Supplementary Information on manuscript: Can the roles of polar and non-polar moieties be reversed in non-polar solvents?

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Free energy differences between initial and final states can be computed using Eq.1 below :

$$\Delta G_{AB} = \int_{\lambda_A}^{\lambda_B} d\lambda \left\langle \frac{\partial V(\mathbf{r};\lambda)}{\partial \lambda} \right\rangle_{\lambda} \tag{1}$$

where V($\mathbf{r}$, λ) is the potential energy of the system as a function of the coordinate vector $\mathbf{r}$, and λ is a switching-on parameter allowing to go from state A to state B by changing its value from λ_A to λ_B.

The λ-dependence of the potential in bonded interaction is linear while non-bonded interaction can be described with linear dependence or with Soft-core interaction. It should be noted that in our simulations we are analyzing only small molecules, so we are only interested in turning off the inter-molecular interactions such as Lennard-Jones and Coulomb potentials. We used the standard linear interpolation shown in Eq.2

$$\begin{aligned} V &= (1-\lambda)V^A + \lambda V^B \\ \frac{\partial V}{\partial \lambda} &= V^B - V^A \end{aligned} \tag{2}$$

However, near off-states i.e. for values of λ equal to 0 and 1 large numerical fluctuations are sometimes recorded leading to clashes between decoupling atoms, thereby preventing a smooth derivative of the potential in Eq.2. A core sotftening (Eq.3) interacting potential was used to circumvent this issue

$$\begin{aligned} V_{soft-core}(r) &= (1-\lambda)V^A(r_A) + \lambda V^B(r_B) \\ r_A &= (\alpha R_A^6 \lambda^p + r^6)^{1/6} \\ r_B &= (\alpha R_B^6 (1-\lambda)^p + r^6)^{1/6} \end{aligned} \tag{3}$$

where λ and p are respectively the soft-core and the soft-core power parameters, and R is the interaction radius, which is equal to the ratio between the Lennard-Jones parameters σ_{ij}.

S1. SUPPLEMENTARY TABLES

TABLE SI: The correspondence between the 20 amino acids and their neutral analog equivalent.

Character	Amino acid	Short name	Single letter	Equivalent
Hydrophobic	Alanine	ALA	A	Methane
Hydrophobic	Valine	VAL	V	Propane
Hydrophobic	Isoleucine	ILE	I	Butane
Hydrophobic	Leucine	LEU	L	Isobutane
Hydrophobic	Methionine	MET	M	Methyl-ethylsulfide
Hydrophobic	Glycine	GLY	G	Hydrogen
Hydrophobic	Phenylalanine	PHE	F	Toluene
Hydrophobic	Tyrosine	TYR	Y	4-Methylphenol
Hydrophobic	Tryptophan	TRP	W	3-Methylindole
Polar	Serine	SER	S	Methanol
Polar	Asparagine	ASN	N	Acetamide
Polar	Glutamine	GLN	Q	Propionamide
Polar	Cysteine	CYS	C	Methanethiol
Polar	Threonine	THR	T	Ethanol
Polar	Histidine	HIS	H	Methylimidazole
Polar	Lysine	LYS	K	n-Butylamine
Polar	Arginine	ARG	R	n-Propylguanidine
Polar	Aspartic acid	ASP	D	Acetic Acid
Polar	Glutamic acid	GLU	E	Propionic Acid
-	Proline	PRO	P	-

TABLE SII: Solvation free energies ($kJ\,mol^{-1}$) for hydrophobic and polar amino acid side chain analogs in water H_2O.

Hydrophobic	This work, 25°C	Ref.[a]	Ref.[b]	Ref.[c]
Methane(Ala)	8.47 ± 0.12	9.20	8.12	8.12
Propane(Val)	6.93 ± 0.50	10.70	8.33	8.33
Butane (Ile)	7.11 ± 1.83	10.70	9.00	9.00
Isobutane (Leu)	7.24 ± 1.34	10.40	9.54	9.55
Methyl-ethylsulfide (Met)	-0.80 ± 1.69	−6.19	−14.52	−6.20
3-methylindole (Trp)	-29.09 ± 2.34	−12.30	−24.60	−24.62
4-methylphenol (Tyr)	-33.79 ± 3.04	−22.40	−25.56	−25.58
Toluene (Phe)	-7.62 ± 1.12	−3.40	−3.18	−3.18
Polar	**This work, 25°C**	**Ref.[a]**	**Ref.[b]**	**Ref.[c]**
Methanol (Ser)	-21.92 ± 0.21	−14.10	−21.17	−21.19
Ethanol (Thr)	-21.41 ± 0.35	−13.70	−20.42	−20.43
Acetamide (Asn)	-41.75 ± 0.95	−18.80	−40.50	−40.53
Propionamide (Gln)	-44.97 ± 1.41	18.70	−38.25	−39.27
Methanethiol (Cys)	-8.70 ± 2.88	5.50	−5.19	−5.28
Methylimidazole (His)	-32.16 ± 1.74	−27.40	−42.97	−43.00
n-butylamine (Lys)	-18.11 ± 1.31	−15.50	—	−39.86
n-propylguanidine (Arg)	-50.05 ± 1.47	−30.10	—	−83.40
Acetic acid (Asp)	-28.98 ± 0.50	−18.20	—	−45.85
Propionic acid (Glu)	-31.55 ± 0.88	−16.20	—	−42.87

[a] Villa & Mark (2002), 20°C
[b] Chang *et al.* (2007), 25°C
[c] Radzicka & Wolfenden (1988), 20°C

TABLE SIII: Solvation free energies ($kJ\,mol^{-1}$) for hydrophobic and polar amino acid side chain analogs in cyclohexane cC_6H_{12}.

Hydrophobic	This work, 25°C	Ref.[a]	Ref.[b]	Ref.[c]
Methane(Ala)	0.60 ± 0.11	0.8 ± 0.6	1.05	0.54
Propane(Val)	-8.39 ± 0.25	-6.7 ± 0.9	−6.61	−8.58
Butane (Ile)	-11.60 ± 0.89	-13 ± 1.5	−9.91	−11.59
Isobutane (Leu)	-11.23 ± 0.86	-9.8 ± 1.5	−9.16	−11.05
Methyl-ethylsulfide (Met)	-15.77 ± 0.61	-14.4 ± 1.3	−14.52	−16.02
3-methylindole (Trp)	-36.55 ± 2.37	-35.9 ± 2.8	−38.12	−34.35
4-methylphenol (Tyr)	-24.38 ± 0.77	-28.3 ± 1.2	−22.68	−24.98
Toluene (Phe)	-21.27 ± 1.65	-25.2 ± 1.0	−19.71	−15.65
Polar	**This work, 25°C**	**Ref.[a]**	**Ref.[b]**	**Ref.[c]**
Methanol (Ser)	-4.73 ± 0.13	-3.5 ± 0.9	−3.22	−6.94
Ethanol (Thr)	-7.89 ± 0.20	-7.8 ± 0.8	−6.57	−9.66
Acetamide (Asn)	-12.57 ± 0.41	-14.3 ± 1.0	−13.68	−12.72
Propionamide (Gln)	-15.32 ± 0.63	-19.3 ± 0.9	−16.82	−16.07
Methanethiol (Cys)	-8.55 ± 0.18	-7.9 ± 0.8	−8.95	−10.54
Methylimidazole (His)	-19.34 ± 1.03	-21.1 ± 1.0	−19.04	−23.47
n-butylamine (Lys)	-13.71 ± 0.55	-16.8 ± 1.8	—	−16.61
n-propylguanidine (Arg)	-17.74 ± 2.08	-24 ± 1.8	—	−20.92
Acetic acid (Asp)	-14.22 ± 0.18	-15.6 ± 1.1	—	−9.33
Propionic acid (Glu)	-19.13 ± 0.55	-18.6 ± 1.1	—	−14.35

[a] Villa & Mark (2002), 20°C
[b] Chang et al. (2007), 25°C
[c] Radzicka & Wolfenden (1988), 20°C

TABLE SIV: Solvation free energies ($kJ\,mol^{-1}$) for hydrophobic and polar amino acid side chain analogs in ethanol EtOH. Note that here and below, results from Damodaran & Song (1986) are those from Nozaki & Tanford (1971) estrapolated at higher temperatures, and are included here for completeness.

Hydrophobic	This work, 25°C	Ref.[a]	Ref.[b]	Ref.[c]
Methane(Ala)	2.79 ± 0.17	5.92	4.75	5.05
Propane(Val)	-4.79 ± 0.71	2.03	0.50	1.13
Butane (Ile)	-6.23 ± 0.76	—	−4.46	−1.33
Isobutane (Leu)	-9.24 ± 0.47	0.01	0.40	3.03
Methyl-ethylsulfide (Met)	-12.52 ± 1.01	—	−12.93	−11.54
3-methylindole (Trp)	-33.43 ± 1.43	−33.77	−40.27	—
4-methylphenol (Tyr)	-43.01 ± 0.95	35.20	−36.38	−37.21
Toluene (Phe)	-18.07 ± 0.68	−13.98	−15.15	−14.19
Polar	**This work, 25°C**	**Ref.[a]**	**Ref.[b]**	**Ref.[c]**
Methanol (Ser)	-23.56 ± 0.37	−19.54	−20.67	−20.97
Ethanol (Thr)	-25.56 ± 0.20	—	−19.97	−21.94
Acetamide (Asn)	-44.24 ± 0.58	—	−39.86	−39.86
Propionamide (Gln)	-48.46 ± 0.42	—	−38.28	−38.28
Methanethiol (Cys)	-15.64 ± 0.41	—	−11.28	—
Methylimidazole (His)	-32.29 ± 0.57	−44.02	−45.45	—
n-butylamine (Lys)	-21.83 ± 1.80	—	−24.70	—
n-propylguanidine (Arg)	-42.24 ± 1.18	—	−48.06	—
Acetic acid (Asp)	-33.72 ± 0.62	−26.87	−29.94	−29.76
Propionic acid (Glu)	-37.71 ± 0.42	−25.51	−29.08	−28.90

[a] Nozaki & Tanford (1971), 25.10°C
[b] Damodaran & Song (1986), 37°C
[c] Tanford (1962), 20°C

TABLE SV: Classic SPT estimates of the Gibbs energy change, ΔG_0, associated with the creation in water H_2O, cyclohexane cC_6H_{12} and ethanol EtOH of a spherical cavity suitable to host methane, propane, toluene and methanol, at 28° and 1 atm; estimates of the solute-solvent interaction energy, consisting of a van der Waals contribution (assumed to be solvent-independent) and a H-bond contribution. A comparison between the $\Delta G_0 + E_a$ values and the experimental ΔG is shown in the last two columns (no optimization has been performed). For each solute, the first line refers to water H_2O, the second to cyclohexane cC_6H_{12}, and the third to ethanol EtOH. Units are ($kJ\,mol^{-1}$).

	ΔG_0	E_a	$\Delta G_0 + E_a$	ΔG
Methane(ALA) $\sigma = 3.70$ Å	22.9	-15.0	7.9	8.3
	16.0	-15.0	1.0	0.8
	17.7	-15.0	2.7	1.6
Propane(VAL) $\sigma = 5.06$ Å	38.7	-31.0	7.7	8.2
	25.7	-31.0	-5.3	-7.6
	29.0	-31.0	-2.0	-5.2
Toluene(PHE)$\sigma = 5.64$ Å	46.7	-50.0	-3.3	-3.7
	30.6	-50.0	-19.4	-18.7
	34.7	-50.0	-15.3	-14.2
Methanol(SER)$\sigma = 3.83$ Å	24.2	-45.0	-20.8	-21.4
	16.8	-22.0	-5.2	-5.3
	18.7	-39.0	-20.3	-21.0

TABLE SVI: Enthalpic and entropic contributions to the solvation free energies (kJ mol^{-1}) for hydrophobic and polar amino acid side chain analogs in water H_2O.

	This work, 25°C			Baldwin (2014), 25°C		
Hydrophobic	ΔG	ΔH	−TΔS	ΔG	ΔH	−TΔS
Methane(Ala)	8.47 ± 0.12	-3.14 ± 1.55	11.61 ± 1.55	8.29	−2.61	4.61
Propane(Val)	6.93 ± 0.50	-11.17 ± 9.09	18.10 ± 9.25	8.21(8.21)	−5.02(−4.83)	6.98(6.79)
Butane (Ile)	7.11 ± 1.83	-28.28 ± 5.66	35.39 ± 6.52	8.75	−5.66	7.75
Isobutane (Leu)	7.24 ± 1.34	-9.46 ± 8.56	16.69 ± 8.30	9.71	−5.23	7.55
Methyl-ethylsulfide (Met)	-0.80 ± 1.69	-24.04 ± 14.04	23.23 ± 12.94	−−	−−	−−
3-methylindole (Trp)	-29.09 ± 2.34	-88.50 ± 23.89	59.41 ± 24.22	−−	−−	−−
4-methylphenol (Tyr)	-33.79 ± 3.04	-104.73 ± 13.86	70.93 ± 11.17	−−	−−	−−
Toluene (Phe)	-7.62 ± 1.12	-53.44 ± 7.56	45.83 ± 7.73	−−	−−	−−
Polar	ΔG	ΔH	−TΔS	ΔG	ΔH	−TΔS
Methanol (Ser)	-21.92 ± 0.21	-42.73 ± 1.38	20.82 ± 1.43	−−	−−	−−
Ethanol (Thr)	-21.41 ± 0.35	-43.56 ± 5.82	22.14 ± 6.08	−−	−−	−−
Acetamide (Asn)	-41.75 ± 0.95	-69.62 ± 7.73	27.87 ± 7.19	−−	−−	−−
Propionamide (Gln)	-44.97 ± 1.41	-71.56 ± 15.02	26.57 ± 15.64	−−	−−	−−
Methanethiol (Cys)	-8.70 ± 2.88	-25.67 ± 5.21	16.97 ± 5.30	−−	−−	−−
Methylimidazole (His)	-32.16 ± 1.74	-63.02 ± 8.18	30.86 ± 9.45	−−	−−	−−
n-butylamine (Lys)	-18.11 ± 1.31	-47.43 ± 9.80	29.32 ± 8.88	−−	−−	−−
n-propylguanidine (Arg)	-50.05 ± 1.47	-124.34 ± 26.07	74.29 ± 24.94	−−	−−	−−
Acetic acid (Asp)	-28.98 ± 0.50	-52.89 ± 8.53	24.59 ± 8.28	−−	−−	−−
Propionic acid (Glu)	-31.55 ± 0.88	-56.98 ± 16.34	25.43 ± 16.84	−−	−−	−−

TABLE SVII: Enthalpic and entropic contributions to the solvation free energies (kJ mol^{-1}) for hydrophobic and polar amino acid side chain analogs in cyclohexane cC_6H_{12}.

	This work, 25°C			Abraham (1979,1982), 25°C		
Hydrophobic	ΔG	ΔH	−TΔS	ΔG	ΔH	−TΔS
Methane(Ala)	0.60 ± 0.11	-3.38 ± 1.37	3.98 ± 1.36	0.8	−0.9	1.7
Propane(Val)	-8.39 ± 0.25	-14.22 ± 4.31	5.84 ± 4.18	−7.6	−13.9	6.29
Butane (Ile)	-11.60 ± 0.89	-21.31 ± 2.25	9.71 ± 2.66	−11.1	−−	−−
Isobutane (Leu)	-11.23 ± 0.86	-18.88 ± 9.48	7.62 ± 9.12	−9.7	−−	−−
Methyl-ethylsulfide (Met)	-15.77 ± 0.61	24.59 ± 6.73	-40.37 ± 7.24	−−	−−	−−
3-methylindole (Trp)	-36.55 ± 2.37	14.60 ± 9.40	-51.16 ± 8.67	−−	−−	−−
4-methylphenol (Tyr)	-24.38 ± 0.77	-58.46 ± 19.00	34.08 ± 19.35	−−	−−	−−
Toluene (Phe)	-21.27 ± 1.65	-45.74 ± 12.23	24.47 ± 13.06	−−	−−	−−
Polar	ΔG	ΔH	−TΔS	ΔG	ΔH	$-T\Delta S$
Methanol (Ser)	-4.73 ± 0.13	-11.83 ± 0.74	7.10 ± 0.73	−−	−−	−−
Ethanol (Thr)	-7.89 ± 0.20	-15.00 ± 2.78	7.11 ± 2.86		−−	−−
Acetamide (Asn)	-12.57 ± 0.41	-20.88 ± 2.18	8.30 ± 1.98	−−	−−	−−
Propionamide (Gln)	-15.32 ± 0.63	-25.10 ± 5.02	9.78 ± 4.93	−−	−−	−−
Methanethiol (Cys)	-8.55 ± 0.18	-17.85 ± 1.08	9.30 ± 1.30	−−	−−	−−
Methylimidazole (His)	-19.34 ± 1.03	-30.98 ± 12.85	11.64 ± 13.74	−−	−−	−−
n-butylamine (Lys)	-13.71 ± 0.55	-25.71 ± 9.33	12.00 ± 9.27	−−	−−	−−
n-propylguanidine (Arg)	-17.74 ± 2.08	-54.12 ± 15.35	36.38 ± 14.06	−−	−−	−−
Acetic acid (Asp)	-14.22 ± 0.18	-26.42 ± 3.00	12.20 ± 3.00	−−	−−	−−
Propionic acid (Glu)	-19.13 ± 0.55	-30.74 ± 3.26	11.61 ± 3.59	−−	−−	−−

TABLE SVIII: Enthalpic and entropic contributions to the solvation free energies ($kJ\,mol^{-1}$) for hydrophobic and polar amino acid side chain analogs in ethanol EtOH.

	This work, 25°C			Abraham (1979,1982), 25°C		
Hydrophobic	ΔG	ΔH	−TΔS	ΔG	ΔH	−TΔS
Methane(Ala)	2.79 ± 0.17	-0.43 ± 1.50	3.22 ± 1.43	1.6	−2.1	3.7
Propane(Val)	-4.79 ± 0.71	-16.44 ± 5.15	11.65 ± 5.19	−5.2	−12.4	7.22
Butane (Ile)	-6.23 ± 0.76	-17.25 ± 10.92	11.02 ± 11.10	−8.1	−17.7	9.6
Isobutane (Leu)	-9.24 ± 0.47	-16.86 ± 6.96	7.62 ± 7.16	−6.9	−16.1	9.21
Methyl-ethylsulfide (Met)	-12.52 ± 1.01	-25.82 ± 9.72	13.31 ± 9.65	−−	−−	−−
3-methylindole (Trp)	-33.43 ± 1.43	-56.80 ± 22.95	23.37 ± 23.62	−−	−−	−−
4-methylphenol (Tyr)	-43.01 ± 0.95	-90.35 ± 9.04	47.34 ± 9.08	−−	−−	−−
Toluene (Phe)	-18.07 ± 0.68	-28.56 ± 13.07	10.49 ± 13.08	−−	−−	−−
Polar	ΔG	ΔH	−TΔS	ΔG	ΔH	−TΔS
Methanol (Ser)	-23.64 ± 0.37	-43.22 ± 3.87	19.62 ± 3.69	−−	−−	−−
Ethanol (Thr)	-25.56 ± 0.20	-47.06 ± 2.70	21.50 ± 2.76	−−	−−	−−
Acetamide (Asn)	-44.24 ± 0.58	-70.71 ± 7.82	26.47 ± 7.78	−−	−−	−−
Propionamide (Gln)	-48.46 ± 0.42	-84.15 ± 16.67	35.69 ± 16.98	−−	−−	−−
Methanethiol (Cys)	-15.64 ± 0.41	-31.89 ± 4.51	16.25 ± 4.67	−−	−−	−−
Methylimidazole (His)	-32.29 ± 0.57	-54.20 ± 8.45	21.91 ± 8.57	−−	−−	−−
n-butylamine (Lys)	-21.83 ± 1.80	-37.84 ± 12.64	16.01 ± 11.80	−−	−−	−−
n-propylguanidine (Arg)	$--\pm---$	$--\pm---$	$--\pm---$	−−	−−	−−
Acetic acid (Asp)	-33.72 ± 0.62	-58.71 ± 5.25	24.99 ± 5.24	−−	−−	−−
Propionic acid (Glu)	-37.70 ± 0.42	-68.60 ± 7.06	30.90 ± 6.95	−−	−−	−−

TABLE SIX: Enthalpic and entropic contributions to the transfer free energies ($kJ\,mol^{-1}$) from water H_2O to cyclohexane cC_6H_{12} for hydrophobic and polar amino acid side chain analogs.

	This work, 25°C			Wolfenden (2015), 25°C			Abraham (1979,1982), 25°C		
Hydrophobic	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS
Methane(Ala)	-7.87 ± 0.23	-0.24 ± 2.92	-7.63 ± 2.91	−12.02	10.68	−22.69	−7.50	10.00	−17.5
Propane(Val)	-15.32 ± 0.75	-3.05 ± 13.40	-12.26 ± 13.44	−23.28	6.20	−29.48	−15.80	7.10	−22.29
Butane (Ile)	-18.71 ± 2.72	6.97 ± 7.91	-25.68 ± 9.18	−24.16	4.31	−28.47	−19.80	−−	−−
Isobutane (Leu)	-18.47 ± 2.20	-10.42 ± 18.04	-8.03 ± 17.42	−24.16	2.51	−26.67	−19.40	−−	−−
Methyl-ethylsulfide (Met)	-14.97 ± 2.30	48.63 ± 20.77	-66.60 ± 20.18	−10.89	3.35	−14.24	−−	−−	−−
3-methylindole (Trp)	-7.46 ± 4.71	103.1 ± 33.29	-110.57 ± 32.89	−10.42	−0.54	−9.88	−−	−−	−−
4-methylphenol (Tyr)	9.41 ± 3.81	46.27 ± 32.86	-36.85 ± 30.52	1.76	18.21	−16.45	−−	−−	−−
Toluene (Phe)	-13.65 ± 2.77	7.70 ± 19.79	-21.36 ± 20.79	−15.04	−1.05	−13.98	−−	−−	−−
Polar	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS
Methanol (Ser)	17.19 ± 0.34	30.91 ± 2.12	-13.71 ± 2.16	16.08	26.00	−9.92	−−	−−	−−
Ethanol (Thr)	13.52 ± 0.55	28.56 ± 8.60	-15.03 ± 8.94	10.42	28.14	−17.71	−−	−−	−−
Acetamide (Asn)	29.18 ± 1.36	48.74 ± 9.91	-19.57 ± 9.17	27.80	29.89	−2.14	−−	−−	−−
Propionamide (Gln)	29.65 ± 2.04	46.46 ± 20.04	-16.79 ± 20.54	23.19	36.80	−13.61	−−	−−	−−
Methanethiol (Cys)	0.15 ± 3.06	7.72 ± 6.29	-7.67 ± 6.6	−8.71	13.06	−21.77	−−	−−	−−
Methylimidazole (His)	12.82 ± 2.77	32.04 ± 21.03	-19.22 ± 23.19	19.89	48.53	−28.64	−−	−−	−−
n-butylamine (Lys)	4.40 ± 1.86	21.72 ± 19.13	-17.32 ± 18.15	1.55	22.23	−20.68	−−	−−	−−
n-propylguanidine (Arg)	32.31 ± 3.55	70.22 ± 41.42	-37.91 ± 39.00	24.62	57.53	−32.91	−−	−−	−−
Acetic acid (Asp)	14.76 ± 0.68	26.47 ± 11.53	-12.39 ± 11.28	18.71	34.92	−16.16	−−	−−	−−
Propionic acid (Glu)	12.42 ± 1.61	26.24 ± 19.59	-13.82 ± 20.41	12.85	43.43	30.48	−−	−−	−−

TABLE SX: Enthalpic and entropic contributions to the transfer free energies kJ mol^{-1}) from water H_2O to ethanol EtOH for hydrophobic and polar amino acid side chain analogs.

	This work, 25°C			Abraham (1979,1982), 25°C		
Hydrophobic	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS
Methane(Ala)	-5.68 ± 0.29	2.71 ± 3.05	-8.39 ± 2.98	−6.70	8.8	−15.50
Propane(Val)	-11.72 ± 1.21	-5.27 ± 14.24	-6.45 ± 14.44	−13.40	8.6	−21.97
Butane (Ile)	-13.34 ± 2.59	11.03 ± 16.58	-24.37 ± 17.62	−16.80	5.9	−22.69
Isobutane (Leu)	-16.48 ± 1.81	-7.40 ± 15.52	-9.07 ± 15.46	−16.60	5.8	−22.39
Methyl-ethylsulfide (Met)	-11.72 ± 2.70	-1.78 ± 23.76	-9.92 ± 22.59	−−	−−	−−
3-methylindole (Trp)	-4.34 ± 3.77	31.70 ± 46.84	-36.04 ± 47.84	−−	−−	−−
4-methylphenol (Tyr)	-9.22 ± 3.99	14.38 ± 22.90	-23.59 ± 20.25	−−	−−	−−
Toluene (Phe)	-10.45 ± 1.80	24.88 ± 20.63	-35.34 ± 20.81	−−	−−	−−
Polar	ΔΔG	ΔΔH	−TΔΔS	ΔΔG	ΔΔH	−TΔΔS
Methanol (Ser)	-1.75 ± 0.58	-0.31 ± 5.25	-1.46 ± 5.12	−−	−−	−−
Ethanol (Thr)	-3.87 ± 0.55	-3.47 ± 8.52	-0.39 ± 8.84	−−	−−	−−
Acetamide (Asn)	-2.60 ± 1.53	-1.43 ± 15.55	-1.17 ± 14.96	−−	−−	−−
Propionamide (Gln)	-3.17 ± 1.83	-20.90 ± 31.69	17.75 ± 35.62	−−	−−	−−
Methanethiol (Cys)	-6.95 ± 3.29	-4.96 ± 9.72	-1.99 ± 9.97	−−	−−	−−
Methylimidazole (His)	-0.05 ± 2.31	8.24 ± 16.63	-8.26 ± 18.02	−−	−−	−−
n-butylamine (Lys)	-3.75 ± 3.11	9.72 ± 22.44	-13.47 ± 20.68	−−	−−	−−
n-propylguanidine (Arg)	$---\pm---$	$---\pm---$	$---\pm---$	−−	−−	−−
Acetic acid (Asp)	-4.74 ± 1.12	-5.93 ± 13.78	0.51 ± 13.58	−−	−−	−−
Propionic acid (Glu)	-6.16 ± 1.30	-10.47 ± 23.40	4.31 ± 23.79	−−	−−	−−

TABLE SXI: Fitting coefficients for different amino acid side chain analogs used to compute the thermodynamics parameters along with their Pearson's correlation coefficient R^2.

	cC_6H_{12}				EtOH				H2O			
Hydrophobic	a	b	c	R^2	a	b	c	R^2	a	b	c	R^2
Methane(Ala)	−29.3694	0.5972	−0.0872	0.95818	10.4955	−0.2346	0.0366	0.99678	−64.9942	1.4308	−0.2079	0.99676
Propane(Val)	8.9816	−0.5017	0.0778	0.96322	−7.3071	−0.1660	0.0306	0.97862	−111.8008	2.3413	−0.3409	0.90212
Butane (Ile)	−93.0027	1.6432	−0.2405	0.97181	−104.5813	1.9986	−0.2929	0.92449	−577.1131	12.5018	−1.8502	0.95994
Isobutane (Leu)	74.7048	−2.0768	0.3139	0.94533	252.7160	−6.0302	0.9042	0.87209	−137.4634	2.9061	−0.4250	0.88111
Methyl-ethylsulfide (Met)	1117.2886	−24.6814	3.6649	0.92475	−182.5088	3.5643	−0.5255	0.98937	139.2361	−3.5924	0.5486	0.82625
3-methylindole (Trp)	2288.4173	−51.2502	7.6264	0.95952	−93.8153	0.9098	−0.1241	0.92019	−185.8273	2.3960	−0.3275	0.93339
4-methylphenol (Tyr)	−339.6722	6.4313	−0.9432	0.93764	−55.0555	−0.6341	0.1184	0.95091	307.8364	−9.0299	1.3837	0.94686
Toluene (Phe)	−52.8578	0.2420	−0.0239	0.93993	−243.1799	4.8563	−0.7198	0.80403	−35.5509	0.0252	0.0130	0.90851
Polar	a	b	c	R^2	a	b	c	R^2	a	b	c	R^2
Methanol (Ser)	−27.2782	0.3709	−0.0518	0.96906	−11.5717	−0.6459	0.1063	0.99971	−35.3124	−0.0971	0.0249	0.99909
Ethanol (Thr)	−15.8606	0.0431	−0.0029	0.97949	14.7211	−1.3157	0.2072	0.98123	−110.9791	1.5442	−0.2182	0.98312
Acetamide (Asn)	55.8768	−1.6963	0.2574	0.94491	89.5388	−3.5109	0.5374	0.97194	8.7707	−1.6703	0.2635	0.98706
Propionamide (Gln)	50.8798	−1.6739	0.2548	0.93166	−39.9522	−0.8732	0.1482	0.95726	−105.0984	0.8572	−0.1151	0.92632
Methanethiol (Cys)	−52.2218	0.8032	−0.1153	0.95474	−68.3014	0.8724	−0.1221	0.98555	−116.9340	2.1153	−0.3076	0.98041
Methylimidazole (His)	−64.2742	0.7870	−0.1117	0.98703	−108.2614	1.2879	−0.1813	0.90130	−517.3281	10.3350	−1.5278	0.83670
n-butylamine (Lys)	−13.7771	−0.2279	0.0400	0.93944	−221.8295	4.1868	−0.6171	0.94929	−206.4630	3.6800	−0.5349	0.91925
n-propylguanidine (Arg)	−941.5227	20.1262	−2.9884	0.90171	−−	−−	−−	−−	526.5740	−14.5680	2.2182	0.84896
Acetic acid (Asp)	104.4444	1.79371	−0.26170	0.98557	−129.4953	1.6740	−0.2374	0.99669	−90.2838	0.9694	−0.1338	0.98984
Propionic acid (Glu)	34.5187	−1.4269	0.2189	0.94840	47.2406	−2.4766	0.3847	0.99048	−216.3530	3.6654	−0.5345	0.92398

S2. SUPPLEMENTARY FIGURES

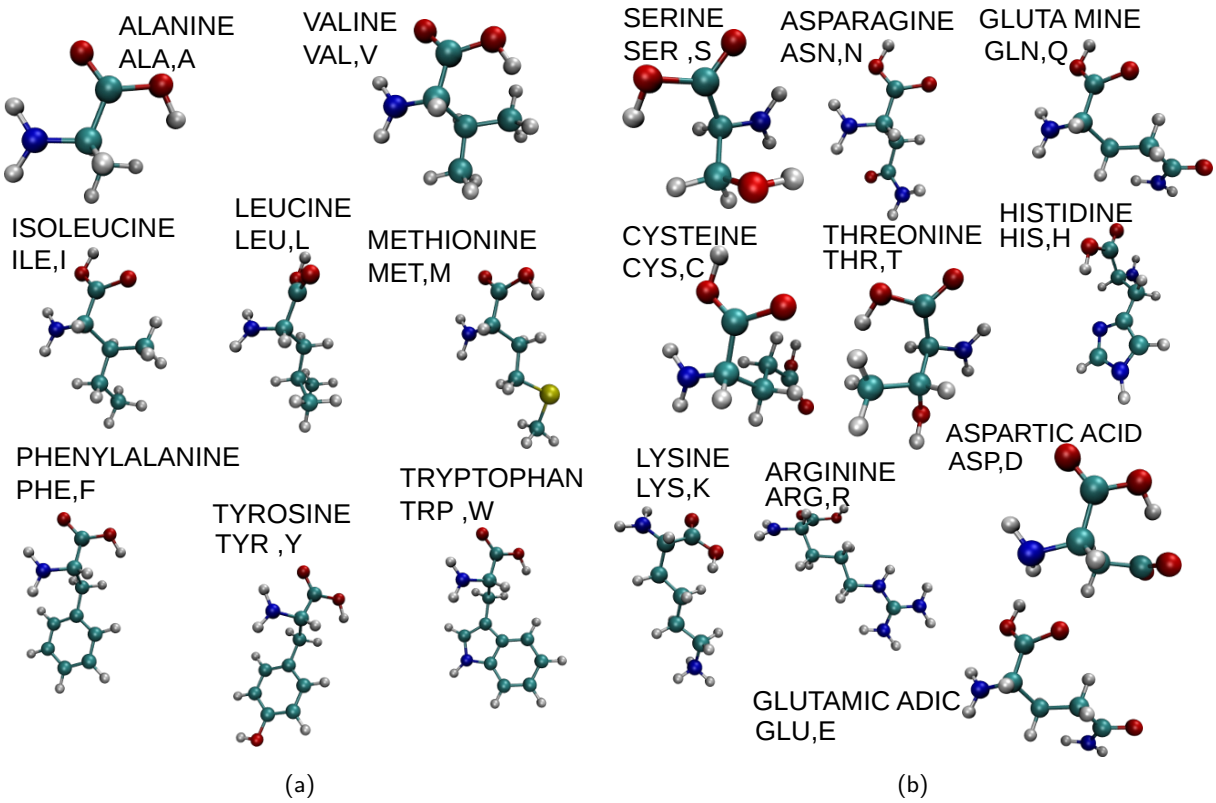

FIG. SI: (a) Hydrophobic amino acids. (b) Polar amino acids.

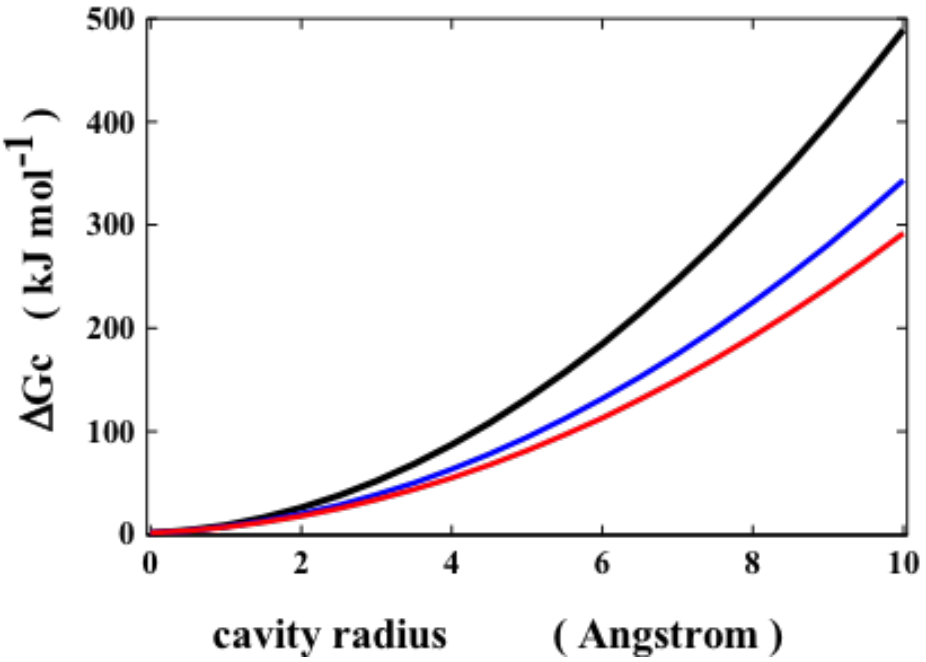

FIG. SII: Trend of the free energy of cavity creation in the three liquids versus the radius of the spherical cavity, calculated by means of classic SPT at 28°C and 1 atm; black line refers to water H_2O, blue line refers to ethanol EtOH , and red line refers to cyclohexane cC_6H_{12}.

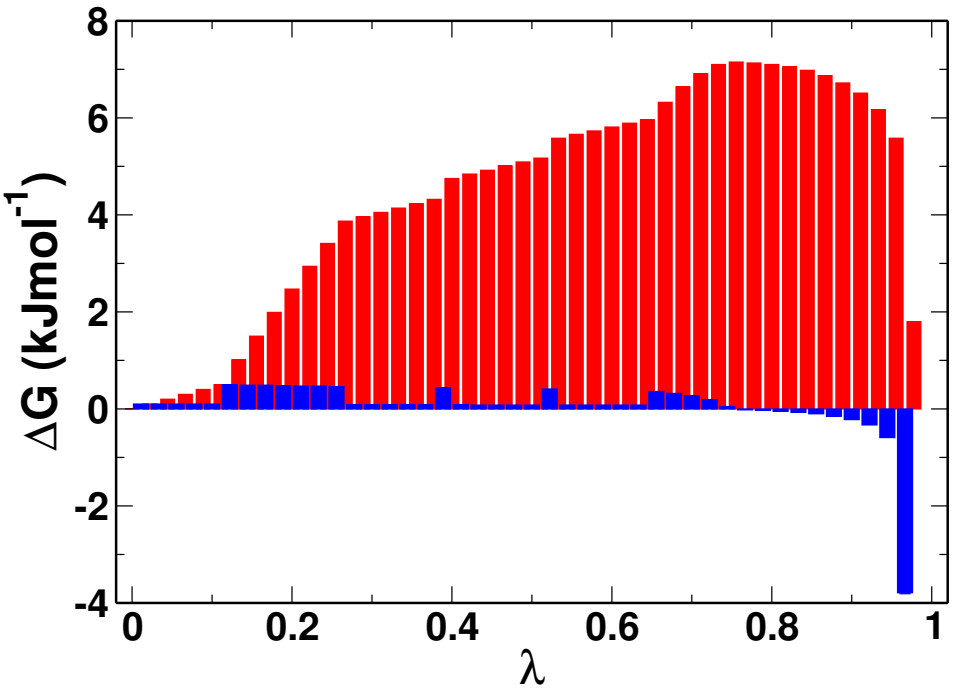

FIG. SIII: Illustrative case of the decoupling process for Methanol, SER in cyclohexane, cC6H12. **Blue** histograms show the free energy difference between two consecutive lambda points while **red** ones display the integral i.e. the cumulative free energy change as a function of lambda. While throughout the work 21 lambda points were used, in this particular case the plot is displayed for 45 lambda points.

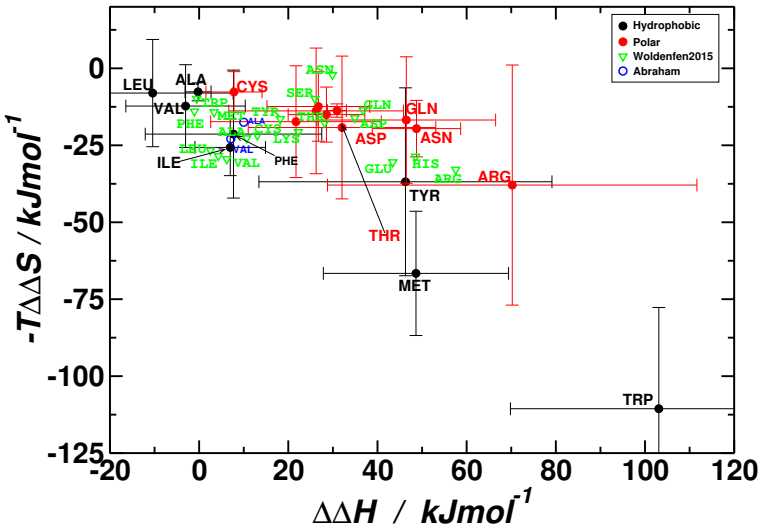

FIG. SIV: Change in the entropic term $-T\Delta\Delta S$ as a function of the change in the entropic part $\Delta\Delta H$ in the case of (a) water to cyclohexane; (b) water to ethanol . In the case of water to cyclohexane, results from Wolfenden *et al* are also included. Units are in kJ mol^{-1}).

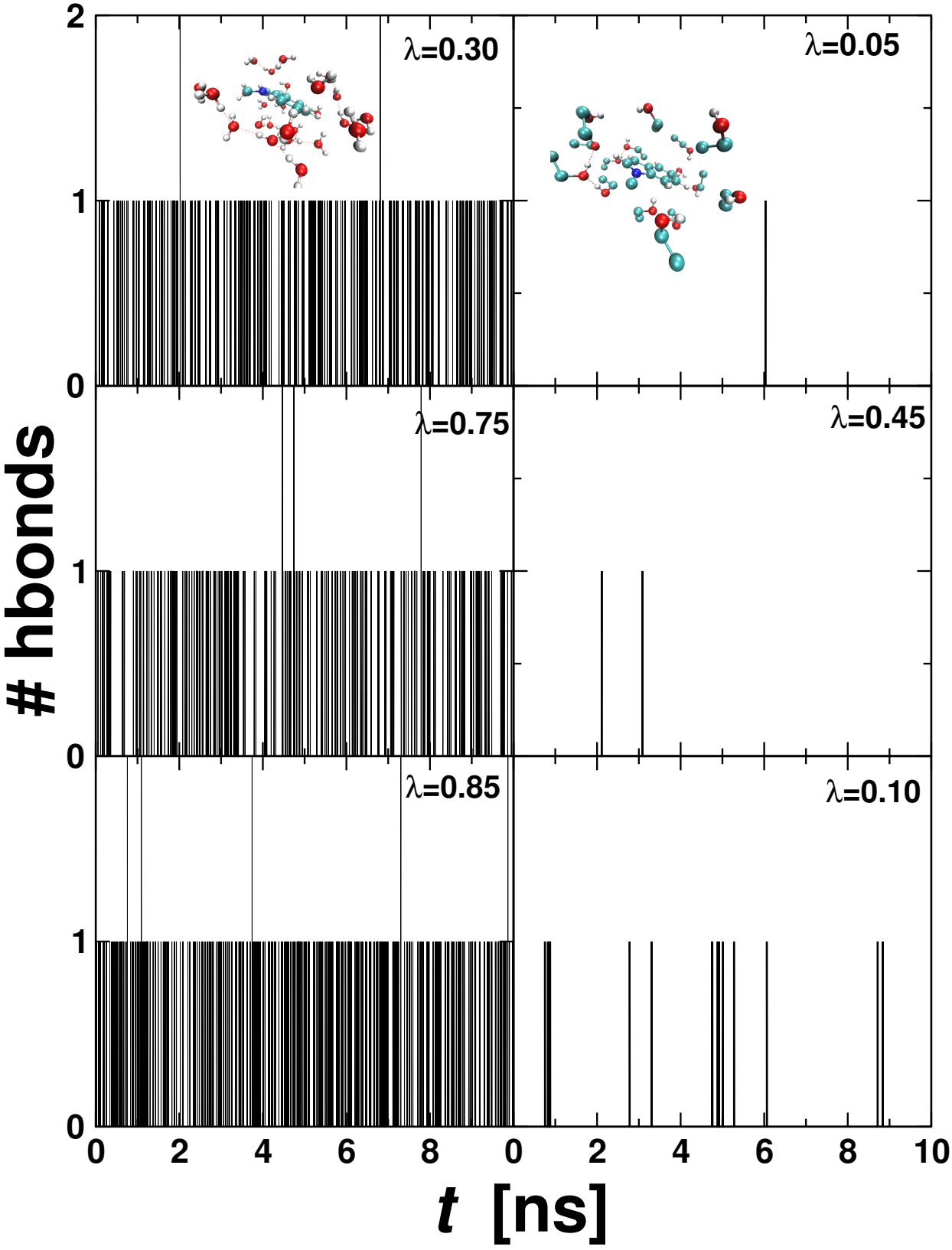

FIG. SV: Time-based number of hydrogen bonds change for 3-methylindole in water, H_2O (**left panel**) and in ethanol, EtOH (**right panel**) at three different temperatures 280, 290 and 300 K upon moving from the **top** to the **bottom**, respectively. Insets are representative snapshots. Hydrogen bonds are computed using *gmx hbond* tool of Gromacs package implying that both faces of the phenyl rings are potentially involved in the geometric consideration for Hbond existence.

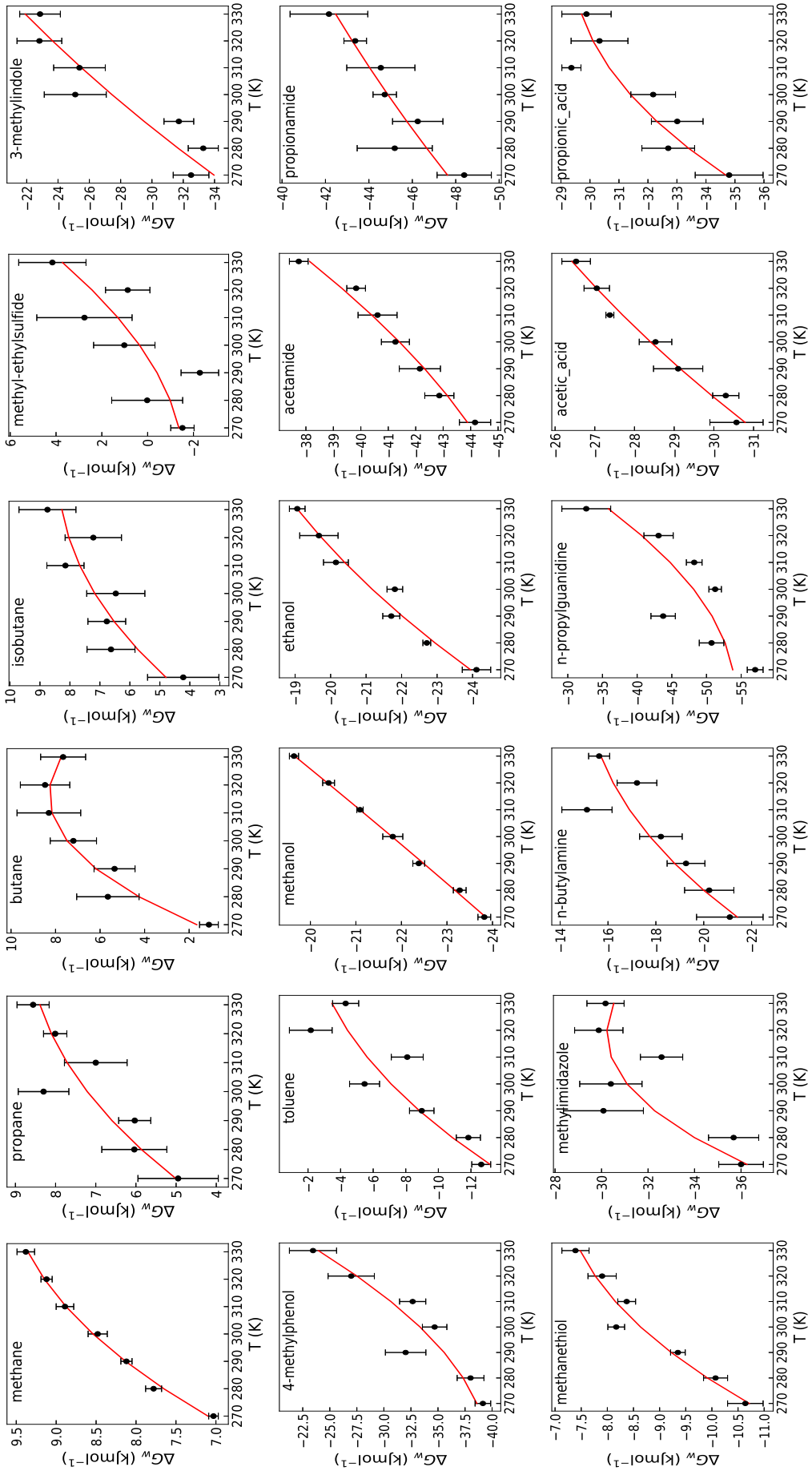

FIG. SVI: Temperature dependence of the solvation free energy from gas to water H_2O, ΔG_w.

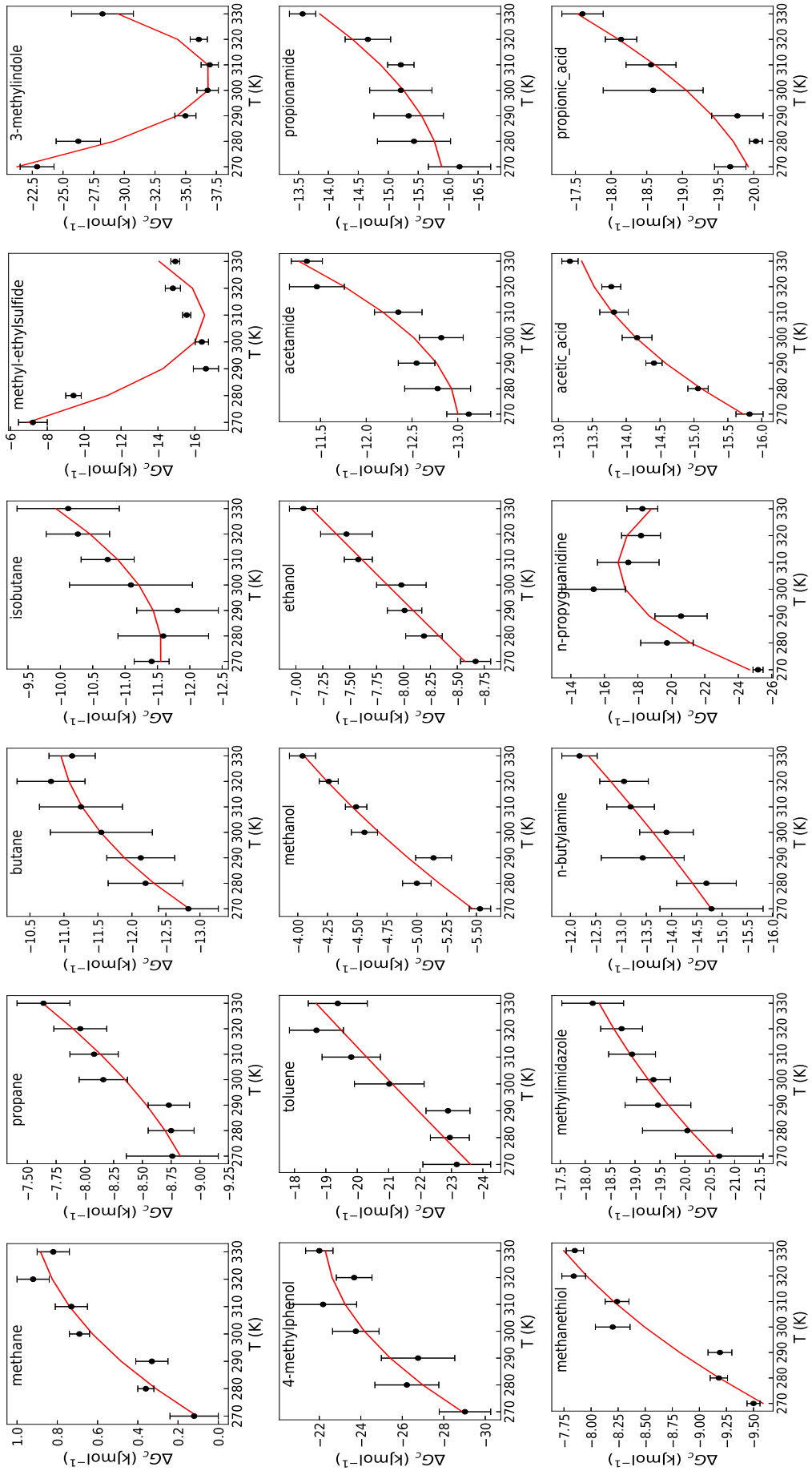

FIG. SVII: Temperature dependence of the solvation free energy from gas to cyclohexane cC_6H_{12}, ΔG_c

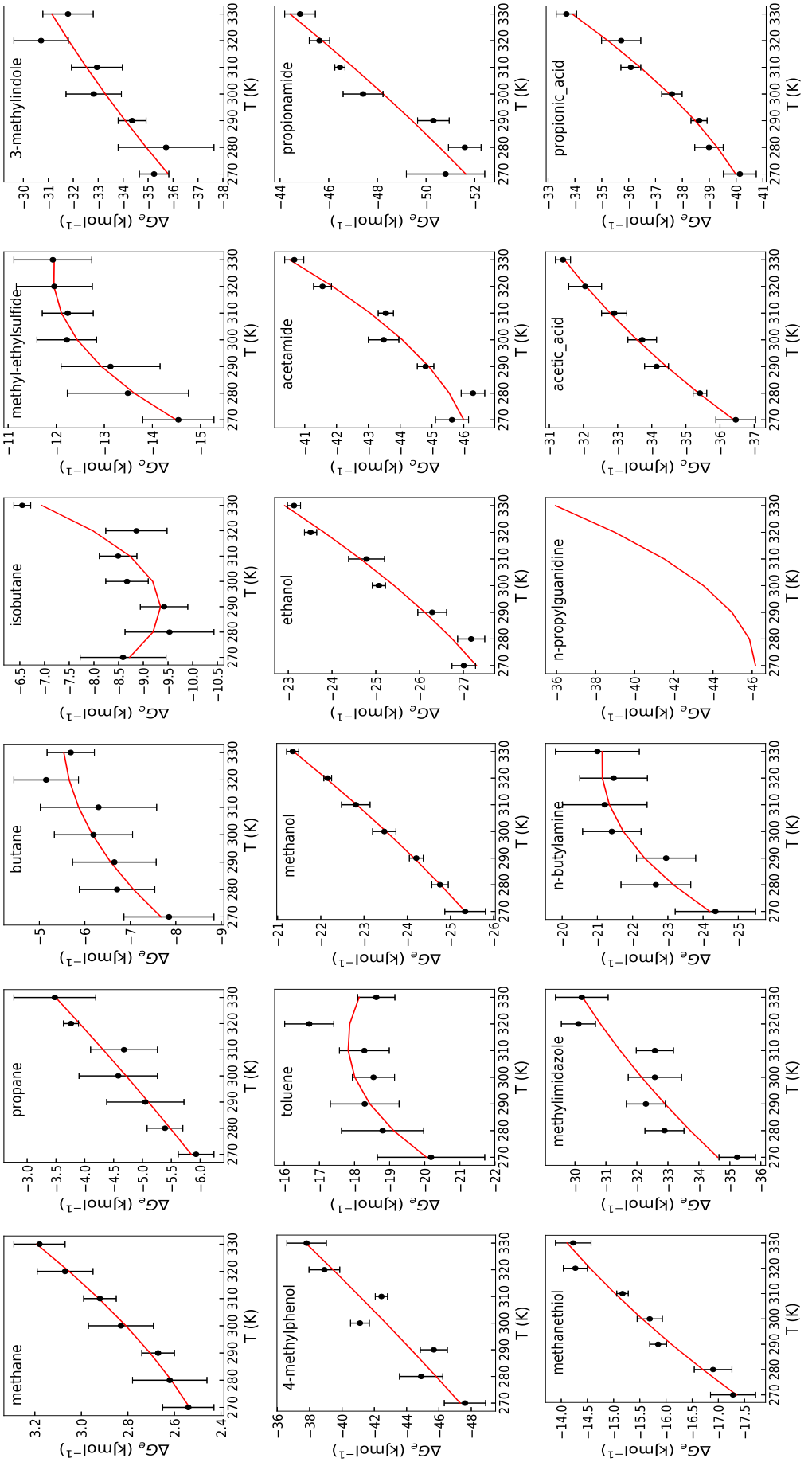

FIG. SVIII: Temperature dependence of the solvation free energy from gas to ethanol EtOH, ΔG_e. It should be noted that large numerical fluctuations prevent the data collection in the case of n-propylguanidine (ARG). Therefore the corresponding plot should be viewed as an *empirical*-like fitting which doesn't enable reliable extraction of thermodynamics constants.