Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information: The Entropic Penalty for Associative Reactions and their Physical Treatment during Routine Computations

Jama Ariai* and Urs Gellrich*

Justus Liebig University, Institute of Organic Chemistry, Heinrich-Buff-Ring 17, 35392 Giessen, Germany.

E-mail: urs.gellrich@org.chemie.uni-giessen.de

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1 Derivation of the Equations of Solvation Entropy

We present a detailed derivation of the translational entropy of solvation (eq 4), rotational entropy of solvation (eq 5), and cavitation entropy (eq 6) based on the formalism presented by Garza.[1] We recall the equations mentioned in the original manuscript by Garza with the prefix 'G', so that G2 refers to eq 2 in the original manuscript by Garza.

1.1 Translational Entropy of Solvation

We start with the general expression of the translational entropy (G3 in G2)

$$S_{\text{trans}} = R\left(\ln q_{\text{trans}} + \frac{5}{2}\right) \tag{S1}$$

where $q_{\text{trans}} = V(2\pi m k_B T/h^2)^{3/2}$ is the translational partition function (G3). For solution-phase, the volume is the product of the number of accessible cavities and the cavity volume ($N_{\text{cav}}V_{\text{cav}}$), while the ideal gas volume $V_{\text{gas}}^{\text{ideal}}$ is used for the gas-phase. Thus, the translational entropy of solvation

$$\Delta_{\text{solv}}S^{\text{trans}} = S_{\text{soln}}^{\text{trans}} - S_{\text{gas}}^{\text{trans}} = R\ln\left(\frac{q_{\text{trans,soln}}}{q_{\text{trans,gas}}}\right) \tag{S2}$$

which simplifies to the final expression $\Delta_{\text{solv}}S^{\text{trans}} = R\ln\left(N_{\text{cav}}V_{\text{cav}}/V_{\text{gas}}^{\text{ideal}}\right)$ for the translational entropy of solvation (eq 4).

1.2 Rotational Entropy of Solvation

The rotational solution-phase entropy is

$$S_{\text{rot}} = R\left(\ln\left(q_{\text{rot}}\right) + T\left(\frac{\partial \ln\left(q_{\text{rot}}\right)}{\partial T}\right)_V\right) + S_{\text{trans}}^{'} - S_{\text{trans}}^{''} \tag{G11}$$

where $S_{\text{trans}}^{'}$ and $S_{\text{trans}}^{''}$ are the translational solution-phase entropy at volume $V' = N_{\text{cav}}4\pi(r_{\text{cav}}-r_{\text{gyr}})^3/3$ and $V'' = N_{\text{cav}}4\pi r_{\text{cav}}^3/3$, respectively. The first two terms are identical to the gas-phase formalism, hence the rotational entropy of solvation simplifies to

$$\Delta_{\text{solv}}S^{\text{rot}} = S_{\text{soln}}^{\text{rot}} - S_{\text{gas}}^{\text{rot}} = S_{\text{trans}}^{'} - S_{\text{trans}}^{''} \tag{S3}$$

which is a scenario comparable to the translational entropy of solvation ($S_{trans}(V_1)-S_{trans}(V_2)$). Accordingly, the final expression is

$$\Delta_{solv}S^{rot} = R\ln\left(\frac{(r_{cav}-r_{gyr})^3}{r_{cav}{}^3}\right) = 3R\ln\left(1-\frac{r_{gyr}}{r_{cav}}\right) \quad \text{(S4)}$$

which is identical to eq 5.

1.3 Cavitation Entropy

The cavitation entropy is calculated according to the original formulation (G25 in G32) with the only exception that $y' = (3y/(1-y))+4.5(y/(1-y)^2$ was condensed for brevity.

2 Computed Gibbs Free Energies

2.1 Scatter Plots for Reactions with Decreasing Particle Number

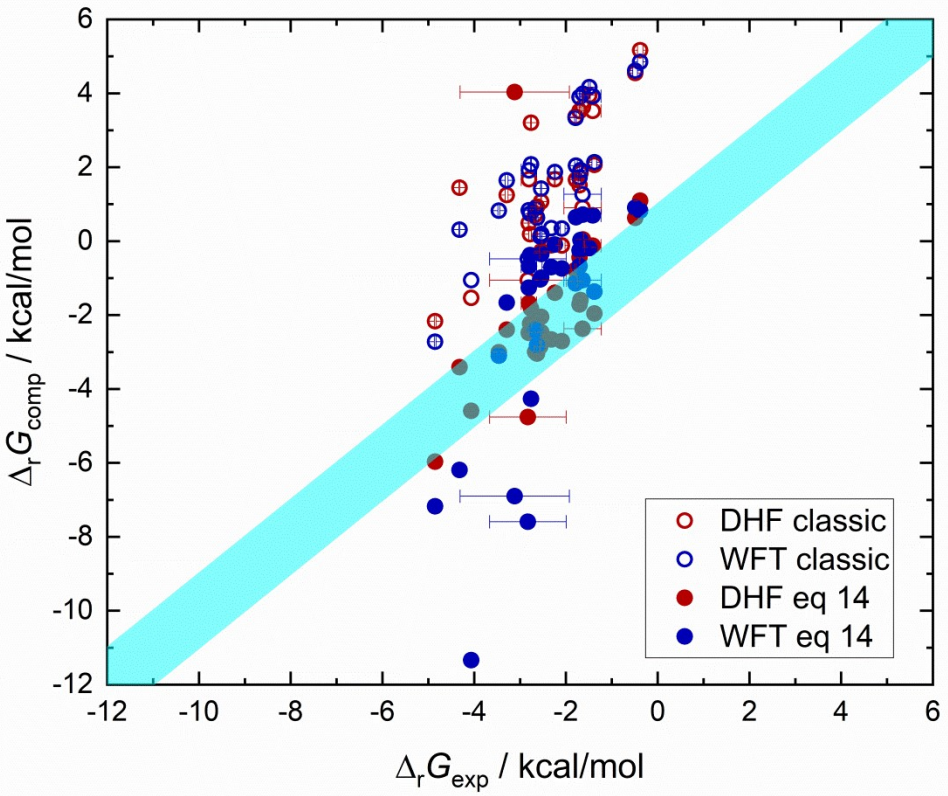

Figure S1: Scatter plot of computed Gibbs free solution-phase reaction energies versus experimental values for reactions with decreasing particle number. The red and blue circles refer to revDSD-PBEP86-D4 and DLPNO-CCSD(T) level of theory, respectively. Hollow and filled symbols refer to uncorrected (i.e., classic approach) and corrected values according to eq 14, respectively. The blue shaded area denotes the regime of chemical accuracy (±1 kcal/mol). Uncorrected values for entry 39 (>14 kcal/mol) are omitted for clarity.

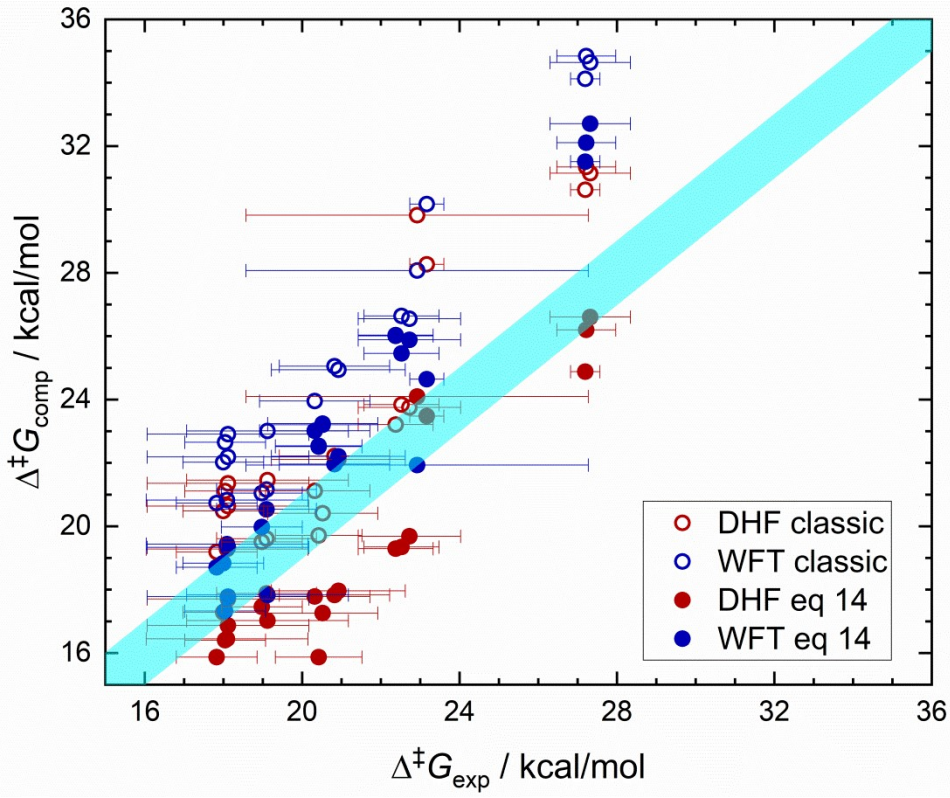

Figure S2: Scatter plot of computed Gibbs free solution-phase activation energies versus experimental values for reactions with decreasing particle number. The red and blue circles refer to revDSD-PBEP86-D4 and DLPNO-CCSD(T) level of theory, respectively. Hollow and filled symbols refer to uncorrected (i.e., classic approach) and corrected values according to eq 14, respectively. The blue shaded area denotes the regime of chemical accuracy (±1 kcal/mol).

2.2 Statistics

Table S1: Mean absolute error (MAE), mean signed error (MSE), mean absolute deviation (MAD), minimum error (min), and maximum error (max) of the Gibbs free energies (comp−exp) regarding bimolecular reactions in kcal/mol. Values in parentheses and brackets are corrected for the entropic penalty using eq 13 and 14, respectively.

	$\Delta^{\ddagger}G_{soln}$		$\Delta_r G_{soln}$	
	WFT	DHF	WFT	DHF
MAE	4.2 (1.6) [0.8]	2.2 (2.8) [2.0]	4.4 (1.5) [1.1]	4.3 (1.5) [1.0]
MSE	4.2 (−0.4) [0.3]	2.1 (−2.5) [−1.8]	4.4 (1.3) [0.7]	4.3 (1.1) [0.5]
MAD	1.2 (1.5) [0.8]	1.5 (1.7) [1.1]	1.5 (1.3) [1.0]	1.5 (1.4) [0.9]
min	2.1 (−3.6) [−1.7]	−0.7 (−6.5) [−4.6]	2.1 (−1.3) [−1.7]	1.8 (−1.5) [−1.9]
max	7.6 (3.7) [2.8]	6.9 (1.8) [1.2]	19.4 (14.6) [8.8]	17.7 (13.0) [7.2]

Table S2: Mean absolute error (MAE), mean signed error (MSE), mean absolute deviation (MAD), minimum error (min), and maximum error (max) of the solution-phase entropy (comp−exp) regarding bimolecular reactions in kcal/mol.

	$-T\Delta^{\ddagger}S_{soln}$	$-T\Delta_r S_{soln}$
MAE	1.6	2.3
MSE	−0.7	2.2
MAD	1.6	1.0
min	−4.0	−0.5
max	3.4	4.4

2.3 Bimolecular Reactions

Table S3: Computed Gibbs free reaction energies for bimolecular reactions. Energies are given as the difference to experimental values. WFT and DHF denote DLPNO-CCSD(T) and revDSD-PBEP86-D4 level of theory, respectively. Entropy-corrected values are given according to eq 13 and eq 14.

				classic		eq 13		eq 14		exp error
Entry	Reaction	Solvent	*T* / K	WFT	DHF	WFT	DHF	WFT	DHF	
9	7a	DCM	270	3.0	2.5	−0.2	−0.7	−0.1	−0.5	0.0
10	7b	C_6H_6	314	2.3	1.8	−0.9	−1.5	−1.4	−1.9	0.8
11	8a	CCl_4	298	5.2	5.5	1.8	2.1	1.2	1.5	0.1
12	8b	CCl_4	298	5.1	5.0	1.8	1.8	1.2	1.1	0.1
13	8c	CCl_4	298	3.5	3.4	0.1	0.1	−0.5	−0.6	0.1
14	8d	CCl_4	298	5.7	5.4	2.3	2.1	1.5	1.3	0.0
15	8e	CCl_4	298	5.6	5.3	2.6	2.3	2.0	1.7	0.0
16	8f	CCl_4	298	3.6	3.5	0.4	0.3	0.2	0.1	0.0
17	8g	CCl_4	298	5.6	5.2	2.4	2.0	1.6	1.3	0.0
18	8h	CCl_4	298	3.4	3.2	0.6	0.4	0.2	0.0	0.0
19	8i	CCl_4	298	3.8	3.4	0.7	0.3	1.1	0.7	0.0
20	8j	CCl_4	298	5.1	5.2	1.9	1.9	1.0	1.0	0.0
21	8k	CCl_4	298	4.0	3.6	0.7	0.4	0.8	0.5	0.0
22	8l	CCl_4	298	2.7	2.2	−0.3	−0.7	0.2	−0.3	0.0
23	8m	CCl_4	298	3.3	3.6	−0.1	0.2	−0.7	−0.4	0.0
24	8n	CCl_4	298	3.6	3.4	0.6	0.4	−0.1	−0.3	0.0
25	8o	CCl_4	298	4.8	6.0	1.2	2.3	−0.2	0.9	0.0
26	8p	CCl_4	298	3.5	3.0	0.7	0.1	1.1	0.5	0.0
27	8q	CCl_4	298	3.6	3.3	1.1	0.8	0.7	0.3	0.0
28	8r	CCl_4	298	4.9	4.5	1.9	1.5	1.3	0.9	0.0
29	8s	CCl_4	298	4.3	4.3	1.1	1.1	0.5	0.5	0.0
30	8t	CCl_4	298	4.6	5.8	1.0	2.2	−0.2	0.9	0.0
31	8u	CCl_4	298	2.1	2.7	−1.3	−0.7	−1.7	−1.1	0.0
32	8v	CCl_4	298	4.1	3.9	1.2	1.0	1.0	0.8	0.0
33	8w	CCl_4	298	2.9	2.5	0.0	−0.4	−0.4	−0.7	0.4
34	8x	CCl_4	298	5.3	4.9	2.3	1.9	1.7	1.3	0.2

Entry	Reaction	Solvent	T / K	classic		eq 13		eq 14		exp error
				WFT	DHF	WFT	DHF	WFT	DHF	
35	8y	CCl_4	298	4.7	4.5	1.9	1.6	1.4	1.1	0.2
36	8z	CCl_4	298	2.7	2.2	−0.3	−0.8	0.1	−0.3	0.2
37	8z	C_6H_6	298	2.4	2.0	−0.6	−1.1	−0.2	−0.6	0.1
38	8z	C_6H_{12}	298	2.7	2.3	0.0	−0.4	0.5	0.1	0.0
39	9	diglyme	348	19.4	17.7	14.6	13.0	8.8	7.2	1.2

Table S4: Computed Gibbs free activation barriers for bimolecular reactions. Energies are given as the difference to experimental values. WFT and DHF denote DLPNO-CCSD(T) and revDSD-PBEP86-D4 level of theory, respectively. Entropy-corrected values are given according to eq 13 and eq 14.

Entry	Reaction	Solvent	T / K	classic		eq 13		eq 14		exp error
				WFT	DHF	WFT	DHF	WFT	DHF	
40	10	CCl_4	301	7.0	5.1	3.7	1.8	2.2	0.3	0.4
41	11	C_6H_{12}	301	4.0	1.2	0.1	−2.7	−0.1	−3.0	1.7
42	11	C_6H_6	301	4.2	1.4	0.1	−2.7	−0.2	−3.0	1.4
43	11	1,4-dioxane	301	3.6	0.8	−0.5	−3.4	0.3	−2.5	1.4
44	11	*i*PrOH	301	2.7	−0.1	−1.9	−4.8	−0.4	−3.3	1.4
45	11	MeOH	301	2.1	−0.7	−3.6	−6.5	−1.7	−4.6	1.1
46	12	C_6H_{12}	301	3.8	1.0	−0.9	−3.7	−0.2	−3.0	1.3
47	12	C_6H_6	301	4.1	1.3	−0.8	−3.6	−0.4	−3.2	1.0
48	12	1,4-dioxane	301	3.6	0.8	−1.4	−4.2	−0.3	−3.1	1.0
49	13	C_6H_{12}	348	7.3	3.8	2.6	−0.9	2.8	−0.7	1.0
50	13	C_6H_6	348	7.6	4.1	2.5	−1.0	2.5	−1.0	0.7
51	13	acetone	348	6.9	3.4	0.9	−2.6	1.2	−2.3	0.4
52	14a	*n*-hexane	303	4.8	3.2	1.8	0.3	0.3	−1.3	2.1
53	14a	$CHCl_3$	303	3.9	2.3	0.1	−1.5	−0.6	−2.1	2.1
54	14a	*n*PrOH	303	4.1	2.5	−0.2	−1.7	1.1	−0.4	2.1
55	14a	H_2O	303	2.7	1.2	−3.2	−4.7	−0.1	−1.6	2.1
56	14a	TFEI	303	2.1	0.5	−2.3	−3.8	0.3	−1.2	1.3
57	14b	*n*-hexane	303	4.6	3.1	1.4	−0.2	−0.1	−1.6	1.0
58	14b	*n*PrOH	303	4.0	2.5	−0.5	−2.0	0.8	−0.7	1.0

Entry	Reaction	Solvent	*T* / K	classic		eq 13		eq 14		exp error
				WFT	DHF	WFT	DHF	WFT	DHF	
59	14b	TFE	303	2.1	0.5	−2.5	−4.1	0.0	−1.5	1.0
60	14b	H_2O	303	2.9	1.4	−3.4	−4.9	−0.4	−2.0	1.0
61	15	THF	308	5.2	6.9	−0.1	1.6	−0.6	1.2	4.3

2.4 Calculated Entropy-Correction term

Table S5: Calculated correction for the entropic penalty ΔG_{corr} (eq 16) given as additive correction to $\Delta_r G_{soln}$ and $\Delta^{\ddagger} G_{soln}$ (in kcal/mol) following the formalisms according to eq 13 and eq 14 (superior, cf. eq 15).

Entry	Reaction	Solvent	T / K	eq 13	eq 14
9	7a	DCM	270	−3.2	−3.1
10	7b	C_6H_6	314	−3.3	−3.7
11	8a	CCl_4	298	−3.4	−4.1
12	8b	CCl_4	298	−3.3	−3.9
13	8c	CCl_4	298	−3.4	−4.0
14	8d	CCl_4	298	−3.3	−4.1
15	8e	CCl_4	298	−3.0	−3.6
16	8f	CCl_4	298	−3.2	−3.4
17	8g	CCl_4	298	−3.2	−4.0
18	8h	CCl_4	298	−2.8	−3.2
19	8i	CCl_4	298	−3.1	−2.8
20	8j	CCl_4	298	−3.3	−4.1
21	8k	CCl_4	298	−3.2	−3.1
22	8l	CCl_4	298	−3.0	−2.5
23	8m	CCl_4	298	−3.3	−4.0
24	8n	CCl_4	298	−3.0	−3.7
25	8o	CCl_4	298	−3.6	−5.0
26	8p	CCl_4	298	−2.9	−2.4
27	8q	CCl_4	298	−2.5	−3.0
28	8r	CCl_4	298	−3.0	−3.6
29	8s	CCl_4	298	−3.2	−3.8
30	8t	CCl_4	298	−3.6	−4.9
31	8u	CCl_4	298	−3.4	−3.8
32	8v	CCl_4	298	−2.9	−3.1
33	8w	CCl_4	298	−2.9	−3.3
34	8x	CCl_4	298	−3.0	−3.6
35	8y	CCl_4	298	−2.9	−3.4
36	8z	CCl_4	298	−3.0	−2.6

Entry	Reaction	Solvent	*T* / K	eq 13	eq 14
37	8z	C_6H_6	298	−3.0	−2.6
38	8z	C_6H_{12}	298	−2.7	−2.2
39	9	diglyme	348	−4.7	−10.5
40	10	CCl_4	301	−3.3	−4.8
41	11	C_6H_{12}	301	−3.9	−4.1
42	11	C_6H_6	301	−4.1	−4.4
43	11	1,4-dioxane	301	−4.2	−3.3
44	11	*i*PrOH	301	−4.7	−3.1
45	11	MeOH	301	−5.8	−3.8
46	12	C_6H_{12}	301	−4.7	−4.1
47	12	C_6H_6	301	−5.0	−4.5
48	12	1,4-dioxane	301	−5.0	−3.9
49	13	C_6H_{12}	348	−4.7	−4.5
50	13	C_6H_6	348	−5.1	−5.1
51	13	acetone	348	−6.0	−5.7
52	14a	*n*-hexane	303	−3.0	−4.5
53	14a	$CHCl_3$	303	−3.8	−4.4
54	14a	*n*PrOH	303	−4.3	−2.9
55	14a	H_2O	303	−5.9	−2.8
56	14a	TFE	303	−4.4	−1.7
57	14b	*n*-hexane	303	−3.2	−4.7
58	14b	*n*PrOH	303	−4.5	−3.2
59	14b	TFE	303	−4.6	−2.1
60	14b	H_2O	303	−6.3	−3.3
61	15	THF	308	−5.3	−5.7

Table S6: Computed solution-phase reaction/activation entropies given as the difference to experimental values. All entropies are given as $-TS$ in kcal/mol at the given temperature.

Entry	Reaction	Solvent	T / K	$-T(\Delta_r S_{comp} - \Delta_r S_{exp})$	exp error
9	7a	DCM	270	3.3	—
10	7b	C_6H_6	314	4.0	0.4
11	8a	CCl_4	298	4.1	0.4
12	8b	CCl_4	298	3.2	0.2
13	8c	CCl_4	298	1.4	0.1
14	8d	CCl_4	298	2.9	0.1
15	8e	CCl_4	298	3.1	0.1
16	8f	CCl_4	298	2.3	0.1
17	8g	CCl_4	298	2.5	0.4
18	8h	CCl_4	298	1.8	0.1
19	8i	CCl_4	298	1.7	0.2
20	8j	CCl_4	298	2.2	0.2
21	8k	CCl_4	298	1.8	0.1
22	8l	CCl_4	298	0.8	0.1
23	8m	CCl_4	298	0.4	0.1
24	8n	CCl_4	298	3.6	0.1
25	8o	CCl_4	298	4.4	0.3
26	8p	CCl_4	298	1.8	0.1
27	8q	CCl_4	298	1.9	0.1
28	8r	CCl_4	298	2.6	0.1
29	8s	CCl_4	298	3.5	0.1
30	8t	CCl_4	298	4.1	0.1
31	8u	CCl_4	298	3.6	0.4
32	8v	CCl_4	298	1.4	0.3
33	8w	CCl_4	298	1.0	0.2
34	8x	CCl_4	298	2.5	0.1
35	8y	CCl_4	298	2.1	0.1
36	8z	CCl_4	298	0.5	0.2
37	8z	C_6H_6	298	1.2	0.2

38	8z	C_6H_{12}	298	0.2	0.1
39	9	diglyme	348	−0.5	0.6
Entry	Reaction	Solvent	*T* / K	$-T(\Delta^{\ddagger}S_{comp}-\Delta^{\ddagger}S_{exp})$	exp error
40	10	CCl_4	301	1.5	0.2
41	11	C_6H_{12}	301	0.1	0.9
42	11	C_6H_6	301	−0.7	0.6
43	11	1,4-dioxane	301	0.5	0.6
44	11	*i*PrOH	301	−1.2	0.6
45	11	MeOH	301	−0.8	0.3
46	12	C_6H_{12}	301	−1.5	0.6
47	12	C_6H_6	301	−2.4	0.5
48	12	1,4-dioxane	301	−2.3	0.5
49	13	C_6H_{12}	348	−2.5	0.5
50	13	C_6H_6	348	−2.9	0.3
51	13	acetone	348	−4.0	0.2
52	14a	*n*-hexane	303	1.5	0.5
53	14a	$CHCl_3$	303	1.9	0.5
54	14a	*n*PrOH	303	0.2	0.5
55	14a	H_2O	303	0.4	0.5
56	14a	TFE	303	−2.8	0.5
57	14b	*n*-hexane	303	0.9	0.2
58	14b	*n*PrOH	303	−0.4	0.2
59	14b	TFE	303	−3.2	0.2
60	14b	H_2O	303	−0.2	0.2
61	15	THF	308	3.4	2.2

2.5 Computed Gibbs Free Energies

Table S7: Computed Gibbs free energies (kcal/mol) for unimolecular (entries 1−8) and bimolecular (entries 9−61) reactions. WFT and DHF refer to DLPNO-CCSD(T) and revDSD-PBEP86-D4 level of theory, respectively. Bulk solvation was considered implicitly with the SMD model.

Entry	Reaction	Solvent	T / K	Δ_rG_{soln}		Δ_rG_g		$\Delta_r\Delta_{solv}G$	Δ_rE_e
				WFT	DHF	WFT	DHF		
1	1	decalin	411	−0.9	−0.9	−1.1	−1.1	0.2	0.2
Entry	Reaction	Solvent	T / K	$\Delta^‡G_{soln}$		$\Delta^‡G_g$		$\Delta^‡\Delta_{solv}G$	$\Delta^‡E_e$
				WFT	DHF	WFT	DHF		
2	1	decalin	411	34.5	32.6	34.2	32.3	0.4	0.1
3	2	1-decene	396	29.5	29.9	30.4	30.8	−0.9	−0.1
4	2	PhCN	383	29.1	27.2	30.4	28.4	−1.3	−0.1
5	3	*n*-hexane	303	19.4	18.4	19.4	18.4	0.0	0.5
6	4	C_6H_6	340	31.9	28.9	32.5	29.5	−0.6	−0.9
7	5	C_6H_6	337	31.0	28.3	31.4	28.7	−0.4	−0.9
8	6	$CHCl_3$	329	21.0	21.1	20.2	20.4	0.8	0.3
Entry	Reaction	Solvent	T / K	Δ_rG_{soln}		Δ_rG_g		$\Delta_r\Delta_{solv}G$	Δ_rE_e
				WFT	DHF	WFT	DHF		
9	7a	DCM	270	−1.1	−1.5	−8.3	−8.8	7.2	9.1
10	7b	C_6H_6	314	−0.5	−1.1	−3.9	−4.5	3.4	5.0
11	8a	CCl_4	298	4.8	5.2	4.9	5.2	0.0	1.2

12	8b	CCl_4	298	4.6	4.6	4.8	4.8	−0.2	1.0
13	8c	CCl_4	298	2.1	2.1	2.7	2.6	−0.5	0.8
14	8d	CCl_4	298	4.2	3.9	3.9	3.7	0.2	1.4
15	8e	CCl_4	298	4.0	3.6	4.3	3.9	−0.3	1.0
16	8f	CCl_4	298	1.9	1.8	3.5	3.4	−1.5	0.1
17	8g	CCl_4	298	3.9	3.5	3.7	3.3	0.2	1.4
18	8h	CCl_4	298	1.7	1.5	2.5	2.3	−0.8	0.7
19	8i	CCl_4	298	2.0	1.7	3.4	3.0	−1.4	0.9
20	8j	CCl_4	298	3.3	3.4	3.0	3.0	0.3	1.3
21	8k	CCl_4	298	1.4	1.1	2.1	1.8	−0.7	1.3
22	8l	CCl_4	298	0.1	−0.3	1.5	1.1	−1.4	1.0
23	8m	CCl_4	298	0.6	0.9	1.2	1.4	−0.5	0.7
24	8n	CCl_4	298	0.9	0.7	1.3	1.1	−0.4	0.8
25	8o	CCl_4	298	2.1	3.2	0.8	1.9	1.3	1.8
26	8p	CCl_4	298	0.7	0.2	2.0	1.5	−1.3	1.0
27	8q	CCl_4	298	0.8	0.5	1.7	1.4	−0.9	0.6
28	8r	CCl_4	298	1.6	1.2	2.0	1.6	−0.3	0.9
29	8s	CCl_4	298	0.8	0.8	0.7	0.7	0.1	1.4
30	8t	CCl_4	298	0.3	1.4	−1.3	−0.2	1.6	2.3
31	8u	CCl_4	298	−2.7	−2.2	−3.4	−2.8	0.7	2.1

32	8v	CCl_4	298	1.9	1.7	3.0	2.8	−1.1	0.7
33	8w	CCl_4	298	1.3	0.9	2.2	1.8	−0.9	0.6
34	8x	CCl_4	298	3.9	3.5	4.3	3.9	−0.4	0.9
35	8y	CCl_4	298	1.9	1.7	2.7	2.4	−0.8	0.7
36	8z	CCl_4	298	0.3	−0.1	1.8	1.4	−1.5	0.8
37	8z	C_6H_6	298	0.3	−0.1	1.8	1.4	−1.5	0.8
38	8z	C_6H_{12}	298	0.2	−0.3	1.8	1.4	−1.7	0.7
39	9	diglyme	348	16.3	14.6	3.7	2.0	12.6	9.1

Entry	Reaction	Solvent	T / K	$\Delta^{\ddagger}G_{soln}$		$\Delta^{\ddagger}G_g$		$\Delta^{\ddagger}\Delta_{solv}G$	$\Delta^{\ddagger}E_e$
				WFT	DHF	WFT	DHF		
40	10	CCl_4	301	30.2	28.3	29.4	27.5	0.7	1.2
41	11	C_6H_{12}	301	24.9	22.1	26.3	23.5	−1.4	0.6
42	11	C_6H_6	301	25.0	22.2	26.3	23.5	−1.3	0.6
43	11	1,4-dioxane	301	23.9	21.1	26.3	23.5	−2.4	0.6
44	11	*i*PrOH	301	23.2	20.4	26.3	23.5	−3.1	0.6
45	11	MeOH	301	22.5	19.7	26.3	23.5	−3.8	0.3
46	12	C_6H_{12}	301	26.5	23.7	29.9	27.1	−3.4	−0.6
47	12	C_6H_6	301	26.6	23.8	29.9	27.1	−3.3	−0.7
48	12	1,4-dioxane	301	26.0	23.2	29.9	27.1	−3.9	−0.7
49	13	C_6H_{12}	348	34.6	31.1	37.2	33.8	−2.6	−0.2

50	13	C_6H_6	348	34.8	31.3	37.2	33.8	−2.4	−0.2
51	13	acetone	348	34.1	30.6	37.2	33.8	−3.1	−0.6
52	14a	*n*-hexane	303	22.9	21.4	22.3	20.7	0.6	1.1
53	14a	$CHCl_3$	303	23.0	21.5	22.3	20.7	0.7	2.1
54	14a	*n*PrOH	303	22.2	20.6	22.3	20.7	−0.1	3.2
55	14a	H_2O	303	20.8	19.3	22.3	20.7	−1.4	3.6
56	14a	TFE	303	21.2	19.6	22.3	20.7	−1.1	3.5
57	14b	*n*-hexane	303	22.6	21.1	22.0	20.5	0.6	1.1
58	14b	*n*PrOH	303	22.0	20.5	22.0	20.5	0.0	3.2
59	14b	TFE	303	21.0	19.5	22.0	20.5	−1.0	3.5
60	14b	H_2O	303	20.7	19.2	22.0	20.5	−1.3	3.6
61	15	THF	308	28.1	29.8	27.7	29.4	0.4	2.2

2.6 Computed Entropies

Table S8: Computed entropies for unimolecular (entries 1−8) and bimolecular (entries 9−61) reactions. All entropies are given as $-TS$ in kcal/mol at the given temperature.

Entry	Reaction	Solvent	T / K	Δ_rS_{soln}	$\Delta_r\Delta_{solv}S$	$\Delta_rS_{g,trans}$	$\Delta_rS_{g,rot}$	$\Delta_rS_{g,vib}$	$\Delta_r\Delta_{solv}S_{trans}$	$\Delta_r\Delta_{solv}S_{rot}$	Δ_rS_{cav}	$\Delta_r\Delta S_{conc}$	Δ_rV_{vdW}
1	1	decalin	411	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	−0.
Entry	Reaction	Solvent	T / K	$\Delta^‡S_{soln}$	$\Delta^‡\Delta_{solv}S$	$\Delta^‡S_{g,trans}$	$\Delta^‡S_{g,rot}$	$\Delta^‡S_{g,vib}$	$\Delta^‡\Delta_{solv}S_{trans}$	$\Delta^‡\Delta_{solv}S_{rot}$	$\Delta^‡S_{cav}$	$\Delta^‡\Delta S_{conc}$	$\Delta^‡V_{vdW}$
2	1	decalin	411	0.3	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.9
3	2	1-decene	396	1.3	0.0	0.0	0.1	1.3	0.0	0.0	0.0	0.0	−1.
4	2	PhCN	383	1.3	−0.1	0.0	0.1	1.3	0.0	0.0	0.0	0.0	−1.
5	3	*n*-hexane	303	2.4	−0.5	0.0	0.1	2.7	0.0	−0.5	0.0	0.0	−2.
6	4	C_6H_6	340	−1.0	0.0	0.0	0.0	−0.9	0.0	0.0	0.0	0.0	3.9
7	5	C_6H_6	337	−0.6	−0.1	0.0	0.0	−0.6	0.0	−0.1	0.0	0.0	3.9
8	6	$CHCl_3$	329	−0.1	0.0	0.0	0.0	−0.1	0.0	0.0	0.0	0.0	4.2
Entry	Reaction	Solvent	T / K	Δ_rS_{soln}	$\Delta_r\Delta_{solv}S$	$\Delta_rS_{g,trans}$	$\Delta_rS_{g,rot}$	$\Delta_rS_{g,vib}$	$\Delta_r\Delta_{solv}S_{trans}$	$\Delta_r\Delta_{solv}S_{rot}$	Δ_rS_{cav}	$\Delta_r\Delta S_{conc}$	Δ_rV_{vdW}
9	7a	DCM	270	6.5	−4.9	10.0	6.1	−4.7	−2.5	−0.1	−0.6	−1.7	0.8
10	7b	C_6H_6	314	8.1	−5.3	12.0	8.0	−6.6	−2.9	−0.2	−0.2	−2.0	0.4
11	8a	CCl_4	298	5.7	−5.3	11.5	6.8	−7.3	−2.6	−0.6	−0.2	−1.9	0.2
12	8b	CCl_4	298	5.9	−5.2	11.3	6.7	−7.0	−2.6	−0.4	−0.2	−1.9	0.2
13	8c	CCl_4	298	5.6	−5.3	11.1	6.0	−6.2	−2.7	−0.5	−0.2	−1.9	0.3
14	8d	CCl_4	298	6.2	−5.3	11.2	6.6	−6.4	−2.7	−0.5	−0.2	−1.9	0.3
15	8e	CCl_4	298	6.7	−4.9	11.1	6.3	−5.8	−2.7	−0.1	−0.2	−1.9	0.3

16	8f	CCl_4	298	6.4	−5.1	11.3	6.8	−6.6	−2.6	−0.3	−0.2	−1.9	0.3
17	8g	CCl_4	298	6.4	−5.1	11.5	6.8	−6.8	−2.6	−0.4	−0.2	−1.9	0.3
18	8h	CCl_4	298	5.7	−4.7	11.1	5.8	−6.4	−2.6	0.0	−0.2	−1.9	0.3
19	8i	CCl_4	298	6.1	−5.0	11.5	6.6	−6.9	−2.7	−0.3	−0.2	−1.9	0.3
20	8j	CCl_4	298	6.2	−5.2	11.3	6.7	−6.6	−2.7	−0.4	−0.2	−1.9	0.3
21	8k	CCl_4	298	6.6	−5.1	11.4	6.8	−6.6	−2.6	−0.4	−0.2	−1.9	0.3
22	8l	CCl_4	298	5.3	−4.9	11.2	5.9	−6.9	−2.7	−0.1	−0.2	−1.9	0.3
23	8m	CCl_4	298	6.7	−5.2	11.3	6.3	−5.6	−2.6	−0.5	−0.2	−1.9	0.4
24	8n	CCl_4	298	6.4	−4.9	11.0	5.9	−5.6	−2.4	−0.4	−0.2	−1.9	0.3
25	8o	CCl_4	298	7.9	−5.5	11.6	7.5	−5.7	−2.6	−0.8	−0.2	−1.9	0.4
26	8p	CCl_4	298	6.3	−4.8	11.2	6.5	−6.7	−2.7	0.0	−0.2	−1.9	0.3
27	8q	CCl_4	298	5.7	−4.4	11.1	6.3	−7.3	−2.6	0.3	−0.2	−1.9	0.4
28	8r	CCl_4	298	6.7	−4.9	11.2	6.5	−6.1	−2.7	−0.1	−0.2	−1.9	0.4
29	8s	CCl_4	298	6.8	−5.1	11.2	6.3	−5.5	−2.6	−0.5	−0.2	−1.9	0.4
30	8t	CCl_4	298	7.1	−5.5	11.6	7.1	−6.1	−2.6	−0.8	−0.2	−1.9	0.5
31	8u	CCl_4	298	6.7	−5.3	11.5	6.6	−6.0	−2.6	−0.6	−0.2	−1.9	0.4
32	8v	CCl_4	298	6.7	−4.8	11.0	6.0	−5.5	−2.5	−0.3	−0.2	−1.9	0.3
33	8w	CCl_4	298	4.9	−4.8	11.0	5.7	−6.6	−2.6	−0.1	−0.2	−1.9	0.3
34	8x	CCl_4	298	6.3	−4.9	11.0	6.2	−6.0	−2.7	−0.2	−0.2	−1.9	0.3
35	8y	CCl_4	298	6.1	−4.8	11.1	6.2	−6.3	−2.6	−0.1	−0.2	−1.9	0.3

36	8z	CCl_4	298	5.2	−4.9	11.1	5.7	−6.8	−2.7	−0.1	−0.2	−1.9	0.3
37	8z	C_6H_6	298	5.1	−4.9	11.1	5.7	−6.8	−2.7	−0.1	−0.2	−1.9	0.3
38	8z	C_6H_{12}	298	5.5	−4.6	11.1	5.7	−6.8	−2.4	−0.1	−0.2	−1.9	0.3
39	9	diglyme	348	10.1	−7.1	14.0	8.6	−5.4	−2.9	−1.1	−0.7	−2.3	2.8
Entry	Reaction	Solvent	T / K	$\Delta^{\ddagger}S_{soln}$	$\Delta^{\ddagger}\Delta_{solv}S$	$\Delta^{\ddagger}S_{g,trans}$	$\Delta^{\ddagger}S_{g,rot}$	$\Delta^{\ddagger}S_{g,vib}$	$\Delta^{\ddagger}\Delta_{solv}S_{trans}$	$\Delta^{\ddagger}\Delta_{solv}S_{rot}$	$\Delta^{\ddagger}S_{cav}$	$\Delta^{\ddagger}\Delta S_{conc}$	$\Delta^{\ddagger}V_{vdW}$
40	10	CCl_4	301	8.4	−5.3	11.0	5.7	−2.9	−2.5	−0.6	−0.2	−1.9	−6.
41	11	C_6H_{12}	301	10.3	−6.1	12.9	7.6	−4.1	−2.9	−0.8	−0.2	−2.2	−5.
42	11	C_6H_6	301	10.1	−6.3	12.9	7.6	−4.1	−3.0	−0.8	−0.3	−2.2	−5.
43	11	1,4-dioxane	301	10.1	−6.3	12.9	7.6	−4.1	−3.1	−0.8	−0.3	−2.2	−5.
44	11	*i*PrOH	301	9.6	−6.8	12.9	7.6	−4.1	−3.0	−0.8	−0.9	−2.2	−5.
45	11	MeOH	301	8.5	−7.9	12.9	7.6	−4.1	−3.3	−1.0	−1.5	−2.2	−5.
46	12	C_6H_{12}	301	10.5	−6.9	12.9	7.9	−3.4	−2.9	−1.6	−0.2	−2.2	−5.
47	12	C_6H_6	301	10.3	−7.1	12.9	7.9	−3.4	−3.0	−1.7	−0.3	−2.2	−5.
48	12	1,4-dioxane	301	10.2	−7.2	12.9	7.9	−3.4	−3.0	−1.7	−0.3	−2.2	−5.
49	13	C_6H_{12}	348	12.1	−7.0	13.1	8.3	−2.3	−2.9	−1.6	−0.2	−2.3	−5.
50	13	C_6H_6	348	11.7	−7.4	13.1	8.3	−2.3	−3.1	−1.7	−0.3	−2.3	−5.
51	13	acetone	348	10.8	−8.3	13.1	8.3	−2.3	−3.2	−1.7	−1.1	−2.3	−5.
52	14a	*n*-hexane	303	9.5	−4.9	11.6	7.0	−4.2	−2.3	−0.5	−0.2	−1.9	−5.
53	14a	$CHCl_3$	303	8.6	−5.8	11.6	7.0	−4.2	−2.7	−0.6	−0.5	−1.9	−5.
54	14a	*n*PrOH	303	8.2	−6.2	11.6	7.0	−4.2	−2.7	−0.6	−1.0	−1.9	−5.

2		Computed			Gibbs			Free			Energies		
55	14a	H_2O	303	6.5	−7.9	11.6	7.0	−4.2	−3.2	−0.7	−2.0	−1.9	−5.
56	14a	TFE	303	8.1	−6.3	11.6	7.0	−4.2	−2.8	−0.6	−1.0	−1.9	−5.
57	14b	*n*-hexane	303	9.2	−5.2	11.7	7.2	−4.5	−2.4	−0.7	−0.2	−1.9	−5.
58	14b	*n*PrOH	303	8.0	−6.4	11.7	7.2	−4.5	−2.7	−0.8	−1.0	−1.9	−5.
59	14b	TFE	303	7.9	−6.5	11.7	7.2	−4.5	−2.7	−0.8	−1.1	−1.9	−5.
60	14b	H_2O	303	6.2	−8.2	11.7	7.2	−4.5	−3.1	−1.0	−2.1	−1.9	−5.
61	15	THF	308	10.1	−7.5	13.4	8.7	−4.5	−2.9	−1.5	−0.9	−2.2	−8.

3 Black-Box Algorithm for Solvation Entropy

The algorithm consists of four different bash-scripts. The main script is *calcEntropySolv* that is invoked by the user. The remaining scripts are then invoked internally throughout the calculation and do not require manipulation by the user.

calcEntropySolv calculates the solvation entropy of a given solute in the desired solute (*vide infra* for numerical examples).

readSolventLibrary extracts the required physical data from a desired solvent from the solvent library.

convertPTE converts the element symbol into its physical quantities (e.g. standard atomic weight).

calcVolume_vdW calculates the molecular vdW volume using Petitjean's algorithm (*vide infra*).[2] The binary must be stored in the same directory.

This section is divided as follows. First, we outline the general procedure of the black-box algorithm. Then, we give detailed information about the calculation of the molecular volume and initial test calculations. Finally, we conclude with the deposited databases and numerical examples for reproduction/documentation purposes.

3.1 General Procedure: Flow-Chart

The flow chart illustrates the single steps of our script for the computation of $S°_{soln}$ and $\Delta_{solv}S°$ for any solute (Figure S3). It is mandatory to request a solvent and to provide an input file. This can be either a XYZ file or an output file from a preceding frequency computation (Gaussian/ORCA). Either way the required properties of the solute, i.e., molar mass, the radius of gyration, and van der Waals volume, are calculated. The solvent can be requested either by selecting one of the 187 implemented ones or specified manually. The latter requires the relative permittivity, molar mass, density, and molecular volume of the solvent. Subsequently, the properties of the solute and the solvent are used to calculate the solvation entropy $\Delta_{solv}S°$, and its components, according to Garza's formalism.[1] If the input file contains a frequency computation, the gas-phase rotational entropy is read and the gas-phase vibrational entropy is calculated according to Grimme's qRRHO approach (100 cm^{-1} cutoff compatible with ORCA).[3] This allows calculating the solution-phase entropy $S°_{soln}$.

To summarize, it requires no more than an optimized molecular structure to compute the solvation entropy $\Delta_{solv}S°$. If a frequency computation is present, the solution-phase entropy $S°_{soln}$ is additionally calculated.

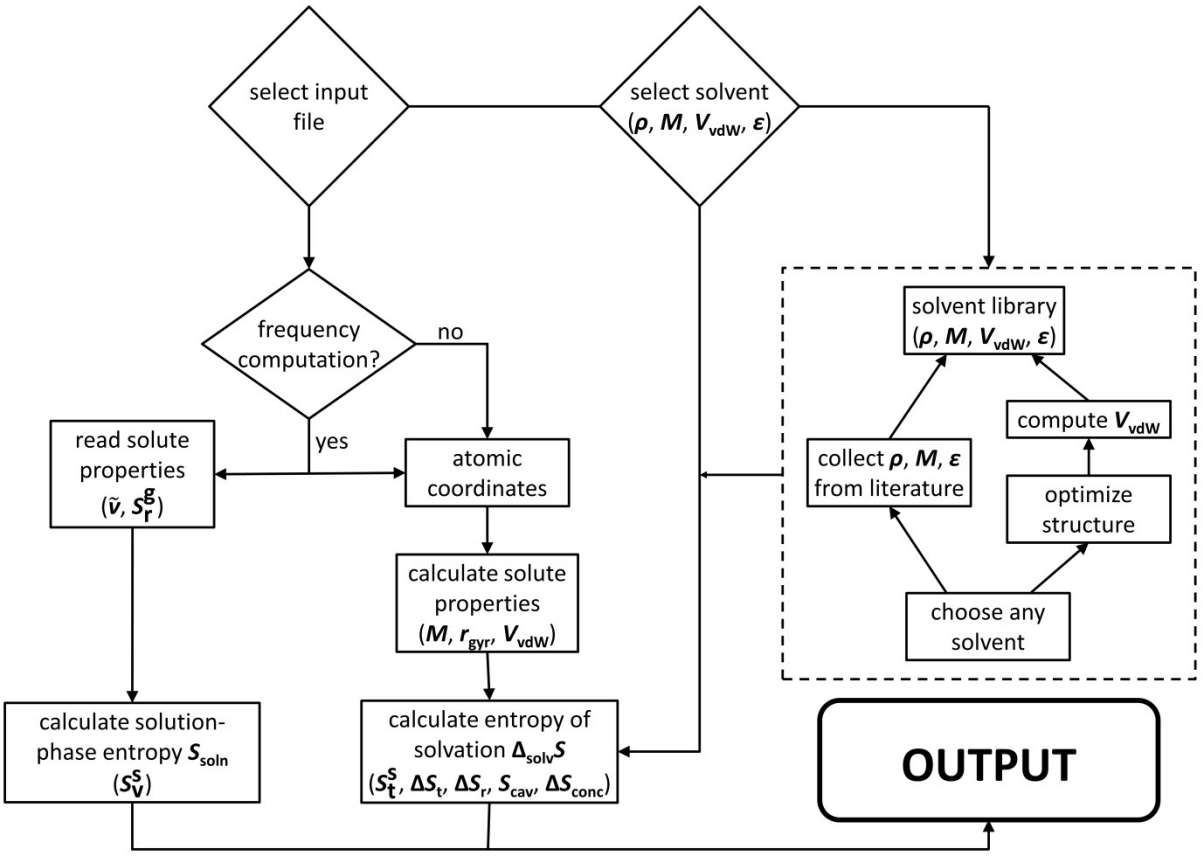

Figure S3. Flowchart illustrating the black-box algorithm to compute $\Delta_{solv}S°$ and $S°_{soln}$.

3.2 Benchmark of Molecular Volume

The method by Petitjean offers two important tools EPSTAB (=0 by default) and NPERM (=0 by default) to avoid numerical instabilities.[2] The former randomly perturbs the atomic coordinates and the latter performs redundant runs with randomly rotated and renumbered copies of the molecule. Especially the EPSTAB keyword is crucial to avoid artifacts. For iodobenzene we obtained different volumes with deviations >1 Å^3 from redundant runs (NPERM>1). Increasing EPSTAB eliminates the numerical instabilities at the cost of increased numerical noise. Tests showed that EPSTAB=$5\cdot10^{-5}$ is a good compromise as it did not produce any artifacts for any solvent molecule. To counteract the numerical noise, we employ redundant runs and discard potential outliers, i.e., deviations greater than 0.01 Å^3 from the

median. The final molecular volume is the arithmetic mean of the remainder. We found that NPERM=7 offers a good compromise between robustness and speed. All in all the computed molecular volume is converged to 10^{-4} Å^3.

3.3 Database

For the calculation of the vdW volume of the solute and solvent, we used the appropriate radii from Bondi with the additions from Rowland and Taylor, and Truhlar (Table S9). Any comparable radii should be feasible as long as they are used consistently.

Table S9: Bondi's set of atomic van der Waals radii for main group elements with additions from Rowland and Taylor, and Truhlar.[4–6]

1	**2**	**13**	**14**	**15**	**16**	**17**	**18**
H 1.10							He 1.40
Li 1.82	Be 1.53	B 1.92	C 1.70	N 1.55	O 1.52	F 1.47	Ne 1.54
Na 2.27	Mg 1.73	Al 1.84	Si 2.10	P 1.80	S 1.80	Cl 1.75	Ar 1.88
K 2.75	Ca 2.31	Ga 1.87	Ge 2.11	As 1.85	Se 1.90	Br 1.85	Kr 2.02
Rb 3.03	Sr 2.49	In 1.93	Sn 2.17	Sb 2.06	Te 2.06	I 1.98	Xe 2.16
Cs 3.43	Ba 2.68	Tl 1.96	Pb 2.02	Bi 2.07	Po 1.97	At 2.02	Rn 2.20
Fr 3.48	Ra 2.83						

The solvent library requires four parameters which are the relative permittivity, molar mass, density, and molecular volume. All but the latter were collected from the literature. The vdW volume was computed analytically from molecular structures, optimized at PBEh-3c level of theory, using Petitjean's algorithm.[2] Altogether, The implemented solvent library consists of 187 entries (Table S10). Alternatively, any arbitrary solvent can be specified manually. The employed standard atomic weights are given in Table S11.

Table S10: Solvent library containing the relative permittivity (ε_r), molar mass (M in g/mol), density (ρ in g/cm^3), and molecular van der Waals volume (V_{vdW} in Å^3).

Entry	Solvent	ε_r[a]	M[a]	ρ[a]	V_{vdW}[b]
1	Acetaldehyde	21	44.052	0.7834	44.86
2	Acetic Acid	6.2	60.052	1.0446	52.62
3	Acetone	21.01	58.079	0.7845	60.09
4	Acetonitrile	36.64	41.052	0.7857	43.4
5	Acetophenone	17.44	120.149	1.0281	113.23
6	Aniline	7.06	93.127	1.0217	89.28
7	Anisole	4.3	108.138	0.994	102.4
8	Argon	1.3247	39.948	1.396	27.83
9	Benzaldehyde	17.85	106.122	1.0401	98.12
10	Benzene	2.2825	78.112	0.8765	78.86
11	Benzonitrile	25.9	103.122	1.0093	96.68
12	Benzyl Alcohol	11.916	108.138	1.0419	102.37
13	Bromobenzene	5.45	157.008	1.495	97.61
14	Bromoethane	9.01	108.965	1.4604	59.93
15	Bromoform	4.404	252.731	2.8788	82.5
16	1-Bromo-2-methylpropane	7.7	137.018	1.272	90.43
17	1-Bromooctane	5.0957	193.125	1.1072	151.74
18	1-Bromopentane	6.31	151.045	1.2182	105.83
19	1-Bromopropane	8.09	122.992	1.3537	75.22
20	2-Bromopropane	9.46	122.992	1.314	75.16
21	Butanal	13.45	72.106	0.8016	75.41
22	Butanoic Acid	2.98	88.106	0.9528	83.25
23	1-Butanol	17.84	74.121	0.8095	79.59
24	2-Butanol	17.26	74.121	0.8063	79.62
25	Butanone	18.56	72.106	0.7999	75.32
26	Butyronitrile	24.83	69.106	0.7936	74.01
27	Butylamine	4.71	73.137	0.7414	82.22
28	*n*-Butylbenzene	2.359	134.218	0.8601	139.97
29	*sec*-Butylbenzene	2.357	134.218	0.8621	139.87
30	*tert*-Butylbenzene	2.359	134.218	0.8665	139.43
31	Butyl Acetate	5.07	116.158	0.8825	114.22
32	Carbon Disulfide	2.632	76.141	1.2632	52.39
33	Carbon Tetrachloride	2.2379	153.823	1.594	84.07
34	Chlorobenzene	5.6895	112.557	1.1058	93.34
35	2-Chlorobutane	8.564	92.567	0.8857	86.1
36	Chloroform	4.8069	119.378	1.4788	69.55
37	1-Chlorohexane	6.104	120.62	0.8781	116.78
38	1-Chloropentane	6.654	106.594	0.882	101.47
39	1-Chloropropane	8.588	78.541	0.8899	70.87
40	*m*-Chlorotoluene	5.763	126.584	1.075	108.55
41	*o*-Chlorotoluene	4.721	126.584	1.0825	108.41
42	*p*-Chlorotoluene	6.25	126.584	1.0697	108.55

Entry	Solvent	ε_r[a]	M[a]	ρ[a]	V_{vdW}[b]
43	*m*-Cresol	12.44	108.138	1.0339	102.01
44	*o*-Cresol	6.76	108.138	1.0327	101.91
45	Cyclohexane	2.0243	84.159	0.7739	92.15
46	Cyclohexanone	16.1	98.142	0.9478	96.22
47	Cyclopentane	1.9687	70.133	0.7457	77.71
48	Cyclopentanol	18.5	86.132	0.9488	85.91
49	Cyclopentanone	13.58	84.117	0.9487	81.65
50	Decalin	2.201	138.25	0.8812	143.41
51	*cis*-Decalin	2.219	138.25	0.8965	143.47
52	*trans*-Decalin	2.184	138.25	0.8659	143.35
53	*n*-Decane	1.9853	142.282	0.7266	163.17
54	1-Decanol	7.93	158.281	0.8297	171.41
55	1-Decene	2.136	140.266	0.7408	159.03
56	1,2-Dibromoethane	4.9612	187.861	2.1683	79.08
57	Dibutyl Ether	3.083	130.228	0.7684	141.12
58	*o*-Dichlorobenzene	10.12	147.002	1.3059	107.61
59	1,1-Dichloroethane	10.1	98.959	1.1757	70.21
60	1,2-Dichloroethane	10.42	98.959	1.2454	70.35
61	*E*-1,2-Dichloroethene	2.14	96.943	1.2565	65.68
62	*Z*-1,2-Dichloroethene	9.2	96.943	1.2837	65.51
63	Dichloromethane	8.93	84.933	1.3266	54.98
64	Diethylamine	3.68	73.137	0.7056	82.55
65	Diethyl Ether	4.2666	74.121	0.7138	79.92
66	Diethyl Sulfide	5.723	90.187	0.8362	90.09
67	Diglyme	7.23	134.173	0.94342	127.81
68	Diiodomethane	5.32	267.836	3.3211	76.38
69	Diisopropyl Ether	3.805	102.174	0.7192	110.56
70	*N*,*N*-Dimethylacetamide	38.85	87.12	0.9372	86.16
71	Dimethyl Disulfide	9.6	94.199	1.0625	78.22
72	*N*,*N*-Dimethylformamide	38.25	73.094	0.9445	71.21
73	2,4-Dimethylpentane	1.902	100.202	0.6727	117.06
74	2,4-Dimethylpyridine	9.6	107.153	0.9309	105.22
75	2,6-Dimethylpyridine	7.33	107.153	0.9226	105.22
76	Dimethyl Sulfoxide	47.24	78.133	1.101	67.36
77	1,4-Dioxane	2.2189	88.106	1.0337	79.04
78	*n*-Dodecane	2.012	170.334	0.7495	193.78
79	Diphenyl Ether	3.726	170.206	1.06613	155.64
80	Dipropylamine	2.923	101.19	0.74	113.15
81	1,2-Ethanediol	41.4	62.068	1.1135	57.28
82	Ethanethiol	6.667	62.134	0.8315	59.1
83	Ethanol	25.3	46.068	0.7893	48.99
84	Ethylbenzene	2.4463	106.165	0.8626	109.38
85	Ethylene	1.4833	28.053	0.5678	36.72
86	Ethyl Acetate	6.0814	88.106	0.9003	83.62

Entry	Solvent	ε_r[a]	M[a]	ρ[a]	V_{vdW}[b]
87	Ethyl Formate	8.57	74.079	0.9208	68.47
88	Ethyl Phenyl Ether	4.216	122.164	0.9651	117.68
89	Fluorobenzene	5.465	96.102	1.0225	84.23
90	1-Fluorooctane	3.89	132.219	0.8116	138.19
91	Formamide	111	45.041	1.1334	39.81
92	Formic Acid	51.1	46.026	1.22	37.44
93	Helium	1.055683	4.0026	0.141227	11.49
94	Heptane	1.9209	100.202	0.6795	117.26
95	1-Heptanol	11.75	116.201	0.8219	125.5
96	2-Heptanone	11.95	114.185	0.8111	121.23
97	4-Heptanone	12.6	114.185	0.8174	121.18
98	*n*-Hexadecane	2.046	226.441	0.7701	255
99	1,1,1,3,3,3-Hexafluoro-2-propanol	16.7	168.037	1.46	96.48
100	*n*-Hexane	1.8865	86.175	0.6606	101.95
101	Hexanoic Acid	2.6	116.158	0.9212	113.76
102	1-Hexanol	13.03	102.174	0.8136	110.19
103	2-Hexanone	14.56	100.158	0.81132	105.93
104	1-Hexene	2.077	84.159	0.6685	97.82
105	1-Hexyne	2.621	82.143	0.7155	94.07
106	Iodobenzene	4.59	204.008	1.8308	104
107	1-Iodobutane	6.27	184.018	1.6154	96.89
108	Iodoethane	7.82	155.965	1.9357	66.29
109	1-Iodohexadecane	3.57	352.337	1.1213	280.53
110	Iodomethane	6.97	141.939	2.2789	50.96
111	1-Iodopentane	5.78	198.045	1.5161	112.19
112	1-Iodopropane	7.07	169.992	1.7489	81.58
113	Isopentane	1.845	72.149	0.6201	86.56
114	Isopropylbenzene	2.381	120.191	0.864	124.61
115	*p*-Isopropyltoluene	2.2322	134.218	0.8573	139.81
116	Isoquinoline	11	129.159	1.091	117.08
117	Krypton	1.664	83.8	2.418	34.53
118	Mesitylene	2.279	120.191	0.8615	124.47
119	Methanol	33	32.042	0.7914	33.74
120	2-Methoxyethanol	17.2	76.095	0.9647	72.94
121	*N*-Methylaniline	5.96	107.153	0.9891	104.88
122	Methyl Benzoate	6.642	136.149	1.0837	121.47
123	Methyl Butyrate	5.48	102.132	0.8984	98.88
124	Methylcyclohexane	2.024	98.186	0.7694	107.34
125	Methyl Acetate	7.07	74.079	0.9342	68.33
126	Methyl Formate	9.2	60.052	0.9713	53.18
127	2-Methylpentane	1.886	86.175	0.65	101.87
128	4-Methyl-2-pentanone	13.11	100.158	0.7965	105.87
129	Methyl Propionate	6.2	88.106	0.915	83.58
130	2-Methyl-1-propanol	17.93	74.121	0.8018	79.53

Entry	Solvent	ε_r[a]	M[a]	ρ[a]	V_{vdW}[b]
131	2-Methyl-2-propanol	12.47	74.121	0.7887	79.44
132	2-Methylpyridine	10.18	93.127	0.9443	90.03
133	3-Methylpyridine	11.1	93.127	0.9566	90.04
134	4-Methylpyridine	12.2	93.127	0.9548	90.03
135	Neon	1.1907	20.18	1.204	15.3
136	Nitrobenzene	35.6	123.11	1.2037	102.14
137	Nitroethane	29.11	75.067	1.0448	64.33
138	Nitromethane	37.27	61.041	1.1371	49.18
139	1-Nitropropane	24.7	89.094	0.9961	79.63
140	2-Nitropropane	26.74	89.094	0.9821	79.72
141	*o*-Nitrotoluene	26.26	137.137	1.1611	117.14
142	*n*-Nonane	1.9722	128.255	0.7192	147.87
143	1-Nonanol	8.83	144.254	0.828	156.1
144	5-Nonanone	10.6	142.238	0.8217	151.78
145	*n*-Octane	1.948	114.229	0.6986	132.56
146	*n*-Octanol	10.3	130.228	0.8262	140.8
147	2-Octanone	9.51	128.212	0.82	136.53
148	*n*-Pentadecane	2.0391	212.415	0.7685	239.69
149	Pentanal	10	86.132	0.8095	90.71
150	*n*-Pentane	1.8371	72.149	0.6262	86.65
151	Pentanoic Acid	2.661	102.132	0.9339	98.46
152	1-Pentanol	15.13	88.148	0.8144	94.89
153	2-Pentanone	15.45	86.132	0.809	90.63
154	3-Pentanone	17	86.132	0.8098	90.55
155	1-Pentene	2.011	70.133	0.6405	82.51
156	Pentylamine	4.27	87.164	0.7544	97.52
157	Pentyl Acetate	4.79	130.185	0.8756	129.52
158	Hexafluorobenzene	2.029	186.054	1.6184	110.99
159	Propanal	18.5	58.079	0.8657	60.1
160	Propanoic Acid	3.44	74.079	0.9882	67.86
161	1-Propanol	20.8	60.095	0.7997	64.28
162	2-Propanol	20.18	60.095	0.7809	64.25
163	Propionitrile	29.7	55.079	0.7818	58.73
164	Allyl Alcohol	19.7	58.079	0.854	60.19
165	Propylamine	5.08	59.11	0.7173	66.91
166	Propyl Acetate	5.62	102.132	0.8878	98.91
167	Pyridine	13.26	79.101	0.9819	74.84
168	Quinoline	9.16	129.159	1.0977	117.1
169	Tetrachloroethene	2.268	165.833	1.623	94.08
170	Tetrahydrofuran	7.52	72.106	0.8833	71.1
171	Tetralin	2.771	132.202	0.9645	130.03
172	Thiophene	2.739	84.14	1.0649	71.5
173	Thiophenol	4.26	110.177	1.0775	96.88
174	Toluene	2.379	92.139	0.8668	94.06

Entry	Solvent	ε_r[a]	M[a]	ρ[a]	V_{vdW}[b]
175	1,1,1-Trichloroethane	7.243	133.404	1.339	84.76
176	1,1,2-Trichloroethane	7.1937	133.404	1.4397	84.91
177	Trichloroethene	3.39	131.388	1.4642	79.9
178	Triethylamine	2.418	101.19	0.7275	113.32
179	2,2,2-Trifluoroethanol	27.68	100.039	1.3842	65.13
180	1,2,4-Trimethylbenzene	2.377	120.191	0.8758	124.34
181	2,2,4-Trimethylpentane	1.943	114.229	0.6878	132.17
182	*n*-Undecane	1.9972	156.309	0.7402	178.47
183	Water	80.1	18.015	0.998	17.69
184	Xenon	1.88	131.29	2.953	42.21
185	*m*-Xylene	2.359	106.165	0.8596	109.27
186	*o*-Xylene	2.562	106.165	0.8802	109.12
187	*p*-Xylene	2.2735	106.165	0.8566	109.27

[a] Unless stated otherwise taken from ref. [7]. [b] Analytical van der Waals volume of the optimized molecular structure (PBEh-3c) using Petitjean's algorithm as described above.[2]

Table S11: Standard atomic weights of the elements (1 December 2018, IUPAC).

Element	Symbol	Atomic Number	Standard Atomic Weight
hydrogen	H	1	1.008
helium	He	2	4.0026
lithium	Li	3	6.94
beryllium	Be	4	9.0122
boron	B	5	10.81
carbon	C	6	12.011
nitrogen	N	7	14.007
oxygen	O	8	15.999
fluorine	F	9	18.998
neon	Ne	10	20.18
sodium	Na	11	22.99
magnesium	Mg	12	24.305
aluminium	Al	13	26.982
silicon	Si	14	28.085
phosphorus	P	15	30.974
sulfur	S	16	32.06
chlorine	Cl	17	35.45
argon	Ar	18	39.95
potassium	K	19	39.098
calcium	Ca	20	40.078
scandium	Sc	21	44.956
titanium	Ti	22	47.867
vanadium	V	23	50.942
chromium	Cr	24	51.996
manganese	Mn	25	54.938
iron	Fe	26	55.845

Element	Symbol	Atomic Number	Standard Atomic Weight
cobalt	Co	27	58.933
nickel	Ni	28	58.693
copper	Cu	29	63.546
zinc	Zn	30	65.38
gallium	Ga	31	69.723
germanium	Ge	32	72.63
arsenic	As	33	74.922
selenium	Se	34	78.971
bromine	Br	35	79.904
krypton	Kr	36	83.798
rubidium	Rb	37	85.468
strontium	Sr	38	87.62
yttrium	Y	39	88.906
zirconium	Zr	40	91.224
niobium	Nb	41	92.906
molybdenum	Mo	42	95.95
ruthenium	Ru	44	101.07
rhodium	Rh	45	102.91
palladium	Pd	46	106.42
silver	Ag	47	107.87
cadmium	Cd	48	112.41
indium	In	49	114.82
tin	Sn	50	118.71
antimony	Sb	51	121.76
tellurium	Te	52	127.6
iodine	I	53	126.9
xenon	Xe	54	131.29
caesium	Cs	55	132.91
barium	Ba	56	137.33
lanthanum	La	57	138.91
cerium	Ce	58	140.12
praseodymium	Pr	59	140.91
neodymium	Nd	60	144.24
samarium	Sm	62	150.36
europium	Eu	63	151.96
gadolinium	Gd	64	157.25
terbium	Tb	65	158.93
dysprosium	Dy	66	162.5
holmium	Ho	67	164.93
erbium	Er	68	167.26
thulium	Tm	69	168.93
ytterbium	Yb	70	173.05
lutetium	Lu	71	174.97
hafnium	Hf	72	178.49
tantalum	Ta	73	180.95
tungsten	W	74	183.84

Element	Symbol	Atomic Number	Standard Atomic Weight
rhenium	Re	75	186.21
osmium	Os	76	190.23
iridium	Ir	77	192.22
platinum	Pt	78	195.08
gold	Au	79	196.97
mercury	Hg	80	200.59
thallium	Tl	81	204.38
lead	Pb	82	207.2
bismuth	Bi	83	208.98
thorium	Th	90	232.04
protactinium	Pa	91	231.04
uranium	U	92	238.03

3.4 Numerical Examples

The script ‘calcEntropySolv’ calculates the solvation entropy of a given solute in the specified solvent. Figure S4 shows a representative example for the routine calculation of the solvation entropy and solution-phase entropy of pyridone (specified as output file from preceding ORCA computation) in benzene at 298 K. Likewise, the solvation entropy can be calculated from the atomic coordinates specified as XYZ file in xmol format (Figure S5). More options are invoked by setting different flags. An example illustrating the optional modifications is provided in Figure S6. Thus, manual solvent specification (permittivity [-P], molar mass [-M], density [-D], molecular vdW volume [-V], deuteration [-d]), and change in rotational symmetry number [-S], and temperature [-T] are implemented. The availability of *solvent* as solvent is checked with ‘readSolventLibrary *solvent*’. Furthermore, if the solute is at the time the solvent, then a different standard state correction must be applied [-c without additional arguments] (not shown below). Besides the direct output, two output files are generated as TXT files that summarize the data during the calculation. One file gives a detailed documentation on the calculation of the molecular vdW volume of the solute, and the second file summarizes the entropy-related calculation following Garza’s formalism for documentation purposes.

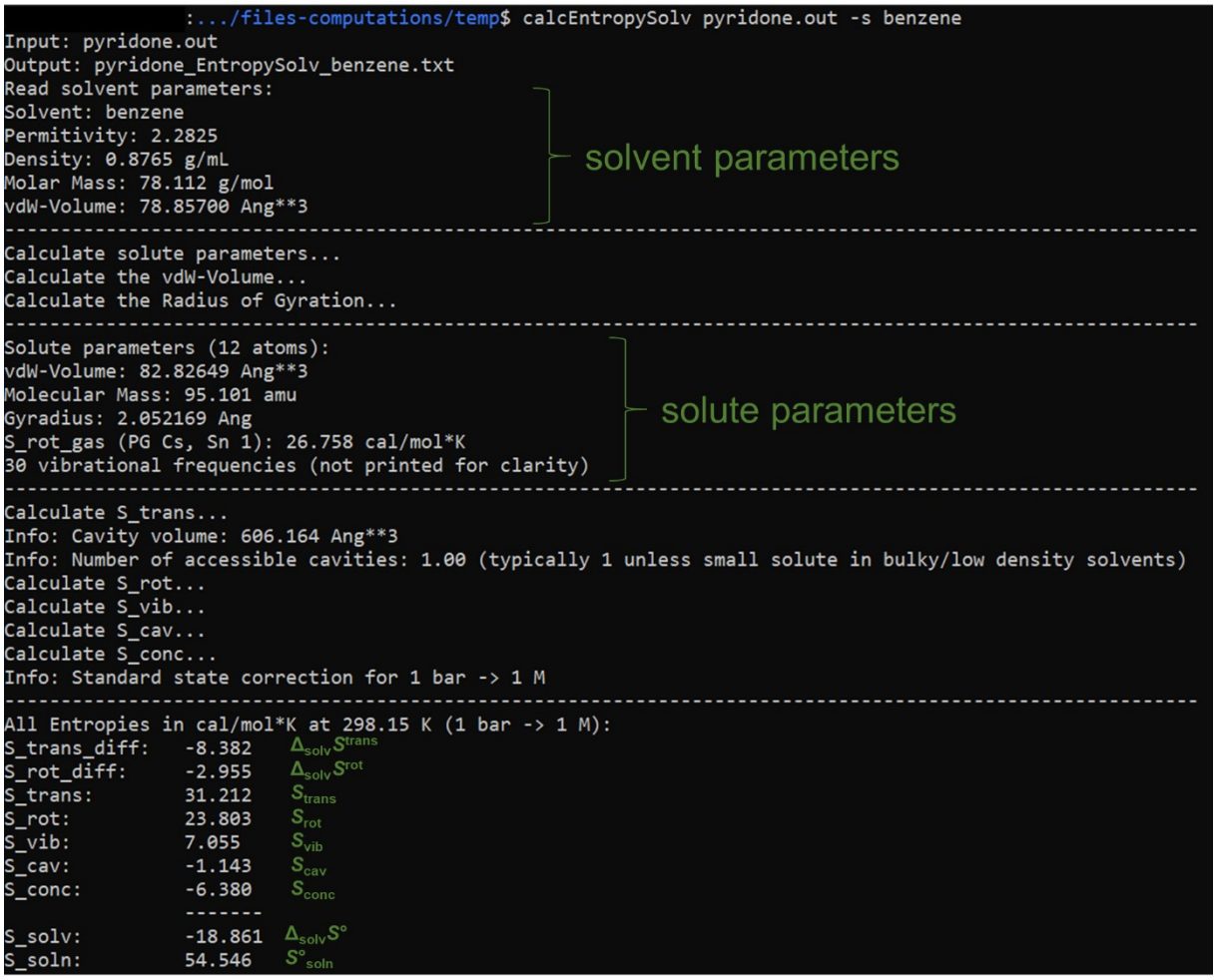

Figure S4: Routine application of the ‘calcEntropySolv’ script to calculate the solvation entropy and solution-phase entropy of a given solute specified as output file from preceding ORCA computation (here: entropy of pyridone in benzene at 298 K).

```
              :.../files-computations/temp$ calcEntropySolv pyridone.xyz -s benzene
Input: pyridone.xyz
Output: pyridone_EntropySolv_benzene.txt
Read solvent parameters:
Solvent: benzene
Permitivity: 2.2825
Density: 0.8765 g/mL
Molar Mass: 78.112 g/mol
vdW-Volume: 78.85700 Ang**3
-------------------------------------------------------------------------------------------------------
Calculate solute parameters...
Calculate the vdW-Volume...
Calculate the Radius of Gyration...
-------------------------------------------------------------------------------------------------------
Solute parameters (12 atoms):
vdW-Volume: 82.82649 Ang**3
Molecular Mass: 95.101 amu
Gyradius: 2.052169 Ang
0 vibrational frequencies (not printed for clarity)
-------------------------------------------------------------------------------------------------------
Calculate S_trans...
Info: Cavity volume: 606.164 Ang**3
Info: Number of accessible cavities: 1.00 (typically 1 unless small solute in bulky/low density solvents)
Calculate S_rot...
Calculate S_cav...
Calculate S_conc...
Info: Standard state correction for 1 bar -> 1 M
-------------------------------------------------------------------------------------------------------
All Entropies in cal/mol*K at 298.15 K (1 bar -> 1 M):
S_trans_diff:   -8.382
S_rot_diff:     -2.955
S_trans:        31.212
S_cav:          -1.143
S_conc:         -6.380
                -------
S_solv:         -18.861
```

Figure S5: Routine application of the ‘calcEntropySolv’ script to calculate the solvation entropy a given solute specified as XYZ file (here: entropy of pyridone in benzene at 298 K).

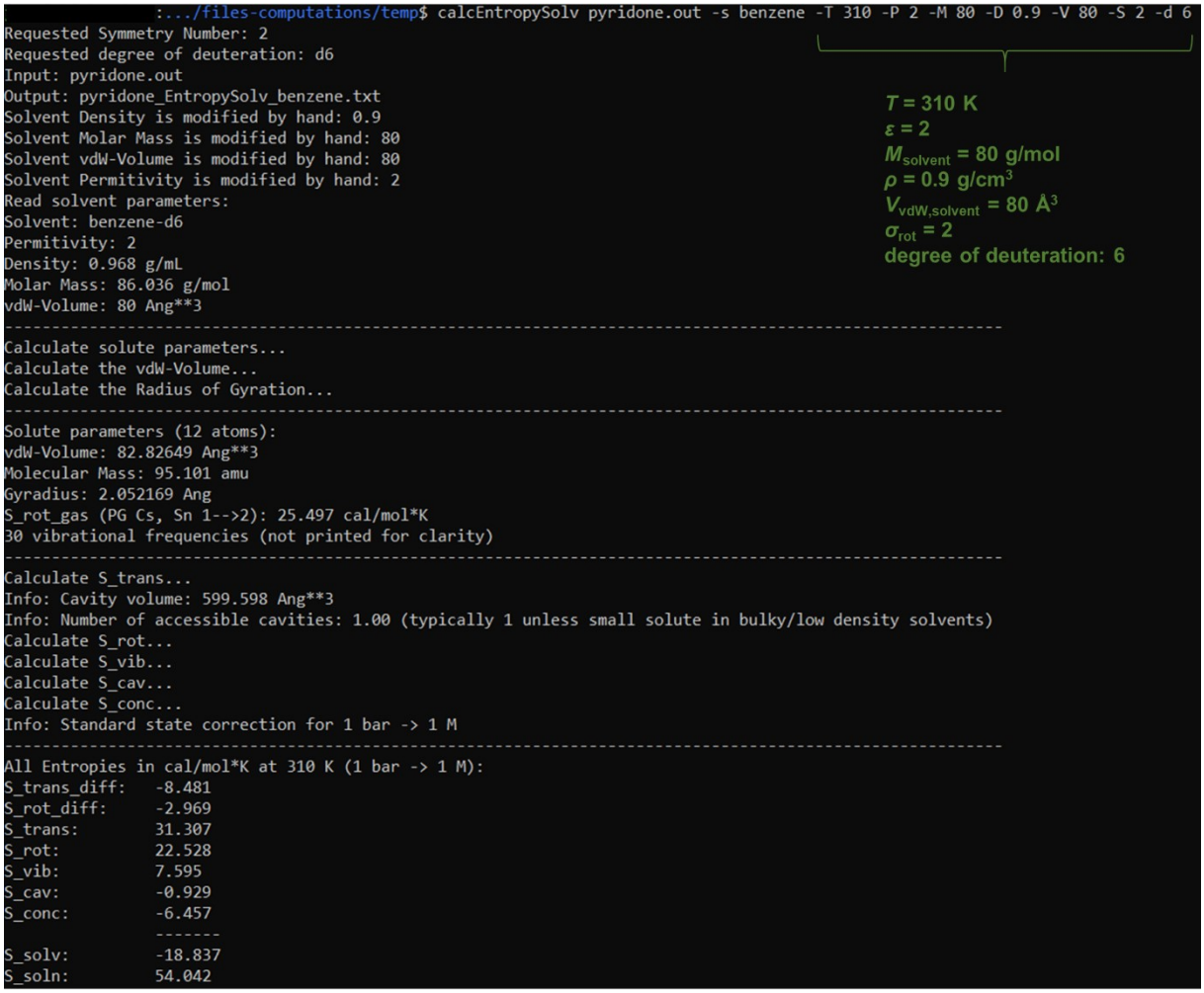

Figure S6: Expert application of the 'calcEntropySolv' script to calculate the solvation entropy and solution-phase entropy of a given solute specified as output file from preceding ORCA computation (here: entropy of pyridone with a rotational symmetry number of 2 in arbitrarily modified benzene-d_6 at 310 K).

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