Supplementary information: Free-energy decomposition of salt effects on the solubilities of small molecules and the role of excluded-volume effects

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	Solute	Ca	lc. $\Delta \mu$ [kcal/mo	l] Exp. $\Delta \mu$ [kcal/mol]			
		Neat water	2.18 M NaCl	2.18 M KI	Neat water	2.18 M NaCl	2.18 M KI
	methane	2.54	2.58	2.32	2.00	2.37	2.67
	ethane	2.60	2.77	2.36	1.83	2.31	2.73
	propane	2.80	2.94	2.35	2.00	2.54	2.96
	n-butane	3.06	3.40	2.77	2.10	2.72	3.20
	n-pentane	3.37	3.67	2.77	2.30	2.98	-
	n-hexane	3.77	4.02	3.33	2.48	3.30	-
	methanol	-4.55	-4.31	-4.51	-5.10	-	-
	ethanol	-4.58	-4.31	-4.61	-5.00	-	-
	n-propanol	-4.27	-3.90	-4.33	-4.85	-	-
	n-butanol	-4.05	-3.68	-4.18	-4.72	-	-
	n-pentanol	-3.86	-3.38	-3.99	-4.57	-	-
	n-hexanol	-3.66	-3.21	-3.81	-4.40	-3.71	_

S1 Calculated and experimental solvation free energies $\Delta \mu$

Solute	Calc. $\Delta \mu \; [\text{kcal/mol}]$			Exp. $\Delta \mu [\text{kcal/mol}]$		
	Neat water	$2.18 \mathrm{~M}$ NaCl	$2.18 \mathrm{~M~KI}$	Neat water	$2.18 \mathrm{~M}$ NaCl	$2.18 \mathrm{~M~KI}$
methane	2.55	2.65	2.42	2.00	2.37	2.67
ethane	2.84	3.05	2.80	1.83	2.31	2.73
propane	3.24	3.51	3.18	2.00	2.54	2.96
n-butane	3.68	4.03	3.56	2.10	2.72	3.20
n-pentane	4.14	4.50	3.92	2.30	2.98	-
n-hexane	4.66	5.05	4.49	2.48	3.30	-
methanol	-3.33	-3.08	-3.27	-5.10	-	-
ethanol	-3.12	-2.81	-3.06	-5.00	-	-
n-propanol	-2.62	-2.25	-2.58	-4.85	-	-
n-butanol	-2.23	-1.80	-2.19	-4.72	-	-
n-pentanol	-1.93	-1.43	-1.89	-4.57	-	-
n-hexanol	-1.51	-0.93	-1.49	-4.40	-3.71	-

Table S1: Calculated and experimental solvation free energies for the solutes treated in this work in neat water and 2.18 M NaCl and KI. The calculated solvation free energies in the presence of 2.18 M NaCl and KI were obtained by linear extrapolation of the regression (cf. Figs. 2 and GSH2) to the Setschenow equation (eqn 7). The experimental solvation free energies in neat water, NaCl, and KI solutions were taken from Mobley and Guthrie¹, Xie *et al.*², and Morrison and Billett³, respectively. The values in the salt solutions were determined using experimental Setschenow coefficients and the hydration free energies for the Sage/OPC/Sengupta&Merz (SOS) force field and the bottom table for GAFF/SPCE/Heyda (GSH).

For the simulations conducted with the GSH force field (Table S1, bottom), less accurate hydration free energies were obtained. This is considered to be due to the choice of force field since it has been observed that the performance of the energy-representation method is rather insensitive to the force field employed.^{4,5} It is found for the SOS force field that the *salting-out* ability is the strongest for K^+ , rather than Na⁺, for the majority of solutes, while for GSH, Na⁺ is marginally the cation to *salt-out* the most. With the GSH force field, furthermore, KI acts in agreement with the experiment³ to weakly *salt-out* small *n*-alkanes, rather than to (weakly) *salt-in* as observed with the SOS force field.

S2 Convergence of the solvation free energy

The solvent species' contributions to the cumulative solvation free energy and averaged solute-solvent interaction energy are shown in Fig. S1 as functions of the MD time from a 100 ns simulation run of methanol in ~0.5 M NaCl solution. While the total and chloride contributions converge fast within 10 ns, the water and sodium contributions are slower in convergence. The standard errors are close between the sodium and water contributions, while these two vary in opposite directions. The rate of convergence corresponds to the time dependence of the RDF of the oxygen atom of the hydroxyl group in methanol with Na⁺ and Cl⁻ depicted in Fig. S2. At the time window of 20 ns, the RDF varies more slowly with the cation than with the anion. The interaction between the hydroxyl group and cation is observed to be a slow mode of motion and limits the convergence of the cation contribution.



Figure S1: Cumulative solvation free energy (left) and averaged solute-solvent interaction energy (right) of methanol in ~0.5 M NaCl as functions of the simulation time of the solution system. The top and bottom figures are for the Sage/OPC/Sengupta&Merz (SOS) and GAFF/SPCE/Heyda (GSH) force fields, respectively. The total values and the sodium, chloride, and water contributions are shown by the colours indicated by the legend. The standard errors are visualised as the shaded area obtained from block averaging with each having a length of 1 ns.



Figure S2: Radial distribution function (RDF) in ~0.5 M NaCl solution of methanol oxygen with Na⁺ (left) and Cl⁻ (right) for 5 time windows of 20 ns length as distinguished by the legend. The top and bottom figures are for the Sage/OPC/Sengupta&Merz (SOS) and GAFF/SPCE/Heyda (GSH) force fields, respectively. The dashed lines refer to the RDF values at the first peaks.

S3 Correlations of the Setschenow coefficient with the changes in the direct interaction energies of the solute with the anion and water upon addition of the salt



Figure S3: Correlation between the total Setschenow coefficient and the solute-anion interaction energy. Data are shown for all the combinations of cations (Na⁺, K⁺, and Rb⁺) and anions (F⁻, Cl⁻, and I⁻). The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Rb⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively. The Sage/OPC/Sengupta&Merz force field was used here.



Figure S4: Correlation between the total Setschenow coefficient and the change in the solute-water interaction energy upon addition of the salt. Data are shown for all the combinations of cations (Na⁺, K⁺, and Rb⁺) and anions (F⁻, Cl⁻, and I⁻). The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Rb⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively. The Sage/OPC/Sengupta&Merz force field was used here.

S4 Decomposition of the partial contributions from the direct solute-solvent interaction and associated solvent reorganisation to the Setschenow coefficient



Figure S5: Species decomposition of the partial contributions from the direct solute-solvent interaction and associated solvent reorganisation to the Setschenow coefficient (*cf.* eqn (12)) for *n*-alcohols (top) and *n*-alkanes (bottom) in potassium salt solutions, with potassium as the cation and F^- (blue), Cl^- (orange), and I^- (green) as the anions. The error bars shown report the 95% confidence interval determined by non-parametric bootstrapping⁶ ($N = 10^5$) assuming the individual solvent contributions to vary linearly. The Sage/OPC/Sengupta&Merz force field was used here.

Results of GAFF/SPCE/Heyda (GSH) Force Field

The following section presents the results obtained from the simulations using the GAFF⁷, SPC/E^{8,9}, and Heyda¹⁰ force field.¹¹ The captions are labelled such that Figures GSH2-10 corresponds to Figs. 2-10 in the main text, while GSH11-13 corresponds to Figs. S3-5 in ESI. With the GSH force field, Cs^+ was adopted instead of Rb⁺ due to the availability of the parameters..





Figure GSH2: Solvation free energies, $\Delta \mu$, of *n*-alcohols (top) and *n*-alkanes (bottom) as functions of potassium salt concentration, with the corresponding anions F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The lines are the best fits using the common value in neat water (zero concentration of the salt) for each solute.

Setschenow coefficients, k_s , for *n*-hexanol and *n*-hexane



Figure GSH3: Setschenow coefficients, k_s , for *n*-hexanol (left) and *n*-hexane (right) for all combinations of the cations: Na⁺, K⁺, and Cs⁺ and anions: F⁻, Cl⁻, and I⁻. k_s are visualised as points, and the planes connecting adjacent points have been added for guidance.



Solvent species decomposition of the Setschenow coefficient, k_s

Figure GSH4: Setschenow coefficient, k_s , and the contributions from the solvent species, namely cations, anions, and water, for *n*-alcohols (top) and *n*-alkanes (bottom) with potassium as the cation and F^- (blue), Cl⁻ (orange), and I⁻ (green) as the anions. The cation, anion, and water contributions correspond to the first, second, and third terms of eqn (9). The self-energy correction was found not to vary with the salt concentration. The error bars shown report the 95% confidence interval as determined by non-parametric bootstrapping⁶ ($N = 10^5$) assuming the individual solvent contributions to vary linearly.



Solvent species decomposition of the direct interaction energy between the solute and solvent

Figure GSH5: Species decomposition of the contributions to the Setschenow coefficient from the direct interaction energies between the solute and solvent for *n*-alcohols (top) and *n*-alkanes (bottom), with potassium as the cation and F^- (blue), Cl^- (orange), and I^- (green) as the anions. The error bars shown report the 95% confidence interval determined by non-parametric bootstrapping⁶ ($N = 10^5$) assuming the individual solvent contributions to vary linearly.

Radial distribution functions of n-hexane and solvent



Figure GSH6: Radial distribution functions (RDFs) in the ~ 1 M salt solutions of the carbon of *n*-hexane with potassium as the cation and F⁻ (blue), Cl⁻ (orange), and I⁻ (green) as the anions. The distributions of water oxygen are also shown (black). The water RDF is insensitive to the choice of the salt, and its differences among the salt species are not appreciable within the resolution of the figure. The RDFs for the 6 carbon atoms are averaged in this figure.



Correlation between the total Setschenow coefficient and the excluded-volume component

Figure GSH7: Correlation between the total Setschenow coefficient and the excluded-volume component obtained from integration over the high-energy domain. Data are shown for all the combinations of cations $(Na^+, K^+, and Cs^+)$ and anions $(F^-, Cl^-, and I^-)$. The data symbols are shaped depending on the cation species: Na^+ (triangle), K^+ (circle), and Cs^+ (inverse triangle) and coloured depending on the anion species: F^- (blue), Cl^- (orange), and I^- (green). The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively.



Species decomposition of the excluded-volume component in the Setschenow coefficient

Figure GSH8: Species decomposition of the excluded-volume component in the Setschenow coefficient for n-alcohols (top) and n-alkanes (bottom) with potassium as the cation and F^- (blue), Cl^- (orange), and I^- (green) as the anions. The error bars shown report the 95% confidence interval determined by non-parametric bootstrapping⁶ ($N = 10^5$) assuming the individual solvent contributions to vary linearly.

Correlation between the total excluded-volume component in the Setschenow coefficient and the water contribution



Figure GSH9: Correlation between the total excluded-volume component in the Setschenow coefficient and the water contribution. Data are shown for all the combinations of cations (Na⁺, K⁺, and Cs⁺) and anions (F⁻, Cl⁻, and I⁻). The solid lines connect the data with the same length of the alkyl chain (N_{carbon}) and varied species of salts. The dashed lines are for fixed salts with varied solutes. The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Cs⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively.

Correlation between the derivative of the water molarity with respect to the salt concentration and the water contribution to the excluded-volume component in the Setschenow coefficient



Figure GSH10: Correlation between the derivative of the water molarity with respect to the salt concentration and the water contribution to the excluded-volume component in the Setschenow coefficient. Data are shown for all the combinations of cations (Na⁺, K⁺, and Cs⁺) and anions (F⁻, Cl⁻, and I⁻). The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Cs⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The solute refers to ethanol and ethane with $N_{\text{carbon}} = 2$, to *n*-butanol and *n*-butane with $N_{\text{carbon}} = 4$, and to *n*-hexanol and *n*-hexane with $N_{\text{carbon}} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively.

Correlations of the Setschenow coefficient with the changes in the direct interaction energies of the solute with the anion and water upon addition of the salt



Figure GSH11: Correlation between the total Setschenow coefficient and the solute-anion interaction energy. Data are shown for all the combinations of cations (Na⁺, K⁺, and Cs⁺) and anions (F⁻, Cl⁻, and I⁻). The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Cs⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively.



Figure GSH12: Correlation between the total Setschenow coefficient and the change in the solute-water interaction energy upon addition of the salt. Data are shown for all the combinations of cations (Na⁺, K⁺, and Cs⁺) and anions (F⁻, Cl⁻, and I⁻). The data symbols are shaped depending on the cation species: Na⁺ (triangle), K⁺ (circle), and Cs⁺ (inverse triangle) and coloured depending on the anion species: F⁻ (blue), Cl⁻ (orange), and I⁻ (green). The solute refers to ethanol and ethane with $N_{carbon} = 2$, to *n*-butanol and *n*-butane with $N_{carbon} = 4$, and to *n*-hexanol and *n*-hexane with $N_{carbon} = 6$. The symbols are filled and open for the *n*-alcohols and *n*-alkanes, respectively.

Decomposition of the partial contributions from the direct solute-solvent interaction and associated solvent reorganisation to the Setschenow coefficient



Figure GSH13: Species decomposition of the partial contributions from the direct solute-solvent interaction and associated solvent reorganisation to the Setschenow coefficient (*cf.* eqn (12)) for *n*-alcohols (top) and *n*-alkanes (bottom) in potassium salt solutions, with potassium as the cation and F^- (blue), Cl^- (orange), and I^- (green) as the anions. The error bars shown report the 95% confidence interval determined by nonparametric bootstrapping⁶ ($N = 10^5$) assuming the individual solvent contributions to vary linearly.

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