Thermodynamics of Solutions I: Benzoic Acid and Acetylsalicylic Acid as Models for Drug Substances and the Prediction of Solubility

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Purpose. To investigate the solution process of drug substances (exemplified by benzoic acid, BA, and acetylsalicylic acid, ASA), particularly the interrelation between enthalpic and entropic terms of Gibbs energy, in different solvents. To develop an approach for the estimation of standard solution enthalpies based on a self-consistent thermochemical scale.

Method. Two independent methods, solubility experiments (concentrations of saturated solutions) and solution calorimetry (standard solution enthalpies) in aliphatic alcohols and individual organic solvents were used. Correlation between the thermodynamic functions in various solvents were analyzed by standard statistical methods. Multiple regression analysis between ΔH^0_{sol} values and the parameters of the solvents was run on the Koppel–Palm equation.

Results. Based on experimental data, a compensation effect between thermodynamic functions was observed. Correlation was found between ΔH^0_{sol} (BA) and ΔH^0_{sol} (ASA) [where the ΔH^0_{sol} (BA)-values were used as a self-consistent thermochemical scale]. Furthermore, ΔH^0_{sol} correlated with the Koppel–Palm basicity of the solvents.

Conclusions. The model based on solubility and solution experiments might be useful for the prediction of solubility or solvation of drug substances in different media. The regression equation based on the self-consistent thermochemical scale makes it possible to approximate the ability to solvate a drug substance in comparison with structure-relative substances.

KEY WORDS: benzoic acid; acetylsalicylic acid; solubility; solution enthalpy; compensation effect; alcohols; organic solvents.

INTRODUCTION

Transport of pharmaceuticals in biologic tissues includes solvation in and distribution between environments of different properties in terms of lipophilicity, basicity, etc. Prediction thereof is made by several approaches, including structure–activity relationships, the Hansch lipophilicity parameter, calculated distribution coefficients (summation of Hansch parameters), and linear solvation energy relationships in water. Here, studies in organic solvents of different properties are done.

Theoretical approaches describe excess Gibbs energy of drugs in various solvents in order to understand the physical processes of dissolution and solvation. These are, among others, deviation of regular solution behavior from ideal introduced by Hildebrand *et al.* (1), accounting for the entropy of mixing by the Flory–Huggins (2,3) parameter, and the mobile order in H-bonded liquids (4).

Furthermore, approaches with different kinds of multiple regression equations to approximate the experimental values of a Gibbs function have been introduced by Hansen and Skaarup (5), Karger *et al.* (6), Kamlet *et al.* (7), Chawla *et al.* (8), Hammet (9), Reichardt (10), Gutman (11), Koppel and Palm (12), and others. These approaches have in common that they were developed for strictly defined substance classes. Therefore, each of the correlation equations has both advantages and disadvantages, and their validity is satisfactory only within strict limits. However, in order to overcome this problem, equations can be extended by additional parameters. These essentially complicate the interpretation of the physical processes, which are back-dissolution and solvation.

Another approach is to study the dissolution process by simultaneously analyzing the thermodynamic potentials ΔG^0_{sol} and ΔH^0_{sol} (13–15). Knowledge of such parameters essentially expands understanding of solubility and solvation phenomena and creates a foundation for analyses of the interrelation between enthalpy and entropy terms. Several decades ago, Tomlinson (16) paid close attention to this approach. He stated that because these functions are, as a rule, obtained from the same experiment (for example, solubility at different temperatures) (13), correlations found are prone to systematic errors. Therefore, we have investigated the regularities in dissolution behavior by means of independent methods (solubility and calorimetric experiments) in various organic solvents.

The choice of benzoic acid (BA) and acetylsalicylic acid (ASA) as model compounds is based on the following reasons: First, both of them are well known and have a lot of experimental data available, e.g., BA solubility (17,18), BA solution enthalpies (19), and values of BA sublimation enthalpy measured by different methods (20). Second, both BA and ASA represent structures that form part of many drug substances (benzene ring and carboxyl group). Moreover, ASA is a derivative of BA with an additional substituent in the *ortho* position, which may sterically hinder access of solvent molecules to the carboxyl motif.

MATERIALS AND METHODS

Materials and Solvents

Acetylsalicylic acid (Aspirin, ASA, $C_9H_8O_4$, MW 180.16) and benzoic acid (BA, $C_7H_6O_2$, MW 122.12), analytic reagent grade, were from Norsk Medisinaldepot (Oslo, Norway). The alcohols were as follows: methanol (MeOH, CH_3OH, MW 32.04), HPLC grade, from Merck (Germany), lot K27636907; ethanol (EtOH, CH_3CH_2OH, MW 46.2), extra pure grade (99.6% v/v, maximum water content 0.4%); 1-propanol [*n*-propanol, $CH_3(CH_2)_2OH$, MW 60.10], HPLC grade, from Aldrich (Germany), lot U00874; 1-butanol [BuOH, $CH_3(CH_2)_3OH$, MW 74.12], analytic reagent grade (ARG), from Merck (Germany), lot K22047090; 1-pentanol [*n*-pentanol, $CH_3(CH_2)_4OH$, MW 88.15], ARG, from Aldrich (Germany), lot 35757–101; 1-Hexanol [*n*-Hexanol, $CH_3(CH_2)_5OH$, MW 102.18), ARG, from Aldrich (Germany), lot 31562-011; 1-heptanol [*n*-heptanol, $CH_3(CH_2)_6OH$, MW 116.2], ARG, from Sigma Chemical Co.

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(USA), lot 60K3706; 1-octanol [*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2], ARG, from Sigma Chemical Co. (USA), lot 11K3688. The hydrocarbons were as follows: *n*-pentane (C_5H_{12}, MW 72.15), ARG, from SDS (Peypin, France), lot 10020005; *n*-hexane (C_6H_{14}, MW 86.18), ARG, from SDS (Peypin, France), lot 07059903C; *n*-heptane (C_7H_{16}, MW 100.21), ARG, from SDS (Peypin, France), lot 16039901; *n*-octane (C_8H_{18}, MW 114.2), ARG, from Sigma Chemical Co. (USA), lot 51K3681. The organic solvents were as follows: benzene (C_6H_6, MW 78.12), ARG, from Merck (Germany), lot K26454983; toluene (C_7H_8, MW 92.14), ARG, from Merck (Germany), lot K23559425; acetonitrile (AN, C_2H_3N, MW 41.05), HPLC grade, from Merck (Germany), lot I894030; 1,4-dioxane ($C_4H_8O_2$, MW 88.11), ARG, from Sigma Chemical Co. (USA), lot 70K3697; tetrahydrofuran (THF, C_4H_8O, MW 72.10), HPLC grade, from SDS (Peypin, France), lot 23049704C; ethyl acetate (EtAc, $C_4H_8O_2$, MW 88.11), ARG, from Merck (Germany), lot K25821023; N,N-dimethylformamide (DMF, C_3H_7NO, MW 73.09), ARG, from Sigma Chemical Co. (USA), lot 11K1321; dimethylsulfoxide (DMSO, C_2H_6SO, MW 78.13), ARG, from Sigma Chemical Co. (USA), lot 129H0068; acetone (C_3H_6O, MW 58.08), ARG, from SDS (Peypin, France), lot 02069901; pyridine (Py, C_5H_5N, MW 79.10), ARG, from Sigma Chemical Co. (USA), lot 10K1128; piperidine (hexahydropypidine, Pip, $C_5H_{11}N$, MW 85.15), ARG, from Sigma Chemical Co. (USA), lot 98H1198; chloroform ($CHCl_3$, MW 119.38), ARG, from Merck (Germany), lot K27794045.

Solubility Determination

Solubilities of BA and ASA were obtained at 25 ± 0.1°C. Solubilities of ASA in benzene, toluene, EtAc, and acetone were determined by the weighing method with a reproducibility of about 3%. The other experiments were carried out spectrophotometrically after the protocol described previously (24), with an accuracy of about 2.5%.

Solution Calorimetry

Enthalpies of solution (ΔH^m_{sol}) at a concentration *m* were measured using a Precision Solution Calorimeter in the 2277 Thermal Activity Monitor Thermostat (both from Thermometric AB, 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 each investigated sample approximately 18 mg. The accuracy of weight measurements corresponded to ±0.0005 mg. The calorimeter was calibrated using KCl (analytic 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 ΔH^0_{sol} = 17,225 ± 50 J·mol^{-1}. This is in good agreement with the value established by IUPAC of ΔH^0_{sol} = 17,217 ± 33 J·mol^{-1} (26). The number of individual dissolution experiments for the each of the solvents was between three and five for the organic solvents and five to eight for the alcohols and hydrocarbons. The difference in the number of experimental data points results from the behavior of the function $\Delta H^0_{sol} = f(n)$. In the case of the alcohols, the values of this function at $n > 3$ appear to fluctuate to only a small degree (see results below), and therefore, more data points are needed for statistical significance of the differences. In the case of the hydrocarbons, the large number of experimental data points is necessary because of the slow dissolution rate of the investigated drugs, which makes increased experimental time necessary. The values ΔH^m_{sol} of investigated compounds in the solvents do not depend on concentration, *m*, in the range of $m = 10^{-4}/1.5\cdot10^{-3}$ mol·kg^{-1}. Therefore, the average of obtained experimental points has been taken as the standard value for ΔH^0_{sol}.

Differential Scanning Calorimetry (DSC)

In order to exclude solvate formation during solubility experiments, analysis of the bottom phase was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin Elmer Analytical Instruments, Norwalk, Connecticut, 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 aluminum sample pans. The DSC 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.

Statistical Analysis

Multiple regression analysis of the data was performed using standard statistical procedures and in-house software.

RESULTS AND DISCUSSION

With the DSC method, in no case were any solutes detected in the bottom phases of the saturated solutions.

Solubility of Benzoic Acid and Acetylsalicylic Acid in Aliphatic Alcohols

The thermodynamic functions of the solubility process (solubility; deviation from ideal solubility, solution enthalpy, calculated entropies terms, calculated free enthalpy) of BA and ASA in aliphatic alcohols are presented in Tables I and II. For comparison reasons analogous literature values for parabens (*para*-hydroxybenzoic esters) are taken from Alexander *et al.* (13).

In order to analyze specific and nonspecific terms of the solvation process, values of ΔH^0_{sol} are also presented on an adjusted scale where enthalpies of an imaginary transfer from the "inert" solvent into the solvent under investigation (ΔH_{tr}) were calculated in each case. The choice of the "inert" solvent needs to be explained. As a rule, a solvent that only nonspecifically interacts with the solute is selected. Ideal solubility is then observed in solvents with similar structure to the solute, as is well known (21). Because both investigated compounds are benzene derivatives, benzene was chosen as the standard ′inert′ solvent.

The dependencies of the transfer enthalpies, ΔH_{tr}, and the entropic term, $T\cdot\Delta S_{tr}$, vs. the alcohol chain length (n) are shown in Fig. 1a and Fig. 1b, respectively.

In general, benzoic acid interacts more strongly with the alcohols than does acetylsalicylic acid. It should be noted that

Table I. Thermodynamic Functions of the Benzoic Acid Solubility Process in Aliphatic Alcohols and Organic Solvents at 25°C

Solvents	X_2[a]	γ[d]	ΔG^0_{sol} (kJ · mol^{-1})	ΔH^0_{sol} (kJ · mol^{-1})	$T \cdot \Delta S^0_{sol}$ (kJ · mol^{-1})	ΔS^0_{sol} (J · K^{-1} · mol^{-1})	ΔH^{BA}_{tr} (kJ · mol^{-1})	ΔS^{BA}_{tr} (J · mol^{-1}·K^{-1})	ε^f_H (%)
MeOH	0.1632	1.38	4.5	18.9 ± 0.2	14.4	48.3	−10.2	−61.4	16.6
EtOH	0.1789	1.25	4.3	14.5 ± 0.3	34.2	34.3	−14.6	−65.3	23.8
n-Propanol	0.1791	1.26	4.3	14.0 ± 0.3	9.7	32.7	−15.3	−65.8	24.6
n-BuOH	0.2016	1.12	4.0	14.8 ± 0.2	10.8	36.3	−14.3	−64.7	23.3
n-Pentanol	0.1839	1.22	4.2	14.4 ± 0.1	10.2	34.2	−14.7	−65.3	23.9
n-Hexanol	0.1905	1.18	4.1	13.4 ± 0.2	9.3	31.2	−15.7	−66.2	25.6
n-Heptanol	0.1946[b]	1.16	4.1	12.7 ± 0.2	8.6	29.0	−16.4	−66.9	26.7
n-Octanol	0.1987	1.13	4.0	11.8 ± 0.3	7.8	26.2	−17.3	−67.7	28.2
n-Pentane	0.0059	43.3	13.0	34.2 ± 0.2	21.2	71.0	—	—	—
n-Hexane	0.0095	24.0	11.5	23.6 ± 0.2	12.1	40.6	—	—	—
n-Heptane	0.0117	19.2	11.0	20.5 ± 0.2	9.5	31.8	—	—	—
n-Octane	0.0129[b]	17.4	10.8	19.5 ± 0.2	8.7	29.2	—	—	—
Benzene	0.0689	3.26	6.6	29.1 ± 0.2	22.5	75.5	0	0	(−61.4)[g]
Toluene	0.0734	3.07	6.5	28.0 ± 0.2	21.5	72.1	−1.1	−3.4	1.8
AN	0.0539[b]	4.17	7.2	19.7 ± 0.3[e]	12.4	41.8	−9.4	−33.7	15.3
1,4-Dioxane	0.2853	0.789	3.1	12.1 ± 0.3[e]	9.0	30.2	−17.0	−45.3	27.7
THF	0.3348[c]	0.672	2.7	6.3 ± 0.3[e]	3.6	12.1	−22.8	−63.4	37.1
EtAc	0.1649	1.37	4.5	11.7 ± 0.3[e]	7.2	24.1	−17.4	−51.4	28.3
DMF	0.4909	0.458	1.8	3.3 ± 0.3[e]	1.5	5.2	−25.8	−70.3	42.0
DMSO	0.5102	0.441	1.7	5.0 ± 0.3[e]	3.3	11.1	−24.1	−64.4	39.3
Acetone	0.1857	1.21	4.2	11.3 ± 0.3[e]	7.1	23.8	−17.8	−51.7	29.0
Pyridine	0.5348	0.421	1.6	−10.0 ± 0.2	−11.6	−38.9	−39.1	−114.4	63.7
Piperidine	—	—	—	−39.7 ± 0.3[e]	—	—	−68.8	—	112
$CHCl_3$	0.1283	1.75	5.1	6.4 ± 0.2	1.3	4.3	−22.7	−71.2	37.0

[a] Ref. 17, accuracy < 3%.
[b] This work.
[c] Ref. 18, accuracy 2%.
[d] $\gamma = X_2^{id}/X_2$; $X_2^{id} = 0.2251$ (17).
[e] Ref. 19.
[f] $\varepsilon_H = (\Delta H_{spec}/\Delta H_{nonspec}) \cdot 100\%$.
[g] $\Delta H_{nonspec} = -61.4$ kJ · mol^{-1}; $\Delta H_{sub} = 90.5 \pm 0.3$ kJ · mol^{-1} (20).

Table II. Thermodynamic Functions of the Acetylsalicylic Acid Solubility Process in Aliphatic Alcohols and Organic Solvents at 25°C

Solvents	X_2	γ[a]	ΔG^0_{sol} (kJ · mol^{-1})	ΔH^0_{sol} (kJ · mol^{-1})	$T \cdot \Delta S^0_{sol}$ (kJ · mol^{-1})	ΔS^0_{sol} (J · K^{-1} · mol^{-1})	ΔH^{ASA}_{tr} (kJ · mol^{-1})	ΔS^{ASA}_{tr} (J · mol^{-1} · K^{-1})
MeOH	0.0719	0.433	6.5	25.0 ± 0.2	18.5	62.0	−15.5	−16.4
EtOH	0.0855	0.364	6.1	25.9 ± 0.3	19.8	66.4	−14.6	−12.0
n-Propanol	0.0418	0.744	7.9	26.5 ± 0.2	18.6	62.5	−14.0	−15.9
n-BuOH	0.0453	0.687	7.7	27.0 ± 0.2	19.3	64.8	−13.5	−13.6
n-Pentanol	0.0395	0.787	8.0	27.2 ± 0.2	19.2	64.3	−13.3	−14.1
n-Hexanol	0.0393	0.791	8.0	26.2 ± 0.2	18.2	61.0	−14.3	−17.4
n-Heptanol	0.0386	0.806	8.1	25.8 ± 0.3	17.7	59.5	−14.7	−18.9
n-Octanol	0.0341	0.912	8.4	25.5 ± 0.2	17.1	57.4	−15.0	−21.0
n-Hexane	—	—	—	40.0 ± 0.2	—	—	—	—
Benzene	0.00101	30.8	17.1	40.5 ± 0.2	23.4	78.4	0	0
Toluene	0.00129	24.1	16.5	34.3 ± 0.2	17.8	59.7	−6.2	−18.7
AN	0.0185	1.68	9.9	25.6 ± 0.2	15.7	52.7	−14.9	−25.7
1,4-Dioxane	0.0516	0.603	7.3	18.8 ± 0.2	11.5	38.4	−21.7	−40.0
THF	—	—	—	8.8 ± 0.3	—	—	−31.7	—
EtAc	0.0448	0.694	7.7	20.8 ± 0.3	13.1	43.9	−19.7	−34.5
DMF	—	—	—	7.5 ± 0.2	—	—	−33.0	—
DMSO	—	—	—	9.3 ± 0.1	—	—	−31.2	—
Acetone	0.0828	0.376	6.2	22.3 ± 0.2	16.1	54.0	−18.2	−24.4
Pyridine	—	—	—	−20.8 ± 0.2	—	—	−61.3	—
$CHCl_3$	0.206	0.151	3.9	10.7 ± 0.3	6.8	22.8	−29.8	−55.6

[a] $\gamma = X_2^{id}/X_2$, $X_2^{id} = 0.0311$ calculated by data from Perlovich and Brandl-Bauer (25).

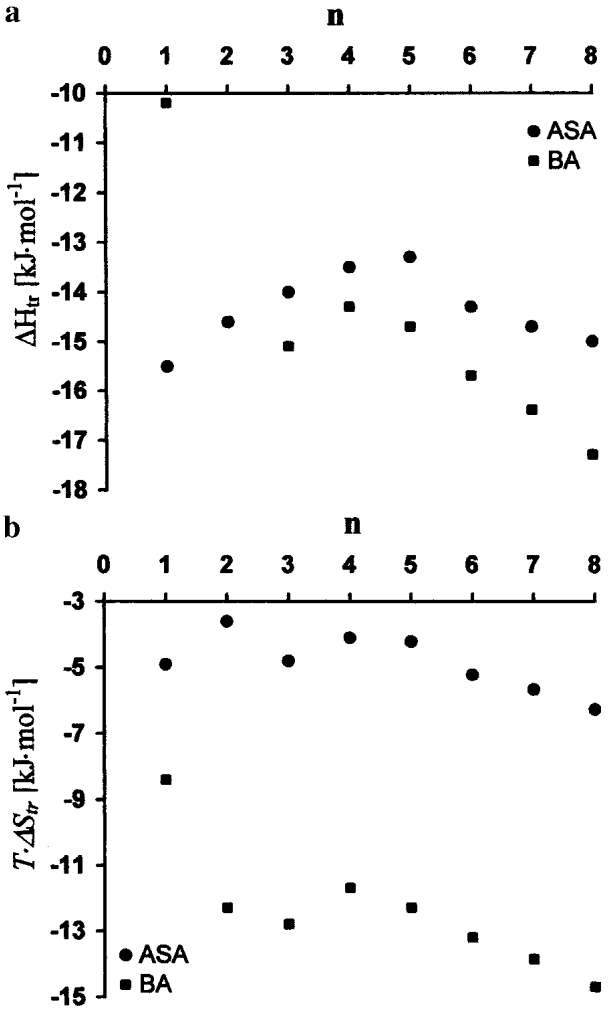

Fig. 1. Dependencies of transfer enthalpies, ΔH_{tr}, (a) and entropy terms of transfer Gibbs energy, $T\cdot\Delta S_{tr}$, (b) vs. the alcohol chain length (n).

the function $\Delta H^0_{sol} = f(n)$ has its maximum at $n = 5$ for ASA, and shows a more complex behavior for BA with the two maxima at $n = 1$ and $n = 4$, respectively. This may be explained by the competition of several factors: (a) the strength of solute–solvent hydrogen bonds (enthalpic factor); (b) the difference in the molecular volumes of solute and solvent, V_2/V_1, (entropic factor); and (c) topology of the molecules (steric factor, which influences both the enthalpic and the entropic terms of Gibbs energy). In some cases it is difficult to divide the solvation process into these simpler steps when enthalpic and entropic effects are closely connected. Therefore, it is problematic to choose only one parameter to describe it. It is supposed that if the function ΔH^0_{sol} is varied slightly vs. the alcohol chain length, the main contribution to Gibbs energy is the entropic term because ΔG^0_{sol} may be smoothed by the independent variable $(A\cdot\Phi_1\cdot V_2)/(\Phi_2\cdot V_1)$ (where A is a parameter that characterizes energies of interaction between solute molecules, between solvent molecules, and solute–solvent interaction, and Φ_i is the volume fraction) (4). As seen in the data, the solvation process of BA and ASA is sensitive to both the enthalpic and the entropic terms. Therefore, it is assumed that there is a compensation effect between them, and, as a result of this phenomenon, ΔG^0_{sol} values are less sensitive to variation of n. The ΔG^0_{sol} function of benzoic acid serves as an example: the maximum difference, $\max|\Delta G^0_{sol}|$, is only 1.5 kJ·mol^{-1}, whereas $\max|\Delta H^0_{sol}|$is 7.1 kJ·mol^{-1}, H^0_{sol} and $\max|T\cdot\Delta S^0_{sol}|$is 6.3 kJ·mol^{-1}. Therefore, the thermodynamic potentials ΔH^0_{sol} and $T\cdot\Delta S^0_{sol}$ are more sensitive tools for study of the solvation process in alcohols.

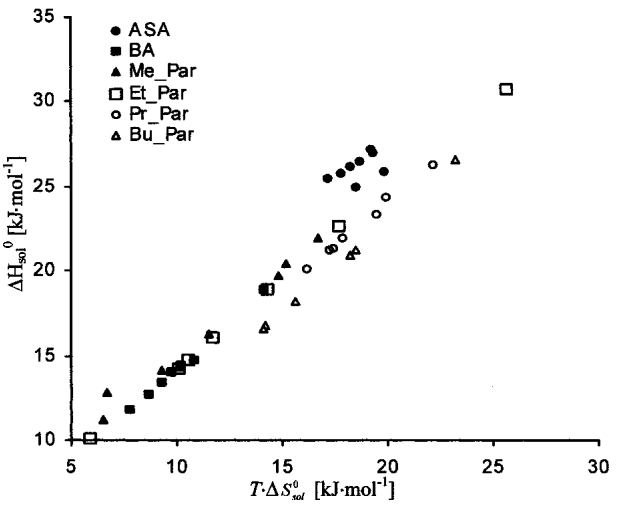

Fig. 2. The experimental results in coordinates ΔH^0_{sol} vs. $T\cdot\Delta S^0_{sol}$ for BA, ASA, and parabens [from Alexander *et al.* (13)].

The experimental results in coordinates ΔH^0_{sol} vs. $T\cdot\Delta$

Table III. The Results of Regression Analysis for Eq. (l): $\Delta H^0_{sol} = A_0 + A_1\cdot(T\cdot\Delta S^0_{sol})$

Compounds	A_0	A_1	σ	R	F	$F^{2.5\%}_{tab}$	n
In alcohols							
Benzoic acid	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
Methylparaben[b]	5.3 ± 0.6	0.98 ± 0.05	0.511	0.994	384	6.978	7
Ethylparaben[b]	3.8 ± 0.1	1.055 ± 0.009	0.142	0.999	13652	6.978	7
Propylparaben[b]	2.8 ± 0.7	1.07 ± 0.04	0.195	0.997	732	6.978	7
Butylparaben[b]	1.3 ± 0.3	1.083 ± 0.016	0.131	0.999	4676	6.978	7
In organic solvents							
Benzoic acid	2.9 ± 0.5	1.17 ± 0.05	1.38	0.993	659	2.132	11
In hydrocarbons							
Benzoic acid	9.3 ± 0.08	1.173 ± 0.006	0.0573	0.999	41319	39.17	4

[a] Without MeOH and EtOH.
[b] Data taken from Alexander *et al.* (13).

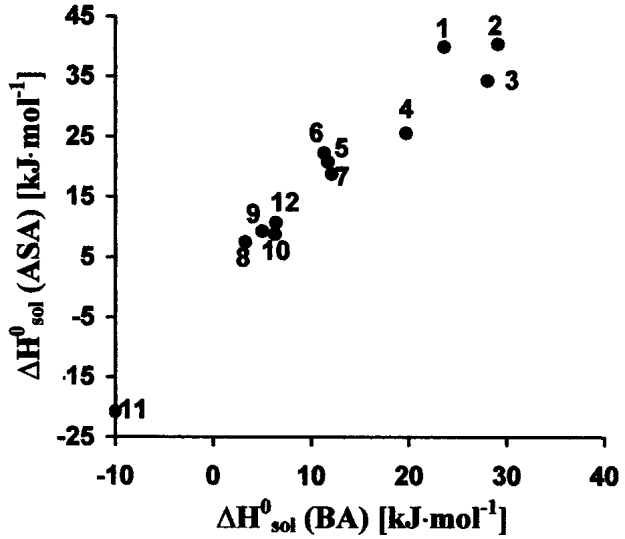

Fig. 3. Relationship between ΔH^0_{sol} (ASA) and ΔH^0_{sol} (BA) in different solvents: 1, n-hexane; 2, benzene; 3, toluene; 4, acetonitrile; 5, EtAc; 6, acetone; 7, 1,4-dioxane; 8, THF; 9, DMF; 10, DMSO; 11, pyridine; 12, $CHCl_3$.

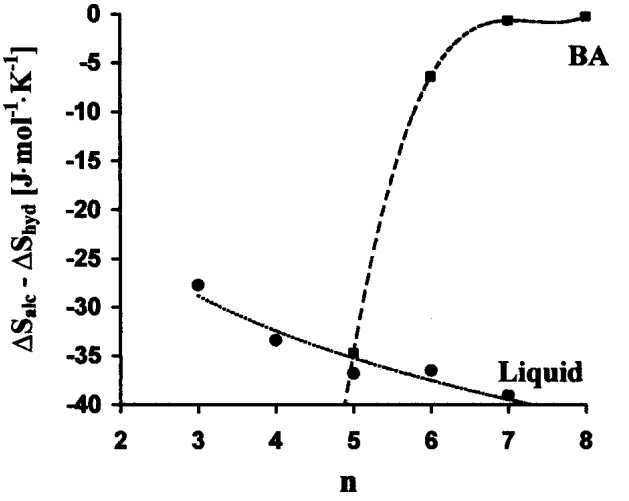

Fig. 4. The transfer entropies of benzoic acid molecules from the hydrocarbons to their homomorphous alcohols (BA). The differences between standard molar entropies of alcohols and of their homomorphous hydrocarbons in liquid phase (liquid).

S^0_{sol} for BA, ASA, and parabens (13) in the alcohols are presented in Fig. 2.

It should be noted that the compensation effect between ΔH^0_{sol} and $T{\cdot}\Delta S^0_{sol}$ is observed for both benzoic acid and acetylsalicylic acid (where the data are from independent experimental methods) and for parabens (where the data are obtained by the solubility method only). The two extraordinary data points in Fig. 2 are ASA in MeOH and EtOH, which may be explained by an essential deviation of this solute from ideal. The maximum difference between ΔH^0_{sol} values of BA in alcohols is 35 times greater than the experimental accuracy, whereas for the $T{\cdot}\Delta S^0_{sol}$ term, the analogous value is 14. From this it may be concluded that the observed regularity is not a result of the correlation between experimental errors. The complex process of solvation of drugs in alcohols may be reduced to the correlation line, which makes it possible to estimate the thermodynamic behavior of the system. The results of this correlation analysis for Eq. (1) are presented in Table III.

$$\Delta H^0_{sol} = A_0 + A_1 \cdot (T \cdot \Delta S^0_{sol}) \quad (1)$$

From Table III it follows that the correlation coefficients on Eq. 1 for the two compounds under investigation are practically the same within statistical errors. This indicates approximately equal sensitivity of the Gibbs energy of the two substances in the solvation process in alcohols.

Results of correlation analysis using Eq. (1) for benzoic acid in all organic solvents except alcohols, and in hydrocarbons only, are also shown in Table III and Fig. 3. Coefficients A_1 for the solvents and the hydrocarbons also have values that are, within statistical errors, equal to the analogous values for the alcohols.

It is interesting to analyze the behavior of the enthalpic and entropic terms of the Gibbs energy by imagining a transfer of benzoic acid molecules from hydrocarbon solution into the corresponding homomorphous alcohol. The results of these calculations are presented in Table IV and Fig. 4. The differences in standard molar entropies between alcohols and their homomorphous hydrocarbons in the liquid phase (4) are also shown in Fig. 4. From the data it can be concluded that as the alcohol length increases, the effect of the hydrogen network on the dissolution process of solute molecules decreases.

Solubilities of Benzoic Acid and Acetylsalicylic Acid in Organic Solvents

The thermodynamic functions of the solubility process of BA and ASA in some selected organic solvents are presented in Tables I and II. In order to compare the heat effects of specific and nonspecific solvation of the investigated compounds, the ′pure base method′ of Arnett *et al.* (22) was used. Anisole was chosen as the reference compound because it does not specifically interact with organic solvents and mimics

Table IV. The Enthalpic and Entropic Terms of the Gibbs Energy of Transfer of Benzoic Acid Molecules from Hydrocarbons into their Homomorphous Alcohols[a]

Alcohol	Hydrocarbon	ΔH_{tr} (hyd→alc) kJ · mol^{-1}	$T \cdot \Delta S_{tr}$ (hyd→alc) kJ · mol^{-1}	ΔS_{tr} (hyd→alc) J · mol^{-1} · K^{-1}
n-BuOH	*n*-Pentane	−19.4	−10.4	−34.9
n-Pentanol	*n*-Hexane	−9.2	−1.9	−6.3
n-Hexanol	*n*-Heptane	−7.1	−0.21	−0.7
n-Heptanol	*n*-Octane	−6.8	−0.08	−0.3

[a] ΔH_{tr} (hyd→alc) = ΔH^0_{sol} (alcohol) − ΔH^0_{sol} (hydrocarbon). ΔS_{tr} (hyd→alc) = ΔS^0_{sol} (alcohol) − ΔS^0_{sol} (hydrocarbon).

the size and structure of the investigated solutes. According to Arnett's approach, the enthalpy of specific interaction is calculated as follows:

$$\Delta H^{PB}_{spec}(\mathrm{i}) = \Delta H^{Comp}_{tr}(\mathrm{i}) - \Delta H^{Anisol}_{tr}(\mathrm{i}) \quad (2)$$

where $\Delta H^{Comp}_{tr}(\mathrm{i}) = \Delta H^{Comp}_{sol}(\mathrm{i}) - \Delta H^{Comp}_{sol}$ (benzene) is the transfer enthalpy of the compound from "inert" solvent (benzene) to investigated solvent (i):

$$\Delta H^{Anisol}_{tr}(\mathrm{i}) = \Delta H^{Anisol}_{sol}(\mathrm{i}) - \Delta H^{Anisol}_{sol}(\text{benzene})$$

is the transfer enthalpy of anisol from "inert" solvent (benzene) to investigated solvent (i). The results of calculations of ΔH^{BA}_{tr} (i), ΔH^{ASA}_{tr} (i), ΔH^{Anisol}_{tr}, and ΔH^{PB}_{spec} (i) are presented in Table V.

As follows from the data in Table V, ASA interacts more strongly than BA with solvents. To quantify this difference, we carried out a correlation analysis between ΔH^{ASA}_{sol} and ΔH^{BA}_{sol}. The result of this analysis is presented in Fig. 3 and can be described by the following correlation equation:

$$\Delta H^{ASA}_{sol} = (0.4 \pm 1.8) + (1.5 \pm 0.1) \cdot \Delta H^{BA}_{sol} \quad (3)$$

$$\sigma = 4.31;\ R = 0.970;\ F^{2.5\%}_{tab} = 2.571;\ F = 161;\ n = 12$$

where σ is the standard deviation, $F^{2.5\%}_{tab}$ is the Fisher distribution tabulated value with confidence interval 2.5%, and F is the calculated Fisher distribution value.

From the regression coefficient $A_1 = 1.5$ it follows that the ASA molecule is 1.5 times more sensitive to interaction with a Brønsted base than is BA.

The analogous equation for the investigated compounds in alcohols follows:

$$\Delta H^{ASA}_{sol} = (18.6 \pm 1.1) + (0.57 \pm 0.8) \cdot \Delta H^{BA}_{sol} \quad (4)$$

$$\sigma = 2.07 \cdot 10^{-2};\ R = 0.960;\ F^{2.5\%}_{tab} = 9.365;\ F = 47.64;\ n = 6$$

Thus, ASA molecules are about two times less sensitive to interaction with alcohols than is BA.

It is interesting to estimate the specific, ΔH_{spec}, and nonspecific, $\Delta H_{nonspec}$, solvation enthalpies and their relative ratio $\varepsilon_H = (\Delta H_{spec}/\Delta H_{nonspec}) \cdot 100\%$. However, in order to calculate these parameters, knowledge of the sublimation enthalpy, ΔH_{sub}, is needed. Unfortunately, these values are unknown for many drug substances. Benzoic acid, however, is the standard substance for testing sublimation equipment, and therefore, this value has been measured very accurately by various methods ($\Delta H_{sub} = 90.5 \pm 0.3$ kJ·mol^{-1}) (20). The results of ε_H value calculations are presented in Table I and show that the enthalpy of nonspecific solvation of the benzoic acid in benzene is –61.4 kJ·mol^{-1}, whereas the value of specific solvation lies between 1.8% in toluene and 112% in piperidine. For example, in *n*-octanol, this value is about 30%. Because of the lack of ΔH_{sub} values, this discussion is not possible for ASA.

In order to analyze the energetic effects of solute–solvent interactions in more detail, a multiple regression analysis was carried out using the Koppel–Palm equation (12):

$$\Delta H^0_{sol} = A_0 + A_1 \cdot B + A_2 \cdot E + A_3 \cdot f(\varepsilon) + A_4 \cdot f(n) \quad (5)$$

where B and E are basicity and electophilicity of the solvent, respectively;

$f(\varepsilon) = (\varepsilon - 1)/(2 \cdot \varepsilon + 1)$ is the function of a polarity of the solvent; $f(n) = (n^2 - 1)/(n^2 + 2)$ is the function of a polarizability of the solvent;

Choice of this equation is based on following reasons: The Koppel–Palm basicity scale (23) was created based on shifts of the OH^- absorption band of phenol in the presence of Brønsted base. Because the phenol structure is related to the studied compounds, and the solution enthalpy of this group of substances is very sensitive to the noted shifts (22) and correlates with them, this particular scale was chosen. The parameters of the investigated solvents are presented in Table VI.

From correlation analysis it follows that for acetylsalicylic acid, the ΔH^0_{sol} function can be described by regression Eq. (6) with three independent, statistically significant variables (B, E, $f(n)$), whereas for benzoic acid the ΔH^0_{sol} function is described by Eq. (7) with variables (B, $f(\varepsilon)$, $f(n)$). The cross-correlation matrices are shown in Table VII.

$$\Delta H^0_{sol} = (37 \pm 2) - (0.137 \pm 0.012) \cdot B + (2.5 \pm 0.7) \cdot E + (20 \pm 15) \cdot f(\varepsilon) \quad (6)$$

$$r = 0.989;\ r_d = 0.986;\ \sigma = 2.7;\ F^{2.5\%}_{tab} = 5.52;\ F = 91.3;\ n = 10$$

Table V. The Results of Analysis of the Specific Interactions of the Solute Molecule with the Solvent

	Anisol[a]		Benzoic acid		Acetylsalicylic acid		Pure base method	
Solvents	ΔH^0_{sol} (kJ · mol^{-1})	ΔH^{Anisol}_{tr} (kJ · mol^{-1})	ΔH^0_{sol} (kJ · mol^{-1})	ΔH^{BA}_{tr} (kJ · mol^{-1})	ΔH^0_{sol} (kJ · mol^{-1})	ΔH^{ASA}_{tr} (kJ · mol^{-1})	$\Delta H^{BA}_{tr} - \Delta H^{Anisol}_{tr}$ (kJ · mol^{-1})	$\Delta H^{ASA}_{tr} - \Delta H^{Anisol}_{tr}$ (kJ · mol^{-1})
Benzene	0.00 ± 0.04	0	29.1 ± 0.2	0	40.5 ± 0.2	0	0	0
Toluene	–0.25 ± 0.13	–0.25	28.0 ± 0.2	–1.1	34.3 ± 0.2	–6.2	–0.85	–5.95
AN	—	—	19.7 ± 0.3	–9.4	25.6 ± 0.2	–14.9	—	—
1,4-Dioxane	0.25 ± 0.04	0.25	12.1 ± 0.3	–17.0	18.8 ± 0.2	–21.7	–17.25	–21.95
THF	–2.13 ± 0.08	–2.13	6.3 ± 0.3	–22.8	8.8 ± 0.3	–31.7	–20.67	–29.57
EtAc	–0.71 ± 0.04	–0.71	11.7 ± 0.3	–17.4	20.8 ± 0.3	–19.7	–16.69	–18.99
DMF	–0.42 ± 0.13	–0.42	3.3 ± 0.3	–25.8	7.5 ± 0.2	–33.0	–25.38	–32.58
DMSO	2.47 ± 0.13	2.47	5.0 ± 0.3	–24.1	9.3 ± 0.1	–31.2	–26.57	–33.67
Acetone	—	—	11.3 ± 0.3	–17.8	22.3 ± 0.2	–18.2	—	—
Pyridine	0.13 ± 0.04	0.13	–10.0 ± 0.2	–39.1	–20.8 ± 0.2	–61.3	–39.23	–61.17
Piperidine	—	—	–39.7 ± 0.3	–68.8	—	—	—	—
$CHCl_3$	—	—	6.4 ± 0.2	–22.7	10.7 ± 0.3	–29.8	—	—

[a] Ref. 22.

Table VI. Parameters of Organic Solvents after Koppel—Palm (23)

Solvents	*B*	*E*	*f*(ε)	*f*(*n*)
n-Hexane	0	0	0.185	0.2289
Benzene	48	1.93	0.231	0.2947
Toluene	58	1.13	0.239	0.2926
AN	160	5.21	0.480	0.2106
EtAc	181	0	0.374	0.2275
Acetone	224	2.13	0.465	0.2201
1,4-Dioxane	237	3.98	0.223	0.2543
THF	287	0	0.404	0.2451
DMF	291	2.6	0.488	0.2584
DMSO	362	3.7	0.485	0.2826
Pyridine	472	0	0.441	0.2989
Piperidine	647	0	0.381	0.2702

where r is the multiple correlation coefficient, r_d is the multiple correlation coefficient adjusted to the degree of freedom.

$$\Delta H^0_{sol} = (-9 \pm 2) - (0.121 \pm 0.006) \cdot B + (50 \pm 14) \cdot f(\varepsilon) + (111 \pm 37) \cdot f(n) \quad (7)$$

$$r = 0.994;\ r_d = 0.992;\ \sigma = 2.26;\ F^{2.5\%}_{tab} = 5.52;\ F = 156.8;\ n = 10$$

These equations may be used to estimate ΔH^0_{sol} for such solvents where carrying out the respective experiments is not possible or difficult.

The compensation effect of BA that was observed in alcohols is also observed in all the other organic solvents apart from alcohols and also if only the hydrocarbons are taken into account. This correlation is presented in Fig. 5, and the regression parameters of equation (1) are summarized in Table III.

Based on the proposed approach, one may estimate solubility of ASA in the hydrocarbons. From the correlation Eq. (3) and experimental ΔH^0_{sol}values of BA (Table I), the following ΔH^0_{sol}values for ASA are calculated: ΔH^{ASA}_{sol} (*n*-pentane) = 51.7 kJ·mol^{-1}; ΔH^{ASA}_{sol} (*n*-hexane) = 40.0 kJ·mol^{-1}; ΔH^{ASA}_{sol} (*n*-heptane) = 31.2 kJ·mol^{-1}; ΔH^{ASA}_{sol} (*n*-octane) = 29.7 kJ·mol^{-1}. If the correlation equation for ASA is used in the form:

$$T \cdot \Delta S^0_{sol} = (1.2 \pm 0.4) + (0.55 \pm 0.02) \cdot \Delta H^0_{sol} \quad (8)$$

Table VII. The Cross-Correlations of the Variables of the Koppel–Palm Fit

Benzoic acid			
	B	*f*(ε)	*f*(*n*)
B	1.000	0.457	0.165
f(ε)		1.000	0.483
f(*n*)			1.000
Acetylsalicylic acid			
	B	*E*	*f*(ε)
B	1.000	0.160	0.788
E		1.000	0.110
f(ε)			1.000

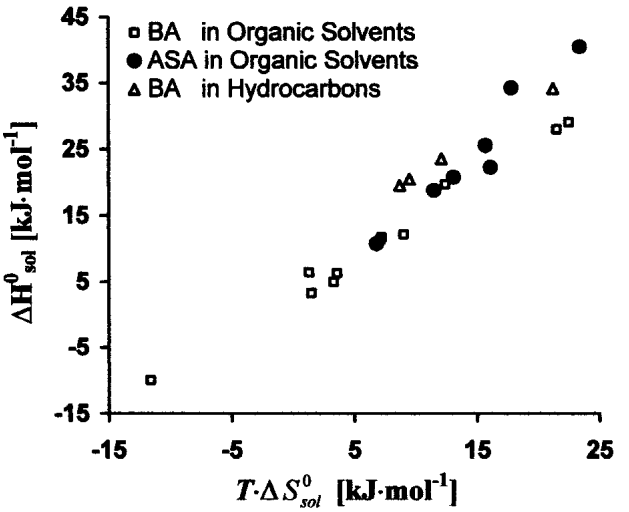

Fig. 5. Relationship between the enthalpic and entropic terms of Gibbs energy for the dissolution process of BA and ASA in organic solvents.

$$r = 0.999;\ \sigma = 3.74 \cdot 10^{-1};\ F^{2.5\%}_{tab} = 15.1;\ F = 1070.6;\ n = 5$$

Both solubility and the entropic term at 25°C (in parentheses) of ASA can be calculated: X_2 (*n*-pentane) = $1.34 \cdot 10^{-4}$ (29.6 kJ·mol^{-1}); X_2 (*n*-hexane) = $1.14 \cdot 10^{-3}$ (23.2 kJ·mol^{-1}); X_2 (*n*-heptane) = $5.72 \cdot 10^{-3}$ (28.4 kJ·mol^{-1}); X_2 (*n*-octane) = $7.29 \cdot 10^{-3}$ (17.5 kJ·mol^{-1}).

CONCLUSION

Based on the present experimental data, it can be concluded that a compensation effect between enthalpic and entropic terms of the Gibbs energy is observed for the dissolution of BA and ASA in alcohols and organic solvents. Therefore, solution enthalpy (especially in combination with ΔG^0_{sol}) is a powerful tool for studying the thermodynamics of solubility of drugs.

However, for more universally valid regularities and relationships, additional experiments need to be carried out in order to create individual thermochemical scales for definite groups of drugs with similar structures. It would be regarded a success to find correlation between the regression coefficient A_1 in Eq. (3) and the structure of the drug compound. This would enable prediction of the thermodynamic functions of solubility of other drug substances (e.g., including solubility in *n*-octanol), based on regression of thermodynamic compensation.

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