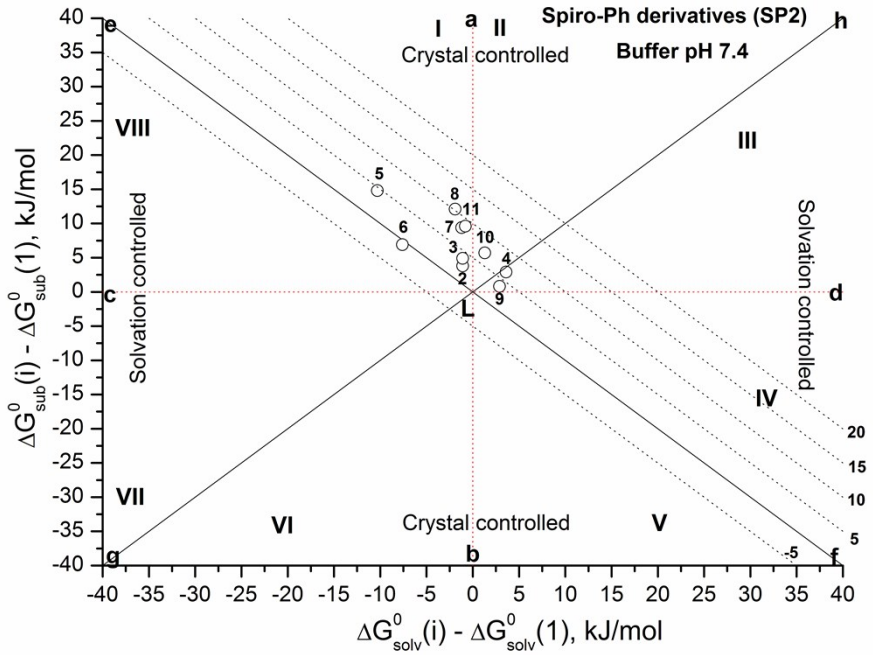
SUPPORTING INFORMATION FOR PUBLICATION

Poorly Soluble Drugs: Disbalance of Thermodynamic Characteristics of Crystal Lattice and Solvation

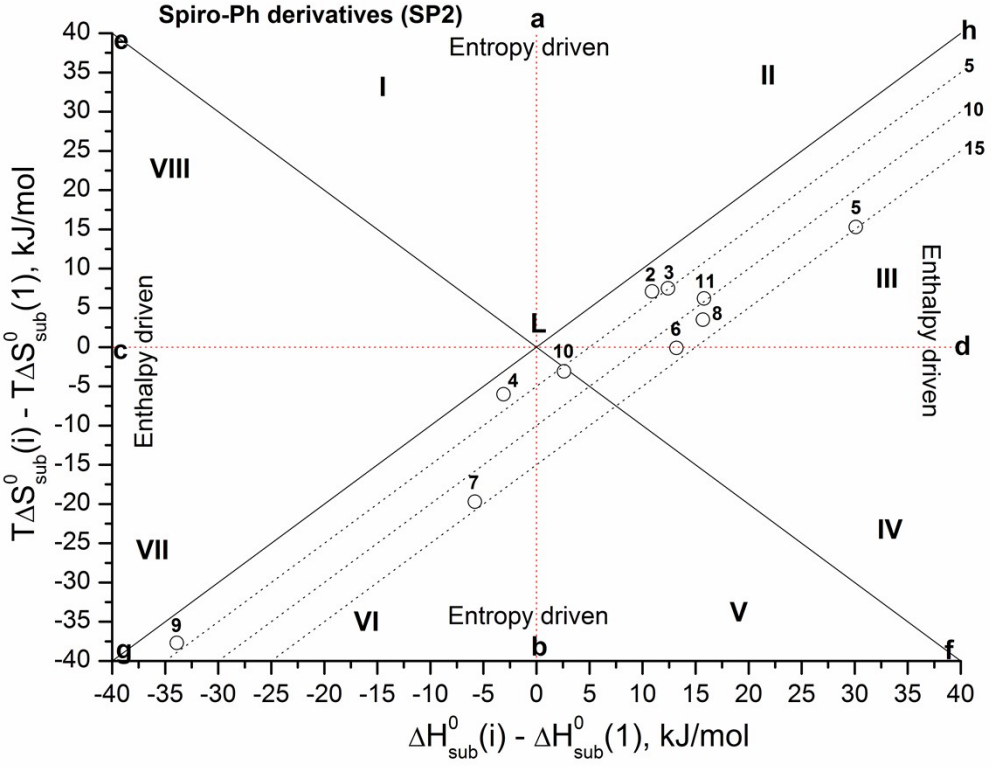
German L. Perlovich[a,b]

[a]*Department of Physical Chemistry of Drugs, Krestov's Institute of Solution Chemistry, Russian Academy of Sciences, 153045, 1 Akademicheskaya St., Ivanovo, Russia;*
[b]*Department of Computer-Aided Molecular Design, Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432, Chernogolovka, Russia;*

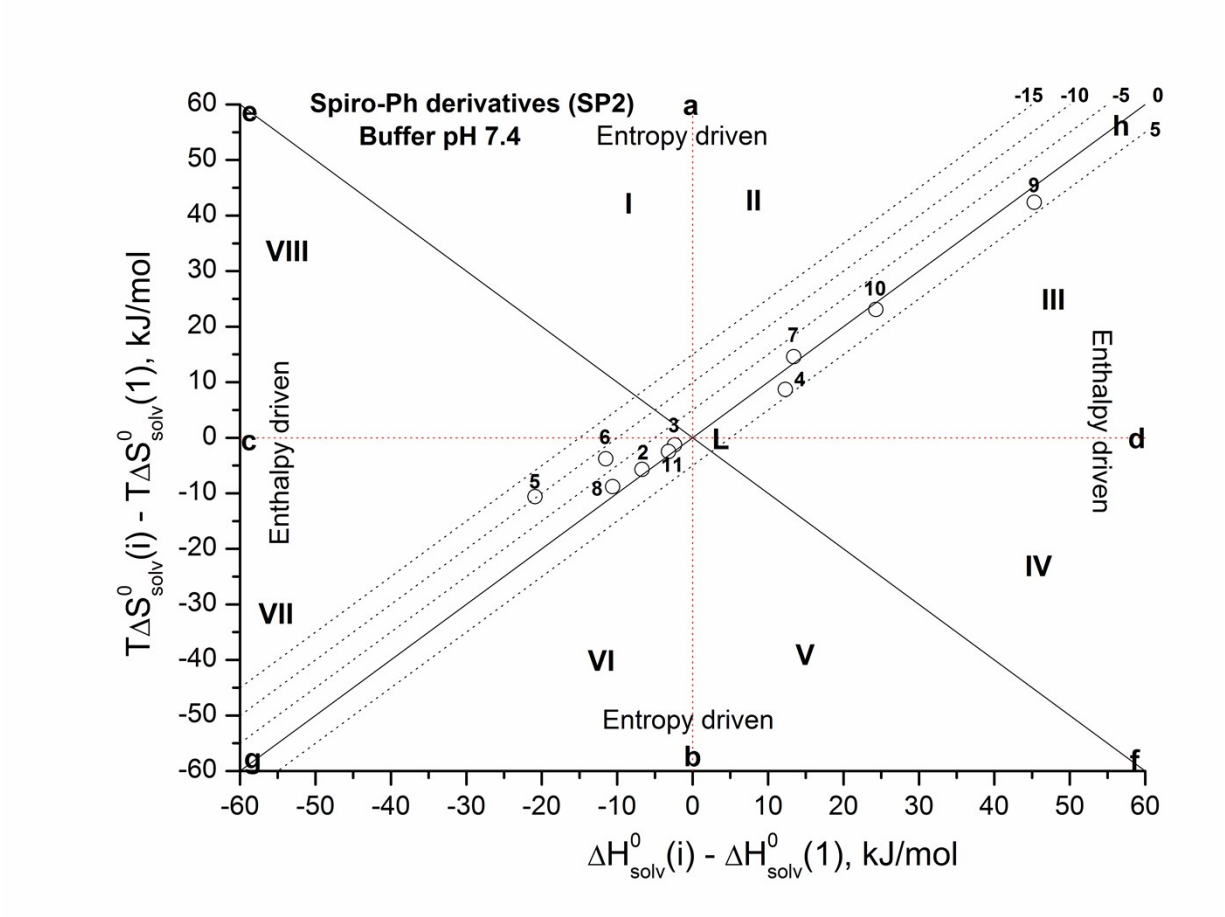
Corresponding author: Perlovich, G.L. (glp@isc-ras.ru)


Spiro-Ph derivatives (SP2)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
20
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

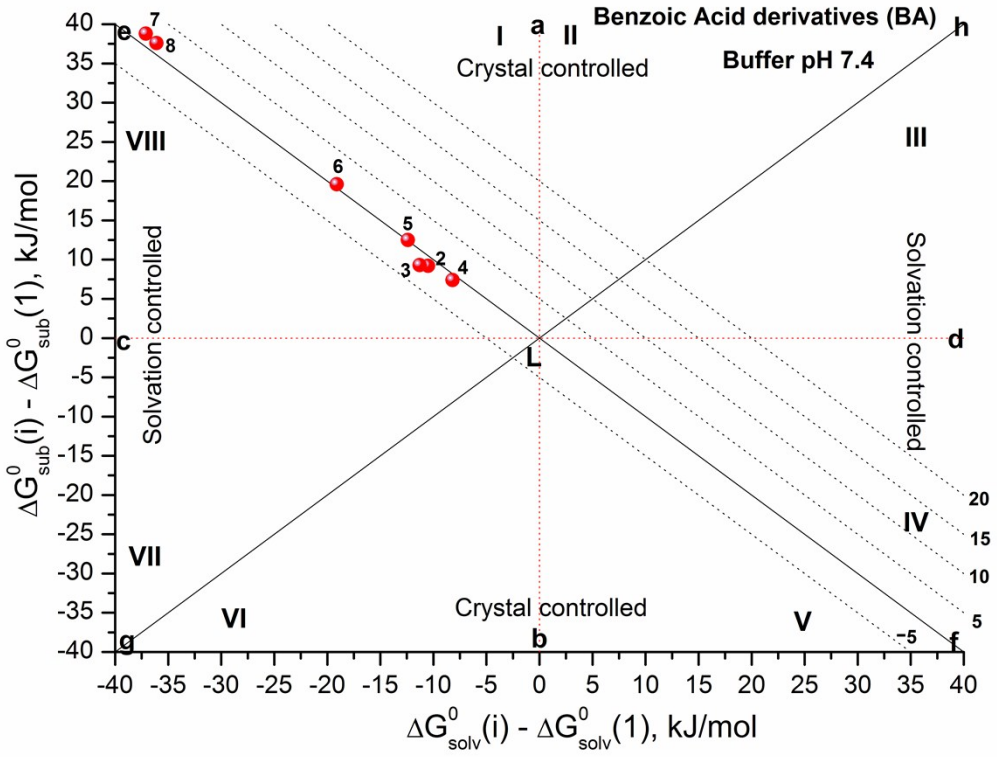

Spiro-Ph derivatives (SP2)
Entropy driven
Enthalpy driven
Entropy driven
Enthalpy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
5
10
15
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b

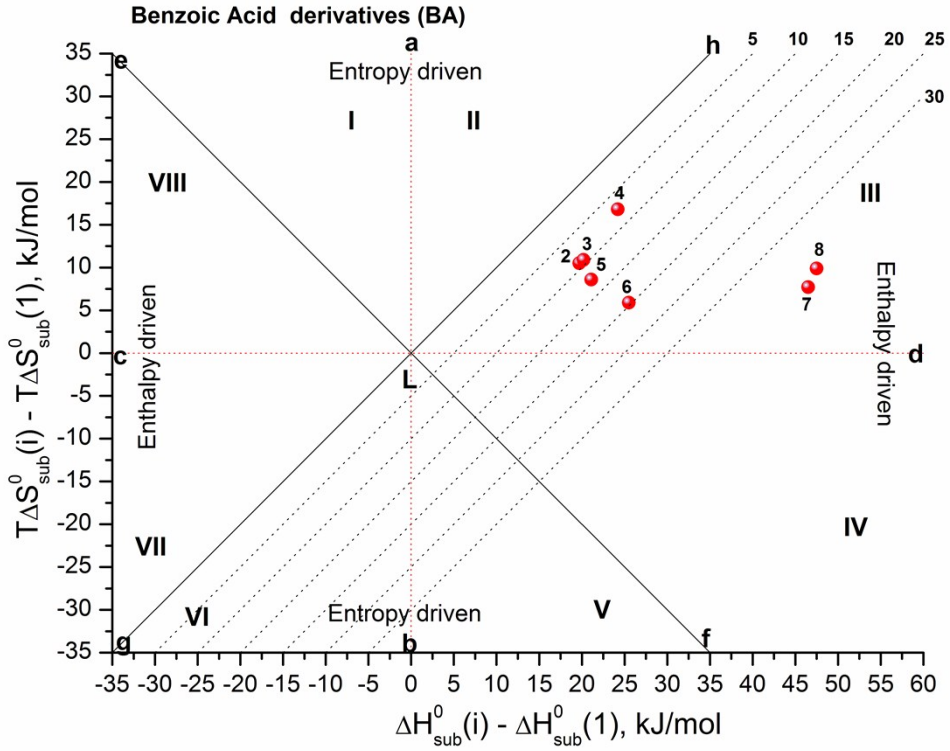


c

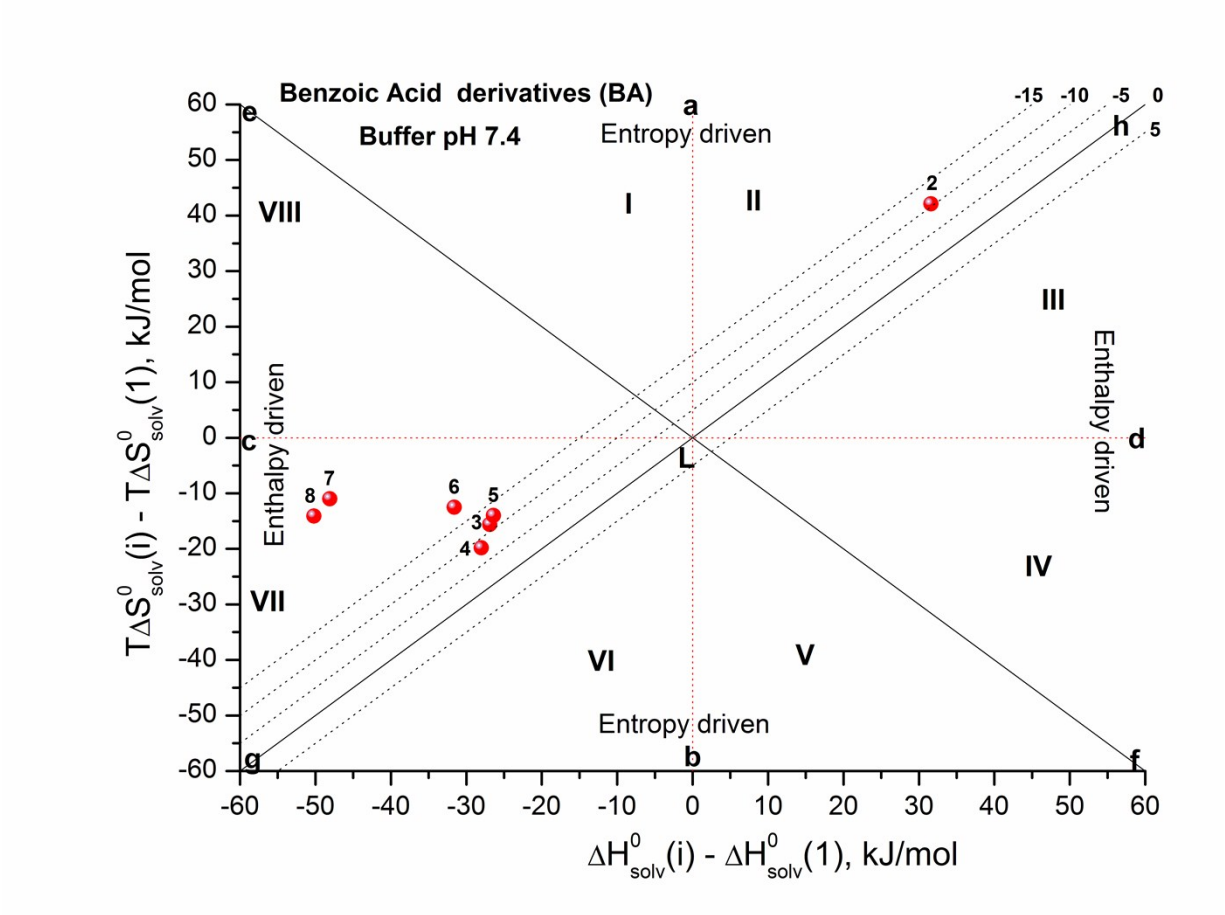
Figure 1SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the spiro derivatives type 2 (SP2) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.


Benzoic Acid derivatives (BA)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
6
7
8
20
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

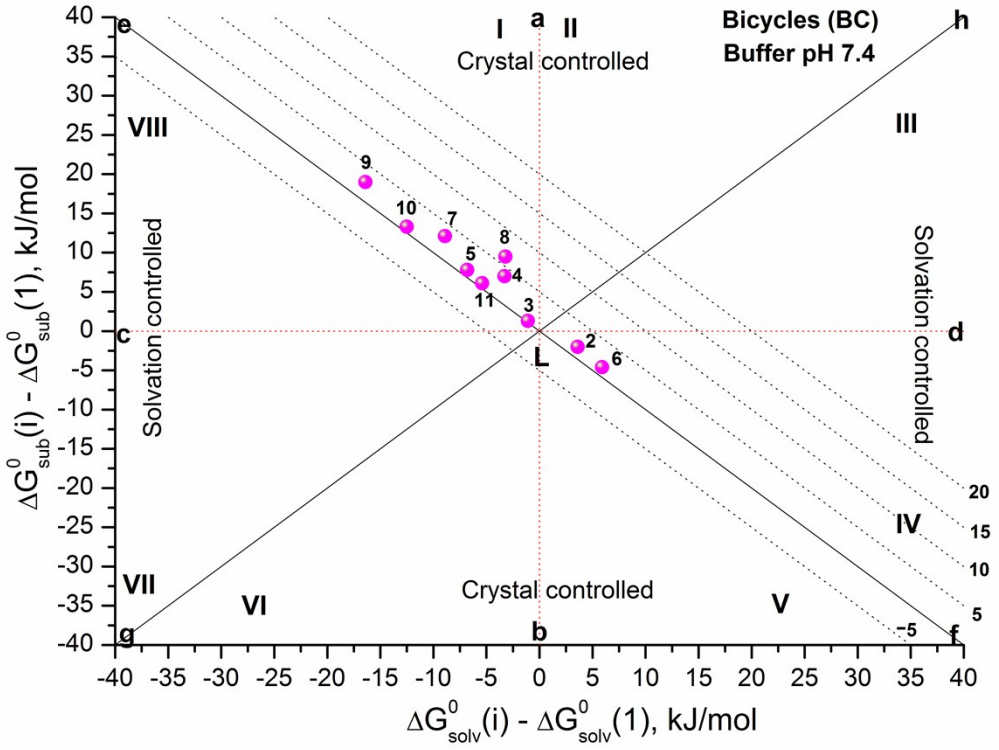

Benzoic Acid derivatives (BA)
Entropy driven
Entropy driven
Enthalpy driven
Enthalpy driven
Entropy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
6
7
8
5
10
15
20
25
30
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b

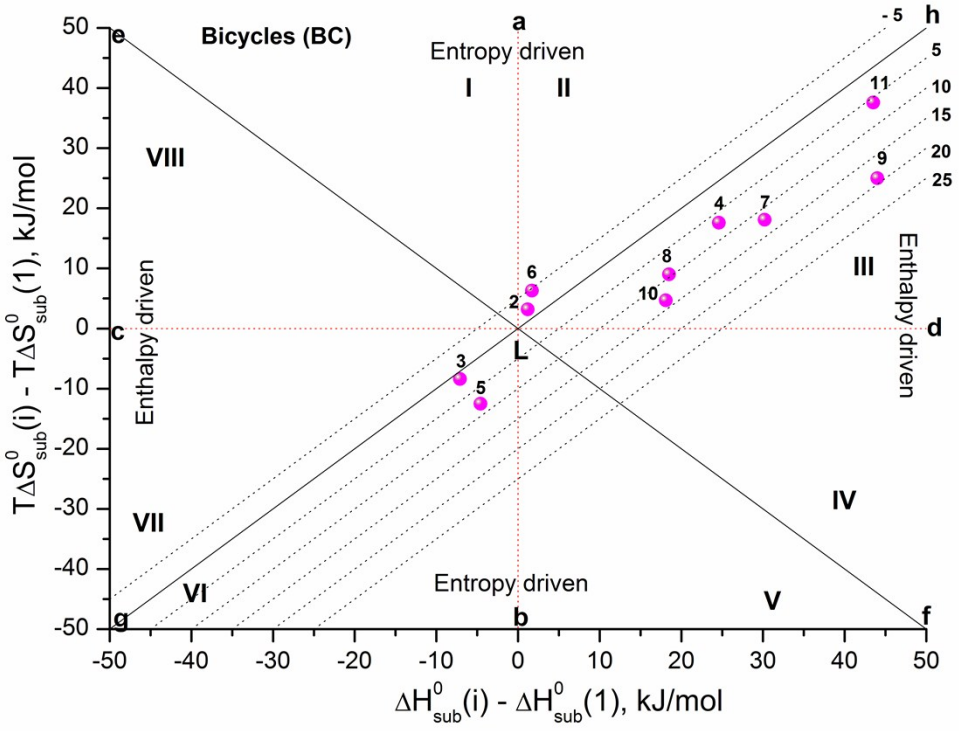


c

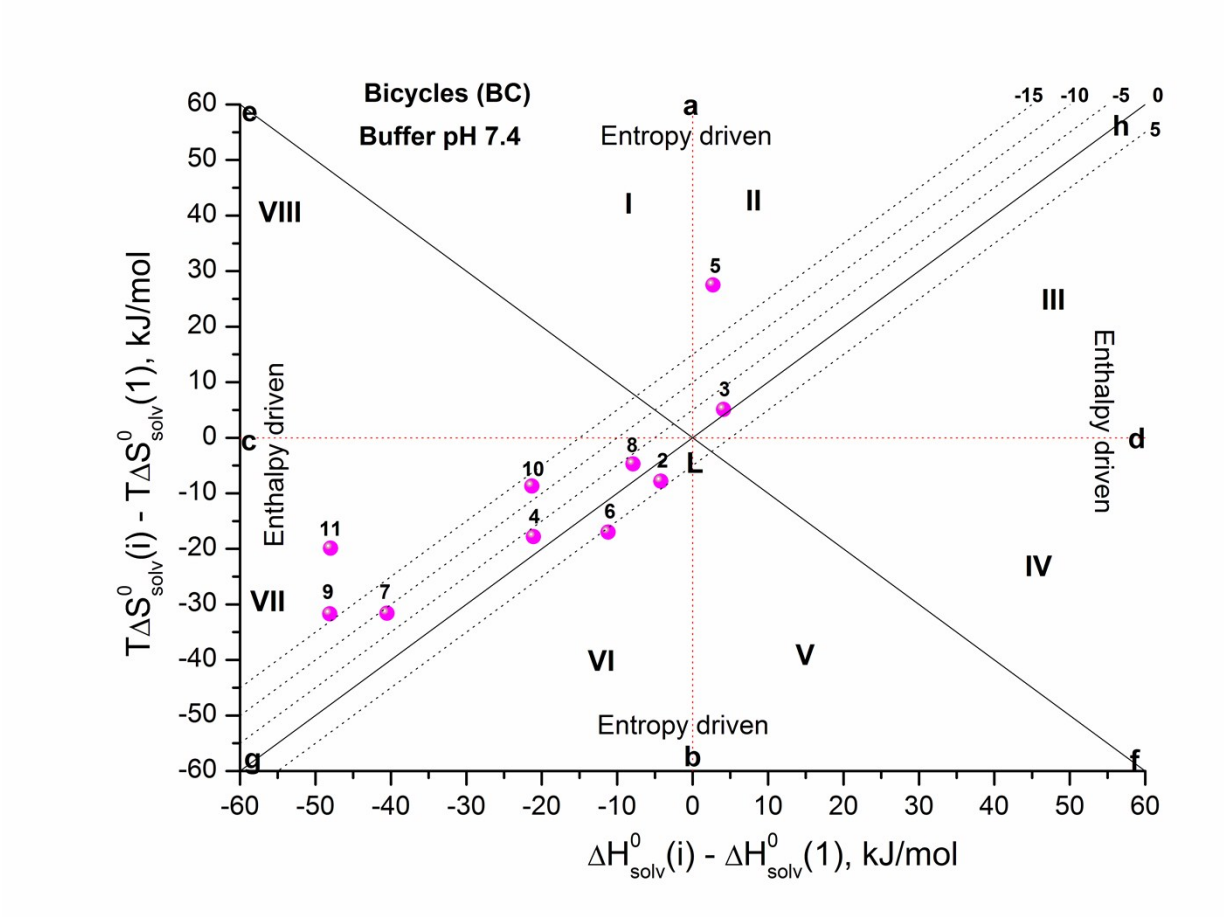
Figure 2SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the benzoic acid and their derivatives (BA) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.


Bicycles (BC)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
20
15
10
5
-5
ΔG⁰sub(i) - ΔG⁰sub(1), kJ/mol
ΔG⁰solv(i) - ΔG⁰solv(1), kJ/mol

a

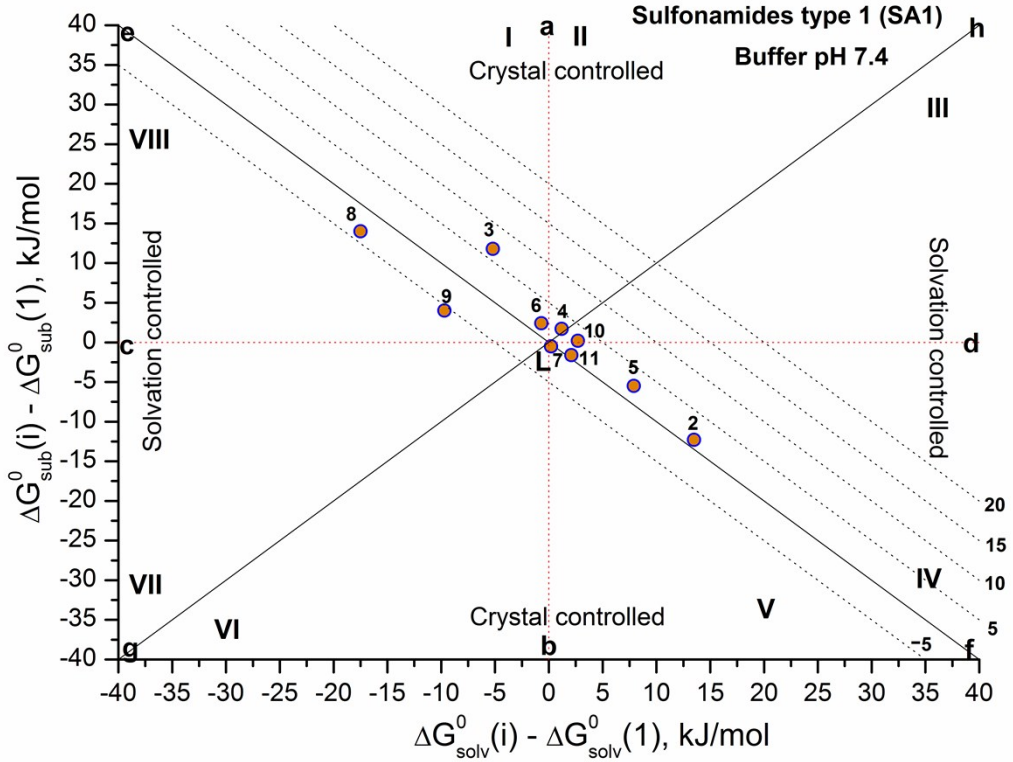

Bicycles (BC)
Entropy driven
Entropy driven
Enthalpy driven
Enthalpy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
-5
5
10
15
20
25
TΔS⁰sub(i) - TΔS⁰sub(1), kJ/mol
ΔH⁰sub(i) - ΔH⁰sub(1), kJ/mol

b

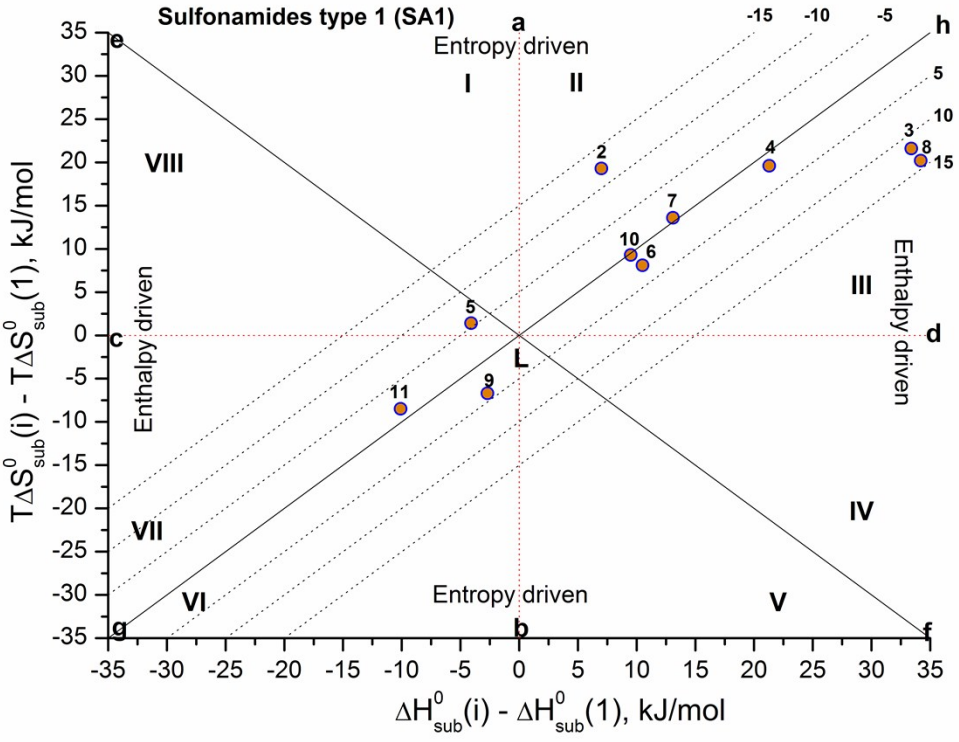


c

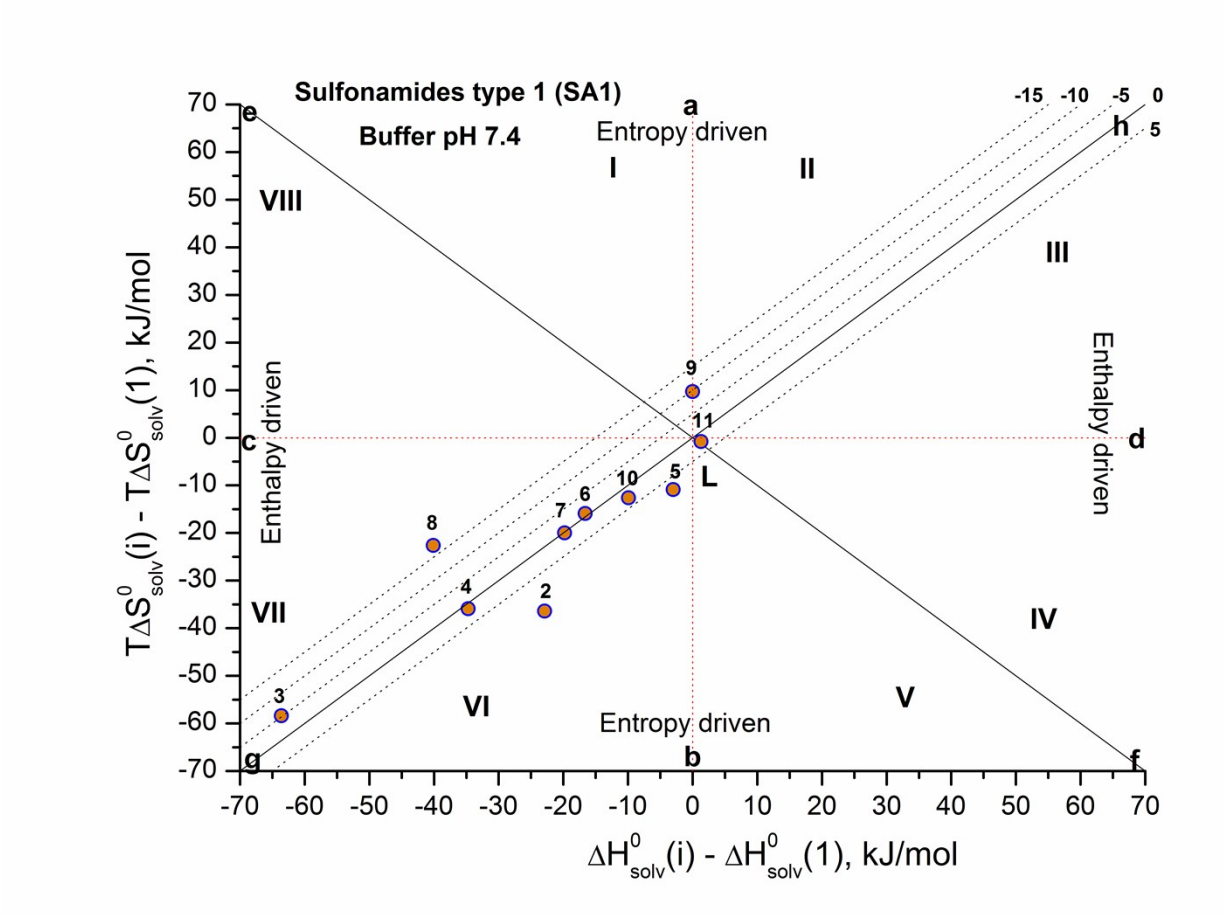
Figure 3SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the Bicycles (BC) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.


Sulfonamides type 1 (SA1)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
20
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

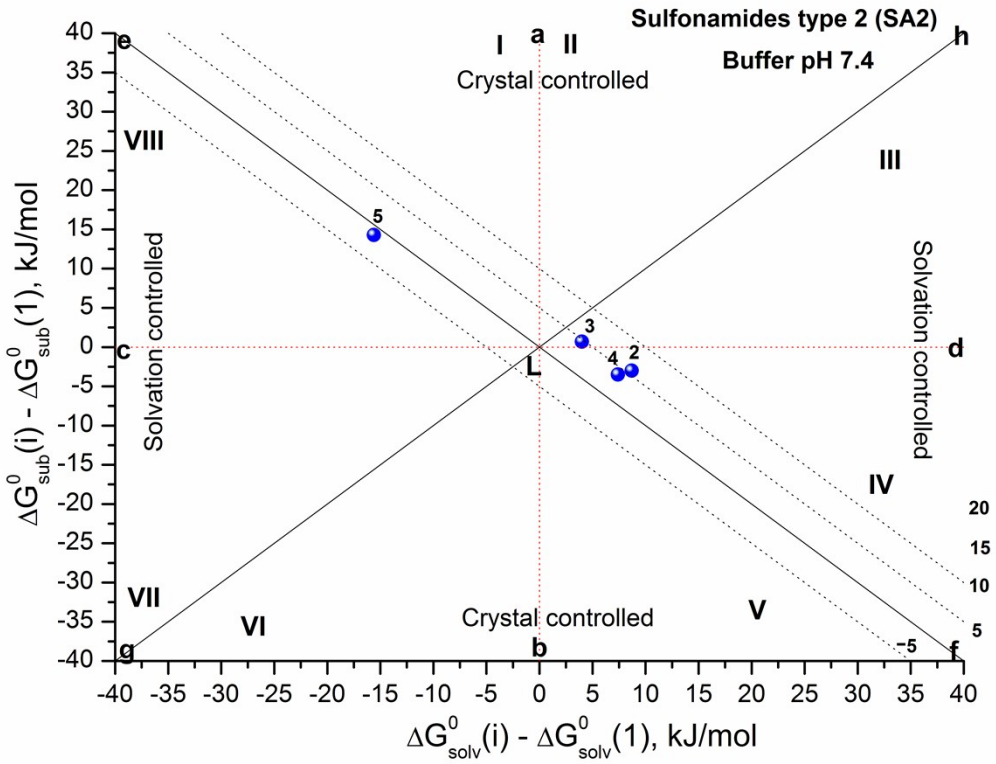

Sulfonamides type 1 (SA1)
Entropy driven
Entropy driven
Enthalpy driven
Enthalpy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
-15
-10
-5
5
10
15
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b

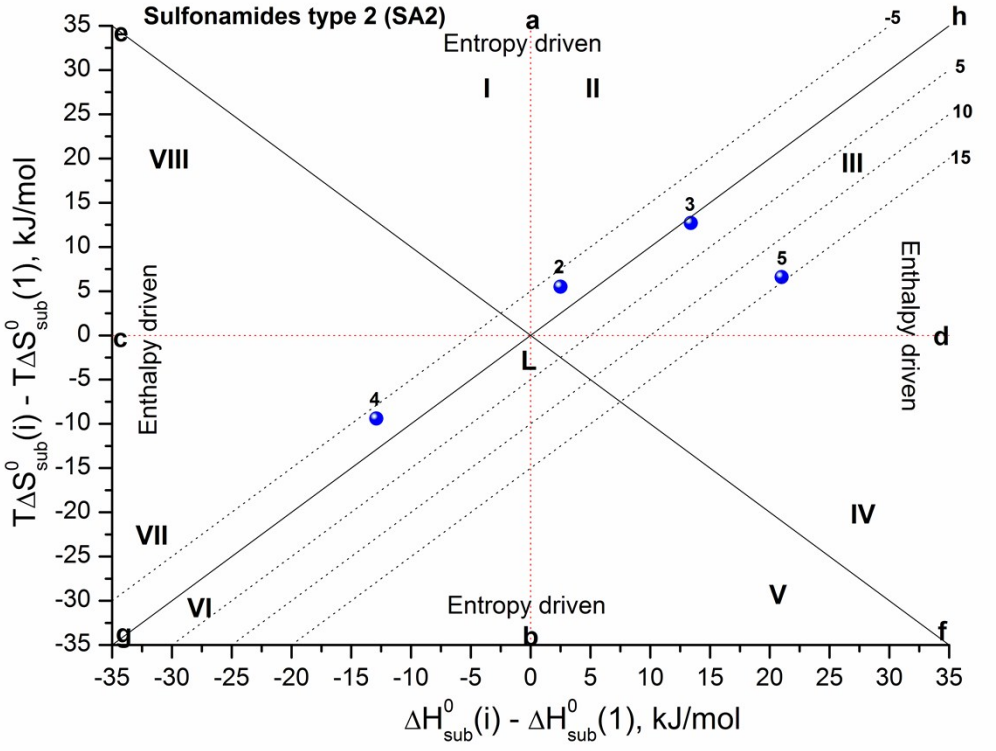


c

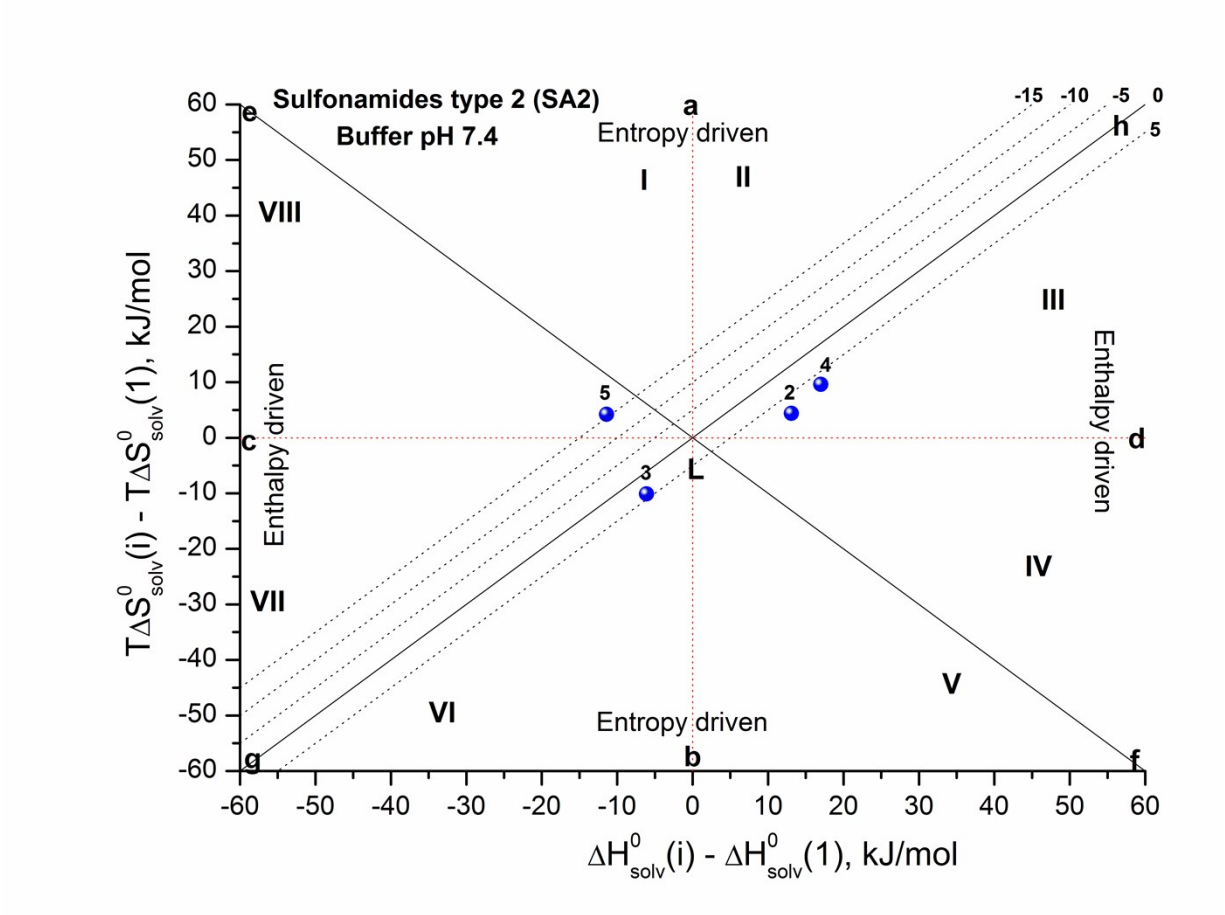
Figure 4SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the Sulfonamides type 1 (SA1) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.


Sulfonamides type 2 (SA2)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
20
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

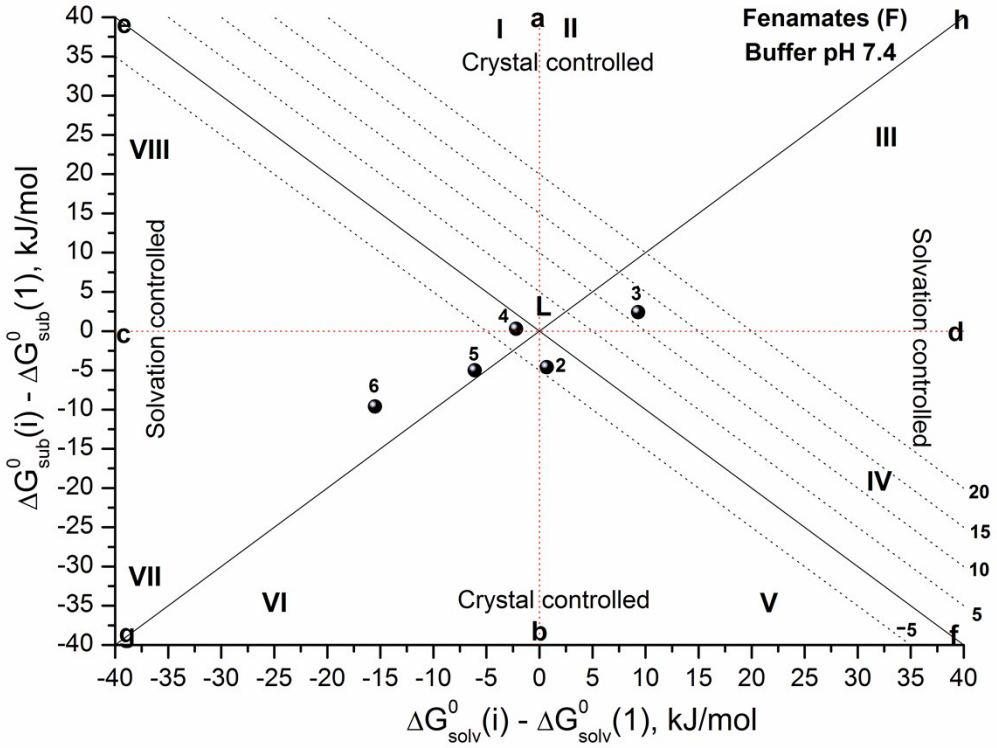

Sulfonamides type 2 (SA2)
Entropy driven
Enthalpy driven
Enthalpy driven
Entropy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
-5
5
10
15
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b

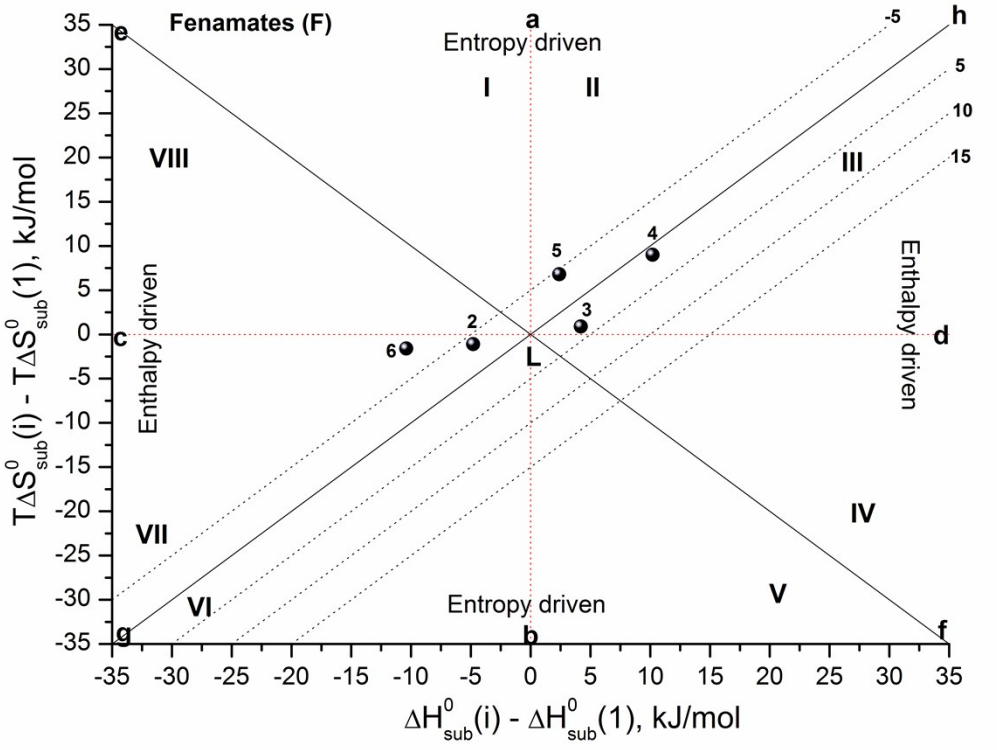


c

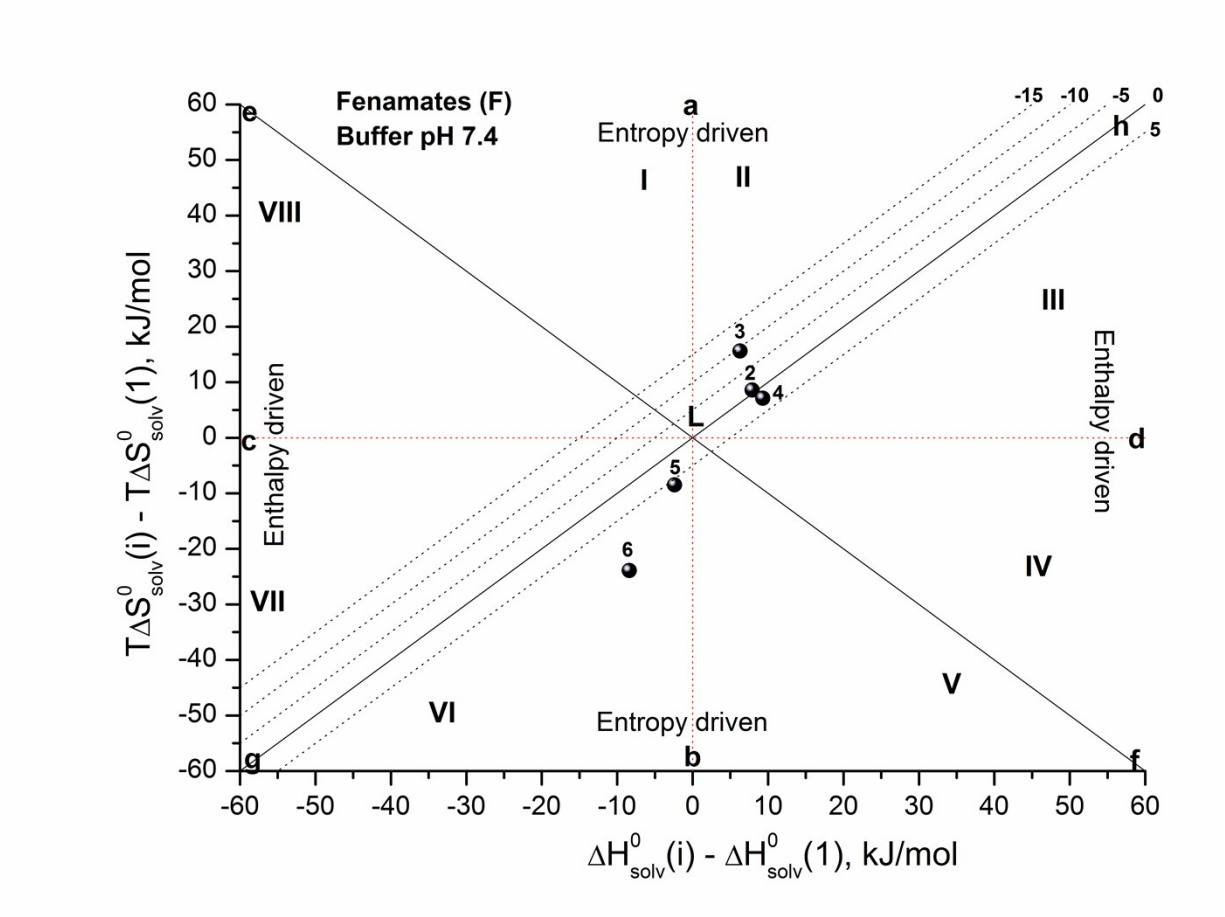
Figure 5SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the Sulfonamides type 2 (SA2) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.


Fenamates (F)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
6
20
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

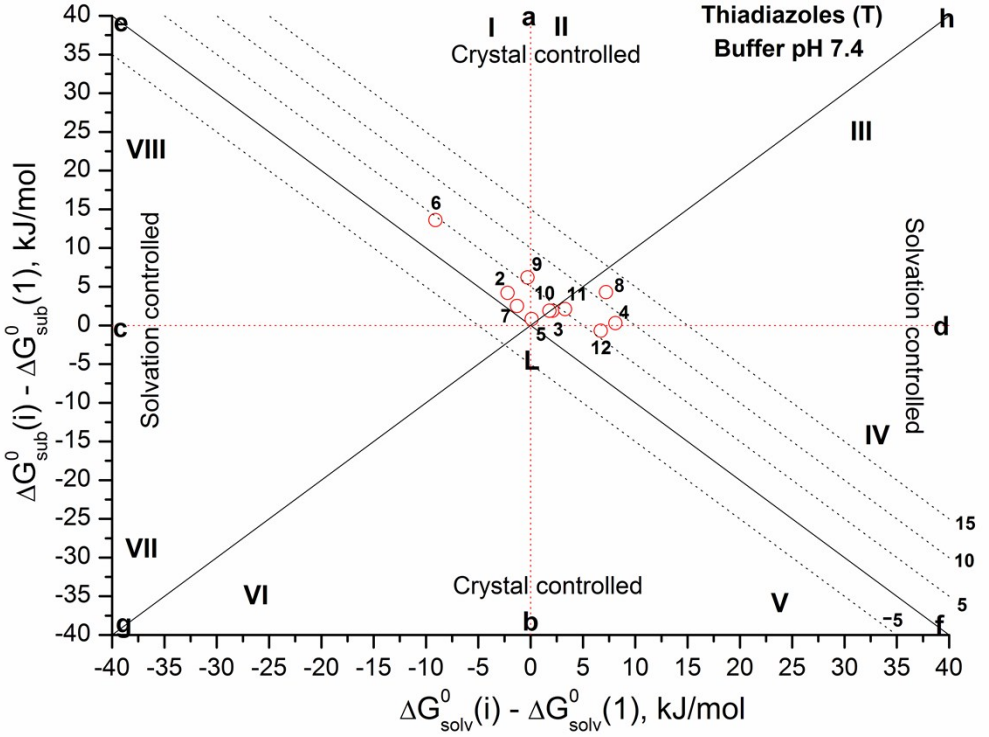

Fenamates (F)
Entropy driven
Entropy driven
Enthalpy driven
Enthalpy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
1
2
3
4
5
6
-5
5
10
15
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b

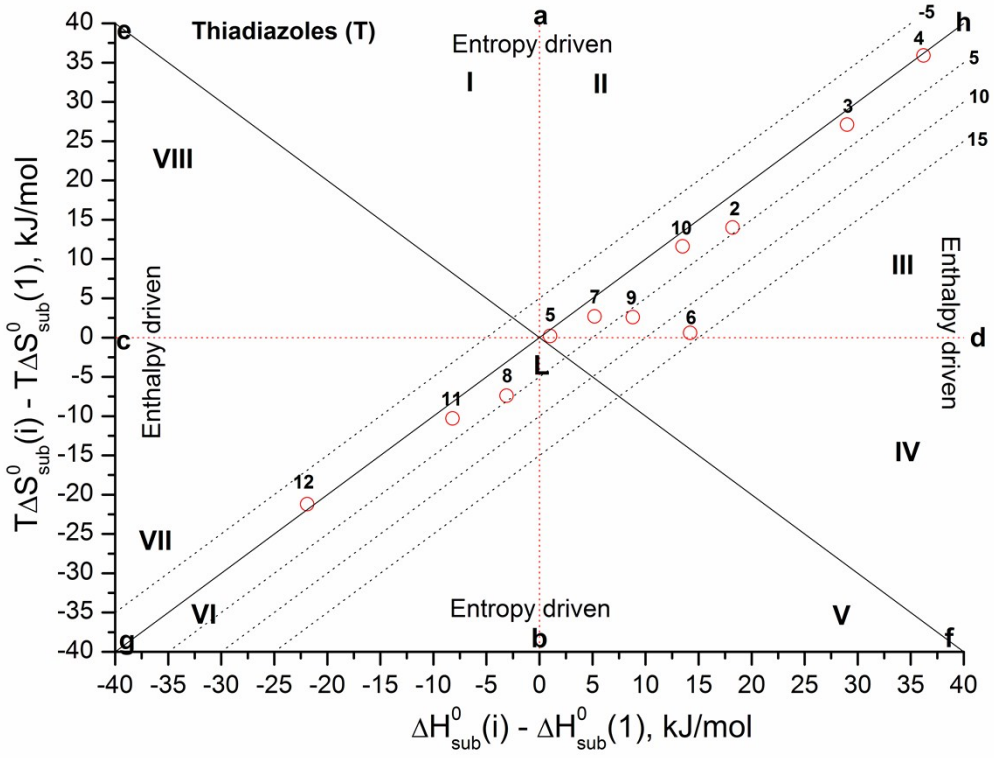


c

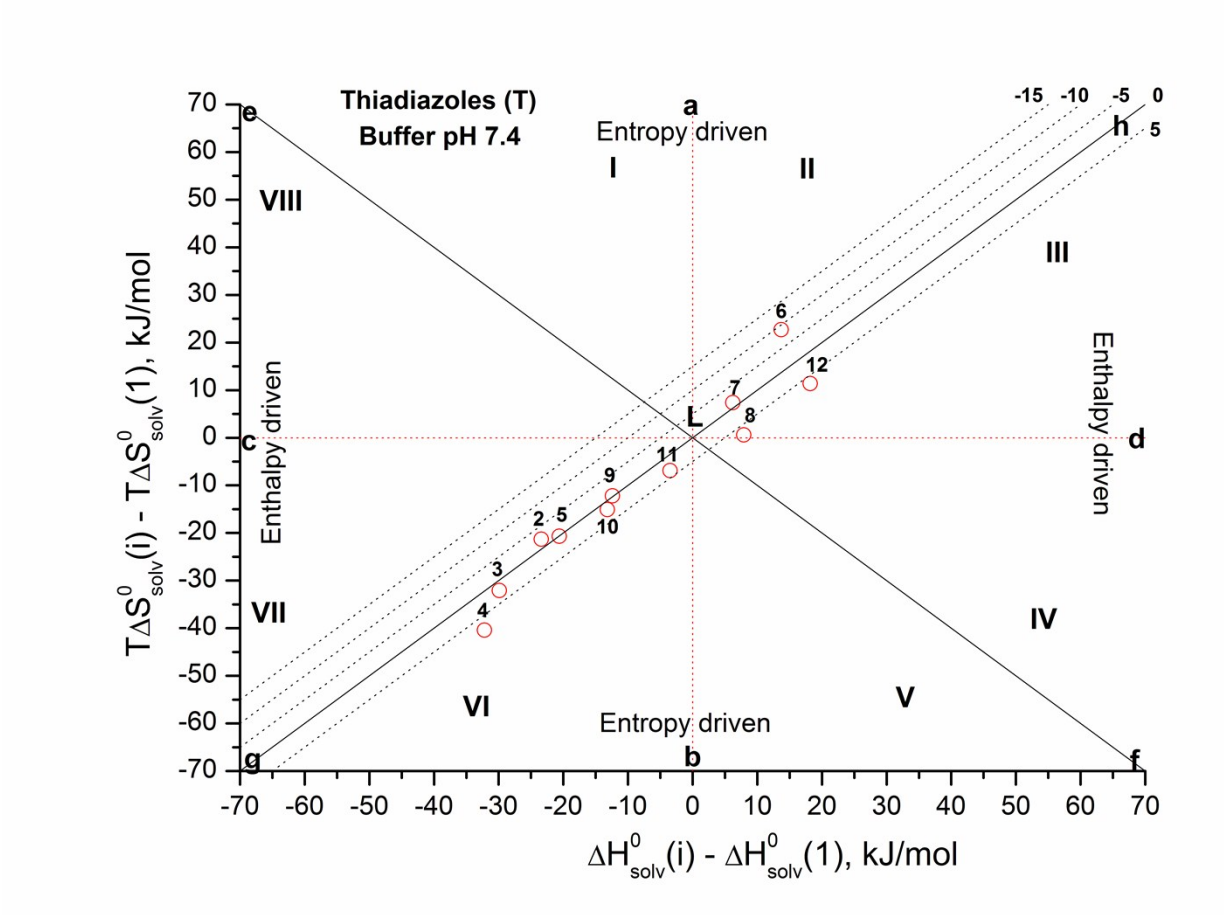
Figure 6SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the N-phenyl-anthranilic acid and their derivatives (fenamates) in comparison to the reference compound: a) experimental data in co-coordinates ($\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$) vs ($\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$); b) experimental data in co-coordinates ($T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$) vs ($\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$); c) experimental data in co-coordinates ($T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1)$) vs ($\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1)$). Numbering corresponds to Figure 1.


Thiadiazoles (T)
Buffer pH 7.4
Crystal controlled
Solvation controlled
Solvation controlled
Crystal controlled
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
15
10
5
-5
$\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1)$, kJ/mol
$\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1)$, kJ/mol

a

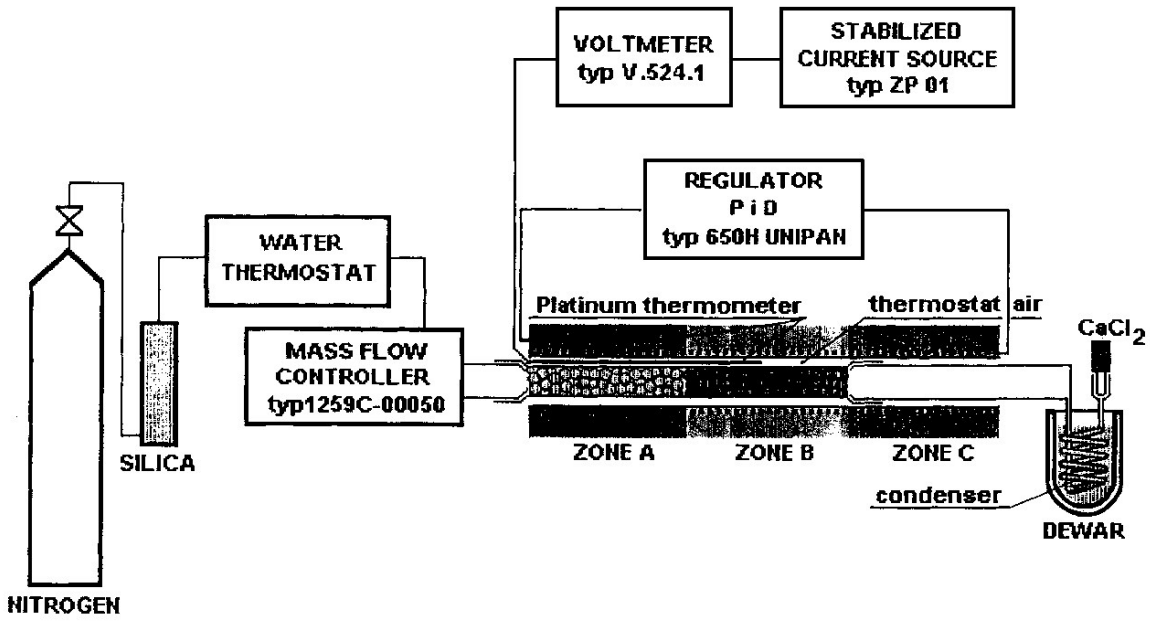

Thiadiazoles (T)
Entropy driven
Entropy driven
Enthalpy driven
Enthalpy driven
I
II
III
IV
V
VI
VII
VIII
a
b
c
d
e
f
g
h
L
-5
5
10
15
$T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1)$, kJ/mol
$\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1)$, kJ/mol

b



c

Figure 7SI. Diagrams for experimental data of sublimation, solvation and dissolution processes of the Thiadiazoles (T) in comparison to the reference compound: a) experimental data in co-coordinates $(\Delta G^0_{sub}(i) - \Delta G^0_{sub}(1))$ vs $(\Delta G^0_{solv}(i) - \Delta G^0_{solv}(1))$; b) experimental data in co-coordinates $(T\Delta S^0_{sub}(i) - T\Delta S^0_{sub}(1))$ vs $(\Delta H^0_{sub}(i) - \Delta H^0_{sub}(1))$; c) experimental data in co-coordinates $(T\Delta S^0_{solv}(i) - T\Delta S^0_{solv}(1))$ vs $(\Delta H^0_{solv}(i) - \Delta H^0_{solv}(1))$. Numbering corresponds to Figure 1.



Scheme 1SI. The scheme of device based on the flow inert gas method

Table 1SI

Energies Gibbs of solubility processes (ΔG^0_{sol} in kJ·mol^{-1}) and solubility values (X_2^{298} in mol. fraction) of the compounds studied in buffer with pH 7.4 at 298 K; thermodynamic sublimation functions (Gibbs energies - ΔG^0_{sub} in kJ·mol^{-1}. enthalpies - ΔH^0_{sub} in kJ·mol^{-1} and entropy terms - $T\Delta S^0_{sub}$ in kJ·mol^{-1}) at 298 K; thermodynamic solvation/hydration functions in buffer with pH 7.4 (Gibbs energies - ΔG^0_{solv} in kJ·mol^{-1}. enthalpies - ΔH^0_{solv} in kJ·mol^{-1} and entropy terms - $T\Delta S^0_{solv}$ in kJ·mol^{-1}) at 298 K.

Compound	X_2^{298}	ΔG^0_{sol}	ΔG^0_{sub}	ΔH^0_{sub}	$T\Delta S^0_{sub}$	ΔG^0_{solv}	ΔH^0_{solv}	$T\Delta S^0_{solv}$
SP1-1	$3.01\cdot10^{-4}$	20.1	39.9	100.7	60.8	-19.8	-86.2	-66.4
SP1-2	$1.71\cdot10^{-4}$	21.5	38.4	95.1	56.7	-16.9	-83.7	-66.6
SP1-3	$6.74\cdot10^{-4}$	18.1	40.9	100.8	59.9	-22.8	-64.4	-41.6
SP2-1	$7.35\cdot10^{-6}$	29.3	56.8	125.9	69.1	-27.5	-123.3	-95.8
SP2-2	$2.47\cdot10^{-6}$	32.0	60.6	136.8	76.2	-28.6	-130.0	-101.5
SP2-3	$1.59\cdot10^{-6}$	33.1	61.7	138.3	76.6	-28.6	-125.7	-97.1
SP2-4	$5.34\cdot10^{-7}$	35.8	59.7	122.8	63.1	-23.9	-111.0	-87.1
SP2-5	$1.20\cdot10^{-6}$	33.8	71.6	156	84.4	-37.8	-144.2	-106.4
SP2-6	$9.75\cdot10^{-6}$	28.6	63.7	139.1	69	-35.1	-134.8	-99.6
SP2-7	$2.69\cdot10^{-7}$	37.5	66.2	120.1	49.4	-28.7	-109.9	-81.2
SP2-8	$1.20\cdot10^{-7}$	39.5	68.9	141.6	72.6	-29.4	-133.9	-104.6
SP2-9	$1.65\cdot10^{-6}$	33.0	57.6	92	31.4	-24.6	-78.0	-53.4
SP2-10	$4.37\cdot10^{-7}$	36.3	62.5	128.5	66	-26.2	-99.0	-72.7
SP2-11	$2.11\cdot10^{-7}$	38.1	66.4	141.7	75.3	-28.3	-126.5	-98.3
BA-1	$1.51\cdot10^{-3}$	16.1	34.4	90.5	56.1	-18.3	-80.4	-62.1
BA-2	$2.55\cdot10^{-3}$	14.8	43.6	110.2	66.6	-28.8	-48.8	-20.0
BA-3	$3.39\cdot10^{-3}$	14.1	43.7	110.7	67.0	-29.6	-107.3	-77.7
BA-4	$2.09\cdot10^{-3}$	15.3	41.8	114.7	72.9	-26.5	-108.4	-81.9
BA-5	$1.45\cdot10^{-3}$	16.2	46.9	111.6	64.7	-30.7	-106.8	-76.1
BA-6	$1.23\cdot10^{-3}$	16.6	54.0	116.0	62.0	-37.4	-112.0	-74.6
BA-7	$7.61\cdot10^{-4}$	17.8	73.2	137.0	63.8	-55.4	-128.5	-73.1
BA-8	$8.25\cdot10^{-4}$	17.6	72.0	138.0	66.0	-54.4	-130.6	-76.2

Table 1SI (Continued)

Compound	X_2^{298}	ΔG^0_{sol}	ΔG^0_{sub}	ΔH^0_{sub}	$T\Delta S^0_{sub}$	ΔG^0_{solv}	ΔH^0_{solv}	$T\Delta S^0_{solv}$
BC-1	$7.35\cdot10^{-6}$	29.3	48.6	106.5	57.9	-19.3	-83.3	-64.0
BC-2	$3.86\cdot10^{-6}$	30.9	46.6	107.7	61.1	-15.7	-87.5	-71.8
BC-3	$6.78\cdot10^{-6}$	29.5	49.9	99.4	49.5	-20.4	-79.2	-58.9
BC-4	$1.65\cdot10^{-6}$	33.0	55.6	131.1	75.5	-22.6	-104.4	-81.8
BC-5	$4.91\cdot10^{-6}$	30.3	56.4	101.9	45.4	-26.1	-80.6	-36.5
BC-6	$4.35\cdot10^{-6}$	30.6	44.0	108.2	64.2	-13.4	-94.5	-81.0
BC-7	$2.02\cdot10^{-6}$	32.5	60.7	136.7	76.0	-28.2	-123.8	-95.6
BC-8	$5.79\cdot10^{-7}$	35.6	58.1	125.0	66.9	-22.5	-91.2	-68.7
BC-9	$2.58\cdot10^{-6}$	31.9	67.6	150.5	82.9	-35.7	-131.4	-95.7
BC-10	$4.02\cdot10^{-6}$	30.8	61.9	124.6	62.6	-31.8	-104.6	-72.7
BC-11	$5.54\cdot10^{-6}$	30.0	54.7	150.0	95.5	-24.7	-131.3	-83.9
SA1-1	$1.35\cdot10^{-6}$	33.5	74.0	134.1	60.1	-40.5	-81.2	-40.7
SA1-2	$8.33\cdot10^{-7}$	34.7	61.7	141.1	79.4	-27.0	-104.1	-77.1
SA1-3	$9.43\cdot10^{-8}$	40.1	85.8	167.5	81.7	-45.7	-144.8	-99.1
SA1-4	$4.19\cdot10^{-7}$	36.4	75.7	155.4	79.7	-39.3	-115.9	-76.6
SA1-5	$5.13\cdot10^{-7}$	35.9	68.5	130.0	61.5	-32.6	-84.2	-51.6
SA1-6	$6.81\cdot10^{-7}$	35.2	76.4	144.6	68.2	-41.2	-97.8	-56.6
SA1-7	$1.52\cdot10^{-6}$	33.2	73.5	147.2	73.7	-40.3	-101.0	-60.7
SA1-8	$5.54\cdot10^{-6}$	30.0	88.0	168.3	80.3	-58.0	-121.3	-63.3
SA1-9	$1.35\cdot10^{-5}$	27.8	78.0	131.4	53.4	-50.2	-81.2	-31.0
SA1-10	$4.19\cdot10^{-7}$	36.4	74.2	143.6	69.4	-37.8	-91.1	-53.3
SA1-11	$1.10\cdot10^{-6}$	34.0	72.4	124.0	51.6	-38.4	-79.9	-41.5
SA2-1	$7.35\cdot10^{-6}$	29.3	53.4	111.5	58.1	-24.1	-69.0	-44.9
SA2-2	$7.38\cdot10^{-7}$	35.0	50.4	114.0	63.6	-15.4	-55.9	-40.5
SA2-3	$1.10\cdot10^{-6}$	34.0	54.1	124.9	70.8	-20.1	-75.1	-55.0
SA2-4	$1.52\cdot10^{-6}$	33.2	49.9	98.6	48.7	-16.7	-52.0	-35.3
SA2-5	$1.24\cdot10^{-5}$	28.0	67.7	132.5	64.7	-39.7	-80.4	-40.7

Table 1SI (Continued)

Compound	X_2^{298}	ΔG^0_{sol}	ΔG^0_{sub}	ΔH^0_{sub}	$T\Delta S^0_{sub}$	ΔG^0_{solv}	ΔH^0_{solv}	$T\Delta S^0_{solv}$
F-1	$1.29\cdot10^{-5}$	27.9	58.9	126.0	68.0	-31.0	-97.0	-66.0
F-2	$1.10\cdot10^{-4}$	22.6	54.3	121.2	66.9	-31.7	-89.1	-57.4
F-3	$2.09\cdot10^{-4}$	21.0	61.3	130.2	68.9	-40.3	-90.7	-50.4
F-4	$4.72\cdot10^{-6}$	30.4	59.2	136.2	77.0	-28.8	-87.7	-58.9
F-5	$8.30\cdot10^{-6}$	29.0	53.9	128.4	74.8	-24.9	-99.4	-74.5
F-6	$1.20\cdot10^{-6}$	33.8	49.3	115.6	66.4	-15.5	-105.4	-89.9
T-1	$8.97\cdot10^{-5}$	23.1	58.3	123.8	65.5	-35.2	-101.5	-66.2
T-2	$4.00\cdot10^{-5}$	25.1	62.5	142.0	79.5	-37.4	-124.9	-87.5
T-3	$1.79\cdot10^{-5}$	27.1	60.2	152.8	92.6	-33.1	-131.4	-98.3
T-4	$3.03\cdot10^{-6}$	31.5	58.6	160.0	101.4	-27.1	-133.7	-106.6
T-5	$6.24\cdot10^{-5}$	24.0	59.1	124.8	65.7	-35.1	-122.1	-86.9
T-6	$1.46\cdot10^{-5}$	27.6	71.9	138.0	66.1	-44.3	-87.8	-43.5
T-7	$5.53\cdot10^{-5}$	24.3	60.8	129.0	68.2	-36.5	-95.3	-58.8
T-8	$9.40\cdot10^{-7}$	34.4	62.6	120.7	58.1	-28.0	-93.6	-65.6
T-9	$8.30\cdot10^{-6}$	29.0	64.5	132.6	68.1	-35.5	-113.9	-78.4
T-10	$2.02\cdot10^{-5}$	26.8	60.2	137.3	77.1	-33.4	-114.7	-81.3
T-11	$1.02\cdot10^{-5}$	28.5	60.4	115.6	55.2	-31.9	-105.0	-73.1
T-12	$7.97\cdot10^{-6}$	29.1	57.6	101.9	44.3	-28.5	-83.3	-54.8