Supporting Information for "Assessment of GAFF2 and OPLS-AA general force fields in combination with the three-point site water models TIP3P, SPCE and OPC3 for the solvation free energy of drug-like organic molecules"

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HREM-TT stage: Equilibrium conformational data

We report here the probability distribution functions of some key internal coordinates for the selected set of organic molecules for all force field/water model combinations. The data have been computed using 1682 configurations of the target state (p=1 atm, T=300 K) taken at regular interval in 8 ns eight-replica HREM-TT simulation.

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2-propoxyethanol

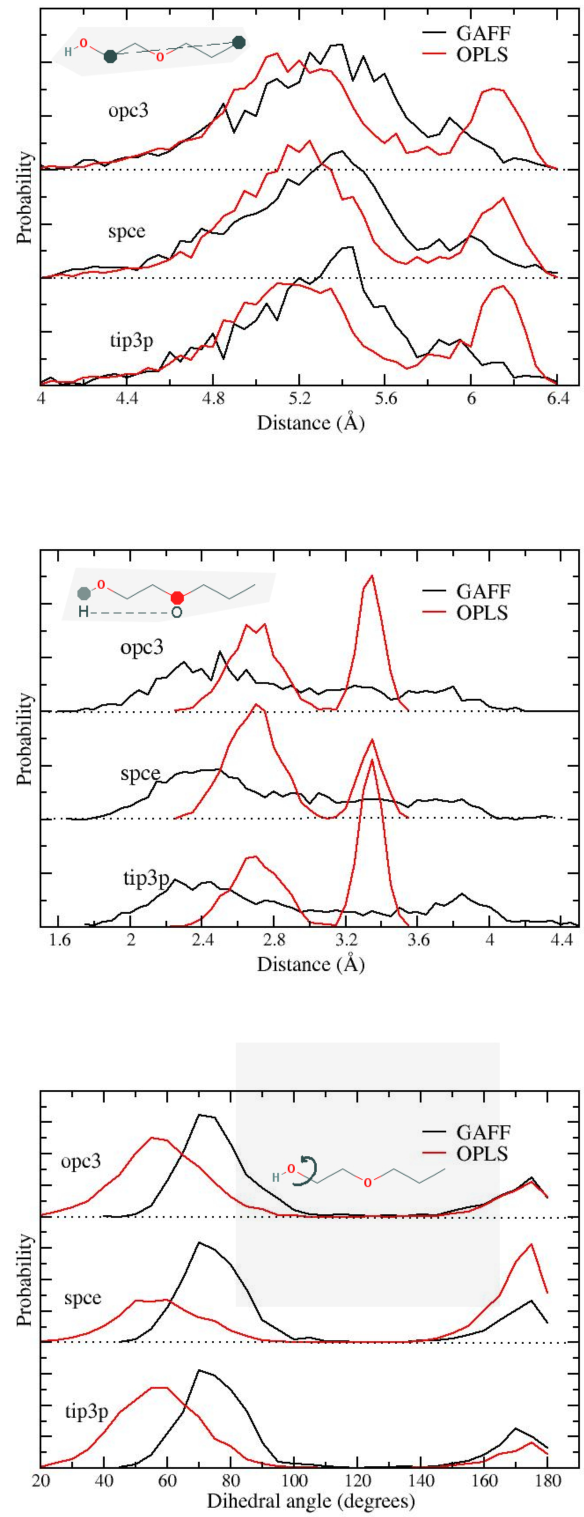
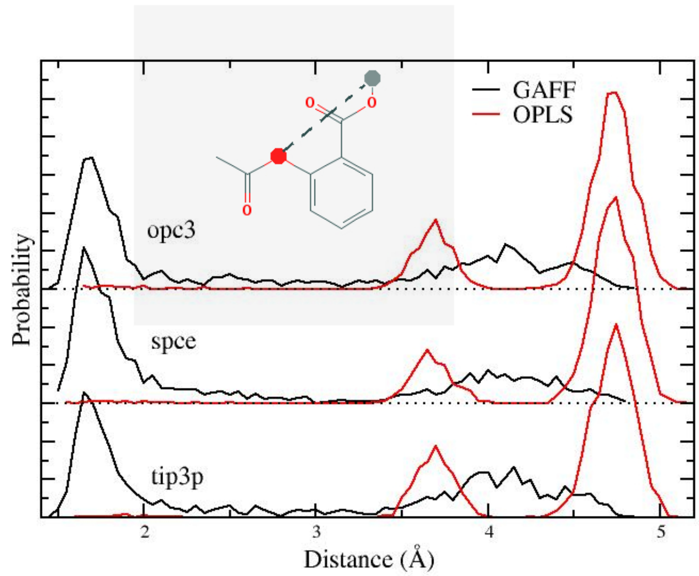


Figure 1: Top panel: C1-C4 distance. Mid panel: O(oxy)-H(hydroxy) distance. Low panel: Torsion around the C1-O(hydroxy) bond.

Acetylsalicylic acid



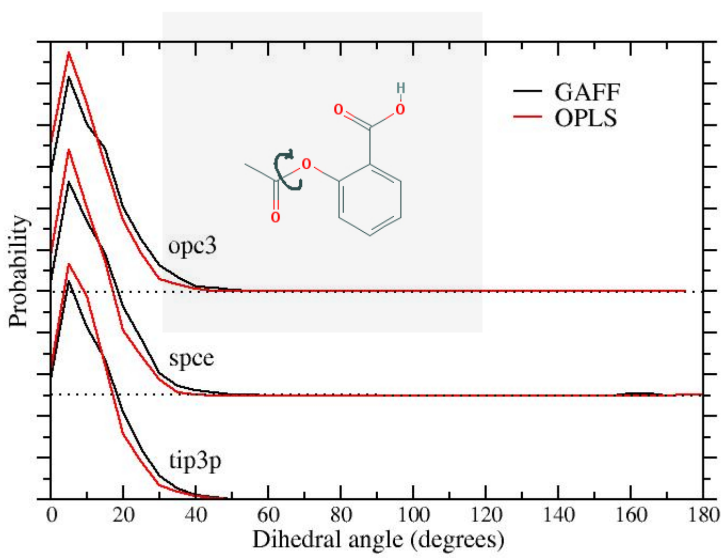
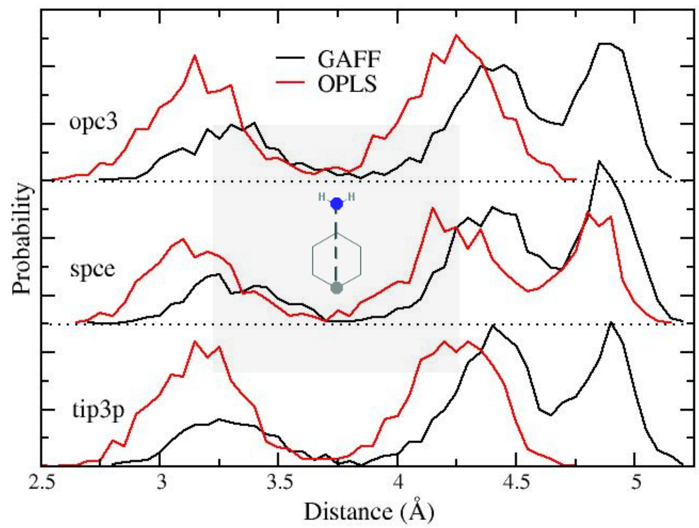


Figure 2: Top panel: O(esteric)-H(hydroxy) distance. Low panel: Torsion around the C-O bond

Cyclohexanamine



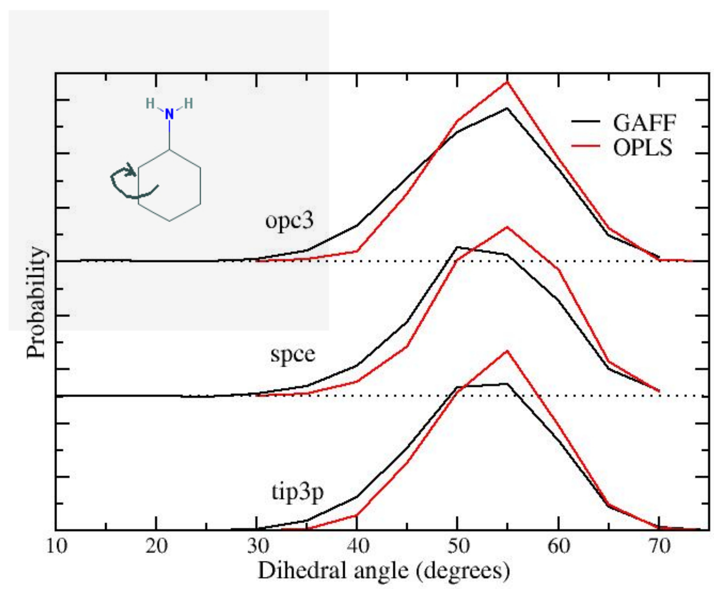
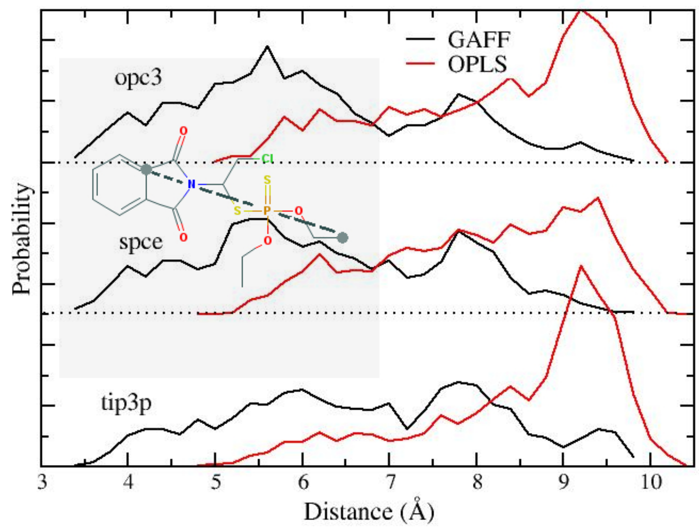


Figure 3: Top panel: C4-N distance. Low panel: Torsion around the C2-C3 bond

Dialifor



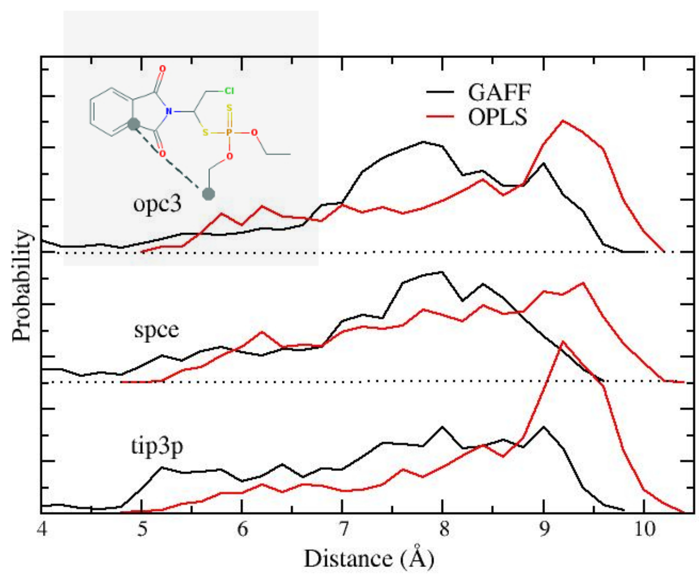
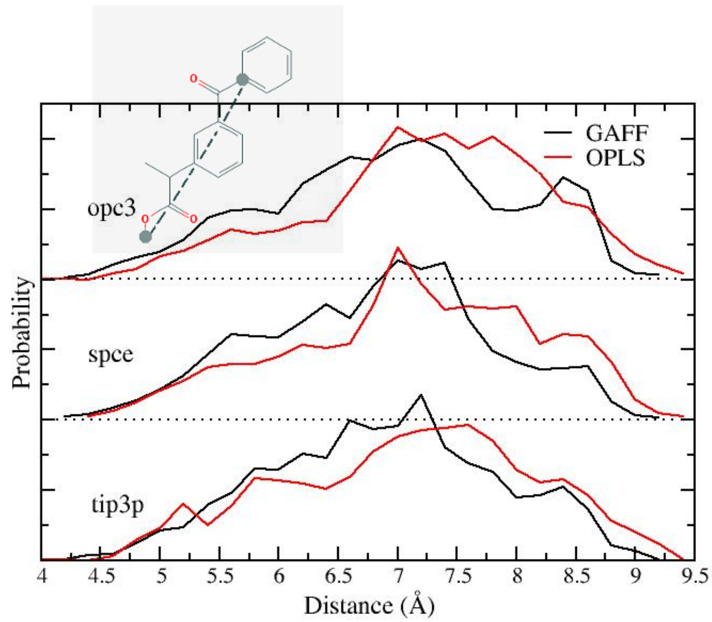


Figure 4: Ring-ethyl distances.

Ketoprophene



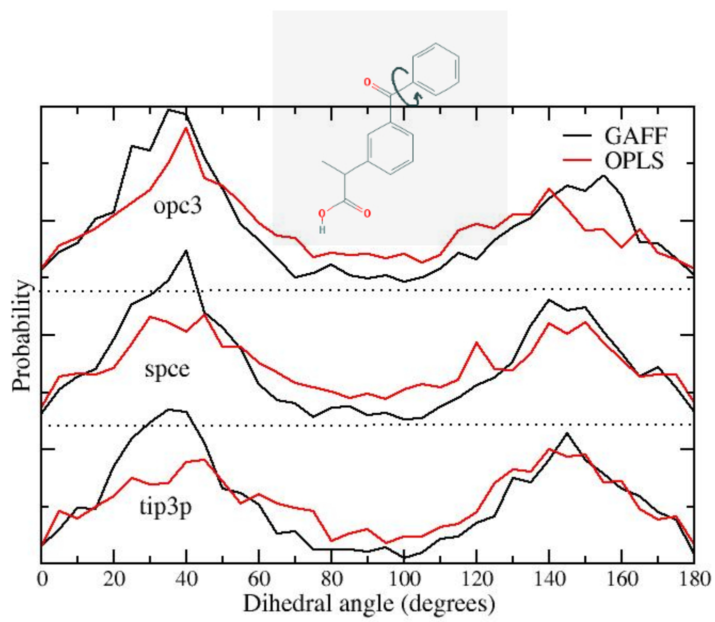
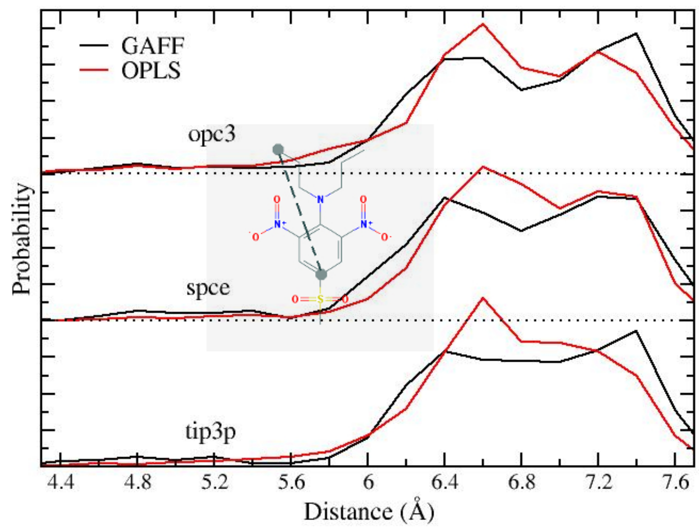


Figure 5: Top panel: H(hydroxy)-phenyl(C1) distance. Low panel: Torsion around C1(phenyl)-C(carboxy) bond.

Nitralin



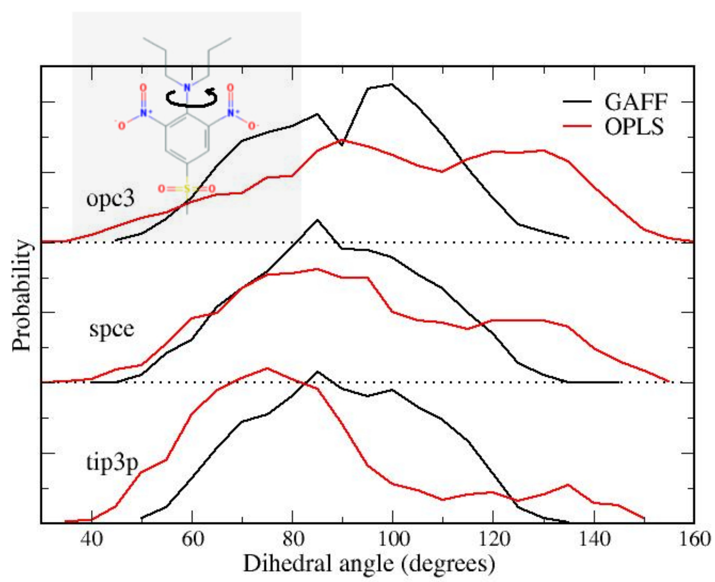


Figure 6: Top panel: C1(phenyl)-C3(propyl) distance. Low panel: torsion around the N-C1(phenyl) bond.

Profluralin

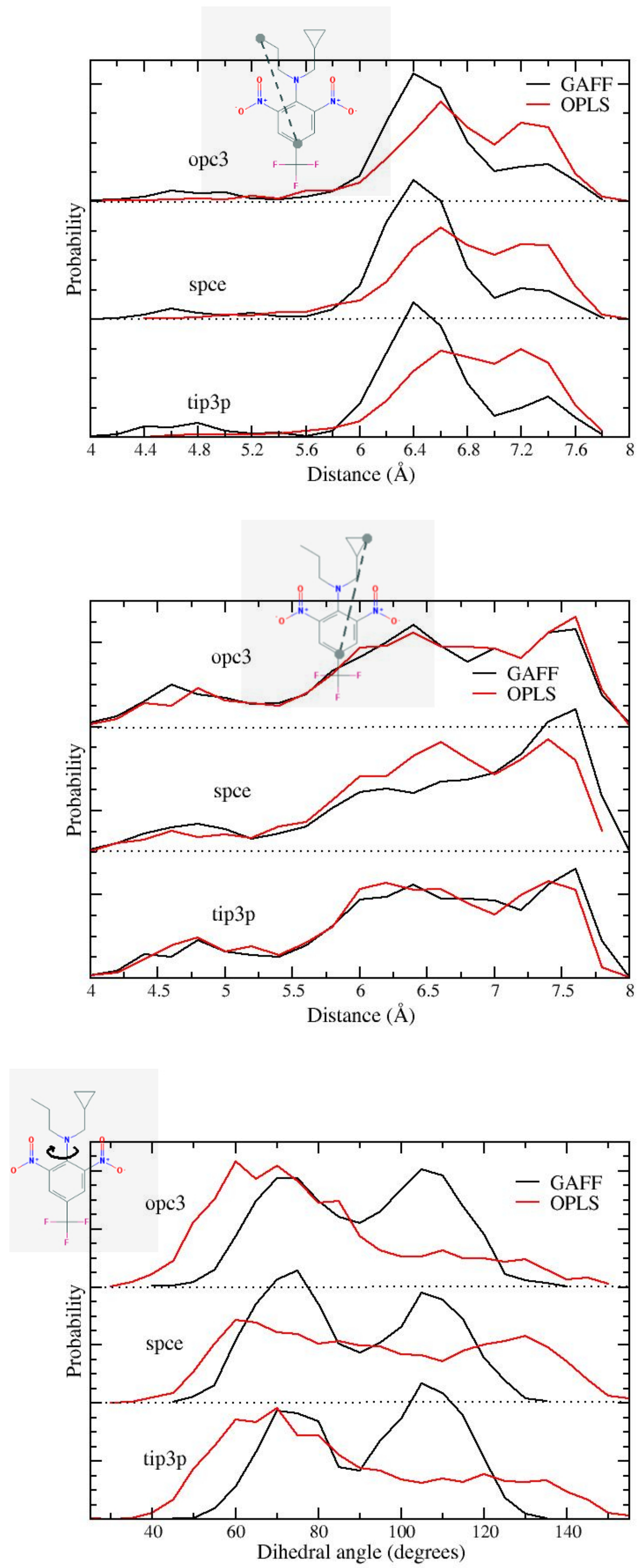


Figure 7: Top panel: C4(phenyl)-1-propyl(C3) distance. Low panel: C4(phenyl)-1-cyclopropyl(C3) distance

Terbacil

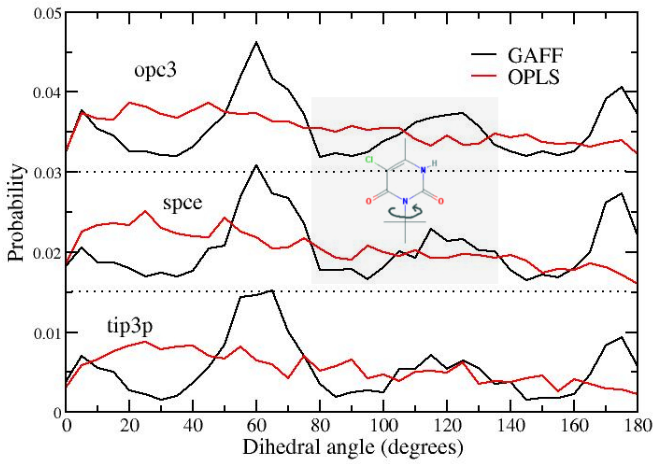


Figure 8: Torsional distribution function of the isobuthyl group

FSAM-NE stage

Gaussian estimate as a function of the annihilation time

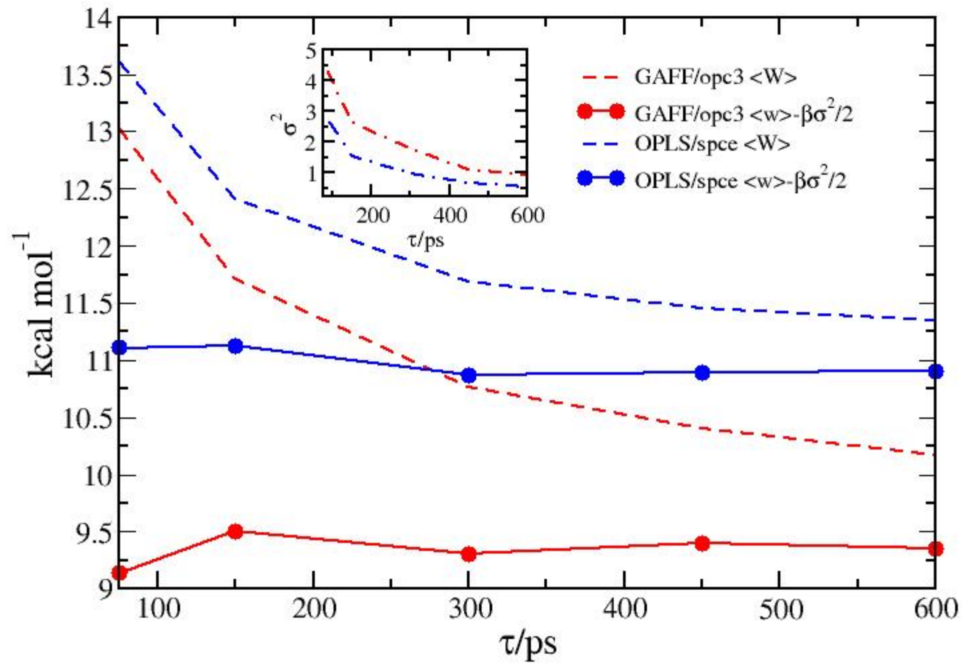


Figure 9: Plot of the Gaussian estimate $\langle W\rangle - \frac{1}{2}\beta\sigma^2$ (solid lines) compared to the mean work $\langle W\rangle$ (dashed line) as a function of the annihilation time for the GAFF/OPC3 and OPLS/SPCE combinations for Acetylsalicylic acid in water. In the inset, the corresponding variance σ^2 are reported.

In Figure 9, we show the Gaussian based estimate and the mean work obtained for various annihilation times in Acetylsalicylic acid in water. As is can be seen, for both analyzed combinations, while the mean work is steadily decreasing along with the variance (see the inset), the Gaussian estimate, $\langle W\rangle - \frac{1}{2}\beta\sigma^2$, starts to be stationary (with oscillations in the order of 0.1 kcal mol^{-1}) for $\tau > 150$ ps.

Work distribution data

Table 1: Mean solvation work in water, $\langle W \rangle$ (kcal mol^{-1}) , variance, σ^2 (kcal^2 mol^{-2}), and Anderson Darling test A^2 for the 48 annihilation work distributions in water. Annihilation time in all cases are set to $\tau = 300$ ps. Bold font in the A^2 entry column indicates failure of the AD test. Reported errors are obtained by standard bootstrap with resampling.

GAFF									
	opc3			spce			tip3p		
	$\langle W \rangle$	σ^2	A^2	$\langle W \rangle$	σ^2	A^2	$\langle W \rangle$	σ^2	A^2
2pro	3.68±0.08	0.84±0.11	0.38	3.69±0.10	0.91±0.13	**1.72**	3.61±0.06	0.56±0.08	**4.32**
acet	10.76±0.11	1.80±0.22	0.42	10.66±0.10	1.53±0.26	**0.90**	10.73±0.08	0.85±0.10	0.78
cycl	0.10±0.08	0.65±0.08	0.25	0.07±0.07	0.58±0.08	0.25	0.21±0.05	0.30±0.03	0.26
dial	14.04±0.14	2.59±0.32	0.18	13.82±0.15	2.55±0.33	**1.26**	14.01±0.10	1.57±0.19	0.34
keto	12.86±0.14	3.06±0.37	**1.14**	12.72±0.14	2.72±0.30	**1.61**	12.90±0.13	2.08±0.25	**9.06**
nitr	13.11±0.11	1.80±0.23	0.23	13.02±0.12	1.56±0.17	0.34	13.42±0.07	0.82±0.10	0.35
prof	5.04±0.12	1.83±0.20	0.67	4.75±0.10	1.53±0.20	0.35	5.52±0.09	0.87±0.11	0.55
terb	16.64±0.10	1.20±0.10	0.62	16.59±0.10	1.16±0.19	0.36	15.77±0.07	0.66±0.07	**0.92**
OPLS									
	opc3			spce			tip3p		
	$\langle W \rangle$	σ^2	A^2	$\langle W \rangle$	σ^2	A^2	$\langle W \rangle$	σ^2	A^2
2pro	4.59±0.11	1.47±0.14	**1.11**	4.44±0.09	1.32±0.16	**2.11**	4.02±0.09	0.84±0.08	**7.42**
acet	11.89±0.10	1.17±0.13	**1.38**	11.68±0.08	0.98±0.11	**1.63**	12.02±0.07	0.62±0.10	**1.03**
cycl	4.96±0.07	0.70±0.07	0.68	4.93±0.08	0.65±0.08	0.48	4.44±0.05	0.35±0.05	0.34
dial	26.40±0.15	3.39±0.40	0.78	26.19±0.14	3.13±0.37	0.72	25.48±0.13	2.32±0.26	**2.27**
keto	12.17±0.13	1.70±0.22	0.46	11.95±0.09	1.45±0.18	0.29	12.39±0.08	0.74±0.11	0.25
nitr	14.66±0.11	2.00±0.24	0.79	14.52±0.11	1.66±0.20	0.39	14.91±0.09	0.91±0.10	0.20
prof	8.89±0.11	2.08±0.26	0.19	8.81±0.09	1.42±0.18	0.21	9.27±0.09	0.93±0.13	0.41
terb	12.02±0.08	1.31±0.16	0.63	11.76±0.09	0.93±0.13	0.31	11.73±0.06	0.49±0.06	0.27

Table 2: Standardized skewness and kurtosis for the 48 work distributions in water. N_g represents the number of normal components in the work distribution. Reported errors are obtained by standard bootstrap with resampling.

	GAFF								
	opc3			spce			tip3p		
	γ	κ	N_g	γ	κ	N_g	γ	κ	N_g
2pro	-0.05±0.29	0.34±0.61	1	0.32±0.21	0.01±0.27	**2**	0.89±0.30	1.67±1.16	**3**
acet	0.04±0.16	-0.24±0.30	1	0.45±0.59	1.71±2.96	**2**	0.12±0.24	0.20±0.47	1
cycl	0.10±0.21	0.04±0.37	1	-0.15±0.20	0.10±0.41	1	-0.08±0.16	-0.04±0.34	1
dial	0.13±0.17	-0.06±0.37	1	-0.38±0.27	0.47±0.52	**2**	-0.06±0.23	0.15±0.58	1
keto	-0.23±0.19	-0.19±0.34	**2**	-0.35±0.21	0.01±0.36	**2**	-0.80±0.20	0.46±0.57	**2**
nitr	-0.20±0.35	0.45±0.94	1	-0.16±0.23	0.54±0.51	1	-0.08±0.21	0.01±0.41	1
prof	-0.23±0.21	-0.12±0.59	1	-0.05±0.27	0.09±0.68	1	-0.18±0.19	-0.08±0.37	1
terb	-0.03±0.20	-0.31±0.30	1	-0.20±0.39	0.86±1.58	**2**	-0.21±0.21	0.27±0.53	1
	OPLS								
	opc3			spce			tip3p		
	γ	κ	N_g	γ	κ	N_g	γ	κ	N_g
2pro	0.17±0.17	-0.40±0.23	**2**	0.28±0.15	-0.18±0.28	**2**	0.75±0.14	0.34±0.41	**2**
acet	-0.39±0.23	0.36±0.46	**2**	-0.40±0.20	0.52±0.42	**3**	-0.35±0.31	0.69±0.89	**2**
cycl	-0.13±0.16	-0.33±0.22	1	-0.26±0.26	0.17±0.58	1	-0.10±0.16	-0.12±0.27	1
dial	0.21±0.23	0.23±0.45	1	0.14±0.16	-0.14±0.22	1	0.40±0.23	-0.15±0.47	**2**
keto	-0.11±0.14	-0.28±0.26	1	0.05±0.20	-0.13±0.28	1	-0.01±0.26	0.16±0.38	1
nitr	-0.28±0.22	0.25±0.44	1	-0.11±0.24	0.30±0.76	1	-0.12±0.19	-0.12±0.34	1
prof	-0.04±0.24	0.10±0.52	1	-0.04±0.16	-0.17±0.28	1	0.02±0.29	0.05±0.64	1
terb	-0.27±0.27	0.57±0.61	1	-0.04±0.22	0.05±0.38	1	-0.12±0.16	-0.24±0.28	1

Table 3: Mean (kcal mol^{-1}), variance (kcal^2 mol^{-2}), third and forth standardized moments of the annihilation work distribution in 1-octanol. Reported errors are obtained by standard bootstrap with resampling. Annihilation time in all cases are set to $\tau = 600$ ps. Bold font in the A^2 entry column indicates failure of the AD test.

	GAFF				
	$\langle W \rangle$	σ^2	γ	κ	A^2
2pro	5.62 ± 0.09	0.96 ± 0.14	-0.07 ± 0.20	-0.12 ± 0.20	0.228
acet	13.49 ± 0.14	2.42 ± 0.32	-0.05 ± 0.30	0.37 ± 0.59	0.375
cycl	4.87 ± 0.07	0.62 ± 0.07	-0.20 ± 0.22	-0.03 ± 0.35	0.470
dial	23.54 ± 0.21	4.03 ± 0.40	0.18 ± 0.25	0.08 ± 0.33	0.523
keto	18.54 ± 0.15	4.08 ± 0.48	-0.10 ± 0.25	0.13 ± 0.43	0.157
nitr	22.98 ± 0.17	3.68 ± 0.50	-0.06 ± 0.21	-0.09 ± 0.28	0.238
prof	15.89 ± 0.10	2.16 ± 0.25	-0.07 ± 0.19	-0.15 ± 0.36	0.270
terb	21.81 ± 0.17	3.72 ± 0.43	-0.19 ± 0.27	-0.15 ± 0.35	0.649
	OPLS				
	$\langle W \rangle$	σ^2	γ	κ	A^2
2pro	5.89 ± 0.13	2.02 ± 0.20	0.52 ± 0.16	-0.32 ± 0.35	**4.474**
acet	15.03 ± 0.31	4.05 ± 0.35	0.10 ± 0.16	-0.28 ± 0.23	0.574
cycl	6.30 ± 0.08	1.01 ± 0.13	0.09 ± 0.21	0.05 ± 0.35	0.152
dial	30.87 ± 0.21	6.42 ± 1.05	-0.00 ± 0.21	0.25 ± 0.34	0.396
keto	19.20 ± 0.17	3.40 ± 0.35	0.13 ± 0.20	0.14 ± 0.48	0.397
nitr	22.05 ± 0.17	3.87 ± 0.49	-0.04 ± 0.15	-0.37 ± 0.29	0.309
prof	17.09 ± 0.14	2.67 ± 0.35	0.12 ± 0.21	0.04 ± 0.58	0.513
terb	18.47 ± 0.12	2.04 ± 0.20	-0.04 ± 0.25	0.07 ± 0.36	0.270