INTERACTION OF DRUGS WITH SOIL ORGANIC MATTER STUDIED BY MICROCALORIMETRY

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Abstract

The usage of pharmaceuticals increases worldwide every year. The residues of these substances are excreted by the human or animal bodies and thus come into direct contact with the environment, mainly soils and ground water. The accumulation of pharmaceuticals in natural ecosystems may be problematic in the future therefore the knowledge of their behaviour, transport and interactions in the ecosystems is essential for their treatment. The most reactive substances in soils are humic as well as fulvic substances. Two fulvic acids stand as the model reactants with different pharmaceuticals in this study. These reactive compounds contain several kinds of active functional groups, such as hydrophilic hydroxylic or carboxylic groups, and also diverse hydrophobic structures. The interactions between fulvic acids and solutions of pure drugs were studied by isothermal titration calorimetry. The aim of the study was to observe the heat effects of the interactions and to describe the intensity of the binding process.

Keywords: Humic substances, drug, interaction, microcalorimetry

1. INTRODUCTION

Soils can be contaminated by pharmaceuticals [1-3]. It has been documented [4-6] that pharmaceuticals are not entirely removed from wastewater in wastewater treatment plants. As a result, pharmaceuticals contaminate surface and ground waters [4,7]. Municipal and hospital wastewater is the main sink of human pharmaceuticals, which are in the end predominantly degraded through processing in sewage treatment plants. However, balances of the input and output of pharmaceuticals into sewage sludge after technological treatment usually reveal that many pharmaceuticals are recalcitrant to biological and abiotic degradation and are therefore not removed quantitatively, thus entering the environment where they represent a risk for both aquatic and terrestrial ecosystems [8-10]. Introduction of drugs to the environment via irrigation is a highly relevant exposure route in semiarid zones where recycled wastewater is an important source of irrigation water [10,11]. Highly mobile drugs have the potential to leach to the groundwater, whereas strongly sorbing pharmaceuticals can accumulate in the top-soil layer. These compounds can subsequently affect the soil microbial community and may be taken up by plants [10,12]. Dissolved organic matter can affect transport and sorption of organic compounds in soils [10,13]. Dissolved organic matter can increase the solute’s apparent solubility and therefore enhance its mobility. Alternatively, dissolved organic matter can reduce mobility due to sorption to the soil solid phases. These processes are controlled by the binding affinity of the contaminant to organic matter [10,13].

The most important constituents of organic matter are humic substances [14,15]. There is a growing interest in the investigation of their interactions with different types of pollutants [1-3,14-16]. Limited research has been conducted to determine the occurrence and direct health risks of primary drugs, environmental degradation, transformation, and the fate of pharmaceuticals are poorly understood [17]. Recently published studies are focused mainly on adsorption processes and determination of parameters of different adsorption isotherms, e.g. [2,8,17]. Some authors calculated thermodynamics parameters (as $\Delta G°$, $\Delta S°$ etc.) on the basis of experimentally determined adsorption characteristics [18-20]. Thermodynamic parameters reflecting interactions of drugs in soils have been determined indirectly, usually batch sorption techniques performed at various temperatures. There are no direct, calorimetric studies. On general level, there is a very little knowledge on the thermodynamic consistency and true relevance of indirectly determined parameters. We hope that the thermodynamic parameters have high impact for the behaviour of drugs in nature, their mobility and immobilization ability in soils. However, our approach is different. This contribution is focused on direct determination of the thermodynamic parameters by means of microcalorimetry (similarly as in ref. [21]). The directly determined changes in Gibbs energy, enthalpy, and entropy can provide true values characterized interactions between humic substances and used pharmaceuticals.

2. MATERIALS AND METHODS

Standards of fulvic acids (FA1 – Fulvic acid Nordic Aquatic 1R105F, FA2 – Fulvic acid Pahokee Peat 2S103F) were purchased from the International Humic Substances Society, USA. The pharmaceuticals diclofenac and ibuprofen were purchased from Sigma-Aldrich, Germany. Stock solutions of fulvic acids were prepared by dissolving the precise amount of its powder in pure water (ELGA PURELAB flex), molar concentrations of both acids were 8.56 mM. The solutions of pharmaceuticals were prepared in pure water (diclofenac $6.75 \cdot 10^{-5}$ M, ibuprofen 24.2 mM) as well and all the solutions were stirred overnight.

The calorimetric experiments were performed using the microcalorimeter PEAQ-ITC, Malvern Instruments, at 25°C. The method is based on the titration of one solution with higher concentration from the syringe (40 μl) into the second solution of lower concentration filled in the measuring cell of the instrument (200 μl) under constant temperature. The heat effects (exothermic or endothermic) occurred during the experiment after each injection are observed as separated peaks on the raw signal of the heat flow detected as the temperature difference between the sample and reference cell of the instrument. The solution of FA was filled in the measuring cell in the case of ibuprofen and filled in the syringe in the case of diclofenac. Experimental setup: 19 aliquots, titration interval 150 s.

3. RESULTS AND DISCUSSION

This study was based on the determination of the thermodynamic parameters and on the comparison of two different fulvic acids (they have different origin) from the calorimetric point of view. The obtained results were evaluated in the instrument software according to the standard procedure. The signal of the blank experiments was subtracted from the real experiment data. Then, in the first step of the data evaluation from the enthalpogram (**Figure 1**) the peaks were integrated to obtain the enthalpies for every single injection.

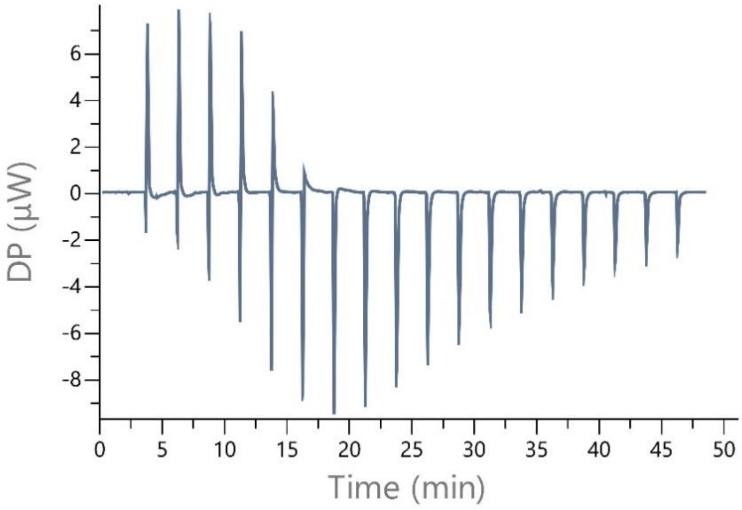

Figure 1 Raw titration data for the interaction of ibuprofen and FA2. DP stands for differential power (heat flow), after the baseline correction, at 25 °C. Initial concentration of ibuprofen in the syringe was 24.2 mM and FA2 in the measuring cell 8.56 mM.

Further, the dependence of the enthalpy change was plotted versus molar ratio of the reactants or concentration as presented in **Figure 2** and **Figure 3**. The experimental conditions should be set as good as to get the S-shape curve suitable for fitting in the software. Without the satisfactory shape of the fitting curve there are no reliable parameters determined.

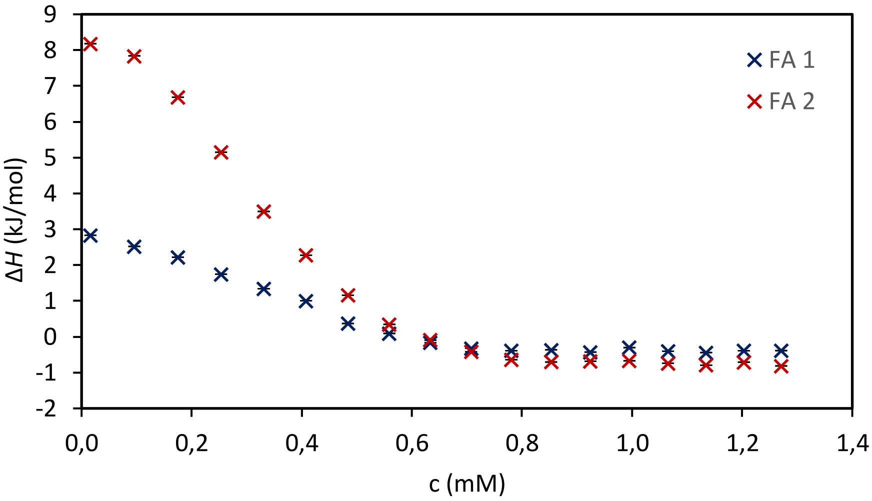

Figure 2 Calorimetric titration curves at 25 °C obtained after the raw data integration, titration of fulvic acid (initial conc. 8.56 mM) into diclofenac (initial conc. 0.0675 mM). Exothermic binding process, higher enthalpy change observed for interaction between diclofenac and FA2.

The main aim of this study was to observe and compare the behaviour of the soil organic matter with the pharmaceuticals and describe the basic parameters of these interactions, mainly the intensity of the binding process. As shown in **Figure 2** and **Figure 3**, there are significant differences between the intensities of the binding process when compared two selected pharmaceuticals.

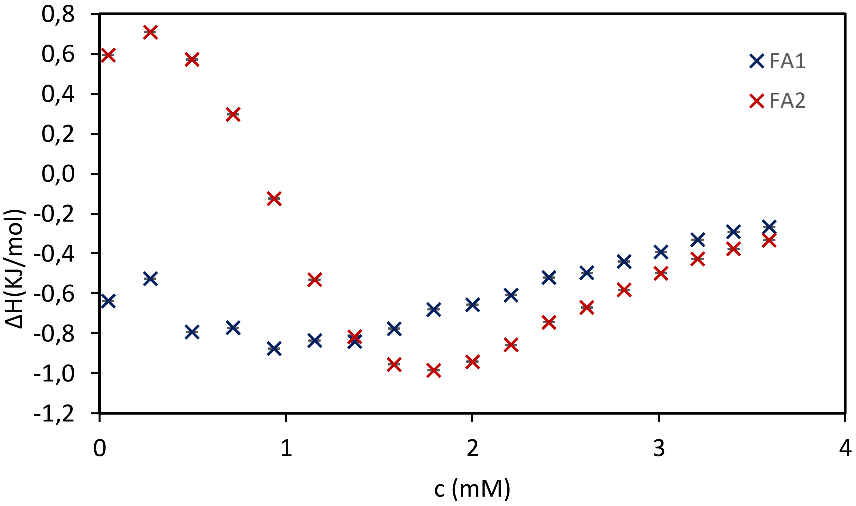

Figure 3 Calorimetric titration curves at 25 °C obtained after the raw data integration, titration of ibuprofen (initial conc. 24.2 mM) into fulvic acid (initial conc. 8.56 mM). Extremely low heat effects observed, different shapes of the curves occurred in comparison to behaviour with diclofenac.

The obtained thermodynamic parameters for diclofenac are summarized in **Table 1**, they were calculated automatically in the software after the data fitting process.

Table 1 Thermodynamic parameters of interactions between both fulvic acids and diclofenac

	Δ*H* (kJ/mol)	**Δ*G* (kJ/mol)**
FA 1	-16	-23
FA 2	-15	-22

The results of the titration of ibuprofen into the solution of fulvic acids are presented in **Figure 3**. It was quite complicated to fit the data for ibuprofen because of the presence of the minimum around 1.5 mM. This unusual shape can be evaluated using another fitting model (two sets of sites).

We observe different shapes of the curves in both figures which is caused by the variety of functional groups of the pharmaceutical molecules. Diclofenac shows more intensive interaction with both fulvic acids. Moreover, the enthalpy of binding FA2 with diclofenac is almost ten times higher than with ibuprofen which might be caused by better reactivity of FA2 (higher amount of reactive functional groups in FA structure) or better combination of those functional groups with diclofenac.

4. CONCLUSION

This paper describes the interactions between widely used pharmaceuticals ibuprofen and diclofenac with soil organic matter, standards of two different fulvic acids. The interactions were studied by a microcalorimetry technique isothermal titration calorimetry to obtain main thermodynamics parameters such as enthalpy or Gibbs energy of the binding process. The concentrations of pharmaceuticals used in this study was set according to the previous preliminary results of our research team as well as the knowledge of the possible concentration in the soils or wastewater. This study provided the basis for the subsequent research in this topic.

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