SUPPORTING INFORMATION

Thermodynamic Approaches to the Challenges of Solubility in Drug Discovery and Development

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Table 1SI.
Thermodynamic characteristics of sublimation, solubility and hydration processes of the sulfonamides studied in water at 298 K

Drug	ΔG^0_{sub} (kJ·mol^{-1})	ΔH^0_{sub} (kJ·mol^{-1})	$T\Delta S^0_{sub}$ (kJ·mol^{-1})	ΔG^0_{sol} (kJ·mol^{-1})	ΔH^0_{sol} (kJ·mol^{-1})	$T\Delta S^0_{sol}$ (kJ·mol^{-1})	$-\Delta G^0_{hyd}$ (kJ·mol^{-1})	$-\Delta H^0_{hyd}$ (kJ·mol^{-1})	$-T\Delta S^0_{hyd}$ (kJ·mol^{-1})
0[a]	53.4	111.5 ± 1.1	58.1 ± 2.3	29.0	27.4 ± 0.9	-1.6 ± 0.3	24.4	84.1 ± 2.0	59.7 ± 2.6
4[b]	67.7	132.5 ± 1.6	64.7 ± 2.1	32.7	36.1 ± 0.4	3.4 ± 0.4	35.0	96.4 ± 2.0	61.4 ± 2.5
5[c]	50.4	114 ± 1	63.6 ± 0.9	34.6	14.6 ± 0.8	-20.0 ± 0.9	15.8	99.4 ± 1.8	83.6± 1.8
6[c]	54.1	124.9 ± 1.6	70.8 ± 1.5	36.4	28.3 ± 0.8	-8.1 ± 0.6	17.7	96.6 ± 2.4	78.9± 2.1
8	57.1[d]	126.8 ± 0.9[d]	69.7 ± 1.8[d]	32.7[a]	34.2 ± 1.2[a]	1.5 ± 0.6[a]	24.4	92.6 ± 2.1	68.2 ± 2.4
9[c]	49.9	98.6 ± 1.6	48.7 ± 1.5	33.0	37.9 ± 1.4	4.9 ± 1.1	16.9	60.7 ± 3.0	43.8 ± 2.6
15	78.0[b]	131.4 ± 2.6[b]	53.4 ± 2.1[b]	31.0[b]	43.0 ± 1.0[b]	12.0 ± 0.6[b]	47.0	88.4 ± 3.7	41.4 ± 2.7
19[e]	74.0	134.1 ± 1.2	60.1 ± 0.9	33.8	38.0 ± 2	4.2 ± 0.7	41.0	96.1 ± 3.2	55.1 ± 1.6
20[f]	74.2	143.6 ± 0.9	69.4 ± 0.6	35.9	49.3 ± 1.3	13.4 ± 0.6	38.3	94.3 ± 2.2	56.0 ± 1.2
22[f]	72.4	124 ± 1	51.6 ± 0.6	33.5	42.6 ± 1.2	9.1 ± 0.6	38.9	81.4 ± 2.2	42.5 ± 1.2
23[e]	61.7	141.1 ± 0.7	79.4 ± 0.6	37.0	14.0 ± 0.6	-23.0 ± 1.3	24.7	127.1 ± 1.3	102.4 ± 3.2
24[e]	85.8	167.5 ± 3.6	81.7 ± 2.4	38.2	30.0 ± 0.8	-8.2 ± 0.8	47.6	137.5 ± 4.4	89.9 ± 3.2
25[b]	88.0	168.3 ± 2.3	80.3 ± 2.7	30.0	45.9 ± 0.6	15.9 ± 0.6	58.0	122.4 ± 2.9	64.4 ± 3.3
26[e]	75.7	155.4 ± 1.6	79.7 ± 1.2	35.1	24.2 ± 0.9	-10.9 ± 0.9	40.6	131.2 ± 2.5	90.6 ± 2.1
38[f]	68.5	130.0 ± 1	61.5 ± 0.6	34.9	46.9 ± 1.5	12.0 ± 0.3	33.6	83.1 ± 2.5	49.5 ± 0.9
41	76.4[d]	144.6 ± 1.6[d]	68.2 ± 2.1[d]	38.9[a]	24.7 ± 0.7[a]	-14.2 ± 0.3[a]	37.5	119.9 ± 2.3	82.4 ± 2.4
42	73.5[d]	147.2 ± 1.5[d]	73.7 ± 2.1[d]	33.7[a]	44.9 ± 1.2[a]	11.2 ± 0.6[a]	39.8	102.3 ± 2.7	62.5 ± 2.7
43	72.3[d]	142.8 ± 1.9[d]	70.5 ± 2.4[d]	37.2[a]	37.7 ± 0.6[a]	0.5 ± 0.2[a]	35.1	105.1 ± 2.5	70 ± 2.6

[a] Ref. [1];
[b] Ref. [2];
[c] Ref. [3];
[d] Ref. [4];
[e] Ref. [5];
[f] Ref. [6].

Table 2SI.
Thermodynamic characteristics of solubility and solvation processes of the sulfonamides studied in 1-octanol at 298 K

Drug	ΔG^0_{sol} (kJ·mol^{-1})	ΔH^0_{sol} (kJ·mol^{-1})	$T\Delta S^0_{sol}$ (kJ·mol^{-1})	$-\Delta G^0_{solv}$ (kJ·mol^{-1})	$-\Delta H^0_{solv}$ (kJ·mol^{-1})	$-T\Delta S^0_{solv}$ (kJ·mol^{-1})
0[a]	8.4	26.8 ± 0.7	18.4 ± 0.6	45.0	84.7 ± 1.8	39.7 ± 2.9
4[b]	11.1	29.1 ± 0.7	18.0 ± 0.6	56.6	103.4 ± 2.3	46.8± 2.7
5[c]	13.9	33 ± 1	19.1 ± 1.1	36.5	81.0 ± 2.0	44.5 ± 2.0
6[c]	10.6	23 ± 1	12.4 ± 0.9	43.5	101.9 ± 2.6	58.4 ± 2.4
8[a]	11.3	4.1 ± 0.1	-7.2 ± 0.3	45.8	122.7 ± 1.0	76.9 ± 2.1
9[c]	7.85	24 ± 1	16.15 ± 1.16	42.05	74.6 ± 2.6	32.55± 2.66
15[b]	14.4	27.5 ± 1.0	13.1 ± 0.6	63.6	103.9 ± 3.6	40.3 ± 2.7
19[b]	16.2	10.7 ± 0.7	-5.5 ± 0.5	57.8	123.4 ± 1.9	65.6 ± 1.4
20[e]	17.0	33.0 ± 1.1	16.0 ± 0.6	57.2	110.6 ± 2.0	53.4 ± 1.2
22[e]	20.7	35.4 ± 0.8	14.7 ± 0.6	51.7	88.6 ± 1.8	36.9 ± 1.2
23[d]	18.1	36.5 ± 0.7	18.4 ± 0.8	43.6	104.6 ± 1.4	61.0 ± 1.4
24[d]	19.3	25.0 ± 0.4	5.7 ± 0.5	66.5	142.5 ± 4.0	76.0 ± 2.9
25[b]	16.4	25.8 ± 0.7	9.4 ± 0.6	71.6	142.5 ± 3.0	70.9 ± 3.3
26[d]	18.7	35.1 ± 0.8	16.4 ± 0.8	57.0	120.3 ± 2.4	63.3 ± 2.0
38[e]	15.6	25.7 ± 0.6	10.1 ± 0.3	52.9	104.3 ± 1.6	51.4 ± 0.9
41[a]	18.6	21.6 ± 0.7	3.0 ± 0.3	57.8	123.0 ± 2.3	65.2 ± 2.4
42[a]	13.8	24.5 ± 0.6	10.7 ± 0.6	59.7	122.7 ± 2.1	63.0 ± 2.7
43[a]	20.0	37.3 ± 0.2	17.3 ± 0.3	52.3	105.5 ± 2.1	53.2 ± 2.7

[a] Ref. [3];
[b] Ref. [7];
[c] Ref. [6];
[d] Ref. [2];
[e] Ref. [1];

Table 3SI.
Thermodynamic characteristics of sublimation, solubility and hydration processes of the compounds studied in buffer with pH 7.4 at 298 K

Drug	ΔG^0_{sub} (kJ·mol^{-1})	ΔH^0_{sub} (kJ·mol^{-1})	$T\Delta S^0_{sub}$ (kJ·mol^{-1})	ΔG^0_{sol} (kJ·mol^{-1})	ΔH^0_{sol} (kJ·mol^{-1})	$T\Delta S^0_{sol}$ (kJ·mol^{-1})	$-\Delta G^0_{hyd}$ (kJ·mol^{-1})	$-\Delta H^0_{hyd}$ (kJ·mol^{-1})	$-T\Delta S^0_{hyd}$ (kJ·mol^{-1})
KETO	57.0[a]	110.1 ± 0.5[a]	53.1 ± 0.3[a]	27.0[b]	16.0 ± 0.3[b]	-11.0 ± 0.3[b]	30.0	95.9 ± 0.8	65.9 ± 0.6
(+)-IBP	41.6[c]	107.7 ± 0.5[c]	66.1 ± 0.3[c]	28.8[b]	13.9 ± 0.5[b]	-14.9 ± 0.3[b]	12.8	93.8 ± 1.0	81.0 ± 0.6
IBP	44.2[c]	116.1 ± 0.6[c]	71.9 ± 0.3[c]	29.8[b]	19.5 ± 0.4[b]	-10.3 ± 0.3[b]	14.4	96.6 ± 1.0	82.2 ± 0.6
(+)-NAP	58.5[d]	130.1 ± 0.5[d]	71.6 ± 0.6[d]	27.7[b]	5.2 ± 0.4[b]	-22.5 ± 0.1[b]	30.8	124.9 ± 0.9	94.1 ± 0.7
FBP	53.3[e]	110.2 ± 0.5[b]	56.9 ± 0.6[b]	28.7[b]	6.7 ± 0.5[b]	-22.0 ± 0.6[b]	24.6	103.5 ± 1.0	78.9 ± 1.2
4-benzyl[f]	57.8	111.0 ± 3.0	53.2 ± 3.0	18.0	22.5 ± 0.9	4.5 ± 0.9	39.8	88.5 ± 3.9	48.7 ± 3.9
BA	34.4[h]	90.5 ± 0.3[h]	56.1 ± 0.3[h]	16.1	10.1 ± 0.2	-6.0 ± 0.3	18.3	80.4 ± 0.5	50.1 ± 0.6
ASA	43.6[g]	110.2 ± 0.5[b]	66.6 ± 0.6[b]	14.8[b]	61.4 ± 0.9[b]	46.6 ± 0.9[b]	28.8	48.8 ± 1.4	20.0 ± 1.5
DIF	57.6[e]	120.1 ± 0.6[b]	62.5 ± 0.6[b]	29.2[b]	7.9 ± 0.5[b]	-21.3 ± 0.6[b]	28.4	112.2 ± 1.1	83.8 ± 1.2
2-OMe-BA[j]	43.7	110.7 ± 0.8	67.0 ± 0.6	14.1	3.4 ± 0.1	-10.7 ± 0.3	29.6	107.3 ± 0.9	77.7 ± 0.9
3-OMe-BA[j]	41.8	114.7 ± 0.8	72.9 ± 0.6	15.3	6.3 ± 0.1	-9.0 ± 0.3	26.5	108.4 ± 0.9	81.9 ± 0.9
4-OMe-BA[j]	46.9	111.6 ± 0.6	64.7 ± 0.6	16.2	4.8 ± 0.1	-11.4 ± 0.3	30.7	106.8 ± 0.9	76.1 ± 0.9
2-OH-BA[i]	38.5	96.6 ± 0.8	58.1 ± 0.9	20.3	25.5 ± 0.6	5.2 ± 0.3	18.2	71.1 ± 1.4	52.9 ± 1.2
3-OH-BA[i]	50.6	105.2 ± 0.8	54.6 ± 0.6	16.2	32.1 ± 0.6	15.9 ± 0.7	34.4	73.1 ± 1.4	38.7 ± 1.3
4-OH-BA[i]	55.0	113.3 ± 0.7	58.3 ± 0.6	17.7	40.3 ± 0.8	22.6 ± 0.1	37.3	73.0 ± 1.5	35.7 ± 0.7
Fluf(form I)[l]	54.3	121.2 ± 0.7	66.9 ± 1.1	22.8	37.4 ± 0.7	14.6 ± 0.6	31.5	83.8 ± 1.4	52.3 ± 1.7
Niflum[l]	61.3	130.2 ± 0.8	68.9 ± 1.2	21.0	39.5 ± 0.5	18.5 ± 0.6	40.3	90.7 ± 1.3	50.4 ± 2.5
Mefen(form I)	59.2[m]	136.2 ± 0.8[m]	76.2 ± 0.9[m]	30.4[o]	48.5 ± 0.4[o]	18.1 ± 0.5[o]	28.8	87.7 ± 1.2	58.9 ± 1.4
Tolf(form I)	53.9[m]	128.4 ± 0.8[m]	74.8 ± 1.2[m]	28.9[n]	38.0 ± 1.2[n]	9.0 ± 0.6[n]	25.0	90.5 ± 2.0	65.5 ± 1.8
N-Ph-Ant	58.9[m]	126.0 ± 1.3[m]	68.0 ± 1.8[m]	27.9[o]	29.0± 0.4[o]	1.1 ± 0.1[o]	31.0	97.0 ± 1.7	66.0 ± 1.9
Dic(form II)[k]	49.3	115.6 ± 1.3	66.3 ± 1.6	33.8	10.2 ± 1.0	-23.6 ± 1.2	15.5	105.4 ± 2.3	89.9 ± 2.8
MePB[p]	42.2	98.8 ± 0.8	56.6 ± 0.6	20.5	27.2 + 0.9	6.7 ± 1.2	21.9	71.6 ± 1.7	49.7 ± 1.8
EtPB[p]	43.4	100.9 ± 0.7	57.5 ± 0.6	22.9	28.9 + 0.8	6.0 ± 1.1	20.5	72.0 ± 1.5	51.5 ± 1.7
PrPB[p]	46.7	123.7 ± 0.6	77.0 ± 0.6	25.3	35.1 + 0.9	9.8 ± 1.2	21.4	88.6 ± 1.5	67.2 ± 1.8
BuPB[p]	45.0	108.4 ± 0.8	63.4 ± 0.6	26.5	36.7 + 1.2	10.2 ± 1.4	18.5	71.7 ± 2.0	53.2 ± 2.0

Table 3SI. (Continued)

Drug	ΔG^0_{sub} (kJ·mol^{-1})	ΔH^0_{sub} (kJ·mol^{-1})	$T\Delta S^0_{sub}$ (kJ·mol^{-1})	ΔG^0_{sol} (kJ·mol^{-1})	ΔH^0_{sol} (kJ·mol^{-1})	$T\Delta S^0_{sol}$ (kJ·mol^{-1})	$-\Delta G^0_{hyd}$ (kJ·mol^{-1})	$-\Delta H^0_{hyd}$ (kJ·mol^{-1})	$-T\Delta S^0_{hyd}$ (kJ·mol^{-1})
AcAm[r]	40.5	99.8 ± 0.8	59.3 ± 0.3	17.7	17.3 ± 0.5	-0.4 ± 0.2	22.8	82.5 ± 1.3	59.7 ± 0.5
2-OH-AcAm[q]	52.8	121.8 ± 0.9	69.0 ± 0.3	22.1	20.7 ± 0.7	-1.4 ± 0.2	30.7	101.1 ± 1.6	70.4 ± 0.5
3-OH-AcAm[q]	56.4	111 ± 1	54.6 ± 0.2	16.0	35.6 ± 0.9	19.6 ± 0.3	40.4	75.4 ± 1.9	35.0 ± 0.5
Parac(form I)[r]	60.0	117.9 ± 0.7	57.9 ± 0.6	15.8	21.8 ± 0.1	6.0 ± 0.2	44.2	96.1 ± 0.8	51.9 ± 0.8
Phenac[r]	52.3	121.8 ± 0.7	69.5 ± 0.3	24.5	31.1 ± 1.6	6.6 ± 0.5	27.8	90.7 ± 2.3	62.9 ± 0.8
2-AcAm-BA[t]	54	116 ± 1	62 ± 2	17.0	1.4 ± 0.1	-15.6 ± 0.3	37.4	112.0 ± 1.1	74.6 ± 2.3
3-AcAm-BA[t]	73.2	137 ± 1	63.8 ± 1.8	17.8	7.9 ± 0.3	-9.9 ± 0.7	55.4	128.5 ± 1.3	73.1 ± 2.5
4-AcAm-BA[t]	72	138 ± 2	66 ± 3	17.9	7.4 ± 0.7	-10.5 ± 1.3	54.4	130.6 ± 2.7	76.2 ± 4.3
2-OH-BZA	44.4[s]	106.6 ± 1.0[s]	62.2 ± 2.3[s]	19.6[t]	41.9 ± 1.1[t]	22.3 ± 1.3[t]	24.8	64.2 ± 2.1	39.4 ± 3.6
3-OH-BZA	60.3[s]	122 ± 1[s]	61.7 ± 2.8[s]	15.9[t]	32.9 ± 0.8[t]	16.9 ± 0.9[t]	44.5	87.3 ± 1.8	42.8 ± 3.7
4-OH-BZA	58.9[s]	117.8 ± 1.0[s]	58.9 ± 2.8[s]	15.3[t]	36.3 ± 1.7[t]	21.0 ± 1.0[t]	43.7	79.4 ± 2.7	35.7 ± 3.8

[a] Ref. [8];
[b] Ref. [9];
[c] Ref. [10];
[d] Ref. [11];
[e] Ref. [12];
[f] Ref. [13];
[g] Ref. [14];
[h] Ref. [15];
[i] Ref. [16];
[j] Ref. [17];
[k] Ref. [18];
[l] Ref. [19];
[m] Ref. [20];
[n] Ref. [21];
[o] Ref. [22];
[p] Ref. [23];
[q] Ref. [24];

[r] Ref. [25];
[s] Ref. [26];
[t] Ref. [27];

Table 4SI.
Thermodynamic characteristics of solubility and solvation processes of the compounds studied in 1-octanol at 298 K

Drug	ΔG^0_{sol} (kJ·mol^{-1})	ΔH^0_{sol} (kJ·mol^{-1})	$T\Delta S^0_{sol}$ (kJ·mol^{-1})	$-\Delta G^0_{solv}$ (kJ·mol^{-1})	$-\Delta H^0_{solv}$ (kJ·mol^{-1})	$-T\Delta S^0_{solv}$ (kJ·mol^{-1})
KETO[a]	6.6	45.5 ± 1.3	38.9 ± 1.5	50.4	66.4 ± 1.8	16.0 ± 1.8
(+)-IBP[a]	7.1	20.3 ± 1.2	13.2 ± 1.2	34.5	87.4 ± 1.5	52.9 ± 1.5
IBP[a]	12.9	26.5 ± 1.1	13.6 ± 1.2	31.3	89.3 ± 1.7	58.0 ± 1.5
(+)-NAP[a]	10.5	23.8 ± 0.7	13.3 ± 0.6	48.0	106.3 ± 1.2	58.3 ± 1.2
FBP[a]	13.7	27.9 ± 0.8	14.2 ± 0.6	39.6	82.3 ± 1.3	42.7 ± 1.2
4-benzyl[b]	9.9	33.6 ± 0.7	23.7 ± 0.6	47.9	77.4 ± 3.7	29.5 ± 3.6
BA[c]	4.0	11.8 ± 0.3	7.8 ± 0.3	-30.4	-78.7 ± 0.6	-48.3 ± 0.6
ASA[a]	8.4	22.5 ± 1.4	14.1 ± 1.5	35.2	87.7 ± 1.9	52.5 ± 2.1
DIF[a]	8.3	10.2 ± 0.3	1.9 ± 0.3	49.3	109.9 ± 0.9	60.6 ± 0.9
2-OMe-BA[e]	7.8	32.1 ± 0.6	24.3 ± 0.9	35.9	78.6 ± 1.4	42.7 ± 1.5
3-OMe-BA[e]	5.0	24.4 ± 0.2	19.4 ± 0.9	36.8	90.3 ± 1.0	53.5 ± 1.5
4-OMe-BA[e]	10.4	28.6 ± 0.3	18.2 ± 0.6	36.5	83.0 ± 0.9	46.5 ± 1.2
2-OH-BA[d]	4.2	13.1 ± 0.6	8.9 ± 0.7	34.3	83.5 ± 1.4	49.2 ± 1.6
3-OH-BA[d]	5.9	12.9 ± 0.7	7.0 ± 0.6	44.7	92.3 ± 1.5	47.6 ± 1.2
4-OH-BA[d]	4.9	13.5 ± 0.6	8.6 ± 0.6	50.1	99.8 ± 1.3	49.7 ± 1.2
Fluf(form I)[g]	5.9	22.6 ± 0.7	16.7 ± 0.6	48.4	98.6 ± 1.4	50.2 ± 1.7
Niflum[g]	8.7	20.7 ± 0.4	12.0 ± 0.6	52.6	109.5 ± 1.2	56.9 ± 2.4
Mefen(form I)[i]	12.2	32.0 ± 1.2	19.7 ± 1.2	47.0	104.2 ± 2.0	57.3 ± 2.1
Tolf(form I)[h]	8.4	15.9 ± 0.4	7.5 ± 0.3	45.5	112.8 ± 1.2	67.3 ± 1.5
N-Ph-Ant[i]	9.1	16.8 ± 0.2	7.7 ± 0.2	49.8	109.2 ± 1.5	59.4 ± 2.0
Dic(form II)[f]	11.4	29.1 ± 0.3	17.7 ± 0.3	37.9	86.5 ± 1.6	48.6 ± 1.9
MePB[j]	5.45	21.9 ± 0.4	16.5 ± 0.5	37.0	76.9 ± 1.2	39.9 ± 1.1
EtPB[j]	4.61	18.9 ± 0.6	14.3 ± 0.6	38.8	82.0 ± 1.3	43.2 ± 1.2
PrPB[j]	3.99	21.2 ± 0.5	17.2 ± 0.7	42.7	102.5 ± 1.1	59.8 ± 1.3
BuPB[j]	2.74	21.2 ± 0.7	18.5 ± 0.8	42.3	87.2 ± 1.5	44.9 ± 1.4
AcAm[k]	4.9	19.9 ± 0.6	15.0 ± 1.0	35.6	79.9 ± 1.4	44.3 ± 1.3
2-OH-AcAm	12.8	24.6 ± 0.7	11.8 ± 0.5	40.0	97.2 ± 1.6	57.2 ± 0.8
3-OH-AcAm	8.1	18.2 ± 0.3	10.1 ± 0.6	48.3	92.8 ± 1.3	44.5 ± 0.8
Parac(form I)[k]	6.0	11.7 ± 0.2	5.7 ± 0.3	54.0	106.2 ± 0.9	52.2 ± 0.9
Phenac[k]	9.4	27.7 ± 0.7	18.3 ± 0.2	42.9	94.1 ± 1.4	51.2 ± 0.5
2-AcAm-BA[l]	9.4	13.3 ± 0.2	3.9 ± 0.2	45.0	100.1 ± 1.2	55.1 ± 2.2
3-AcAm-BA[l]	15.1	13.0 ± 0.4	-2.3 ± 1.4	58.1	123.4 ± 1.4	65.3 ± 3.2
4-AcAm-BA[l]	13.3	13.1 ± 0.5	0.2 ± 1.4	59.0	124.9 ± 2.5	65.9 ± 4.4
2-OH-BZA[l]	8.3	30.7 ± 1.0	22.4 ± 1.4	36.1	75.4 ± 2.0	39.3 ± 3.7
3-OH-BZA[l]	10.4	20.7 ± 1.8	10.3 ± 1.2	50.0	99.5 ± 2.8	49.5 ± 4.0
4-OH-BZA[l]	8.9	19.8 ± 1.0	10.8 ± 0.9	50.0	95.9 ± 2.0	45.9 ± 3.7

[a] Ref. [9];
[b] Ref. [13];
[c] Ref. [28];
[d] Ref. [16];
[e] Ref. [17];
[f] Ref. [18];
[g] Ref. [19];
[h] Ref. [21];
[i] Ref. [22];

[j] Ref. [23];
[k] Ref. [25];
[l] Ref. [27];

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