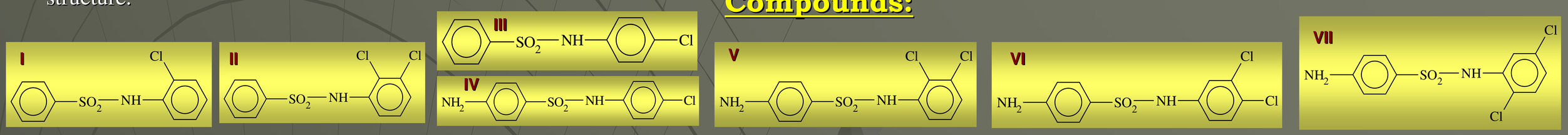
Sulfonamides as a subject to study molecular interactions in crystals and solutions: sublimation, solubility, solvation, distribution

Perlovich G.L.[a], Strakhova N.N.[a], Kazachenko V.P.[a], Schaper K.-J.[b], Raevsky O.A.[a]
[a] Department of Computer-Aided Molecular Design, Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432, Chernogolovka, Russia;
[b] Research Centre Borstel, Centre for Medicine and Biosciences, D-23845 Borstel, Germany;
E-mail address: germanper@yandex.ru

Introduction: Sulfonamides are drugs extensively used for the treatment of certain infections caused by Gram-positive and Gram-negative microorganisms, some fungi, and certain protozoa. Unfortunately, the action of sulfonamides is complicated and can not be described in simple way. There is not enough information to propose suitable mechanisms for the transfer process of sulfonamides between immiscible liquid phases, and between aqueous media and biological membrane models, in order to explain the differences in the pharmacological power as a function of the molecular structure.

Aim:
- to study sublimation process;
- to investigate solubility in water and n-octanol;
- to describe solvation characteristics;
- to analyse partitioning processes in water-octanol system;

Compounds:



Material and Methods:

- The compounds studied have been synthesized.
- Sublimation experiments have been carried out by transpiration method;
- Solubility and partitioning experiments at various temperatures have been realized by solubility saturation method;
- Thermo-chemical measurements have been carried out by differential scanning calorimeter (Perkin-Elmer Pyris 1 DSC)

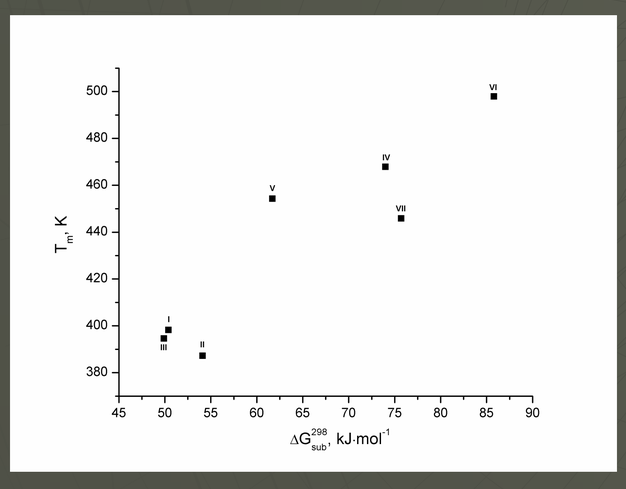
Thermodynamic Characteristics of Solubility Processes of the Compounds Studied in Water and n-Octanol

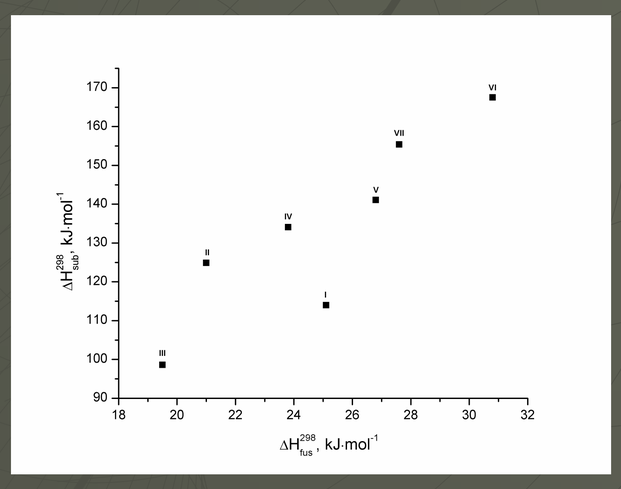
Drugs	X_2^{298} mol fr	ΔG_{sol}^{298} [kJ·mol^{-1}]	ΔH_{sol}^{298} [kJ·mol^{-1}]	$T\Delta S_{sol}^{298}$ [kJ·mol^{-1}]	ΔS_{sol}^{298} [J·mol^{-1}·K^{-1}]
Water					
I	$8.64\cdot10^{-7}$	34.6	14.6 ± 0.8	-20.0	-67 ± 3
II	$4.06\cdot10^{-7}$	36.4	28.3 ± 0.8	-8.1	-27 ± 2
III	$1.68\cdot10^{-6}$	33.0	37.9 ± 1.4	4.9	17 ± 2
IV	$1.19\cdot10^{-6}$	33.8	38 ± 2	4.2	14 ± 2
V	$3.32\cdot10^{-7}$	37.0	14.0 ± 0.6	-23.0	-77 ± 2
VI	$2.05\cdot10^{-7}$	38.2	30.0 ± 0.8	-8.2	-28 ± 2
VII	$7.25\cdot10^{-7}$	35.1	24.2 ± 0.9	-10.9	-37 ± 2

Drugs	X_2^{298} mol fr	ΔG_{sol}^{298} [kJ·mol^{-1}]	ΔH_{sol}^{298} [kJ·mol^{-1}]	$T\Delta S_{sol}^{298}$ [kJ·mol^{-1}]	ΔS_{sol}^{298} [J·mol^{-1}·K^{-1}]
n-octanol					
I	$3.60\cdot10^{-3}$	13.9	33 ± 1	19.1	64 ± 2
II	$1.41\cdot10^{-2}$	10.6	23 ± 1	12.4	42 ± 2
III	$4.21\cdot10^{-2}$	7.85	24 ± 1	16.15	54 ± 2
IV	$1.45\cdot10^{-3}$	16.2	10.7 ± 0.7	-5.5	-18 ± 1
V	$6.84\cdot10^{-4}$	18.1	36.5 ± 0.7	18.4	62 ± 1
VI	$4.22\cdot10^{-4}$	19.3	25.0 ± 0.4	5.7	19 ± 1
VII	$5.29\cdot10^{-4}$	18.7	35.1 ± 0.8	16.4	55 ± 1

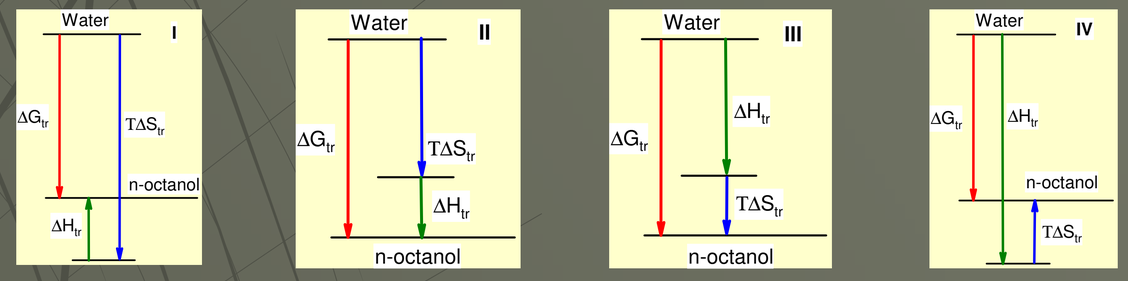
Thermodynamic Characteristics of Sublimation Processes of the Compounds Studied

	I	II	III	IV	V	VI	VII
ΔG_{sub}^{298} [kJ·mol^{-1}]	50.4	54.1	49.9	74.0	61.7	85.8	75.7
ΔH_{sub}^{298} [kJ·mol^{-1}]	113 ± 1	123.4 ± 1.6	97.3 ± 1.9	134.1 ± 1.2	141.1 ± 0.7	167.5 ± 3.6	155.4 ± 1.6
$T\Delta S_{sub}^{298}$ [kJ·mol^{-1}]	62.6	69.3	47.4	60.1	79.4	81.7	79.7
ΔS_{sub}^{298} [J·mol^{-1}·K^{-1}]	210 ± 3	232 ± 5	159 ± 5	202 ± 3	266 ± 2	274 ± 8	268 ± 4
ζ_H [%]	64.4	64.0	67.2	69.1	64.0	67.2	66.1
ζ_{TS} [%]	35.6	36.0	32.8	30.9	36.0	32.8	33.9
T^f [K]	398.2 ± 0.2	387.2 ± 0.2	394.6 ± 0.2	467.9 ± 0.2	454.3 ± 0.2	497.9 ± 0.2	445.9 ± 0.2
ΔH_{fus} [kJ·mol^{-1}]	33.5 ± 0.5	27.2 ± 0.5	25.8 ± 0.5	37.3 ± 0.5	40.9 ± 0.5	51.5 ± 0.5	41.3 ± 0.5
ΔS_{fus} [J·mol^{-1}·K^{-1}]	84 ± 2	70 ± 2	65 ± 2	79.7	90.0	103.4	92.6





Dependencies of the sublimation thermodynamic parameters versus characteristics of the fusion processes of the molecular crystals under investigation



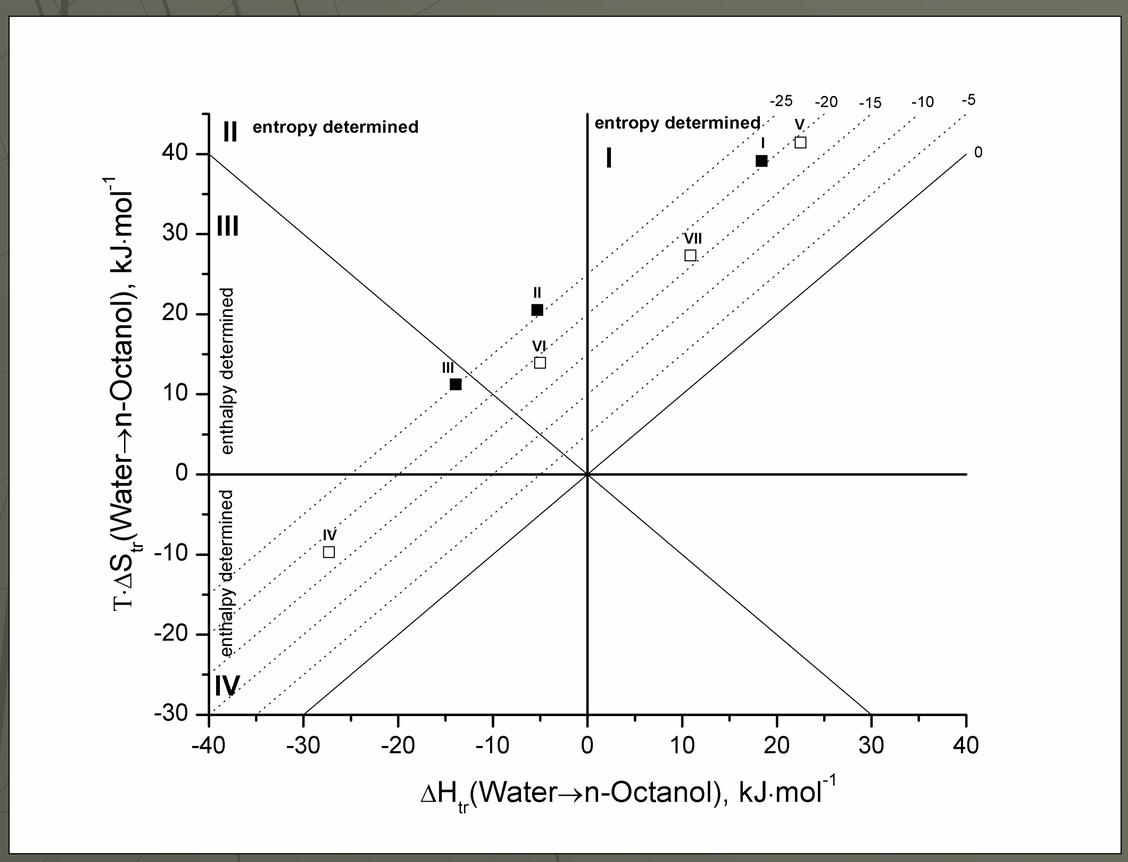
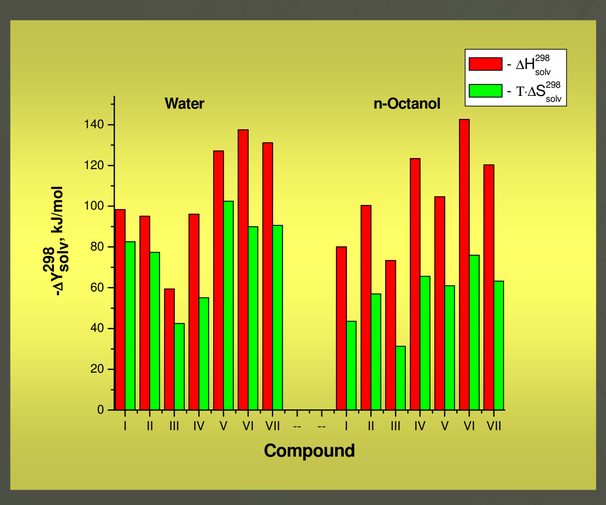
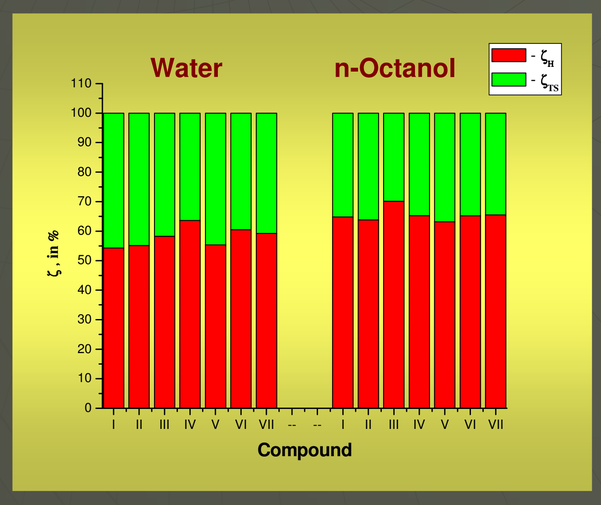


Diagram which gives opportunity to analyze driving forces of the partitioning (transfer) processes of compounds studied in the Water-Octanol system depending on structure and topology molecule





Solvation characteristics of the compounds studied in Water and n-Octanol

$\zeta_H = [\Delta H_{solv}/(|\Delta H_{solv}|+|T\cdot\Delta S_{solv}|)]\cdot100\%$; $\zeta_{TS} = [T\cdot\Delta S_{solv}/(|\Delta H_{solv}|+|T\cdot\Delta S_{solv}|)]\cdot100\%$

Conclusion:

Distinguishing between enthalpy and entropy, as is possible through the present approach, leads to the insight that the mechanism is different for the different molecules (entropy- or enthalpy determined). Thus, in contrast to interpretation of Gibbs energy of transfer, being excessively used for pharmaceuticals in the form of the partition coefficient and logP, analysis of thermodynamic functions of the transfer process provides additional mechanistic information. This may be of importance for further evaluation of distribution of drug molecules and provide a better understanding of biopharmaceutical properties of drugs.

Acknowledgments

This work was supported by ISTC (project No. 0888).

[1] Perlovich, G.L., Strakhova, N.N., Kazachenko, V.P., Volkova, T.V., Tkachev, V.V., Schaper, K.J., Raevsky O.A. 2007. Int. J. Pharm. 334, 115–124.