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THERMODYNAMIC INVESTIGATIONS OF SUBLIMATION, SOLUBILITY AND SOLVATION OF [4-(BENZYLOXY)-PHENYL]ACETIC ACID

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Temperature dependences of solubility, saturated vapour pressure and crystal heat capacity of [4-(Benzyloxy)phenyl]acetic acid were determined. The solubility of this compound was investigated in *n*-hexane, buffered water solutions with pH 2.0 and 7.4 and *n*-octanol. The enthalpy of sublimation and vaporization as well as the fusion temperature were determined. Solvation and solubility processes have been analyzed. The thermodynamics of transfer processes from one buffer to another (protonation process), from buffers to 1-octanol (partitioning process), and from *n*-hexane to the applied solvents (specific interaction) have been calculated and compared to those of other NSAIDs. The relevant shares of specific and non-specific interactions in the process of solvation have been investigated and discussed.

Keywords: *[4-(benzyloxy)phenyl]acetic acid, DSC, fusion, heat capacity, solubility, solvation, sublimation, thermodynamic functions, thermogravimetry, transfer process, vaporization, water/octanol system*

Introduction

The understanding of drug passive transport mechanism through different kind of biological barriers is of a great interest for biomedical chemistry and pharmacy. An important role is played here by the mechanism of diffusion into biological membranes (e.g. the nature and dimension of the units that are transferred by the diffusion process). However, so far this issue has not been given proper attention. The purpose of the present work is to look at this problem through the examination of energetic aspects of the interaction of drugs with different media and first of all with *n*-octanol known as a structural analog for lipids (in particular, phospholipids) [1], and with buffered water. So far the most attention has been paid to the *n*-octanol/water partitioning studies of drugs which are characterized by partitioning coefficient log*P* [2–5]. Nevertheless, the better understanding of its mechanism is achieved when water–*n*-octanol transfer thermodynamic functions are analyzed. They allow to estimate the partitioning driving forces in absolute scale [6, 7].

As it is known, the dissolution process is determined by the crystal lattice energy of solute as well as by the interaction energy solute–solvent [8]. The lack of data for thermodynamic functions characterizing the sublimation process made it impossible to give an accurate characteristic of the solvation process. What is more the knowledge of these functions allows to assume the influence of the structure and constitution of a drug molecule and opens new possibilities/opportunities in drug optimization and drug design.

This work is a continuation of our study of drugs solvation phenomenon in pharmaceutically relevant mediums [9, 10–14].

Experimental

Materials

The studies of [4-(benzyloxy)phenyl]acetic acid, (4-boph), ($C_{15}H_{14}O_3$, *MW* 242.27), a non-steroidal representative (Fig. 1), were carried out using commercially available substance of 98% purity from Aldrich, lot No. 555398.

The solvents were as follows: *n*-octanol (1-octanol, $CH_3(CH_2)_7OH$, *MW*=130.2) ARG from Sigma Chemical Co. (USA), lot 11K3688; *n*-hexane (C_6H_{14}, *MW*=86.18) ARG from SDS (Peypin, France), lot 07059903C. The buffer solutions have been prepared by mixing solutions of hydrochloric acid and potassium chloride for the pH 2.0, and appropriate sodium and potassium salts of phosphoric acid for the pH 7.4 as described elsewhere [15]. All the chemicals where of AR grade. The pH values have been controlled using Toledo MP 220 pH meter (Mettler, USA) standardized with pH 1.68 and 9.22 solutions.

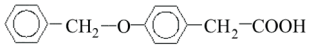

Fig. 1 Structure formula of [4-(benzyloxy)phenyl]acetic acid

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Methods

Solubility determination

Solubilities of 4-boPh were determined within a wide range of temperature (15–42)±0.1°C by an isothermal saturation technique. The solid phase was removed by centrifuging and then by filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size), and the bulk solution was measured spectrophotometrically using UV-2401 PC spectrophotometer (Shimadzu, Japan) according to the previously described schedule [16]. The experimental results are the average of at least three replicated experiments with the statistical errors within 2.5%.

Thermogravimetric experiments

Thermogravimetric investigations were carried out within the temperature range of 20–400°C, heating rate of 10°C min^{-1} and flow rate of dry argon gas 5.4 L h^{-1} using TG Analyzer 951 with a horizontal furnace by DuPont Instr. (USA). The calibration of the TG cell was performed using a sample of calcium oxalate monohydrate in an atmosphere of flowing dry argon (6 L h^{-1}) at heating rate of 5°C min^{-1}. Samples were placed in the aluminum pans of the type used for DSC measurements with the intrinsic surface area equal $1.43 \cdot 10^{-4}$ m^2. The samples were spread uniformly until they completely covered the bottom surface. The measurements were repeated three times. The determinations were off by 3%.

Sublimation experiments

Sublimation experiments were carried out with the transpiration method as described elsewhere [17]. The equipment was calibrated using benzoic acid (standard substance obtained from the Polish Committee of Quality and Standards) with enthalpy of combustion being $\Delta H_c = -3228.07$ kJ mol^{-1} and heat of fusion corresponding to ΔH_{fus}=18.0 kJ mol^{-1}. The standard value of the obtained sublimation enthalpy was ΔH^0_{sub} =90.5±0.3 kJ mol^{-1}. This is in good agreement with the value recommended by IUPAC of ΔH^0_{sub} =89.7±0.5 kJ mol^{-1} [18]. The saturated vapor pressures were measured at each temperature at least 5 times with the statistical error being within 3–5%. The experimentally determined vapor pressure data were described in (ln$P$; 1/T) co-ordinates by Eq. (1):

$$\ln P = A + B/T \quad (1)$$

The value of the enthalpy of sublimation is calculated by the Clausius–Clapeyron equation:

$$\Delta H^{T}_{sub} = \frac{-R\partial(\ln P)}{\partial(1/T)} \quad (2)$$

Whereas the entropy of sublimation at a given temperature T was calculated from the following relation:

$$\Delta S^{T}_{sub} = (\Delta H^{T}_{sub} - \Delta G^{T}_{sub}) / T \quad (3)$$

where $\Delta G^{T}_{sub} = RT\ln(P/P_0)$ and $P_0 = 1.013 \cdot 10^5$ Pa.

Differential scanning calorimetry (DSC)

The temperature dependencies of heat capacities in the process of fusion were obtained using a TG-DSC 111 Setaram differential scanning calorimeter (Setaram, France). DSC runs were performed in an atmosphere of dry nitrogen of high purity 99.99% using standard stainless steel sample crucibles. The equipment was calibrated with indium. The value for the enthalpy of fusion equaled 28.48 J g^{-1} (reference value 28.45 J g^{-1}). The melting point was 156.5±0.1°C (n=10). All the DSC experiments were carried out at a heating rate of 0.5 K min^{-1}. The accuracy of mass measurements was ±0.0005 mg.

Statistical analysis

Regression analysis of the data has been performed using standard statistical procedures (the least square method).

Calculation procedure

There is a series of methods of the determination of vaporization enthalpy through the simultaneous thermogravimetry–differential thermal analysis (TG-DTA) is based on the recording of the sample mass loss from an unchanging surface area in a regulated inert gas flow. For future calculations the ascending DTA curve region has been considered. The parameters of experiment, i.e. the sample preparation procedure, both heating and inert gas flow rates were optimized by Wright *et al*. [19] using benzoic acid which corresponds to the compound studied by us. Moreover, the method has been successfully applied to drug studies (in particular for parabens which have similar molecular structure to 4-boph) [20, 21]. Those are the main reasons of the TG-DTA technique chosen, though many other methods are employed successfully for studying of vaporization process of complex organic compounds [22].

The evaporation process could be described by Langmuir equation:

$$\frac{dm}{dt} = P\alpha\left(\frac{M}{2\pi RT}\right)^{1/2} \quad (4)$$

where dm/dt is the rate of mass loss per area, P is the pressure, α is the vaporization constant, M is the molecular mass of the compound studied, R is the gas constant, and T is the absolute temperature.

It should be noted that α is an equal unity in vacuum only and it is not so in gas flow conditions. If the vapor under investigation is non-associated then Eq. (4) could be rewritten as:

$$P = [\alpha^{-1}(2\pi R)^{1/2}]\left[\left(\frac{T}{M}\right)^{1/2}\left(\frac{dm}{dt}\right)\right] = kv \qquad (5)$$

where $k=\alpha^{-1}(2\pi R)^{1/2}$ and $v=(T/M)^{1/2}(dm/dt)$.

As it follows from the equation, k does not depend on the compound nature and is a universal constant, whereas v does. The k-value was measured earlier using Antoine constants for methylparaben [20] and is nearly equal to 124525 in SI units, while the v-value is a constant within a given series of measurements. E_{act} may be estimated by the Arrhenius equation:

$$\ln k_{vap} = \ln A_{vap} - \frac{E_{act}}{RT} \qquad (6)$$

where k_{vap} is the coefficient of evaporation and is equal to mass loss per surface area of a sample, i.e. $k_{vap}=dm/Sdt$. A sure sign of the non-associated vaporization is the equality of both the activation energy of evaporation, E_{act}, and the vaporization enthalpy, ΔH_{vap}, (zero-order process).

Table 1 The Arrhenius equation parameters and vaporization enthalpy experimental values of [4-(benzyloxy)phenyl]acetic acid

No.	E_{act}[a]/kJ mol^{-1}	lnA_{vap}	R	ΔH_{vap}/kJ mol^{-1}
1	75.1	28.16	0.997	77.4
2	78.1	29.27	0.998	78.7
3	72.9	28.03	0.994	75.1

[a] $\ln k_{vap}=\ln A_{vap}-E_{act}/RT$

The Arrhenius equation parameters and vaporization enthalpy experimental values (calculated from the Clausius–Clapeyron equation) of [4-(benzyloxy)phenyl]acetic acid are shown in Table 1. As follows from Table 1, a zero-order process is observed at 4-boph evaporation.

Results and discussion

Sublimation thermodynamics

Temperature dependence of [4-(benzyloxy)phenyl]acetic acid saturated vapor pressure and thermodynamic functions of sublimation process are summarized in Table 2.

The crystal structure of 4-boph has been characterized by Bats using X-ray diffraction experiment [23]. It showed that the crystal lattice had triclinic symmetry with two independent molecules in the unit cell. The

Table 2 Temperature dependence of saturated vapor pressure and some thermodynamic parameters of [4-(benzyloxy)phenyl]acetic acid

T/°C	P/Pa	T/°C	P/Pa
103.0	$5.73\cdot10^{-2}$	111.0	$1.24\cdot10^{-1}$
105.0	$7.35\cdot10^{-2}$	112.0	$1.29\cdot10^{-1}$
106.5	$8.29\cdot10^{-2}$	113.0	$1.47\cdot10^{-1}$
110.0	$1.11\cdot10^{-1}$	114.0	$1.56\cdot10^{-1}$

$\ln(P/\text{Pa})=(31.5\pm0.9)-(12909\pm362)/T$

$R=0.9977$; $\sigma=2.64\cdot10^{-2}$; $n=8$

ΔH_{sub}/kJ mol^{-1}	107±3
ΔH_{sub} (calc.)[a]/kJ mol^{-1}	106.4±2.6
ΔG^0_{sub}/kJ mol^{-1}	57.8
ΔH^0_{sub} [b]/kJ mol^{-1}	111±3
$T\Delta S^0_{sub}$/kJ mol^{-1}	53.2
ΔS^0_{sub}/J K^{-1} mol^{-1}	178±10
ς_H/%	67.6
ς_{TS}/%	32.4
C^{cr}_p (298.15) (exp.)/J K^{-1} mol^{-1}	340±3
C^{cr}_p (298.15) (calc.)/J K^{-1} mol^{-1}	339.7
ΔH_{vap}/kJ mol^{-1}	77.1±1.8
ΔS_{vap}/J K^{-1} mol^{-1}	104
ΔH_{fus}/kJ mol^{-1}	29.3±0.8
T_{fus}/K	396.1±0.7
ΔS_{fus}/J K^{-1} mol^{-1}	74±2

[a] $\Delta H_{sub}=\Delta H_{vap}+\Delta H_{fus}$;
[b] $\Delta H^0_{sub}=\Delta H^T_{sub}+[0.75+0.15C^{cr}_p(298.15)][T_m-298.15]$

phenyl rings form the dihedral angle around 64.0°C. The molecules create dimmers by the carboxyl groups in the crystal lattice (Fig. 2) and the packing architecture looks like parallel stacks along the c-axis.

It should be noted that the temperature range of the vapor pressure experiment is far from ambient. In our previous works [10–14] we considered that the enthalpy of sublimation did not depend on temperature (the influence of heat capacity changes was to be negligible), but as a matter of fact it caused a small systematic error. Taking this into account in the present work the heat capacity of the crystal was experimentally determined in the temperature range 20–125°C. The obtained data were used to determine the standard subli-

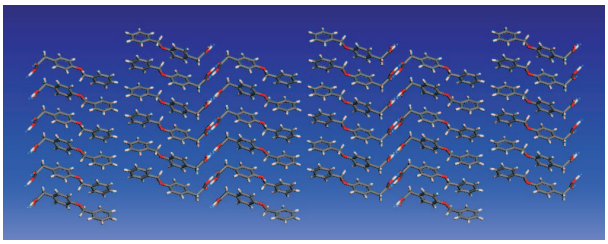


Fig. 2 Packing architecture of [4-(benzyloxy)phenyl]acetic acid

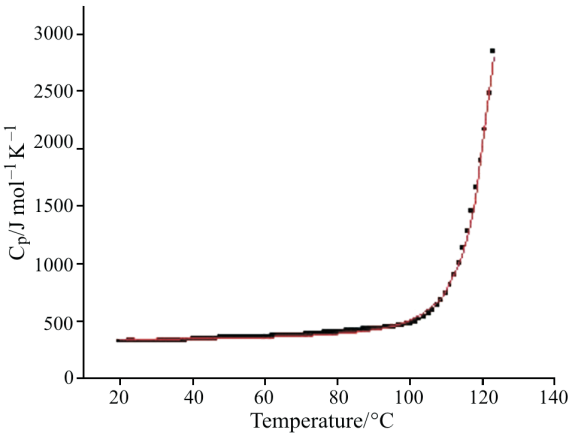


Fig. 3 Temperature dependence of heat capacity ΔC_p of [4-(benzyloxy)phenyl]acetic acid

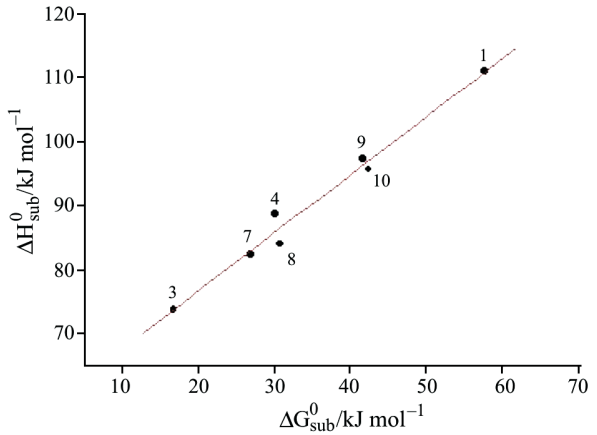


Fig. 4 Sublimation Gibbs energy, ΔG^0_{sub}, *vs*. sublimation enthalpy, ΔH^0_{sub}, for [4-(benzyloxy)phenyl]acetic acid relative compounds (numbering corresponds to Table 3)

mation thermodynamic functions. The temperature dependence of heat capacity ΔC_p of [4-(benzyloxy)phenyl]acetic acid is shown in Fig. 3.

Regardless of the experimentally determined specific heat, C_p value at 25°C was calculated using the group additivity method described by Chickos *et al*. [24]. Both the experimental and the calculated values are given in Table 2 and show an excellent agreement.

The main problem lies in unavailability of gas phase heat capacity values for Kirchhoff's equation. Nevertheless, there are numerous estimation methods that allow to overcome this problem. In our opinion one of the most appropriate approaches is the one proposed by Chickos *et al*. [25] for its sensitivity to molecular structure:

$$\Delta H^0_{sub} = \Delta H^T_{sub} + \\ +[0.75 + 0.15C^{cr}_p(298.15)][T_m - 298.15] \quad (7)$$

The standard sublimation thermodynamic functions are presented in Table 2. In order to find out the main driving force of the sublimation process the relative parameters of enthalpic and entropic terms were calculated with the following equations:

$$\varsigma_H = \frac{\left|\Delta H^0_{sub}\right|}{\left|\Delta H^0_{sub}\right| + \left|T\Delta S^0_{sub}\right|} \cdot 100\% \quad (8)$$

$$\varsigma_{TS} = \frac{\left|T\Delta S^0_{sub}\right|}{\left|\Delta H^0_{sub}\right| + \left|T\Delta S^0_{sub}\right|} \cdot 100\% \quad (9)$$

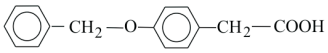
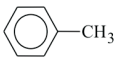
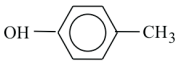
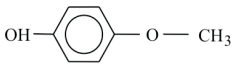
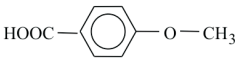
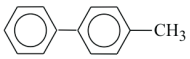
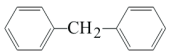
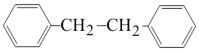
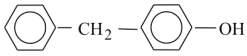
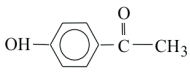
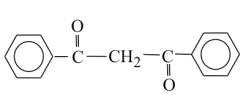
As it follows from Table 2, the process noted is enthalpy driven as for the drugs studied by us earlier [10–14].

The determined sublimation thermodynamic functions were compared with the data on these functions found in literature for the compounds which have a similar molecular structure. The data outlined as well as the structural formulas are collected in Table 3. The dependence between the Gibbs energy of sublimation, ΔG^0_{sub}, and the enthalpy of sublimation, ΔH^0_{sub}, is presented in Fig. 4.

As can be seen from Table 3, the enthalpy sublimation term (~60%) outweigh entropy one for all the considered compounds. Moreover, a compensation effect can be observed between the thermodynamic functions ΔG^0_{sub} and ΔH^0_{sub} (Fig. 4). Thus, it may be concluded that a systematic relation between the thermodynamics of sublimation and the compounds' structure takes place.

It seems obvious that the crystal lattice energy strongly depends on nature and position of functional groups. Addition of any substituent (–O– (**3**, **4**, **5**), –OH (**3**, **4**), –COOH (**5**), $-C_6H_5$ (**6**, **7**), $-C_6H_5OH$ (**9**)) to the toluene molecule (as the simplest compound in the series) causes an increase of crystal lattice energy. Molecules able to form H-bonds (–OH; –COOH containing) show an enhanced increase of lattice energy compared to those which do not form H-bonds: (**2**)<(**3**, **4**, **10**, **5**); (**6**, **7**, **8**)<(**9**, **1**). However, there is a competition between van der Waals (non-specific) and H-bond (specific) forces: (**3**)<(**6**, **7**, **8**)≈(**4**). As to [4-(benzyloxy)phenyl]acetic acid, it has a similar sublimation enthalpy value as (**5**). It could be explained by the fact that the additional $-CH_2-$ and $C_6H_5CH_2-$ groups do not influence the crystal lattice energy essentially. Moreover, if (**2**), (**3**) and (**6**) are compared, evidence comes up indicating that enlarging of van der Waals surface of molecule by the addition of the benzene ring causes almost the same increase as the addition of hydroxylic substitute. Thus, it may be concluded that H-bonding plays a significant role in strengthening of intermolecular forces in crystal.

Table 3 Thermodynamic parameters of sublimation process of some compounds

No.	Compound	ΔH^0_{sub}/ kJ mol^{-1}	ΔG^0_{sub}/ kJ mol^{-1}	$T\Delta S^0_{sub}$/ kJ mol^{-1}	ς_H[a]/ %	ς_{TS}[b]/ %	Reference
1	 [4-(benzyloxy)phenyl]acetic acid	111±3	57.8	53.2	67.6	32.4	this work
2	 toluene	43.1					[24]
3	 4-methylphenol	73.9±1.5	16.8	57.1	56.4	43.6	[26]
4	 4-methoxyphenol	88.7	30.1	58.6	60.2	39.8	[26]
5	 4-methoxybenzoic acid	109.8±0.6					[24]
6	 4-methylbiphenyl	80.2±1.4					[24]
7	 diphenylmethane	82.5±0.6	27.0	55.5	59.8	40.2	[27]
8	 dibenzyl	84.0±0.5	30.8	53.2	61.2	38.8	[27]
9	 4-benzylphenol	97.4	41.7	55.7	63.6	36.4	[26]
10	 4-hydroxyacetophenone	95.7	42.5	53.2	64.3	35.7	[26]
11	 dibenzoylmethane	115.7±0.9					[24]

[a] $\varsigma_H = [\Delta H^0_{sub} / (\Delta H^0_{sub} + T\Delta S^0_{sub})] \cdot 100\%$; [b] $\varsigma_{TS} = [T\Delta S^0_{sub} / (\Delta H^0_{sub} + T\Delta S^0_{sub})] \cdot 100\%$

Table 4 Temperature dependencies of [4-(benzyloxy)phenyl]acetic acid solubility in buffers with pH 2.0 and 7.4, *n*-hexane and *n*-octanol

T/°C	pH 2.0	pH 7.4	*n*-hexane	*n*-octanol
	$X_2 \cdot 10^6$	$X_2 \cdot 10^4$	$X_2 \cdot 10^5$	$X_2 \cdot 10^2$
15	–	5.23	–	–
19	–	–	3.36	–
20	4.88	5.81	3.62	1.53
25	6.68	6.95	5.20	1.88
30	11.41	8.20	7.78	2.29
37	13.13	9.99	10.85	3.18
42	–	–	–	4.34
A[a]	6.0±0.7	1.8±0.4	9.8±0.4	9.6±0.3
B[a]	5613±364	2701±108	5883±105	4043±85
R[b]	0.9986	0.9976	0.9995	0.9993
σ[c]	$2.72 \cdot 10^{-2}$	$2.08 \cdot 10^{-2}$	$1.73 \cdot 10^{-2}$	$1.63 \cdot 10^{-2}$

[a]parameters of the correlation equation: $\ln X_2 = A - B/T$;
[b]R – pair correlation coefficient; [c]σ – standard deviation

On the basis of the thermodynamic parameters of fusion and vaporization processes (Table 2) we tried to estimate the sublimation enthalpy value by the well known equation $\Delta H_{sub} = \Delta H_{fus} + \Delta H_{vap}$. The calculated value is in a good agreement with the experimental one: 106.4±2.6 and 107±3 kJ mol^{-1}, respectively. Moreover, the sublimation process is determined in ~70% by vaporization, whereas fusion term contributes to ~30% only.

Solubility and solvation

The temperature dependencies of 4-boph solubility in the buffers with pH 2.0 and 7.4, *n*-hexane (chosen as a solvent which interacts with solute non-specifically) and *n*-octanol are collected in Table 4. The solution and solvation thermodynamic functions of the drug under investigation in the considered solvents are presented in Table 5.

The solvation enthalpies and entropies are negative in both buffers. In addition, the driving force is the enthalpy, for both acidic and basic media, which corresponds to a hydrophobic hydration [28, 29]. As can be seen from Table 5, 4-boph is solvated stronger in buffer with pH 7.4 than with pH 2.0. It results from the fact that in pH 7.4 drug molecules exist in an ionic form, thus the coulombic term (i.e. specific interaction) of solvation process increases considerably. Another prerequisite to admit this assumption arises from the analysis of the transfer thermodynamic functions from the appropriate buffer to *n*-hexane (Table 6); the absolute values of the thermodynamic functions for the outlined transfer process (Gibbs energy, enthalpy and entropy) are increased for pH 7.4 in comparison to pH 2.0. Moreover, the ε_H parameter, which describes the ratio of specific and non-specific (solute–solvent) interactions in terms of enthalpies, shows that specific interactions in the buffer of pH 7.4 outweigh the analogous interactions in pH 2.0 approximately 6 times. Though the enthalpic term is governed by a non-specific solute–solvent interaction for both pHs, the specific one is expressed to a greater extent in basic media.

Table 5 Thermodynamic functions of solubility and solvation processes of [4-(benzyloxy)phenyl]acetic acid in solvents studied

Solvent	X_2^{25} (mol. fract.)	ΔG^0_{sol}/kJ mol^{-1}	ΔH^0_{sol}/kJ mol^{-1}	$T\Delta S^0_{sol}$/kJ mol^{-1}	ΔS^0_{sol}/J K^{-1} mol^{-1}	
pH 2.0	$6.66 \cdot 10^{-6}$	29.5	44.4±1.6	14.9	50±5	
pH 7.4	$6.95 \cdot 10^{-4}$	18.0	22.5±0.9	4.5	15±3	
n-hexane	$5.22 \cdot 10^{-5}$	24.4	48.8±0.8	24.4	82±3	
n-octanol	$1.88 \cdot 10^{-2}$	9.9	33.6±0.7	23.7	80±2	
	$-\Delta G^0_{solv}$/kJ mol^{-1}	$-\Delta H^0_{solv}$/kJ mol^{-1}	$-T\Delta S^0_{solv}$/kJ mol^{-1}	$-\Delta S^0_{solv}$/J K^{-1} mol^{-1}	ς_{Hsolv}/%	ς_{TSsolv}/%
pH 2.0	28.3	67.6	38.3	129±16	63.5	36.5
pH 7.4	39.8	88.5	48.7	163±13	64.5	35.5
n-hexane	33.4	62.2	28.8	97±13	68.4	31.6
n-octanol	47.9	77.4	29.5	99±13	72.4	27.6

Table 6 Thermodynamic parameters of transfer processes of [4-(benzyloxy)phenyl]acetic acid

	ΔG^0_{tr}/kJ mol^{-1}	ΔH^0_{tr}/kJ mol^{-1}	$T\Delta S^0_{tr}$/kJ mol^{-1}	ς_{Htr}/%	ς_{Str}/%	ε_H/%
n-hexane→pH 2.0	5.1	–4.4	–9.5	31.7	68.3	7.1
n-hexane→pH 7.4	–6.4	–26.3	–19.9	56.9	43.1	42.3
n-hexane→*n*-octanol	–14.5	–15.2	–0.7	95.6	4.4	24.4
pH 7.4→pH 2.0	11.5	21.9	10.4	67.8	32.2	–
pH 2.0→*n*-octanol	–19.6	–10.8	8.8	55.1	44.9	–
pH 7.4→*n*-octanol	–8.1	11.1	19.2	36.6	63.4	–

The driving forces of the (*n*-hexane→buffer) transfer process (specific interaction) are enthalpy driven for the pH 7.4, whereas for the pH 2.0 they are entropy driven.

Based on data obtained, there is a possibility to estimate the protonation energy by considering the pH 7.4→pH 2.0 transfer process. It constitutes 21.9 kJ mol^{-1}, which is in good agreement with the analogous data for other NSAIDs [7]. From the point of view of passive transport, 4-boph has better transport ability in acidic environment due to smaller energetic expenses for solvation.

Transfer characteristics of (buffer→n-octanol) process

The solvation thermodynamic functions of drug under investigation in *n*-octanol are presented in Table 5. As can be seen, the driving force of the process is enthalpic term. The transfer *n*-hexane→*n*-octanol thermodynamic functions for [4-(benzyloxy)phenyl]acetic acid are shown in Table 6. The specific interactions of the drug with *n*-octanol molecules is determined by enthalpy mainly, whereas the entropic factor is negligible. In addition, the ε_H-value shows that the specific interactions make 24.4% from non-specific ones.

It was interesting to analyze the drug transfer processes from buffers to *n*-octanol as it helps to understand deeper the mechanism of partitioning between water and lipid phases. The advantage of such analysis is that the data obtained represent the pure forces of transfer process without any side effects (such as mutual dissolution of solvents). The resulting data of such analysis are presented in Table 6. It should be noted, that pH of aqueous phase strongly affects the mechanism of partitioning (transfer process). In the case of acidic media it is driven enthalpically, whereas for basic one the driving force is entropy. The reason lies in peculiarities of solvation shells structure in different pHs. In order to partition the drug molecule needs both to escape the hydration shell and to be solvated by *n*-octanol molecules. Obviously, the hydration shell in pH 7.4 is more ordered and linked stronger to drug anion (due to increased electrostatic forces) than in pH 2.0. As a consequence, the drug transfer from acidic environment to lipid one accomplishes with less energetic expenses. Moreover, the solvation enthalpy in *n*-octanol does not compensate the solvation enthalpy in pH 7.4. This fact probably indicates that the drug molecule is still partly hydrated while transfer to *n*-octanol. Thus, the analysis of a full transfer thermodynamics set lets one to look into partitioning process deeper unlike log*P* consideration only.

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