Supporting Information

Efficient Combination of Environment Change and Alchemical Perturbation Within the Enveloping Distribution Sampling (EDS) Scheme: Twin-System EDS and Application to the Determination of Octanol-Water Partition Coefficients

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(Date: January 16, 2013)

Table S1: Relevant non-bonded interaction parameters[a] used for the $-CH_2-O-H$ headgroup in alcohols (A), the CH_x groups in aliphatic hydrocarbon chains (B) and the ether function in 1,2-dimethoxyethane (C), in the 54A7[1,2] and 53A6$_{OXY}$[3]/53A6$_{OXY+D}$[4] versions of the GROMOS force field. For each atom type, denoted by the atom type code IAC, they include the Lennard-Jones (LJ) dispersion parameter, $C_6^{1/2}$, repulsion parameter for non-hydrogen-bonding interactions, $C_{12,I}^{1/2}$, and repulsion parameter for hydrogen-bonding interactions, $C_{12,II}^{1/2}$, as well as the atomic partial charges q. The funtional forms of the corresponding terms and the applied (geometric-mean) combination rule for LJ parameters are described in Refs 5,6. For alcohols, 54A7 and 53A6$_{OXY}$ differ in the LJ parameters and charges for the atom type OA and in the charges for the atom types H and CH2, connected to OA. For alkanes the two versions are identical. For ethers, 54A7 and 53A6$_{OXY}$ differ in the LJ parameters and charges for the atom type OE and in the charges for the atom types CH3 and CH2 connected to OE. 53A6$_{OXY}$ and 53A6$_{OXY+D}$ differ only in the torsional-energy parameters for the dihedral types OCCO and CCOC, which are reported in Figure S1.

			54A7				53A6$_{OXY(+D)}$			
				$C_{12}^{1/2}$				$C_{12}^{1/2}$		
group	IAC	type	$C_6^{1/2}$	I	II	q	$C_6^{1/2}$	I	II	q
	21	H	–	–	–	0.408	–	–	–	0.410
A	3	OA	0.04756	1.100	1.227	−0.674	0.04500	1.150	1.350	−0.700
	15	CH2	0.08642	5.828	–	0.266	0.08642	5.828	–	0.290
B	16	CH3	0.09805	5.162	–	0.000	0.09805	5.162	–	0.000
	15	CH2	0.08642	5.828	–	0.000	0.08642	5.828	–	0.000
	16	CH3	0.09805	5.162	–	0.162	0.09805	5.162	–	0.290
C	4	OE	0.04756	1.100	1.227	−0.324	0.04123	1.5297	1.5297	−0.580
	15	CH2	0.08642	5.828	–	0.162	0.08642	5.828	–	0.290

[a]The units of $C_6^{1/2}$, $C_{12}^{1/2}$ and q are $(\mathrm{kJ\,mol^{-1}nm^6})^{1/2}$, $(10^{-3}[\mathrm{kJ\,mol^{-1}nm^{12}}]^{1/2})$ and (e).

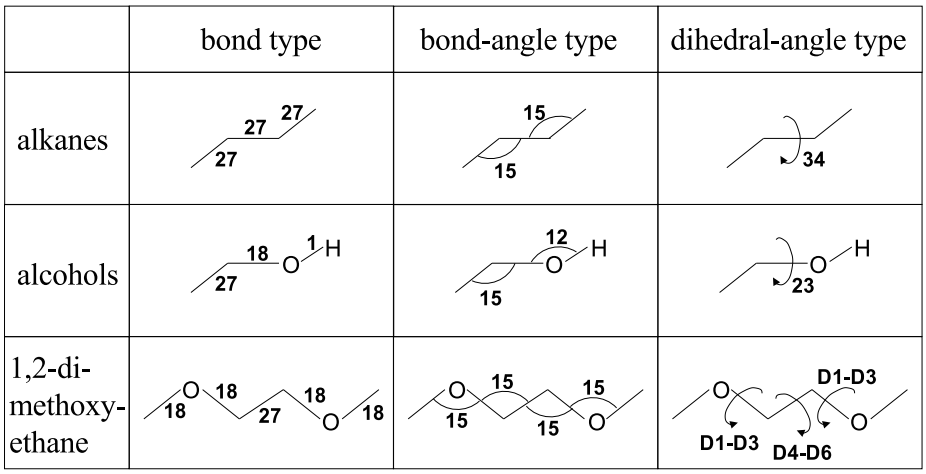

Figure S1: Covalent interaction types (bond stretching, bond-angle bending and dihedral-angle torsion) used in the present work. The numbers refer to the type codes of the 54A7 parameter set,[1,2] except for the dihedral-angle types of 1,2-dimethoxyethane which are defined in the $53A6_{OXY+D}$ parameter set (see Table IV in Ref. 4).

Table S2: EDS reference-state parameters s and E_B^R (kJ mol^{-1}) used in the twin-system EDS production simulations to obtain free enthalpy differences between hexane$^{a}_{(+D)}$ and compounds X in dry octanol or wet octanol and water. E_A^R was fixed to zero in all cases.

	54A7				$53A6_{OXY(+D)}$	
	dry octanol		wet octanol		wet octanol	
Compound X	s	E_B^R	s	E_B^R	s	E_B^R
butane	0.25	7.0	0.25	8.0	0.25	8.0
pentane	0.40	3.0	0.40	3.0	0.40	2.0
heptane	0.60	−3.0	0.60	−3.0	0.60	−4.0
octane	0.25	−7.0	0.25	−7.0	0.25	−7.0
hexanol	0.08	11.0	0.085	11.0	0.085	14.0
1,2-dimethoxy-ethane[b]	–	–	–	–	0.128	26.6

[a] the +D version applies only for 1,2-dimethoxyethane.

[b] for this compound an additional calculation considering an octanol-water mixture with a water mole fraction of 0.27 (experimental saturation concentration) instead of 0.16 was carried out using EDS parameters of $s = 0.128$ and $E_B^R = 26.0\,\mathrm{kJ\,mol^{-1}}$.

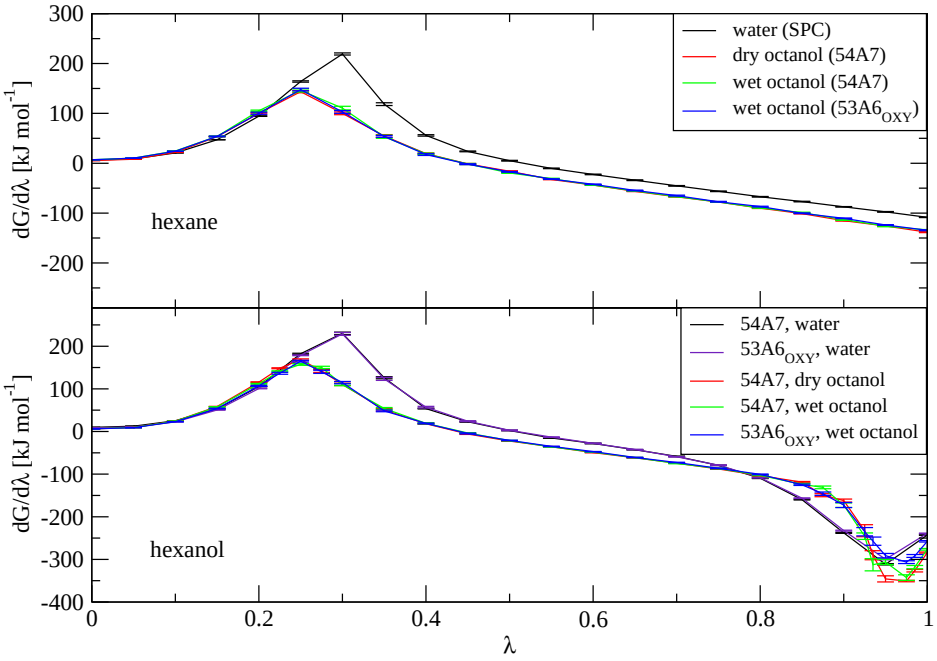

Figure S2: Average of the derivative of the Hamiltonian with respect to the coupling parameter λ as a function of λ for the process of gradually activating the solute-solvent interactions from no interactions at $\lambda = 0$ to full interactions at $\lambda = 1$. The upper panel summarizes the results obtained for hexane in different solvents, the lower panel summarizes the results obtained for hexanol.

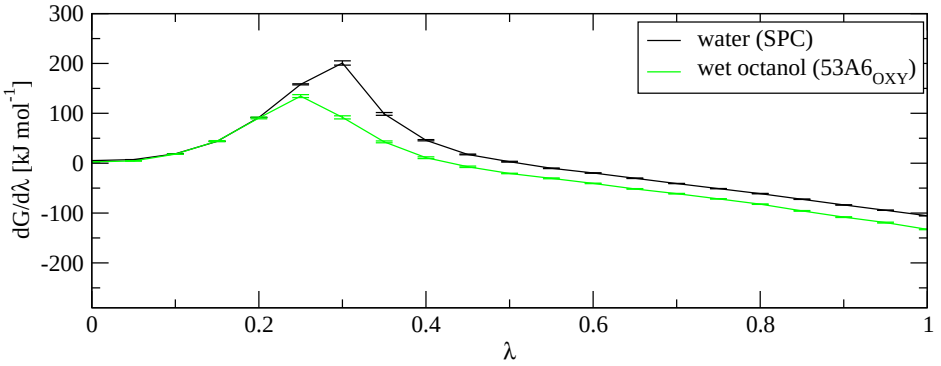

Figure S3: Average of the derivative of the Hamiltonian with respect to the coupling parameter λ as a function of λ for the process of gradually activating the solute-solvent interactions of hexane with modified torsional-energy parameters[4] from no interactions at $\lambda = 0$ to full interactions at $\lambda = 1$. The solvents employed were SPC water and wet octanol.

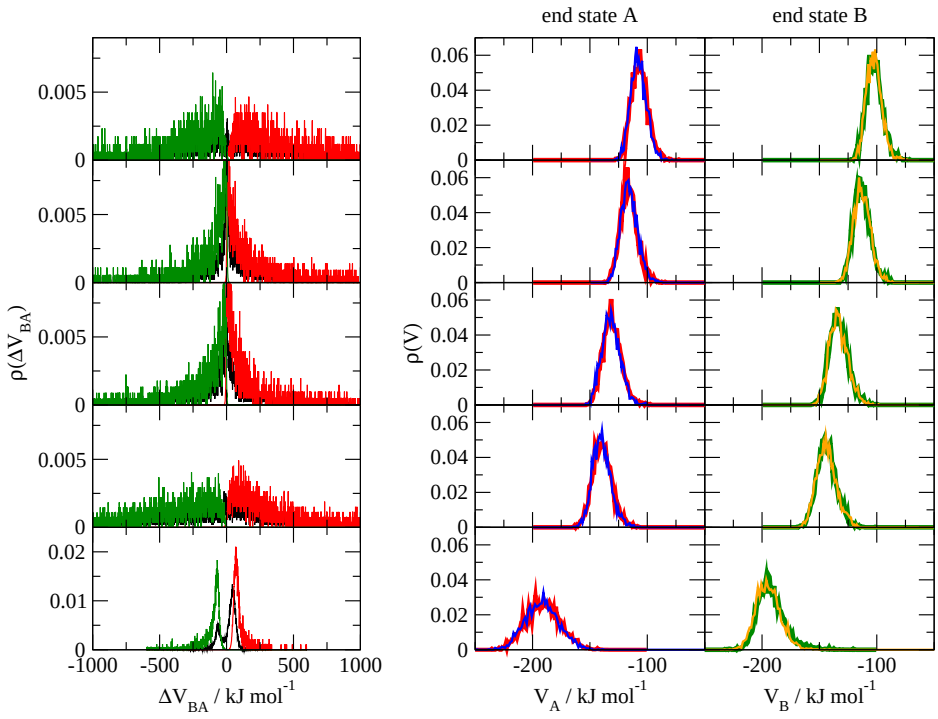

Figure S4: Left: Energy difference distributions for the reference state, $\rho_{\mathrm{R}}(\Delta V_{\mathrm{BA}})$ (black), and the two end states, $\tilde{\rho}_{\mathrm{A}}(\Delta V_{\mathrm{BA}})$ (red), $\tilde{\rho}_{\mathrm{B}}(\Delta V_{\mathrm{BA}})$ (green), as obtained from twin-system EDS simulations. State B represents the combined Hamiltonians of solute X solvated in dry octanol (X = butane, pentane, heptane, octane, hexanol; from top to bottom) and solute M solvated in water (M = hexane). State A represents the combined Hamiltonians of solute X solvated in water and solute M solvated in dry octanol. The simulations were performed with the 54A7[1,2] force field. The energy difference distributions of the end states were determined by reweighting. Right: Nonbonded solute-solute plus solute-solvent energy distributions of the EDS end states obtained *via* reweighting from EDS reference-state simulations ($\tilde{\rho}_{\mathrm{A}}(V_{\mathrm{A}})$ and $\tilde{\rho}_{\mathrm{B}}(V_{\mathrm{B}})$, red and green) and from independent MD simulations of the end states ($\rho_{\mathrm{A}}(V_{\mathrm{A}})$ and $\rho_{\mathrm{B}}(V_{\mathrm{B}})$, blue and orange).

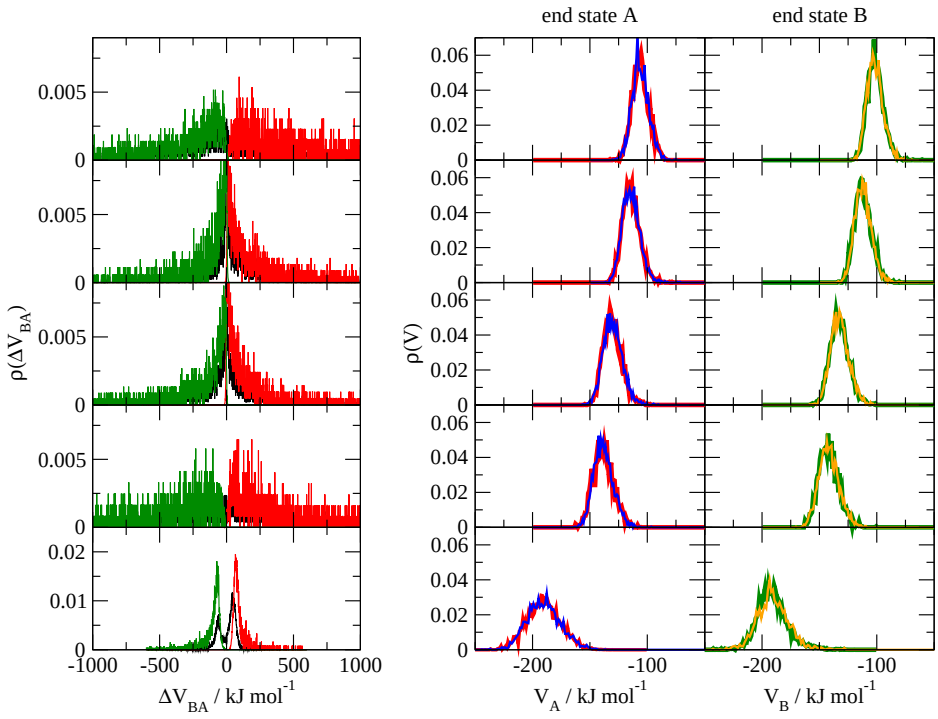

Figure S5: Energy difference distributions for the reference state, $\rho_{\mathrm{R}}(\Delta V_{\mathrm{BA}})$ (black), and the two end states, $\tilde{\rho}_{\mathrm{A}}(\Delta V_{\mathrm{BA}})$ (red), $\tilde{\rho}_{\mathrm{B}}(\Delta V_{\mathrm{BA}})$ (green), as obtained from twin-system EDS simulations. State B represents the combined Hamiltonians of solute X solvated in wet octanol (X = butane, pentane, heptane, octane, hexanol; from top to bottom) and solute M solvated in water (M = hexane). State A represents the combined Hamiltonians of solute X solvated in water and solute M solvated in wet octanol. The simulations were performed with the 54A7[1,2] force field. The energy difference distributions of the end states were determined by reweighting. Right: Nonbonded solute-solute plus solute-solvent energy distributions of the EDS end states obtained *via* reweighting from EDS reference-state simulations ($\tilde{\rho}_{\mathrm{A}}(V_{\mathrm{A}})$ and $\tilde{\rho}_{\mathrm{B}}(V_{\mathrm{B}})$, red and green) and from independent MD simulations of the end states ($\rho_{\mathrm{A}}(V_{\mathrm{A}})$ and $\rho_{\mathrm{B}}(V_{\mathrm{B}})$, blue and orange).

References

[1] D. Poger, W. F. van Gunsteren, A. E. Mark, A new force field for simulating phosphatidylcholine bilayers, *J. Comput. Chem.* **2010**, 31, 1117–1125.

[2] N. Schmid, A. Eichenberger, A. Choutko, S. Riniker, M. Winger, A. E. Mark, W. F. van Gunsteren, Definition and testing of the GROMOS force-field versions: 54A7 and 54B7, *Eur. Biophys. J.* **2011**, 40, 843–856.

[3] B. A. C. Horta, P. F. J. Fuchs, W. F. van Gunsteren, P. H. Hünenberger, New interaction parameters for oxygen compounds in the GROMOS force field: Improved pure-liquid and solvation properties for alcohols, ethers, aldehydes, ketones, carboxylic acids, and esters, *J. Chem. Theory Comput.* **2011**, 7, 1016–1031.

[4] P. F. J. Fuchs, H. S. Hansen, P. H. Hünenberger, B. A. C. Horta, A GROMOS parameter set for vicinal diether functions: Properties of polyethyleneoxide and polyethyleneglycol, *J. Chem. Theory Comput.* **2012**, 8, 3943–3963.

[5] http://www.gromos.net.

[6] W. F. van Gunsteren, S. R. Billeter, A. A. Eising, P. H. Hünenberger, P. Krüger, A. E. Mark, W. R. P. Scott, I. G. Tironi, *Biomolecular Simulation: The GROMOS96 Manual and User Guide*, Vdf Hochschulverlag AG an der ETH Zürich, Zürich, Groningen **1996**.