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Thermodynamic studies of Fenbufen, Diflunisal, and Flurbiprofen: Sublimation, solution and solvation of biphenyl substituted drugs

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Abstract

Temperature dependency of saturated vapour pressure for Fenbufen (FBF) was obtained. Heat capacities for Fenbufen, Diflunisal (DIF), and Flurbiprofen (FBP) were measured, and standard thermodynamic functions of sublimation were calculated (FBF: $\Delta G^{298}_{sub} = 74.0\,kJ\,mol^{-1}$; $\Delta H^{298}_{sub} = 155.0 \pm 0.8\,kJ\,mol^{-1}$; $\Delta S^{298}_{sub} = 272 \pm 3\,J\,mol^{-1}\,K^{-1}$; DIF: $\Delta G^{298}_{sub} = 57.6\,kJ\,mol^{-1}$; $\Delta H^{298}_{sub} = 120.1 \pm 0.6\,kJ\,mol^{-1}$; $\Delta S^{298}_{sub} = 210 \pm 2\,J\,mol^{-1}\,K^{-1}$; FBP: $\Delta G^{298}_{sub} = 53.3\,kJ\,mol^{-1}$; $\Delta H^{298}_{sub} = 110.2 \pm 0.5\,kJ\,mol^{-1}$; $\Delta S^{298}_{sub} = 191 \pm 2\,J\,mol^{-1}\,K^{-1}$). Thermochemical parameters of fusion process for FBF were obtained, and evaporation enthalpy was estimated from fusion and sublimation enthalpies. Temperature dependencies of the solubility in buffer solutions (pHs 2.0 and 7.4), *n*-Octanol, and *n*-Hexane were measured, and solution and solvation thermodynamic functions were calculated. The transfer thermodynamic functions from *n*-Hexane to solvents used (imitating specific "drug–solvent" interaction), and from buffer solutions to *n*-Octanol (imitating partitioning/distribution processes) were analyzed. Specific/non-specific "drug–solvent" interaction ratios in terms of solvation enthalpies were estimated. All studied solutions are characterized by prevalence of non-specific "drug–solvent" interactions. A difference exists between mechanisms of partitioning and distribution of studied drugs.

Keywords: Fenbufen; Diflunisal; Flurbiprofen; Sublimation; Solubility; Solvation; Transfer thermodynamics; Partitioning; Distribution

1. Introduction

Fenbufen, Diflunisal, and Flurbiprofen are nonsteroidal anti-inflammatory, analgesic, and antipyretic drugs. From a chemical point of view, they belong to biphenyl homologues series (Fig. 1). Consideration of drugs with similar molecular structure helps to isolate and to interpret the nature and position of functional groups' impact on drug affinity with hydrophilic and hydrophobic media of pharmaceutical interest (Perlovich et al., 2007), such as *n*-Octanol and buffer solutions. Thus, simultaneous studying of chosen compounds' behavior in the context of thermodynamic approach either in crystalline state or in solutions opens new opportunities in understanding structural and energetic peculiarities of drug interactions with physiological fluids and model media.

Regarding Fenbufen, there are poor literature data about its solubility (in tetrahydrofuran (Di Martino et al., 1999), buffer solution with pH 2.0, and *n*-Octanol (Fini et al., 1986)), and few reports about its thermochemical properties (Fini et al., 1986; Cousse et al., 1987). As to Diflunisal and Flurbiprofen, their sublimation, solution and solvation thermodynamics in some organic (Perlovich et al., 2003) and buffer solutions (Perlovich et al., 2006) have been reported by us earlier. Within this work, the existing data on DIF and FBP are enlarged, systematized and compared to newly obtained data on FBF.

2. Materials and methods

2.1. Compounds and solvents

Fenbufen (FBF) (3-[4-biphenylcarbonyl]propionic acid, $C_{16}H_{14}O_3$, MW 254.28), was from Sigma–Aldrich Inc. (Oslo, Norway), lot no. 538515; Diflunisal (DIF) (5-[2,4-difluorophenyl]salicylic acid, $C_{13}H_8F_2O_3$, MW 250.2) was from ICN Biomedicals (Aurora, OH, USA), lot No. 89887; Flurbiprofen (FBP) ([±]-2-fluoro-α-methyl-4-biphenylacetic acid, $C_{15}H_{13}FO_2$, MW 244.3) was from Sigma (St. Louis, MO, USA), lot 38H1398. The solvents were as follows: *n*-Octanol

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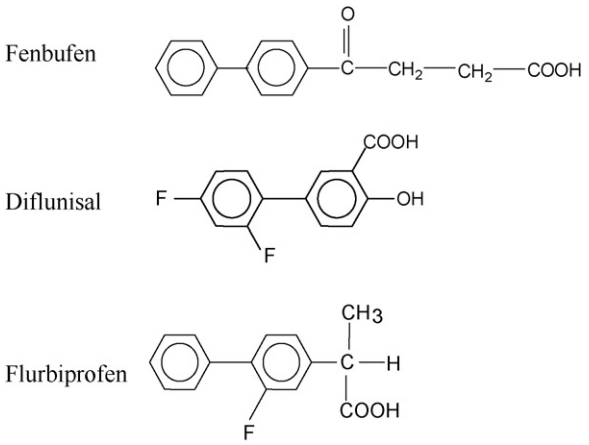


Fig. 1. Structures of the studied drugs' molecules.

($CH_3(CH_2)_7OH$, 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 components of buffer solutions were as follows: hydrochloric acid and potassium chloride (pH 2.0); potassium phosphate monosubstituted and sodium phosphate disubstituted (pH 7.4). All the chemicals were of AR grade.

The pH values have been controlled using pH/ion analyzer OP-300 (Radelkis, Hungary) supplied with a combination-type electrode and standardized with pH 4.00 ± 0.01 and 7.00 ± 0.01 solutions.

2.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was carried out using a PerkinElmer Pyris 1 DSC differential scanning calorimeter (PerkinElmer Analytical Instruments, Norwalk, CT, USA) with Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing (20 ml min^{-1}) dry helium gas of high purity 99.996% using standard aluminium sample pans and a heating rate of 10 K min^{-1}. The accuracy of weight measurements was ±0.001 mg. The DSC was calibrated with the indium from PerkinElmer (P/N 0319-0033). The value determined for the enthalpy of fusion corresponded to 28.48 J g^{-1} (reference value 28.45 J g^{-1}). The melting point was 156.5 ± 0.1 °C ($n = 10$). The enthalpy of fusion at 298.15 K was calculated by the following equation:

$$\Delta H^{298}_{fus} = \Delta H^{T}_{fus} - \Delta S^{T}_{fus}(T_{fus} - 298.15) \quad (1)$$

and the enthalpy of evaporation by:

$$\Delta H^{298}_{vap} = \Delta H^{298}_{sub} - \Delta H^{298}_{fus} \quad (2)$$

2.3. Sublimation experiments

Sublimation experiments were carried out by the transpiration method as described elsewhere (Zielenkiewicz et al., 1999). In brief, a stream of an inert gas passes the sample at a given constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapour of the substance under investigation. The vapour is condensed at some point downstream, and the mass of sublimate as well as its purity is determined. The vapour pressure over the sample at this temperature can be calculated from the amount of sublimated material and the volume of the inert gas used. The equipment was calibrated using benzoic acid (standard substance obtained from the Polish Committee of Quality and Standards). The standard value of the obtained sublimation enthalpy was $\Delta H^{298}_{sub} = 90.5 \pm 0.3$ kJ mol^{-1}. This is in good agreement with the value recommended by IUPAC of $\Delta H^{298}_{sub} = 89.7 \pm 0.5$ kJ mol^{-1} (Cox and Pilcher, 1970). The saturated vapour pressures were measured at each temperature at least three times with the statistical error being within 3–5%. The experimentally determined vapour pressure data were described in ($\ln p$; $1/T$) co-ordinates by equation:

$$\ln p = A + \frac{B}{T} \quad (3)$$

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

$$\Delta H^{T}_{sub} = -\frac{R\partial(\ln p)}{\partial(1/T)} \quad (4)$$

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

$$\Delta S^{T}_{sub} = \frac{\Delta H^{T}_{sub} - \Delta G^{T}_{sub}}{T} \quad (5)$$

where $\Delta G^{T}_{sub} = -RT \ln(p/p^0)$ and $p_0 = 1.013 \times 10^5$ Pa.

The standard sublimation enthalpy, ΔH^{298}_{sub}, was calculated by equation proposed by Chickos and Acree (2002):

$$\Delta H^{298}_{sub} = \Delta H^{T}_{sub} + [0.75 + 0.15 Cp^{298}_{cr}][T - 298.15], \quad (6)$$

where ΔH^{T}_{sub} is the sublimation enthalpy at temperature T, Cp^{298}_{cr} is the standard heat capacity value of crystalline Fenbufen, and T corresponds to the average temperature of sublimation experiment.

2.4. Solubility determination

Solubility determination was undertaken within a temperature range of $(18 \div 42) \pm 0.1$ °C by an isothermal saturation technique. The solid phase was separated by centrifuging in the case of *n*-Octanol and *n*-Hexane solutions, and by filtration in the case of buffer solutions (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size). The bulk solutions were measured spectrophotometrically using SF-46 spectrophotometer (LOMO, Russia) according to the previously described protocol (Perlovich and Bauer-Brandl, 2003) with an accuracy of 2–2.5%. The resulting values are the average of at least four replicated experiments.

The standard solution Gibbs energies were calculated using following equation:

$$\Delta G^{0}_{sol} = -RT \ln X_2, \quad (7)$$

where X_2 is the molar fraction of a solute in a saturated solution. The standard solution enthalpies were derived from temperature

dependences of drugs solubilities expressed in molar fractions (van't Hoff equation):

$$\frac{d\ln X_2}{dT} = \frac{\Delta H^0_{sol}}{RT^2} \quad (8)$$

For rightful use of Eq. (8) the following assumptions were made: (a) the activity coefficients of dissolved drugs do not deviate from unit and (b) the solution enthalpies do not depend on concentration. The solution heat capacities are considered to be constant within studied temperature range, since the temperature dependence of solubilities is described by linear equations.

2.5. Statistical analysis

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

3. Results and discussion

3.1. Sublimation thermodynamics

The sublimation thermodynamic parameters of DIF and FBP have been published by us earlier (Perlovich et al., 2003). Temperature dependence of Fenbufen saturated vapour pressure and thermodynamic functions of sublimation process along with some thermochemical data are summarized in Table 1.

In order to calculate the standard values of sublimation enthalpies, the experimental values of drugs' heat capacities at 298.15 K were determined using DSC technique.

Table 1
Temperature dependence of saturated vapour pressure and some thermochemical parameters of Fenbufen

t (°C)	p (Pa)	t (°C)	p (Pa)
105.5	5.41×10^{-3}	131.0	1.10×10^{-1}
110.0	9.56×10^{-3}	134.5	1.57×10^{-1}
114.0	1.46×10^{-2}	136.0	1.88×10^{-1}
116.0	1.93×10^{-2}	138.0	2.49×10^{-1}
120.0	3.08×10^{-2}	140.0	2.95×10^{-1}
124.5	5.18×10^{-2}	142.5	4.02×10^{-1}
127.0	7.23×10^{-2}	147.5	6.53×10^{-1}

$\ln(p(\text{Pa})) = (43.0 \pm 0.2) - (18280 \pm 97)/T$

$R = 0.9998$; $\sigma = 2.85 \times 10^{-2}$; $F = 35732$; $n = 14$

p^{298} (Pa)	1.12×10^{-8}
ΔG^{298}_{sub} (kJ mol^{-1})	74.0
ΔH^{T}_{sub} (kJ mol^{-1})	152.0 ± 0.8
ΔH^{298}_{sub} (kJ mol^{-1})	154.9 ± 0.8
Cp^{298}_{cr} (J K^{-1} mol^{-1})[a]	187 ± 3
$T\,\Delta S^{298}_{sub}$ (kJ mol^{-1})	80.9
ΔS^{298}_{sub} (J K^{-1} mol^{-1})	271 ± 2
T_{fus} (K)	462.9 ± 0.2
ΔH^{T}_{fus} (kJ mol^{-1})	41.1 ± 0.5
ΔH^{298}_{fus} (kJ mol^{-1})	24.2
ΔS^{T}_{fus} [b] (J K^{-1} mol^{-1})	89 ± 1
ΔH^{298}_{vap} (kJ mol^{-1})	130.7

[a] 99 ± 1 (DIF); 270 ± 3 (FBP).
[b] $\Delta S^{T}_{fus} = \Delta H^{T}_{fus}/T_{fus}$.

Table 2
Crystal lattice parameters of Fenbufen, Diflunisal, and Flurbiprofen

Parameters	FBF	DIF	FBP
Ref. cod.	SAFNIW	–	FLUBIP
Graph-set	$R^2_2(8)$	$R^2_2(8)S(6)$	$R^2_2(8)$
a (Å)	31.918(10)	34.666(6)	9.315(4)
b (Å)	5.550(2)	3.743(1)	12.734(9)
c (Å)	15.078(9)	20.737(4)	5.823(2)
α (°)	90.00	90.00	83.0(1)
β (°)	90.00	110.57(2)	107.2(1)
γ (°)	90.00	90.00	90.00
	Orthorhombic	Monoclinic	Triclinic
V_{cell} (Å^3)	2670.98	2519.4(4)	624.7(6)
V_{mol} (Å^3)	333.9	314.9	312.4
Space group	$Pca2_1$	$C2/c$	$P\bar{1}$
Z	8	8	2
D_{obs} (g CM^{-3})	1.264	–	–
D_{calc} (g CM^{-3})	1.265	1.324	1.29
T (K)	298	298	298
Reference	Kim et al. (1988)	Kim and Park (1996)	Flippen and Gilardi (1975)

Since the sublimation behavior is defined mostly by crystal structure of a compound, the crystalline state of compounds studied is to be described in short. Based on the results of X-ray structural analysis by Kim et al. (1988) and Kim and Park (1996), and Flippen and Gilardi (1975), the crystal structure parameters of FBF, DIF, and FBP are summarized in Table 2.

In all three cases the molecules form cyclic dimers retained by two H-bonds between adjacent carboxylic groups. Packing architectures of drugs studied were constructed using Endeavour software (Brandenburg and Putz, 2007), they are shown in Fig. 2.

It was interesting to compare the sublimation thermodynamics of FBF with the ones of DIF and FBP.

As follows from Table 3, the compounds studied may be arranged by sublimation enthalpy increase as follows: FBP < DIF < FBF. It means that Fenbufen has the strongest crystal lattice, whereas Flurbiprofen has the weakest one. This fact may be explained by a couple of reasons: firstly, the orthorhombic unit cell of Fenbufen is more ordered (characterized by the most number of symmetry elements), than both monoclinic unit cell of Diflunisal and the most disordered triclinic unit cell of Flurbiprofen; secondly, a long hydrocarbon "tail" of FBF-molecule presumably increases the van der Waals interaction between molecules in crystal to a greater extent than the halogen atoms do in the cases of DIF and FBP.

It is worth mentioning, that a correlation takes place between the standard sublimation entropies and the molecular volumes in crystal lattices of studied compounds (Fig. 3): the more the molecular volumes, the more disordering occurs during sublimation process.

Perhaps, an explanation of this phenomenon lies in the studied crystals symmetry. As follows from Table 2, for a series of considered compounds molecular volume is proportional to complexity of crystal lattice structure. Thus, an increase of symmetry elements amount leads to an increase of molecules

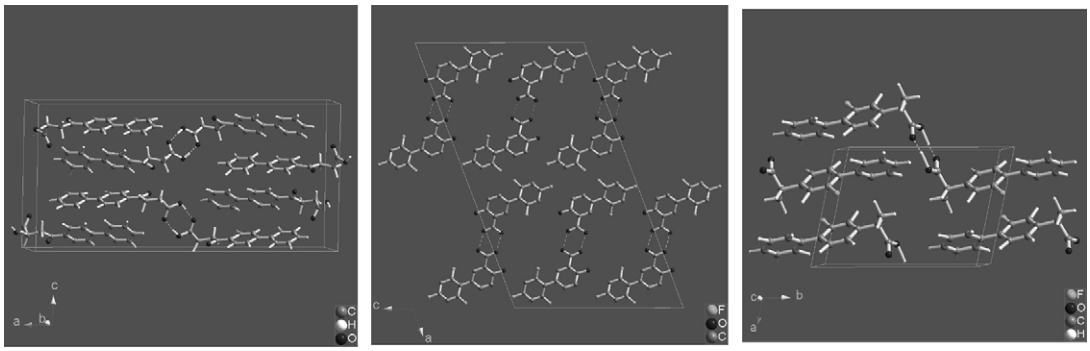


Fig. 2. Molecular packing architectures of Fenbufen, Diflunisal, and Flurbiprofen in the crystal lattices.

Table 3
Thermodynamic parameters of sublimation process of some biphenyl homologues

Compound	ΔH^{298}_{sub} (kJ mol^{-1})	ΔG^{298}_{sub} (kJ mol^{-1})	$T\,\Delta S^{298}_{sub}$ (kJ mol^{-1})	ς_H[a] (%)	ς_{TS}[b] (%)	Reference
FBF	155.0 ± 0.8	74.0	81.0	65.7	34.3	This work
DIF	120.1 ± 0.6	57.6	62.5	65.8	34.2	Perlovich et al. (2003)[c]
FBP	110.2 ± 0.5	53.3	56.9	65.9	34.1	Perlovich et al. (2003)[c]

[a] $\varsigma_H = (|\Delta H^{298}_{sub}|/(|\Delta H^{298}_{sub}| + |T\,\Delta S^{298}_{sub}|)) \times 100\%$.
[b] $\varsigma_{TS} = (|T\,\Delta S^{298}_{sub}|/(|\Delta H^{298}_{sub}| + |T\,\Delta S^{298}_{sub}|)) \times 100\%$.
[c] Sublimation enthalpies were corrected by Eq. (6).

ordering in crystal, which consequently causes the sublimation entropy growth.

As can be seen from Table 3, the sublimation process of all drugs studied is enthalpically determined with analogous ratio between enthalpic and entropic terms.

3.2. Solubility and solvation

The solubilities of FBF, DIF and FBP, evaluated in molar fractions at various temperature points in *n*-Octanol, buffer solutions, and *n*-Hexane are presented in Table 4.

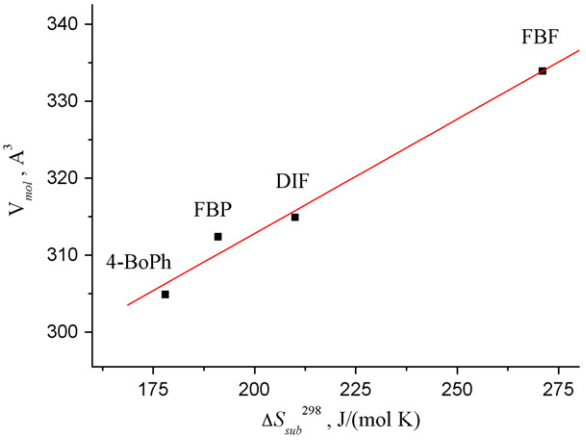


Fig. 3. Dependence between the sublimation entropies (ΔS^{298}_{sub}) and molecular volumes (V_{mol}) in the crystal lattices of the drugs (FBF, Fenbufen; DIF, Diflunisal; FBP, Flurbiprofen; 4-Boph, [4-(benzyloxy)phenyl]acetic acid (Kurkov et al., 2006)).

The following fact takes place: the arrangement by increasing solubility of studied drugs is identical and looks as pH 2.0 < pH 7.4 < *n*-Hexane < *n*-Octanol.

The solvation thermodynamic parameters of solutes can be deduced from sublimation and solubility data using the following expression:

$$\Delta Y^0_{solv} = \Delta Y^0_{sol} - \Delta Y^{298}_{sub}, \quad (9)$$

where $Y \equiv G, H, S$.

The thermodynamic functions of solubility and solvation processes at 298.15 K are summarized in Tables 5 and 6, respectively. The negative solution entropies in the buffer solutions may be a consequence of water molecules ordering around hydrophobic fragments of drug particles, known as "hydrophobic effect".

Concerning DIF and FBP, their solution enthalpies in *n*-Octanol have been measured earlier calorimetrically (Perlovich et al., 2006). In present work, these magnitudes were calculated using solubility experimental results with following correction of solution entropies. The results of using two independent methods show good agreement.

It is noticeable, that the solvation enthalpies of FBF in *n*-Octanol and pH 2.0 are approximately equal ($\Delta H^0_{solv} \approx -114$ kJ/mol). Moreover, FBF and DIF interact stronger with solvents in comparison with FBP. In other words, hydrocarbon "tail" of FBF as well as additional halogen atom together with extra hydrophilic center (OH-group) of DIF enhances solvation energy. All studied compounds demonstrate the strongest solvation in pH 7.4 and the weakest one in *n*-Hexane. These facts are due to the ionized state of drug particles in pH 7.4 solution and due to the absence of specific interaction centers in *n*-Hexane molecules.

Table 4
The temperature dependencies of Fenbufen, Diflunisal, and Flurbiprofen solubility, X_2 (molar fraction), in solvents used

T (K)	FBF				DIF[d]		FBP[d]	
	pH 2.0 $X_2 \times 10^7$	pH 7.4 $X_2 \times 10^5$	*n*-Octanol $X_2 \times 10^3$	*n*-Hexane $X_2 \times 10^6$	*n*-Octanol $X_2 \times 10^2$	*n*-Hexane $X_2 \times 10^6$	*n*-Octanol $X_2 \times 10^2$	*n*-Hexane $X_2 \times 10^4$
291.15	–	–	–	–	–	–	6.08	–
293.15	1.35	4.45	1.06	–	3.33	9.00	6.50	3.28
298.15	1.80	5.55	1.29	–	3.43	11.15	7.06	4.43
303.15	2.31	6.99	1.78	1.04	3.55	14.34	7.96	6.66
305.15	–	–	–	1.26	–	–	–	–
308.15	–	–	–	1.53	–	–	–	–
310.15	3.28	9.28	2.66	1.85	3.80	18.58	–	10.59
313.15	–	–	–	2.24	–	–	–	–
315.15	4.38	11.70	3.32	2.46	4.21	22.47	–	16.91
A[a]	0.8 ± 0.3	3.7 ± 0.3	9.7 ± 0.3	9.1 ± 0.9	0.8 ± 0.1	1.6 ± 0.3	8.7 ± 0.3	15 ± 1
B[a]	4880 ± 97	4038 ± 77	4843 ± 83	6921 ± 268	1222 ± 41	3872 ± 97	3356 ± 101	6838 ± 322
R[b]	0.9994	0.9995	0.9996	0.9970	0.9984	0.9991	0.9990	0.9967
σ[c]	1.86×10^{-2}	1.48×10^{-2}	1.59×10^{-2}	2.89×10^{-2}	6.10×10^{-3}	1.86×10^{-2}	6.05×10^{-3}	6.18×10^{-2}

[a] Parameters of the correlation equation: $\ln X_2 = A - B/T$.
[b] R: Pair correlation coefficient.
[c] σ: Standard deviation.
[d] Solubilities of DIF and FBP in buffer solutions see in Perlovich et al. (2006).

As to solvation entropies, they are almost identical for appropriate solutions containing molecules of FBF and DIF, and equally greater in absolute values, than solutions containing FBP molecules. Regarding pH 7.4 solutions, the ratio between solvation entropies changes crucially, as specific forces grow stronger in polar medium, and the presence of electronegative substitutes becomes significant. Besides, the solvation entropies in both buffers are enhanced in comparison with *n*-Octanol; it may be again a consequence of hydrophobic hydration effect. Finally, the solvation process of studied drugs in all solvents is enthalpically determined.

3.3. Transfer [n-Hexane → solvent] thermodynamics

To estimate the intensity of specific "drug–solvent" interactions, the transfer thermodynamics from *n*-Hexane to solvents under consideration were calculated and analyzed. The resulting data are presented in Table 7.

As one may see, specific "drug–solvent" interactions are accompanied with heat liberation and promote ordering of solutions under study.

A parameter ε_H, which describes the relative ratio between specific and non-specific "drug–solvent" interactions in terms of solvation enthalpy, was firstly introduced in (Perlovich and

Table 5
Solubility thermodynamic functions of Fenbufen, Diflunisal, and Flurbiprofen in solvents used at 298.15 K

Compound	X_2 (molar fraction)	ΔG^0_{sol} (kJ mol^{-1})	ΔH^0_{sol} (kJ mol^{-1})	$T\,\Delta S^0_{sol}$ (kJ mol^{-1})	ΔS^0_{sol} (J mol^{-1} K^{-1})
pH 2.0					
FBF	1.80×10^{-7}	38.5	40.6 ± 0.8	2.1	7 ± 3
DIF[a]	4.45×10^{-7}	36.3	21.5 ± 1.0	−14.8	−50 ± 3
FBP[a]	4.97×10^{-7}	36.0	43.2 ± 0.5	7.2	24 ± 2
pH 7.4					
FBF	5.55×10^{-5}	24.3	33.6 ± 0.6	9.3	31 ± 2
DIF[a]	7.72×10^{-6}	29.2	7.9 ± 0.5	−21.3	−72 ± 2
FBP[a]	9.44×10^{-6}	28.7	10.2 ± 0.3	−22.0	−74 ± 2
n-Octanol					
FBF	1.29×10^{-3}	16.5	40.3 ± 0.7	23.8	80 ± 2
DIF[b]	3.55×10^{-2}	8.3	10.2 ± 0.3	1.9	6 ± 1
FBP[b]	7.96×10^{-2}	6.3	27.9 ± 0.8	21.6	72 ± 3
n-Hexane					
FBF	7.43×10^{-7}	35.0	57.5 ± 2.2	22.5	75 ± 8
DIF	1.12×10^{-5}	28.3	32.2 ± 0.8	3.9	13 ± 3
FBP	4.43×10^{-4}	19.1	56.9 ± 2.7	37.8	127 ± 9

[a] Perlovich et al. (2006).
[b] Corrected values from Perlovich et al. (2003) (see text for details).

Table 6
Solvation thermodynamic functions of Fenbufen, Diflunisal, and Flurbiprofen in solvents used at 298.15 K

Compound	$-\Delta G^0_{solv}$ (kJ mol^{-1})	$-\Delta H^0_{solv}$ (kJ mol^{-1})	$-T\,\Delta S^0_{solv}$ (kJ mol^{-1})	$-\Delta S^0_{solv}$ (J mol^{-1} K^{-1})	ς_H[c] (%)	ς_{TS}[d] (%)
pH 2.0						
FBF	35.5	114.3	78.8	264	59.2	40.8
DIF[a]	21.3	98.6	77.3	259	56.1	43.9
FBP[a]	17.3	67.0	49.7	167	57.4	42.6
pH 7.4						
FBF	49.7	121.4	71.7	240	62.9	37.1
DIF[a]	28.4	112.2	83.8	281	57.2	42.8
FBP[a]	24.6	103.5	78.9	265	56.7	43.3
n-Octanol						
FBF	57.5	114.6	57.1	192	66.7	33.3
DIF[b]	49.3	109.9	60.6	203	64.5	35.5
FBP[b]	47.0	82.3	35.3	118	70.0	30.0
n-Hexane						
FBF	39.0	97.4	58.4	196	62.5	37.5
DIF	29.3	87.9	58.6	197	60.0	40.0
FBP	34.2	53.3	19.1	64	73.6	26.4

[a] Values from Perlovich et al. (2006), corrected for standard sublimation enthalpies, ΔH^{298}_{sub}.
[b] Values from Perlovich et al. (2003), corrected for standard sublimation enthalpies, ΔH^{298}_{sub}.
[c] $\varsigma_H = (|\Delta H^0_{solv}|/(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|)) \times 100\%$.
[d] $\varsigma_{TS} = (|T\,\Delta S^0_{solv}|/(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|)) \times 100\%$.

Bauer-Brandl, 2003). It is defined as:

$$\varepsilon_H = \left| \frac{\Delta H_{spec}}{\Delta H_{nonspec}} \right| \times 100\%, \quad (10)$$

where $\Delta H_{spec} = \Delta H^{Hex\rightarrow Solvt}_{tr}$; $\Delta H_{nonspec} = \Delta H^{0,Hex}_{solv}$.

As follows from Table 7, all studied systems are characterized by prevalence of non-specific "drug–solvent" interactions. An exception is demonstrated by FBP in pH 7.4: specific term of "drug–solvent" interaction is briefly equal to non-specific one.

From Tables 6 and 7 one may conclude, that similar ΔS^0_{solv} values of FBF and DIF in *n*-Octanol are determined by van der Waals forces, whereas in pH 2.0 solutions this phenomenon is explained by equivalent role of both specific and non-specific interactions (if compare FBF and DIF) in system ordering.

Besides, it is interesting to note that FBP appears to stand out among drugs studied with respect to the ratio of enthalpic/entropic terms of solvation Gibbs energy in organic solvents (approximately 70/30 for FBP and 60/40 respectively for the rest drugs in per cent). This fact can be explained in a following way: the molecules of FBF and DIF contain fragments – ketonic, hydroxyl and carboxylic motifs – which are able to form intramolecular hydrogen bonds. Presumably, the conformational changes of FBF and DIF molecules in *n*-Hexane and *n*-Octanol solutions make distances between and orientation of acceptor

Table 7
Thermodynamic parameters of transfer processes of Fenbufen, Diflunisal, and Flurbiprofen from *n*-Hexane to the solvents used at 298.15 K

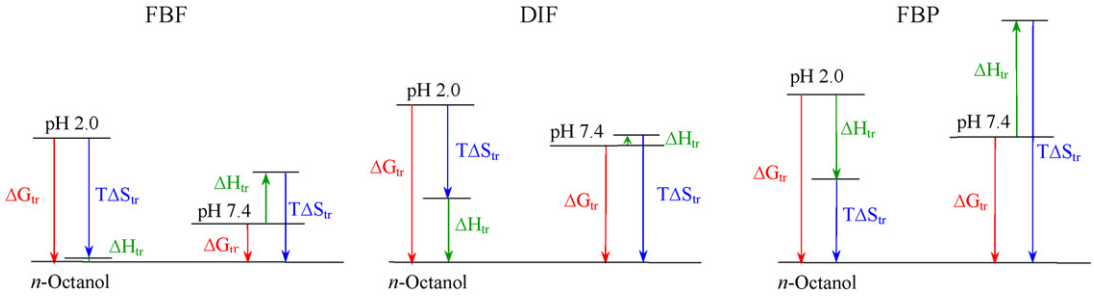
Solvents	$\Delta G^{Hex\rightarrow Solvt}_{tr}$ (kJ mol^{-1})	$\Delta H^{Hex\rightarrow Solvt}_{tr}$ (kJ mol^{-1})	$T\,\Delta S^{Hex\rightarrow Solvt}_{tr}$ (kJ mol^{-1})	ε_H[a] (%)
FBF				
n-Hexane	(−39.0)[b] 0	(−97.4)[b] 0	(−58.4)[b] 0	0
pH 2.0	3.5	−16.9	−20.4	17.4
pH 7.4	−10.7	−24.0	−13.3	24.6
n-Octanol	−18.5	−17.2	1.3	17.7
DIF				
n-Hexane	(−29.3)[b] 0	(−87.9)[b] 0	(−58.6)[b] 0	0
pH 2.0	8.0	−10.7	−18.7	12.2
pH 7.4	0.9	−24.3	−25.2	12.9
n-Octanol	−20.0	−22.0	−2.0	25.0
FBP				
n-Hexane	(−34.2)[b] 0	(−53.3)[b] 0	(−19.1)[b] 0	0
pH 2.0	16.9	−13.7	−30.6	25.7
pH 7.4	9.6	−50.2	−59.8	94.1
n-Octanol	−5.4	−29.0	−23.6	54.4

[a] $\varepsilon_H = |\Delta H_{spec}/\Delta H_{nonspec}/| \times 100\%$.
[b] Solvation thermodynamics in *n*-Hexane.

Table 8
Thermodynamic parameters of transfer processes of Fenbufen, Diflunisal, and Flurbiprofen from buffer solutions to *n*-Octanol at 298.15 K

Compound	$\Delta G_{tr}^{Buf\rightarrow Oct}$ (kJ mol^{-1})	$\Delta H_{tr}^{Buf\rightarrow Oct}$ (kJ mol^{-1})	$T\,\Delta S_{tr}^{Buf\rightarrow Oct}$ (kJ mol^{-1})	$\Delta S_{tr}^{Buf\rightarrow Oct}$ (J mol^{-1} K^{-1})	ς_H[a] (%)	ς_{TS}[b] (%)
pH 2.0						
FBF	−22.0	−0.3	21.7	73	1.4	98.6
DIF	−28.0	−11.3	16.7	56	40.4	59.6
FBP	−29.7[c]	−15.3[d]	14.4	48	51.5	48.5
pH 7.4						
FBF	−7.8	6.8	14.6	49	31.8	68.2
DIF	−20.9	2.3	23.2	78	9.0	91.0
FBP	−22.4	21.2	43.6	146	32.7	67.3

[a] $\varsigma_H = (|\Delta H_{tr}^{Buf\rightarrow Oct}|/(|\Delta H_{tr}^{Buf\rightarrow Oct}| + |T\,\Delta S_{tr}^{Buf\rightarrow Oct}|)) \times 100\%$.
[b] $\varsigma_{TS} = (|T\,\Delta S_{tr}^{Buf\rightarrow Oct}|/(|\Delta H_{tr}^{Buf\rightarrow Oct}| + |T\,\Delta S_{tr}^{Buf\rightarrow Oct}|)) \times 100\%$.
[c] −23.8 (Burgot and Burgot, 1995).
[d] −15.6 (Burgot and Burgot, 1995).



Scheme 1.

and donor groups within the same molecule favorable for formation of H-bond. An argument for this assumption comes from Table 7. One may see that FBF and DIF experience weaker specific interaction with *n*-Octanol in comparison with FBP, which may be a consequence of partial saturation of hydrogen bonding sites of first two drugs.

In addition, another useful measure of specific "drug–solvent" interaction – the parameter $\Delta\log P$ – can be estimated. For this purpose, molar partitioning coefficients are calculated from solubility data:

$$\log P_{Solvt\rightarrow Buf} = \frac{c_{Solvt}}{c_{Buf}}, \quad (11)$$

where c is the molar solubility of drug, and Solvt means *n*-Octanol or *n*-Hexane. Then, $\Delta\log P$ is determined as:

$$\Delta\log P = \log P_{Oct\rightarrow Buf} - \log P_{Hex\rightarrow Buf} \quad (12)$$

The resulting values of $\Delta\log P$ for FBF, DIF, and FBP are as follows: 2.98; 3.31; 2.05, respectively.

3.4. Transfer [buffer → n-Octanol] thermodynamics

To analyze the affinity of drugs with different media $\log P$ and $\log D$ are commonly used. Yet, drug transfer process consideration from buffer solutions to *n*-Octanol lets one to discuss energetic aspects of drug partitioning and distribution in detail. The thermodynamic functions of noted transfer processes for studied drugs are presented in Table 8.

Our results show good agreement with literature data, merely available for partitioning of Flurbiprofen (Burgot and Burgot, 1995). As can be seen, in most cases the transfer of drug particles (molecules and ions) from hydrophilic to lipophilic liquid is entropically determined. Nevertheless, there is a difference between mechanisms of partitioning and distribution of studied drugs, as partitioning of the drugs constitutes an exothermic process, whereas distribution is an endothermic one. It is illustrated by Scheme 1.

Perhaps, qualitatively similar behavior of the studied drugs either at partitioning or at distribution means that the major role in it plays the identical biphenyl skeleton. Still, quantitative comparative analysis of transfer thermodynamic parameters of different homologues is a useful instrument in the selection of an appropriate candidate with relation to its passive transport properties.

4. Conclusion

Based on carried out experiments the thermodynamic functions of sublimation and solution together with fusion and evaporation parameters were obtained. The solvation thermodynamic functions in *n*-Octanol, *n*-Hexane and water buffers were calculated and analyzed. The studied drugs demonstrate the most affinity with lipophilic liquid media, they belong to amphiphilic substances though. For all studied compounds in all considered solutions the dominant term of solvation Gibbs energy is enthalpic one. The results of

comparative analysis among biphenyl substituted drugs show that a long hydrocarbon chain increases the crystal energy, leads to the solubility decrease and strengthens solvation in all considered solvents compared to the halogen atoms influence. The "drug–solvent" specific/non-specific interaction balance may be stipulated not only by nature and position of substitutes, but also by conformational state of dissolved molecules. As to partitioning and distribution processes, their mechanisms seem to be different and insensitive to discrepancies of the molecular composition of studied set of drugs.

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