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Modelling of pH dependent n-octanol/water partition coefficients of ionizable pharmaceuticals

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ABSTRACT

The lipophilicity of a compound is generally described by its n-octanol/water partition coefficient. Lipophilicity is an important descriptor, e.g. to correlate the toxic effect of substances or adsorption and transport properties of drug molecules in the human body.

Often drug molecules contain one or more ionizable groups, hence the lipophilicity is strongly pH-dependent.

The thermodynamic model COSMO-RS is a widely accepted method to predict partition coefficients of neutral compounds between neutral solvents and ionic liquids, thus COSMO-RS is principally able to handle molecules containing ionizable groups. In this work the model COSMO-RS was used to predict lipophilicity profiles of ionizable pharmaceuticals containing one acidic group. Under consideration of ion paring the partition of ionizable drugs can be calculated. The predicted pH dependent lipophilicities are in good agreement with literature data and own measurements.

1. Introduction

Lipophilicity represents the affinity of a molecule or moiety for a lipophilic environment. It is commonly measured by its distribution behavior in a biphasic system, like n-octanol/water (e.g., partition coefficient in n-octanol/water). The lipophilicity of a compound is an important property for the design of separation processes, for the characterization of hazardous compounds and for the evaluation of pharmaceutical active compounds [1]. Therefore methods to predict the partition coefficient are of special interest, especially those which require only structural information. The standard method in the field of drug design is the fragmental method clog *P* introduced by Hansch and Leo [2]. Thermodynamic based models like UNIFAC (KOW-UNIFAC) [3] and COSMO-RS [4] also proofed their predictive power for neutral compounds. However more than 60% of all listed pharmaceuticals have an ionizable group [5], despite various separation processes base on the varying lipophilicity of the neutral and the dissociated form of the target compounds.

The model by Hansch and Leo [2] is not able to describe the partition of ionizable compounds explicitly, where as UNIFAC is principally able to do so. The overall quality of COSMO-RS predictions cannot reach that of group contribution methods for systems were they are well-parameterized. However COSMO-RS predictions can be applied to problems where group contribution methods and other prediction tools cannot be used because of unknown interaction parameters or unknown group increments [6]. This is the case for many charged molecules like ionic liquids [7] and ionic surfactants [8] where the model COSMO-RS has shown to yield good qualitative and satisfying quantitative predictions. Wille et al. [9] demonstrated that COSMO-RS can qualitatively predict the influence of electrolytes on the partition coefficients of pharmaceuticals in their molecular form. However pH dependent partition coefficients of dissociating pharmaceuticals were calculated assuming that the ionized molecules partition between both phase corresponding to the amount of water in each phase. Hence the partition coefficient of all ionized species in n-octanol/water was assumed to be equal. Though partition coefficients of ionized compounds differ significantly from each other, furthermore a strong influence of the background salt concentration on the partition coefficient of the ionized species was reported by various authors [10,11].

The present work aims to predict the pH dependent lipophilicity profiles of acidic pharmaceuticals. Under consideration of ion

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pairing partition coefficients of neutral and charged pharmaceuticals are predicted and compared with literature data and own measurements.

2. Materials and methods

2.1. Modelling

2.1.1. COSMO-RS

COSMO-RS (Conductor like Screening Model for Real Solvents) is a predictive method for thermodynamic properties such as activity coefficients. The only input required is the molecular structure of all relevant compounds [4]. In a first step, three-dimensional structures of all involved molecules are generated with Hyperchem (Version 8.5) and conformational analysis is carried out using the semi-empirical force field method Amber99. Afterwards, the quantum chemical model COSMO (Conductor like Screening Model), is applied to each obtained conformer using density functional theory (DFT) at BP-TZVP-level with the program package Turbomole (Version 5.10) [12].

Result is an optimized geometry as well as screening charges of the molecule in an ideal conductor, from which interaction of the molecule with its surroundings can be derived [12]. Finally, COSMO-RS predicts the chemical potential of the component i in the mixture using statistical thermodynamics. The activity coefficient γ_i of component i can be written as:

$$\gamma_i = \exp\left(\frac{\mu_i^* - \mu_i^0}{RT}\right) \tag{1}$$

μ_i^* and μ_i^0 are the chemical potentials of component i in the mixture and in the reference state of pure liquid, respectively. x_i is the mole fraction of component i.

All COSMO-RS calculations have been performed using the program COSMOtherm (Version 2.1.01.08) [13]. Within a few internal model parameters the only required information is the molecular structure to predict n-octanol/water partition coefficients [14]. One of the internal parameters is the COSMO-radius of single elements. Whereas for most elements optimized COSMO-radii have been fitted, no COSMO-radius has been fitted yet for elements like sodium, potassium or lithium. Crude default values (Table 1), recommended by Eckert and Klamt [13] were used without any adjustment [15].

The probability of a conformer to occur is taken into account in COSMO-RS according to the Boltzmann distribution of the conformers total free energies [4].

2.1.2. Prediction of n-octanol/water partition coefficients

For prediction of n-octanol/water partition coefficients, infinite dilution activity coefficients of a solute i in the n-octanol-rich ($\gamma_i^{\infty,o}$) and the water-rich ($\gamma_i^{\infty,w}$) phase are calculated with COSMO-RS. The compositions of both phases are taken from literature [16]: The n-octanol-rich phase includes 28.9 mol% water whereas the aqueous phase is nearly free of n-octanol (0.00932 mol% n-octanol). The partition coefficient is then calculated as follows [17]:

$$K = \frac{x_i^o}{x_i^w} = \frac{\gamma_i^{\infty,w}}{\gamma_i^{\infty,o}}; \quad x_i \to 0 \tag{2}$$

Mostly, partition coefficients available in literature are molarity-based (indicated as P). With COSMO-RS calculated mole-fraction-based partition coefficients K are recalculated to P taking into account the molar volumes v of both phases at 25 °C.

$$P = \frac{v^w}{v^o} \cdot K \tag{3}$$

Table 1
Compounds investigated in this work.

Drug	Provider/purity	pK_a
Sodium Diclofenac	ABCR/98%	4.50 [27]
Sodium Ibuprofen	Fluka/>99.5%	4.45 [11]
Sodium Salicylat	Sigma/>99.5%	2.97 [27]

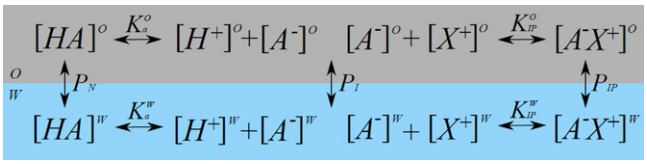

Fig. 1. Partition mechanisms of a monoacid HA between an aqueous phase (w) and a n-octanol-rich phase (o). Dissociated monoacids can be present in both phases either as free ions or as ion pairs. It is assumed that K_a is not affected by this consideration.

2.1.3. pH dependence and ion pairing

Most pharmaceutical solutes have ionizable groups and are partly or fully dissociated, depending on the actual pH value. Furthermore ion pair formation may occur, where the ionized species pairs up with simple ions of the background salt. Effects of ion strength have also to be taken into account. All reaction and partition mechanisms considered in this work are shown in a schematic diagram in Fig. 1.

The partition coefficient of the unionized species P_N refers to the ratio of concentrations in the water-rich (w) and n-octanol-rich (o) phase:

$$P_N = \frac{[HA]^o}{[HA]^w} \tag{4}$$

Square brackets indicate molar concentrations of the unionized species HA. Furthermore the partitioning of the ionic species A^- can be expressed as follows.

$$P_I = \frac{[A^-]^o}{[A^-]^w} \tag{5}$$

Because the electroneutrality must be maintained in each phase, the ionic species A^- can only transfer from one phase to another together with an equivalent amount of ions of opposite charge. Besides free ions associate in solution into pairs. The partition coefficient of ion pairs is given as follows.

$$P_{IP} = \frac{[A^-X^+]^o}{[A^-X^+]^w} \tag{6}$$

A major role in the association is played by long-range electrostatic forces between the ions [18]. It is generally accepted that free ions can be considered to be at chemical equilibrium with ion pairs. Therefore the association of ionic species A^- and counter ion X^+ can be quantified analogue to K_a by an ion pair formation constant K_{IP}.

$$K_{IP} = \frac{[A^-X^+]}{[A^-]\cdot[X^+]} \tag{7}$$

As mentioned above, the conventional view is that ion pairs are held together by long-range, nondirectional electrostatic forces, without having a covalent character [18].