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Thermodynamics of solutions
II. Flurbiprofen and diflunisal as models for studying solvation of drug substances

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Abstract

Three independent methods (sublimation, solubility and solution calorimetry) were used to study the dissolution and solvation processes of diflunisal (DIF) and flurbiprofen (FBP). Thermodynamic functions for the sublimation of DIF and FBP were obtained. Concentrations of saturated solutions and standard solution enthalpies of DIF and FBP in aliphatic alcohols and individual organic solvents were measured. Correlation analysis between: (a) the thermodynamic functions for a substance in various solvents, and (b) the same functions for different compounds was carried out. The investigated substances can be arranged with increasing Gibbs energy of solvation as follows: benzoic acid<DIF<FBP. Enthalpy is found to be the major driving force of the solvation process for all the studied compounds. The ratio of specific and nonspecific solute–solvent interaction in terms of enthalpies (ε_H) and in terms of entropies (ε_S) was analyzed. Based on the experimental data, a compensation effect of thermodynamic solubility functions of the investigated substances both in alcohols and in organic solvents was found.

Keywords: Flurbiprofen; Diflunisal; Sublimation; Solubility; Solvation; Compensation effect; Organic solvents

1. Introduction

The balance between lipophilic and hydrophilic properties is one of the most important characteristics of drug compounds with respect to their biopharmaceutical properties. The regularities, how lipophilic and hydrophilic properties affect the solvation process and dissolution, are of special interest. As these regularities are based on thermodynamic functions, simultaneous analysis of both the enthalpic and the entropic terms of Gibbs energy can provide a deeper understanding of the processes. For this approach there is a need to carry out methodically independent experiments in order to exclude artifacts due to correlating experimental errors.

Therefore, in the present study, three individual experimental methods are used in order to be able to distinguish between solution enthalpy (solution calorimetry) and entropy of solution (via solubility). Moreover, in order to enable distinguishing between the enthalpy of dissolution of solid substances and—as a part thereof—solvation processes of individual molecules, sublimation enthalpy is measured as well. These data enable comparison between compounds based on thermodynamically defined descriptors.

The present work continues previous studies on the dissolution process of model substances (benzoic acid, BA, and acetylsalicylic acid, ASA) in aliphatic alcohols and individual organic solvents (Perlovich and Bauer-Brandl, 2002). In the present study, flurbiprofen, FBP, and diflunisal, DIF, were chosen as more complicated subjects (Fig. 1): in contrast to BA and ASA, these compounds are biphenylfluor derivatives. However, like BA and ASA, they include carboxyl groups in their structures, where the diflunisal molecule has one extra hydrophilic center, which is the hydroxyl group.

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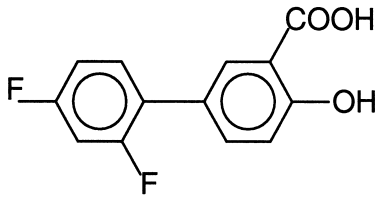
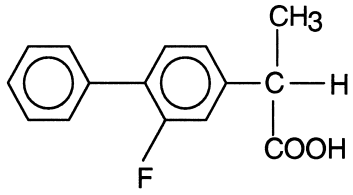


Diflunisal



Flurbiprofen

Fig. 1. Structure formulas of the investigated drugs.

2. Materials and methods

2.1. Materials and solvents

The studies of FBP ([±]-2-fluoro-α-methyl-4-biphenylacetic acid, $C_{15}H_{13}FO_2$, molecular mass, M_r 244.3) and diflunisal (5-[2,4-difluorophenyl]salicylic acid; $C_{13}H_8F_2O_3$, M_r 250.2) were carried out using commercially available substance from Sigma (St. Louis, MO, USA) (lot 38H1398) and ICN Biomedicals (Aurora, OH, USA) (lot No. 89887), respectively. The alcohols were as follows: methanol (MeOH, CH_3OH, M_r 32.04) HPLC grade from Merck (Germany), lot K27636907; ethanol (EtOH, CH_3CH_2OH, M_r 46.2) extra pure grade (99.6%, v/v, maximum water content 0.4%); 1-propanol [*n*-propanol, $CH_3(CH_2)_2OH$, M_r 60.10] HPLC grade from Aldrich (Germany), lot U00874; 1-butanol [BuOH, $CH_3(CH_2)_3OH$, M_r 74.12] analytical-reagent grade (ARG) from Merck, lot K22047090; 1-pentanol [*n*-pentanol, $CH_3(CH_2)_4OH$, M_r 88.15] ARG from Aldrich, lot 35757-101; 1-hexanol [*n*-hexanol, $CH_3(CH_2)_5OH$, M_r 102.18] ARG from Aldrich, lot 31562-011; 1-heptanol [*n*-heptanol, $CH_3(CH_2)_6OH$, M_r 116.2] ARG from Sigma, lot 60K3706; 1-octanol [*n*-octanol, $CH_3(CH_2)_7OH$, M_r 130.2] ARG from Sigma, lot 11K3688. The hydrocarbons were as follows: *n*-pentane (C_5H_{12}, M_r 72.15) ARG from SDS (Peypin, France), lot 10020005; *n*-hexane (C_6H_{14}, M_r 86.18) ARG from SDS, lot 07059903C; *n*-heptane (C_7H_{16}, M_r 100.21) ARG from SDS, lot 16039901; *n*-octane (C_8H_{18}, M_r 114.2) ARG from Sigma, lot 51K3681. The organic solvents were as follows: benzene (C_6H_6, M_r 78.12) ARG from Merck, lot K26454983; toluene (C_7H_8, M_r 92.14) ARG from Merck, lot K23559425; acetonitrile (AN, C_2H_3N, M_r 41.05) HPLC grade from Merck, lot I894030; 1,4-dioxane ($C_4H_8O_2$, M_r 88.11) ARG from Sigma, lot 70K3697; tetrahydrofuran (THF, C_4H_8O, M_r 72.10) HPLC grade from SDS, lot 23049704C; ethyl acetate (EtAc, $C_4H_8O_2$, M_r 88.11) ARG from Merck, lot K25821023; *N*,*N*-dimethylformamide (DMF, C_3H_7NO, M_r 73.09) ARG from Sigma, lot 11K1321; dimethylsulfoxide (DMSO, C_2H_6SO, M_r 78.13) ARG from Sigma, lot 129H0068; acetone (C_3H_6O, M_r 58.08) ARG from SDS, lot 02069901; pyridine (Py, C_5H_5N, M_r 79.10) ARG from Sigma, lot 10K1128; piperidine (hexahydropypidine, Pip, $C_5H_{11}N$, M_r 85.15) ARG from Sigma, lot 98H1198; chloroform ($CHCl_3$, M_r 119.38) ARG from Merck, lot K27794045; 1,2-dichloroethane ($C_2H_4Cl_2$, M_r 98.97) ARG from Merck, lot S21118814.

2.2. Solubility determination

Solubilities of FBP and DIF were obtained at 25±0.1 °C as follows: the solubilities of FBP in acetone, 1,4-dioxane, ethyl acetate, and DIF in benzene, toluene and acetonitrile were determined by the weighing method with a reproducibility of about 3%. All the other experiments were carried out by a spectrophotometrical method with an accuracy of about 2.5% using the protocol described previously (Zielenkiewicz et al., 1999a).

2.3. Solution calorimetry

Enthalpies of solution at a concentration m (ΔH^m_{sol}) were measured using a Precision Solution Calorimeter in the 2277 Thermal Activity Monitor Thermostat (both from Thermometric, Järfälla, Sweden). The software SolCal Version 1.2 (Thermometric) was applied to all calculations. The measuring temperature was 25 ± 10^{-4} °C, volume of the vessel 100 ml, stirrer speed 500 rpm and the mass of the each sample approximately 18 mg. The accuracy of weight measurements corresponded to ±0.0005 mg. The number of repetitions of experiments for each solvent was 5. The calorimeter was calibrated using KCl (analytical grade >99.5%, from Merck) in water in a wide concentration interval with more than 10 measurements. The standard value of solution enthalpy obtained was $\Delta H^0_{sol}=17225\pm50$ J mol^{-1}. This is in good agreement with the value recommended by IUPAC of $\Delta H^0_{sol}=17217\pm33$ J mol^{-1} (Cox and Pilcher, 1970). The values ΔH^m_{sol} of the compounds investigated in the solvents do not depend on concentration, m, in the range between $m=10^{-4}$ and $m=1.5\cdot10^{-3}$ mol kg^{-1}. Therefore, the mean of the 5–7 experimental points was taken as the standard value of ΔH^0_{sol}.

2.4. Sublimation experiments

Sublimation experiments were carried out by the transpiration method as was described previously (Zielenkiewicz et al., 1999b). The equipment was calibrated using benzoic acid (standard substance obtained from Polish Committee

of Quality and Standards) with enthalpy of combustion being $H_c = -3228.07$ kJ mol^{-1} and heat of melting corresponding to $H_{fus} = 18.0$ kJ mol^{-1}. The standard value of sublimation enthalpy obtained was $\Delta H^0_{sub} = 90.5 \pm 0.3$ J mol^{-1}. This is in good agreement with the value recommended by IUPAC of $\Delta H^0_{sol} = 89.7 \pm 0.5$ J mol^{-1} (Cox and Pilcher, 1970). The saturated vapor pressures were measured at each temperature at least five times with the statistical error being within 3–5%. The experimentally determined vapor pressure data were described in ($\ln P$; $1/T$) coordinates by Eq. (1):

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

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

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

Whereas the entropy of sublimation at a given temperature T was calculated form 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.

2.5. Differential scanning calorimetry (DSC)

In order to exclude the formation of solvates during solubility experiments, the bottom phases in the vials were studied using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, CT, USA) and Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing (20 ml min^{-1}) dry argon gas of high purity 99.990% using standard aluminium sample pans. The DSC system was calibrated with indium from Perkin-Elmer (P/N 0319-0033). The value for 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 ($n = 10$). All the DSC experiments were carried out at a heating rate of 10 K min^{-1}. The accuracy of weight measurements was ±0.0005 mg.

2.6. Statistical analysis

Regression analysis of the data was performed using standard statistical procedures by in-house software.

3. Results and discussion

3.1. Thermodynamics of flurbiprofen and diflunisal sublimation

Temperature dependencies of vapor pressure of FBP and DIF and thermodynamic parameters of sublimation are summarized in Table 1.

It should be noted that, within the studied temperature interval between 70 and 140 °C, a temperature dependence of ΔH_{sub} was not observed. Therefore, the dependences of the vapor pressure of the compounds on the temperature may be described by linear regression equations, which are presented in Table 1.

In order to compare the present experimental data with literature data for diflunisal (Cotton and Hux, 1985), the vapor pressure values were extrapolated to lower temperatures using the equations presented in Table 1 (the literature data from (Cotton and Hux, 1985) is given in parentheses): $P(30\,°C) = 1.78 \cdot 10^{-5}$ Pa ($2.13 \cdot 10^{-5}$); $P(40\,°C) = 6.61 \cdot 10^{-5}$ Pa ($1.00 \cdot 10^{-4}$). These data are judged as being not in bad agreement.

It is interesting to compare the obtained values of sublimation enthalpies with the analogous value of biphenyl (BP) taken from the literature (Cox and Pilcher, 1970): $\Delta H_{sub}(DIF) = 119.3 \pm 0.6$ kJ mol^{-1} > $\Delta H_{sub}(FBP) =$

Table 1
Vapor pressure at temperatures t and thermodynamic parameters of diflunisal and flurbiprofen sublimation

DIF				FBP			
t (°C)	P (Pa)	t (°C)	P (Pa)	t (°C)	P (Pa)	t (°C)	P (Pa)
76.0	$8.99 \cdot 10^{-3}$	106.0	$2.32 \cdot 10^{-1}$	68.5	$1.26 \cdot 10^{-2}$	99.0	$2.86 \cdot 10^{-1}$
81.0	$1.56 \cdot 10^{-2}$	113.0	$4.58 \cdot 10^{-1}$	70.0	$1.45 \cdot 10^{-2}$	104.5	$4.78 \cdot 10^{-1}$
87.0	$3.27 \cdot 10^{-2}$	117.0	$7.20 \cdot 10^{-1}$	73.7	$2.24 \cdot 10^{-2}$		
94.0	$7.14 \cdot 10^{-2}$	120.0	$9.50 \cdot 10^{-1}$	77.5	$3.27 \cdot 10^{-2}$		
97.0	$9.82 \cdot 10^{-2}$	125.0	1.38	82.5	$5.51 \cdot 10^{-2}$		
98.5	$1.12 \cdot 10^{-1}$	128.0	1.79	86.0	$7.89 \cdot 10^{-2}$		
101.0	$1.42 \cdot 10^{-1}$	132.5	2.95	88.0	$9.48 \cdot 10^{-2}$		
104.5	$2.02 \cdot 10^{-1}$	137.0	4.01	94.0	$1.74 \cdot 10^{-1}$		
$\ln(P[\text{Pa}]) = (36.4 \pm 0.2) - (14400 \pm 8000)/T$				$\ln(P\ [\text{Pa}]) = (33.8 \pm 0.2) - (13040 \pm 60)/T$			
$R = 0.9997$; $\sigma = 3.72 \cdot 10^{-2}$;				$R = 0.9998$; $\sigma = 1.62 \cdot 10^{-2}$;			
$F^{2.5\%}_{tab} = 2.95$; $F = 36261$; $n = 16$				$F^{2.5\%}_{tab} = 4.36$; $F = 52994$; $n = 10$			
$\Delta H_{sub} = 119.3 \pm 0.6$ kJ mol^{-1}				$\Delta H_{sub} = 108.4 \pm 0.5$ kJ mol^{-1}			
$\Delta S_{sub} = 207 \pm 2$ J mol^{-1} K^{-1}				$\Delta S_{sub} = 185 \pm 1$ J mol^{-1} K^{-1}			

$108.4 \pm 0.5 > \Delta H_{sub}(BP) = 81.6 \pm 2.1$. One may assume that introducing big substituents into the biphenyl fragment, as is the case in both DIF and FBP, would decrease the density of the packing of the molecules in the solid state, and, as a consequence, decrease van der Waals's interactions between the molecules. However, as follows from the data, a hydrogen bond network yields grave stabilization of the crystal lattice.

3.2. Thermodynamics of flurbiprofen and diflunisal solvation in aliphatic alcohols

The thermodynamic parameters of dissolution and solubility (ΔG^0_{sol}, ΔH^0_{sol}, $T\Delta S^0_{sol}$) and of the solvation processes (ΔG^0_{solv}, ΔH^0_{solv}, $T\Delta S^0_{solv}$) of diflunisal and flurbiprofen in aliphatic alcohols are presented in Tables 2 and 3, respectively, where $\Delta H^0_{solv} = \Delta H^0_{sol} - \Delta H_{sub}$; $\Delta S^0_{solv} = \Delta S^0_{sol} - \Delta S_{sub}$.

In order to compare the ability of the noted substances to be solvated, dependencies of Gibbs energies of solvation ΔG^0_{solv} versus the chain length of the alcohol (n) are depicted in Fig. 2. For convenience of comparison, analogous data of benzoic acid (taken from Perlovich and Bauer-Brandl, 2002) are presented in the same figure.

As can be seen from Fig. 2, the solvation of both FBP and DIF is approximately 1.7 times stronger in comparison with BA. Moreover, the solvation between the diflunisal molecule and the alcohols is in general stronger in comparison with flurbiprofen.

Based on the experimental data one may estimate the major driving force of the solvation process. For this procedure the following parameters were introduced which split the respective Gibbs energy into the relative fractions of enthalpy and entropy:

$$s_H = (|\Delta H^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)) \cdot 100\% \quad (4)$$

$$s_S = (|T\Delta S^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)) \cdot 100\% \quad (5)$$

where again $\Delta H^0_{solv} = \Delta H^0_{sol} - \Delta H_{sub}$; $\Delta S^0_{solv} = \Delta S^0_{sol} - \Delta S_{sub}$.

The results of these calculations are presented in Table 4 for DIF, FBP from the present experiments, and for benzoic acid from the literature (Perlovich and Bauer-Brandl, 2002) for comparison. Dependencies of the introduced parameters versus the alcohol chain length (n) are shown in Fig. 3 (again analogous data of benzoic acid from Perlovich and Bauer-Brandl (2002) are presented in the same figure). As can be seen from Table 4 and Fig. 3, enthalpy is main driving force of the solvation process for the all studied compounds. It should be noted that the enthalpic term is approximately double the value of the entropic one. The investigated substances can be arranged according to increasing enthalpic terms as follows: BA < DIF < FBP. The rank order of solubilities of the substances and consequently entropies is contradictory to the expected.

Furthermore, it is the present authors' opinion that not only the main driving force of the solvation process of drug molecules is important, but also the balance between specific and nonspecific solute–solvent interactions as well. Therefore, parameters which describe the relative ratio of specific and nonspecific solute–solvent interaction

Table 2
Thermodynamic functions of the diflunisal solubility and solvation processes in aliphatic alcohols and organic solvents at 25 °C

Solvent	X_2	γ[a]	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})	ΔH^{DIF}_{tr} (kJ mol^{-1})	ΔS^{DIF}_{tr} (J mol^{-1} K^{-1})	$-\Delta G^0_{solv}$ (kJ mol^{-1})	$-\Delta H^0_{solv}$ (kJ mol^{-1})	$-T\Delta S^0_{solv}$ (kJ mol^{-1})
MeOH	0.0151	0.243	10.4	21.7±0.4	11.3	37.9	−12.0 (1.7)[b]	−11.4	47.2	97.6	50.4
EtOH	0.0191	0.192	9.8	19.4±0.2	9.6	32.2	−14.3 (1.6)	−17.1	47.8	99.9	52.1
n-Propanol	0.0236	0.156	9.3	17.2±0.3	7.9	26.5	−16.5 (1.8)	−22.8	48.3	102.1	53.8
n-BuOH	0.0266	0.156	9.0	16.2±0.3	7.2	24.2	−17.5 (1.8)	−25.1	48.6	103.1	54.5
n-Pentanol	0.0326	0.113	8.5	15.1±0.2	6.6	22.2	−18.6 (1.9)	−27.1	49.1	104.2	55.1
n-Hexanol	0.0331	0.113	8.4	13.6±0.2	5.2	17.4	−20.1 (2.0)	−31.9	49.2	105.7	56.5
n-Heptanol	0.0383	0.0958	8.1	11.5±0.2	3.4	11.4	−22.2 (2.1)	−37.9	49.5	107.8	58.3
n-Octanol	0.0352	0.104	8.3	10.7±0.2	2.4	8.0	−23.0 (2.2)	−41.3	49.3	108.6	59.3
Benzene	0.000471	7.79	19.0	33.7±0.2	14.7	49.3	0	0	38.6	85.6	47.0
Toluene	0.000568	9.97	18.5	28.3±0.2	9.8	32.9	−5.4	−16.4	39.1	91.0	51.9
AN	0.00355	1.03	14.0	27.1±0.4	13.1	43.9	−6.6	−5.4	43.6	92.2	48.6
Acetone	–	–	–	24.1±0.2	–	–	−9.6	–	–	95.2	–
1,4-Dioxane	–	–	–	13.6±0.3	–	–	−20.1	–	–	105.7	–
THF	–	–	–	7.0±0.3	–	–	−26.7	–	–	112.3	–
EtAc	–	–	–	15.2±0.2	–	–	−18.5	–	–	104.1	–
$CHCl_3$	–	–	–	10.9±0.3	–	–	−22.8	–	–	108.4	–
DMF	–	–	–	2.5±0.2	–	–	−31.2	–	–	116.8	–
DMSO	–	–	–	7.8±0.2	–	–	−25.9	–	–	111.5	–
Pyridine	–	–	–	−43.5±0.2	–	–	−77.2	–	–	162.8	–

[a] $\gamma = X_2^{id}/X_2$, $X_2^{id} = 0.00367$ (Perlovich et al., 2002a).
[b] $\Delta H^{DIF}_{tr}/\Delta H^{FBP}_{tr}$.

Table 3
Thermodynamic functions of the flurbiprofen solubility and solvation processes in aliphatic alcohols and organic solvents at 25 °C

Solvent	X_2	γ[a]	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})	ΔH_{tr} (kJ mol^{-1})	ΔS_{tr} (J mol^{-1} K^{-1})	$-\Delta G^0_{solv}$ (kJ mol^{-1})	$-\Delta H^0_{solv}$ (kJ mol^{-1})	$-T\Delta S^0_{solv}$ (kJ mol^{-1})
MeOH	0.0478	1.83	7.5	25.3±0.4	17.8	59.6	−7.1	−26.8	45.8	83.1	37.3
EtOH	0.0612	1.43	6.9	23.4±0.4	16.5	55.3	−9.0	−31.2	46.4	85.0	38.6
n-Propanol	0.0668	1.31	6.7	23.1±0.1	16.4	55.0	−9.3	−31.5	46.6	85.3	38.7
n-BuOH	0.0667	1.31	6.7	22.8±0.1	16.1	54.0	−9.6	−32.5	46.6	85.6	39.0
n-Pentanol	0.0716	1.22	6.5	22.5±0.2	16.0	53.5	−9.9	−32.9	46.8	85.9	39.1
n-Hexanol	0.0716	1.22	6.5	22.2±0.2	15.7	52.5	−10.2	−33.9	46.8	86.2	39.4
n-Heptanol	0.0760	1.15	6.4	22.0±0.2	15.6	52.4	−10.4	−34.2	46.9	86.4	39.5
n-Octanol	0.0817	1.07	6.2	21.9±0.3	15.7	52.7	−10.5	−33.9	47.1	86.5	39.4
n-Pentane	0.000350	250	19.7	26.0±0.2	6.3	21.1	–	–	33.6	82.4	48.8
n-Hexane	0.000494	177	18.9	27.7±0.2	8.8	29.6	–	–	34.4	80.7	46.3
n-Heptane	0.000631	143	18.3	29.9±0.3	11.6	38.9	–	–	35.0	78.5	43.5
n-Octane	0.000616	142	18.3	32.5±0.5	14.2	47.5	–	–	35.0	75.9	40.9
Benzene	0.0682	1.28	6.6	32.4±0.2	25.8	86.3	0	0	46.7	76.0	29.3
Toluene	0.0767	1.14	6.4	30.5±0.3	24.1	80.9	−1.9	−5.7	46.9	77.9	31.0
AN	0.0308	2.84	8.6	27.3±0.2	18.7	62.6	−5.1	−23.8	44.7	81.1	36.4
Acetone	0.124	0.705	5.2	25.4±0.3	20.2	67.8	−7.0	−18.8	48.1	83.0	34.9
1,4-Dioxane	0.175	0.500	4.3	17.5±0.3	13.2	44.2	−14.9	−42.3	49.0	90.9	41.9
THF	–	–	–	9.5±0.3	–	–	−22.9	–	–	98.9	–
EtAc	0.111	0.788	5.5	20.7±0.3	15.2	51.1	−11.7	−35.6	47.8	87.7	39.9
$CHCl_3$	–	–	–	11.4±0.2	–	–	−21.0	–	–	97.0	–
$C_2H_4Cl_2$	–	–	–	37.9±0.2	–	–	5.5	–	–	70.5	–
DMF	–	–	–	7.2±0.1	–	–	−25.2	–	–	101.2	–
DMSO	–	–	–	10.4±0.3	–	–	−22.0	–	–	98.0	–
Pyridine	–	–	–	2.3±0.1	–	–	−30.1	–	–	106.1	–
Piperidine	–	–	–	−32.4±0.2	–	–	−64.8	–	–	140.8	–

[a] $\gamma = X_2^{id}/X_2$, $X_2^{id} = 0.08745$ (Perlovich et al., 2002b).

in terms of enthalpies (ε_H) and in terms of entropies (ε_S), were defined according to the following definitions:

$$\varepsilon_H = |\Delta H_{spec}/\Delta H_{nonspec}| \cdot 100\% \quad (6)$$

$$\varepsilon_S = |\Delta S_{spec}/\Delta S_{nonspec}| \cdot 100\% \quad (7)$$

where

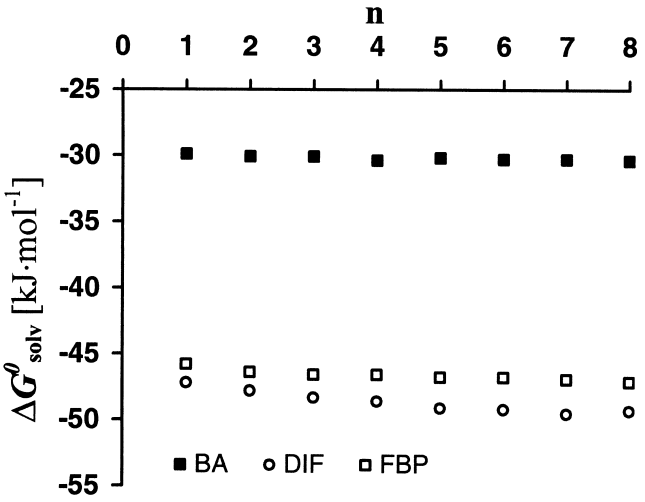


Fig. 2. Dependence of Gibbs energies of solvation, ΔG^0_{solv}, on the chain length (n) of the alcohol (solvent).

$$\Delta H_{spec} = \Delta H^0_{sol,i} - \Delta H^0_{sol,benzene};$$

$$\Delta H_{nonspec} = \Delta H^0_{sol,benzene} - \Delta H_{sub};$$

$$\Delta S_{spec} = \Delta S^0_{sol,i} - \Delta S^0_{sol,benzene};$$

$$\Delta S_{nonspec} = \Delta S^0_{sol,benzene}.$$

Benzene was chosen as an ‘‘inert’’ solvent, which interacts with drug molecules solely by a nonspecific interaction (as was done in Perlovich and Bauer-Brandl (2002)). The ε_H and ε_S values for the studied substances are presented in Table 4. These values indicate that during dissolution of both diflunisal and benzoic acid in aliphatic alcohols, specific solute–solvent interactions affect the entropic term of Gibbs energy to a greater extent than nonspecific interactions, whereas the noted regularity is not observed for FBP. With regard to the enthalpic term, in all studied cases the nonspecific solute–solvent interaction predominates. It appears that the introduced parameters ε_H and ε_S describe the ability of a solvent to solvate molecules. The parameters would then be a useful tool for understanding the distribution of drug molecules between different environments, and consequently may help to more rationally choose appropriate drug candidates.

Entropy/enthalpy compensation has been studied in a number of investigations into pharmaceutical, biochemical and biological systems (Tomlinson, 1983; Manzo and

Table 4
Relative enthalpic and entropic parameters of solvation process of the diflunisal, flurbiprofen and benzoic acid in aliphatic alcohols and organic solvents at 25 °C

Solvent	DIF				FBP				BA[a]			
	ς_H[b] (%)	ς_S[c] (%)	ε_H[d] (%)	ε_S[e] (%)	ς_H (%)	ς_S (%)	ε_H (%)	ε_S (%)	ς_H (%)	ς_S (%)	ε_H (%)	ε_S (%)
MeOH	65.9	34.1	14.0	23.1	69.0	31.0	9.3	31.1	63.2	36.8	16.6	36.0
EtOH	65.7	34.3	16.7	37.7	68.8	31.2	11.8	36.2	62.3	37.7	23.8	54.6
n-Propanol	65.5	34.5	19.3	46.2	68.8	31.2	12.2	36.5	62.2	37.8	24.6	56.7
n-BuOH	65.4	34.6	20.4	50.9	68.7	31.3	12.6	37.7	62.6	37.4	23.3	51.9
n-Pentanol	65.4	34.6	21.7	55.0	68.7	31.3	13.0	38.1	62.4	37.6	23.9	54.7
n-Hexanol	65.2	34.8	23.5	64.7	68.6	31.4	13.4	39.3	62.2	37.8	25.6	58.7
n-Heptanol	64.9	35.1	25.9	76.9	68.6	31.4	13.7	39.6	62.1	37.9	26.7	61.6
n-Octanol	64.7	35.3	26.9	83.8	68.7	31.3	13.8	39.3	62.0	38.0	28.2	65.3
n-Pentane	–	–	–	–	62.8	37.2	–	–	61.7	38.3	–	–
n-Hexane	–	–	–	–	63.5	36.5	–	–	60.3	39.7	–	–
n-Heptane	–	–	–	–	64.3	35.7	–	–	60.0	40.0	–	–
n-Octane	–	–	–	–	65.0	35.0	–	–	60.0	40.0	–	–
Benzene	64.6	35.4	(−85.6)[f]	0	72.2	27.8	(−76.0)	0	64.6	35.4	(−61.4)	0
Toluene	63.7	36.3	6.3	33.3	71.5	28.5	2.5	6.6	64.4	35.6	1.8	4.5
AN	65.5	34.5	7.7	11.0	69.0	31.0	6.7	27.6	61.8	38.2	15.3	44.6
Acetone	–	–	11.2	–	70.4	29.6	9.2	21.8	61.8	38.2	29.0	68.5
1,4-Dioxane	–	–	23.5	–	68.4	31.6	19.6	49.0	62.5	37.5	27.7	60.0
THF	–	–	31.2	–	–	–	30.1	–	61.6	38.4	37.1	84.0
EtAc	–	–	21.6	–	68.7	31.3	15.4	41.3	61.7	38.3	28.3	68.1
$CHCl_3$	–	–	26.6	–	–	–	27.6	–	–	–	37.0	94.3
DMF	–	–	36.4	–	–	–	33.2	–	61.5	38.5	42.0	93.1
DMSO	–	–	30.3	–	–	–	28.9	–	61.8	38.2	39.3	85.3
Pyridine	–	–	90.2	–	–	–	39.6	–	59.8	40.2	63.7	151.5
Piperidine	–	–	–	–	–	–	85.3	–	–	–	–	–

[a] Perlovich and Bauer-Brandl (2002).
[b] $\varsigma_H = (|\Delta H^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)) \cdot 100\%$.
[c] $\varsigma_S = (|T\Delta S^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)) \cdot 100\%$.
[d] $\varepsilon_H = (\Delta H_{spec}/\Delta H_{nonspec}) \cdot 100\%$.
[e] $\varepsilon_S = (\Delta S_{spec}/\Delta S_{nonspec}) \cdot 100\%$.
[f] $\Delta H_{nonspec} = -85.6$ kJ mol^{-1}.

Ahumada, 1990; Bustamante et al., 1998). In this respect, particular attention should be paid to the accuracy of the experimental data. It has been discussed that the compensation effects described in the literature could possibly be pure artifacts due to the correlation of experimental errors in non-independent experiments (Exner, 1964, 1973). Therefore, in the present study, ΔH^0_{sol} and ΔG^0_{sol} values were obtained by independent methods (solubility experiment and solution calorimetry). In the present study, such artifacts can be excluded because for diflunisal in alcohols, the variation of ΔH^0_{sol} values in all the experiments was found to be 28-fold the experimental error. The analogous value for ΔG^0_{sol} equals 12. For convenience, regression analysis between the enthalpic and entropic terms of the Gibbs energy was carried out in coordinates ΔH^0_{sol} and $T\Delta S^0_{sol}$, and the observed regularities are kept in the dimension plane (ΔH^0_{sol}; ΔG^0_{sol}) as well. The experimental data for diflunisal, flurbiprofen, benzoic and acetylsalicylic acids in alcohols are collected in Fig. 4. As follows from Fig. 4, the compensation effect is observed for all four substances.

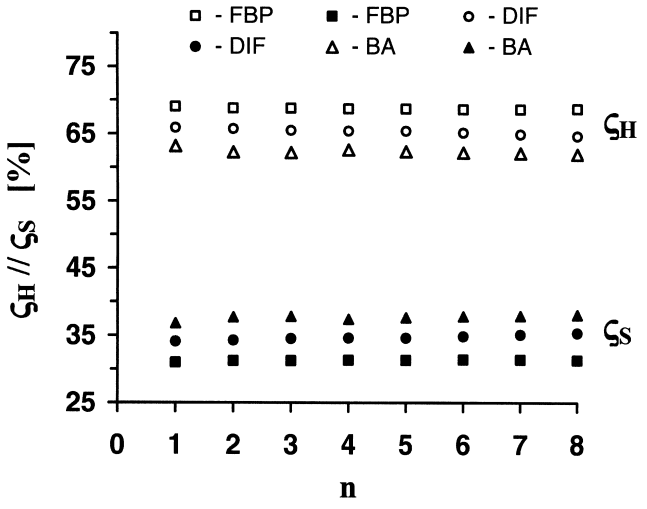


Fig. 3. Dependence of relative enthalpic/entropic terms of the solvation process, expressed as ς_H and ς_S parameters versus the chain length (*n*) of the alcohol.

For a quantitative description of the compensation effect, regression analysis by Eq. (8) was used and the results are listed in Table 5:

$$\Delta H^0_{sol} = A_0 + A_1(T\Delta S^0_{sol}) \quad (8)$$

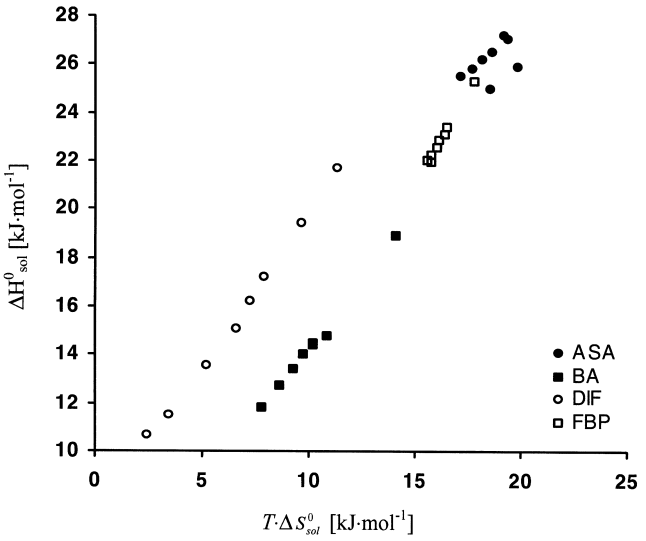


Fig. 4. The experimental results in coordinates ΔH^0_{sol} versus $T\Delta S^0_{sol}$ for BA, ASA, DIF and FBP.

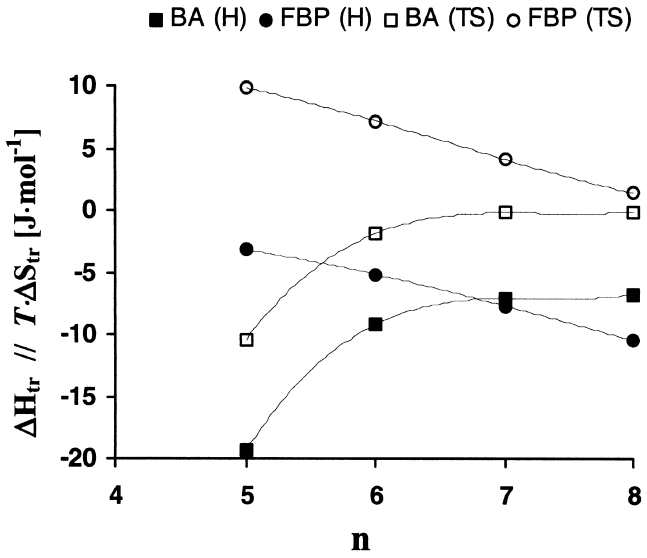


Fig. 5. Transfer functions, ΔH_{tr} or $T\Delta S_{tr}$, respectively, of benzoic acid and flurbiprofen molecules being transferred from the hydrocarbons into their homomorphous alcohols.

It should be noted that the regression coefficients A_1 of FBP and DIF differ significantly from each other: the enthalpic term of flurbiprofen is more sensitive to changes of the entropic term compared to diflunisal.

It is interesting to analyze the changes of the enthalpic and entropic terms of Gibbs energy under an imagined transfer of the drug molecules from a hydrocarbon environment into their homomorphous alcohols. The results of such calculations are presented in Table 6 and Fig. 5. For comparison, similar dependencies are also shown for BA (Perlovich and Bauer-Brandl, 2002) in Fig. 5. For diflunisal, similar data could not be yielded due to extremely low solubility of this substance in the respective

Table 5
The results of regression analysis for Eq. (8): $\Delta H^0_{sol} = A_0 + A_1(T\Delta S^0_{sol})$

Compound	A_0	A_1	σ	R	F	$F^{2.5\%}_{tab}$	n
In alcohols							
Flurbiprofen	−1.4±0.8	1.50±0.05	0.0882	0.998	898	9.365	6
Diflunisal	10.2±0.7	0.91±0.09	1.02	0.968	90.6	5.696	8
Benzoic acid[a]	3.0±0.1	1.12±0.03	0.146	0.998	1456	5.696	8
Acetylsalicylic acid[a]	12±1	0.76±0.06	0.123	0.986	140	9.365	6
In organic solvents							
Flurbiprofen	2.6±0.9	1.15±0.04	0.479	0.998	693	15.10	5
Benzoic acid[a]	2.9±0.5	1.17±0.05	1.38	0.993	659	2.132	11
In hydrocarbons							
Flurbiprofen	20.6±0.5	0.82±0.05	0.293	0.996	274	39.17	4
Benzoic acid[a]	9.3±0.08	1.173±0.006	0.0573	0.999	41319	39.17	4

[a] Perlovich and Bauer-Brandl (2002).

Table 6
The enthalpic and entropic terms of the Gibbs energy of transfer flurbiprofen molecules from hydrocarbons to their homomorphous alcohols[a]

Alcohol	Hydrocarbon	ΔH_{tr}(hyd→alc) (kJ mol^{-1})	$T\Delta S_{tr}$(hyd→alc) (kJ mol^{-1})	ΔS_{tr}(hyd→alc) (J mol^{-1} K^{-1})
n-BuOH	*n*-Pentane	−3.2	9.8	32.9
n-Pentanol	*n*-Hexane	−5.2	7.2	24.1
n-Hexanol	*n*-Heptane	−7.7	4.1	13.8
n-Heptanol	*n*-Octane	−10.5	1.4	4.7

[a] $\Delta H_{tr}(\text{hyd}\rightarrow\text{alc}) = \Delta H^0_{sol}(\text{alcohol}) - \Delta H^0_{sol}(\text{hydrocarbon})$; $\Delta S_{tr}(\text{hyd}\rightarrow\text{alc}) = \Delta S^0_{sol}(\text{alcohol}) - \Delta S^0_{sol}(\text{hydrocarbon})$.

organic solvents, which makes experimental determination of solution enthalpies impossible.

The behavior of enthalpic and entropic terms of Gibbs energy is essentially different: For flurbiprofen, with increasing n, the absolute value of transfer enthalpy increases while the transfer entropy decreases and converges to zero. For benzoic acid, in contrast to this, the absolute value of transfer enthalpy decreases and the transfer entropy increases and also converges to zero—as is the case with FBP, but from the opposite side. Since at $n=8$ the entropic term converges to zero in both cases, it may be assumed that the driving force then is the enthalpic term. However, at $n=5$, the opposite effect is observed for FBP: dissolution is entropically driven. Obviously, as the length of the chain of the alcohol increases, the thermodynamic behavior of the transfer process is essentially modified. Probably, as n is small, the big FBP molecule destroys the network of hydrogen bonds in the alcohol in such a strong way that the extra (now nonbonded) hydrogen atom can interact with appropriate electron donors, which leads to the essential reorganization of the network of the hydrogen bonds around the solute molecule (=solvation shell) compared to the pure alcohol. However, as the chain length n increases, the flurbiprofen molecule is better adjusted to the hydrogen bond network of the solvent and does not disturb it so much. Similar processes occur with transfer of benzoic acid: however, with small n, both the enthalpic and the entropic terms have significant impact on dissolution.

3.3. Thermodynamics of flurbiprofen and diflunisal solvation in organic solvents

In addition to the above discussed parameters, the thermodynamic functions of the solubility and solvation processes of diflunisal and flurbiprofen in a selection of organic solvents are presented in Tables 2 and 3 as well. In order to compare the heat effects of the specific and the nonspecific solvation in organic solvents, the pure base method of Arnett et al. (1970) was used. The biphenyl molecule was chosen as the model compound, which mimics size and structure of the investigated solute and at the same time does not specifically interact with organic solvents. According to Arnett's approach, the enthalpy of the specific interaction of a compound is calculated as follows:

$$\Delta H_{\mathrm{spec}}^{\mathrm{Comp}}(\mathrm{i}) = \Delta H_{\mathrm{tr}}^{\mathrm{Comp}}(\mathrm{i}) - \Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}(\mathrm{i}) \quad (9)$$

where $\Delta H_{\mathrm{tr}}^{\mathrm{Comp}}(\mathrm{i}) = \Delta H_{\mathrm{sol}}^{\mathrm{Comp}}(\mathrm{i}) - \Delta H_{\mathrm{sol}}^{\mathrm{Comp}}(\mathrm{benzene})$ is the transfer enthalpy of the noted compound from the ''inert'' solvent (benzene) into the investigated solvent (i); $\Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}(\mathrm{i}) = \Delta H_{\mathrm{sol}}^{\mathrm{Biphenyl}}(\mathrm{i}) - \Delta H_{\mathrm{sol}}^{\mathrm{Biphenyl}}(\mathrm{benzene})$ is the transfer enthalpy of the biphenyl molecule from the ''inert'' solvent (benzene) into investigated solvent (i).

The results of the calculations of $\Delta H_{\mathrm{tr}}^{\mathrm{DIF}}(\mathrm{i})$, $\Delta H_{\mathrm{tr}}^{\mathrm{FBP}}(\mathrm{i})$, $\Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}$ and $\Delta H_{\mathrm{spec}}^{\mathrm{Comp}}(\mathrm{i})$ are presented in Table 7.

As follows from Table 7, diflunisal in general interacts stronger with the respective solvents in comparison with flurbiprofen. It should be noted that these differences for weak bases lie within approximately 8 kJ mol^{-1}, whereas for the strong base (pyridine) the corresponding value is 46 kJ mol^{-1}. Probably, in solvents of lower basicity, the diflunisal molecule forms an intramolecular hydrogen bond, whereas in a strong base this bond is destroyed (due to competition with the stronger electron donor) and one extra proton donor center appears for interaction with the solvent. This fact would consequently lead to an essentially increased solvation effect.

The structures of both studied drugs contain very

Table 7
The results analysis of the specific interactions of the solute molecule with the solvent

Solvent	Biphenyl		Flurbiprofen		Diflunisal		Pure base method	
	$\Delta H_{\mathrm{sol}}^{0}$ (kJ mol^{-1})	$\Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{sol}}^{0}$ (kJ mol^{-1})	$\Delta H_{\mathrm{tr}}^{\mathrm{FBP}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{sol}}^{0}$ (kJ mol^{-1})	$\Delta H_{\mathrm{tr}}^{\mathrm{DIF}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{tr}}^{\mathrm{FBP}} - \Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{tr}}^{\mathrm{DIF}} - \Delta H_{\mathrm{tr}}^{\mathrm{Biphenyl}}$ (kJ mol^{-1})
Benzene	18.14[a]	0	32.4±0.2	0	33.7±0.2	0	0	0
Toluene	16.34[a]	−1.8	30.5±0.3	−1.9	28.3±0.2	−5.4	−0.1	−3.6
AN	21.32[a]	3.18	27.3±0.2	−5.1	27.1±0.4	−6.6	−8.3	−9.8
Acetone	19.27[a]	1.13	25.4±0.3	−7.0	24.1±0.2	−9.6	−8.1	−10.7
1,4-Dioxane	16.85[a]	−1.29	17.5±0.3	−14.9	13.6±0.3	−20.1	−13.6	−18.8
THF	14.25[a]	−3.89	9.5±0.3	−22.9	7.0±0.3	−26.7	−19.0	−22.8
EtAc	17.14[a]	−1.0	20.7±0.3	−11.7	15.2±0.2	−18.5	−10.7	−17.5
$CHCl_3$	–	–	11.4±0.2	−21.0	10.9±0.3	−22.8	–	–
$C_2H_4Cl_2$	17.52[a]	−0.62	37.9±0.2	5.5	–	–	6.1	–
DMF	15.42[b]	−2.72	7.2±0.1	−25.2	2.5±0.2	−31.2	−22.5	−28.5
DMSO	19.69[c]	1.55	10.4±0.3	−22.0	7.8±0.2	−25.9	−23.4	−27.5
Pyridine	16.89[a]	−1.25	2.3±0.1	−30.1	−43.5±0.2	−77.2	−28.9	−76.3
Piperidine	–	–	−32.4±0.2	−64.8	–	–	–	–

[a] Solomonov et al. (1984).
[b] Fuchs and Rodewald (1973).
[c] Krishnan and Friedmann (1969).

electronegative F-atoms, which are supposed to induce an essential contribution to specific solvation, particularly in alcohols which would act as H-donors. Indeed, as may be seen from Tables 2 and 3, the value for ΔH_{tr} is bigger for DIF, having two F-atoms, compared to FBP, which only has one. Looking at the ratio of enthalpies of transition as $\beta = \Delta H_{tr}^{DIF} / \Delta H_{tr}^{FBP}$, the value β increases from 1.7 to 2.2 with the chain length n of the respective alcoholic solvent. This value is in good agreement with the ratio of F-atoms in the structures of the considered substances.

In all the organic solvents under investigation, as well as in the alcohols, the compensation effect is observed for FBP. This correlation is presented in Fig. 6 (analogous results for benzoic acid from Perlovich and Bauer-Brandl (2002) are shown in the same figure) and the regression parameters of Eq. (8) are summarized in Table 5. It is not difficult to see that the experimental values for FBP and BA in the hydrocarbons lie on distinguished regression lines and do not coincide with the line for the organic solvents. On the other hand, the experimental data points for FBP and BA in organic solvents are situated approximately on the same regression line.

It should be noted that in the vials of the solubility experiments, the bottom phases of flurbiprofen and diflunisal in all the investigated solvents were examined by DSC. Not any heat effects attributed to desolvation processes of whatever solvates were seen with the only exception being (FBP + AN). Probably, this fact is the reason of the observed deviation of the experimental point from the common regression line in coordinates (ΔH_{sol}^0, $T\Delta S_{sol}^0$) due to errors in the solubility data. Thus, this point was omitted in the graph and in the regression analysis.

Based on the present experimental data, a couple of conclusions may be drawn:

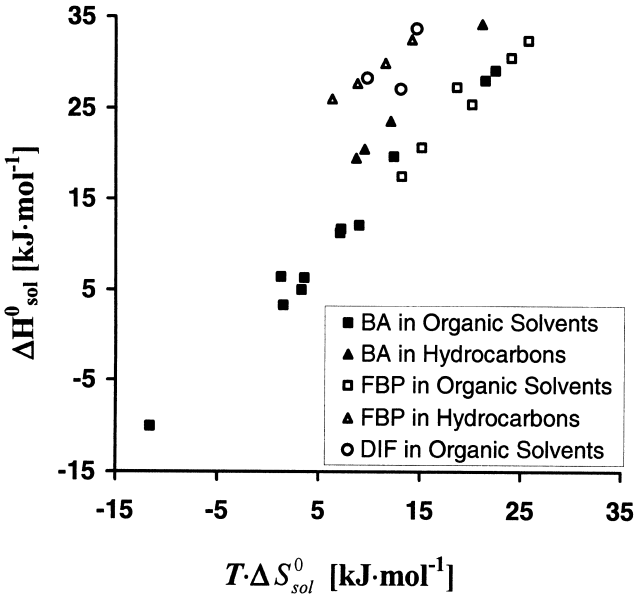


Fig. 6. Relationship between the enthalpic and entropic terms of Gibbs energy of dissolution of BA, FBP and DIF in the organic solvents.

(a) Enthalpy is the major driving force of the solvation process for all the studied compounds in both alcohols and organic solvents.
(b) With dissolution of DIF and FBP in alcohols and organic solvents a compensation effect between enthalpic and entropic terms of the Gibbs energy is observed. Therefore, solution enthalpy (particularly in combination with ΔG_{sol}^0) is a powerful tool to study thermodynamics of solubility of these drug substances.

However, for finding general regularities and relationships there is a need to carry out additional experiments in order to create special (individual) thermochemical scales for strictly definite groups of drugs with similar structure. Then it may be possible to find a correlation between the regression coefficient of the compensation effect (parameter A_1 in Eq. (8)) and the structure of the drugs. This would enable prediction of the thermodynamic functions of the solubility process (including solubility in n-octanol with impact on partitioning) exclusively based on the compensation regression lines.

Acknowledgements

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