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Thermodynamic Study of Sublimation, Solubility, Solvation, and Distribution Processes of Atenolol and Pindolol

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Abstract: Temperature dependency of saturated vapor pressure, thermochemical, and thermodynamic characteristics of sublimation, as well as fusion and vaporization processes, for atenolol and pindolol was studied. Specific and nonspecific energetic terms in the crystal lattices were estimated. Temperature dependencies of solubility in buffer (pH 7.4), in *n*-octanol, and in *n*-hexane were measured. Thermodynamic functions of solubility, solvation, and transfer processes were deduced. It was found that transfer processes for the drugs moving from water into *n*-octanol are determined mainly by the entropy term. Distribution coefficients of the compounds in the water/*n*-octanol system were derived and compared with analogous coefficients calculated from saturation solubility data in the individual solvents. The impact of mutual dissolution of water and *n*-octanol molecules in the water/*n*-octanol system on distribution coefficients is discussed.

Keywords: Thermodynamics; sublimation; solubility; solvation; transfer; specific and nonspecific interactions; distribution; atenolol; pindolol; water/*n*-octanol system

Introduction

Pharmacokinetic characteristics of drugs for drug delivery processes are frequently described by *in vitro* parameters such as solubility in both hydrophilic and lipophilic systems, partitioning experiments, and diffusion studies. Both the *in vivo* behavior and the mentioned experimental parameters are determined by the molecular structure of the drug molecules, particularly by the solvation properties of the molecules. Usually, to analyze absorption and partitioning of molecules in various media, terminologies with regard to lipophilic and hydrophilic molecular properties are used which are not strictly quantitative. Introducing a thermodynamic description of the outlined processes provides an opportunity both for a deeper understanding and for quantitative characterization thereof. Moreover, the proposed approach enables us to estimate enthalpic and entropic effects on an absolute energy scale for the steps of passive drug transport and delivery.

This work is a continuation of the cycle of studies devoted to solvation properties of drugs based on molecular crystals.[1–5] The two compounds chosen for this study,

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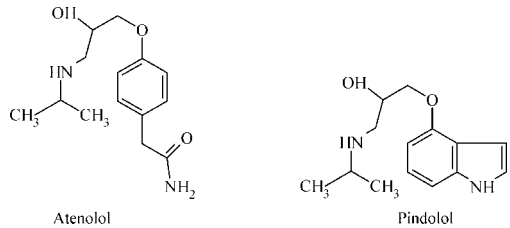

Figure 1. Structures of atenolol and pindolol.

atenolol and pindolol (Figure 1), are β-blockers, used in the treatment of hypertension and angina pectoris, and cardiac arrhythmia.[6] For this group, there is a distinctive relationship between hydrophilic/lipophilic properties and both pharmacodynamic (selectivity) and pharmacokinetic properties (degree and kinetics of absorption, distribution, and elimination) *in vivo*. Furthermore, the distinctive peculiarity of the drug molecules is their low partitioning coefficients in a water/octanol system, which makes the compounds attractive subjects for studying differences in the solvation effects in both phases.

Experimental Section

Materials and Solvents. Atenolol (benzeneacetamide, 4-{2-hydroxy-3-[(1-methylethyl)amino]propoxy}-, $C_{14}H_{22}N_2O_3$, FW 266.34, 98%, lot 99H1339) and pindolol {2-propanol, 1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]-, $C_{14}H_{20}N_2O_2$, FW 248.33, 98%, lot P-0778} were from Sigma (Sigma-Aldrich Co. Ltd., Gillingham, U.K.).

1-Octanol [*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2, lot 11K3688], AR grade, was from Sigma Chemical Co., and *n*-hexane (C_6H_{14}, MW 86.18, lot 07059903C), AR grade, was from SDS (Peypin, France). The buffer solution for pH 7.4 was prepared by mixing solutions of appropriate sodium and potassium salts of phosphoric acid. All the chemicals were AR grade. pH values were checked using a Toledo MP 220 pH meter (Mettler) standardized with pH 1.68 and 9.22 solutions.

Determination of Solubilities. Solubilities of the drugs were determined over a wide temperature range 15–42 $\pm$ 0.1 °C by an isothermal saturation technique. Upon centrifugation of the solid phase, the rest was removed by filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size), and the bulk solution was measured spectrophotometrically using a UV-2401 PC spectrophotometer (Shimadzu) according to the previously described protocol.[1] The extinction coefficients in *n*-octanol are as follows: $\varepsilon(\lambda=227\text{ nm}) = 1.047 \times 10^4$ for atenolol and $\varepsilon(\lambda=219\text{ nm}) = 2.892 \times 10^4$ for pindolol. In buffer (pH 7.4), the extinction coefficients are as follows: $\varepsilon(\lambda=274.5\text{ nm}) = 1.239 \times 10^3$ for atenolol and $\varepsilon(\lambda=218\text{ nm}) = 4.558 \times 10^4$ for pindolol. The experimental results are given as the average of at least three replicated experiments with statistical errors being within 2.5%.

Determination of Partition Coefficients. The method of isothermal saturation was used for the determination of partition coefficients $P(D_{7.4})$. The procedure was as follows. *n*-Octanol solutions at a fixed concentration were prepared, varying the concentrations between one-tenth and the maximum solubility value. The respective solution was left in a thermostated ampule, with the same volume of water added. Equilibration took 24 h under continuous stirring. The initial concentration in the octanol solutions and the final concentration of the substance after equilibration were determined by spectrophotometry. All experiments were carried out at 25 °C.

The partition coefficient was calculated as

$$P = C_{ow}/C_{wo} \tag{1}$$

where C_{ow} and Cwo are the molar concentrations of the solute in the mutually saturated phases of octanol and water, respectively. The correctness of the P value was verified by checking the mass balance of the starting amount of substance i compared to total amount of the substance partitioned between the two phases

$$m_i = m_{ow} + m_{wo} \tag{2}$$

where m_i (C_iV_i) is the starting mass (in moles) of the substance, m_{ow} ($C_{ow}V_{ow}$) is the mass of the substance dissolved in the water-saturated octanol phase, and m_{wo} ($C_{wo}V_{wo}$) is the mass of the substance dissolved in the octanol-saturated water phase. Each experiment was conducted in at least triplicate.

DSC Experiments. Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin Elmer Analytical Instruments, Norwalk, CT) and Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing (20 mL/min) dry nitrogen gas of high purity (99.990%) using standard closed aluminum sample pans. The differential scanning calorimeter was calibrated with indium from Perkin-Elmer (P/N 0319-0033). The value of the determined enthalpy of fusion corresponded to 28.48 J/g (reference value of 28.45 J/g). The melting point was 429.7 $\pm$ 0.1 K (n = 10). All the DSC experiments were carried out at a heating rate of 10 K/min. The accuracy of weight measurements was $\pm$0.005 mg. The enthalpy of fusion at 298 K was calculated with the following equation under the assumption that $\Delta C_p \approx \Delta S_{fus}$ (where ΔC_p is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the melt):

$$\Delta H_{fus}^{298} = \Delta H_{fus} - \Delta S_{fus}(T_m - 298.15) \tag{3}$$

The difference between heat capacities of the melt and the solid states is approximated by the entropy of fusion (as a "worst case" estimate). This approach has been used by Dannenfelser and Yalkowsky[20] and by Verevkin et al.[21]

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Vaporization enthalpy was evaluated by

$$\Delta H_{vap} = \Delta H_{sub}^{298} - \Delta H_{fus}^{298} \quad (4)$$

The ideal solubility value, X_2^{id}, was derived via eq 5 as proposed by Hildebrand[22] under the assumption that $\Delta C_p \approx \Delta S_{fus}$:

$$\ln X_2^{id} = (\Delta H_{fus}/R)(1/T_m - 1/T) - \Delta S_{fus}/R[\ln(T_m/T) - (T_m/T) + 1] \quad (5)$$

Detailed analysis of the adaptability of eq 5 has been described by Neau et al.[23]

Sublimation Experiments. Sublimation experiments were carried out with the transpiration method as described elsewhere.[7] The equipment was calibrated using benzoic acid (standard substance obtained from the Polish Committee of Quality and Standards) with the enthalpy of combustion (ΔH_c) being −3228.07 kJ/mol and the heat of fusion (ΔH_{fus}) corresponding to 18.0 kJ/mol. The standard value of the obtained sublimation enthalpy (ΔH_{sub}^0) was 90.5 ± 0.3 kJ/mol. This is in good agreement with the value recommended by IUPAC of 89.7 ± 0.5 kJ/mol.[8] 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

$$\ln(P) = A + B/T \quad (6)$$

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

$$\Delta H_{sub}^T = -R\partial(\ln P)/\partial(1/T) \quad (7)$$

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

$$\Delta S_{sub}^T = (\Delta H_{sub}^T - \Delta G_{sub}^T)/T \quad (8)$$

where $\Delta G_{sub}^T = -RT \ln(P/P_0)$ and $P_0 = 1.013 \times 10^5$ Pa.

Results and Discussion

Sublimation Thermodynamics. The temperature dependencies of saturation vapor pressure of atenolol and pindolol are presented in Table 1. The thermodynamic characteristics of sublimation, fusion, and vaporization (calculated from the former two) are summarized in Table 2.

Sublimation data are yielded at elevated temperatures for experimental reasons. To improve the extrapolation to room conditions, the heat capacity [C_{pc}^{298}(ad) value] of the crystals was estimated using the additive scheme proposed by Chickos et al.[9] The experimental heat capacity value at 298 K was estimated with the following correlation equation proposed by Chickos et al.:[9] $C_{pc}^{298}(ex) = 0.75 + 0.15C_{pc}^{298}(ad)$. Heat capacity was introduced as a correction for the recalculation of the ΔH_{sub}^T value at 298 K (ΔH_{sub}^{298} value), according to eq 9:[9]

$$\Delta H_{sub}^{298} = \Delta H_{sub}^T + \Delta H_{cor} = \Delta H_{sub}^T + (C_{pc} - C_{pg})(T - 298.15) = \Delta H_{sub}^T + [0.75 + 0.15C_{pc}^{298}(ad)](T - 298.15) \quad (9)$$

where C_{pc} and C_{pg} are heat capacities of the crystal and gas phase, respectively; the heat capacity of the gas phase is negligibly small compared to that of the crystal.

Unfortunately, the crystal structures of the substances studied are not satisfactorily described in literature, and this fact makes it difficult to characterize the specific and nonspecific terms of the molecules in the crystal lattices. To overcome this problem, the following approach was used. The sublimation enthalpies for a selection of molecular crystals were taken from the database of Chickos et al.[10]

Table 1. Temperature Dependencies of Saturation Vapor Pressure of Atenolol and Pindolol

atenolol[a]		pindolol[b]	
t (°C)	P (Pa)	t (°C)	P (Pa)
123.0	3.34×10^{-2}	82.0	1.28×10^{-3}
126.1	4.55×10^{-2}	84.0	1.87×10^{-3}
128.9	5.61×10^{-2}	91.0	3.38×10^{-3}
130.1	6.52×10^{-2}	95.0	6.81×10^{-3}
131.1	7.07×10^{-2}	96.0	7.08×10^{-3}
135.0	1.18×10^{-1}	99.0	1.01×10^{-2}
139.6	1.70×10^{-1}	104.0	2.07×10^{-2}
142.0	1.94×10^{-1}	106.0	2.82×10^{-2}
145.1	2.92×10^{-1}	108.0	3.21×10^{-2}
		109.0	3.54×10^{-2}
		110.0	3.88×10^{-2}
		112.0	5.50×10^{-2}
		114.5	7.89×10^{-2}
		121.0	1.39×10^{-1}
		122.0	1.48×10^{-1}
		123.0	1.77×10^{-1}
		126.5	2.73×10^{-1}
		133.5	5.33×10^{-1}
		136.0	6.64×10^{-1}
		141.0	9.90×10^{-1}
		142.0	1.36
		152.0	4.14
		154.0	4.48

[a] Where ln[P (Pa)] = (37 ± 1) − (16149 ± 442)/T, $\sigma = 5.65 \times 10^{-2}$, $r = 0.9973$, $F = 1332.7$, and $n = 9$. [b] Where ln[P (Pa)] = (41.7 ± 0.4) − (17184 ± 150)/T, $\sigma = 9.52 \times 10^{-2}$, $r = 0.9992$, $F = 13122$, and $n = 23$.

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Table 2. Thermodynamic Characteristics of Sublimation, Fusion, and Vaporization Processes of Atenolol and Pindolol

	ΔG_{sub}^{298} [a] (kJ/mol)	ΔH_{sub}^{T} [b] (kJ/mol)	ΔH_{sub}^{298} [c] (kJ/mol)	C_{pc}^{298}(ad) (J mol^{-1} K^{-1})	ΔS_{sub}^{298} (J mol^{-1} K^{-1})	T_m (K)	ΔH_{fus} (kJ/mol)	ΔH_{fus}^{298} [d] (kJ/mol)	ΔS_{fus} [e] (J mol^{-1} K^{-1})	ΔH_{vap}^{298} [f] (kJ/mol)	X_2^{id} [g]
atenolol	71.1	134.3 ± 3.7	140.0 ± 3.7	381.5	215 ± 9	426.1 ± 0.2	38.7 ± 0.5	27.1	91 ± 1	101.3	2.02×10^{-2}
pindolol	68.0	142.9 ± 1.2	146.0 ± 1.2	354.9	251 ± 3	423.6 ± 0.2	60.6 ± 0.5	42.7	143 ± 1	103.3	2.37×10^{-3}

[a] $\Delta G_{sub}^{298} = -298.15RT\ln(P^{298}/P_0)$, where $P_0 = 101300$ Pa. [b] Without correction. [c] With correction on ΔC_p:[9] $\Delta H_{cor} = (C_{pc} - C_{pg})(T - 298.15) = [0.75 + 0.15C_{pc}^{298}(ad)](T - 298.15)$, where C_{pc} and C_{pg} are heat capacities for the crystal and gas phase, respectively; $\Delta H_{sub}^{298} = \Delta H_{sub}^{T} + \Delta H_{cor}$. [d] $\Delta H_{fus}^{298} = \Delta H_{fus} - \Delta S_{fus}(T_m - 298.15)$. [e] $\Delta S_{fus} = \Delta H_{fus}/T_m$. [f] $\Delta H_{vap} = \Delta H_{sub}^{298} - \Delta H_{fus}^{298}$. [g] Where $\ln X_2^{id} = (\Delta H_{fus}/R)(1/T_m - 1/T) - \Delta S_{fus}/R[\ln(T_m/T) - (T_m/T) + 1]$.

van der Waals molecular volumes were calculated with GEPOL[18] using Kitaigorodsky's atomic radii.[19] To estimate the energetic level of nonspecific molecular interaction within crystal lattices, which at the same time includes the respective contribution of the molecular conformational strength, those crystal structures of molecules meeting the following requirements were selected: (a) crystals without any hydrogen bond networks, (b) molecules that include groups of compounds with various topological structures [benzene, biphenyl, naphthalene, benzophenone, biphenyl ether, diphenylamine derivatives, and other bicyclic substances with a connecting bridge between the cyclic motifs of several atoms (not more than three)], and (c) molecules in which the size of substituents does not exceed the size of the *tert*-butyl fragment. Seventy-one molecular crystals were thus selected from the database, and for this group, the relationship between van der Waals volume and sublimation enthalpy can be described by the following correlation equation (Figure 2):

$$\Delta H_{sub}^{vdw} = (11 \pm 2) + (0.46 \pm 0.02)V^{vdw} \qquad (10)$$

where $r = 0.973$, $\sigma = 4.1$, and $n = 71$.

The results of this calculation are presented in Table 3. It is not difficult to see that the values of specific interactions in the crystal lattices for both substances are within 18–20 kJ/mol. This fact probably means that it is due to the creation of one hydrogen bond (because this value corresponds to the energy of one hydrogen bond), which contributes to the crystal lattice energy 15% of the energy of the nonspecific interactions.

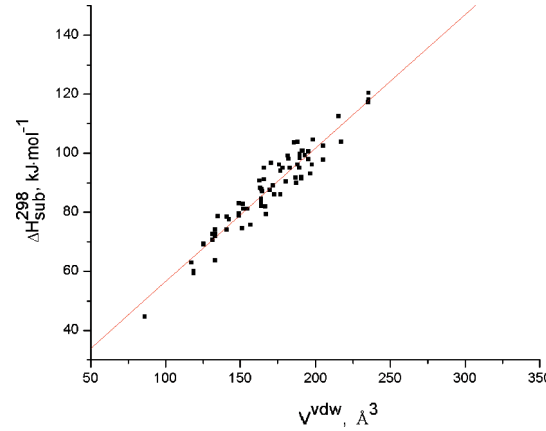

Figure 2. Relationship between sublimation enthalpies (ΔH_{sub}^{298}) and van der Waals volumes (V^{vdw}) of selected molecular crystals (see the text).

Few data for sublimation enthalpies of compounds with structures similar to atenolol and pindolol have been published (Table 4). If atenolol is compared with 2-phenylacetamide, it may be concluded that an additional substituent in the para position (atenolol) increases the crystal lattice energy by 41.9 kJ/mol. Analogously, indole compared to pindolol leads to a crystal lattice energy increased by 68.2 kJ/mol. It should be noted that introducing substituents into the 3-position of the indole molecule also increases the crystal lattice energy (3-methylindole and L-tryptophan). Moreover, the increment of this value does not essentially depend on the nature of the substituent.

As follows from Table 2, the enthalpies of vaporization for the studied drugs coincide within experimental errors.

Solubility and Solvation Processes. The partitioning process between water and octanol is the phase transition of the solute molecules across the interphase between the two phases (water and octanol) due to a thermodynamic driving force, which is defined by the difference in the chemical potentials of solute molecules dissolved in water and in octanol, respectively. However, sticking to the thermodynamic formalism, we find many questions remain about a model describing the elementary steps of the partitioning process. First of all, it is obvious that the solute molecules in the solution interact with their nearest neighbor solvent molecules in a stronger way compared to molecules farther out in the bulk. Therefore, a so-called solvation shell is

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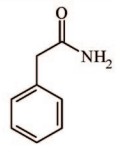
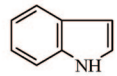
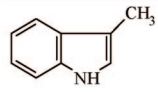
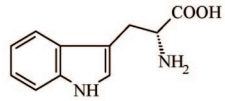
Table 3. Calculated Values of Nonspecific, $\Delta H_{sub}^{non\text{-}spec}$, and Specific, ΔH_{sub}^{spec}, Sublimation Enthalpy Terms of the Compounds under Investigation

	V^{vdw} (Å^3)	ΔH_{sub}^{298} (kJ/mol)	$\Delta H_{sub}^{non\text{-}spec}$ [a] (kJ/mol)	ΔH_{sub}^{spec} (kJ/mol)	ε_{sub} [b] (%)
atenolol	241.0	146.0 ± 1.2	126.4	19.6	15.5
pindolol	250.9	140.0 ± 3.7	121.9	18.1	14.8

[a] Calculated by the correlation equation (*eq 10*) $\Delta H_{sub}^{non\text{-}spec} = \Delta H_{sub}^{vdw}$; statistical error within 4 kJ/mol. [b] $\varepsilon_{sub} = (\Delta H_{sub}^{spec}/\Delta H_{sub}^{non\text{-}spec}) \times 100\%$; experimental error within 6%.

Table 4. Sublimation Enthalpies of Compounds with Structures Similar to Those of the Drugs Studied

Compounds	ΔH_{sub}	Ref
Atenolol	140.0 ± 3.7	tw[a]
	98.1 ± 0.9	(11)
		
2-phenylacetamide		
Pindolol	146.0 ± 1.2	tw[a]
	77.8 ± 1.6	(12)
		
Indole		
	83.3	(13)
		
3-methylindole		
	87.9 ± 8	(14)
		
L-tryptophane		

[a] tw – this work

created around each solute molecule. The strength and nature of the drug–solvent interactions within this solvation shell are nonhomogeneous (nonuniform): there are weak van der Waals interactions as well as stronger donor–acceptor interactions, hydrogen bonds (as in the extreme case of a donor–acceptor interaction), and electrostatic interactions, each being of different reach. Since most drug compounds are able to create hydrogen bonds, these molecules are solvated in solutions, particularly in aqueous solutions, by strong hydrogen bonds. During the partitioning–distribution process, a molecule solvated in water must rebuild this solvation shell into the octanol solvation shell (resolvation).

Temperature dependencies of solubility in water and *n*-octanol were measured. The experimental results for solubility and solvation processes are summarized in Tables 5 and 6.

To distinguish specific and nonspecific interaction by the outlined terms, *n*-hexane was used as a reference solvent, which interacts with the molecules only by nonspecific forces. In contrast to our previous works,[1–5] the solution enthalpy values of atenolol (16.4 ± 2.1 kJ/mol) and pindolol (10.2 ± 2.5 kJ/mol) in *n*-hexane are in most cases lower than analogous values for buffer (14.9 ± 0.7 kJ/mol for atenolol and 14.5 ± 0.7 kJ/mol for pindolol) and *n*-octanol (34.1 ± 1.0 kJ/mol for atenolol and 28.4 ± 1.0 kJ/mol for pindolol). In other words, *n*-hexane cannot be used as an "inert" solvent for the compounds studied. In our opinion, this fact may be explained by the extremely low solubility of the molecules in *n*-hexane ($X_2 \sim 10^{-7}$), and as a consequence, the molecules form associates (larger than dimers) in the solution. Confirmation of this fact comes in the high values of the activity coefficients (calculated on the basis of ideal solubility values): γ_2(atenolol) = 5.36 × 10^4 and γ_2(pindolol) = 6.42 × 10^3.

The dissolution processes of atenolol and pindolol in the buffer solution are accompanied by a decrease in entropy. This behavior may be connected with the hydrophobic effect (i.e., ordering of water molecules caused by hydrophobic fragments of the drug molecules). It should be mentioned that the outlined effect is 8 times more pronounced for pindolol than for atenolol, and this may be explained by the fact that the volume of the hydrophobic fragment of the pindolol molecule is larger than that of atenolol. In contrast to buffer, the solubility entropy terms in *n*-octanol are positive for both compounds, and for atenolol, this term is 1.6 times higher than for pindolol.

Pindolol is more strongly solvated in each of the considered solvents than atenolol is. The solvents can be arranged in the rank order of decreasing absolute value of solvation enthalpy for atenolol (water > *n*-hexane > *n*-octanol) and for pindolol (*n*-hexane > water > *n*-octanol).

To compare enthalpic and entropic terms of solvation, parameters ς_H and ς_{TS} are used to describe the relative fraction of enthalpy and entropy of solvation, respectively, which has been introduced elsewhere:[5]

$$\varsigma_{Hsolv} = [|\Delta H^0_{solv}|/(|\Delta H^0_{solv}|+|T\Delta S^0_{solv}|)] \times 100\% \quad (11)$$

$$\varsigma_{TSsolv} = (|T\Delta S^0_{solv}|/(|\Delta H^0_{solv}|+|T\Delta S^0_{solv}|)] \times 100\% \quad (12)$$

As one can see from the data in Table 6, for the considered compounds and solvents, the solvation processes are dominated by the enthalpy term over the entropy term; however, the contribution of the terms depends essentially on the nature of the solvent. As mentioned above, for the drugs studied in *n*-hexane, the ς_{TSsolv} value overweighs the analogous values for the other solvents. It should be noted that the minimum value of ς_{TSsolv} corresponds to that in *n*-octanol.

In our previous work,[5] a correlation was observed between the mean plasma half-life values, PHL_m, for some NSAIDs and the solvation enthalpies in octanol as a model for a lipophilic compartment. Unfortunately, definite half-life values for the compounds studied are to our knowledge not found in the literature probably because they are widely

Table 5. Temperature Dependencies of Atenolol and Pindolol Solubility, X_2[mole fraction], in *n*-Hexane, Aqueous Buffer at pH 7.4, and *n*-Octanol

	atenolol			pindolol		
t (°C)	*n*-hexane $X_2 \times 10^7$	water (pH 7.4) $X_2 \times 10^3$	*n*-octanol $X_2 \times 10^3$	*n*-hexane $X_2 \times 10^7$	water (pH 7.4) $X_2 \times 10^5$	*n*-octanol $X_2 \times 10^3$
15	2.63	–	–	3.02	–	–
20	3.05	1.27	3.38	3.81	2.21	1.61
25	3.77	1.37	4.09	3.69	2.49	2.05
30	3.81	1.49	5.30	4.08	2.65	2.36
37	3.05	1.75	7.30	4.00	3.04	3.09
42	5.04	1.93	8.74	4.84	3.40	3.70
A[a]	-8.3 ± 0.8	-0.6 ± 0.3	8.3 ± 0.4	-11 ± 1	-4.8 ± 0.3	5.2 ± 0.4
B[a]	1967 ± 253	1788 ± 95	4097 ± 118	1223 ± 300	1749 ± 89	3416 ± 115
R[b]	0.9684	0.9958	0.9988	0.898	0.9961	0.9983
σ[c]	6.37×10^{-2}	1.82×10^{-2}	2.26×10^{-2}	7.53×10^{-2}	1.71×10^{-2}	2.21×10^{-2}

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

Table 6. Thermodynamic Functions of Atenolol and Pindolol Solubility and Solvation Processes in Some Solvents at 298 K

solvent	X_2	γ_2[a]	ΔG_{sol} (kJ/mol)	ΔH_{sol} (kJ/mol)	$T\Delta S_{sol}$ (kJ/mol)	ΔS_{sol} (J K^{-1} mol^{-1})	$-\Delta G_{solv}$[b] (kJ/mol)	$-\Delta H_{solv}$[c] (kJ/mol)	$-T\Delta S_{solv}$ (kJ/mol)	ς_H[d] (%)	ς_{TS}[e] (%)
Atenolol											
n-hexane	3.77×10^{-7}	5.36×10^4	36.7	16.4 ± 2.1	-20.3	-68.1	34.4	123.6	89.2	58.1	41.9
water (pH 7.4)	1.37×10^{-3}	14.7	16.3	14.9 ± 0.7	-1.4	-4.7	54.8	125.1	70.3	64.0	36.0
n-octanol	4.09×10^{-3}	4.9	13.6	34.1 ± 1.0	20.5	68.8	57.5	105.9	48.4	68.6	31.4
Pindolol											
n-hexane	3.69×10^{-7}	6.42×10^3	36.7	10.2 ± 2.5	-26.5	-88.9	31.3	135.8	104.5	56.5	43.5
water (pH 7.4)	2.49×10^{-5}	95.2	26.3	14.5 ± 0.7	-11.8	-39.6	41.7	131.5	89.8	59.4	40.6
n-octanol	2.05×10^{-3}	1.2	15.3	28.4 ± 1.0	13.1	43.9	52.7	117.6	64.9	64.4	35.6

[a] $\gamma_2 = X_2^{id}/X_2$. [b] $\Delta G^0_{solv} = \Delta G^0_{sol} - \Delta G^0_{sub}$. [c] $\Delta H^0_{solv} = \Delta H^0_{sol} - \Delta H^0_{sub}$. [d] $\varsigma_H = [|\Delta H^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)] \times 100\%$. [e] $\varsigma_{TS} = [|T\Delta S^0_{solv}|/(|\Delta H^0_{solv}| + |T\Delta S^0_{solv}|)] \times 100\%$.

dependent on both first-pass effect and renal clearance, indicating both hydrophilic and lipophilic mechanisms.[16] Atenolol is reported to have a longer half-life (6–9 h) than pindolol (3–4 h).[16] Further, we tried to compare experimentally derived protein binding values with the solvation enthalpies in *n*-octanol. Pindolol has a higher level of plasma protein binding (60%) than atenolol (3%).[24] As the pindolol molecules are also more strongly solvated in *n*-octanol (−117.6 kJ/mol) than atenolol molecules (−105.9 kJ/mol), this is not unexpected because the plasma protein binding is thought to have comparably lipophilic characteristics.

Distribution and Transfer Characteristics (Buffer → *n*-Octanol). The thermodynamic functions of the transfer process (buffer → *n*-octanol) of the drugs under investigation are presented in Table 7, and the distribution parameters in water (buffer)/octanol phases obtained in this study and those collected from the literature are summarized in Table 8. Here, the transfer enthalpies were calculated as the difference between the solution enthalpies in *n*-octanol and water obtained from the temperature dependencies in the solubility experiments.

Table 7. Thermodynamic Parameters of Transfer Processes from Water (pH 7.4) to *n*-Octanol for Atenolol and Pindolol

	ΔG^0_{tr} (kJ/mol)	ΔH^0_{tr} (kJ/mol)	$T\Delta S^0_{tr}$ (kJ/mol)	ς_{Htr}[a] (%)	ς_{TStr}[b] (%)
atenolol	−2.7	19.2	21.9	46.7	53.3
pindolol	−11.0	13.9	24.9	35.8	64.1

[a] $\varsigma_{Htr} = [\Delta H^0_{tr}/(|\Delta H^0_{tr}| + |T\Delta S^0_{tr}|)] \times 100\%$. [b] $\varsigma_{TStr} = [T\Delta S^0_{tr}/(|\Delta H^0_{tr}| + |T\Delta S^0_{tr}|)] \times 100\%$.

Table 8. Distribution Parameters of Atenolol and Pindolol

	$D_{7.4}$[a]	P_{RS}[b]	$D_{7.4}$[c]	$D_{7.4}$[d]	P_{ACD}[e]	pK_a[f]	ionization (mol %, pH 7.4)[f]
atenolol	0.04 ± 0.07	3.0	0.005	0.78	1.25	9.55	99.3
pindolol	0.29 ± 0.09	82	0.2	1.2	93	8.80	96.2

[a] Mean from seven measurements at the different drug concentrations of the initial octanol phase. [b] $P_{RS} = X_2^{oct}/X_2^{w}$ at 25 °C. [c] From ref 15. [d] From ref 16 at 37 °C. [e] Calculated using Advanced Chemistry Development (ACD/Laboratories) Software Solaris, version 4.67.[17] [f] From ref 16.

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It is interesting to note that the drug transfer processes from buffer to *n*-octanol may help us to better understand the mechanism of partitioning between water and lipid phases. The advantage of such an approach is that the data obtained represent the pure forces of the transfer process (for all the thermodynamic parameters) without any side effects (such as mutual dissolution of solvents). In opposition to that, distribution experiments include the analysis of the influence of mutual saturation of the solvents. As one can see from the data in Table 7, the transfer processes for both compounds have negative Gibbs energy values; however, the actual value for atenolol is 4 times less than that of pindolol. The entropy terms of the considered drugs outweigh the enthalpy terms [and, moreover, this tendency prevails for pindolol: ς_{TStr}(pindolol) = 64.1% vs ς_{TStr}(atenolol) = 53.3.1%]. Thus, it may be assumed that distribution processes of the substances in water/octanol phases are entropy-driven. Because the mutual saturation of the water/octanol system can lead to a decreased entropy in each phase (ordering the solvent molecules around the solute molecules), it should be expected that during the distribution processes in the system (drug/water/*n*-octanol), the enthalpy term will be comparable with the entropy term. As a consequence, the distribution coefficients are close to zero. This tendency is observed in particular in partitioning experiments with drugs in water/octanol systems. From Table 8, it follows that the $D_{7.4}$ value of atenolol is close to zero; therefore, it is difficult to measure the value, as the experimental errors may exceed the parameter. The values obtained in this study are in good agreement with the values determined by Palm et al.[15] It is not difficult to see that the experimental and calculated distribution coefficients are significantly different from the ratio of solubilities in the isolated phases: $(P_{RS}/D_{7.4})(M_w/M_o)$(atenolol) = 10 and $(P_{RS}/D_{7.4})(M_w/M_o)$(pindolol) = 39 [i.e., the relation between the distribution coefficients calculated as the ratio of the concentration expressed in mole fraction ($P = X_2^{oct}/X_2^w$) and moles per liter ($D_{7.4} = C_{ow}/C_{wo}$) is $P_{RS} = D_{7.4}(M_o/M_w)$]. It is concluded that the values are very sensitive to mutual saturation of the water/octanol system.

It is our opinion that the compounds with partition coefficient values between 0 and 1 are particularly difficult cases for studying distribution processes. First, the experimental errors of the partition coefficient determination for these substances are in a range comparable to the values themselves. Second, the water and octanol molecules in octanol and water phases, respectively, act as a cosolvent in relation to the main solvent, which strongly influences the partitioning process. Therefore, the question of how likely it is that the approach proposed by us sufficiently describes the partitioning processes for the outlined drugs is raised. Probably, for the mentioned (anomalous) cases, this approach can be used as a "zero" approximation to evaluate the behavior of the system without cosolvent effects on the molecules and compare this to the impact of the cosolvent effect by mutual saturation on these molecules. It may be assumed that the drug molecules transfer from one phase to the other together with their respective solvation shells, because the chemical potentials of the studied molecules in both the water and the *n*-octanol phases are close to one another. Therefore, in these particular cases, we should not consider individual molecules, but more complicated systems comprising the molecule together with its solvation shell. Therefore, comparison of experimentally derived partition coefficients with calculated transfer functions (as discussed in this paper) provides us with the opportunity to analyze the impact of the solvation shells on partitioning processes.

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