Complex oiling-out behavior of procaine with stable and metastable liquid phases

SUPPLEMENTAL INFORMATION

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Predictions based on gPROMS SAFT-γ-Mie database parameters

I. Model Regression

The smiles string for procaine is CCN(CC)CCOC(=O)c1ccc(cc1)N.

The measured crystalline solubility data of procaine in pure solvents is provided in Figure 1 below.

Table S1: Solubility data used in model regression

Solvent	Temperature	Experimental
	K	g/100g solution
ethanol	277.15	60.9341
ethanol	283.15	65.9765
ethanol	298.15	85.3618
n-heptane	277.15	0.0854
n-heptane	283.15	0.1452
n-heptane	298.15	0.4592
n-heptane	310.15	1.0938
n-heptane	323.15	2.1699
water	277.15	0.244755146
water	283.15	0.350518446
water	298.15	0.942607692
water	310.15	2.869227165
water	323.15	7.557664293

I.1 Database Model

The predicted solubility data using the database model, as well as the associated deviation analysis is shown below.

Table S2: Database model predictions

Solvent	Temperature	Solubility			Solute - Solvent interaction coverage	Use data point for estimation
		Experimental	Predicted	Deviation		
	K	g/100g solution	g/100g solution	%	%	
ethanol	277.15	60.9341	32.77	46.21%	86%	☑
ethanol	283.15	65.9765	52.14	20.98%	86%	☑
ethanol	298.15	85.3618	76.35	10.56%	86%	☑
n-heptane	277.15	0.0854	4.50E-03	94.73%	88%	☑
n-heptane	283.15	0.1452	8.01E-03	94.48%	88%	☑
n-heptane	298.15	0.4592	3.06E-02	93.34%	88%	☑
n-heptane	310.15	1.0938	8.14E-02	92.56%	88%	☑
n-heptane	323.15	2.1699	0.22	89.94%	88%	☑
water	277.15	0.244755146	0.31	25.48%	86%	☑
water	283.15	0.350518446	0.33	5.72%	86%	☑
water	298.15	0.942607692	0.41	56.39%	86%	☑
water	310.15	2.869227165	0.50	82.43%	86%	☑
water	323.15	7.557664293	0.65	91.44%	86%	☑

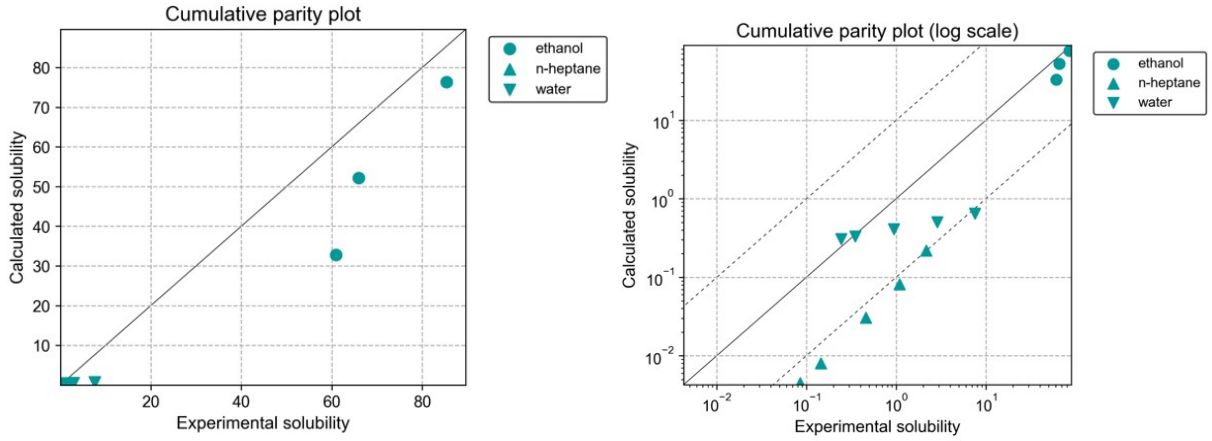

Figure S1: Parity plots for database model predictions.

I.2 Molecular Model

The predicted solubility data using the molecular model, as well as the associated deviation analysis is shown below.

Note, for the majority of the modelling work performed in this study used a beta version of the gPROMS Solvent Selection (gSS) tool (v 1.0.0-beta 4). After extensive testing by the one of the authors (FR), some unphysical behavior was predicted for procaine (e.g., unphysical melting

temperatures). The software developers (formerly Process Systems Enterprise, and now Siemens) noted that this was due to the fact that the gSS regression algorithm purposefully neglected the presence of the vapor-phase root generated by the equation of state. Hence, the Siemens subject matter expert fit the experimental data for this study in-house, using an amended algorithm which did not neglect the vapor-phase root, thereby leading to an improved parameter search, and the corrected molecular model was sent to the author for subsequent prediction. The regressed parameters are provided in Figure S3 below.

Table S3: Molecular model predictions

SOLVENT	T [K]	Csat (exp) [wt%]	Csat (pred) [wt%]	%Deviation
ethanol	277.15	60.9341	62.35673386	2.334708904
ethanol	283.15	65.9765	67.22187727	1.887607355
ethanol	298.15	85.3618	80.41127709	5.799459366
n-heptane	277.15	0.0854	0.089217128	4.469705213
n-heptane	283.15	0.1452	0.145716784	0.355911696
n-heptane	298.15	0.4592	0.449919467	2.021022018
n-heptane	310.15	1.0938	1.010221999	7.641067965
n-heptane	323.15	2.1699	2.236176405	3.054352983
water	277.15	0.244755146	0.19711273	19.46533786
water	283.15	0.350518446	0.33953004	3.134901144
water	298.15	0.942607692	1.178694883	25.046177
water	310.15	2.869227165	2.855157215	0.490374214
water	323.15	7.557664293	6.706214835	11.26603967
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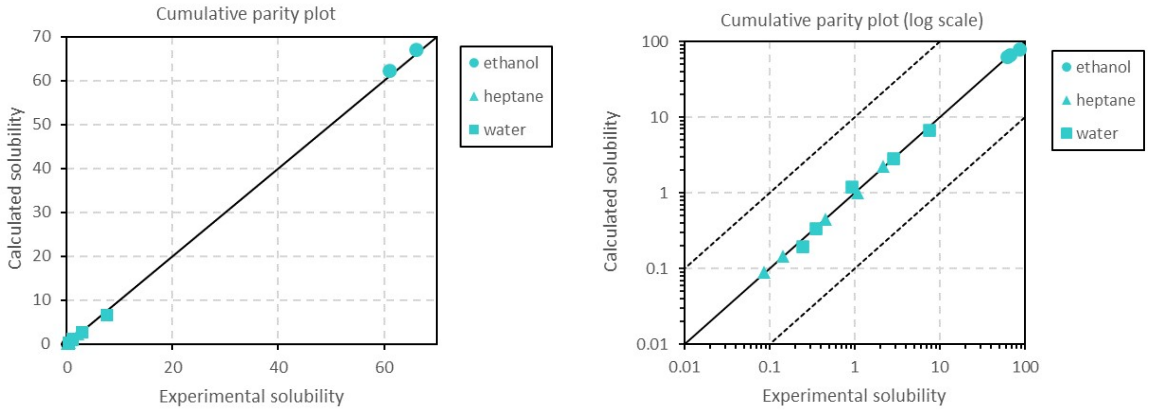

Figure S2: Parity plots for molecular model predictions.

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Figure S3: Molecular model regressed parameter values, as reported in gSS .xml file.

II. Experimental phase boundary data

II.1 Crystalline solubility

i. Neat heptane

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
4	0.8546±0.3231	0	99.91±0.03	0.08538±0.03226
10	1.454±0.062	0	99.85±0.01	0.1452±0.0061
RT	4.613±0.068	0	99.54±0.01	0.4592±0.0068
37	11.06±0.25	0	98.91±0.02	1.094±0.024
50	22.19±4.12	0	97.83±0.40	2.170±0.395

ii. Neat ethanol

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
4	1560±4	39.07±0.06	0	60.93±0.06
10	1940±41	34.02±0.48	0	65.98±0.48
RT	5837±230	14.64±0.48	0	85.36±0.48

iii. 0.6 v/v ethanol in heptane

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
4	492.9±26.3	42.80±0.75	24.20±0.42	33.00±1.17
10	700.4±31.3	37.58±0.70	21.25±0.39	41.18±1.09
RT	1814±295	22.86±2.29	12.92±1.30	64.22±3.59
37	11319±4733	5.666±1.901	3.204±1.075	91.13±2.98

iv. 0.8 v/v ethanol in heptane

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
4	968.3±41.2	41.93±0.89	8.890±0.188	49.18±1.08
10	1239±19	36.85±0.31	7.812±0.067	55.34±0.38
RT	3680±258	17.66±0.95	3.745±0.202	78.59±1.15
37	13151±4816	6.311±2.157	1.338±0.457	92.35±2.61

II.2 Oiling out limits

i. Antisolvent titration

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
4	106.4	37.85	52.54	9.617

	98.40	36.54	54.50	8.958
	86.44	34.75	57.29	7.956
	76.35	33.02	59.88	7.093
	67.22	31.14	62.56	6.299
	63.43	30.35	63.69	5.965
	57.00	28.99	65.62	5.393
	51.76	27.87	67.21	4.921
	46.85	26.63	68.89	4.475
	37.16	23.90	72.51	3.583
	30.11	21.60	75.47	2.923
	24.49	19.39	78.22	2.391
	14.37	13.53	85.05	1.417
	13.16	14.28	84.42	1.299
	12.06	14.82	83.99	1.192
	6.385	1.279	98.09	0.6344
	6.385	1.279	98.09	0.6344
	6.320	0.8688	98.50	0.6280
	12.45	7.532	91.24	1.230
	9.388	6.279	92.79	0.9301
	239.8	44.56	36.10	19.34
	183.2	44.05	40.46	15.48
	160.0	43.72	42.48	13.79
	142.0	43.46	44.11	12.43
	110.0	41.07	49.02	9.909
	97.12	39.09	52.06	8.853
	152.2	40.56	46.23	13.21
10	113.4	27.87	61.94	10.18
	181.0	38.08	46.60	15.32
	294.9	39.11	38.11	22.78
	253.7	38.84	40.92	20.24
	71.08	16.91	76.45	6.636
	158.9	35.00	51.30	13.71
	14.25	2.832	95.76	1.404
	18.78	2.550	95.61	1.843
RT	23.66	7.835	89.85	2.312
	114.9	24.58	65.12	10.30
	16.59	6.513	91.86	1.632
	22.05	6.755	91.09	2.158
	101.1	24.35	66.47	9.178
	93.07	24.22	67.27	8.514
	332.1	34.17	40.90	24.93
	290.0	32.95	44.57	22.48
	316.9	35.25	40.69	24.06
	403.6	36.07	35.17	28.76
	123.4	25.33	63.68	10.98
	257.8	34.95	44.56	20.49

	115.8	25.18	64.45	10.37
	87.07	22.33	69.66	8.010
	67.59	19.93	73.74	6.331
	51.68	17.24	77.84	4.914
	34.98	13.69	82.93	3.380
	31.37	12.87	84.09	3.042
	23.84	10.90	86.77	2.328
	122.5	29.77	59.32	10.91
	463.6	38.99	29.33	31.67
	352.1	39.36	34.60	26.04
	291.5	38.35	39.08	22.57
	254.7	36.38	43.32	20.30
	226.1	34.78	46.78	18.44
	203.3	33.44	49.66	16.90
	186.3	31.82	52.48	15.70
	170.5	30.88	54.55	14.57
	158.4	29.62	56.71	13.67
	147.9	28.51	58.61	12.88
	138.7	27.52	60.30	12.18
	122.6	26.21	62.87	10.92
	25.30	3.413	94.12	2.467
	28.21	5.533	91.72	2.744
37	179.6	25.58	59.19	15.23
	25.16	6.896	90.65	2.455
	33.40	7.255	89.51	3.232
	28.70	7.051	90.16	2.790
	179.6	25.58	59.19	15.23
	128.1	19.12	69.53	11.35
	84.61	11.35	80.85	7.801
	342.9	31.79	42.68	25.53
	67.68	15.04	78.62	6.339
	64.05	14.56	79.42	6.019
	61.52	14.29	79.92	5.796
	44.82	11.72	83.99	4.289
	298.3	25.93	51.09	22.98
	275.9	26.05	52.33	21.62
	244.3	25.14	55.22	19.64
	216.1	24.11	58.12	17.77
	193.8	23.25	60.51	16.23
	173.6	22.32	62.89	14.79
	154.1	21.16	65.49	13.35
	138.5	20.20	67.63	12.17
	124.8	19.26	69.64	11.09
	113.5	18.48	71.33	10.19
	104.1	17.81	72.76	9.428
	85.32	16.04	76.10	7.861

	54.16	10.36	84.50	5.138
	37.47	7.283	89.11	3.612
	37.86	5.047	91.30	3.648
55	50.84	8.001	87.16	4.838
	41.12	6.568	89.48	3.950
	47.46	6.518	88.95	4.531
	146.9	21.81	65.37	12.81
	108.7	21.98	68.21	9.802
	138.6	22.53	65.29	12.17
	110.2	20.01	70.06	9.929
	84.24	16.93	75.30	7.770
	67.74	14.87	78.79	6.344
	47.84	11.45	83.98	4.566
	164.5	15.18	70.69	14.13
	75.57	10.08	82.90	7.026
	63.99	7.501	86.49	6.014
	465.5	25.33	42.90	31.76
	435.1	25.62	44.06	30.32
	408.5	25.89	45.11	29.00
	373.1	25.55	47.27	27.17
	343.4	25.26	49.18	25.56
	310.0	24.51	51.82	23.67
	284.2	23.97	53.90	22.13
	251.1	23.65	56.27	20.07
	223.0	22.80	58.97	18.24
	195.8	21.64	61.99	16.37

ii. Cooling experiments

Temperature (°C)	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
RT	11.75	0	98.84	1.162
	12.94	0	98.72	1.278
	9.873	0	99.02	0.978
37	16.20	0	98.41	1.594
	16.02	0	98.42	1.577
	16.88	0	98.34	1.660
50	29.30	0	97.15	2.847
	26.75	0	97.39	2.605
	29.87	0	97.10	2.900
55	33.32	0	96.78	3.224
	33.09	0	96.80	3.203
	34.16	0	96.70	3.303
60	37.78	0	96.36	3.641
	38.08	0	96.33	3.668
	38.62	0	96.28	3.718
65	38.66	0	96.28	3.722

	38.89	0	96.26	3.743
	38.28	0	96.31	3.687

iii. Heating experiments

Temperature (°C)	Phases	Solubility (API mg/g solvent)	Wt.% Ethanol	Heptane	Procaine
55	Heptane	26.87	0	97.38	2.617
		22.29	0	97.82	2.180
		23.97	0	97.66	2.341
		22.58	0	97.79	2.208
	Procaine	14493	0	6.454	93.55
		13317	0	6.985	93.02
		11988	0	7.700	92.30
		14532	0	6.438	93.56
60	Heptane	34.66	0	96.65	3.350
		35.75	0	96.55	3.451
		40.24	0	96.13	3.869
		43.73	0	95.81	4.190
	Procaine	10330	0	8.826	91.17
		11457	0	8.028	91.97
		12256	0	7.544	92.46
		5667	0	15.00	85.00
70	Heptane	52.15	0	95.04	4.956
		63.07	0	94.07	5.933
		51.61	0	95.09	4.908
		53.76		94.90	5.102
	Procaine	7000	0	12.50	87.50
		7305	0	12.04	87.96
		8024	0	11.08	88.92
		6970	0	12.55	87.45
85	Heptane	85.56	0	92.12	7.882
		84.95	0	92.17	7.830
		85.84	0	92.09	7.905
	Procaine	6219	0	13.85	86.15
		5759	0	14.79	85.21
		6062	0	14.16	85.84
95	Heptane	134.4	0	88.15	11.85
		135.4	0	88.07	11.93
		135.3	0	88.08	11.92
	Procaine	4455	0	18.33	81.67
		4528	0	18.09	81.91
		4345	0	18.71	81.29