

Electronic Supplementary Information

Dichloromethane replacement: towards greener chromatography via statistical thermodynamics

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S1. Materials and Methods

S1.1 Materials

DCM (99%), MeOH (99.9%), EtOAc (98%), and EtOH (99.8%), were obtained from Fisher Scientific (Loughborough, England). Heptane (99%), ethyl isobutyrate (99%), and methyl pivalate (99.9%) were obtained from Sigma-Aldrich (Merck). *tert*-Butyl acetate (99%), and *sec*-butyl acetate were obtained from Fluorochem (UK) and Thermo Scientific, respectively. Analytes ibuprofen (99.1%), ketoprofen (99.51%), and acetaminophen (99.96%) were obtained from APExBIO (USA), caffeine (99%) and 4-aminophenol (99%) were obtained Sigma-Aldrich (Merck), and *o*-acetylsalicylic acid (99%) was obtained from Alfa Aesar and used without any further purification. For Kamlet-Taft tests, dyes *N,N*-diethyl-4-nitroaniline (97%) and 4-nitroaniline (99%) were obtained from Fluorochem (UK) and Sigma-Aldrich, respectively. TLC plates (TLC Silica gel 60 F254, aluminium support, 20 cm x 20 cm, Merck) were cut to 2.0 cm x 8.0 cm plates and analysed via a 254 nm UV lamp (UVP UVGL-55 Handheld UV Lamp, 254/365 nm, multi-band split tube) and viewing cabinet.

S1.2 Calculation of Kamlet-Taft Parameters

The π^* and β Kamlet-Taft parameters for test solvents (S) *tert*-butyl acetate and *sec*-butyl acetate were determined in this work; the α parameter was not calculated as this was assumed to be zero. Dyes *N,N*-diethyl-4-nitroaniline (*D-NA*) and 4-nitroaniline (NA) were dissolved in the both solvents and mixtures were subsequently scanned on a Jasco 550 UV-Vis spectrometer to determine the $\nu_{max}(N,N)$ and $\nu_{max}(NA)$. The π^* parameter was determined using equation S1^{1,2} and the β parameter was determined using equations S2 and S3 from the original literature.³ Experimental wavelength values were converted to kilokaiser (kK) before use in calculations.

$$\pi^* = \frac{\nu_{\max(N,N)}[S] - \nu_{\max(N,N)}[\text{cyclohexane}]}{\nu_{\max(N,N)}[\text{DMSO}] - \nu_{\max(N,N)}[\text{cyclohexane}]} \quad (\text{Eq. S1})$$

$$\nu_{\max(NA)}[S_{\text{calculated}}] = 1.035(\nu_{\max(D-NA)}[S_{\text{observed}}]) + 2.64 \text{ kK} \quad (\text{Eq. S2})$$

$$\beta = \frac{\nu_{\max(NA)}[S_{\text{calculated}}] - \nu_{\max(NA)}[S_{\text{observed}}]}{2.8} \quad (\text{Eq. S3})$$

S1.3 Calculation of the Solvent Strength Parameter (\mathcal{E}^o)

The solvent strength parameter (\mathcal{E}^o) can be estimated through eq. S4 for silica⁴:

$$\mathcal{E}^o = -0.264V + 0.199S + 0.384A + 0.535B + 0.272 \quad (\text{Eq. S4})$$

where, for a given solvent, V is the McGowan's characteristic volume⁵, S is dipolarity/polarisability, A is effective hydrogen-bond acidity, and B is effective hydrogen bond basicity. Through a ranking system of increasing polarity, wherein \mathcal{E}^o (pentane) is arbitrarily set to zero, one can select a potential alternative based on similar solvent strength values.

S2. Experimental Data and Analysis

S2.1 Thin Layer Chromatography (TLC) - Test Solvents Modified with MeOH

Table 1. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in DCM modified with 0-20% MeOH.

Analyte A (DCM-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
2	0.17	0.19	0.17	0.18	0.013
5	0.43	0.40	0.40	0.41	0.016
10	0.54	0.54	0.54	0.54	0
20	0.80	0.77	0.80	0.79	0.016
Analyte B (DCM-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
2	0.17	0.20	0.17	0.18	0.016
5	0.29	0.31	0.31	0.30	0.016
10	0.54	0.51	0.54	0.53	0.016
20	0.86	0.83	0.88	0.85	0.025
Analyte C (DCM-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
2	0.057	0.057	0.057	0.057	0
5	0.20	0.20	0.20	0.20	0
10	0.51	0.51	0.51	0.51	0
20	0.83	0.86	0.86	0.85	0.016
Analyte D (DCM-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.025	0.025	0.025	0.03	0
2	0.048	0.071	0.071	0.06	0.014
5	0.32	0.35	0.35	0.34	0.017
10	0.62	0.59	0.62	0.61	0.017
20	0.96	0.94	0.92	0.94	0.020

Table 2. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *tert*-butyl acetate (1) modified with 0-20% MeOH.

Analyte A (1-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.22	0.22	0.24	0.23	0.013
2	0.37	0.34	0.34	0.35	0.016
5	0.56	0.58	0.57	0.57	0.011
10	0.65	0.68	0.68	0.67	0.017
20	0.73	0.72	0.72	0.72	0.002
Analyte B (1-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.33	0.33	0.38	0.35	0.026
2	0.41	0.38	0.40	0.40	0.014
5	0.53	0.53	0.54	0.54	0.006
10	0.68	0.68	0.71	0.69	0.019
20	0.83	0.78	0.79	0.80	0.026
Analyte C (1-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.022	0.022	0	0.01	0.013
2	0.061	0.060	0.060	0.06	0.001
5	0.16	0.16	0.15	0.15	0.002
10	0.33	0.35	0.34	0.34	0.013
20	0.40	0.40	0.40	0.40	0
Analyte D (1-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.16	0.18	0.16	0.17	0.013
2	0.29	0.28	0.26	0.28	0.014
5	0.44	0.47	0.46	0.46	0.011
10	0.65	0.68	0.66	0.66	0.013
20	0.73	0.70	0.70	0.71	0.015

Table 3. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *sec*-butyl acetate (2) modified with 0-20% MeOH.

Analyte A (2-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.32	0.32	0.34	0.33	0.013
2	0.42	0.40	0.40	0.41	0.013
5	0.49	0.50	0.54	0.51	0.026
10	0.54	0.58	0.59	0.57	0.027
20	0.62	0.66	0.62	0.63	0.023
Analyte B (2-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.48	0.48	0.45	0.47	0.014
2	0.56	0.56	0.54	0.55	0.011
5	0.58	0.58	0.55	0.57	0.014
10	0.61	0.61	0.61	0.61	0
20	0.64	0.64	0.67	0.65	0.015
Analyte C (2-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.04	0.06	0.06	0.06	0.012
2	0.04	0.04	0.04	0.04	0.002
5	0.10	0.10	0.10	0.10	0.002
10	0.27	0.27	0.28	0.27	0.003
20	0.36	0.36	0.33	0.35	0.013
Analyte D (2-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.18	0.14	0.14	0.15	0.024
2	0.30	0.30	0.40	0.33	0.056
5	0.40	0.40	0.44	0.41	0.023
10	0.5	0.52	0.53	0.52	0.016
20	0.60	0.60	0.60	0.60	0

Table 4. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in ethyl isobutyrate (3) modified with 0-20% MeOH.

Analyte A (3-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.17	0.17	0.20	0.18	0.013
2	0.33	0.29	0.31	0.31	0.018
5	0.48	0.48	0.46	0.47	0.013
10	0.50	0.52	0.51	0.51	0.010
20	0.66	0.63	0.65	0.65	0.013
Analyte B (3-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.33	0.33	0.33	0.33	0
2	0.36	0.33	0.35	0.35	0.018
5	0.50	0.50	0.48	0.49	0.013
10	0.54	0.54	0.55	0.54	0.004
20	0.68	0.65	0.65	0.66	0.017
Analyte C (3-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
2	0.05	0.05	0.05	0.05	0
5	0.13	0.13	0.13	0.13	0.003
10	0.27	0.24	0.27	0.26	0.018
20	0.38	0.37	0.39	0.38	0.013
Analyte D (3-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.16	0.14	0.14	0.15	0.012
2	0.20	0.22	0.20	0.21	0.010
5	0.38	0.35	0.37	0.37	0.011
10	0.48	0.50	0.53	0.50	0.023
20	0.60	0.60	0.61	0.60	0.006

Table 5. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in methyl pivalate (4) modified with 0-20% MeOH.

Analyte A (4-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.20	0.17	0.17	0.18	0.014
2	0.30	0.32	0.32	0.31	0.009
5	0.46	0.44	0.44	0.45	0.011
10	0.52	0.52	0.53	0.52	0.006
20	0.69	0.63	0.67	0.66	0.032
Analyte B (4-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.24	0.27	0.24	0.25	0.014
2	0.28	0.30	0.30	0.29	0.009
5	0.48	0.48	0.48	0.48	0
10	0.54	0.52	0.55	0.54	0.016
20	0.73	0.73	0.71	0.73	0.013
Analyte C (4-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
2	0.04	0.04	0.04	0.04	0.002
5	0.10	0.10	0.10	0.10	0.002
10	0.27	0.27	0.28	0.27	0.003
20	0.36	0.36	0.33	0.35	0.013
Analyte D (4-MeOH)					
% MeOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.11	0.11	0.13	0.12	0.013
2	0.17	0.19	0.19	0.19	0.010
5	0.33	0.30	0.30	0.31	0.019
10	0.54	0.54	0.54	0.54	0
20	0.64	0.64	0.64	0.64	0

S2.2 Thin Layer Chromatography (TLC) – Test Solvents Modified with 3:1 EtOAc-EtOH

Table 6. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in DCM modified with 0-75% 3:1 EtOAc-EtOH.

Analyte A (DCM-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
10	0.27	0.29	0.29	0.28	0.013
25	0.62	0.62	0.60	0.61	0.012
50	0.71	0.73	0.73	0.73	0.013
75	0.79	0.77	0.79	0.78	0.013
Analyte B (DCM-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
10	0.38	0.38	0.36	0.37	0.013
25	0.68	0.68	0.66	0.67	0.012
50	0.80	0.80	0.79	0.80	0.007
75	0.86	0.84	0.86	0.86	0.010
Analyte C (DCM-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
10	0.22	0.22	0.22	0.22	0
25	0.45	0.45	0.45	0.45	0
50	0.48	0.48	0.46	0.47	0.012
75	0.55	0.53	0.53	0.54	0.007
Analyte D (DCM-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.03	0.03	0.03	0.03	0
10	0.17	0.17	0.13	0.16	0.025
25	0.48	0.46	0.46	0.46	0.013
50	0.71	0.71	0.73	0.72	0.013
75	0.82	0.84	0.82	0.83	0.012

Table 7. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *tert*-butyl acetate (1) modified with 0-75% 3:1 EtOAc-EtOH.

Analyte A (1-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.22	0.22	0.24	0.23	0.013
10	0.31	0.31	0.33	0.32	0.013
25	0.47	0.45	0.45	0.45	0.012
50	0.59	0.63	0.63	0.62	0.025
75	0.78	0.80	0.80	0.79	0.012
Analyte B (1-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.29	0.28	0.30	0.29	0.011
10	0.48	0.50	0.52	0.50	0.023
25	0.54	0.57	0.76	0.62	0.120
50	0.72	0.72	0.74	0.73	0.012
75	0.88	0.86	0.88	0.87	0.012
Analyte C (1-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.02	0.02	0	0.01	0.013
10	0.05	0.07	0.07	0.06	0.013
25	0.11	0.09	0.09	0.10	0.013
50	0.29	0.29	0.31	0.30	0.013
75	0.38	0.38	0.40	0.39	0.011
Analyte D (1-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.16	0.18	0.16	0.17	0.013
10	0.36	0.36	0.34	0.36	0.013
25	0.44	0.46	0.48	0.46	0.021
50	0.68	0.68	0.68	0.68	0
75	0.91	0.89	0.91	0.91	0.012

Table 8. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *sec*-butyl acetate (2) modified with 0-75% 3:1 EtOAc-EtOH.

Analyte A (2-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.32	0.32	0.34	0.33	0.013
10	0.48	0.50	0.46	0.48	0.021
25	0.46	0.47	0.44	0.45	0.016
50	0.69	0.69	0.64	0.67	0.026
75	0.73	0.75	0.73	0.74	0.012
Analyte B (2-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.51	0.53	0.53	0.53	0.013
10	0.65	0.63	0.65	0.64	0.012
25	0.63	0.63	0.60	0.62	0.018
50	0.80	0.82	0.84	0.82	0.023
75	0.85	0.83	0.83	0.84	0.012
Analyte C (2-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.04	0.06	0.06	0.06	0.012
10	0.13	0.08	0.10	0.10	0.021
25	0.16	0.18	0.16	0.17	0.012
50	0.40	0.40	0.40	0.40	0
75	0.56	0.54	0.54	0.55	0.012
Analyte D (2-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.18	0.14	0.14	0.15	0.024
10	0.22	0.23	0.23	0.23	0.004
25	0.34	0.36	0.38	0.36	0.021
50	0.65	0.59	0.59	0.61	0.036
75	0.86	0.79	0.81	0.82	0.035

Table 9. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in ethyl isobutyrate (3) modified with 0-75% 3:1 EtOAc-EtOH.

Analyte A (3-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.18	0.18	0.20	0.19	0.012
10	0.30	0.27	0.27	0.28	0.013
25	0.42	0.44	0.44	0.44	0.013
50	0.58	0.56	0.63	0.59	0.032
75	0.70	0.70	0.68	0.69	0.012
Analyte B (3-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.32	0.34	0.34	0.33	0.012
10	0.48	0.48	0.45	0.47	0.014
25	0.56	0.53	0.58	0.56	0.023
50	0.69	0.69	0.71	0.70	0.012
75	0.80	0.80	0.80	0.80	0
Analyte C (3-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.02	0.05	0	0.02	0.023
10	0.08	0.08	0.08	0.08	0
25	0.10	0.13	0.15	0.13	0.025
50	0.32	0.32	0.30	0.31	0.012
75	0.40	0.43	0.49	0.44	0.044
Analyte D (3-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.16	0.14	0.14	0.15	0.012
10	0.21	0.23	0.23	0.22	0.012
25	0.38	0.38	0.40	0.38	0.011
50	0.57	0.59	0.59	0.58	0.013
75	0.81	0.79	0.81	0.81	0.011

Table 10. R_f values (n=3) for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in methyl pivalate (4) modified with 0-75% 3:1 EtOAc-EtOH.

Analyte A (4-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.20	0.17	0.17	0.18	0.014
10	0.31	0.29	0.29	0.30	0.013
25	0.43	0.40	0.40	0.41	0.012
50	0.62	0.62	0.6	0.61	0.013
75	0.76	0.74	0.74	0.75	0.012
Analyte B (4-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.24	0.27	0.24	0.25	0.014
10	0.42	0.42	0.44	0.43	0.013
25	0.51	0.49	0.49	0.50	0.012
50	0.70	0.65	0.67	0.67	0.022
75	0.80	0.80	0.78	0.80	0.011
Analyte C (4-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0	0	0	0	0
10	0.07	0.09	0.07	0.07	0.013
25	0.12	0.14	0.14	0.13	0.013
50	0.38	0.33	0.33	0.35	0.026
75	0.46	0.48	0.44	0.46	0.019
Analyte D (4-3:1 EtOAc-EtOH)					
% 3:1 EtOAc-EtOH	R_f (1)	R_f (2)	R_f (3)	R_f (average)	Std. dev.
0	0.11	0.11	0.13	0.12	0.013
10	0.23	0.23	0.26	0.24	0.012
25	0.39	0.39	0.41	0.39	0.012
50	0.62	0.62	0.64	0.63	0.013
75	0.80	0.78	0.78	0.79	0.012

S2.3 Thin Layer Chromatography (TLC) - Test Solvent Mixtures Modified with 3:1 EtOAc-EtOH

Table 11 . R_f values for analyte mixtures 4-aminophenol/acetaminophen and ibuprofen/ ketoprofen run in DCM modified with 10% 3:1 EtOAc-EtOH and *tert*-butyl acetate (1), *sec*-butyl acetate (2), ethyl isobutyrate (3) and methyl pivalate (4) modified with 25% 3:1 EtOAc-EtOH.

4-Aminophenol					
% 3:1 EtOAc-EtOH	R_f (DCM)	R_f (1)	R_f (2)	R_f (3)	R_f (4)
10	0.25	-	-	-	-
25	-	0.52	0.52	0.48	0.48
Acetaminophen					
% 3:1 EtOAc-EtOH	R_f (DCM)	R_f (1)	R_f (2)	R_f (3)	R_f (4)
10	0.14	-	-	-	-
25	-	0.41	0.40	0.35	0.37
Ibuprofen					
% 3:1 EtOAc-EtOH	R_f (DCM)	R_f (1)	R_f (2)	R_f (3)	R_f (4)
10	0.43	-	-	-	-
25	-	0.74	0.74	0.63	0.75
Ketoprofen					
% 3:1 EtOAc-EtOH	R_f (DCM)	R_f (1)	R_f (2)	R_f (3)	R_f (4)
10	0.70	-	-	-	-
25	-	0.57	0.52	0.48	0.50

S2.4 Linear Regression Analysis

Simple linear regressions were performed in Excel (ANOVA) on TLC data sets that would yield undefined KBI results. These cases include analytes A, B, and C run in DCM and analyte C run in methyl pivalate wherein, at the dilute eluent limit, $\ln(k)$ is undefined ($R_f = 0$). Predicted R_f are used in the calculation of KBIs and linear equations, R^2 values, and p-values are shown in the tables below.

Table 12 . Linear regression analysis data (linear equation for predicted R_f values, R^2 , p-value) for acetylsalicylic acid (A), ketoprofen (B) and caffeine (C) run in DCM modified with MeOH.

DCM-MeOH			
Analyte	Equation	R^2	p-value
A	$y = 0.1493x + 0.1112$	0.914	0.01
B	$y = 0.1656x + 0.0718$	0.976	0.002
C	$y = 0.1742x + 0.0014$	0.981	0.001

Table 13 . Linear regression analysis data (linear equation for predicted R_f values, R^2 , p-value) for acetylsalicylic acid (A), ketoprofen (B) and caffeine (C) run in DCM modified with 3:1 EtOAc-EtOH.

DCM-3:1 EtOAc-EtOH			
Analyte	Equation	R^2	p-value
A	$y = 0.0869x + 0.1689$	0.804	0.04
B	$y = 0.0919x + 0.211$	0.778	0.05
C	$y = 0.0566x + 0.1332$	0.757	0.05

Table 14 . Linear regression analysis data (linear equation for predicted R_f values, R^2 , p-value) for caffeine (C) run in methyl pivalate (4) modified with MeOH.

4-MeOH			
Analyte	Equation	R^2	p-value
C	$y = 0.0733x + 0.0191$	0.923	0.009

Table 15 . Linear regression analysis data (linear equation for predicted R_f values, R^2 , p-value) for caffeine (C) run in methyl pivalate (4) modified with 3:1 EtOAc-EtOH.

4-3:1 EtOAc-EtOH			
Analyte	Equation	R^2	p-value
C	$y = 0.0565x + 0.001$	0.986	0.0006

S2.5 Calculation of $\ln(k)$ Terms

Table 16. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in DCM modified with MeOH. R_f terms used in calculations for analytes A, B, and C are the predicted terms calculated from linear regression (LR) analysis found in S2.4.

Analyte A (DCM-MeOH)			
MeOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.11	7.99	2.08
0.49	0.19	4.40	1.48
1.2	0.30	2.38	0.867
2.5	0.48	1.08	0.079
4.9	0.85	0.177	-1.73
Analyte B (DCM-MeOH)			
MeOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.07	12.9	2.56
0.49	0.15	5.51	1.71
1.2	0.28	2.62	0.962
2.5	0.48	1.08	0.075
4.9	0.89	0.12	-2.10
Analyte C (DCM-MeOH)			
MeOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.001	731	6.59
0.49	0.09	10.4	2.34
1.2	0.22	3.62	1.29
2.5	0.43	1.32	0.274
4.9	0.86	0.16	-1.84
Analyte D (DCM-MeOH)			
MeOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.03	39.0	3.66
0.49	0.06	14.8	2.69
1.2	0.34	1.91	0.649
2.5	0.61	0.645	-0.438
4.9	0.94	0.07	-2.71

Table 17. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *tert*-butyl acetate (1) modified with MeOH.

Analyte A (1-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.23	3.35	1.21
0.49	0.35	1.86	0.623
1.2	0.57	0.766	-0.266
2.5	0.67	0.494	-0.705
4.9	0.72	0.382	-0.963
Analyte B (1-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.35	1.87	0.627
0.49	0.40	1.52	0.422
1.2	0.54	0.863	-0.147
2.5	0.69	0.458	-0.780
4.9	0.80	0.255	-1.37
Analyte C (1-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.01	68.0	4.22
0.49	0.06	15.6	2.74
1.2	0.15	5.48	1.70
2.5	0.34	1.95	0.669
4.9	0.40	1.51	0.412
Analyte D (1-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.17	5.00	1.609
0.49	0.28	2.63	0.968
1.2	0.46	1.19	0.177
2.5	0.66	0.512	-0.669
4.9	0.71	0.413	-0.884

Table 18. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *sec*-butyl acetate (2) modified with MeOH.

Analyte A (2-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.33	2.069	0.727
0.49	0.41	1.46	0.383
1.2	0.51	0.961	-0.041
2.5	0.57	0.747	-0.291
4.9	0.64	0.579	-0.547
Analyte B (2-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.47	1.14	0.134
0.49	0.55	0.814	-0.206
1.2	0.57	0.765	-0.268
2.5	0.61	0.630	-0.463
4.9	0.65	0.539	-0.617
Analyte C (2-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.06	17.0	2.83
0.49	0.04	22.8	3.13
1.2	0.103	8.73	2.17
2.5	0.27	2.67	0.981
4.9	0.35	1.87	0.627
Analyte D (2-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.15	5.50	1.704
0.49	0.33	2.01	0.700
1.2	0.41	1.42	0.350
2.5	0.52	0.934	-0.069
4.9	0.60	0.667	-0.405

Table 19. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in ethyl isobutyrate (3) modified with MeOH.

Analyte A (3-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.18	4.52	1.51
0.49	0.31	2.23	0.804
1.2	0.47	1.12	0.114
2.5	0.51	0.962	-0.039
4.9	0.65	0.545	-0.607
Analyte B (3-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.33	2.00	0.693
0.49	0.35	1.89	0.639
1.2	0.49	1.03	0.029
2.5	0.54	0.847	-0.166
4.9	0.66	0.514	-0.665
Analyte C (3-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.01	87.0	4.47
0.49	0.05	17.3	2.85
1.2	0.13	6.89	1.93
2.5	0.26	2.84	1.04
4.9	0.38	1.64	0.493
Analyte D (3-MeOH)			
MeOH (mol/dm ³)	R _f	k	ln (k)
0	0.15	5.82	1.76
0.49	0.21	3.85	1.35
1.2	0.37	1.73	0.548
2.5	0.50	0.990	-0.011
4.9	0.60	0.663	-0.411

Table 20. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in methyl pivalate (4) modified with MeOH. R_f terms used in calculations for analyte C are the predicted terms calculated from linear regression (LR) analysis found in S2.4.

Analyte A (4-MeOH)			
MeOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.18	4.59	1.52
0.49	0.31	2.18	0.779
1.2	0.45	1.25	0.219
2.5	0.52	0.906	-0.098
4.9	0.66	0.515	-0.664
Analyte B (4-MeOH)			
MeOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.25	2.97	1.09
0.49	0.29	2.41	0.878
1.2	0.48	1.09	0.082
2.5	0.54	0.857	-0.155
4.9	0.73	0.378	-0.974
Analyte C (4-MeOH)			
MeOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.02	51.3	3.94
0.49	0.06	17.1	2.84
1.2	0.11	8.12	2.09
2.5	0.20	3.99	1.38
4.9	0.38	1.62	0.483
Analyte D (4-MeOH)			
MeOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.12	7.44	2.01
0.49	0.19	4.39	1.48
1.2	0.31	2.21	0.795
2.5	0.54	0.846	-0.167
4.9	0.65	0.552	-0.595

Table 21. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in DCM modified with 3:1 EtOAc-EtOH. R_f terms used in calculations for analytes A, B, and C are the predicted terms calculated from linear regression (LR) analysis found in S2.4.

Analyte A (DCM-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.17	4.92	1.59
1.1	0.27	2.75	1.01
2.8	0.41	1.42	0.356
5.6	0.66	0.53	-0.641
8.4	0.89	0.113	-2.18
Analyte B (DCM-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.21	3.74	1.32
1.1	0.31	2.19	0.782
2.8	0.47	1.14	0.128
5.6	0.73	0.379	-0.970
8.4	0.98	0.018	-4.01
Analyte C (DCM-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.13	6.51	1.87
1.1	0.20	4.09	1.41
2.8	0.29	2.43	0.889
5.6	0.45	1.22	0.202
8.4	0.61	0.645	-0.438
Analyte D (DCM-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.03	39.0	3.66
1.1	0.16	5.27	1.66
2.8	0.46	1.16	0.145
5.6	0.72	0.392	-0.937
8.4	0.83	0.210	-1.56

Table 22. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *tert*-butyl acetate (1) modified with 3:1 EtOAc-EtOH.

Analyte A (1-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.23	3.35	1.21
1.1	0.32	2.14	0.761
2.8	0.45	1.20	0.185
5.6	0.62	0.62	-0.472
8.4	0.79	0.26	-1.35
Analyte B (1-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.29	2.4	0.906
1.1	0.50	1.00	0
2.8	0.62	0.605	-0.503
5.6	0.73	0.369	-0.997
8.4	0.87	0.148	-1.91
Analyte C (1-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.01	68.0	4.22
1.1	0.06	15.1	2.72
2.8	0.10	9.38	2.24
5.6	0.30	2.38	0.865
8.4	0.39	1.56	0.443
Analyte D (1-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.17	5.00	1.609
1.1	0.36	1.81	0.593
2.8	0.46	1.18	0.167
5.6	0.68	0.467	-0.762
8.4	0.91	0.102	-2.29

Table 23. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in *sec*-butyl acetate (2) modified with 3:1 EtOAc-EtOH.

Analyte A (2-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.33	2.10	0.727
1.1	0.48	1.087	0.083
2.8	0.45	1.20	0.186
5.6	0.67	0.484	-0.727
8.4	0.74	0.358	-1.03
Analyte B (2-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.53	0.901	-0.104
1.1	0.64	0.565	-0.571
2.8	0.62	0.613	-0.490
5.6	0.82	0.223	-1.50
8.4	0.84	0.190	-1.66
Analyte C (2-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.06	17.0	2.83
1.1	0.10	8.60	2.15
2.8	0.17	5.00	1.61
5.6	0.40	1.47	0.386
8.4	0.55	0.829	-0.187
Analyte D (2-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.15	5.50	1.70
1.1	0.23	3.41	1.23
2.8	0.36	1.77	0.569
5.6	0.61	0.645	-0.439
8.4	0.82	0.218	-1.52

Table 24. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in ethyl isobutyrate (3) modified with 3:1 EtOAc-EtOH.

Analyte A (3-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.19	4.36	1.47
1.1	0.28	2.57	0.943
2.8	0.44	1.29	0.253
5.6	0.59	0.694	-0.365
8.4	0.69	0.442	-0.816
Analyte B (3-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.33	2.00	0.693
1.1	0.47	1.14	0.134
2.8	0.56	0.792	-0.234
5.6	0.70	0.427	-0.851
8.4	0.80	0.250	-1.39
Analyte C (3-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.01	87.0	4.47
1.1	0.08	12.3	2.51
2.8	0.13	7.00	1.95
5.6	0.31	2.19	0.785
8.4	0.44	1.27	0.242
Analyte D (3-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R _f	k	ln (k)
0	0.15	5.82	1.76
1.1	0.22	3.50	1.25
2.8	0.38	1.61	0.474
5.6	0.58	0.725	-0.322
8.4	0.81	0.242	-1.42

Table 25. Calculation of $\ln(k)$ terms for acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) run in methyl pivalate (4) modified with 3:1 EtOAc-EtOH. R_f terms used in calculations for analyte C are the predicted terms calculated from linear regression (LR) analysis found in S2.4.

Analyte A (4-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.18	4.59	1.52
1.1	0.30	2.38	0.865
2.8	0.41	1.43	0.358
5.6	0.61	0.627	-0.468
8.4	0.75	0.339	-1.08
Analyte B (4-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.25	2.97	1.09
1.1	0.43	1.33	0.28
2.8	0.50	1.01	0.014
5.6	0.67	0.483	-0.726
8.4	0.80	0.254	-1.37
Analyte C (4-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f (LR)	k	$\ln(k)$
0	0.0001	1020	6.93
1.1	0.06	14.6	2.68
2.8	0.16	5.29	1.67
5.6	0.32	2.16	0.768
8.4	0.47	1.11	0.101
Analyte D (4-3:1 EtOAc-EtOH)			
3:1 EtOAc-EtOH (mol/dm ³)	R_f	k	$\ln(k)$
0	0.12	7.44	2.01
1.1	0.24	3.15	1.15
2.8	0.39	1.53	0.428
5.6	0.63	0.588	-0.531
8.4	0.79	0.271	-1.30

S.26 Calculation of KBI Terms with Fitting

Table 26. Calculation of KBI terms for analytes acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) analytes in test solvents DCM, *tert*-butyl acetate (1), *sec*-butyl acetate (2), ethyl isobutyrate (3), and methyl pivalate (4), modified with MeOH. The ln(k) data from S2.5 was fit to a convenient function which is reported in the above table along with R² values and KBIs.

Analyte A (MeOH)			
Solvent	Equation	R ²	KBI term
DCM	$y = -0.0358x^3 + 0.2797x^2 - 1.2764x + 2.0698$	0.9999	1.28
1	$y = -0.0425x^3 + 0.4577x^2 - 1.6705x + 1.2501$	0.9954	1.67
2	$y = -0.0254x^3 + 0.253x^2 - 0.8885x + 0.7383$	0.9989	0.889
3	$y = -0.0831x^3 + 0.6989x^2 - 1.8555x + 1.5243$	0.9991	1.86
4	$y = -0.0681x^3 + 0.5893x^2 - 1.6884x + 1.5102$	0.9993	1.69
Analyte B (MeOH)			
Solvent	Equation	R ²	KBI term
DCM	$y = -0.0625x^3 + 0.4854x^2 - 1.8104x + 2.5386$	0.9997	1.81
1	$y = 0.0144x^3 - 0.0351x^2 - 0.5877x + 0.655$	0.9973	0.588
2	$y = -0.0196x^3 + 0.1754x^2 - 0.534x + 0.0986$	0.9631	0.534
3	$y = -0.0117x^3 + 0.1279x^2 - 0.634x + 0.7624$	0.964	0.634
4	$y = -0.0341x^3 + 0.3004x^2 - 1.084x + 1.1654$	0.9787	1.08
Analyte C (MeOH)			
Solvent	Equation	R ²	KBI term
DCM	$y = 0.4034x^2 - 3.4176x + 5.3763$	0.8823	3.42
1	$y = 0.2823x^2 - 2.1118x + 3.9867$	0.9828	2.11
2	$y = 0.1074x^2 - 1.0597x + 3.1909$	0.9196	1.06
3	$y = 0.1872x^2 - 1.5637x + 3.6658$	0.9951	1.56
4	$y = 0.1506x^2 - 1.3923x + 3.7207$	0.9779	1.39
Analyte D (MeOH)			
Solvent	Equation	R ²	KBI term
DCM	$y = -0.0882x^3 + 0.8253x^2 - 3.2407x + 3.7959$	0.9933	3.24
1	$y = -0.0058x^3 + 0.212x^2 - 1.4112x + 1.611$	1	1.41
2	$y = -0.0743x^3 + 0.6562x^2 - 1.8399x + 1.6295$	0.9795	1.84
3	$y = -0.0147x^3 + 0.2277x^2 - 1.2146x + 1.8016$	0.9951	1.21
4	$y = 0.0146x^3 + 0.0335x^2 - 1.0478x + 2.0006$	0.9999	1.05

Table 27. Calculation of KBI terms for analytes acetylsalicylic acid (A), ketoprofen (B), caffeine (C), and acetaminophen (D) analytes in test solvents DCM, *tert*-butyl acetate (1), *sec*-butyl acetate (2), ethyl isobutyrate (3), and methyl pivalate (4), modified with 3:1 EtOAc-EtOH. The $\ln(k)$ data from S2.5 was fit to a convenient function which is reported in the above table along with R^2 values and KBIs.

Analyte A (3:1 EtOAc-EtOH)			
Solvent	Equation	R^2	KBI term
DCM	$y = -0.006x^3 + 0.066x^2 - 0.5807x + 1.5924$	1	0.581
1	$y = -0.0039x^3 + 0.0545x^2 - 0.4852x + 1.2193$	0.9998	0.485
2	$y = 0.0011x^3 - 0.0061x^2 - 0.2259x + 0.6142$	0.9285	0.226
3	$y = -0.0026x^3 + 0.0572x^2 - 0.5711x + 1.4842$	0.9995	0.571
4	$y = -0.0027x^3 + 0.0516x^2 - 0.5509x + 1.4936$	0.9976	0.551
Analyte B (3:1 EtOAc-EtOH)			
Solvent	Equation	R^2	KBI term
DCM	$y = -0.0146x^3 + 0.1239x^2 - 0.6524x + 1.3358$	0.9998	0.652
1	$y = -0.0119x^3 + 0.1659x^2 - 0.8859x + 0.875$	0.9975	0.886
2	$y = 0.0056x^3 - 0.0623x^2 - 0.044x - 0.2059$	0.9359	0.044
3	$y = -0.0034x^3 + 0.0551x^2 - 0.4695x + 0.6641$	0.9964	0.469
4	$y = -0.0056x^3 + 0.0847x^2 - 0.6011x + 1.0202$	0.9854	0.601
Analyte C (3:1 EtOAc-EtOH)			
Solvent	Equation	R^2	KBI term
DCM	$y = 0.011x^2 - 0.3621x + 1.8381$	0.9984	0.362
1	$y = 0.0503x^2 - 0.8446x + 4.0049$	0.9724	0.845
2	$y = 0.0209x^2 - 0.5363x + 2.8148$	0.9947	0.536
3	$y = 0.064x^2 - 0.9864x + 4.1046$	0.8532	0.986
4	$y = 0.1486x^2 - 1.9059x + 5.9605$	0.8792	1.91
Analyte D (3:1 EtOAc-EtOH)			
Solvent	Equation	R^2	KBI term
DCM	$y = -0.0172x^3 + 0.3086x^2 - 2.0002x + 3.6266$	0.9991	2
1	$y = -0.0121x^3 + 0.1501x^2 - 0.864x + 1.5444$	0.9945	0.864
2	$y = -0.0015x^3 + 0.0206x^2 - 0.4513x + 1.705$	1	0.451
3	$y = -0.0046x^3 + 0.0645x^2 - 0.5955x + 1.7856$	0.9989	0.595
4	$y = -0.0048x^3 + 0.0865x^2 - 0.7782x + 1.9798$	0.9988	0.778

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Appendix A

Here we provide the derivations of key relationships that have been used in Section 2.4. Following the standard chromatography theory, we consider the two phases, the mobile phase ($\alpha = M$) and the stationary phase ($\alpha = S$) under instantaneous equilibrium. The molecular species present are analyte ($i = a$) solvent ($i = s$), and two eluents ($i = e_1$ and e_2). Our presentation here is restricted up to two eluent species, yet it is possible to extend this theory to incorporate more solvent species. Under constant pressure and temperature, the solvation free energy an analyte, $\mu_a^{(\alpha)*}$, in phase α can be expressed as^{1,2}

$$-d\mu_a^{(\alpha)*} = \sum_{i=s,e_1,e_2} c_i G_{ai}^{(\alpha)} d\mu_i \quad (\text{A.1})$$

where μ_i is the chemical potential of the species i , $G_{ai}^{(\alpha)}$ is the Kirkwood-Buff integral (KBI) between analyte and species i , and c_i is the bulk number density of the species i which has been assumed to be the same for both phases; following the standard chromatography theory, μ_i is the same for both phases due to instantaneous equilibrium³ and the presence of the stationary objects affects the distribution of analytes only. The chemical potentials in eq A.1 are linked via the Gibbs-Duhem equation away from the analyte under constant T and P .^{3,4}

$$0 = \sum_{i=s,e_1,e_2} c_i d\mu_i \quad (\text{A.2})$$

Eliminating $d\mu_s$ via eqs A.1 and A.2 yields

$$-d\mu_a^{(\alpha)*} = \sum_{i=e_1,e_2} c_i \left(G_{ai}^{(\alpha)} - G_{as}^{(\alpha)} \right) d\mu_i \quad (\text{A.3})$$

Differentiating eq (A.3) at the $c_{e_1} \rightarrow 0$ limit in the presence of a dilute e_2 yields

$$\begin{aligned} & - \left(\frac{\partial \mu_a^{(\alpha)*}}{\partial c_{e_1}} \right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} \\ &= c_{e_1} \left(G_{ae_1}^{(\alpha)} - G_{as}^{(\alpha)} \right) \left(\frac{\partial \mu_{e_1}}{\partial c_{e_1}} \right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} + c_{e_2} \left(G_{ae_2}^{(\alpha)} - G_{as}^{(\alpha)} \right) \left(\frac{\partial \mu_{e_2}}{\partial c_{e_1}} \right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} \\ &\simeq G_{ae_1}^{(\alpha)} - G_{as}^{(\alpha)} \quad (\text{A.4a}) \end{aligned}$$

For the final step of eq (A.4), we have used: (i) From Raoult's Law, $\mu_{e_1} = \mu_{e_1}^\infty + RT \ln x_{e_1}$, where $\mu_{e_1}^\infty$ is the dilute ideal standard state and x_{e_1} is the mole fraction of e_1 . Since $x_{e_1} = \frac{c_{e_1}}{c_{e_1} + c_{e_2} + c_s + c_a} \simeq \frac{c_{e_1}}{c_s^0}$ with the bulk solvent concentration c_s^0 , because e_1 , e_2 and a are all dilute, and c_s^0 is a constant when carrying out differentiation; (ii) From Raoult's Law, $\mu_{e_2} = \mu_{e_2}^\infty + RT \ln x_{e_2}$, where $\mu_{e_2}^\infty$ is the dilute ideal standard state and x_{e_2} is the mole fraction of e_2 . Since $x_{e_2} = \frac{c_{e_2}}{c_{e_1} + c_{e_2} + c_s + c_a} \simeq \frac{c_{e_2}}{c_s^0}$, x_{e_2} is not affected by the introduction of dilute c_{e_1} , leading to $\left(\frac{\partial \mu_{e_2}}{\partial c_{e_1}} \right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} \simeq 0$. Likewise,

$$-\left(\frac{\partial \mu_a^{(\alpha)*}}{\partial c_{e_2}}\right)_{T,P,c_{e_1};c_{e_2} \rightarrow 0} \simeq G_{ae_2}^{(\alpha)} - G_{as}^{(\alpha)} \quad (\text{A.4b})$$

can also be derived.

Taking the difference between the mobile and stationary phases, eqs A.4a and A.4b can be rewritten as

$$-\left(\frac{\partial \Delta \mu_a^*}{\partial c_{e_1}}\right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} \simeq \Delta G_{ae_1} - \Delta G_{as} \quad (\text{A.5a})$$

$$-\left(\frac{\partial \Delta \mu_a^*}{\partial c_{e_2}}\right)_{T,P,c_{e_1};c_{e_2} \rightarrow 0} \simeq \Delta G_{ae_2} - \Delta G_{as} \quad (\text{A.5b})$$

where the KBI difference has been introduced via eq 5 (in the direction of stationary \rightarrow mobile). Using $\Delta \mu_a^* = RT \ln K$ (noting how K is defined in eq 1 for the sign), in combination with eq 2 (noting that the c_{e_1} and c_{e_2} dependence of k comes from K), we obtain from eqs A.5a and A.5b,

$$-\left(\frac{\partial \ln k}{\partial c_{e_1}}\right)_{T,P,c_{e_2};c_{e_1} \rightarrow 0} \simeq \Delta G_{ae_1} - \Delta G_{as} \quad (\text{A.6a})$$

$$-\left(\frac{\partial \ln k}{\partial c_{e_2}}\right)_{T,P,c_{e_1};c_{e_2} \rightarrow 0} \simeq \Delta G_{ae_2} - \Delta G_{as} \quad (\text{A.6b})$$

When there is only one solvent species, eq A.6 automatically reduces to eq 8 in the main text.

Now we show that the effects of eluents are additive at the dilute eluent limit. (Note that the additivity may break down when e_1 and e_2 are concentrated). It is customary in experimental practice to use a prepared mixture that contains the fixed fractions of e_1 and e_2 . In this context, increasing the “eluent” concentration c_e means

$$-\left(\frac{\partial \ln k}{\partial c_e}\right)_{T,P} = -\left(\frac{\partial \ln k}{\partial c_{e_1}}\right)_{T,P} \left(\frac{\partial c_{e_1}}{\partial c_e}\right)_{T,P} - \left(\frac{\partial \ln k}{\partial c_{e_2}}\right)_{T,P} \left(\frac{\partial c_{e_2}}{\partial c_e}\right)_{T,P} \quad (\text{A.7})$$

In the dilute region, $\left(\frac{\partial c_e}{\partial c_{e_1}}\right)_{T,P} = \left(\frac{\partial c_{e_1}}{\partial c_{e_1}}\right)_{T,P} + \left(\frac{\partial c_{e_2}}{\partial c_{e_1}}\right)_{T,P} = 1$ because the presence of e_1 does not affect c_{e_2} . Likewise, $\left(\frac{\partial c_e}{\partial c_{e_2}}\right)_{T,P} = 1$. Consequently, we arrive at

$$-\left(\frac{\partial \ln k}{\partial c_e}\right)_{T,P} = -\left(\frac{\partial \ln k}{\partial c_{e_1}}\right)_{T,P} - \left(\frac{\partial \ln k}{\partial c_{e_2}}\right)_{T,P} \quad (\text{A.8})$$

Which means that the eluent gradients are additive at dilution.

Appendix A References

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