.1	0.003	0.01	2.4	1.2	0.095	0.14
3	**3-chlorophenol**	57 ± 2	13 ± 4	0.11	0.22	13	5.0	0.39	0.39
4	**2-chlorophenol**	25.9 ± 0.5	4.2 ± 1	0.035	0.055	5.9	2.1	0.24	0.28
5	**3-methoxyphenol**	10.4 ± 0.1	single phase	0.04	single phase	3.3	single phase	0.3	single phase
6	**2-ethylphenol**	14.6 ± 0.1	3.7 ± 0.1	0.007	0.02	4.2	1.62	0.17	0.21
7	**2-sec-butylphenol**	8.5 ± 0.1	2.1 ± 0.2	0.001	0.007	2.2	1.2	0.062	0.1
8	**phenol**	14.1 ± 0.7	single phase	0.18	single phase	5.4	single phase	0.51	single phase
9	**4-chlorophenol**	52.0 ± 0.6	13 ± 3	0.065	0.23	12.2	3.6	0.32	0.59
10	**1-butanol**	1.58 ± 0.01	single phase	0.036	single phase	1.1	single phase	0.78	single phase
11	**1-hexanol**	0.85 ± 0.01	1.24 ± 0.03	0.0043	0.02	0.52	0.81	0.41	0.43
12	**1-nonanol**	0.41 ± 0.01		0					
13	**2-pentanone**	1.72 ± 0.01	1.31 ± 0.04	0	0.005	0.82	0.74	0.77	0.47
14	**2-heptanone**	0.91 ± 0.01		0		0.35		0.32	
15	**2-decanone**	0.4 ± 0.01		0					

16	**cyclohexanone**	2.7 ± 0.2	2.03 ± 0.06	0	0.057	1.5	1.20	1.28	0.695
17	**cycloheptanone**	2.3 ± 0.1	1.88 ± 0.03	0	0.014	1.12	0.96	0.9	0.51
18	**gamma-valerolactone**	single phase		single phase		single phase		single phase	
19	**MIBK**	1.04 ± 0.01	0.9 ± 0.02	0	0.0015	0.47	0.46	0.45	0.3
20	**2-butanol**	1.5 ± 0.02	single phase	0.15	single phase	1.2	single phase	1.1	single phase
21	**2-pentanol**	1.33 ± 0.02	1.35 ± 0.04	0.008	0.04	0.82	1.13	0.69	0.66
22	**2-octanol**	0.58 ± 0.01		0					
23	**ethyl acetate**	1.33 ± 0.01	1.03 ± 0.08	0	0.007	0.7*	N/A	0.65	0.69
24	**butyl acetate**	0.64± 0.01							
25	**methyl butyrate**	0.71± 0.01	0.74 ± 0.01	0	0.002	0.31	0.42	0.26	0.28
26	**pentane**	0.0007 ± 0.0001							
27	**octane**	0.0006 ± 0.0001							
28	**cyclohexane**	0.002 ± 0.0001							
29	**1-hexene**	0.0024 ± 0.0001							
30	**1-octene**	0.0015 ± 0.0001							
31	**cyclopentanol**	1.91 ± 0.02	1.78 ± 0.05	0.04	0.29	1.1	1.34	0.81	0.91
32	**benzyl alcohol**	3.78 ± 0.04	2.51 ± 0.02	0.012	0.18	1.8	1.6	0.49	0.59
33	**cyclooctanol**	1.08 ± 0.01		0					
34	**2-MTHF**	2.0 ± 0. 2	1.11 ± 0.05	0	0.004	1.4	0.85	1.6	0.61
35	**tetrahydropyran**	1.51 ± 0. 08	1.06 ±	0	0.003	1.0	0.76	1.0	0.48

			0.02						
36	**diethylether**	0.3 ± 0.06							
37	**dioxane**	single phase		single phase		single phase		single phase	
38	**dipropylether**	0.14 ± 0.02							
39	**pentanoic acid**	1.75 ± 0.01		0.017		0.9		0.29	
40	**hexanoic acid**	0.85 ± 0.01		0.001		0.46		0.13	
41	**octanoic acid**	0.28 ± 0.01		0					
42	**butyric acid**	single phase		single phase		single phase		single phase	
43	**toluene**	0.05 ± 0.0001							
44	**m-cresol**	20.6 ± 0.2	4.2 ± 0.9	0.027	0.18	3.9	2.54	0.22	0.47
45	**chlorobenzene**	0.06 ± 0.001							
46	**o-cresol**	22 ± 2	5 ± 0.2	0.025	0.072	5.3	2.44	0.25	0.36
47	**pentanal**	reactive		reactive		reactive		reactive	
48	**hexanal**	reactive		reactive		reactive		reactive	
49	**octanal**	reactive		reactive		reactive		reactive	
50	**Aniline**	reactive		reactive		reactive		reactive	
51	**2-chloroaniline**	reactive		reactive		reactive		reactive	
52	**3-chloroaniline**	reactive		reactive		reactive		reactive	
53	**m-toluidine**	reactive		reactive		reactive		reactive	
54	**1-chloro-3-propanol**	single phase		single phase		single phase		single phase	

Table S4. Water (% v/v) in organic and organic (% v/v) in aqueous phase, and change (%) in P_{HMF} and water (% v/v) in organic phase on 20 wt.% fructose solution at 298 K.

#	Solvents	Change (%) in P_{HMF} with fructose (20 wt. %)	% Water (v/v) in organic phase	% Organic(v/v) in aqueous phase	Change (%) in water in organic phase with fructose (20 wt. %)
1	**Pentafluorophenol**		43.1	3.5	

2	**2-Isopropyl Phenol**	6.82	5.07	5.7	-0.2
3	**3-Chlorophenol**	-7.18	19.82	3.23	-2.72
4	**2-Chlorophenol**	-1.54	13.72	4.13	
5	**3-Methoxy Phenol**	8.97	18.42	7.9	
6	**2-ethyl phenol**	21.92	8.25	1.7	-8.5
7	**2-sec-Butyl Phenol**	9.41	3.20	0.5	
8	**phenol**	-0.42	29.12	8.4	-12.5
9	**4-chlorophenol**	-9.67	17.92	3.03	-4.3
10	**1-butanol**	19.62	16.58	15.13	-20.1
11	**1-hexanol**	16.47	5.59	7.63	
12	**1-nonanol**		3.13	7.88	
13	**2-pentanone**	4.65	3.37	10.33	
14	**2-heptanone**	19.78	0.79	7.56	
15	**2-decanone**		0.24	6.01	
16	**cyclohexanone**	28.89	5.77	17.50	-14.6
17	**cycloheptanone**	34.48	3.33	9.55	-9.43
18	**MIBK**	14.42	1.61	2.77	-7.7
19	**2-butanol**	27.33	32.32	27.6	-42.07
20	**2-pentanol**	17.29	9.46	18.53	-14.98
21	**2-octanol**		2.93	4.94	
22	**ethyl acetate**	18.80	3.03	10.53	-10.45
23	**butyl acetate**		1.00	7.5	
24	**methyl butyrate**	22.53	1.24	7.81	
25	**pentane**		Undetectable	0.22	
26	**octane**		Undetectable	0.05	
27	**cyclohexane**		Undetectable	2.11	

28	**1-hexene**		Undetectable	1.26	
29	**1-octene**		Undetectable	0.3	
30	**cyclopentanol**	11.52	16.41654387	18.07	
31	**benzyl alcohol**	13.76		2.89	-22.55
32	**cyclooctanol**		5.07	2.74	
33	**2-MTHF**	7.14	4.25	17.02	
34	**Tetrahydropyran**	15.23	2.45	10.01	
35	**diethylether**		0.83	2	
36	**dipropylether**		0.21	3.55	
37	**Pentanoic Acid**	14.86	13.60	8.65	
38	**Hexanoic Acid**	0	5.64	14.96	
39	**Octanoic Acid**		1.92	5.53	
40	**Toluene**		Undetectable	0	
41	**m-cresol**	-13.59	12.72	4.37	-7.82
42	**chlorobenzene**		Undetectable	1.13	
43	**o-cresol**	-5.09	12.87	7.46	

Table S5. Safety, Health and Environmental scores for solvent toxicity using the CHEM21 interactive solvent guide (R= Recommended, P= Problematic, H=Hazardous).

#	Solvents	*Safety Score*	*Health Score*	*Environmental Score*	*Recommendation*
1	**pentafluorophenol**	1	5	5	P
2	**2-isopropylphenol**	1	7	7	H
3	**3-chlorophenol**	1	5	7	P
4	**2-chlorophenol**	1	7	7	H
5	**3-methoxyphenol**	1	6	7	P
6	**2-ethylphenol**	1	5	5	P
7	**2-sec-butylphenol**	1	7	7	H

8	**phenol**	1	7	7	H
9	**4-chlorophenol**	1	2	7	P
10	**1-butanol**	3	4	3	R
11	**1-hexanol**	3	2	5	R
12	**1-nonanol**	1	2	7	P
13	**2-pentanone**	4	2	3	R
14	**2-heptanone**	3	2	5	R
15	**2-decanone**	1	5	7	P
16	**cyclohexanone**	3	2	5	R
17	**cycloheptanone**	3	4	5	P
18	**MIBK**	4	2	3	R
19	**2-butanol**	3	2	3	R
20	**2-pentanol**	3	2	3	R
21	**2-octanol**	1	4	5	P
22	**ethyl acetate**	5	3	3	R
23	**butyl acetate**	4	2	3	R
24	**methyl butyrate**	4	5	5	P
25	**pentane**	8	3	7	H
26	**octane**	4	2	7	P
27	**cyclohexane**	6	3	7	P
28	**1-hexene**	8	3	7	H
29	**1-octene**	5	2	7	P
30	**cyclopentanol**	3	1	5	R
31	**benzyl alcohol**	1	2	7	P
32	**cyclooctanol**	1	5	7	P
33	**2-MTHF**	6	5	3	P
34	**tetrahydropyran**	5	6	5	P
35	**diethylether**	10	3	7	H
36	**dipropylether**	9	3	5	H
37	**pentanoic acid**	1	7	3	P
38	**hexanoic acid**	1	7	7	H
39	**octanoic acid**	1	7	7	H
40	**toluene**	5	6	3	P
41	**m-cresol**	1	7	7	H
42	**chlorobenzene**	3	2	7	P
43	**o-cresol**	1	7	7	H

The CHEM21 ranking methodology for solvent toxicity is based on solvent physical properties (boiling point, flash point, autoignition temperature) and GHS statements.[1] It

establishes safety, health, and environment criteria (SHE criteria), each scored from 1 to 10, with a higher figure representing a higher hazard. These individual scores are combined in an overall score (recommended, problematic, or hazardous) for each solvent.

References

1. The CHEM21 solvent selection guide interactive tool: solvent ranking, http://learning.chem21.eu/methods-of-facilitating-change/tools-and-guides/solvent-selection-guides/interactive-tool-chem21-guide/, (accessed November 4, 2020).